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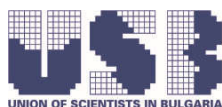
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Invited Speakers

The Why, the What and the How of Dynamical Time Series Modeling

Prof. Maia Angelova

School of IT at the Deakin Melbourne Burwood Campus, Australia

In this talk I will share our current research on modelling complex physiological time series data for objective evaluation of health, physical and cognitive performance. The advances of health and performance monitoring with wearable devices have created new challenges for data science and mathematical modelling by providing massive volumes of continuous time series data in different form, shape and size, captured from our locomotor movements, heart rate, respiration and brain waves. Often for evaluating our physical and cognitive performance, as well as our wellbeing and the quality of life, specialists use different questionnaires. This inevitably brings elements of subjectiveness in the evaluation, which can on occasions provide inadequate or wrong evaluation of the conditions. One aim of our research program is to develop, based on the sensor signals, objective tools for evaluation and classification of physical and cognitive conditions. This brings new challenges in the automatic learning from these signals mainly due to volume and complexity of the data, as well as the inadequacy, or the need of generalisation or adaptation of current metrics used in data mining, machine and deep learning algorithms.

Curriculum Vitae

Maia Angelova is a Professor of Data Analytics and Machine Learning at the School of IT at the Deakin Melbourne Burwood Campus. She is the Director of the Data to Intelligence (D2I) Research Centre and leads the Data Analytics Research Lab at the School of IT. Maia joined Deakin in January 2017. Prior to this, she was a Professor of Mathematical Physics and Leader of the Mathematical Modelling Research Lab at Northumbria University at Newcastle upon Tyne UK since 2004 and before that a Lecturer in Physics in Somerville College at the University of Oxford UK from 1991 to 1996. Maia's research expertise and interests are in modelling: data-driven modelling of complex physiological systems with specific interests in modelling sleep and insomnia, diabetes, dementia, depression, ageing including healthy ageing. She has strong expertise in time series analysis, spectral analysis and dynamical systems. She uses symmetry and is an expert in representations of groups with anti-unitary operators. She has worked on coherent and squeezed states, which find applications in quantum optics, quantum computing and quantum control. She is the co-author of a Machine Learning (ML) model "Targeted Projection Pursuit" TPP, for dimensionality reduction and visualisation of multivariate data, and a the corresponding tool in Java is available in the WEKA. She was the Coordinator and Principal Investigator of European Framework Program 7 Marie Curie project MATSIQEL, "Models of ageing and technological solutions for improving and enhancing the quality of life" with 86 participants from 6 countries and 4 continents. Maia is a Fellow of The Institute of Physics, a member of The London Mathematical Society, the Australian Mathematical Society and the International Union of Crystallography. Maia is a member of the Editorial Board of Frontiers of Physics, Bioinformatics and Biology Insights and a member of Program Committee and Technical Committees of several international conferences in mathematical and theoretical physics, applied mathematics, data analytics and complex systems. Maia's research is at the boundary between theory and applications and she is increasingly interested in translational research into the areas of health, medicine and health care. She has been funded by the Australian Defence, Medical Research Council UK, EPSRC UK, European FP6 and FP7 Programs, The Royal Society, The London Mathematical Society, The Australian Mathematical Society and AMSI. She is a Fellow of The Institute of Physics UK, member of the Council in Complex Systems Society (CSS), member of Society of Mathematical Biology, The Australian Mathematical Society and The London Mathematical Society.



AI Approach to Predict Inhibitors of Drug Metabolizing Enzymes

Prof. Maria A. Miteva

Centre national de la recherche scientifique, INSERM, France

Artificial Intelligence (AI) and Machine Learning (ML) are more than just buzz words being used in the pharmaceutical and biotechnology industry. There is now a steady stream of publications and evidence outlining what these terms really mean, how they can be applied in a drug discovery and development setting, and how much value they add in terms of saving time, effort and costs. AI and ML can be used for target identification, drug design and optimization, predicting drug toxicity and adverse events. We will present in silico study integrating structural bioinformatics and machine learning approaches to predict inhibition of drug-metabolizing enzyme. Drug metabolizing enzymes (DME) play a key role in the metabolism, elimination and detoxification of xenobiotics, drugs and endogenous molecules. While their principal role is to detoxify organisms by modifying compounds, such as pollutants or drugs in some cases they render their substrates more toxic thereby inducing adverse drug reactions, or their inhibition can lead to drug-drug interactions. Predicting potential inhibition of DME is important in early-stage drug discovery. We focus on Cytochrome P450 (CYP) responsible for the metabolism of 90 % drugs and on sulfotransferases (SULT), phase II conjugate drug metabolizing enzymes, acting on a large number of drugs, hormones and natural compounds. We performed modeling using two learning algorithms, Support Vector Machine (SVM) and RandomForest combining chemicals, protein-ligand interactions and protein structure and dynamics information. Our inhibition models predict CYP and SULT inhibition for three isoforms with an accuracy of >80 % and are implemented in the new software DrugME.



Curriculum Vitae

Maria Miteva is a Research Director at INSERM. She has been working in Bulgaria (Bulgarian Academy of Sciences), Sweden (Karolinska Institutet), and France (CNRS, Inserm). She joined INSERM in 2002 and is currently co-directing the INSERM Unit ERL U1268 “Medicinal Chemistry and Translational Research”, at the Faculty of Pharmacy, University of Paris. She has strong expertise in medicinal chemistry, biophysics, drug-drug interactions, bioinformatics, chemoinformatics and AI for drug discovery and toxicity prediction. She has 4 patents and more than 100 peer-reviewed publications (ID ORCID:N-2419-2018). She edited the book “In silico lead discovery” (Bentham Sci 2011). She is an editorial board member for several reputed journals in the field and an Associated Editor for BMC Pharmacology and Toxicology.

Bio-Inspired Optimization of Type-2 Fuzzy Systems: Theory and Applications

Prof. Oscar Castillo

Tijuana Institute of Technology, Tijuana, Mexico

Type-2 fuzzy systems are powerful intelligent models based on the theory of fuzzy sets, originally proposed by Prof. Zadeh. Most real-world applications up to now are based on type-1 fuzzy systems, which are built based on the original (type-1) fuzzy sets that extend the concept of classical sets. On the other hand, type-2 fuzzy sets extend type-1 fuzzy sets by allowing the membership to be fuzzy, in this way allowing a higher level of uncertainty management for real-world problems. Even with the current successful applications of type-1 fuzzy systems, now many papers have shown that type-2 is able to outperform type-1 in control, pattern recognition, manufacturing, diagnosis and other areas. The key challenge in dealing with type-2 fuzzy models is that their design has a higher level of complexity, and in this regard the use of bio-inspired optimization techniques is of great help in finding the optimal structure and parameters of the type-2 fuzzy systems for particular applications, like in control, robotics, manufacturing and others. Methodologies for designing type-2 fuzzy systems using bio-inspired optimization in different areas of application are presented as illustration. In particular, we will cover Bee Colony Optimization, Particle Swarm Optimization, Gravitational Search and similar approaches to the optimization of fuzzy systems in control applications, robotics and pattern recognition. Finally, we will also consider using fuzzy logic for enhancing the performance of metaheuristics, where also good results have been achieved. In this case, again type-2 fuzzy logic outperforms type-1 and other methods for dynamic parameter adaptation in bio-inspired optimization techniques.

Curriculum Vitae

Prof. Oscar Castillo holds the Doctor in Science degree (Doctor Habilitatus) in Computer Science from the Polish Academy of Sciences (with the Dissertation "Soft Computing and Fractal Theory for Intelligent Manufacturing"). He is a Professor of Computer Science in the Graduate Division, Tijuana Institute of Technology, Tijuana, Mexico. In addition, he is serving as Research Director of Computer Science and head of the research group on Hybrid Fuzzy Intelligent Systems. Currently, he is the President of HAFSA (Hispanic American Fuzzy Systems Association) and Past President of IFSA (International Fuzzy Systems Association). Prof. Castillo is also Chair of the Mexican Chapter of the Computational Intelligence Society (IEEE). He also belongs to the Technical Committee on Fuzzy Systems of IEEE and to the Task Force on "Extensions to Type-1 Fuzzy Systems". He is also a member of NAFIPS, IFSA and IEEE. He belongs to the Mexican Research System (SNI Level 3). His research interests are in Type-2 Fuzzy Logic, Fuzzy Control, Neuro-Fuzzy and Genetic-Fuzzy hybrid approaches. He has published over 300 journal papers, 10 authored books, 40 edited books, 200 papers in conference proceedings, and more than 300 chapters in edited books, in total 886 publications according to Scopus (H-index=62), and more than 1000 publications according to ResearchGate (H-index=73 in Google Scholar). He has been Guest Editor of several successful Special Issues in the past, like in the following journals: Applied Soft Computing, Intelligent Systems, Information Sciences, Non-Linear Studies, Fuzzy Sets and Systems, JAMRIS and Engineering Letters. He is currently Associate Editor of the Information Sciences Journal, Applied Soft Computing Journal, Engineering Applications of Artificial Intelligence, Granular Computing Journal and the International Journal on Fuzzy Systems. Finally, he has been elected IFSA Fellow in 2015 and MICAI Fellow member in 2017. He has been recognized as Highly Cited Researcher in 2017 and 2018 by Clarivate Analytics for his multiple highly cited papers in Web of Science.



Point of Care in the ICU

Dr. Biljana Kuzmanovska

Anesthesiology at Medical Faculty, Ss Cyril and Methodius University, Skopje, N. Macedonia

Point of Care (POC) refers to medical laboratory testing or other diagnostic tools that are performed outside of laboratory settings, such as bedside and near-patient settings. POC is any medical test that is performed ad hoc and provides quick results. POC can be used in community, at home, in ambulances, during patient transport, in emergency rooms and in intensive care units. There is growing need of POC in intensive care units (ICU). Time is of essence for diagnosis and treatment of critically ill patients hospitalized in ICU. These patients often have affection of multiple organ systems, and the complexity of their pathology requires multiple and often repeated diagnostic procedures, which can be time consuming. POC in ICU means fast diagnosis of certain conditions in critically ill patients and enables timely clinical decision making. Very useful POC test in ICU are coagulation tests (thromboelastography TEG), blood gases analysis, rapid microbiological tests. Bedside ultrasound is also a point of care diagnostic tool in ICU, used in detecting changes in internal organs, bleeding, pleural effusion etc., even accessing the state of hemodynamics. POC ultrasound is especially useful in unstable patients that are not fit for transport to radiology department for CT or MRI. In conclusion, Point of Care is diagnostic tools concept, which is particularly useful in care for critically ill patients, enabling fast clinical decision making.



Curriculum Vitae

Dr Biljana Kuzmanovska was born 1972 in Skopje, Macedonia. She is anesthesiologist who obtained her medical degree and specialization in Anesthesiology from Ss Cyril and Methodius University in Skopje, N. Macedonia. She defended Master and PhD Thesis in the field of Anesthesiology at the same university. Dr Kuzmanovska is author of several scientific publications, coauthor of three books in the field of anesthesiology and reanimation, and participant in several international multi centric scientific clinical trials as Principal Investigator for her clinical center. The results of some of the trials are published, and others are ongoing. She is contributor to the following published clinical trials:

- Effect of Intraoperative High Positive End-Expiratory Pressure (PEEP) With Recruitment Maneuvers vs Low PEEP on Postoperative Pulmonary Complications in Obese Patients: A Randomized Clinical Trial
- Writing Committee for the PROBESE Collaborative Group of the PROtective VEntilation Network (PROVENet) for the Clinical Trial Network of the European Society of Anaesthesiology et al. JAMA. 2019.
- Post-anaesthesia Pulmonary Complications After Use of Muscle Relaxants (POPULAR): A Multicentre, Prospective Observational Study
- Eva Kirmeier et al. Lancet Respir Med. 2019 Feb.
- Rivaroxaban for Thromboprophylaxis After Hospitalization for Medical Illness
- Alex C Spyropoulos et al. N Engl J Med. 2018.

Dr. Kuzmanovska was invited speaker to several international scientific conferences and congresses in the field of anesthesiology and intensive care. She currently holds the position of Associate Professor of Anesthesiology at Medical Faculty, Ss Cyril and Methodius University, Skopje, N. Macedonia. Researchgate score: 26.71, h-index: 5.

Integrating Microbiomes in the Context of Lung Disease

Prof. Krasimira Tsaneva-Atanasova

College of Engineering, Mathematics and Physical Sciences, University of Exeter, United Kingdom

Studies have shown that airway composition of microbes relates to diseases. The advent of microbial genomics has enabled the comprehensive characterization of diverse bacteria, fungi and virus found in the airway. While bacteria, fungi and viruses coexist as communities in the airway, most microbiome studies involve singular analysis of bacteria, fungi or viruses in isolation. Here we integrate multi-microbiomes from same samples for the first time using a similarity network fusion strategy. This holistic approach identifies clinically relevant high and low-risk clusters with greater precision. Subsequent weighted ensemble-based co-occurrence analysis between clusters shows that “interactions” between microbes are of equal if not of greater importance than individual microbes, promoting the concept of community as pathogens rather than individual microbes.

Curriculum Vitae

Krasimira Tsaneva-Atanasova earned her undergraduate and MSc degrees in mathematics at the University of Plovdiv, Bulgaria from 1991 until 1996. In September 2001 she started a PhD in applied mathematics at the University of Auckland, New Zealand. After completing her PhD in October 2004 she spent 18 months as a post-doctoral fellow at the Laboratory of Biological Modelling, National Institutes of Health, USA and another 15 months as a post-doctoral fellow at the Department of Mathematics and the Department of Biology at Ecole Normale Supérieure in Paris, France. She joined the Department of Engineering Mathematics at the University of Bristol in October 2007 as a lecturer and was promoted to a Reader in Applied Mathematics in 2012. She moved to the College of Engineering, Mathematics and Physical Sciences, University of Exeter (UoE) in July 2013 where she is currently a Professor of Mathematics for Healthcare.

Prof. Tsaneva-Atanasova ($h=29$, ± 2472 citations) has substantial experience of leading and managing large, multidisciplinary, research projects tackling biomedical and healthcare challenges. She is Associate Dean for Global in the College of Engineering, Mathematics and Physical Sciences, Director of the recently awarded Hub for quantitative Modelling in Healthcare (EP/T017856/1, 2021-2015), Co-director of the University of Exeter ISSF (a £4.8M initiative between UoE and the Wellcome Trust) and an Alan Turing Institute Fellow since October 2018. Her research and professional activities aim to inform novel applications of mathematics to enable the development of quantitative methods for healthcare and healthcare technologies. In her research, she develops and analyses mathematical models for applications to personalised prediction and clinical decision support in prevention, diagnosis or treatment of health-related conditions. Her international reputation in this field is evidenced through regular invitations to meetings such as SIAM DS, ECMTB, Equadiff, ICIAM, and awards like the prestigious Technical University of Munich (TUM) Institute for Advanced Study (IAS) Hans Fischer Senior Fellowship, a 3-year programme of research on Transient Emergent Network Dynamics (since April 2019). She is a Fellow of the Institute of Mathematics and its Applications (since 2020) and is regularly invited to assesses UK and international research activity at the interface between mathematics and medicine.



The New Field of Network Physiology: Mapping the Human Physiome

Prof. Plamen Ch. Ivanov

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The human organism is an integrated network where complex physiological systems continuously interact to optimize and coordinate their function. Organ-to-organ interactions occur at multiple levels and spatiotemporal scales to produce distinct physiologic states. Disrupting organ communications can lead to dysfunction of individual systems or to collapse of the entire organism. Yet, we do not know the nature of interactions among systems and sub-systems, and their collective role as a network in maintaining health. We initiated a new interdisciplinary field, Network Physiology, which aims to address these fundamental questions. Through the prism of concepts and approaches from statistical and computational physics and nonlinear dynamics, we will present a new framework to identify and quantify dynamic networks of organ interactions. We focus on inferring coupling and dynamical interactions among organ systems from continuous streams of synchronized recordings of key physiologic parameters. In contrast to traditional complex networks theory, where edges/links are constant and represent static graphs of association, novel approaches in Network Physiology aim to establish dynamical aspects of organ communications in real time, to track the evolution of organ network interactions and quantify emerging collective network behaviors in response to changes in physiological state and condition. We will report first findings utilizing this new framework to (i) investigate brain-brain network interactions across distinct brain rhythms and locations, and their relation to new aspects of neural plasticity in response to changes in physiologic state; (ii) characterize dynamical features of brain-organ communications as a new signature of neuroautonomic control; and (iii) establish basic principles underlying coordinated organ-organ communications. We will demonstrate how physiologic network topology and systems connectivity lead to integrated global behaviors representative of distinct states and functions. The presented investigations are initial steps in building a first Atlas of dynamic interactions among organ systems and the Human Physiome, a new kind of BigData of blue-print reference maps that uniquely represent physiologic states and functions under health and disease.



Curriculum Vitae

Professor Ivanov, PhD, DSc, is Director of the Keck Laboratory for Network Physiology at Boston University (<https://sites.google.com/site/labnetworkphysiology/home>), Associate Physiologist at the Division of Sleep Medicine, Brigham and Women's Hospital, and Lecturer in Medicine at Harvard Medical School. He has introduced innovative ways to analyze and model physiologic systems, adapting and developing concepts and methods from modern statistical physics, nonlinear dynamics and networks theory. He has investigated the complex dynamics and underlying control mechanisms of a range of physiological systems, including studies on cardiac and respiratory dynamics, sleep-stage transitions, circadian rhythms, locomotion and

brain dynamics, and has uncovered basic laws of physiologic regulation. His work is published in more than 150 publications and book chapters (H-index=60; 26,700 citations), and has been broadly featured in the media, including Scientific American, Science News, Physics World, Nature Research Highlights, Washington Post, Futurity Magazine, the Boston Globe. Professor Ivanov has pioneered the study of dynamical network interactions of physiological and

organ systems, and is the originator and founder of the field of Network Physiology. His current work focuses on developing theoretical framework to investigate network interactions among diverse organ systems, and how physiological systems integrate to generate distinct states and functions at the organism level to produce health or disease. His work lays the foundation of the Human Physiome, a new type of BigData, containing streams of continuously recording, high frequency, synchronized physiological signals under various physiological states and clinical conditions, with an associated Atlas of network maps representing network interactions among physiological systems at different levels in the human organism. Professor Ivanov is one of the nine founding members of PhysioNet (<https://physionet.org/>) — first NIH sponsored data sharing research resource. His research has been funded by the W.M. Keck Foundation, NIH, Office of Naval Research (ONR) and the US-Israel Binational Science Foundation (BSF). He has served as editorial and advisory board member for several leading journals, including EPL (Europhysics Letters), EPJ Nonlinear Biomedical Physics, Journal of Biological Physics (JOBP), Physiological Measurement, New Journal of Physics. He is Editor-in-Chief of the journal Frontiers in Fractal and Network Physiology, and is the founding director of the International Summer Institute on Network Physiology (ISINP, <https://isinp-3.lakecomoschool.org>), Lake Como School of Advanced Study. Professor Ivanov is Elected Fellow of the American Physical Society (2010). He is recipient of the Sustained Research Excellence Award (2009-2011) of the Biomedical Research Institute, Brigham and Women's Hospital, Harvard Medical School; of the Georgi Nadjakov Medal, Bulgarian Academy of Sciences (2012), and of the Pythagoras Award for high achievements in interdisciplinary research bestowed by the President of Bulgaria (2014).

Hybrid Intelligent Systems in Medical Diagnosis

Prof. Patricia Melin

Tijuana Institute of Technology, Tijuana, Mexico

Hybrid intelligent systems are formed by prudent combinations of intelligent models, such as neural networks, fuzzy models and others, to achieve efficient solutions to real-world problems. The main idea is to take advantage of the main characteristics of the individual models. For example, neural networks are good for learning from training data, while fuzzy logic is good for representing expert knowledge and uncertainty management, and evolutionary computing is good for search and optimization. Medical diagnosis are challenging due to their complexity and the uncertainty involved in the inherent decision making process done by Medical Doctors. In our work the proposed approach is to build powerful hybrid intelligent systems for achieving the automated medical diagnosis. The proposed hybrid architecture is based on modular neural networks for learning from large datasets of patients. Then for combining the outputs of the modules an integration based on type-2 fuzzy rules is performed for modeling the involved decision making process, as well as the inherent uncertainty in making the decisions. Finally, evolutionary or bio-inspired optimization techniques are used for optimizing the architectures of the neural networks, as well as the structures of the type-2 fuzzy systems. The proposed hybrid architecture has been tested and applied in different medical diagnosis problems with good results. In particular, we can mention hypertension diagnosis, arrhythmia diagnosis and diabetes diagnosis and detection of pulmonary diseases. We believe that the proposed hybrid intelligent approach can also be used for other diagnosis problem in the future.



Curriculum Vitae

Prof. Patricia Melin holds the Doctor in Science degree (Doctor Habilitatus, D.Sc.) in Computer Science from the Polish Academy of Sciences. She is a Professor of Computer Science in the Graduate Division, Tijuana Institute of Technology, Tijuana, Mexico, since 1998. In addition, she is serving as Director of Graduate Studies in Computer Science and is Head of the research group on Hybrid Neural Intelligent Systems (2000-present). Prof. Melin has published nearly 800 publications in indexed journals, book chapters, and conference proceedings, as well as nearly 50 books, and as consequence of this she has achieved more than 15000 citations with an H-index of 66 in Google Scholar. In addition, she has been awarded the Highly

Cited Researcher recognition in the area of Computer Science in 2017 and 2018 by Clarivate Analytics, being in the top 1% cited authors in this area. She has also been advisor of more than 85 graduate students in computer science at the Ph.D. and master's levels. She has been the President of NAFIPS (North American Fuzzy Information Processing Society) in 2019-2020. Prof. Melin is the founding Chair of the Mexican Chapter of the IEEE Computational Intelligence Society. She is member of the IEEE Neural Network Technical Committee (2007-present), the IEEE Fuzzy System Technical Committee (2014 to present) and is Chair of the Task Force on Hybrid Intelligent Systems (2007-present) and she is currently Associate Editor of the Information Sciences Journal, IEEE Transactions on Fuzzy Systems and Journal of Complex and Intelligent Systems. She is a member of NAFIPS, IFSA, and IEEE. She belongs to the Mexican Research System with level III (highest level). Her research interests are in Modular Neural Networks, Type-2 Fuzzy Logic, Pattern Recognition, Fuzzy Control, Neuro-Fuzzy and Genetic-Fuzzy hybrid approaches. She has served as Guest Editor of several Special Issues in the past, in journals like: Applied Soft Computing, Intelligent Systems, Information Sciences, Non-Linear Studies, Engineering Applications of Artificial Intelligence, Fuzzy Sets and Systems.

