ICCB
2019

VIII International Conference on
Computational Bioengineering
4-6 September 2019, Belgrade, Serbia

ICCB 2019
Proceedings

8th International Conference on Computational Bioengineering

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Organizers

University of Kragujevac

University of Belgrade

Bioengineering Research and Development Centre BioIRC

Faculty of Engineering Kragujevac

Supporting organizations

The Ministry of Education, Science and Technological Development of The Republic of Serbia

European Society of Biomechanics

Contents

Welcome Message

Dear colleagues and students,

On behalf of the Organizing Committee, it is our great pleasure to welcome you to the *8th International Conference on Computational Bioengineering* (ICCB2019) which is taking place in Belgrade, Serbia, from 4th-6th September, 2019.

The ICCB2019 promotes complementary disciplines that hold great promise for the advancement of research and development in complex medical, biological and computer systems. The main conference includes sixteen sections dealing with topics such as biomechanics, cardiovascular engineering, patient-specific modeling, multiscale modelling, data mining, decision support systems, biomaterials and dental biomechanics, nanomedicine, tissue and cell engineering, computational chemistry, sports bioengineering, etc. Within sixteen sections, we also have seven mini symposia dealing with the issues in the fields of artificial intelligence, machine learning, computational chemistry, risk assessment, computational and experimental physiology, augmented reality and multi-scale modelling. The conference is organized, sponsored and supported by the University of Kragujevac, University of Belgrade, Bioengineering Research and Development Center BioIRC, Ministry of Education, Science and Technological Development of the Republic of Serbia and European Society of Biomechanics.

The ICCB is a large international conference with 16 years of tradition and leading reputation. It follows previous successful conferences held in Spain in 2003, in Portugal in 2005, in Venezuela in 2007, in Italy in 2009, in Belgium in 2013, in Spain in 2015, in France in 2017. ICCB gathers eminent scientists and researchers, as well as students aiming to promote interdisciplinary and multidisciplinary approaches needed for solving complex problems, which requires expertise in the field of biomedical sciences and engineering.

This year, the ICCB 2019 has received more than 150 high-quality research papers and the best papers have been chosen for this Book of Abstracts. Each paper has been reviewed by at least 2 scientists in the programe and scientific review committee. As a result of the strict review process and evaluation, the committee has selected papers which will be published as full regular research papers.

We are delighted to announce 10 world renowned scientists as ICCB 2019 keynote speakers:

***Dimitrios Fotiadis**, University of Ioannina, Greece*

***Valentin Djonov**, University of Bern, Switzerland*

***Akira Tsuda**, HSPH, Harvard University, USA*

***Marie-Christine Ho Ba Tho**, University of Technology of Compiegne, France*

***Milos Kojic**, Houston Methodist Research Institute, USA*

***Stephane Avril**, Center for Biomedical and Healthcare Engineering, France*

***Nino Russo**, Universita della Calabria, Italy*

***Erik Klein**, University of Technology in Bratislava, Slovakia*

***Julien Barthes**, PROTIP MEDICAL, Strasbourg, France*

***Atul Bhaskar**, University of Southampton, UK*

We must also say that the conference would certainly not have been so successful without the efforts of many people who were actively engaged in organization of such a major internationally recognized academic event. We give our special gratitude to the members of the program and scientific review committee as well as to all chairs, organizers and committee members for their dedication and support.

This year, ICCB Conference is held in Belgrade, Serbia, a city with rich cultural heritage and extensive and colorful history. We hope that you will find time to explore the city and experience its soul. Serbia already has a number of very good scientists in the area of bioengineering and ICCB2019 is an excellent opportunity to introduce their research and scientific achievements in these challenging areas.

On behalf of the Organizing Committee, we wish you all a pleasant stay in Belgrade and a productive conference.

Prof. Nenad Filipović, Conference Program Chair

Organization and Committees

Local Organization Committee

Nenad Filipovic, University of Kragujevac, (Chairperson)

Milos Kojic, BioIRC - University of Kragujevac

Veljko Milutinovic, University of Belgrade

Miroslav Trajanovic, University of Nis

Neda Vidanovic, University of Kragujevac (Secretariat)

Dalibor Nikolic, BioIRC - University of Kragujevac (Logistics)

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N. Filipovic, Serbia

D. Fotiadis, Greece

J.M. García Aznar, Spain

C. Gasser, Sweden

D. Garzon, Colombia

C. Hellmich, Austria

Program at a Glance

Wednesday 04 September 2019		
08:45 - 09:15	Opening Ceremony - Welcome speech: Dr. Nenad Filipovic, rector of the University of Kragujevac, Conference Chair Dr. Viktor Nedovic, State Secretary, Ministry of Education, Science and Technological Development Dr. Berislav Vekic, State Secretary, Ministry of Health	
09:15- 09:45	Keynote speaker: **Topic: Angiogenesis modeling** **Prof. Valentin Djonov,** *University of Bern, Switzerland*	
09:45 - 10:30	**Session W.1** **Mini-Symposia 4:** COMPUTATIONAL AND EXPERIMENTAL PHYSIOLOGY: NOVEL POTENTIAL ANTINEOPLASTIC COMPOUNDS AND CARDIOVASCULAR SYSTEM	
10:30 - 11:00	Coffee Break	
11:00 - 11:30	Keynote speaker: **Topic: Nanoparticles, pulmonary medicine** **Prof. Akira Tsuda,** *Harvard School of Public Health, Boston, MA, USA*	
11:30 – 13:00	**Session W.2** **Mini-Symposia 6:** MULTISCALE IN-SILICO MODELING OF CARDIOMYOPATHY FROM GENO TYPE TO PHENO TYPE	
13:00 - 14:00	Buffet Lunch	
14:00 - 15:00	**Session W.3** **Biomedical Decision Support System**	
15:00 - 15:30	Keynote speaker: **Topic: In silico and in vitro tissue models for biomaterial risk assessment and tissue engineering** **Julien Barthes,** *PROTIP MEDICAL, Strasbourg, France*	
15:30 - 16:30	**Session W.4** **Mini-Symposia 7:** MULTISCALE MODELLING OF EXPERIMENTAL DATA RELATED TO BIOMATERIAL RISK ASSESSMENT (part I)	
16:30 - 17:00	Coffee Break	
17:00 - 17:45	**Session W.5** **Mini-Symposia 7:** MULTISCALE MODELLING OF EXPERIMENTAL DATA RELATED TO BIOMATERIAL RISK ASSESSMENT (part II)	
17:45 – 18:30	**Session W.6.1** **Gene Expression Analysis and Engineering**	**Session W.6.2** **Mini-Symposia 3:** RISK ASSESSMENT IN CARDIOVASCULAR DISEASES