Angiogenesis in HIV Associated Preeclampsia

Prof. Thajasvarie Naicker

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Introduction: Preeclampsia (PE) is associated with inadequate uteroplacental perfusion and resultant endothelial dysfunction. This hypoxic microenvironment creates an imbalance of circulating angiogenic [vascular endothelial growth factor (VEGF); placental growth factor (PlGF)] and antiangiogenic factors [soluble fms-like tyrosine kinase-1 (sFlt-1) and soluble endoglin (sEng)]. Lymphatic vessels transport lymph fluid, proteins, and other cells that leak into tissues from the bloodstream and return them to the circulatory system. Both blood and lymphatic capillaries are lined by a monolayer of endothelial cells of mesodermal origin. In view of the paradoxical effect of HIV infection on PE development, this study examines angiogenesis (Flt-1, sFlt-1 and Eng) and lymphangiogenesis (lymphatic vessel endothelial-LYVE-1 and podoplanin) in the HIV endemic area of KwaZulu-Natal, South Africa.

Materials and Methods: Placental tissue was obtained from normotensive and preeclamptic women and further stratified by HIV status. Conventional immunohistochemistry performed using VEGF, PlGF, sFlt-1, Eng, LYVE-1 and podoplanin antibodies. Immunostaining within conducting (stem) and exchange (intermediate/terminal) villi at term were morphometrically analysed using the Zeiss Axiovision software.

Results: Flt-1, sFlt-1 and Eng was strongly immunolocalised in the endothelial, syncytio and cytotrophoblast cells as well as the extravillous trophoblast cells. A significant difference was noted in Eng immunoexpression between exchange ($p = 0.02$) and conducting villi ($p < 0.001$), with a higher immunoexpression in both villi types of the preeclamptic compared to the normotensive groups. However, a lack of statistical significance was noted on the effect of HIV status on Flt-1 and sFlt-1 immunoexpression in both exchange and stem villi. A significant difference was observed in the exchange villi for Flt-1 and sFlt-1 immunoexpression ($p < 0.003$) between the preeclamptic vs the normotensive groups, rather than stem villi. Irrespective of pregnancy type (normotensive versus PE), there was no significant effect of HIV status on Flt-1, sFlt-1 and Eng immunoexpression within the exchange and conducting villi. Podoplanin was immunolocalized in a reticular-like stromal complex within the exchange and conducting villi compared to the endothelial localization of LYVE. Both LYVE-1 and podoplanin were upregulated in HIV + vs. HIV- groups regardless of pregnancy and villi type. Both markers were down regulated in PE compared to normotensive pregnancies.

Conclusion: In conclusion, the paradigm shift of an imbalance in the angiogenic and lymphangiogenic transfer predominates in PE pregnancies. In PE comorbid with HIV infection, HIV utilizes its accessory proteins to exploit VEGF's effect. Anti-retroviral therapy leads to endothelial dysfunction and decreased nitric oxide that induce endothelial oxidative stress. Moreover, HAART re-constitutes the immune response in PE, thereby predisposing women to PE development. Further large-scale studies are urgently required to investigate the effect of the duration of HAART on PE development.



Curriculum Vitae

Professor Thajasvarie Naicker holds a Doctor in Philosophy degree (PhD) in Obstetrics & Gynaecology from the University of KwaZulu-Natal (UKZN), South Africa. In addition, she is a qualified microscopist and a Fellow (FRMS) of the Royal Microscopy Society, United Kingdom. She is a Professor within the Nelson R Mandela School of Medicine, College of Health Sciences in UKZN. Prof Naicker is the Research Head of Optics & Imaging Centre, Doris Duke Medical Research Institute and Chair of the Placental Research Group, the largest such group on the African Continent. Her research interests are in pre-eclampsia pathogenesis, HIV associated hypertension in pregnancy and paediatric nephropathy. Due to her experience in electron microscopy she has co-authored a number of papers involving ultrastructure. She is recognized as an established scientific researcher and has published over 324 scientific papers in journals and conference proceedings. She serves on the Editorial Board of journals, reviewer and has been invited as the plenary speaker at meetings. She has received a number of Scholarships. More recently, she received the Africa Oxford University Research Initiative for capacity development in Africa. Prof Naicker has a track record of carrying out capacity development workshops in Africa where she teaches academic staff the latest scientific/research methodologies in medicine. Additionally, she has an excellent track record of supervision having supervised 58 postgraduate degrees (masters and PhD level) to completion.

Understanding the Mystery behind Deep Learning – Deep, Deeper, Deepest

Dr. D. Jude Hemanth

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Deep learning has become an integral part of all automated applications, especially in the medical scenario. Literature reveals the availability of many deep learning models for disease diagnostic applications. In spite of the wide usage of these models, the research works reveal the non-availability of novel/innovative deep learning models which can improve the performance of the overall automated system. One of the significant reasons for this issue is the lack of proper understanding of the deep learning models by the budding researchers. Most of the researchers carry out experiments with standard models/software and report results without a proper discussion on the results. A proper understanding of the concepts will definitely lead the researchers to “out-of-box” thinking which in turn can pay the way for modified deep learning models. In this talk, the basic in-depth concepts of deep learning models will be discussed with an objective to trigger their innovative thoughts for the development of novel deep learning models. The points to be noted during practical implementations will be also discussed. Few conventional models also will be discussed along with the case study of COVID-19 detection from lung images. The details of different publicly available databases for COVID-19 images will be shared along with few experimental results/performance measures. An accuracy level in the range of 85–90% was achieved with the conventional deep learning models. These results clearly highlight the scope for improvement in the deep learning based automated systems. Few open research problems will be shared for the researchers to extend their work further if they are already working with the deep learning models. The contents of this talk are arranged in such a way that it will cater the needs of the beginners, intermediate and the expert researchers in this area. This talk will be beneficial to budding machine learning engineers, researchers working towards medical diagnostic applications and academicians.

Curriculum Vitae

Dr. D. Jude Hemanth received his B.E degree in ECE from Bharathiar University in 2002, M.E. degree in communication systems from Anna University in 2006 and Ph.D. from Karunya University in 2013. His research areas include Computational Intelligence and Image processing. He has authored more than 100 research papers in reputed SCIE indexed International Journal and Scopus indexed International Conferences. His Cumulative Impact Factor is more than 130. He has published 27 edited books with reputed publishers such as Elsevier, Springer and IET. He has been serving as Associate Editor of SCIE Indexed International Journals such as Journal of Intelligent and fuzzy systems. He serves as an Editorial Board member/Guest Editor of many journals with leading publishers such as Elsevier (Soft Computing Letters), Springer (Multidimensional Systems and Signal Processing, SN Computer Science, Sensing and Imaging) and Inderscience (IJAIP, IJICT, IJCVR, IJBET). He is the series editor of “Biomedical Engineering” book series in Elsevier and “Robotics & Healthcare” book series with CRC Press. He has received a project grant with 35,000 UK Pound from Government of UK (GCRF scheme) with collaborators from University of Westminster, UK. He has also completed 1 funded research project from CSIR, Govt. of India and 1 ongoing funded project from DST, Govt. of India.



He also serves as the “Research Scientist” of Computational Intelligence and Information Systems (CI2S) Lab, Argentina; LAPISCO research lab, Brazil; RIADI Lab; Tunisia and Research Centre for Applied Intelligence, University of Craiova, Romania. He has been also the organizing committee member of several international conferences across the globe such as Portugal, Romania, UK, Egypt, China, etc. He has delivered more than 100 Keynote talks/Invited Lectures in International Conferences/workshops. He holds professional membership with IEEE Technical Committee on Neural Networks (IEEE Computational Intelligence Society) and IEEE Technical Committee on Soft Computing (IEEE Systems, Man and Cybernetics Society). Currently, he is working as Associate Professor in Department of ECE, Karunya University, Coimbatore, India.

Session 1

Bioinformatics and Computational Biology

Computational Epigenetic Analysis of Genes for Cellular Stress and Toxicity in Complex Diseases

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Background: Complex diseases, also called multifactorial, are the most frequent and socially significant diseases both influenced by genetic and environmental factors. In recent years, Genome-Wide Association Studies (GWAS) has identified and confirmed a number of genetic variants for susceptibility to many complex diseases and pathological conditions. However, these findings explain only small part of the overall genetic risk for these diseases, which necessitates new studies to clarify the relationship between genetic factors and the clinical manifestation. Epigenetic factors are most likely involved in the complex interaction between genes and the environment. Studies on epigenetic factors in the genesis of the complex diseases are not yet sufficient. Therefore, epigenetic studies could shed light on understanding their pathogenesis. Epigenetic modifications are defined as heritable changes in gene function that occur without a change in the nucleotide sequence. They are mitotically and transgenerationally inheritable and potentially reversible. The most studied mechanisms that are known to affect the epigenome are DNA methylation, histone modification, and aberrant expression of microRNAs. Inherited or sporadic epimutations in different organs could lead to disease development.

Objective: We aimed to determine DNA methylation levels of genes connected to cellular stress and toxicity during the course of two complex diseases – type 2 diabetes mellitus (T2DM) and dermatitis herpetiformis (DH) in order to understand the role of epigenetic regulation in their development.

Materials and methods: We have performed analysis for promoter methylation of 22 such genes in blood samples of patients with these two diseases, compared with healthy controls using Human Stress & Toxicity PathwayFinder EpiTect Methyl II Signature PCR Array. The method is based on detection of remaining input DNA after cleavage with methylation-sensitive and methylation-dependent restriction enzyme. These enzymes digest unmethylated and methylated DNA, respectively. After digestion, the remaining DNA in each individual enzyme reaction is quantified by RT-PCR using primers that flank a promoter of gene of interest. The relative fractions of methylated and unmethylated DNA are subsequently determined by comparing the amount in each digest with that of a mock (no enzymes added) digest using a ΔC_t method and mathematical quotation.

Results and conclusion: We revealed highly increased promoter methylation (associated with gene silencing) of BRCA1, MSH2 and CDKN1a genes in T2DM patients and hypermethylation of CYP1A1 in DH patients. This pilot study paves the way to better understand the complex pathogenesis of diseases with the contribution of epigenetic dysregulation.

Keywords: Computational epigenetics, DNA methylation, Type 2 diabetes mellitus, Dermatitis herpetiformis, Cellular stress and toxicity.

Acknowledgements: The study was supported by Grant KII-06-IIH 33/34/2019 of BNSF.

Modelling Bacterial Classification for Antimicrobial Resistance

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Background: Different bioinformatics and statistical approaches are developed for bacterial antimicrobial resistance classification. Antibiotic resistance genes (ARGs) create a serious health problem that appears not only in clinical settings but also in non-clinical environments harboring many resistant bacteria. With the advance of next generation sequencing technologies complex metagenomes are studied. The objective of our work is to propose a new way to use spatial correlation Bayesian models (e.g. convolution models) to estimate the relative risk of antimicrobial resistance (AMR) abundance related taxomes using the available spatial information of the samples.

Results: The novelty of our approach is that we use a spatial correlation Bayesian model to estimate the epidemiological relative risk of AMR related taxomes. This modelling technique starts with using the AMR taxomes count data which are generated from the raw shotgun sequence files via the software ‘kaiju’. We model the epidemiological relative risk through a convolution model, which is a Bayesian hierarchical model that incorporates explicitly the spatial structure in the data as determined by the longitude and latitude of the samples. We use the Bayesian setting implementation in R as provided in package CARBayes, where inference is based on Markov chain Monte Carlo (MCMC) simulation. We apply a conditional autoregressive (CAR) prior on the spatial effect. The initial values of the response in the model are Standardized Incidence Ratios (SIR): observed vs expected values which are crude estimates of the relative risk. Finally, we generate maps using BatchGeo map tool with the results from the modeling: model estimated AMR relative risk and model estimated AMR relative risk with covariates (e.g. surface material, climate data). The model can also be used for data with excessive zeros by modeling the response as Zero Inflation Poisson (ZIP) process.

Conclusions: We could use relative risk as a new measure for antimicrobial resistance by incorporating the spatial information for the samples as defined by their origin. The level of annotation of the antimicrobial data which is directly related to the number of the identified AMR taxomes further influences the accuracy of classification of the samples. The use of an integrated dataset including a larger database or gene centric database such as Pangea can achieve better assessment of the variation between the samples and help determine their places of origin.

Keywords: Metagenomics, Convolution model, Bayesian hierarchical inference, Spatial correlation, Antimicrobial resistance.

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InterCriteria Analysis Approach for Decision-Making in Virtual Screening: Comparative Study of Various Scoring Functions

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In the last decades, the initial stages of drug design are largely supported by computer-aided approaches, including *in silico* virtual screening (VS). VS is a structure-based method, whose purpose is to discern possible lead compounds by computational evaluation of huge databases of potential drug candidates. The core of the VS is the docking-scoring method, applied to evaluate possible conformations and orientations of the ligand in the binding site of the protein, and rank them by the binding energy of the complex. In the process, the scoring function plays a key role, as it allows prediction of the ligand affinity to the receptor. There are different types of scoring functions, and their performance depends not only on the function per se, but also on the properties of the protein binding pocket (shape, polarity, size, and flexibility). This poses the question about the right selection of the scoring function, and of the final drug candidates in VS projects.

The goal of our study is to evaluate the ability of the recently developed InterCriteria Analysis (ICrA) approach to support decision making in VS. ICrA approach itself is a method for multicriteria analysis whose purpose is to distinguish possible relations in the behavior of pairs of criteria when multiple objects are considered [1]. Two fundamental mathematical concepts underlie ICrA – index matrices and intuitionistic fuzzy sets, allowing to account for the uncertainty in information processing. In the study, ICrA has been applied to compare the performance of diverse scoring functions, implemented in four software platforms for molecular docking and post-docking optimization, namely AMMOS2 [2], DOCK6 [3], X-Score [4], and FRED [5]. Docking and post-docking have been performed on five protein drug targets, selected to represent different physicochemical properties and topologies of the binding sites (estrogen receptor, thymidine kinase, coagulation factor X, ribonuclease, neuraminidase), using receptor-based focused libraries from ChemBridge diversity set of druglike molecules [6].

The ability of the scoring functions to rank active compounds towards receptor-based focused libraries has been examined, and the relationships between the scoring functions have been evaluated, applying ICrA. Our results demonstrated that the employed here empirical scoring functions were more appropriate for pockets of predominant hydrophobic nature, while the force field scoring functions performed better on mixed or polar pockets. We can conclude that more than one scoring function should be used to reveal possible drug candidates with elevated probability to become drug leads in further drug development studies.

Keywords: Structure-based drug design, Virtual screening, Molecular docking, Scoring function, InterCriteria analysis.

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Structure-Based Modelling Study of Multi-Target-Directed Small Molecules against Neurodegenerative Disorders: Exploring the Performance of Various Docking Scoring Functions

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The current therapy of the neurodegenerative diseases (NDDs) is based on the “one molecule-one target” paradigm. To combat the multifactorial nature of NDDs, the focus is now shifted toward development of small molecules that modulate more than one therapeutic CNS target – the so called multi-target-directed ligands [1].

This study presents *in silico* modelling of small molecules (ligands) able to simultaneously interact with three target proteins related to NDD symptomatics – acetylcholin-esterase (AChE), histone deacetylase 2 (HDAC2), and monoamine oxidase B (MAO-B). Docking-based virtual screening of large databases of drug-like molecules was applied. Considering the differences in performance of the scoring functions implemented in the docking programs, the docking of the potential triple hits (molecules able to interact with all three proteins) was done using three widely used molecular modelling software platforms: 1) rigid- and flexible-protein docking in MOE (v. 2019.0102, <https://www.chemcomp.com/>); 2) FlexX docking and HYDE rescoring in SeeSAR (v. 9.2, 2019, www.biosolveit.de); and 3) AutoDock Vina (<http://vina.scripps.edu>).

The binding energies estimated by the scoring functions were further analysed in terms of intercriteria analysis approach (ICrA) [2]. ICrA is based on two mathematical formalisms, namely intuitionistic fuzzy sets and index matrices, and seeks to uncover similarities in the behaviour of criteria when applied in the evaluation of multiple objects. ICrA was exploited as a potential tool to support the selection of an appropriate docking protocol for multi-target-directed ligands. The results on the intercriteria relations between the scoring functions indicate that a precise selection of scoring functions and docking protocols, conformed to available knowledge of the studied objects, is needed. Such analysis could assist in the optimisation of the selected screening protocol and particularly to avoid the computationally expensive docking protocols, which are highly consonant with less expensive ones.

Keywords: Neurodegenerative diseases, Multi-target-directed ligands, Docking, Scoring functions, Intercriteria analysis.

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Probable Hepatic and Skin Metabolic Activation, Predicting Molecular Properties and Bioactivity Score of a Newly Synthesized Bexarotene Derivative as a Potential Drug

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This study aimed to predict probable liver (*in vivo* and *in vitro* rat) and skin metabolites, their DNA and protein binding (mechanism of action), to calculate the molecular properties and bioactivity scores of a newly synthesized compound (4-Isopropyl-phenyl-methyldene-4-[1-(3,5,5,8,8-pentamethyl-6,7-dihydronaphthalen-2-yl)ethenyl]benzohydrazide) as a bexarotene derivative by *in silico* methods (QSAR Toolbox and Molinspiration chemoinformatics software). The parent structure of the newly synthesized compound can bind to DNA (A_N^2 , non-covalent interaction, radical mechanism via ROS formation and S_N^2 mechanism of action) but it cannot bind to protein and experimental metabolic pathways of action were not observed for rat *in vivo* and *in vitro*. The predicted metabolites after hepatic metabolic activation simulator for both conditions (*in vivo* and *in vitro* rat) are forty-nine and thirteen, respectively. The reactive metabolites for both (*in vivo* and *in vitro*) have different mechanism of action (A_N^2 , non-covalent interaction, radical mechanism and S_N^2) by DNA binding. Some reactive metabolites are with the following mechanisms of action (nucleophilic addition, Schiff base formation, S_N^2) by protein binding. One product of the skin metabolism simulator was predicted. The reactive metabolite has the following mechanism of action (A_N^2 , non-covalent interaction, radical mechanism and S_N^2) by DNA binding and the metabolite is not reactive by protein binding. The Molinspiration software has been used for identifying probable parameters - molecular properties (evaluating the descriptors for "drug-like" molecules according to Lipinski's rule) and bioactivity score (from active to moderately active) of the newly synthesized compound as a potential drug.

Keywords: A newly bexarotene derivative, Predict, Metabolic activation, Liver, Skin, Molecular properties, Bioactivity score, OECD QSAR Toolbox, Molinspiration.

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2. Molinspiration Chemoinformatic Software: <https://www.molinspiration.com/>

Generalized Net model of Ant Lion Optimizer

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In the presented paper, the functioning and the results of the work of a metaheuristic algorithm, known as Ant Lion Optimizer (ALO) is described using the apparatus of generalized nets (GNs) [1]. The GNs are proven as an appropriate and efficient tool for describing the essence of various optimization methods, such as metaheuristic algorithms [2]. The developed GN-model mimic the optimization processes based on the behaviour of antlions and their prey in nature. To model such interactions, ants are required to move over the search space, and antlions are allowed to hunt them and become fitter using traps. Since ants move stochastically in nature when searching for food, a random walk models ants' movement. Antlions are able to build traps proportional to their fitness and ants are required to move randomly. The final stage of hunt is when an ant reaches the bottom of the pit and is caught in the antlion's jaw. After this stage, the antlion pulls the ant inside the sand and consumes its body. The proposed GN-model execute the ALO algorithm conducting abovementioned basic steps and thus performing an optimal search. ALO GN-model considered here is another contribution to the open problem specified in [3], namely "to present each of the artificial intelligence areas by GNs". It is shown that the proposed ALO GN-model can be described by the same GN structure as the GN-model of Cuckoo search algorithm. Moreover, the *universal* GN-model [2] can be converted to the herewith presented GN-models of ALO by employing the appropriate hierarchical operators.

Keywords: Generalized nets, Ant Lion Optimizer, Metaheuristic algorithm.

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***In silico* Study of Mono- and Multicomponent Solutions of Antimicrobial Peptides**

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Antimicrobial peptides (AMPs) are small proteins with a molecular weight below 10kDa, 6-100 residues long, mainly cationic and with an amphiphilic nature (see, e.g. [1]). They are a key element in the primary host defense against microbial invasions in all eukaryotes. AMPs exhibit rapid and efficient antimicrobial activity against a range of pathogens – Gram-positive and Gram-negative bacteria, fungi, parasites, and some viruses. Despite the millions of years of co-evolution, bacteria have failed so far to develop even limited resistance against their action. All this makes AMPs a promising therapeutic alternative to the conventional antibiotics in the face of dramatically increasing bacterial multi-drug resistance. The antimicrobial action of AMPs is not completely understood, neither is their behaviour in bodily fluids prior to attacking the target membrane scrutinised. Thus, it is not known when they adopt their biologically active secondary structure and if certain collective phenomena take place. We present the first results of a large-scale *in silico* study of newly isolated peptides from the mucus of the garden snail *Cornu Aspersum* regarding their solvation behavior in mono- and multicomponent solutions and its possible association with their specific biological activity. The obtained results extend our earlier findings on α -helical and intrinsically disordered AMPs (bombinin H2 and indolicidin) [2, 3]. By means of molecular dynamics simulations we demonstrate on these examples that particularly extended AMPs tend to self-associate in clusters and this process not only drives their convergence into the biological fold but also appears essential for their interaction with the targeted bacterial membrane. The cluster formation patterns are analysed in the context of a possible identification of the essentially active components in multicomponent substances of natural origin.

Keywords: Antimicrobial peptides (AMP), Molecular dynamics simulations, Self-association, Cluster size, Cluster formation pattern, Peptide-membrane interaction, Biologicals.

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Session 2

Decision Making in Biomedicine and Healthcare

A Two-level model for Generating Healthy Routes in the Conditions of a Smart City

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One of the most famous applications of modern technologies such as IoT (Internet of Things) and CPSS (Cyber-Physical-Social Systems) is to build smart cities. Among many other things, a smart city supports smart transport, smart traffic control, smart hospitals, smart schools. Furthermore, a smart city provides a variety of services that can improve the quality of life of its citizens.

This paper presents a service for the citizens of a smart city called "healthy route". For people with various lung diseases, it is extremely important to take into account the degree of air pollution when moving from one starting point to a target point. The service offers routes that avoid areas with polluted air. The routes are visualized on the mobile phones of the users.

The article presents mathematical and computer models that are used to implement the service. It is essential that these models take into account the spatial and temporal aspects of the passage through a route and the state of the adjacent airspace. For this reason, the formalism for ambient-oriented modeling known as CCA (Calculus of Context-aware Ambients) is applied to represent the computer model. The algorithm for generating healthy routes, which is a modification of the classic variant of hierarchical search, is also presented.

A prototype of the service and its supporting infrastructure is being implemented for the region of Plovdiv within a project between the University of Plovdiv and North University of China. The supporting infrastructure, consisting of a sensor network, a communication infrastructure and a cloud, is supported by the Center for Excellence in Informatics and Information and Communication Technologies.

The problem presented in this article is a subject of intensive research. Therefore, the results of significant projects are summarized in the "Related Works" section. A comparative analysis of our approach with those known from the specialized literature is also made.

Keywords: Smart Cities, Intelligent Health Services, Mathematical Modeling, Ambient-Oriented Modeling.