Thursday 05 September 2019		
08:30 - 09:00	Keynote speaker: **Topic: Multiscale modeling** **Prof. Dimitrios I. Fotiadis,** *University of Ioannina, Greece*	
09:00 – 09:30	Keynote speaker: **Topic: Smeared multiscale finite element models for drug delivery and in electrophysiology** **Prof. Milos Kojic,** *Houston Methodist Research Institute, USA*	
09:30 - 11:00	**Session T.1** **Computational Modeling**	
11:00 - 11:30	Coffee Break	
11:30 – 12:00	Keynote speaker: **Topic: Inverse problems in cardiovascular continuum mechanics and medical applications** **Prof. Stephane Avril,** *Center for Biomedical and Healthcare Engineering, France*	
12:00 – 13:00	**Session T.2** **Cardiovascular Engineering**	
13:00 - 14:00	Buffet Lunch	
14:00 – 16:00	**Session T.3.1** **Biomechanics (part I)**	**Session T.3.2** **InSilc Workshop**
16:00 - 16:30	Coffee Break	
16:30 - 17:00	Keynote speaker: **Topic: Theoretical Study of Radical Scavenging Activity of Para-Substituted Phenols** **Prof. Erik Klein,** *University of Technology in Bratislava, Slovakia*	
17:00 - 18:45	**Session T.4** **Mini-Symposia 2:** APPLIED COMPUTATIONAL CHEMISTRY (part I)	
20:00 - 23:00	Gala Dinner	

Friday 06 September 2019	
08:30 - 09:00	Keynote speaker: **Topic: Musculoskeletal system** **Prof. Marie-Christine Ho Ba Tho,** *University of Technology of Compiegne, France*
09:00 – 11:00	**Session F.1** **Biomechanics (part II)**
11:00 - 11:30	Coffee Break
11:30 – 12:30	**Session F.2** **Mini-Symposia 1:** ARTIFICIAL INTELLIGENCE AND MACHINE LEARNING IN BIOENGINEERING
12:30 - 13:00	Keynote speaker: **Topic: Computational mechanics of implants and scaffolds** **Prof. Atul Bhaskar,** *University of Southampton, UK*
13:00 – 14:00	Buffet Lunch
14:00 - 14:30	Keynote speaker: **Topic: Metals in cancer therapy. A computational viewpoint** **Prof. Nino Russo,** *Universita della Calabria, Italy*
14:30 - 16:15	**Session F.3** **Mini-Symposia 2:** APPLIED COMPUTATIONAL CHEMISTRY (part II)
16:15 – 17:15	**Session F.4** **Signal Processing**
17:15 – 17:45	**Session F.5** **Mini-Symposia 5:** HOLOGRAM AND AUGMENTED REALITY BIOMECHANICAL MODELS OF A VIRTUAL BALANCE PHYSIOTHERAPIST AND COGNITIVE TRAINING GAMES
17:45 - 18:15	Closing Ceremony

Keynote Speakers

"In vivo and ex vivo tools for modeling of angiogenesis"

Wednesday 4 September 2019

09:15-09:45

Dr. Valentin Djonov,
University of Bern,
Bern, Switzerland

Abstract

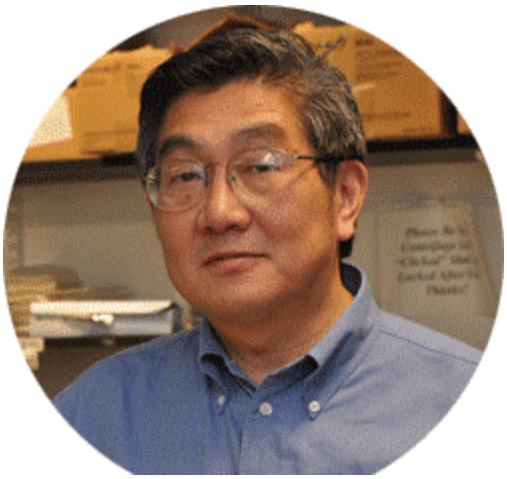
Multiple mathematical and computational models have been developed in the last decades to study diverse aspects of angiogenesis. Different variables such as capillary growth, endothelial motility, vascular morphological changes, signaling, pathways, growth factors, interaction with the surrounding tumor and normal tissue etc. have been employed to study and predict different facets of blood vessel formation and regression. Surprisingly relatively low number of reproducible and robust systems for verification of the mathematical and computational models are available. The rough and insufficient in vivo assessment without reliable 3D visualization and quantification of the vascular response counts, at least partially, to the low transition rate of the modeling to the preclinical and clinical trials.