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Virtual Assisted Technologies as a Helping Tool for Therapists in Assessment of Anxiety. Outcomes of a Pilot Trial with Chatbot Assistance

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As a result of many factors, it is suggested, that mental health issues associated with anxiety, depression and other disorders have been increased lately. Developing appropriate support strategies, especially for highly prevalent problems, such as mood disorders and more specifically for anxiety disorders is a critical public health challenge. Generally, a special topic in the field of healthcare, turns to be accessibility of specialists immediately when needed.

Online interventions have the potential to address this gap for a variety of disorders and mental health issues. Implementation of special support by the means of digital communication provides easy accessibility and anonymity, therefore making it suitable option for clients with variety of psychological issues. Psychology counseling is an area where specific elements, such as evaluation of emotional health, could be supported by the use of appropriate technologies. Such technology could increase accessibility to this type of assistance by reducing lengthy and costly travel to specialized centers. In addition, technology may enable over-burdened professionals to increase the reach of their services, and help people with physical limitations who have restricted ability to travel to receive care.

The present paper puts into discussion and analysis the effective role of so-called 'virtual assistants' (also known as 'chatbots'). The focus is set on technical side of development of electronic questionnaire for anxiety based on standardized test – Anxiety Symptoms Questionnaire [1]. The obtained results are processed by making use of intuitionistic fuzzy set (IFS) techniques. IFSs represent an extension of the concept of fuzzy sets, as defined by Zadeh, exhibiting function $\mu_A(x)$ defining the membership of an element x to the set A , evaluated in the $[0; 1]$ -interval. The difference between fuzzy sets and IFSs is in the presence of a second function $\nu_A(x)$ defining the non-membership of the element x to the set A , where $\mu_A(x) \in [0; 1]$, $\nu_A(x) \in [0; 1]$, under the condition of $\mu_A(x) + \nu_A(x) \in [0; 1]$. The theory of IFS contains many developed techniques not only for registering but also quantification of the so inherent to the real processes and objects imprecision and uncertainty. Based on the received answers, the intuitionistic fuzzy assessments $\mu(x)$ and $\nu(x)$ for determine the degree of calmness and degree of anxiety respectively of each interviewed will be given. The evaluations are formed on the basis of a set of intuitionistic fuzzy estimations $\langle \mu(x), \nu(x) \rangle$ of real numbers from the set $[0, 1] \times [0, 1]$, and $\mu(x) + \nu(x) \leq 1$. The degree of uncertainty $\pi(x) = 1 - \mu(x) - \nu(x)$ represents such cases wherein there is no information for the status of the current interviewed.

Keywords: Virtual assisted diagnosis, Digital healthcare, Anxiety, Mental disorders.

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Comparative Analysis of Decision-making Models in National Healthcare Systems of EU Member-States: Change-Drivers' Identification

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The paper is aiming to outline a typology of decision-making models, applicable at the healthcare systems of EU member-state. By comparing key features relevant to the decision-making processes at a national level we assessed the relevance of the existing principal models of decision-making to the dynamic context of Industry 4.0 and Industry 5.0. The central issue of the article is to find out how the applied decision-making models ensured the conformity between the national and the European healthcare priorities, and from the other side, how these models refer to the ability of rapid and elastic adaptiveness of the national systems to the social needs, the accessibility to information of the stakeholders, as well as the ethical acceptability of the decision making models and their transparency ensured through introducing of emerging technologies.

The sampling of countries examined consists of two old democracies, two member-states from the second enlargement of the Union, and two post-communist countries from the latest accession. The approach represents a consistently applied research method incorporating a system analysis, gap analysis, comparative analysis, which are described in a roadmap of the research.

Both primary and secondary data are used, and the core findings are based on a hybrid background, which is integrating ECHI (European Consumers Healthcare Index) results and HTA (Healthcare technology Assessment) with the purpose to chose comparable indicators, allowing further conclusions on the potential of the identified decision-making models, of being fast adaptive to the dynamically changing contexts. This refers directly to the management quality of the national healthcare systems, but also to their preparedness for digital transformation and their ability to respond to emerging risks.

The contribution of the paper, beyond the results of the comparison of different national decision-making models at the healthcare systems, is the identification of change-drivers which might be used for improvements of the national healthcare systems in conformity with the technological and social-political national developments

Keywords: Healthcare policy, Decision-making models, Healthcare technology assessment, Comparative analysis.

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Unified Approach for Designing a Database for the Needs of the Anesthesiologists in Bulgaria

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This paper addresses the need for building an information system and a database which can improve the functioning of the anesthesiology departments in Bulgaria. It also provides means for the analysis of the collected anesthesiology data.

An overview of already existing similar developments worldwide has been made. Based on the conducted analysis and the experience of the authors in anesthesia and software development, is proposed a set of data on the different medical conditions, the parameters of anesthesia and the information on the postoperative condition of patients. It is proposed a structure of a database and an architecture of an information system which will allow to work with the collected information.

The information system project is designed to operate on two different levels- hospital level and a national level. The separation of data is done based on the possible different usages of the data-storing of a hospital level archive, analyzing national data anesthesiological data with the purpose to improve the results in that area and reducing the complication while applying anesthesia including the post-operative period. A multitier client-server architecture will be used during the design of the system. The back-end provides a REST API that would also allow external system integration. Measures for information protection are proposed, which is especially critical in the analysis of a national database with the possibility of use by all registered medical specialists and organizations. In the national database the patient-sensitive information (e.g. names and identifiers) will be stored using one way encryption. The purpose of the proposed information system and database is to improve the quality of work of anesthesiologists and to use the collected data for future research. At the end of this paper is given a short overview of possible usage of IoT devices to automatically collect data during post-operative conditions.

Keywords: Medical database, Information systems in medicine, Anesthesiology.

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A New Machine Learning Modelling Approach for Patients' Mortality Prediction in Hospital Intensive Care Unit

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The prediction of mortality in a hospital Intensive Care Unit (ICU) is a challenge that must be addressed with high precision [1]. Advancements in collecting Electronic Health Records (EHR), computing processing power and Artificial Intelligence (AI) made it possible to model large medical datasets. Machine Learning (ML) is a subset of AI that is considered a powerful tool in predictive modelling. ML modelling is subject to the problem of class imbalance and is affected by the majority class, increasing the false-negative rate [2].

In this study, we built and evaluated one hundred and twenty-two ML models to predict approximately 36000 patients' mortality from the Medical Information Mart for Intensive Care III (MIMIC-III) dataset after being admitted to the Intensive Care Unit (ICU). Patients mortality is a binary classification task impacted with class imbalance bias towards the majority class. We examined the effect of various strategies on the models when dealing with class imbalance; including the use of sampling techniques [3], appropriate selection of evaluation metrics [4] and algorithmic modifications (Ensemble Learners) [5] combined with feature construction in a clinical setting.

In data preparation, four mortality and severity scoring features were constructed. These features enhanced our ML predictive modelling. The scores are; the Simplified Acute Physiology Score (SAPS II) [6], the Sequential Organ Failure Assessment score (SOFA) [7], the Glasgow Coma Scale (GCS) [8] and Elixhauser Comorbidity Index [9]. The use of standalone scores had some drawbacks regarding models' predictive power and generalization [10, 11].

When modelling, we overtook current published models' performance in testing [12] with our new modelling approach by combining severity and mortality scores with demographical and disease-related features. The combined constructed features with ensemble classifiers had a considerable impact on the classification. They resulted in an improvement in the mortality status prediction by facilitating an increase in the information contained within each variable and the weights for minority class records. For evaluation, the best five classification models for adults' mortality prediction were identified. The Area Under Receiver Operator Characteristic curve [13] of the models tested with isolated data was 0.65 to 0.95. These encouraging results can be used to guide further development of models to allow for a more reliable prediction of mortality status in ICU. This will be useful for ICU admissions planning and ensuring that medical care interventions can be appropriately targeted.

Keywords: Imbalanced Learning, Machine Learning, Mortality, Severity Scores, Classification, Sampling, Ensembles.

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Point of Care Lung Diagnostic in ICU – Our Experience with Bedside Lung Ultrasound

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Introduction: Lung ultrasound as a bedside diagnostic technique might be a helpful tool in clinical decision making in critically ill patients.

Aim of study: The aim of this study is to present 6 months experience of using lung ultrasound as a point of care tool in a tertiary university clinic ICU.

Material and methods: We performed a retrospective study of clinical records in patients with respiratory failure hospitalized in the ICU of Clinical Center “Mother Teresa” in Skopje, N Macedonia for the period from January 1st 2020, till June 1st 2020. We analyzed the use of bedside lung ultrasound. The examination was made according to the BLUE Protocol (1). The LUS exam was made with Ultrasound Machine Mindray TP2200 using the curvilinear probe.

Results: LUS was used in 48 out of 180 critically ill patients (26.6%). Pathological findings were noted in 42 patients (87,5%) , while 6 patients (12,5%) were with normal findings. Pleural effusion was detected in 10 patients (23.8%). Signs of Alveolocapillary syndrome were detected in 21 patients (50%) , and in 2 patients (4.7%) pneumothorax was detected. In 18 patients (42.8%) presence of lung consolidation was found; in 8 patients (44.5%) pneumonia and in 10 patients (55,5%) atelectasis. According to the results of the LUS in 19 patients (45.3%) some sort of invasive procedure was undertaken. In 7 patients (36,8%) thoracic drainage was performed and bronchoaspiration in 4 patients (21%). In 12 patients (63.1%), mechanical ventilation was initiated.

Conclusions: Based on our results we can conclude that Point of Care LUS is a helpful tool for rapid assessment of underlying pathological substrate in critically ill patients with acute respiratory failure and have important role in clinical decision making regarding therapy.

Keywords: Point of care, Lung Ultrasound, Critically ill.

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Computer-Based Rehabilitation of Cognitive Impairments in Patients with Multiple Sclerosis

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Multiple sclerosis (MS) is an inflammatory disease of the central nervous system, which leads to demyelination and subsequent neurodegeneration. The wide distribution of lesions in brain and spinal cord in patients with MS results in manifestation of motor, cognitive and neuropsychological symptoms, which can occur simultaneously or independently of each other. Cognitive impairments affect up to 70% of people with MS and negatively affect employment, social functioning, quality of life and daily activities. General cognitive symptoms, which include attention deficit, speed of information processing, long-term memory and executive functions, are the target of up-to-date research for rehabilitation of neuropsychological disorders in people with MS.

In unison with the global world tendencies, for the first time in Bulgaria a computer system for assessment and rehabilitation of cognitive impairment has been developed. The system is implemented in a cloud infrastructure and will be provided as an IT service for neurological wards and clinics. The system, named COGNI SOFT, consisting of two modules: 1. module for assessment of the cognitive status and 2. module for rehabilitation of the registered cognitive impairment in persons with MS. Patient's data (demographic characteristics, educations, level of computer skills, occupation, disease duration, grade of physical disability according to EDSS, MRI findings, number of relapses etc.) are entered by therapeutic in electronic file-part of the system, and together with the results of the baseline cognitive tests form the system's input. Neurorehabilitation is based on two main approaches – restorative, which depends on the brain's ability for cortical reorganization after injury and leads to alleviation of the patient's deficit in processing and interpreting the information, and compensatory (strategic) approach for training, which is based on strategy to adapt the person to the environment against his/her personal background. The rehabilitation module of the system includes training programs for improving the cognitive skills in terms of working memory, delayed recall, attention, visuo-spatial orientation skills, emotional recognition, executive functions. Rehabilitation is prescribed by a therapist depending on the individual's cognitive status. Based on the affected cognitive domains and degree (severity) of damage, the therapist selects appropriate rehabilitation programs, taking into account the level of difficulty and the frequency of execution.

Using the system, we create our own norm (based on results from 70 healthy persons) for each of the diagnostic tests. A statistically significant difference ($p < 0.05$) in the level of cognition was found between healthy controls and individuals with MS ($n = 23$). After 3-month training period a follow up re-testing of cognition was done. On the basis of statistical analysis including InterCriteria Analysis we revealed that the most MS patients who underwent cognitive rehabilitation training improved their cognitive functioning ($p > 0.05$). The obtained results confirm the prevailing opinion that regular computer-based rehabilitation, adapted to the individual needs of people with MS can cause adaptive cortical reorganization and as a result to improve the cognitive performance. This determines the capacity of cognitive exercises to preserve and improve cognitive brain reserve.

Keywords: Multiple sclerosis, Cognitive impairment, Cognitive rehabilitation, Computer training.

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InterCriteria Decision Making Approach for Osteoarthritis Disease Analysis

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The presented InterCriteria decision making method is based on two fundamental concepts: intuitionistic fuzzy sets and index matrices. This paper continues a series of research on the application of the novel approach of InterCriteria Analysis (ICrA) of medical data. The ICrA analysis is applied on the results of medicine, physiotherapeutic treatment and kinesiotherapeutical program characteristics. The main goal is an improvement of general quality of patients' life through practices of specific methodology of kinesiotherapy.

The knee performs the function of a medial motor link in the kinetic chain of the lower limb. The knee joint endures the weight of the body that is why it must have mobility, stabilization and dynamism in order to hold the body in different postures.

One of the most common diseases of the locomotory system is the osteoarthritis of the knee joint. The osteoarthritis is one of the most devastating chronic conditions that affect people around the world. It affects mainly middle-aged people, prevailing female.

The gonartrosis leads to medical, social and psychological problems, deriving primarily from the accompanying restricted movements of the affected lower limb and the tendency of disabling and incapacitating the people suffering from it. The main reasons why the knee joint is being worn out are old age, static abnormalities (e.g. overloading, traumas, inner joint injuries and diseases). Among the most widespread causes are the constant overloading, obesity, hard physical labor and hypokinesia [1]. For the purposes of this research we analyzed the results received from the observation of 10 patients [2]. The patients have been treated by specialized kinesiotherapy methodology aiming at increasing the volume of movement in the cervical partition and decreasing limited mobility. While taking decisions about the treatment process we have applied InterCriteria Analysis [3] of the data received from the observation of the patient's state in order to find the subordination between the restorations of the separate movements in the cervical partition of the spine.

The article describes an original multicriteria decision making approach of analyzing the treatment results of patients with Osteoarthritis disease in order to improve the process of taking decisions about the treatment course - InterCriteria Decision Making Approach. The results from the InterCriteria Analyses confirm the already known results from previous research, showing that the muscles in the human body are closely connected and improving one movement will lead to improving another one. The present paper proves the application of one original multicriteria decision making approach - InterCriteria, which improved the relations between the criteria analysis, giving better specialized kinesiotherapy methodology.

Keywords: Intelligent systems, Osteoarthritis disease, Human health, Kinesiotherapy, Decision making, InterCriteria analysis.

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Application of Digital Health and Telemedicine to Deal with COVID-19

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Artificial intelligence, digital health, telemedicine, portable sensors, virtual reality - these new technologies will completely change the way patients and doctors perceive healthcare. Digital health already has a huge impact on the way doctors work, it is very important what tasks it allows them to take on. There are many repetitive and monotonous tasks that most medical professionals do not like to do. Digital health solutions can make them better, faster and cheaper. These tasks usually do not require any creativity or empathy. The process of digital technologies entering healthcare is more complex than simply saying that artificial intelligence (AI) or robotics will take over medical work and activities.

We live in unprecedented times. The new strain of coronavirus is spreading at an alarming rate, so much so that the World Health Organization (WHO) declared a pandemic on March 11. However, this strain of COVID-19, which is thought to have originated either by transfer from a non-human host or evolved into a pathogenic strain in the human population, is very real and causes suffering at every level of society. In particular, its virulent nature puts the elderly and the immunocompromised at higher risk.

The development of the pandemic contributes to the widespread use of telemedicine. Prior to the pandemic, only 1 in 10 American patients used telemedicine services, according to a study by J.D. Power. But with COVID-19 the use of telehealth applications is increasing to 158% in the United States. The coronavirus pandemic has caused an explosive increase in the need for digital services, including those related to health and medicine. Many medical organizations (public and private) are starting to use telemedicine platforms and have announced the opening of free remote consultations between patients and doctors on COVID-19.

In this paper we will look at some digital health and telemedicine applications and activities that have proven effective in dealing with COVID-19.

Within the framework of a two-year project in telemedicine, digital health and smart medicine, medical examinations and tests are performed, which include the following activities and procedures – examination of lungs, heart, ears, ECG, blood pressure, pulse, blood oxygenation, body temperature, body mass index, ultrasound of abdominal organs, prostate, breasts, thyroid gland.

The obtained results are summarized statistically by many indicators, some of which are - gender, age, types of diseases, consultations with a specialist.

Through the use of information and communication technologies is provided equal access for health consultation with various specialists of chronically ill and quarantined people with the aim of avoiding contact and travel, which activity is directly related to the new epidemic situation caused by COVID 19. This telemedicine activity is also analyzed in terms of the prevention of COVID 19.

Keywords: Artificial intelligence, Digital health, Telemedicine, COVID-19.

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Session 3

Intuitionistic Fuzzy Sets and Applications

Intuitionistic Fuzzy Representation of Uncertainty in Biomedical Operations

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The paper studies the problem of representation of the uncertainty in biomedical operations. Each operation is considered as a request (e.g., a patient) offered to a virtual service device, representing a manual, semiautomatic or automatic action. Some concepts of Service Systems Theory are justified and/or extended, especially traffic characterization in the International Telecommunication Union recommendations [4]. This allows three service qualifications: (i) flow characterization (e.g., requests' flow intensity (rate), probability of the next service direction, service duration, traffic intensity and volume); (ii) causal classification (offered, blocked, repeated, served, carried, lost, parasitic [5], effective, etc.); (iii) proposed intuitionistic fuzzy service characterization (successful (belonging to a fully completed successful service), uncertain (uncompleted, due to any reason, target service) and unsuccessful (a service not belonging to the desired successful service)). A conceptual model of the causal service structure of a virtual service system is proposed, including graphical representation. A notation system of the devices and the devices' parameters is proposed based on the qualifiers, corresponding to each of the traffic types considered.

For every virtual service device, using the causal conceptual representation, an intuitionistic fuzzy pair [2] is defined which characterizes the uncertainty in the process of servicing of the requests. The degrees of membership, non-membership and uncertainty [1] are expressed as ratios of the parameters of the virtual devices. A comparison with the classical stochastic approach of uncertainty presentation is made. The problem of representing the uncertainty in more complex systems consisting of parallel or consecutive composition of services is also studied. The intuitionistic fuzzy pairs for each of the devices can be aggregated to obtain an intuitionistic fuzzy pair corresponding to comprise devices, a portion of the service system or the whole service system.

The proposed approach is applicable to service systems with and without waiting/queuing and repeated service attempts. The analytical expressions are derived for a system in stationary state. They are important for service system traffic quality estimation and prediction, and dimensioning of operating and waiting rooms. In the present paper, an explicit scalable representation of uncertainty in the service processes is proposed. Additional or repeated examinations may be required in biomedical operations which correspond to the repeated traffic in telecommunication systems [4]. The results obtained can be applied, in particular, to health service systems.

Keywords: Conceptual modelling, Intuitionistic fuzzy pairs, Service systems, Uncertainty.

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Intuitionistic Fuzzy Evaluations for Analysis of the Proximal Humerus Fractures

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In the paper is proposed a method for evaluation of patients with Proximal humerus fractures (PHFx) obtained in the in the period 2017-2019 in Department of orthopedics and traumatology in University hospital for active treatment in Burgas. For the assessment of the PHFx the theory of intuitionistic fuzzy sets is used [1, 2].

Proximal humerus fractures (PHFx), defined as fractures occurring at or proximal to the surgical neck of humerus happen very often. In patients above the age of 65 years, PHFx are second most frequent upper extremity fracture, and the third most common nonvertebral osteoporotic fracture after proximal femur and distal radius fractures [3]. Most of the patients with PHFx are treated nonoperatively. However, surgical treatment is becoming more frequent, with fracture reconstruction increasing at a higher rate than prosthetic replacement [4]. Surgical treatment of displaced proximal humeral fractures with use of the locking proximal humeral plate that was evaluated in our and other studies, can lead to a good functional outcome provided that the correct surgical technique is used [5].

During hospitalization, the demographic and baseline characteristics of the patients were recorded. Fractures were classified according to Neer Classification system by the treating surgeon on the basis of plain radiographs and intraoperative fracture visualization. Scheduled follow-up evaluations were performed three, six, and twelve months postoperatively. At each follow-up visit, the patient was examined and interviewed with regard to pain, Forward Flexion, Abduction, Medial and Lateral Rotation, Constant and DASH score. True anteroposterior and transscapular Y-view radiographs were made postoperatively and at each follow-up visit. Radiographs were primarily evaluated by the treating surgeon for fracture-healing and possible complications.

For the evaluation the patients' Range of Motion (ROM) the theory of intuitionistic fuzzy (IF) and interval valued IF sets is used [1, 2].

The suggested assessments which estimate the PHFx to the respective patient are formed on the basis of a set of IF evaluations $\langle \mu, \nu \rangle$ of real numbers from the set $[0, 1] \times [0, 1]$. These IF estimations reflect the degree of good ROM - μ , or poor ROM ν for each patient, and for them is valid that $\mu + \nu \leq 1$. The degree of uncertainty $\pi = 1 - \mu - \nu$ represents the cases in which the treatment procedure has not been completed or the information for the current patient is not full.

Keywords: Intuitionistic fuzzy assessment, Interval valued intuitionistic fuzzy evaluations, Proximal humerus fractures evaluation.

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Intuitionistic Fuzzy One-Factor Analysis of Covid-19 Cases

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In a previous publication [5,6], we have introduced Intuitionistic Fuzzy One-Factor ANOVA (1-D IFANOVA), which is a modified ANOVA algorithm based on the concepts of Intuitionistic Fuzzy Sets (IFSs, see [1]) and Index Matrices (IMs, [2]). Analysis of variance (ANOVA) is a statistical method concerned with comparing the means of several samples, originally developed by Fisher [4]. As the sample data for ANOVA is placed in a table, Index Matrices (introduced by Atanasov in 1984 [2]) can be a very convenient tool for storing and processing the information used in this analysis. An IM of Intuitionistic Fuzzy Pairs (IFPs, see [2]) is called an Intuitionistic Fuzzy Index Matrix (IFIM, see [3]). 1-D IFANOVA uses IFIM operations to produce its results.

The recent events related to the COVID-19 pandemic have posed many questions regarding the disease's spread rate, including whether various external factors may or may not have an influence upon it. One such factor is the geographic location of countries, which involves differing climate, economic development, population density and other properties.

This prompted us to apply 1-D IFANOVA to analyze how the number of daily reported cases in the European countries depends on their geographic location, e.g. their region. Such an effect would require adjustment of further measures.

When a data set has gaps and irregular changes in consecutive number values (for example, due to varying numbers of tests), this may accumulate a type of uncertainty over multiple reports. Intuitionistic fuzziness provides the means to describe this imprecision more accurately, by allowing a degree of truth and falsity for a particular statement, where the difference between one and their sum corresponds to the hesitation degree. By converting the COVID-19 data to IFPs, we allow this uncertainty to be expressed in numbers.

In this paper we will analyse the effect the "geographic location" factor has on the number of COVID-19 cases by applying 1-D IFANOVA on the dataset of daily cases provided by European Centre for Disease Prevention and Control [7] for the data for the period from March 1 to August 25, 2020.