The Zebrafish Caudal Fin Angiogenesis Assay and Ex vivo microangioCT are appropriated and complementary tools, which could close this gap partially. In addition to the possibility of the almost permanent in vivo monitoring of Zebrafish Caudal Fin blood vessels, different basic vascular parameters (total regenerated area, vascular projection area, contour length, vessel area density) could be extracted from in vivo fluorescence microscopy images using a stereological approach. Skeletonization of the vasculature by our custom-made software Skelios provided additional parameters including "graph energy" and "distance to farthest node". The latter gave important insights into the complexity, connectivity and maturation status of the regenerating vascular network. The employment of a reference point (vascular parameters prior amputation) is unique for the model and crucial for a proper assessment. Additionally, the assay provides exceptional possibilities for correlative microscopy by combining in vivo-imaging and morphological investigation of the area of interest. The 3-way correlative microscopy links the dynamic changes in vivo with their structural substrate at the subcellular level. Ex vivo microangioCT allows time-efficient non-destructive 3D-imaging of the organ and its vasculature including the finest capillaries. Besides the superior visualization, the obtained detailed 3D information on the organ vasculature enables its 3D-skeletonization and further quantitative analysis. Combined with correlative histology, a broad range of complementary structural information can be obtained.

“Lung imaging by synchrotron”

Wednesday 4 September 2019

11:00-11:30



Dr. Akira Tsuda,
Harvard School of Public Health,
Boston, MA, USA

Abstract

Surprisingly, despite decades of studies on lung anatomy and physiology, how the alveolar region (alveoli and ducts) moves during breathing to effect appropriate gas exchange is still not well understood. This gap, in our knowledge is due to the technical limitations of currently available lung imaging, which rely on invasive approaches. A recent technological development, however, allows us now to image the lungs noninvasively at high resolution in vivo using synchrotron-based x-ray imaging.

This talk explains this new technology and addresses a central question of lung mechanics: what are the acinar dynamics associated with breathing. We aim to distinguish between two competing hypotheses:

Hypothesis 1: the alveoli and ducts remain patently open during breathing and

Hypothesis 2: acinar mechanics are dominated by alveolar recruitment and derecruitment.

"In Silico and in vitro tissue models for Biomaterial Risk Assessment and Tissue Engineering"

Wednesday 4 September 2019

15:00-15:30

Julien Barthes,
PROTIP MEDICAL,
Strasbourg, France

Abstract

Biomaterial based solution is now representing a significant portion of remedies offered by the healthcare system. However, technologies currently available to predict biological response of existing or new biomaterials are still limited. In vitro tissue models with for example organ-on-a-chip technologies can simulate the activities, mechanics and physiological response of entire organs and organ systems and so they represent a potential solution to better characterize biomaterials at tissue and organ levels. In vitro approaches require a significant amount of experiments and to reduce this amount, computational bioengineering with the development of in silico models may be of great interest as they can serve as predictive models for biological events and provide additional information. These predictive models are necessary in different areas such as biomaterial risk assessment to quantify biomaterial toxicity and in tissue engineering to predict biomaterial biological outcomes after implantation in terms of inflammation and integration. In this presentation, we will highlight the need of in silico models for biomaterial risk assessment and to predict the cellular colonization of medical implants after implantation.

"Multi-scale modeling of atherosclerotic plaque for the risk stratification, diagnosis, prognosis and treatment of cardiovascular disease"

Thursday 5 September 2019

08:30-09:00

Dr. Dimitrios I. Fotiadis,
University of Ioannina,
Ioannina, Greece

Abstract

Cardiovascular disease (CVD) is the most common cause of death in developing countries. The major consequence is caused by myocardial infarction and stroke in coronary artery disease and carotid artery disease, respectively. Nowadays, tons of data are collected for the clinical understanding of CVD. This information is coming from several types of data including imaging data from computed tomography or magnetic resonance imaging, clinical data and risk factors and biological information such as simple lab tests or more advanced omics analysis of genes, proteome and lipids.

The utilization of these data enables the development of mathematical and computational models for the development of prevention strategies in CVD. More advanced approaches are based on the combination of the available data implementing multi-level and multi-scale support systems for the management of CVD in several stages of the disease.

Carotid artery disease, which refers to the build-up of atherosclerotic plaques in carotid bifurcations, is a highly prevalent and devastating disease, with enormous socioeconomic burden. It constitutes the primary cause of cerebrovascular events and ischaemic stroke, and accounts for up to 30% of all strokes. The determining factors for carotid artery disease management are currently the degree of stenosis, and the presence of symptoms. Patients with 70% stenosis in their carotid artery, either symptomatic or asymptomatic, are considered to be at high risk of cerebrovascular events and are therefore directed to surgical intervention (carotid endarterectomy or stenting). In contrast, patients with <70% stenosis are considered at low-intermediate risk when asymptomatic, and unless other confounding factors exist, they are subjected to medical treatment alone. When the patients are symptomatic with recent events, the cut-off of 50% stenosis is used instead. However, this stratification is rather generic, leading to high levels of unnecessary surgical treatment, and high levels of under treatment in patients with lower levels of stenosis, who are also at high risk of cerebrovascular events. Moreover, the criteria for this stratification have been largely based on clinical trials of the 90's and refer to patient populations that have dramatically changed since then.

"Smeared multiscale finite element models for drug delivery and in electrophysiology"

Thursday 5 September 2019

09:00-09:30

Dr. Milos Kojic,
Houston Methodist Research Institute,
Houston, TX, USA

Abstract

Modeling of a physical field, such as concentration field in case of drug delivery or electrical potential in electrophysiology, in the real physiological conditions, remains a challenge. This is particularly demanding task when considering complex systems as tumors, or entire organs. Today, the goal is to develop methodology which will lead to computational tools applicable to the laboratory and clinical investigations, but also in medical practice.

Motivated by these goals, we have recently developed a robust and generally applicable concept for in silico modeling physical fields within composite media. We have formulated a composite smeared finite element (CSFE) for gradient driven problems where the basic idea is that different domains in a composite medium (capillaries, extracellular space, cells, organelles, neural network) are occupying the corresponding volumes rVV (rV is volumetric fraction) within the element. The fields are coupled by the connectivity elements at each node which serve to model biological barriers between the domains, as capillary or lymph walls (or nerve fibers lateral conductivity), or cell and organelle membranes. Using the CSFE it is possible to model large domains in a simple way – just by continuum FEs. We also briefly present a smeared concept in mechanics as an extension of the field models.