For this purpose, we have created a command-line utility which performs 1-D IFANOVA over an IM of pre-prepared IFPs. We have also analysed the data with classical ANOVA (which does show a dependency) and will perform a comparative analysis of the results obtained from that and from IFANOVA.

Keywords: Covid-19, Index matrix, Intuitionistic fuzzy sets, Variation analysis.

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Opportunity to detect Hazardous Materials in Water Using Intercriteria Analysis

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The detection of hazardous materials in water is crucial part of the water management and monitoring. However, analyzing the entire diversity toxic compounds, potentially presented in the water is not an easy, nor economical task and sometimes it is impossible, as well. This group of chemicals vary from heavy metals ions to complex organic molecules and bio-toxins. Finding a general indicator for the toxicity presented in water and aquatic environments could be an important step toward the development of early warning systems to support decision making in water monitoring.

In this study, an integrated approach combining information from 4 different sensors is used to evaluate the water status in terms of the toxic compounds presented. Bio-electrochemical reactor is used as a sensor to evaluate the specific biological response to the toxic compounds and pH, ORP and conductivity electrodes are used to find additional correlations between the water physical parameters and the inhibitors presented. To represent the two major groups of toxic chemicals, namely the heavy metals and the aromatic hydrocarbons, Cu^{2+} and phenol are used in different concentration in the tested models. The influence of phenol was evaluated both in distilled water media and inorganic matter content of 0.5 d LB/L. The phenol concentration applied is in the range of 0-40g/L. The other group of investigations covers the influence of copper in range of 0-40 mg Cu^{2+} /L. Three parameters were under control, namely, conductivity, ORP and the Bioelectrochemical Response (BeR).

The data obtained showed a good level of correlation and response of all the sensors and electrode used in terms of both presence and concentration of the tested pollutants. Evidently the signal (BeR) depends of organic matter content (positively), phenol content (negatively) and the copper concentration (negatively).

In order to find signal profiles specific for these two groups of pollutants the intercriteria analysis with intuitionist fuzzy logic is applied. In this case we will do comparison with the other methods (for example, Pearson's and Kendall correlations).

In this case the μ coefficient between Bioelectrochemical Response and pH is very high (0.93) – strong positive consonance. In the positive consonance are also the μ coefficient between pH and conductivity (0.805). The relations between these parameters give us the chance to remove one of these parameters depend the situation. If the system need fast result, we have to remove the slower obtaining of the parameters. The coefficients obtained could be further used in machine learning and development of a system able to perform toxicity level assessment and prediction of the type of the source of the inhibitory influence.

Keywords: Detection of hazardous materials in water, Intuitionist fuzzy logic

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Interval-Valued Intuitionistic Fuzzy Estimations of a Radar Image for Recognition Purposes

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In the present research work the authors investigate the process of pattern recognition in terms of an object of interest, obtained by a radar image technique by applying the tools of Interval-Valued Intuitionistic Fuzzy Sets (IVIFS) [1-3]. The process of image acquisition by using the remote sensing approach is usually performed by a fast Fourier transform of the reflected radar signal. Due to the nature of the radio waves, the reflection signal is comprised of direct and reflected signals, causing image blurring and smudging. The approach presented in this research work aims to propose an analytical evaluation of the processed image in comparison to preliminary defined target images such as airborne or marine vessels and vehicles. The algorithm itself uses an interval-valued intuitionistic fuzzy estimations (IVIF-estimations) representing the similarities between the target image and the selected images for the comparison [2]. The IVIF-estimations are defined to evaluate the similarity between the images. In the first step, the target image is juxtaposed to the second image. We have the original pattern $ABCD$ and the other pattern $AGHI$. In the second step of the procedure the sections BC and HI are fuzzified so that they are modified to the regions $BCEF$ and $HIKJ$. In the third step of the algorithm the following regions are determined (Fig.1): $s = \#AGHOCD$, $a = \#AELK$, $b = \#EBML$, $c = \#BGJM$, $d = \#MJHO$, $e = \#KLNI$, $f = \#INFD$, $g = \#NOCF$ and $h = \#LMON$.

Thereafter $s = a + b + c + d + e + f + g + h$. In the fourth step of the procedure the IVIF-degree of coincidence of the second pattern with the original are defined:

$$\langle M, N \rangle = \left\langle \left[\frac{a}{s}, \frac{a+b+e+h}{s} \right], \left[\frac{c}{s}, \frac{c+d}{s} \right] \right\rangle$$

The degree of uncertainty is determined as the interval

$$\left[0, \frac{f+g}{s} \right].$$

The resulted IVIF-estimations represent the similarities between the selected images. According to the quantity of the processed key pixels in the images, there is a tradeoff between performance and quality of recognition. In order to verify the algorithm correctness, a numerical experiment on several radar images with a different degree of blurring has been carried out.

Keywords: Interval-valued intuitionistic fuzzy estimation, Pattern recognition, Radar image.

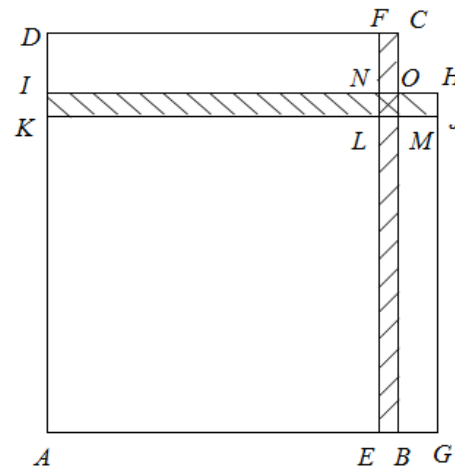


Fig.1. Example

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Session 4

Artificial Intelligence in Biomedicine and Healthcare

In-silico Investigation of Human Visual System

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The paper presents in-silico investigations of effects of brain lesions in different parts of human visual system. For this aim a hierarchical spike timing neural network model reproducing performance of visual tasks with reinforcement learning by humans was implemented in NEST simulator [1, 2]. Its structure and connectivity is designed according to available information about corresponding brain areas organization.

The model has two basic sub-structures shown in Fig. 1: a perceptual part involved in visual information processing and perceptual decision making and basal ganglia that biases taken decisions according to received external reinforcement signal.

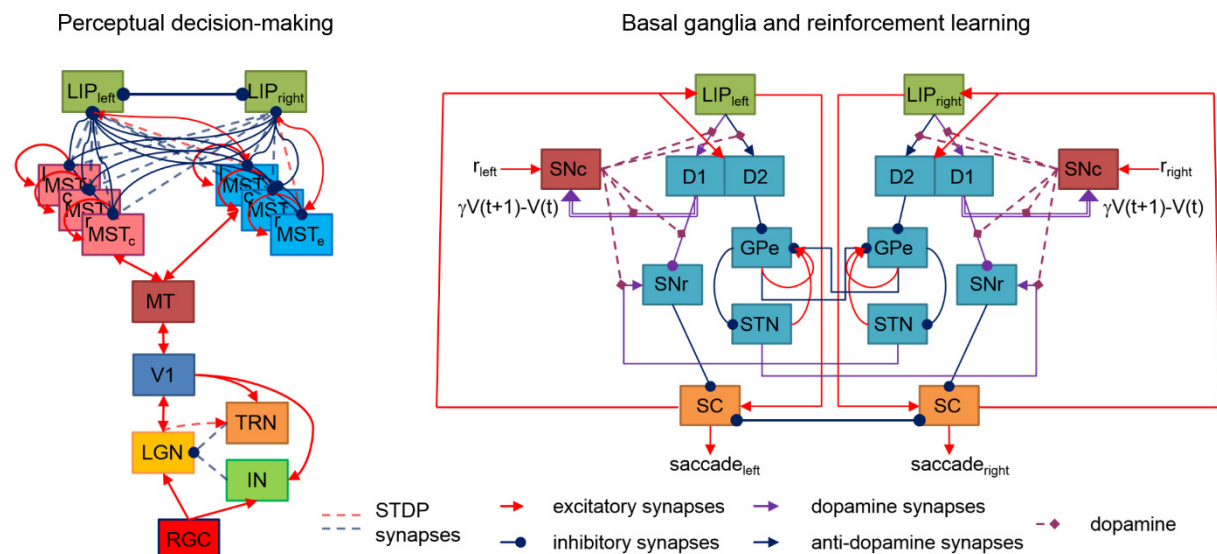


Fig. 1. Model structure.

The perceptual part includes subsequent brain areas involved in visual information processing, perception and decision making as follows: retinal ganglion cells (RGC), thalamic relay consisting of lateral geniculate nucleus (LGN), thalamic reticular nucleus (TRN) and interneurons (IN), visual cortex (V1), middle temporal (MT) and medial superior temporal (MST) areas, and lateral intraparietal cortex (LIP). The basal ganglia (BG) consists of a group of subcortical nuclei including Striatum (with D1 and D1 receptors), Globus Pallidus externa (GPe), Subthalamic Nucleus (STN), Substantia Nigra pars reticulata (SNr) and Substantia Nigra pars compacta (SNc). It uses reward information from the environment to modulate the LIP activity and thus the motor response (voluntary saccade) preparation in Superior Colliculus (SC). The developed software includes also an option to introduce “damage” in each one of the model sub-structures thus allowing performance of in-silico investigations of effect of brain lesions. The simulations were performed by stimulation of the model input using dynamic visual scenarios consisting of moving dots. Different scenarios including damage

in single or several brain areas were prepared and model reactions were collected. Observed deterioration of visual task performance were summarized and commented in relation to simulated types of brain lesions.

Keywords: Spike-timing neural network, Visual system, Decision making, Reinforcement learning.

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Fuzzy U-Net Neural Network Design for Image Segmentation

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Detection and instance segmentation of cellular nuclei is an important step in the analysis of microscopic images. It allows locating the cells in the image and precedes all information extraction and evaluation tasks. The automation of this step is needed to facilitate the analysis of the data from high-throughput imaging experiments. The microscopic images are highly sensitive to experimental conditions, which often leads to increased variability of the final images even in slides processed in one batch. The introduction of Fuzzy Logic into already successful segmentation scenarios has proven itself to be extremely helpful [1].

The fuzziness allows for seemingly more real results by preserving the uncertainty inherent to natural images [2]. The U-Net model is widely used for image segmentation [7].

In the article a segmentation model is proposed, which is designed as a combination of a U-Net architecture [3] and Fuzzy Layers. The U-net alone is a CNN developed for semantic segmentation of biomedical images. The aim of this model's architecture is to produce more accurate results with a smaller amount of training data compared to other convolutional neural networks. For training and testing the model was used the Kaggle dataset [8] which contains just under 700 images. Currently, the process is divided into two main parts – 1) training of a deep learning neural network model; 2) creation of a bitmask as the final outcome. In the first step, a Fuzzy U-Net model is constructed by concatenating one or more Fuzzy Layers between the contracting and expanding path of a standard U-Net model. The latter consists of four convolution and four deconvolution sets of layers. In the second step, we tested several thresholding techniques (manual thresholding, Global isodata thresholding, Adaptive Mean, Adaptive Gaussian and Otsu Thresholding). The Otsu Thresholding [3], coupled with a Gaussian Filter, used for smoothing the sharp differences, has proved to be the best amongst the tested.

Furthermore, the Fuzzy U-Net model for Image Segmentation has been subjected to optimization with analysing the usage of different approaches. This was conducted with automated machine learning practices applying Keras Tuner (a hyperparameter tuning tool for deep learning models) and hyperparameter optimization with Bayesian Optimization [4], and Hyperband [5].

Keywords: Fuzzy layer, U-Net, Otsu thresholding, Keras tuner, Deep learning, Semantic segmentation, Hyperparameter optimization, Grid search, Automated ML

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Effects of Variable Impulsive Perturbations on the Stability of Fractional-order Cohen-Grossberg Neural Networks with Respect to Functions

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The class of Cohen-Grossberg neural networks (CGNNs) introduced in 1983 [1] has been intensively studied in the existing literature because of the great opportunity of applications in emerging areas as associative memory, parallel computing, pattern recognition, signal and image processing, etc. that are important to science, engineering, biology and medicine.

On the other side, because of the boundless opportunities for modelling applications and generalizations, fractional-order derivatives have been intensively introduced in numerous real-world models [2, 3]. In fact, it has been theoretically and experimentally proven that fractional-order derivatives can capture non-local relations as well as memory and hereditary properties the processes. However, the results on fractional-order CGNNs are still very few [4, 5] and the theory of this important class of models is still under the development.

In addition, in the existing results on fractional CGNNs impulsive effects have been ignored so far. Note that, the behavior of impulsive CGNNs have been studied by some authors [6, 7, 8]. However, corresponding results on fractional-order impulsive CGNNs do not exist, and this is the main goal of our research.

In this paper, we study the problems of stability of the equilibrium with respect to a manifold defined by a function for impulsive fractional-order Cohen-Grossberg neural networks. The effects of variable impulsive perturbations are investigated. The impulses are realized as continuous functions and can be considered as a control. Indeed, since impulsive phenomena exist in numerous fields of science and engineering [9, 10, 11] and the impulsive control methods are found to be more efficient than other control strategies, there has been an increasing research interest on the impulsive generalizations of different neural network systems.

The main results in our research are obtained by employing the Lyapunov method and comparison principle.

Keywords: H-manifold, Mittag-Leffler stability, Variable impulses, Cohen-Grossberg neural networks, Lyapunov method.

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Visualization on stability of Impulsive Cohen-Grossberg Neural Networks with Time-Varying Delays

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Neural networks of type Cohen-Grossberg (CGNNs) were introduced by Cohen and Grossberg in [1]. Since it releases in 1983 many scientists were working for application of such models in different research fields. One of the most important roles of such systems is the stability it provides within the potential application therefore it is necessary to be investigated. In real-world, both biological and artificial neural networks have time delays due mainly to the limited speed of signal transmissions and amplifiers switching. Such time delays may affect the dynamic behavior of the network making it unstable or diverge. Due to the countless different possibilities for modelling, behaviors of impulsive CGNNs have been investigated by many researchers. Some of the examples, as theoretical results, given in those results [2–6] are used in this paper as real-world neural networks in order to be viewed their graphical representation of a computer simulation. The effect of the time-varying delays over the stability of the system is investigated. It is believed that these graphical results are useful for the design and exploration of impulsive CGNNs by researchers and students.

Keywords: Cohen-Grossberg neural networks, Delay, Stability, Time-varying delays, Graphical results.

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Cascading Approach for Automatic ICD-10 Codes Association to Diseases in Bulgarian

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ICD-10 is the 10th revision of the International Statistical Classification of Diseases and Related Health Problems [1], a medical classification provided by the World Health Organization. This classification is extremely important for physicians to be able to describe a disease in a unified way. The paper explores the problem of the automatic association of ICD-10 codes to diagnoses in Bulgarian. Since this is currently performed manually by medical professionals, the ability to automate this task would save time and allow doctors to focus more on patient care. In addition, many clinical notes contain diagnoses that are not mapped to standard medical classification, which makes their automatic processing very hard. The task of ICD-10 codes is an extreme scale multi-class multi-label classification task, due to the huge number of classes – 11000, and the possibility to assign multiple valid ICD-10 codes to a diagnosis. This makes the task very challenging. Moreover, for the training of such machine learning algorithms, it is necessary to create a big training data set [2], [3]. The Bulgarian language is a low resource language. For training data, we created semi-automatically corpora from linked open data and public documents [4]. The corpora contain about 350 000 diagnoses in Bulgarian language labeled with 3-sign and 4 sign ICD-10 codes.

We propose an innovative cascading approach for the automatic association of ICD-10 codes to diagnoses in Bulgarian language. In this approach, the core functionality is the use of the hierarchical nature of the ICD-10 classification that allows to narrow down the process and to reduce the search space. It is done at levels, starting with defining the first character in the encoding and so on until we define the entire code. As a result, individual classifications are combined into one common classification. The approach is compared to different machine learning approaches, including those based on deep learning [4] transformers like BERT models. The experimental results show that the proposed approach outperforms in accuracy, precision and recall classical approaches, among which Naïve Bayes classifier, SVM, Random Forest, Neural Networks, BERT and others have been tested.

There is already research in this area for other languages such as Spanish [5], Serbian [6], Dutch [7], and Chinese [8]. The proposed approach is relatively language independent and can be easily adapted for other languages.

Keywords: ICD-10 codes, Health Informatics, Big Data, Machine Learning, Text-based classification.

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A Deep Learning Based Approach for Automatic Synthetic Patient Status Corpora Generation

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Clinical narratives play a crucial role in medical research. On daily bases are created millions of patient data in a textual format on different languages. On the other side due to ethical and legal issues, such data cannot be shared and there are a lot of restrictions for their reuse because they contain personal and sensitive information. For knowledge extraction from such records, there is a huge demand for development tools and services for clinical text analytics, which requires the availability of big corpora of training data [1].

The main goal is the development of a system for the automatic generation of synthetic outpatient records (ORs) from real data in unstructured textual format only. The clinical texts used for the model training contain pairs of consecutive sentences taken from anonymized corpora of ORs in the Bulgarian language. Currently, there are no other available corpora with which we can deal. The ORs have special predefined structures and contain sections as a free text for "Anamnesis", "Patient status", "Treatment", "Lab test", etc. For this research, we selected to generate synthetic data for patient status only. This section consists of a description of the current condition of anatomic organs and systems based on observations and manual checks only. However, the proposed approach is applicable to the other ORs section and our plans include experimental work in this direction. The size of the corpora is about a billion of bigrams of sentences. Such an approach using pieces of text allows to preserve partially the context of the clinical information, and on the other side to overcome the problem with patient reidentification.

We propose an innovative approach for automatic synthetic patient status generation, based on deep-learning models. The core of the proposed system is based on a fine-tuned multilingual Bert [2] model based on our corpora for the task next sentence prediction. As a baseline for comparison is used a statistical rule-based model for synthetic clinical text generation. The proposed approach can be applied to other languages as well.

In contrast with other methods for synthetic data validation [3] that deal with semistructured data – the validation of the generated free text is more difficult because it requires the availability of a corpus of full-text ORs. We apply two different validity tests. The results from experiments provide strong evidence that the proposed approach can generate a huge variety of valid synthetic patient statuses.

Keywords: Health Informatics, Big Data, Machine Learning, Synthetic Patient Status Corpora Generation, Deep Learning.

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Artificial Intelligence Techniques for Food-derived Bioactive Peptides Prediction: A Literature Review

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In recent years, there has been a significant increase in interest in food-derived bioactive peptides. This is because bioactive peptides possess a number of properties that allow them to control diseases and support human health. They are used to lower blood pressure (antihypertensive) [1], to improve immunity, to lower cholesterol, have anti-cancer [2] and antidiabetic [3] properties. Thus, bioactive peptides are important sources for alternative medicine and possess therapeutic activity. Hence, biologically active peptides can be used as a basis for functional foods and drugs development.

In date, the most bioactive peptides have been isolated following a so-called “conventional” approach [4]. This includes the experimental *in vivo* and *in vitro* protocols, which are expensive and time consuming. Recently, *in silico* approaches have been used to predict bioactive peptides in a more effective way. These approaches are the basis of the following relatively new scientific fields – bioinformatics, chemoinformatics and chemometrics, which obviously are overlapped. These disciplines are developing rapidly and this is a prerequisite for the emergence of new computational approaches involving databases, online tools, and software for investigating and identifying potential bioactive peptides [5]. Some of them are used different artificial intelligence (AI) techniques such as artificial neural networks (ANN), support vector machine (SVM), random forest, etc. Such AI algorithms are extremely effective at providing accurate predictive models for a wide range of biological and chemical problems. Furthermore, they can considerably assist to reduce the cost and the time to obtain promising peptides by partly replacement on the expensive laboratory experiments. Therefore, the main purpose of this review is to present the basic techniques of artificial intelligence with a brief description and to demonstrate some examples of their use in research concerning the analysis and prediction of bioactive peptides. The current problems and the prospects in the application of AI techniques will be also discussed.

Keywords: Artificial intelligence, Bioinformatics, Cheminformatics, Chemometrics, Bioactive peptides, Food-derived peptides, Prediction.

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Sequence-Based Prediction of Food-originated ACE Inhibitory Peptides Using Deep Learning Algorithm

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In recent years, food originated bioactive peptides became a promising source of potential therapeutic agents. Predicting the biological activity of these peptides is crucial for the discovery and development of functional foods and effective peptides-based drugs. Antihypertensive peptides are certainly the most reported food-derived peptides. These peptides inhibit a key enzyme in renin-angiotensin system named angiotensin-converting enzyme (ACE), resulting in lowering of blood pressure. Hypertension is a serious problem and affects up to 30 % of the adult population in developed and developing countries [1]. It is a major risk factor concomitant with cardiovascular disease (CVD) states such as coronary heart disease, peripheral artery disease and stroke, and kidney disease [2]. So far, various milk proteins have been extensively studied and a number of peptides have been well characterized by antihypertensive effects *in vitro* and *in vivo* [3,4]. These peptides are initially part of protein's structure and may become active after the action of proteolytic enzymes [5]. Moreover, subsequent steps of purification are needed. Meanwhile, it is a rather expensive and time-consuming procedure, and often require months of hard work, which is not always successful. To overcome this shortcoming, machine learning (ML) approaches are increasingly used. The concept of ML is grounded on various techniques, the most used of which are neural networks (NNs), support vector machine (SVM), random forest (RF) and more recently deep neural networks (DNNs).

In this study, *in silico* computational approach is used to predict food-originated ACE inhibitory peptides. Firstly, since there are no automated data collection procedures [7] the food-derived peptide databases such as AHTPDB [7] and PeptideDB [8] were studied to form the needed dataset. It consists of positive and negative samples. The positive ones are formed from the peptides with ACE inhibitor function, while the negative ones are generated from peptides with different functions, for example anticancer function. After that, the feature extraction was done, which is a process to reduce the number of input variables, and also feature descriptors were generated. They are inputted to a deep neural network classifier, where it learns the relationship between feature descriptors (x) and response variable (y), and makes subsequent predictions for any newly provided data sets.

Finally, to assess prediction performance of the model, four metrics were used, namely sensitivity (Sn), specificity (Sp), balanced accuracy (BACC), and Matthews correlation coefficient (MCC). The proposed model is tested with 3125 samples in the positive dataset and 2783 samples in the negative dataset and sequence length from 2 to 20 amino acids. The obtained results show high predictive accuracy, which make the model suitable for identification of ACE inhibitory peptides.

Keywords: Deep learning, machine learning, Neural networks, Bioactive peptides, Sequence-based prediction, Antihypertensive peptides, Food-derived peptide.

Acknowledgements: This research presented in this paper is supported by The Bulgarian National Program “Young Scientists and Postdoctoral Students”.