Several examples illustrate applicability of the smeared methodology which is built in our FE code PAK. The examples include models of drug delivery within liver and pancreas with tumors, and also hart electrophysiology coupled with the mechanical response.

"Inverse problems in cardiovascular continuum mechanics and medical applications"

Thursday 5 September 2019

11:30-12:00

Prof. Stephane Avril,
Center for Biomedical and Healthcare Engineering, France

Abstract

The fluid mechanics community has been interested for many years in hemodynamics. More recently, significant endeavours of the solid mechanics community have permitted to establish constitutive equations and to achieve stress analyses in arterial lesions (atheromatous plaque in coronary or carotid arteries, aneurysms of the aorta). The mechanical properties of blood vessels have often been characterized ex vivo, but medical imaging, including MRI, now allows non-intrusive identifications in vivo. The spatial heterogeneity of these mechanical properties, even at the macroscopic scale, remains poorly explored despite its undeniable interest in understanding the mechanisms of remodeling and degeneration of the tissue. We are interested in the problem of identifying the fields of mechanical properties of aneurysms of the aorta. Scientific barriers are related to the complex geometry, the nonlinear and anisotropic behavior of tissues, the multiaxial loading conditions, and to the measurement of a local response in these tissues. Our identification approaches, based on digital image correlation field measurements and inverse methods, have demonstrated the link between the heterogeneity of mechanical properties and the existence of localized failure modes. A micromechanical approach has also made it possible to develop a mechanobiological model to reproduce the behavior of the aorta in surgical situations and a simulation software is being developed in a start-up for assistance to medicine and personalized surgery in the cardiovascular field. The two complementary in vivo and ex vivo methodologies reported could provide multiple parameters necessary for the reliable mathematical and computational models of angiogenesis.

"Theoretical Study of Radical Scavenging Activity of Para-Substituted Phenols"

Thursday 5 September 2019

16:30-17:00

Prof. Erik Klein,
University of Technology,
Bratislava, Slovakia

Abstract

Phenolic compounds in biological systems can be transformed by enzymatic reactions or by non-catalytic processes, such as oxidation, reduction, or hydrolysis. Radical scavenging activity and subsequent oxidation resulting in quinone products represent one of the important features of phenolics. Based on a generalized reaction scheme, for phenol and 25 para-substituted phenols, we theoretically investigate the thermodynamics of the individual reaction steps, including three hydrogen atom transfers, as well as OH• radical addition, leading to final ortho-quinone formation. All calculations were performed using (SMD) M06-2X/6-311++G** approach for the gas-phase and aqueous solution in order to study the effect of electron-donating and electron-withdrawing substituents and the water solvent effect. Obtained results show that most reaction enthalpies correlate with Hammett constants satisfactorily. Water enhances the substituent effect. Corresponding dependences can be employed for the estimation of studied reaction enthalpies using Hammett constant of a substituent.

"Knowledge extraction from medical imaging for advanced patient specific musculoskeletal models"

Friday 6 September 2019

08:30-09:00

Prof. Marie-Christine Ho Ba Tho,
University of Technology of Compiegne,
France

Abstract

Patient specific computer modelling has been developed since the last decade but still the specificity is not fully described or is limited to patient geometry. Furthermore patient specific models can be obtained with geometry and mechanical properties derived from CT, but one should pay attention to the reliability of the images quality and the control of the acquisition parameters. Besides these extensive numerical models, most of models are derived from CT data and few from MRI. Furthermore few consider appropriate material properties derived from tissue characterization obtained from medical images, as they mostly are issued from literature. The methodology developed in our group is based on material and geometry knowledge extracted from advanced medical imaging. For hard tissue, from Computed Tomography (CT) personalized bone mechanical properties could be extracted and moreover its follow up could provide data for validation of patient specific predictions. For soft tissue, mechanical, physical, biochemical properties can be extracted from MRI. Advanced MRI such as dynamic MRI and MRE allowed respectively to analyse the in vivo forces generated by the muscles in movement but also its mechanical properties in passive and active behavior. Based on these knowledges, patient specific geometry, mechanical properties and forces are assessed derived from advanced medical imaging techniques. These data are of importance for developing patient specific computer modelling for prediction and evaluation of therapeutic, surgical or functional rehabilitation treatments. Notions of reliability of the numerical models and uncertainty are addressed in order to provide an objective tool for aided decision support system to clinicians. Clinical applications will be given as illustrative examples.

"Computational mechanics of implants and scaffolds"

Friday 6 September 2019

12:30-13:00

Prof. Atul Bhaskar,
University of Southampton,
UK

Abstract

The mechanical response of implants and scaffolds, and natural bio-structures, is of great current interest. The advent of additive manufacturing has further facilitated the fabrication of materials and devices with structural hierarchy. In this talk, we present a host of mechanical problems in biological contexts, where computational mechanics provides interesting insights. First, we present the elasto-plastic response of lattice structures and their application to the design of stents. Simple analyses based on the mechanics of elastic lattices—that exploit the translational symmetry—lead to closed form response estimates. Scaling relationship with respect to structural parameters, in conjunction with a "master curve" representing the non-linear elasto-plastic response, are presented. Then we consider the elastic response of scaffold structures in a woodpile arrangement. Micro-mechanical models are developed using flexure of filaments—the analysis is carried out for remotely loaded infinite elastic lattices. Yet again, we are able to obtain scaling relationship for the elastic response. A fifth power scaling relating the apparent modulus of elasticity to the volume fraction is theoretically obtained, and computationally verified.

Following these, fabrication and mechanical characterization of woodpile lattices that possess a variety of novel microstructures—texturally and architecturally—are presented. The fabrication and the response characterization of functionally graded lattice films is discussed next. The use of classical computational mechanics to the instability behaviour of microtubules within the cytoskeleton—organized structurally as mitotic spindles—is taken up next. Finally, spatio-temporal events in a Ca2+ reaction-diffusion system are examined in the spirit of dynamical systems theory.

"In vivo and ex vivo tools for modeling of angiogenesis"

Friday 4 September 2019

14:00-14:30

Prof. Nino Russo,
Universita della Calabria,
Italy

Abstract

The contribution of theoretical and computational chemistry in the field of cancer therapy should be presented and discussed. In particular, the discussion will be focused on the possibility to design new drug active in both chemo- and photo-dynamic therapy, by using density functional theory. Platinum II and IV compounds and the photophysical properties (absorption wavelengths, singlet-triplet energy gaps and spin-orbit matrix elements) of a series of photosensitizers should be presented.

Technical Program

Wednesday 04 September 2019

08:45 - 09:15	Opening Ceremony - Welcome speech: Dr. Nenad Filipovic, rector of the University of Kragujevac, Conference Chair Dr. Vliktor Nedovic, State Secretary, Ministry of Education, Science and Technological Development Dr. Berislav Vekic, State Secretary, Ministry of Health

09:15 - 09:45	Keynote speaker: **Topic: Angiogenesis modeling** **Prof. Valentin Djonov,** *University of Bern, Switzerland* **Chair:** Marko Živanović

Session W.1: 09:45-10:30 Chair: Vladimir Jakovljević
Mini-Symposia 4: COMPUTATIONAL AND EXPERIMENTAL PHYSIOLOGY: NOVEL POTENTIAL ANTINEOPLASTIC COMPOUNDS AND CARDIOVASCULAR SYSTEM

W.1.1 – *Sex differences of doxorubicin-induced cardiotoxicity in a model of isolated rat heart* - Rankovic M, Bradic J, Radonjic K, Srejovic I, Zivkovic V, Jeremic N, Stojic V, Dimitrijevic M, Jakovljevic V

W.1.2 – *The effects of chronic administration of o,o'-diethyl-(s,s–ethylenediamine-n,n'–di–2-(3-cyclohexyl)propanoate dihydrochloride and its octahedral pt(iv) complex on rat heart function: comparison with cisplatin* - Zivkovic V, Smigic J, Sabo T, Vranic A, Krivokapic M, Bolevich S, Stojic V, Kocic V, Jakovljevic V

W.1.3 – *The acute effects of cisplatin and its structural analogues on cardiodynamic and coronary flow of the isolated rat heart* - Milosavljevic I, Novokmet S, Zivkovic V, Srejovic I, Nikolic Turnic T, Jeremic J, Bogojeski J, Bolevich S, Dimitrijevic M, Kocic V, Jakovljevic V

10:30 - 11:00	Coffee Break

11:00 - 11:30	Keynote speaker: **Topic: Nanoparticles, pulmonary medicine** **Prof. Akira Tsuda,** *Harvard School of Public Health, Boston, MA, USA* **Chair:** Nenad Filipović

Session W.2: 11:00-13:00 Chair: Boban Stojanović
Mini-Symposia 6: MULTISCALE IN-SILICO MODELING OF CARDIOMYOPATHY FROM GENO TYPE TO PHENO TYPE

W.2.1 – *Surrogate Models of Huxley Muscle Model Based on Artificial Neural Networks* - Bogdan Milićević, Lazar Vasović, Miloš Ivanović, Boban Stojanović

W.2.2 – *Heart mechanical model based on Holzapfel experiments* - Milos Kojic, Miljan Milosevic, Bogdan Milićević, Vladimir Simic

W.2.3 – *Composite smeared finite element – accuracy in electrical field* - Vladimir Geroski, Miljan Milosevic, Nenad Filipovic, Milos Kojic
W.2.4 – *Application of CSFE for drug delivery in liver model with tumor* - Vladimir Simic, Miljan Milosevic, Arturas Ziemys, Milos Kojic
W.2.5 – *Tuning cooperativity of calcium activation in cardiac muscle* - Momcilo Prodanovic, Boban Stojanovic, Mladen Maric, Danica Prodanovic, Srboljub M. Mijailovich
W.2.6 – *Genetic determinants of clinical phenotype in hypertrophic cardiomyopathy* - Andrej Preveden, Nduka Okwose, Maria Tafelmeier, Fausto Barlocco, Francesco Mazzarotto, Christopher Eggett, Paul Brennan, Lars Maier, Iacopo Olivotto, Dejana Popovic, Arsen Ristic, Aleksandar Redzek, Guy A MacGowan, Nenad Filipovic, Djordje G Jakovljevic, Lazar Velicki

13:00 - 14:00	Buffet Lunch

Session W.3: 14:00-15:00 Chair: Nenad Filipović
Biomedical Decision Support System

W.3.1 – *New Determinants for the Rupture Risk Assessment of the Intracranial Aneurysm* - Romana Perinajová, Merel Toussaint, Bob Kalkman, Pim van Ooij, Saša Kenjereš
W.3.2 – *Development of Virtual Angiography Protocol Combining Computer Graphics and Computational Fluid Dynamics* - Hiroaki Niikura, Hiroyuki Takao, Soichiro Fujimura, Yuya Uchiyama, Makoto Yamamoto, Yuichi Murayama

15:00 - 15:30	Keynote speaker: **Topic: In silico and in vitro tissue models for biomaterial risk assessment and tissue engineering** **Julien Barthes,** *PROTIP MEDICAL, Strasbourg, France* **Chair:** Tijana Šušteršič

Session W.4: 15:30-16:30 Chair: Arban Uka
Mini-Symposia 7: MULTISCALE MODELLING OF EXPERIMENTAL DATA RELATED TO BIOMATERIAL RISK ASSESSMENT (part I)