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Performance Prediction of a Microbial Fuel Cell Based on Artificial Neural Networks

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This study integrates artificial neural network (ANN) processing with microbial fuel cell (MFC)-based on the electricity generation. Innovative treatment of wastewater flows is being applied to the Microbial fuel cell. It is a typical bio-electrochemical system where chemical energy containing in organic matter is converted in electricity by bacteria activity. Constructed MFC with air-cathode presented a single chambered plastic cylindric system ($V = 20$ mL) with a carbon fiber brush anode (surface area of 200 cm^2) and air-cathode (VITO - Belgium) (surface area of 3.77 cm^2). The study is focused on monitoring the operational stability of a cell with a VITO air-cathode and an anode carbone brush. The process is controlled by the potential created through an open circuit potential (OCP) and closed circuit potential (CCP). The obtained voltage is in the range of $45.7 \text{ mV} - 43.9 \text{ mV}$ at CCP, while it is $202.5 - 201.5 \text{ mV}$ at OCP. The extent of the COD removal during the run is 78.6% . To monitor the content of organics in the medium, the tests Hach Lange LCK 514, spectrophotometer Hach Lange DR 3900 and for the voltage was measured with Auto ranging digital Multimeter Model MY-66 were used. The parameters are measured in university lab at every 12 hours. The data obtained were used to train the Neural Network and to predict the generated voltage by the Microbial fuel cell. On the other site, artificial neural networks are a convenient tool for predicting the parameters of various processes. Here we will use a recurrent neural network to predict the loading of the cell. The network is trained with historical experimental data from the process and intuitionistic fuzzy estimates of the coefficient of affiliation, reflecting the degree of depletion of the nutrient medium $\mu = \frac{a_i - A_k}{B - A}$, where $\mu \in [0, 1]$; non-affiliation coefficient – ν , reflecting the degree of saturation of the nutrient medium, $\nu = \frac{B_k - a_i}{B - A}$, where $\nu \in [0, 1]$ and a coefficient of uncertainty reflecting the degree of inertia and inaccurate measurement of the parameters by the measuring instruments $\pi = 1 - \mu - \nu$. These estimates are the basis on which cell loading is managed. In the paper, the membership function is perceived as something negative, and the non-membership function as something positive. Here we will connect the membership function with depletion of nutrient medium and the non-membership function with a degree of saturation of the nutrient medium. Apart from our perception there is no other reason for these two expressions to be in this way, but if necessary they can be exchanged.

Keywords: Neural network, Intuitionistic fuzzy estimations, Microbial fuel cell, Waste water.

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A Concept of Bio-Process Mining applied to Time-Resolved Developmental Dataset of the Roundworm *C. elegans*

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Process mining is a relatively young research discipline that sits between computational intelligence and data mining on the one hand, and process modeling and analysis on the other hand. The idea of process mining is to discover, monitor and improve real processes by extracting knowledge from event logs readily available in today's systems. Process mining includes process discovery, conformance checking, social network/organizational mining, automated construction of simulation models, model extension, model repair, case prediction, and history-based recommendations. (IEEE Task Force on Process Mining). Process mining is an area of research of Aalst for the recent years [1, 2]. It could be applied directly in healthcare if we describe patients as clients [3]. There are some ideas that they could be used in bioinformatics also [4] but in this article, we want to prove that process mining can be mapped to some biological processes.

In order to map a particular process from biology, development, genetics to business process, a set of particular rules are defined as minimum requirements for being a process log: case id – mandatory, event id – mandatory properties – timestamp, activity, etc. (to be mapped to source dataset) and notes on mapping approach (framework).

When such biological processes respond to these requirements, we can describe it as a sequence of events. Following these concepts, we applied process mining techniques to analyze the developmental process of the nematode *C. elegans*. For modelling, the publicly accessible dataset from the lineage-resolved molecular atlas of *C. elegans* was used [5], which contains single-cell RNA sequencing-derived time-resolved gene expression series.

The dataset (GSE126954) contains a cell annotations list of 89,701 cells including arbitrary embryonic time and gene expression data for all genes in the annotated cells.

This data is used to analyze transcription changes and cell differentiation as events occurring at specific time points.

Keywords: Process modelling, Developmental biology, Process mining, Event log.

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Application of Virtual Reality as a Tool for Structural Analysis of Molecules – Steroids, Pharmaceuticals and Pesticides

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The three dimensional nature of chemical interactions requires application of suitable technology for visualization of molecules in order to assess their reactivity. The molecular flexibility of organic chemicals allows those structures to exist in a set of different structural orientations (conformations) as a result of changes of structural variables such as bond rotation, valence angles and many other. Each spatial position may differ significantly in respect to chemical reactivity. Thus, in order to make an overall reactivity profile of a specific chemical all possible 3D positions should be considered and analyzed.

Reality technologies include virtual reality (VR), augmented reality (AR) and mixed reality (MR). From the three aforementioned, VR is proven to be the most suitable technology for demonstrating 3D objects for educational purposes. However, VR systems have its own classification which includes the following types: immersive, semi-immersive and non-immersive. Therefore, these types should be further analyzed by a making a comparison between them which will make the result more comprehensive. In this way, the choice of what type of VR technology should be used in education and especially medicine is even more specified.

In most cases the generation of the total number of possible conformers is not necessary. From practical point of view, a representative set of most structurally distinctive conformers could be used for analysis of the chemical reactivity. The goal here is to create all conformers in 3D scene which will allow further visualization with appropriate VR technology. In order to achieve the goal, the coordinates of conformers for each molecule are generated and provided into a user friendly application, where the user could see each conformer and to observe its 3D molecular structure.

In the current work the focus is set on representative chemicals from groups of steroids, pharmaceuticals and pesticides. In order to analyze the reactivity of those chemicals the following steps are accomplished: 1) generation of initial 3D structures; 2) generation of possible 3D structural orientation; and 3) visualization of the 3D structures in a suitable tool for virtual reality.

Keywords: Virtual reality, Molecular structures, Education.

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Functional Outcome Prediction of Operated Proximal Humerus Fractures by Means of Artificial Neural Networks

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Proximal humerus fractures (PHFx) are very common in patients above 65. PHFx are second most frequent upper extremity fracture accounting about 6 to 10 % of fractures in this patient group [3]. According to Charles Court-Brown PHFx often occur in the fit elderly independent patient - a contributor to society, who might well be converted to a degree of social dependency. PHFx are mainly treated nonoperatively. Surgical treatment is becoming more frequent ranging between 30 % to 60 %. Surgical treatment of such fractures with locking plate has a good functional outcome provided that the correct surgical technique is used. Medical records of patients' demographic and baseline characteristics during hospitalization were created. Fracture classification acc. Neer Classification system based on plain radiographs and intraoperatively.

Follow-up evaluations on the third, sixth and twelfth month postoperatively patient assessed with regard to pain, ROM (Forward Flexion, Medial and Lateral Rotation, Abduction), Constant and DASH score.

The above information is based on studies performed at University Hospital of Burgas by our research team in the period 2017-2019. Neural networks are one useful tools for object recognition and prognosis [1, 2].

The neural network has a structure of 9:66:12. At the input of the neural network is provided information about Age, According Neer's Classification system, the measurements from the third month for Medial Rotation, Lateral Rotation, Forward Flexion, Abduction, Constant and DASH Score assesment. The measured parameters for the sixth and twelfth month for Medial Rotation, Lateral Rotation, Forward Flexion, Abduction, Constant, DASH Score are fed to the output of the neural network.

The aim is to predict the values of Medial Rotation, Lateral Rotation, Forward Flexion, Abduction, Constant and DASH Score without performing the corresponding measurements for the sixth and twelfth month. In the training and testing of the neural network, the data from real measurements of 63 women for 2019 who underwent this procedure at the University Hospital Burgas were used.

Keywords: Neural network, Proximal humerus fractures.

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Programme Product for Index Matrices

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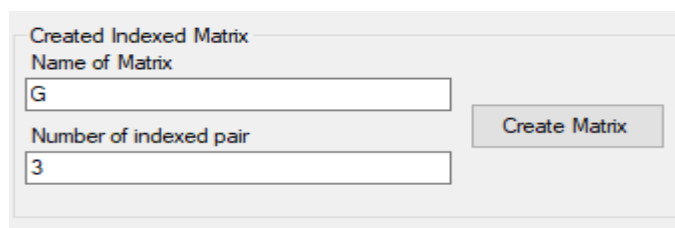
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In the years different types of index matrices (IMs) are defined: index matrices with elements logical variables, propositions, (0, 1)-index matrices or predicates; intuitionistic fuzzy index matrices (IFIMs); extended index matrices (EIMs); temporal intuitionistic fuzzy index matrices (TIFIMs); index matrices with function-type of elements (IMFEs); three dimensional index matrices (3D-IMs); n -dimensional index matrices [3]. Operations which are performed over the IMs and their extensions include addition, termwise multiplication, multiplication, structural subtraction, multiplication with a constant α , termwise subtraction, aggregation operations (max-row aggregation, min-row-aggregation, sum-row-aggregation, average-row-aggregation, max-column-aggregation, min-column aggregation, sum-column-aggregation and average-column-aggregation), reduction, projection, substitution, hierarchical operations over EIMs, specific operations over ETIFIM: $(\circ, *)$ -row-aggregations and $(\circ, *)$ -column aggregations, operation "composition" and its opposite operation, "automatic reduction", "inflating operation". In the theory of IMs level operators and extended modal operators are defined. The OLAP operations as slice, dice [9], roll-up, drill-down [5], transposition, drill-across [6], data cube [10] are presented. New operations over n -dimensional index matrices as sorting operations and reducing operations are described [4, 7]. The relations: strict relation "inclusion about dimension", non-strict relation "inclusion about dimension", strict relation "inclusion about value", non-strict relation "inclusion about value", strict relation "inclusion", non-strict relation "inclusion" over IMs and their extensions are investigated. The theory of IMs is presented in [1, 2].

In the current research work a program product for index matrices is implemented. The implementation of the index matrices is made using programming language C#, the libraries of .NET Framework (.Net Core) and Visual Studio integrated development environment (IDE) [3]. Part of the realization of the program product is presented (Fig. 1–Fig.6). In the first step the skeleton of an indexed matrix is created (Fig. 1 and Fig. 2).

In the next step a name to each indexed pair is given (Fig. 3). The value for indexed pair can be 0 or 1 (Fig. 4). The created index matrix is presented (Fig. 5 and Fig. 6). The program product for realization of IM has the possibility to work with more than one index matrix.

The relations over IM are realized in the next step of the current research work. Depending on the number of similar elements different types of relations are determined. In the end the case of intuitionistic fuzzy index matrix is implemented. An example of fault detection in machine using the programme product for index matrices is presented. The results are important to make decision for the state of the machine.



Created Indexed Matrix

Name of Matrix

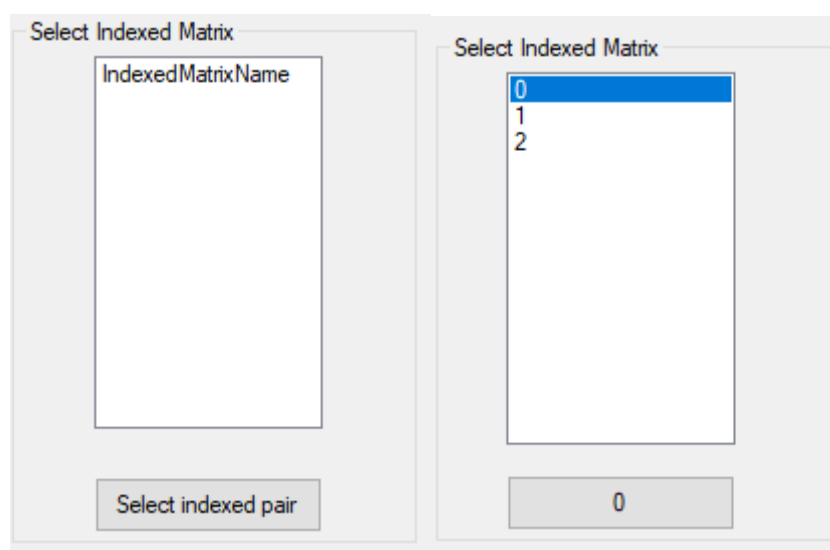
G

Number of indexed pair

3

Create Matrix

Fig.1. Create an index matrix



Select Indexed Matrix

IndexedMatrixName

Select indexed pair

Select Indexed Matrix

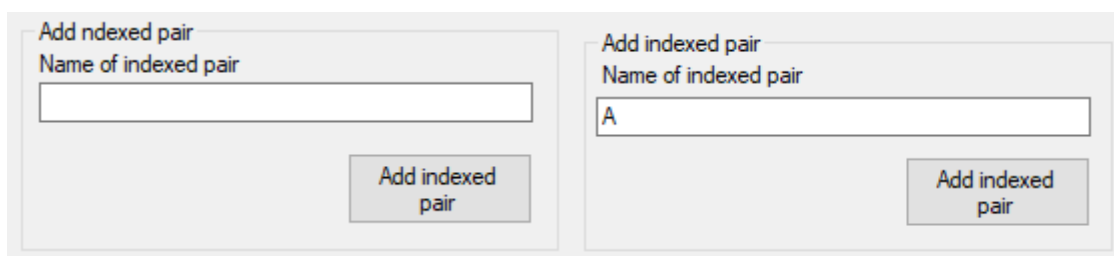
0

1

2

0

Fig.2. Select created index matrix



Add indexed pair

Name of indexed pair

Add indexed pair

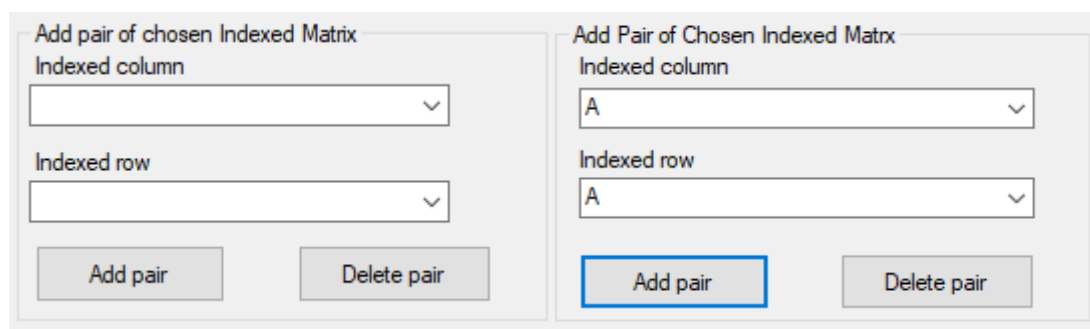
Add indexed pair

Name of indexed pair

A

Add indexed pair

Fig.3. Add indexed pair



Add pair of chosen Indexed Matrix

Indexed column

Indexed row

Add pair

Delete pair

Add Pair of Chosen Indexed Matrix

Indexed column

Indexed row

A

A

Add pair

Delete pair

Fig.4. Select indexed pair to add/remove value in corresponding cell

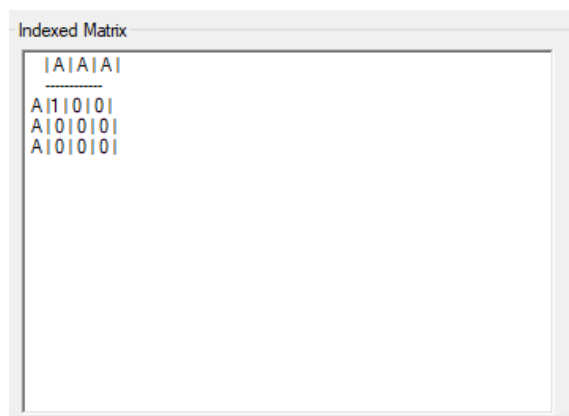


Fig.5. Index matrix

Fig.6. Program product for index matrices

Keywords: Index matrices, Relations, Software.

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Session 5

Biomedical Imaging and Image Processing

Morphometric Image Analysis in Biomedical Research

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Morphometry refers to a quantitative analysis of form, which is a concept that includes both the size and shape of an organism or organ. Morphometric image analysis in biomedical research is a quantitative description of geometric features of structures such as tissues, cells, cell organelles or biomarkers. It utilizes advanced computer-assisted image analysis system where the microscopic image is recorded and a specific software is applied to objectively measure specific histological characteristics. It may be performed on whole image, or on a particular area of interest after image segmentation. Morphometric image analysis is widely used in biomedical studies and pathology. Its applications include differentiating between benign and malignant tissues based on the nuclear morphology of the cells, quantitation of immunohistochemical or immunofluorescent assays for the expression of specific biomarkers in pathological conditions such as preeclampsia *etc.* [1, 2]. Accurate calibration of the instrument and the use of standards and controls is essential for precise and reproducible quantitation. Morphometric image analysis may be performed on plastic or paraffin-embedded and specifically stained tissue sections by use of conventional light, e.g. fluorescence microscopy or on thick specimens by means of confocal laser scanning microscopy. The latter allows for attainment of space-related profiles and performing of volumetric measurement within them – a very useful approach in studies on cortical microcirculation [3]. 3D confocal cell morphometry combines the high image resolution offered by the confocal microscopy with analysis of the time course of morphological changes of tissues and cells *in situ* and *in vivo* [4, 5]. The present review summarizes the significance of morphometric image analysis in biomedical research, the main problems and the general approach to the use of this technique for quantitation of immunohistochemical and immunofluorescent images.

Keywords: Morphometry, Image analysis, Microscopy, Immunohistochemistry, Immunofluorescence

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Comparative Morphometric Image Analysis of LYVE-1 and Podoplanin in HIV Infected Preeclamptic Women

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Introduction: We applied computer assisted morphometric image analysis to quantify the immunohistochemical distribution of two lymphatic markers podoplanin and lymphatic vessel endothelial hyaluronan receptor-1 (LYVE-1) in the placenta of women with HIV associated preeclampsia. Preeclampsia is a serious medical complication and its exact pathogenesis is still unknown. The presence of soluble factors that cause vascular endothelial damage as well as a dysregulation of angiogenesis in preeclampsia is well known [1, 2]. It is thus important to study the possible role of lymphatics and lymphangiogenesis in the synergy of HIV infection and preeclampsia.

Materials and methods: Placental tissue was obtained from normotensive and preeclamptic women stratified according to their HIV status. The preeclamptic group was divided into early (< 34 weeks; EOPE) and late (> 34 weeks; LOPE) onset preeclampsia. Immunostaining was performed on formalin-fixed, paraffin wax-embedded sections using mouse anti-human LYVE-1 and D2-40 podoplanin antibodies. Microscopic images were obtained from at least four randomly selected fields of view per slide. At least 4 slides per tissue block were viewed. The images were viewed with an Axioscope A1 microscope and the morphometric image analyses were performed using the AxioVision software (Carl Zeiss, Germany). The morphometry was performed using the automated mode after calibration with the same settings applied to all images. Our study focused on the conducting (stem) and exchange (intermediate/terminal) villi at term. Hence separate calibration settings for morphometric analyses of each type villi was applied. Single object analysis was used for calculating the immunostaining in conducting villi, while a two phase threshold was applied to the exchange villi.

Results: LYVE-1 immunostaining was localized within endothelium of the arterial supply and venous drainage of both conducting and exchange villi as well as within medial cells of arteries. In contrast, podoplanin was immunolocalized in a reticular-like stromal complex within the exchange and conducting villi. In general, there was a decline in the expression of both lymphatic markers in preeclamptic versus normotensive women, being more prominent during EOPE than LOPE. Both LYVE-1 and podoplanin were upregulated in HIV+ vs. HIV- groups regardless of pregnancy and villi type.

Conclusion: This study provides a novel insight into the LYVE-1 and podoplanin immunoexpression in the fetal circulation of conducting and exchange villi of HIV-infected preeclamptics. It highlights the benefits of computer assisted morphometric image analysis as a reliable tool for quantification of immunostaining in biological tissue.

Keywords: Morphometry, Immunohistochemistry, LYVE-1, Podoplanin, Preeclampsia, Placental villi, HIV infection.

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Morphometric Characteristics of Erythrocytes Derived from Women with Preeclampsia. Pilot Study

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The aging process of erythrocytes is considered an issue of special scientific and clinical interest. Since these cells play an important biological role such as transport of respiratory gases, maintenance of blood rheology and blood flow, investigation of the morphometric characteristics of erythrocytes can give important information about various pathological conditions.

In this study, we apply atomic force microscopy (AFM) imaging to examine the ultrastructural changes occurring during the aging of erythrocytes derived from women with preeclampsia and healthy pregnant and non-pregnant women.

The overall morphological profile of freshly isolated erythrocytes from healthy pregnant and non-pregnant women appear uniform to a large extent, i.e. a typical biconcave structure is found for nearly 80% of the total number of cells. In the course of aging, the percentage of biconcave morphological type gradually decreases at the expense of spiculed, spherocytic or crenated cells. After 30 days of storage the cells with morphology typical for senescent cells (spiculed and spherocytic) become more than 50% of the total number of cells.

The process of structural alteration of erythrocytes obtained from women with preeclampsia begins at an earlier stage compared to the control groups. As early as the 5th day after isolation, we observe 20% spiculed cells, while after 20 – 30 days of storage, the spiculed and spherocytic cells already exceed 50-60% of the total population. Surprisingly, at this point also cells with unusual nanomorphology are observed. The erythrocytes from patients with preeclampsia appear very fragile and often only ghosts are detected instead of intact cells.

Our results show a different pattern of morphological alterations during the aging process of erythrocytes derived from women with preeclampsia compared to the healthy controls. This study provides a basis for conducting further research in the prevention of this pathology.

Keywords: Preeclampsia, Erythrocytes, Cells aging, Atomic force microscopy.

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Gabor Features for the Classification and Evaluation of Chromogenic *in situ* Hybridization Images

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High-throughput chromogenic in-situ hybridization (CISH) is an invaluable technique to study the spatial distribution of gene expression in animal tissues [1]. The specific mRNA fragments of the sought gene product and the cell that produces it are revealed in fixed tissues by the production of colored precipitate that can be easily observed and documented using a standard bright-field microscopic imaging system [2], [3]. The "gold standard" for grading of the CISH-stained tissues involves qualitative scoring of cellular gene expression strength, and/or pattern by a domain-expert [4], [5]. This method is biased and suffers from low reproducibility. Furthermore, it lowers the effectiveness of high-throughput experiments, when large amounts of image data are generated at high speeds. There exist a few quantitative image-analysis approaches to resolve these issues, but the proposed methods are sensitive to experimental conditions or require expert adjustment of multiple parameters [6], [7]. CISH-images have inhomogeneous texture. That is why their analysis requires the usage of a combination of features instead of a particular standard method for specific feature extraction. The idea of the research team is to use different approaches to extract structural information from CISH-images that will be used to generate a feature space for semantic segmentation and functional analysis of gene expression. In our current work, after [8], we explore the idea by unsupervised classification based on features extracted via multidirectional Gabor filters and using them for unsupervised classification with Fuzzy c-means algorithm. The tissue on two chosen images is divided into overlapping tiles of certain size (sampling scale = 100 μ m). The image-tiles are classified based on the extracted features of the filtered region (mean, standard deviation and energy) and are compared to the gold standard evaluations of gene expression in the original images. The rationale behind this is to determine whether the natural grouping of the filtered regions of the image is a useful representation of gene-expression strength to be implemented in a task for semantic segmentation and quantitative evaluation.