W.4.1 – *Computational immunoprofiling predictions of immune response promiscuity to Epstein Barr Virus epitopes and oral biofilm in acute coronary syndrome* - Mariliis Jaago , Arno Pihlak, Helle Sadam, Valentina Bozok, Oliver Nisumaa, Jaak Vilo, Pirkko Pussinen, Nihal Engin Vrana, Kaia Palm
W.4.2 – *Analysis of Focus Measure and Image Fusion of Microscopy Images* - Arban Uka, Florenc Skuka, Latif Xeka, Harry Esmonde, Nihal Engin Vrana
W.4.3 – *Mathematical simulation of biodegradable material cytotoxicity in 3D hepatocellular systems in vitro* - Alexander Makhaniok, Constantin-Edi Tanase, Amir Ghaemmaghami, Nihal Engin Vrana, Vitaly Goranov
W.4.4 – *The Mathematical approach to disclose low Cytotoxicity of material from in vitro co-culture experiment* - Ivan Siutsou, Lydie Ploux, Nihal Engin Vrana, Vitaly Goranov

16:30 - 17:00	Coffee Break

Session W.5: 17:00-17:45 Chair: Julien Barthes
Mini-Symposia 7: MULTISCALE MODELLING OF EXPERIMENTAL DATA RELATED TO BIOMATERIAL RISK ASSESSMENT (part II)

W.5.1 – *Convolutional Neural Networks for Fibroblast Cell Classification and Counting* - Arban Uka, Julien Barthes, Xhoena Polisi, Aleksandros Ruci, Albana Halili, Ali Osman Topal, Nihal Engin Vrana

W.5.2 – *Coupling experimental data and numerical simulation in modelling epithelial barrier formation with A549 cancerous cell line* - Tijana Šušteršič, Milica Nikolić, Julien Barthes, Nihal Engin Vrana, Nenad Filipović

W.5.3 – *Computer Assisted Spheroid Formation Analysis* - Xhoena Polisi, Constantin-Edi Tanase, Arban Uka, Nihal Engin Vrana, Amir Ghaemmaghami

Session W.6.1: 17:45-18:30 Chair: Marko Živanović
Gene Expression Analysis and Engineering

W.6.1.1 – *The logic of regulation design in bacterial restriction-modification systems* - Andjela Rodic, Bojana Blagojevic, Magdalena Djordjevic, Konstantin Severinov, Marko Djordjevic

W.6.1.2 – *Effects of bacterial cell growth rate on dynamics of a natural gene circuit* - Stefan Graovac, Andjela Rodic, Magdalena Djordjevic, Marko Djordjevic

W.6.1.3 – *A simple criteria for predicting direction of CRISPR array: applications to investigating non-canonical CRISPR/Cas functions* - Ognjen Milicevic, Bojan Bozic, Jelena Guzina, Marko Djordjevic

Session W.6.2: 17:45-18:30 Chair: Miroslav Marković
Mini-Symposia 3: RISK ASSESSMENT IN CARDIOVASCULAR DISEASES

W.6.2.1 – *The role of magnetic resonance imaging in the assessment of biological activity of intraluminal thrombus and proteolytic processes in abdominal aortic aneurysm* - Milos Sladojevic, Zeljka Stanojevic, Igor Koncar, Petar Zlatanovic, Sasenka Vidicevic, Jelena Tosic, Aleksandra Isakovic, Miroslav Markovic, Lazar Davidovic

W.6.2.2 – *Identification and assessment of the impact of preoperative mortality predictors within the formulation and validation of outcome prediction models for patients operated on for a ruptured abdominal aortic aneurysm – a study design* - Ivan Tomić, Miroslav Marković, Igor Končar, Miloš Sladojević, Perica Mutavdžić, Lazar Davidović

W.6.2.3 - *Validation of Taxinomisis stratification tool through observational multicentre clinical trial* - P.Mutavdzic, N.Tiemerman, J.Pelisek,D.P.V de Kleijn, G.J. de Borst-2, HH.Eckstein, V.Obach, V.Riambau, D.Palombo, F. Montecucco, F.Sigala, L.Davidovic, D.Fotiadis, I.Koncar

Thursday 05 September 2019

08:30 - 09:00	Keynote speaker: **Topic: Multiscale modeling** **Prof. Dimitrios I. Fotiadis,** *University of Ioannina, Greece* **Chair:** Dalibor Nikolić

09:00 - 09:30	Keynote speaker: **Topic: Smeared multiscale finite element models for drug delivery and in electrophysiology** **Prof. Milos Kojic,** *Houston Methodist Research Institute, USA* **Chair:** Miljan Milošević

Session T.1: 09:30-11:00 Chair: Miljan Milošević
Computational Modeling

T.1.1 – *Mathematical modeling of the passive mechanical properties of human fascia* - Miglena Kirilova-Doneva, Dessislava Pashkouleva, Stoyan Stoytchev
T.1.2 – *Numerical modeling and simulations of magnetic drug delivery for the lung cancer therapy* - S. Kenjereš, P. Bakker
T.1.3 – *Evaluation of Methods for POD Basis Interpolation on Grassmann Manifolds for Simulations of Complex Hyperelastic Structures* - Orestis Friderikos, Mayra Mora, Emmanuel Baranger, David Neron
T.1.4 – *A multi-agent system of the cell membrane: auto-assembly and particle/ion interaction* - Víctor A. Acosta Santamaría, Tien-Tuan Dao, Karim El-Kirat
T.1.5 – *Deterministic and stochastic parameter analysis of the bone cell population model* - Julijana Simonović, Thomas E. Woolley

11:00 – 11:30	Coffee Break

11:30 - 12:00	Keynote speaker: **Topic: Inverse problems in cardiovascular continuum mechanics and medical applications** **Prof. Stephane Avril,** *Center for Biomedical and Healthcare Engineering, France* **Chair:** Igor Saveljić

Session T.2: 12:00-13:00 Chair: Dalibor Nikolić
Cardiovascular Engineering

T.2.1 – *Endothelium resolving simulations of wall shear-stress dependent mass transfer of LDL in arteries* - S. Kenjereš, J.P. van der Krieke, C. Li
T.2.2 – *Optimization of Parameters for 3D-Bioprinting Scaffold Production – Blood Vessel Bioengineering* - Marko N. Živanović, Dalibor D. Nikolić, Nenad D. Filipović

13:00 - 14:00	Buffet Lunch

Session T.3.1: 14:00-16:00 Chair: Igor Saveljić
Biomechanics (part I)

T.3.1.1 – *Technical approach to CFD streamlines calculation in 3D alveolar models* - Danko Milasinovic, Igor Saveljic, Frank Henry, Akira Tsuda, Nenad Filipovic
T.3.1.2 – *Investigation on Effect of Pulsation Condition Involved in Recanalization of Coil Embolized Aneurysms* - Takumi Ishii, Hiroyuki Takao, Soichiro Fujimura, Yuya Uchiyama, Kazutoshi Tanaka, Hiroshi Ono, Takuma Okudaira, Toshihiro Ishibashi, Katharina Otani, Koji Fukudome, Yuichi Murayama, Makoto Yamamoto
T.3.1.3 – *Different hemodynamic metrics induce growth and remodeling of patient-specific ascending thoracic aortas* - S. Jamaleddin Mousavi, Raja Jayendiran, Solmaz Farzaneh, Stéphane Avril
T.3.1.4 – *Numerical simulations of blood flow patterns in the patient-specific left ventricle model with dynamic valves* - Fei Xu, Sasa Kenjeres
T.3.1.5 – *Effect of hip implant surface modification on shear stress distribution – a finite element analysis* - Aleksandra Vulović, Nenad Filipović

Session T.3.2: 14:00-16:00 Chair: Dimitrios Fotiadis
InSilc Workshop

T.3.2.1 – *In-silico module to model transient three-dimensional drug delivery in subject-specific geometries of stented arteries: physics-based simulation of controlled release and tissue retention* - Farhad Rikhtegar Nezami, Abraham R. Tzafriri, Elazer R. Edelman
T.3.2.2 – *The Impact of Various Bioresorbable Scaffold Designs on Hemodynamics* - Imane Tarrahi, Monika Colombo, Eline M.J. Hartman, Maria Natalia Tovar Forero, Ryo Torii; Claudio Chiastra, Joost Daemen; Frank J.H. Gijsen
T.3.2.3 – *Myocardial perfusion modelling for predicting the clinical significance of side-branch occlusions in virtual in-silico trials* - Toni Lassila, Ali Sarrami-Foroushani, Nishant Ravikumar, Andres Diaz-Pinto, Alejandro F. Frangi
T.3.2.4 – *In-silico clinical trial: development of computational models predicting degradation of bioresorbable stents in patient specific coronary arteries* - Katarzyna Polak-Kraśna, Constantino Fiuza, William Ronan, Ted Vaughan
T.3.2.5 – *In-silico clinical trial: development of computational models for virtual deployment of vascular scaffolds in patient specific coronary arteries* - Lorenza Petrini, Luca Antonini, Lorenzo Mandelli, Francesco Migliavacca, Gabriele Dubini, Giancarlo Pennati
T.3.2.6 – *The development of a cloud-based in-silico clinical trial platform* - Peter Mortier, Reinjan Ergo, Dries Desmet, Nic Debusschere, Bjorn Kristinsson
T.3.2.7 – *3d Reconstruction tool of coronary arteries, plaque morphology and "virtual" population* - Karanasiou, G.S., Sakelarios A. I, Kyriakidis S., Pleouras D., Fotiadis, D.I.
T.3.2.8 – *The InSilc Project and the regulatory roadmap* - Karanasiou, G.S., Fotiadis, D.I.

16:00 – 16:30	Coffee Break

16:30 - 17:00	Keynote speaker: **Topic: Theoretical Study of Radical Scavenging Activity of Para-Substituted Phenols** **Prof. Erik Klein,** *University of Technology in Bratislava, Slovakia* **Chair:** Jelena Đorović

Session T.4: 17:00-18:45 Chair: Dejan Milenković
Mini-Symposia 2: APPLIED COMPUTATIONAL CHEMISTRY (part I)

T.4.1 – *Role of atomic and molecular non-observable properties in the understanding and description of real observables of the chemical systems* - Ivan Juranić

T.4.2 – *The interaction of protonated octopamine and norepinephrine whit β1-adrenergic receptor: Molecular docking and dynamical simulation* - Zoran Marković, Žiko Milanović, Dušan Dimić, Jasmina Dimitrić Marković, Marijana Stanojević-Pirković

T.4.3 – *The PCET-RRC mechanism in the reaction of ferulic acid with •OH free radicals* - Ana Amić, Dejan Milenković

T.4.4 – *A combined experimental and theoretical study on vibrational spectra of 3-(1-(m-toluidino)ethylidene)-chroman-2,4-dione* - Zoran Marković, Dejan Milenković, Edina Avdović , Srećko Trifunović, Jelena Đorović

T.4.5 – *An experimental and theoretical study of the reactivity of selected catecholamines and their precursors towards ascorbyl radical* - Dušan Dimić, Đura Nakarada, Miloš Mojović, Zoran Marković, Jasmina Dimitrić-Marković.

T.4.6 – *Graph theory based model for the enthalpy of formation of benzenoid hydrocarbons* - Izudin Redžepović, Svetlana Marković, Boris Furtula.

T.4.7 – *Antioxidative properties of usnic acid and its interaction with tyrosyl-DNK phosphodiesterase 1* - Zoran Marković, Jelena Đorović, Nedeljko Manojlović, Marijana Stanojević-Pirković, Svetlana Jeremić.