Four experts without prior knowledge of the classification results evaluate the strength of gene expression ("none", "low", "moderate" or "strong") and its pattern ("none", "sparse" or "dense") of a set of randomly selected tiles. Afterwards, they independently evaluate each class using the original whole-slide images. Finally, a comparison between the class-scale and tile-scale evaluations is used to assess the usefulness of the selected features. To answer these and similar questions, we constructed a Python workflow for the programmatic access and navigation of the whole-slide images, extraction of the needed information and application of different types of classifications on the generated feature space.

Keywords: Chromogenic in situ hybridization, Texture analysis, Machine learning, Feature extraction, Fuzzy C-means.

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An Approach for Development of a Physical Breast Phantom for X-ray Imaging Using an Inkjet Printer: Preliminary Results

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Anthropomorphic physical body phantoms turn out to be a valuable tool for evaluation, calibration and quality assurance of radiology equipment. Physical shape, composition and radiological equivalency are essential requirements for these phantoms. Nowadays, 3D printing technologies provide vast possibilities for production of anthropomorphic phantoms using various polymer materials and combinations of them. Recently, simple printing on paper sheets was explored to produce realistic phantoms that are less expensive and do not require a specialised equipment.

The current preliminary study evaluates the feasibility of an approach to create a physical anthropomorphic breast phantom using a conventional inkjet printer and plain office paper. Several x-ray contrast substances can be used as ink additives in order to achieve x-ray attenuation. In this study, we use a solution of potassium iodide (KI) in distilled water (0.6 g/ml), due to its low price, easy dissolution and easy insertion into the printer cartridge. Initially, a calibration phantom was created by printing square patterns of size 20 mm x 20 mm with different ink quantities, gradually increasing from 0% to 100%. This calibration phantom was imaged at a general-purpose radiography system using 40 kVp incident x-ray spectrum. The obtained planar x-ray image was used to determine the relation between the linear attenuation coefficient of the printed ink patterns and the grey scale intensity (from 0 to 100%). This served to identify, which grey value corresponds to glandular tissue at this incident energy.

Next, a segmented slice from a patient breast MRI was printed on several sets of paper sheets, each one containing 10 sheets. Sets were imaged at 40 kVp, 60 kVp and 80 kVp at general purpose radiography unit. Regions of Interest (RoI) were assigned on the x-ray image to evaluate several parameters such as minimum, maximum, and average grey value. Consequently, the obtained images were evaluated subjectively and objectively. Subjective evaluation was performed through a visual assessment of the obtained radiographic images. It showed realistic appearance of the glandular tissue on the x-ray images. Objective evaluation was performed through a comparison of calculated values within the RoI between the different sets. The evaluation indicated increase in the incident energy results in lower glandular contrast.

This preliminary study showed that the proposed approach maybe suitable for the development of realistic radiological physical breast phantoms. Future research is related to the fabrication of a complete “paper” phantom and its evaluation for use in x-ray mammography imaging.

Keywords: Anthropomorphic physical phantoms, Breast phantoms, X-ray imaging, Inkjet printed phantoms, Radiology, Mammography.

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Influence of Incident Mammography Spectra and Breast Phantom Characteristics on Mammography Features

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The aim of this work is to evaluate the effect of incident mammography spectra, exposure and breast phantom characteristics on the extracted mammography features. For this purpose, four digital breast phantoms are generated by using a dedicated in-house developed software application. The phantoms differ in the content, the thickness and materials used in to simulate the gland, adipose and skin tissues. The first two breast phantoms, called GAG phantoms, consist of a semicircular container with assigned glandular tissue characteristics and thousands of adipose spheres with different diameters. The two phantoms correspond to two thicknesses of 50 mm and 60 mm. They were filled with glandular tissue. The next two phantoms, called GGA phantoms consist of the same components, but the container and the spheres are simulated from glandular tissue, while the container filling material is made from adipose. Another software tool, XRAYImagingSimulator, is used to generate X-ray images under typical mammography geometry. Photon noise is added by different entrance surface exposures (ESE) 2.5; 3; 3.4mGy. Eight mammography X-ray spectra are used. An image quality platform is used to calculate the following features: kurtosis, skewness, fractal analysis and the β factor from the power law spectra. The results show that for the same type breast phantom (GAG or GGA), the use of higher ESE results in lower fractal dimension. In addition, for the same incident dose, higher breast thickness results in lower skewness, higher kurtosis and higher fractal, while β factor remains constant. For the same breast thickness and both breast types (GAG, GGA), higher skewness values are observed for the GAG combination, which is a sign that this breast phantom represents denser breast than the GGA combination. Fractal values are higher for the less dense breast GGA, while the kurtosis is higher for the GAG breast phantoms. This simulation study concludes that fractal dimension depends on the incident X-ray spectra, while the statistical features kurtosis and skewness remain almost constant. These features may be used as basic parameters in the design of software applications for breast density evaluation. The comparisons between the two basic phantoms (GGA and GAG) reveals which material combination might be use for the representation of a denser breast, i.e. GAG. Currently, the results from more than twenty radiographic features extracted from the images are under evaluation. They will be used in the design of deep learning system to classify mammographic breast density.

Keywords: Breast digital phantoms, Breast imaging techniques, Simulations, Mammography features.

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Session 6

Mathematical Modelling in Biomedicine and Healthcare

Generalized Net Model of Telerehabilitation Program for Patients with Socially Significant Diseases

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The development of telecommunication technologies and artificial intelligence has led to a significant change in the health care trends. A strong example of innovative healthcare provision is the so-called telerehabilitation, which is part of the rapidly evolving field of telemedicine. Telerehabilitation (TR), also known as e-rehabilitation, is a modern form of rehabilitation service that is delivered over the interactive devices. It can address a wide spectrum of health conditions, from minor health issues to emergency medical conditions. It can be especially beneficial to people in rural or remote areas. One of the most advantageous aspects of TR is that it can deliver therapy to individuals that might otherwise be unable to visit a traditional in-person clinic. Many patients with socially significant diseases suffering from disabilities, or other impairments can benefit greatly from TR, as it can reduce the costs and complications related to travel compared to traditional inpatient or person-to-person rehabilitation. Various studies have shown that TR can have similar effects to those of traditional rehabilitation. Nevertheless, adopting TR in clinical practice requires organization changes which may be challenging. In the present paper, an application of the apparatus of generalized nets to telerehabilitation services and the advantages of using such model, is discussed. We propose a reduced GN-model representing a real-time patient/therapist interaction via video-conferencing platform. The model allows different treatment behavior depending on the disease. The model describes a telerehabilitation protocol and algorithm for choosing the best rehabilitation treatment based on the patient dysfunctions and the possible outcomes. The model can be used for simulation of different situations, related to the condition of the patient and the treatment plan in order to observe, and analyze the possible results generated when specific information of the model's parameters is introduced. The results can be used as a powerful tool in the decision making process in order to optimize the telerehabilitation programs for patients with socially significant diseases. Moreover, the model can be complicated and detailed, which will significantly improve the accuracy of the assessment of the patients and the reliability of the proposed algorithm.

Keywords: Telerehabilitation, Generalized nets, Generalized net model.

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A Generalized Net Model for Registration, Assessment and Rehabilitation of Cognitive Impairment in Persons with Multiple Sclerosis

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Cognitive decline occurs along with physical disability in approximately two-thirds of persons suffering from multiple sclerosis (MS) and has devastating influence on quality of life at all stages and in all subtypes of the disease. The modern immunomodulatory therapy has a satisfactory effect on the relapse rate and disease progression, but does not improve the degree of cognitive impairment. Over the last decade, the number of studies on treatment and management of cognitive impairment in people with MS are rapidly growing.

A generalized net model for registration, assessment and rehabilitation of cognitive impairment in persons with MS has been developed. The assessment of cognitive status was made on the basis of results obtained through computer-based neuropsychological tests. Based on comparison of the results from MS patients with those of healthy controls, the degree of cognitive deficit was determined.

The input of the generalized net was formed by the data from patient's medical records, which were categorized according to disease duration, grade of disability, age, sex and employment. As a result of applying the InterCriteria Analysis, the output of the model provides information about the type of impaired cognitive domains and the degree of cognitive deterioration. This allows the therapist to build an appropriate rehabilitation strategy for each individual patient. The rehabilitation module contains a set of different rehabilitation games with several levels of difficulty. The frequency, as well as the degree of complexity of cognitive training is based on the patient's results and the general cognitive reserve registered at baseline.

The system is implemented in a cloud infrastructure and is planned to be provided as an IT service for neurological departments and clinics. In this way, the system is available for testing and rehabilitation of unlimited number of people (both healthy controls and persons with MS) at any time. The developed GN model provides a mechanism for description and simulation of these parallel processes. In this way, the proposed model will be useful in determining the individual approach to each patient and will help optimizing the results of cognitive rehabilitation. The analysis of the model will allow outlining the future directions for therapeutic approaches on cognitive impairments in MS, which will lead to inclusion of cognitive rehabilitation and training programs in routine clinical practice within the next decade.

Keywords: Multiple sclerosis, Cognitive Impairment, Cognitive rehabilitation, Computer training

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A Generalized Net Model with Intuitionistic Fuzzy Assessments of the Process of Cardiopulmonary Resuscitation

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Within the last 20 years a lot of Generalized Net (GN, [1]) models, related to description of biomedical processes in the living organism, and models of the ways of functioning of the different systems and organs in the human body were constructed [3]. The modelling of the such kind of processes and systems with a uniform instrument gives the possibility for their comparing, testing, analysis and control. In this paper a GN model of the Cardiopulmonary Resuscitation (CPR) process is presented. The CPR is a collection of diagnostic and therapeutic actions performed to restore suspended basic vital functions (respiration, cardiac activity, functions of the central nervous system) during cardiac arrest [4, 5]. The developed GN model is a set of transitions that present the sequence of actions of the CPR process with its three interconnected stages: (1) basic life support - refers to maintaining an airway and supporting breathing and the circulation; (2) advanced life support - restoring the spontaneous circulation, stabilization the condition of the patient, and starting the intensive treatment; (3) prolonged life support - intensive treatment of the post-resuscitation syndrome. From the input places of the GN model enter tokens that present the initial status of the person who needs from CPR. The new and enriched knowledge about the process of cardiopulmonary resuscitation of the output of the model is obtained.

In the research, assessments which estimate the execution time of the CPR process are suggested. They are formed on the basis of a set of intuitionistic fuzzy estimations $\langle \mu, \nu \rangle$ of real numbers from the set $[0, 1] \times [0, 1]$, related to the respective patients. The degree of uncertainty $\pi = 1 - \mu - \nu$ represents the cases in which the CPR procedure has not been completed or additional information is needed. Within the paper the ordered pairs were defined in the sense of intuitionistic fuzzy sets [2].

The constructed here GN model can be changed adaptively by using hierarchical operators. It can be used for investigating the behavior of the CPR algorithm. Another application of the model can be prediction of some activities in the CPR and suggesting possible preventive measures, especially in the phase of the prolonged life support. The collecting the information about CPR parameters - fluids, drugs, therapy, ect., as well as qualitative observations can be used for: preparing the recommendations for improving the algorithm; collecting medical information for scientific investigations; training of students.

Keywords: Generalized nets, Modelling, Cardiopulmonary resuscitation, Intuitionistic fuzzy sets.

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Generalized Net Model of the Arterial Supply of the Upper Limb of the Vascular System

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More than 750 Generalized Net models (GN, [1, 2]) of the different systems and organs in the human body are described in a series of paper and several monographs. The global GN model of the human body is presented in [3]. It can be used for investigation the behavior of the different systems of the human body and the relations between them. Each GN model of a particular system or organ can be detailed and made more complex. In the present investigation a GN model of the arterial supply of the upper limb as a part of the vascular system is presented. The vascular system ensures the circulation of blood and lymph in the body. It is composed of a CardioVascular System (CVS) which distributes blood, and a lymphatic system, which distributes lymph. The basic GN model of CVS is presented in [3]. In [4] this GN model is extended with intuitionistic fuzzy estimations. In [5] a GN model which describes the process of circulation of the blood and lymph in the upper limbs is constructed. The transitions of the GN model of the arterial supply of the upper limb proposed in this paper have maximal simple form and present the main arteries that carry oxygenated blood away from the heart to the upper limb are: subclavian artery, axillary artery, brachial artery, radial artery, ulnar artery. They divide into numerous branches. The purpose of the construction of the model is to complement and enrich the knowledge about the CVS, or at least about a part of it.

Keywords: Generalized nets, Modelling, Vascular System, Arterial Supply of the Upper Limb

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Model of the Process of Obtaining and Diagnosing Convalescent Plasma from Patients with COVID-19 by Generalized Nets

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In the Republic of Bulgaria there is a system of centers and wards at three hierarchical levels for collection, processing, diagnosis, storage and distribution of blood and blood products. The leading institution is the National Center for Transfusion Hematology (NCTH). At the next level are five Regional Centers for Transfusion Hematology (RCTH) in Plovdiv, Varna, Pleven and Stara Zagora, plus a Center at the Military Medical Academy, Sofia. At the third level, there are 23 Departments of Transfusion Hematology (OTH).

After the spread of Covid 19 in our country and the introduction of a state of emergency, many hospitals began to hospitalize patients with a positive result for Covid 19 from RT-PCR. Scientific publications subsequently showed that after discharge from hospitals, patients had antibodies to Covid 19. This necessitated the use of plasma with antibodies from patients with Covid 19. They should be monitored, as well as talked to individually to donate plasma either by plasmapheresis or by donating blood and extracting plasma from it. The idea is to take plasma or blood from survivors of Covid 19 in an OTH with the appropriate capacity. It should be transported to the NCTH for the diagnosis of transmissible infections, as is the case with donated blood. Depending on the need, the plasma will be distributed in the medical establishments of the country. Generalized nets (GNs) are one of the tools for modeling parallel processes running in real time. In the present study we propose a GN-model of the process of obtaining and diagnosing convalescent plasma from patients with COVID-19. The presented GN-model describes in details the different steps during the evaluation of the convalescent plasma, which will find expression in process optimization.

Keywords: Convalescent blood plasma, COVID-19, Plasmapheresis, Generalized Nets, Generalized Net Model.

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Possible Application of Generalized Nets in Telemedicine Screening of Corona Virus Disease 2019 (COVID-19)

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The Novel Coronavirus 2019 was first reported in Wuhan, China in late December 2019. Since the beginning of the outbreak, there has been an exponential expansion of the infection and the WHO declared it as a public health emergency of international concern on January 30th. The spread of this virus is now global with lots of casualties of all ages and social groups. The virus has been named SARS-CoV-2 and the disease it causes has become known as coronavirus disease 2019 (COVID-19). The rapid progression of the disease presents a real challenge for the whole world. During the present coronavirus disease (COVID-19) crisis, telemedicine has been recommended to screen suspected patients to limit risk of exposure and maximize medical staff protection. Telehealth can be used to screen for COVID-19 symptoms and assess patients for potential exposure. The use of telehealth can slow transmission of the disease by keeping at-risk people out of waiting rooms and reducing their contact with healthcare facilities. It also enables patients who are not suffering from COVID-19 to continue to receive care. This is particularly important for elderly people, who are at the greatest risk during this pandemic. By improving staff productivity, it stretches the capacity of hospital staff so that more people can be treated. By reducing physical contact with infected patients, telehealth can protect the clinicians. In a view of this, the development of specific screening algorithms and protocols based on the interactive telecommunication technologies and realized via mathematical tools for modeling will permit more efficient collection, transformation and evaluation of significantly large number of patient health data and to report the data into the required form. The purpose of the present paper is to present possible application of GNs with the development of a reduced GN-model as a telemedicine screening tool for COVID-19. The model describes a possible algorithm for remote symptom screening and the different transitions of the model are representing respectively the different criterias of the evaluation process. Moreover, some of the structures of the proposed model represents database storage and processing of COVID-19 data. The GN-model may provide a framework that can be used by primary care practitioners to guide diagnostic processes for patient suspected to have COVID-19, enabling more accurate and efficient identification of that condition and would assist in optimizing patient outcomes and more effective treatment. This model can be complicated and detailed, which will significantly improve the accuracy of the evaluation of the patient and the reliability of the proposed algorithm.

Keywords: COVID-19, Telehealth, Generalized nets.

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A Generalized Net Model of the Pattern of Behavior in Patients with eGFR < 20 ml / min (CKD Stage IV-V)

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Chronic kidney disease (CKD) is a state of progressive loss of kidney function ultimately resulting in the need for renal replacement therapy (dialysis or transplantation). Kidney damage refers to pathologic abnormalities either suggested by imaging studies or renal biopsy, abnormalities in urinary sediment, or increased urinary albumin excretion rates. Patients with CKD and particularly end-stage renal disease (ESRD) are at increased risk of mortality, particularly from cardiovascular disease. The transition from Chronic Kidney Disease (CKD) to the final stage of the course of kidney disease is a process that can take place over a period of time and is not strictly determined in duration. During this period of time it is appropriate to monitor the patient by specialists in various fields - nephrologist, nutritionist, vascular surgeon, urologist, social worker, clinical psychologist. The goal for this multidisciplinary team should be:

1. Monitoring of the main parameters in advanced CKD.
2. Aggressive diet therapy
3. Monitoring of complications in CKD stage IV-V – anemic syndrome, mineral-bone disease, malnutrition, etc.
4. Preparation for kidney transplantation, the possibility of preemptive transplantation is the method of choice in the treatment of these patients.
5. Selection of the appropriate method of dialysis treatment - chemo- or peritoneal dialysis. When choosing a hemodialysis (HD) method of treatment, make appropriate vascular access.
6. Giving the necessary pre-dialysis information to the patient.
7. Determining the exact moment for starting dialysis procedures, in case of previously performed vascular access or access for peritoneal dialysis (PD).

In the present study a multimodal mathematical model of behavior in patients with eGFR <20 ml / min. (CKD stage IV-V) based on generalized nets (GNs) is proposed. The developed reduced GN-model allows for optimization of clinical behavior in patients with CKD stage IV-V, in several ways.

First, the model will permit extraction of clinical data from patients during the different stages of the evaluation process, which will have a great importance in the clinical decision making. Second, the overall result of the model will give a possible information about the patient outcomes related to the clinical decisions.

Keywords: Kidney Disease, CKD stage IV-V, Generalized Nets, Generalized Net Model.

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Generalized Net Model of Biometric Authentication System Based on Palm Geometry and Palm Vein Matching

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The introduction of technological safeguards is more important than ever, but with the increase in networks, devices, connections and applications, this it is extremely complicated. For many people, biometric security is the answer - the technology that can serve and support all industries. The aim of the current investigation is to construct a Generalized net (GN) model of biometric authentication system based on palm geometry and palm vein matching. GNs are suitable instrument for describing parallel processes in their dynamic development [3, 4, 7]. GN models for pattern recognition processes are published [2, 5, 6]. GN model of biometric access-control system and GN model of multimodal biometric identification system are constructed [1, 8]. The processes of iris recognition [11, 14], face recognition [13], fingerprints recognition [9] and signature verification [10] are already modeled using the apparatus of GNs. In the current research work the idea of receiving biometric data through a mobile phone sensor and camera is discussed. The palm of the user is scanned via a sensor placed in the housing of the device. The user's veins data is collected via a scan with the camera of the device. Both processes run simultaneously. The GN model of biometric authentication system based on palm geometry and palm vein matching is constructed using GNDraw software [12]. It contains 6 transitions and 31 places (Fig. 1). The users veins and palm geometry is scanned (transition Z_0) and the received images are preprocessed (transition Z_1). Thereafter the palm veins and the palm geometry are extracted from the input images in parallel (transition Z_2 and transition Z_3). The result is written in the database (transition Z_4). If the database contains the palm vein template and the palm geometry template for the given user the new templates are used for comparison with the extracted user templates (transition Z_5). Additionally, the user has to write one's password which is compared with the previously stored password in the database (transition Z_6). Depending of the received results from the comparison the user can be recognized or not. The presented GN model of biometric authentication system based on palm geometry and palm vein matching can be used to describe and simulate the work process with smart devices. The processes allow for a significant improvement in the quality of work by increasing the security of the device and protection of the user's personal data.

Keywords: Biometric system, Generalized net, Palm vein authentication, Palm geometry, Security.

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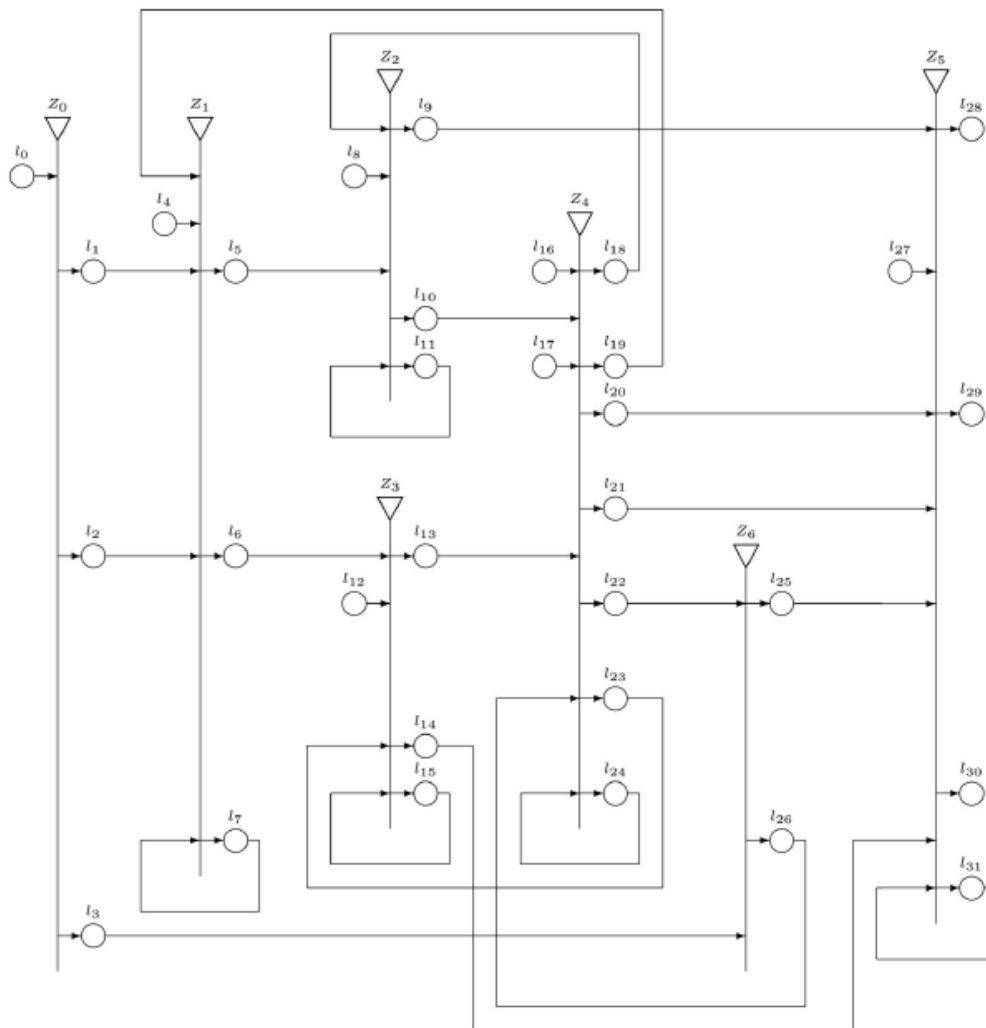


Fig. 1. Generalized net model of biometric authentication system based on palm geometry and palm vein matching

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Implementation of Expanding Hierarchical Operators in GN IDE

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Generalized Nets (GNs) [1–3] are used as a tool to methodically construct reusable models of complex systems that involve parallel or concurrent processes. Over the years, numerous operators have been introduced into the GNs' theory to extend GNs' modelling power.

Generalized Net Integrated Development Environment (GN IDE) [4, 5] is a software tool developed to support the research in the GNs' theory and applications. Initially, the main functionality implemented in GN IDE involved creating GN-models and running simulations for them, with a simplified algorithm of GN functioning integrated into the system. Further, this algorithm in GN IDE has been built up by implementing merging and splitting of tokens.

Recent enhancements in GN IDE involve the integration of GN operators. Two features related to the reducing operators over GNs have been implemented in GN IDE [6]. The first one allows a reduction of components from an already created GN-model without any loss of information. The second feature allows identifying the class of reduced GNs to which a particular GN-model may be referred.

In order to improve GN IDE and to open up new possibilities for its applications, the consistent implementation of GNs' operators in GN IDE has been continued with the implementation of two of the GNs' expanding hierarchical operators, defined to replace a specified transition or place in a GN-model with an entire GN. The implementation of these expanding hierarchical operators in GN IDE and their possible applications are discussed in this paper. The possibility to easily refine a GN-model in details by replacing a GN-transition with a GN has been demonstrated by an example.

Decomposition is a common approach when modelling a complex system. Different subprocesses or states of the system are first described by simpler models and integrated later into one composite model. This approach is often easier than directly creating a detailed version of the model. The states or the subprocesses of a specific system are usually depicted by GN-places or GN-transitions in one rough simplified model. When they are presented in more details, entire GNs are commonly used. To include the detailed models into the overall model of the system, expanding hierarchical operators can be exploited. The implemented expanding hierarchical operators can be conveniently employed further for modelling hierarchically embedded organs or systems of the human body [7].

Keywords: Generalized nets, Expanding hierarchical operators, GN IDE.

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Session 7

Biomedical Approaches and Applications

Biologically Active Acidic and Neutral Heteropolysaccharides from *Geranium sanguineum* L. and *Macrolepiota procera* (Scop.) Singer

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The importance of herbal and mushroom polysaccharides for the support of human health is generally determined by their beneficial effects on the digestive, excretory, cardiovascular, endocrine, nervous, respiratory and musculoskeletal systems. Interestingly, *Geranium sanguineum* is traditionally used in ethnomedicine and *Macrolepiota procera* is a famous delicious edible mushroom, but polysaccharides in both species are not studied enough. Therefore, the aim of the present study was to compare the chemical diversity, immunomodulatory activity on human leukocytes and stimulatory effects on probiotic bacteria of water-extractable polysaccharide complexes (PSCs) from these two species with different physiology. *G. sanguineum* PSC from the leaves (GSL-PSC) consists of pectins with a predominant C-6 methoxylated and O-2/O-3 acetylated homogalacturonan regions, followed by rhamnogalacturonans type I, branched with arabinogalactan structures. *G. sanguineum* PSC from the roots (GSR-PSC) contains starch-type glucans, followed by pectins with smaller homogalacturonan content, which are rich in 1,(3)5-linked arabinans. *M. procera* PSC (MP-PSC) is a mixture of neutral polysaccharides, in which α -1,4-glucans predominate, followed by α -fuco-2-(1,6)-galactans and β -glucomannans, acetylated at mannose residues. GSR-PSC (200 μ g/mL) expressed the most potent *ex vivo* immunomodulatory activity by stimulating human monocytes, granulocytes and acquired immune cells, such as T helper cells and B cells, in a normal and activated state. The three PSCs did not support the growth of 28 strains of different species lactic acid bacteria, isolated from Bulgarian dairy products or humans, when they served as the only carbon source (2%, w/v). However, GSR-PSC (1.4%, w/v) clearly increased biofilm formation of some probiotic bacterial strains, which can be a useful property in the development of symbiotic foods. *G. sanguineum* root polysaccharides need to be added to the active compounds of aqueous root extracts, which have documented immunomodulatory effects.

Keywords: *Geranium sanguineum*, *Macrolepiota procera*, Polysaccharides, NMR, Immunomodulatory activity, Probiotics.

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Fluorescence Spectroscopy of Phosphatidylcholine Bilayers in Mono- and Disaccharide Aqueous Solutions

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The stabilizing effect of sugars is widely used in medicine and industry for cryo- and biopreservation of tissues and materials. An example of its application in nature is the protection of plant cells from the effects of prolonged drought with the help of oligo- and polysaccharides (fructans). On the other hand, sugary foods and drinks have been demonstrated to lower the levels of high-density lipoprotein cholesterol (the so-called "good" cholesterol) and higher the levels of triglycerides, both of which have been shown to increase the risk of cardiovascular disease. In view of describing the mechanisms of the established effects of carbohydrates on a number of biological membranes we address the effect of small carbohydrates (sucrose and glucose) on the bilayer organization. We study their influence on the structure of single-component lipid membranes composed of the monounsaturated lipids 1-palmitoyl-2-oleoyl-sn-glycero-3-phosphocholine (POPC) or 1-stearoyl-2-oleoyl-sn-glycero-phosphocholine (SOPC). The degree of hydration and the rotational order parameter of lipid molecules in the bilayers are assessed by means of 6-Dodecanoyl-N,N-dimethyl-2-naphthylamine (Laurdan) and 1,6-diphenyl-1,3,5-hexatriene (DPH) fluorescence spectroscopy of large unilamellar vesicles. In both types of vesicles, we report reduced lipid ordering at all concentrations of the mono- and disaccharide studied (50-400 mmol/L). The reduced degree of lipid order in the POPC-containing matrix testifies to the interaction of sugar molecules with the lipid bilayer. With increasing the temperature the alteration of lipid packing, defined as the difference between the generalized polarization parameter of Laurdan at 60°C and 20°C, is more pronounced for single-component SOPC vesicles compared to POPC vesicles in sugar solutions (glucose and sucrose). A similar effect of glucose and sucrose solutions is observed on the lipid fluidity, more deeply in the hydrophobic core, estimated via the difference between the fluorescence anisotropy of DPH at 60°C and 20°C. The reported results provide evidences that small carbohydrates are able to change the membrane structure and order related to the membrane homeostasis.

Keywords: Membrane organization, Lipid bilayers, Sucrose, Glucose, 6-Dodecanoyl-N,N-dimethyl-2-naphthylamine (Laurdan), 1,6-diphenyl-1,3,5-hexatriene (DPH).

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Polyphenols Extracted from the Plant *Inula Oculus-Christi* Induced Membrane and Cytoskeleton Reorganisation in Cancer and Non-cancer Cells

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Cellular health and viability relies on the proper structure and function of cell membrane and cytoskeleton associated with it. Interrelations between plasma membrane and cytoskeleton are of crucial importance for essential cellular processes such as endocytosis, formation of intercellular junctions, cell morphology etc. The interactions of membrane constituents with the cytoskeleton can be affected by alterations in membrane fluidity. Many studies validate the beneficial effects of polyphenols as antioxidant and protective agents, but a molecular mechanism of their interaction and transition through the plasma membranes of different cell lines is still missing. In this study, we examined the affinity of flavonoid glycosides (FGs) and phenolic acids (PAs), extracted from the medicinal plant *Inula oculus-christi*, to reorganize the plasma membrane structure and actin cytoskeleton by using confocal microscopy. Assessment of the degree of membrane ordering aiming to distinguish the ordered from disordered domains of the cellular membranes was performed using the fluorescent dye Di-4-ANEPPDHQ and visualization of F-actin was by TRITC-phalloidin.

Two epithelial cell lines with differences in their origin and plasma membrane composition were chosen: the non-malignant MDCK (kidney epithelial cells) and the cancerous A549 (pneumocytes type 2). The tested polyphenolic compounds were able to induce alterations in the plasma membrane and actin organisation in both cell types. FGs exhibited ordering effect on A549 plasma membranes and fluidizing one on MDCK cells. The plasma membranes of both cell lines were fluidized by PAs. Different patterns of the actin reorganisation were observed for both cell lines after treatment with two polyphenolic compounds. Actin cytoskeleton of cancerous A549 cells was more affected whereas changes in MDCK cells were moderate. We suggested that influence of FGs and PAs on membrane fluidity could change affinity of proteins, responsible for actin-membrane connections and thus could affect different cellular functions, including signal transductions pathways and intercellular interactions. The changed membrane fluidity in combination with actin reorganisation could diminish cancerous display of some tumours.

Keywords: Cell membranes, Membrane domains, Actin cytoskeleton, Plant polyphenols, Fluorescence microscopy.

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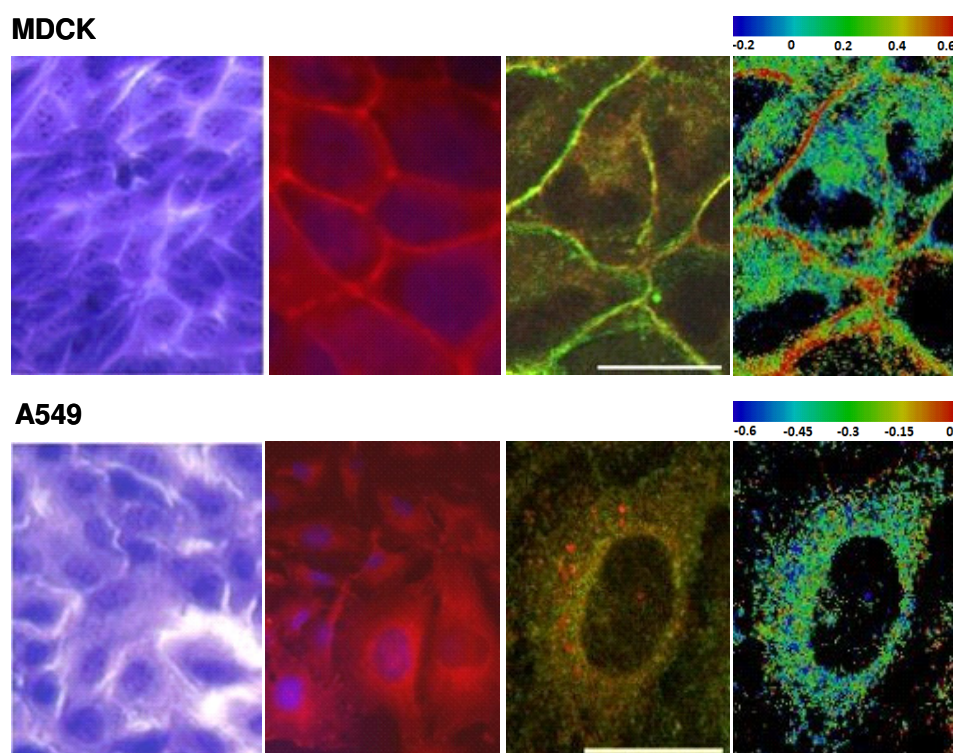


Fig. 1. MDCK and A549 cells morphology (first column), actin labelling, lipid order labelling (merged red and green channels (third column) and GP imaging (fourth column))

Resveratrol Stiffens 1-palmitoyl-2-oleoyl-sn-glycero-3-Phosphocholine Bilayers

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In response to exogenous stress some plant species synthesize the phytoalexine resveratrol (trans-3,5,4'-trihydrostilbene). Found in the skins and seeds of red grapes, red wines, peanuts and other nutrients this polyphenolic compound has been recognized as beneficial in the prevention of oxidative damage in the human organism. The mechanism by which resveratrol exerts its pleiotropic effects is still unclear. Here we study its influence on the structure and mechanics of biomimetic lipid systems composed of the monounsaturated lipid 1-palmitoyl-2-oleoyl-sn-glycero-3-phosphocholine (POPC). The degree of hydration of lipid molecules in the bilayers is assessed by means of Laurdan fluorescence spectroscopy of large unilamellar vesicles. In POPC vesicles, we report enhanced lipid ordering at all concentrations of the polyphenol studied (0-200 $\mu\text{mol/L}$). The increased degree of lipid order in the POPC-containing matrix supports the hypothesis that resveratrol can be considered as a "filler", located parallel to the lipid molecules. Thermal shape fluctuation analysis of nearly spherical giant unilamellar vesicles is applied to probe the membrane mechanics in the presence of resveratrol. Higher bending elasticity modulus of POPC bilayers is measured at increasing the polyphenol concentration. At 200 $\mu\text{mol/L}$ of resveratrol the membrane bending rigidity is reported to increase by nearly 20% compared to its value in bidistilled water. This finding is coherent with the results from fluorescence spectroscopy testifying to the denser packing of POPC molecules induced by resveratrol. The reported results provide knowledge about the phytoalexine's effect on the structural organization of membrane lipids as well as on the bilayer mechanical properties. Revealing the molecular basis of resveratrol-membrane interactions helps developing future applications of the polyphenol in medicinal chemistry and pharmacology.

Keywords: Resveratrol, Membrane organization, Lipid bilayers, Bending elasticity, Giant unilamellar vesicles.

Acknowledgements: Funding from the National Science Fund at the Ministry of Education and Science of Bulgaria (Grant DN18-15/2017) is acknowledged. The authors thank the Bulgarian Ministry of Education and Science for support by the Scientific Infrastructure on Cell Technologies in Biomedicine (SICTB) (DO1-154/28/08/2018). This work is partially supported by COST Action COMULIS CA17121.

Membrane Molecular Mechanisms during Oxidative Stress and Antioxidant Defence

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Many studies have proven the important role of ROS (reactive oxygen species) in the development of oxidative stress. ROS are continuously produced during normal physiologic events, but their elevated levels may cause oxidative modification of lipids. Thus, ROS have damaging potential, leading to disease conditions. Aerobic organisms have antioxidant defences such as food constituents to remove or repair the damaged molecules. Among them, the polyphenol resveratrol (Resv), produced by some plants protects them against environmental stresses. The powerful antioxidant action of this molecule on human health is well documented, but the exact molecular mechanism of action is still unclear. It has been considerable interest in the possibility that the plasma membrane contains lipid “rafts” (L_o, liquid-ordered domains), microdomains enriched in cholesterol, sphingolipids and specialized proteins in a more liquid phospholipid matrix (L_d, liquid-disordered domains). These domains could take part in many cellular processes including cell signaling and trafficking events.

We studied the effect of Resv on the lipid ordering and raft fraction in model membranes composed of palmitoyl-docosahexaenoyl phosphatidylcholine (PDPC), polyunsaturated lipid species which is more prone to oxidation, palmitoyl-oleoyl phosphatidylcholine (POPC), monounsaturated ones, sphingomyelin (SM) and cholesterol (Chol). PDPC/SM/Chol mixtures at 37°C demonstrated a reduced lipid ordering at Resv concentrations close to physiological ones. An opposite trend was observed at amounts higher than physiological ones. POPC/SM/Chol mixtures exhibited only ordering effect for all studied Resv concentrations. Moreover, Resv was able to modulate the raft fraction in POPC ternary mixtures whereas in PDPC ones Resv mostly reduces it (Fig. 1).

We demonstrated changes in the membrane organization induced by Resv and hypothesize that these alterations could be considered as a unique property of the bioactive compound to protect the living cell from oxidative stress.

Keywords: Oxidative stress, Resveratrol, Lipid raft, Docosahexaenoic acid, Oleic acid, Lipid ordering.

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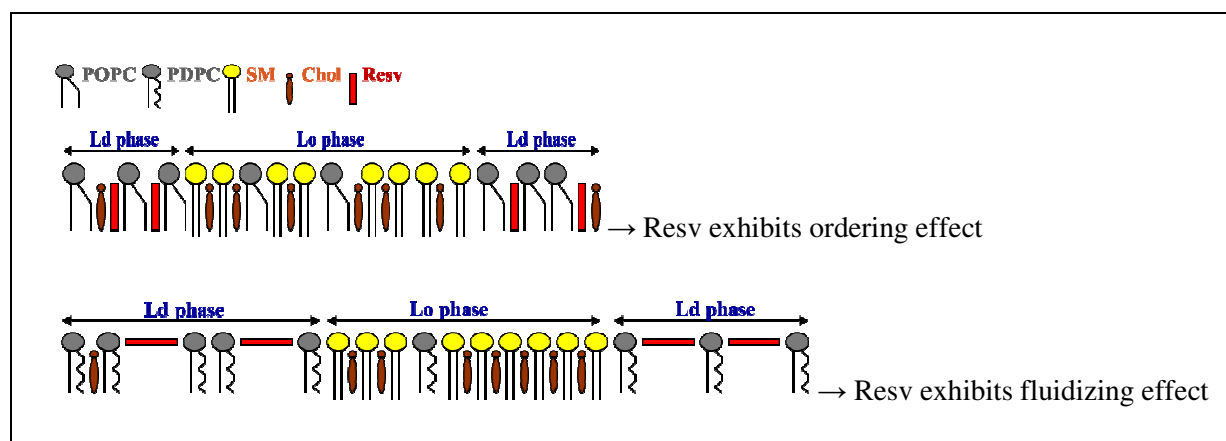


Fig.1. Suggested mechanism by which resveratrol exerts its pleiotropic effects

Membrane Reorganization under Oxidative Stress: Effect of Oxidized Lipids

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Oxidative stress is a major outcome of free radical mediated injury, associated with inflammation and a number of pathologies, such as Alzheimer disease, atherosclerosis, cardiovascular diseases, cancer among others. Alterations in lipid composition and structure are of obvious importance when attempting to understand the consequences of oxidative stress on membrane-associated processes. To examine the physicochemical changes in membrane lateral organization induced by oxidized lipids, we prepared model membranes that mimic the lipid composition of specialized cellular membrane domains, called rafts. Lipid rafts are liquid-ordered (L_o) membrane domains enriched in sphingomyelin (SM) and cholesterol (Chol) that are floating in a sea of unsaturated phospholipids in the non-raft liquid disordered (L_d) phase. These domains play an important role in plasma membrane processes and functions as organizing centers for the assembly and trafficking of signaling molecules. The aim of the present study is to investigate the effect of two of the most physiologically active oxidized phosphatidylcholines (OxPCs), 1-palmitoyl-2-(5'-oxo-valeroyl)-*sn*-glycero-3-phosphocholine (POVPC) and 1-palmitoyl-2-glutaroyl-*sn*-glycero-3-phosphocholine (PGPC), on the membrane packing, raft formation and the size of nanodomains as a function of the degree of fatty acid unsaturation at *sn*-2 position in phosphatidylcholine (PC) molecule. Monounsaturated lipid, 1-palmitoyl-2-oleoyl-*sn*-glycero-3-phosphocholine (POPC), and polyunsaturated one, 1-palmitoyl-2-docosahexaenoyl-*sn*-glycero-3-phosphocholine (PDPC) are compared in different types of mixtures with various PC/SM/Chol ratios.

OxPCs fluidize the domains in L_o phase state as well as "pure" L_d membranes, and this effect is larger in polyunsaturated membranes than in monounsaturated ones. The flicker spectroscopy measurements further support the strong softening of POPC bilayers upon addition of only 5 mol% of POVPC. In ternary L_o/L_d systems, the opposite trend is found, OxPCs have an ordering effect in monounsaturated matrix, while there are no significant differences observed in polyunsaturated one. POVPC demonstrates a greater ability to alter the fluidity of Chol-containing membranes than PGPC. The opposite trend is noticed in membranes without Chol, where PGPC induces much larger changes in membrane packing in comparison to POVPC. Moreover, POVPC exhibits a stronger and concentration-dependent effect on the formation and size of raft domains compared to PGPC.

OxPCs affect the physicochemical properties of membranes and domains in Chol-containing monounsaturated matrix to a greater extent than polyunsaturated one (Fig. 1), demonstrating a protective structural role of docosahexaenoic acid belonging to the omega-3 family against the presence of oxidized lipids.

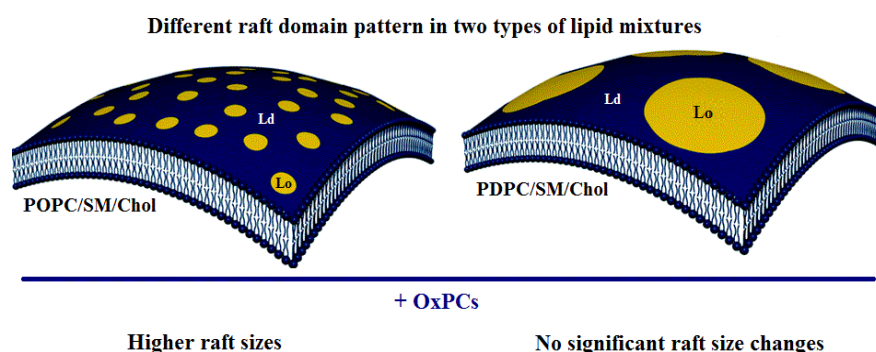


Fig. 1. Lipid domain pattern with and without oxidized lipids in mono- and poly-unsaturated ternary mixtures. Adapted from [1]

Keywords: Oxidized lipids, Lipid rafts, Oxidative stress, Membrane organization, Model membranes.

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Chitosan-Based Nanoparticles Interact with Bio-inspired Membranes. Implications in Biomedical Engineering

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The biodegradable and non-toxic materials are an increasing field of research for maintaining human health. Chitosan (CS) is one of the most studied polysaccharides for this purpose. In our study, we explored the biological activity of newly developed polymeric-based nanoparticles (NPs), including metal oxides, such as ZnO. To understand the complete mechanism of action of these nanoparticles with cell plasma membranes, we focused on their interactions with lipids, assembled in biomimetic membranes.

Large unilamellar vesicles (LUVs) have been prepared and composed of different lipids and their mixtures mimicking the lipid architecture of mammalian plasma membranes. Lipid order was investigated by Laurdan spectroscopy measurements at physiological temperature. We studied LUVs composed of Egg phosphatidylcholine (EPC) in liquid-disordered phase (L_d), equimolar ratios of EPC/Cholesterol (Chol), and ESM/Chol in liquid-ordered phase (L_o), and EPC/ESM/Chol mixtures representing L_o/L_d phase coexistence. The ternary mixtures mimic the formation of raft-like membrane domains implicated in crucial cellular physiological events in health and disease.

LUVs (1 mg/ml) in different lipid phase states were treated by increasing concentration of NPs (up to 1mg/ml) – CS, ZnO NPs, ZnO-CS, ZnO- PEG nanocomposites (NCs). The CS NPs increases the lipid order of membrane in L_d phase. The addition of ZnO alone and ZnO-CS to the model vesicles decreases the lipid packing compared to CS NPs. CS NPs induce larger changes in membranes in L_d phase compared to L_o one, where the alterations in molecular order is much weaker. ZnO-CS NCs show the strongest lipid packing capacity for ESM/Chol mixtures, model of cellular lipid rafts. ZnO-CS NCs effect on L_o/L_d phase coexistence depends on the molar ratio of Chol in the mixtures. In general, the presence of Chol increases the lipid packing. At the highest studied Chol concentration, ZnO-CS NCs make the membrane even more ordered compared to CS. At low Chol levels, these NCs exhibit less membrane packing effect compared to pure CS.

Nanomaterials are able to affect the lipid ordering and organization in biomimetic membranes by changing the degree of hydration at the glycerol level of the lipid membrane. We imply that the obtained results could contribute to deeper understanding of the mechanisms of cell attachment to polymer surfaces and to determine the role of the surface properties of materials by their interaction with the cells.

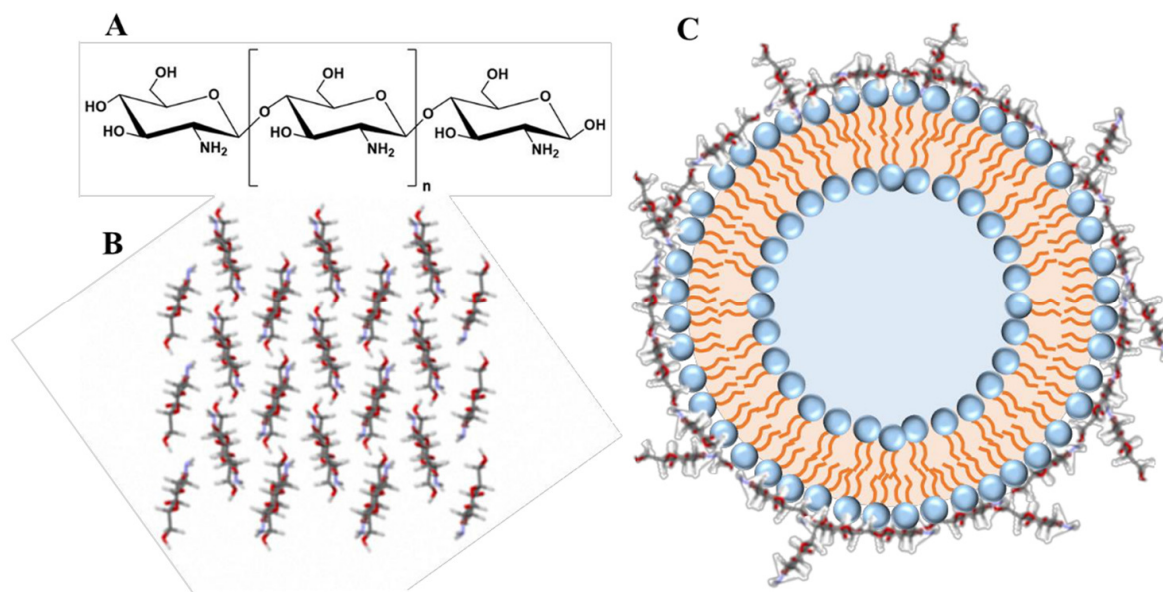


Fig. 1. A – Structure of chitosan; B – Polymerisation of chitosan;
C – Interaction of chitosan with model membrane

Keywords: Chitosan nanoparticles, Sphingomyelin, Cholesterol, Rafts, Liposomes.

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Fluorescence Spectroscopy as Marker for the Study of Unknown Olive Oils

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Fluorescence spectroscopy is a widely used method from biology to agriculture and from the natural to the technical sciences. It is convenient and easy to apply on samples of plant and animal origin. In our work, fluorescence spectroscopy is applied to detect unknown quality olive oils. This method does not perform a quantitative biological and chemical analysis.

Since the fluorescence spectroscopy is often very weak and also in all directions, in order not to saturate the receiver, the useful fluorescence signal is measured in a direction that is below 45° to the excitation radiation. It is preferable to use a laser diode as a source in the circuit, because of its very small spectral width. The LEDs used in the experiment have a relatively wide spectral width of radiation of about 30 - 40 nm and the angular distribution of its radiation is in a large angular range of +/- 300. It was chosen to work with four laser wavelengths of 370 nm, 395 nm, 450 nm and 425 nm. The LED irradiates the sample and its emission wavelength is transmitted through the optical fiber to the spectrometer. The sensitivity of the spectrometer is in the range from 200 nm up to 1100 nm with a resolution of $\delta\lambda = 5$ nm. The results obtained from olive oils are average value of five samples of fluorescent spectra.

In previous works, the authors studied the same types of olive oil and their composition. This study examines different types - extra virgin, virgin, olive pomace oil and salad olive oils (for characterization of the olive oil types COI/OT/NC no. 1 Resolution No. RES-2/91-IV/04 and COI/T.15/NC no 3-25 (revised June 2003) standards are used). Data were obtained for extra virgin and olive pomace oils from the same producers. They show that extra virgin olive oils have a pronounced fluorescence peak of 680 nm followed by 720 nm. While the olive pomace oil and salad olive oils are shifted to the left i.e., about 600 nm with symmetrically arranged additional peaks.

Fluorescence spectra for unknown olive oils were obtained. The data show that fluorescence spectroscopy is a reliable method for detecting olive oils quality.

Fluorescence spectroscopy allows a classification of different olive oil type, thus the most healthy for the human extra virgin olive oils can be selected.

Keywords: Olive oil, Fluorescence spectroscopy.

Aging Patterns of Blood Plasma and Red Blood Cells of Patients with Amyotrophic Lateral Sclerosis

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Amyotrophic lateral sclerosis (ALS) is an uncommon, rapidly progressing neurodegenerative disease associated with significant changes in the motor neurons and motor functions [1, 2]. The ALS pathogenesis is not well understood and most of the proposed biological markers for the diagnosis of ALS are not confirmed as reliable [3, 4]. Recently, efforts to search for novel, non-invasive biomarkers in blood plasma and peripheral blood cells has been stimulated.

In this study we report results of a biophysical characterization of red blood cells (RBCs) and blood plasma from patients diagnosed with ALS, the disease progression was followed along the process of erythrocytes aging.

Calorimetric data reveal that the most abundant proteins of blood plasma and cytoskeletal and major membrane proteins of red blood cells (RBCs) of patients diagnosed with ALS are more stable against the thermal challenge than those of healthy individuals. Strong difference between the aging pattern of the morphology of ALS and healthy RBCs, determined from optical images, is also found.

The important thermodynamic features of plasma and RBCs proteins, and the morphometric types of RBCs are modified along the aging process for patients with ALS:

- (i) The aging is associated with gradual decrease in the temperature of Hb unfolding for both ALS and healthy RBCs, hemoglobin (Hb) in ALS cells, however, remains thermally more stable along the entire aging process under study (ca. 60 days) than in healthy cells.
- (ii) The plasma proteins albumin and transferrin/immunoglobulin G (IgG) are stabilized in ALS plasma.
- (iii) The amplitudes of the transitions assigned to fibrinogen and transferrin/IgG have bigger values compared to the healthy ones, unlikely the thermal transition of immunoglobulins is not as well resolved for ALS plasma as for healthy ones.
- (iv) The transformation of the cells shape along aging occurs much faster for healthy than for ALS cells.

Our pilot investigation of the biophysical features of ALS blood plasma and peripheral blood cells proves higher degree of stability of both plasma and RBCs proteins, and different aging pattern of RBCs compared to healthy ones.

Keywords: Red blood cells, Blood plasma, Amyotrophic lateral sclerosis, Aging process, Thermal stability of plasma and erythrocytes protein, Morphology of red blood cells.

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A FEM Study of Mechanical Behaviour of a New S-Shape-Stents of Different Lengths

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Coronary stents are one of the most used tools for treatment of cardiac diseases caused by reducing of the blood vessel lumen due to plaque. The most studied stents known from the literature are the so called Palmaz-Schatz stent, which struts are parallel before the stent balloon expansion.

The presented study shows the results of studying of mechanical behaviour of a stent of novel S-shaped form at different stent lengths. This shape was presented firstly by the firm ISMA EOOD, Sofia, Bulgaria.

The stent struts can be obtained by copying the shape in both longitudinal and peripheral directions like Escher tessellation. Using this approach, the bridges between the cells, which need cramping in the usual Palmaz-Schatz stents, are obtained in a native way.

In the current presentation following mechanical properties of the stent are estimated: recoil, foreshortening, dogboning, as well as the flexibility. Safety factor for stents with 1, 2, 3, 4, and 5 shapes in longitudinal direction are found. These parameters are very important concerning preservation of desired lumen of blood vessel and safety transportation to the place of implantation.

Mechanical behaviour of the stents, fabricated from medical stainless steel Grade 316L, are simulated using COMSOL Multiphysics.

The mechanical properties of the stent with the suggested shape are compared with the mechanical parameters of traditional Palmaz-Schatz stents known from the literature.

The stents of new design show more negative dogboning which is preferable as found from FEM simulation of traditional Palmaz-Schatz stents.

The recoil and foreshortening is not larger compared with Palmaz-Schatz stents.

The stents with the new stent design reveal a good flexibility and maximal bending angle is found for each stent length.

No von Mises stresses are observed, which exceed the ultimate tensile stresses.

The stents reveal a good safety factor and this is a good prediction of long life of the implant.

Finally, it is proven, that FEM is very versatile and reliable tool for pre-clinic testing of coronary stents.

Keywords: Solid mechanics, Coronary stents, FEM, Comsol.

High-risk Cardiac Patients Follow up via Portable Telemonitoring Personal Analyzer: Accuracy, Reliability and Applicability

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Patients' telemetry deals with remote following of vital parameters and processes without continuous direct contact between physician and patient. The aim of this study is to investigate the accuracy, reliability and applicability of a telemetry system for real-time monitoring of cardiac patients. The system includes personal analyzer (PA), central unit and a console for the cardiologist. PA is portable device performing continuous single-channel electrocardiogram (ECG) acquisition at 250 Hz sampling rate; heartbeat detection and classification (normal/ectopic beats), and heartrate assessment. PA transfers 10 s ECG segments on 3 reasons: regular transfer (5/10/15 min), transfer on demand and when an alarm based on rhythm disorders and/or heartbeat abnormalities is generated.

The ECG telemetry system is tested in the Cardiology unit of University Hospital "Alexandrovska" – Sofia. The research has involved 85 patients (31 male, age 23-91 years, hospital stay 1-14 days) with cardio-vascular diseases – ischemia with or without experienced myocardial infarction, arterial hypertension, heart failure (result of valvular heart disease and cardiomyopathy), myopericarditis, accompanying thyroid pathology, and patients with electrolyte imbalance. In parallel, the patients' ECGs have been recorder by a holter device Signa-Lyzer SD. An experienced cardiologist has performed the following analyses of the collected ECG data:

- Compared the ECG segments that have provoked an alarm to the respective ECG segments in the holter recording and judged about the correctness (accuracy) of the alarm;
- Checked the holter ECG recording for events that are missed by the PA (reliability).

Full correspondence between the PA alarms and the rhythms recorded via the holter has been observed (100% accuracy). Considering the observed holter events, PA reliably warns for 80.6% of the rhythm disorders. In the remaining 19.4% an alarm is not generated mainly due to the fact that the patients have been out of the telemetry range.

The observed results show that the tested PA could support timely diagnosis, prompt reaction and adequate therapeutic treatment in potentially life-threatening clinical conditions, such as:

- Proarrhythmic effects of antiarrhythmic drugs, especially when combined with antidepressants, antihistamines or macrolide antibiotics;
- High-grade conduction disorders, requiring urgent pacemaker implantation;
- Malignant ventricular dysrhythmias;
- Episodes of paroxysmal atrial fibrillation that require anticoagulation for stroke prevention.

The data obtained via PA might draw physicians' attention to undiagnosed thyroid gland dysfunction.

In conclusion, the portable PA could be a useful tool for proper diagnosis and management of high risk patients with cardiomyopathies, congestive heart failure, obstructive sleep apnea and patients in post myocardial infarction state.

Keywords: Wireless electrocardiogram monitoring, Portable ECG module, Telemetry, Cardiac diseases.

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Software Tool for Electrocardiogram Annotation

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Background: Nowadays, many electrocardiograms (ECG) are being daily recorded worldwide for diagnostic purpose. However, if the ECG recordings are not properly annotated, their use is confined only to the particular patient diagnostic process. On the other hand, the development of diagnostic methods requires access to annotated databases for training, testing and validating the models/methods/algorithms.

Aim of the study: The aim of this work is to present the potential of an internet-based software developed for annotating large databases of ECG signals.

Methods: The designed annotation software has two main components as follows:

- A server component which is server-based, written in Python programming language. It contains procedures for managing the ECG records, i.e. reading and saving ECG signals, recording the annotation data as well as the ECG waves delineation data.
- Front-end application written predominantly in Java Script programming language. There are several available frameworks like Angular, Vue.js and React, from which the React Java Script framework has been chosen as the most popular and easy to use.

The annotation system has the following submodules:

- Annotation module – allows marking the new QRS complexes', changing their type or correcting their position;
- Average beats module – averaged beats are generated by the server and displayed in the browser. Using this module the averaged QRS complex delineation markers (P, QRS, T waves begin and end) can be corrected.
- Rhythm type of the ECG record – provides the rhythm type and possibility to change it.

Results: The initial version of the application works with a database based on a local server on a personal computer. It has been tested by four users (annotators). The software is opened for further developments.

Discussion and Conclusions: Currently the presented ECG annotation software is in its test phase and addition of new features is ongoing. This complex tool has the capability to annotate large databases supporting multiple annotations per record. The accumulation of large annotated ECG databases would be of great benefit for development, testing and evaluation of new algorithms for ECG signal analysis.

Keywords: Electrocardiogram (ECG), Annotation software, Heartbeat types, Arrhythmia types.

A Survey on the Application of Mobile Communication Devices in Remote Cardiac Monitoring Systems

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Remote patient monitoring using GSM (Global System for Mobile) technology provides a global connectivity able to transfer and store large amounts of physiological data in the cloud. The rapid improvements in wireless and cellular communication set the new mobile mHealth era of clinical care when physicians can think about their patients outside the traditional in-office setting and patients can be actively engaged in their care by simply using their smart mobile devices connected to different body sensors. Positive effects of early diagnosis and treatment, patient mobility, long-term cost-effectiveness and safety in the spectrum of cardiac morbidity and severity are largely expected. This study aims to perform a systematic literature review (SLR) on the current developments and applications of mobile communication devices (GSM, smart-watches, smartphones) for real-time telemetric monitoring of the cardiac activity based on the electrocardiogram (ECG) and additional body sensors.

SLR was performed in June-2020 in five largest databases for peer-reviewed literature (Scopus, Web-of-Science, PubMed, Springer, Science Direct) on English papers published (2010-2020). First filter included papers with titles, abstracts and keywords: ("GSM"-or-"smartphone"-or-"smartwatch") and (("patient"-and-"telemetry") or ("patient"-and-"remote"-and-"monitoring") or ("ECG"-and-"telemetry") or ("ECG"-and-"remote"-and-"monitoring")), identifying 123 publications: Scopus (10, 8.1%), PubMed (21, 17.1%), Springer (24, 19.5%), Science Direct (21, 17.1%), Web-of-Science (47, 38.2%). Second filter (Python algorithm) removed 9 duplicated publications in search-lists of databases, storing data for 114 unique records. According to the analysis plan, those 114 records were further subjected to analytical screening by two reviewers who comprehensively read the titles and abstracts to pre-select papers answering the specific question: "Does the paper present remote out-of-hospital patient ECG monitoring and transmitting data via mobile communication devices?". A number of 92 articles (80.7%) were excluded non-matching the specific question, covering the following topics: clinical trials in-hospital settings; monitoring of critical patients in intensive care units; management of various communication architectures; stress systems and clinical trials under special conditions; processing and recording of ECG signals with large number of electrodes; ECG telemetry in animals. SLR selected 22 papers by consensus between reviewers [1–22]. They present different technologies for remote patient monitoring (mostly using standard communication modules in smartphones GSM/GPRS/SMS/GPS, rarely other interfaces or mobile ad-hoc networks); sensors (ECG, photoplethysmogram, ballistocardiogram, thermometer, accelerometer, piezo-sensors); continuous measurements (heart-rate, respiratory-rate, non-invasive blood pressure, heart-rhythm, oxygen saturation, energy expenditure, location information); alarm event detection (cardiac arrhythmia, hypertonemia, fall); real-life applications (ambulatory monitoring of cardiac patients, cardiac rehabilitation, mobile ECG-detection system in ambulances, remote follow-up of cardiac implantable

electronic devices, fetus heart-rhythm monitoring, etc.). Benefits and technological challenges behind mHealth are discussed, together with special aspects for patient privacy protection in client side when using mHealth.

Keywords: Electrocardiogram, GSM, Smartphone, mHealth, Remote patient monitoring, Telemetry, Cardiac activity.

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Differences in Ischemia Mechanism in Coronary Artery Disease and Cardiac Syndrome X

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Aim: The Cardiac Syndrome X (CSX) includes patients with the triad of angina pectoris: a positive exercise-strain test and angiographically smooth coronary arteries. The most manifested clinical symptom is chest pain. The aim of the study is to explore the differences in ischemia mechanism in both groups – CSX and patients with Coronary Artery Disease (CAD), based on specific changes in Autonomic Cardiac Control (ACC).

Material and Methods: We used a new method for multicriteria decision making – InterCriteria Analysis (ICrA) [1], to reveal relationships between 13 standard indicators for Heart Rate Variability (HRV) – in resting state (REST) and by sympathetic stimulation (handgrip test, HT) or parasympathetic stimulation (Valsalva manoeuvre, VM), through which we evaluated the activity of ACC in two groups of 40 patients – with CSX and with CAD [2].

Results: In resting state, the PNN50 indicator for the group with CAD is in a weak negative consonance with the indicators for VLF, LF1, and HF for the group with CSX. By stimulation of the sympathetic fraction of ACC (HT), the indicator PNN50 for the CAD group is in a weak negative consonance with the indicators RRMd, Med, dRRMd, PNN50, RMS, LF, and HF for the CSX group. By parasympathetic stimulation (Valsalva manoeuvre, VM), there is no established consonance between the HRV indicators in the two groups. These results give a reason to assume, that in the two groups there is a different response of the sympathetic autonomic system under conditions of stress with a matching parasympathetic tone.

Keywords: Cardiac syndrome X, Coronary artery disease, InterCriteria Analysis, Heart rate Variability, Autonomic cardiac control.

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Session 8

Excitable Structures and Motor Activity

A Risk Assessment Study on Musculoskeletal Disorders in Computer Users Based on a Modified Nordic Musculoskeletal Questionnaire

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We present a recent study on musculoskeletal disorders risk assessment in computer users. For the purpose of our study, we collected data from 60 people who normally use PCs in their work routine. The data collection campaign was implemented by means of a modified Nordic Musculoskeletal Questionnaire (NMQ), which involves self-assessment of pain intensity and localization following the body pose visualizations specified in ISO 11226:2000, and the recommendations for proper arrangement of the workplace according to ISO 9241-6. Specifically, a modified NMQ was implemented as a computer test. Based on the post-test briefings with the participants, we found out that the NMQ brings an educational benefit because it made the participants aware of specific inappropriate habits and body poses. Specifically, the test provoked the participants to think about the proper pose of the trunk, upper and lower limbs, the distance to the screen, the position with respect to the keyboard, and mouse, etc., which was perceived as beneficial and useful. The average age of participants was 39.6 years old and more than half of them admitted the absence of specific knowledge on the regulations for proper body pose or on the deficiency of specific knowledge about the common recommendations related to the proper arrangement of the workplace. Among these are approximately 18.3% of the responders who openly admitted that they are not familiar with the recommendations for the proper position of the body when using computers. Another 36% declared that they are partially acquainted with the good practices and regulations related to the subject. Thought-provoking outcomes of our study are the conclusions that there is an urgent need for proper training of the average computer user on the health compliant work positions and on the development of healthy habits. Furthermore, energetic efforts are required for the popularization of good practices for the safe use of computers and the related standards. The results obtained to this end, motivate the development and promotion of adequate proactive measures for long-term health preservation of computer users. The findings reported here are considered essential for people who use computers on a daily basis.

Keywords: Ergonomics, Musculoskeletal disorders, Computer workplace, Nordic musculoskeletal questionnaire.

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Technological Support to Musculoskeletal Disorders Assessment and Management

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Work efficiency and quality of life largely depend on health. Daily computer use is an integral part of work, educational activities, and entertainment, and as it is already well known, it increases the risk of developing various musculoskeletal disorders (MSD). MSDs are identified as the main reason for chronic body pain, most often in the upper limbs, shoulders, or neck. In this regard, we present the overall concept of our project, which aims to develop appropriate resources and advanced technological tools in support of the early diagnosis and management of MSD among computer users, who use PCs in their work routine. Our concept is based on the assumption that contemporary technology can support well the standard therapeutic procedures used by medical staff for the identification of MSD and the periodic assessment of MSD progress. Specifically, we aim to develop a technological platform and appropriate tools for the automated estimation of the current body position based on video or images, questionnaire-based distress assessment and concentration assessment based on physiological signals. These data will be used in order to develop advanced statistical models that facilitate the early detection of MSD and will help for predicting the MSD symptoms. Among the main objectives of our project is to develop a set of indicators and mobile apps that help the management of MSDs in work-related computer use. The project also has educational aspects as we aim to make computer users aware of the good practices and the relevant regulations for long-term preservation of health and work efficiency.

Keywords: Ergonomics, Musculoskeletal disorders, Computer use, Risk assessment, MSD management.

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Effect of Changes in the Intracellular Resistivity of Skeletal Muscle Fibre on Intracellular and Extracellular Potentials

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The electrically evoked muscle action potential (M-wave) is used as a non-invasive estimate of changes in the functional state of muscle. The strange behavior of the M-wave raises questions about the mechanisms of observed changes and about the site for better M-wave detection. Intensive muscle contractions are accompanied by metabolic changes that could affect the ionic composition of the cytoplasm of muscle fibre and thus its resistivity. We aim to study the effects of intracellular resistivity on intracellular action potentials (IAPs) and extracellular potentials (EPs). The Hodgkin-Huxley type mathematical model was used to simulate the intracellular processes of muscle fibre, for normal human temperature. The spatial potential profile of the IAP obtained for each time point was used to calculate the corresponding point of the EP in the time domain. The results showed that the change in intracellular resistivity had practically no effect on the amplitude and shape of IAP in the temporal domain. The main effect was on the velocity of IAP propagation along the fibre and proportional to velocity length of IAP profile in the spatial domain. Changes in the length of the IAP profile affected the amplitude of the EPs above the end-plate region and above the middle of the fibre semilength to a similar extent. Changes in the velocity of IAP propagation on the duration of the first phase of EPs were similar for detection above the end-plate region and the middle of the fibre semilength. Changes in the velocity of IAP propagation affected the latency of appearance of the second phase of EP and did not affect its amplitude and duration. The results will help in analysis of changes in the M-responses obtained during and after muscle activity.

Keywords: Skeletal muscle fibre, Intracellular resistivity, H-H type model, Intracellular action potential, Extracellular potential, Propagation velocity, Electrode position.