20:00 - 23:00	Gala Dinner

Friday 06 September 2019

08:30 - 09:00	Keynote speaker: **Topic: Musculoskeletal system** **Prof. Marie-Christine Ho Ba Tho,** *University of Technology of Compiegne, France* **Chair:** Smiljana Đorović

Session F.1: 09:00-11:00 Chair: Velibor Isailović
Biomechanics (part II)

F.1.1 – *Hemodynamic Investigation on Growth of Unruptured Cerebral Aneurysms During Follow-up Term* - Takuma Okudaira, Hiroyuki Takao, Soichiro Fujimura, Yuya Uchiyama, Kazutoshi Tanaka, Hiroshi Ono, Takumi Ishii, Toshihiro Ishibashi, Katharina Otani, Koji Fukudome, Yuichi Murayama, Makoto Yamamoto

F.1.2 – *Numerical analysis and virtual surgery for acute aortic dissection* - Igor Saveljic, Lazar Velicki, Dalibor Nikolic, Nenad Filipovic

F.1.3 – *Simulation and experimental validation of pulsatile flow in a compliant tube* - Jiří Jagoš, Darina Jašíková, Michal Knotek, Jiří Burša

F.1.4 – *Advanced modelling approach of carotid artery atherosclerosis* - Smiljana Djorovic, Igor Saveljic, Nenad Filipovic.

F.1.5 – *Combining numerical methods with parametric optimization of stent design* - Dalibor Nikolic, Igor Saveljic, Marija Gacic, Nenad Filipovic

F.1.6 - *In silico stent deployment using finite element method and contact algorithm* - Velibor Isailovic, Milos Kojic, Dalibor Nikolic, Nenad Filipovic

11:00 - 11:30	Coffee Break

Session F.2: 11:30-12:30 Chair: Marie-Christine Ho Ba Tho
Mini-Symposia 1: ARTIFICIAL INTELLIGENCE AND MACHINE LEARNING IN BIOENGINEERING

F.2.1 – *Deep Learning for the Prediction of Lower Limb Muscle Forces* - Tien-Tuan Dao, Marie-Christine Ho Ba Tho

F.2.2 – *Pre-term birth prediction using EHG for home remote monitoring* - Alessandro Galassi, Dan Istrate, Catherine Marque, Charles Muszynski

F.2.3 – *Deep Learning based approach for assessment of Primary Sjögren's Syndrome from salivary gland ultrasonography images* - Milos Radovic, Arso Vukicevic, Alen Zabotti, Vera Milic, Salvatore De Vita, Nenad Filipovic

12:30 - 13:00	Keynote speaker: **Topic: Computational mechanics of implants and scaffolds** **Prof. Atul Bhaskar,** University of Southampton, UK **Chair:** Vladimir Simić

13:00 - 14: 00	Buffet Lunch

14: 00 - 14:30	Keynote speaker: **Topic: Metals in cancer therapy. A computational viewpoint** **Prof. Nino Russo,** *Universita della Calabria, Italy* **Chair:** Dejan Milenković

Session F.3: 14:30-16:15 Chair: Jelena Đorović
Mini-Symposia 2: APPLIED COMPUTATIONAL CHEMISTRY (part II)

F.3.1 – *Combined 3D-QSAR modeling, molecular dynamics and molecular docking studies in rational drug design of novel 5-HT2A antagonists* - Milica Radan, Mirjana Antonijevic, Teodora Djikic, Dusan Ruzic, Katarina Nikolic
F.3.2 – *Vibrational spectroscopy study of coumarine-derived ligand 3-(1-(o-toluidino)ethylidene)-chroman-2,4-dione: A combined theoretical and experimental investigation* - Zoran S. Marković, Edina H.Avdović, Žiko B. Milanović, Dejan Milenković, Svetlana Jeremić, Srećko R.Trifunović
F.3.3 – *Computational Cation Complexation by Cryptands* - Ralph Puchta
F.3.4 – *Scavenger capacity of the 1,2,4-trihydroxyxanthone toward hydroxyl, hydroperoxyl and methylperoxyl radicals* - Zoran Marković, Sanida Šemović, Žiko Milanović, Ana Amić, Svetlana Jeremić
F.3.5 – *Experimental and theoretical study of structure and antioxidant activity of some N'-benzylidene-3,4,5-trihydroxybenzohydrazides* – Vladimir P. Petrović, Vesna Milovanović, Dušica Simijonović, Zorica D. Petrović, Zoran Markovic
F.3.6 – *Influence of circadian function on the dynamical states of the hypothalamic-pituitary-adrenal axis* – Milorad M. Anđelković, Ana D. Stanojević, Željko D. Čupić, Ana Z. Ivanović-Šašić, Ljiljana Z. Kolar-Anić
F.3.7 – *On the thermodynamics of the radical scavenging activity of 3,4-dihydroxybenzohydrazide derivatives* – Denisa Cagardová, Vladimír Lukeš, Erik Klein, Vladimir Petrović, Zoran Marković

Session F.4: 16:15-17:15 Chair: Tijana Šušteršič
Signal Processing

F.4.1 – *Shape characterization of the gonarthrosis in the X-ray images* - Suzana Petrovic Savic, Branko Ristic, Aleksandar Matic, Nikola Prodanovic, Goran Devedzic
F.4.2 – *Evaluation of social and cognitive load stress detection using speech-derived features* - Giorgos Giannakakis, Nikolaos Stefanakis, Angelos Ilias, Panagiotis Simos
F.4.3 – *Medical Image Processing using Xilinx System Generator* – Tijana Šušteršič, Vladimir Milovanović, Vesna Ranković, Nenad Filipović, Aleksandar Peulić
F.4.4 – *Correlation of the Lumbar and Cervical Lordosis with Spinal Inclination in Children with Idiopathic Scoliosis Optically Diagnosed* - Saša Ćuković, Wolfgang Birkfellner, Michele Fiorentino, Tanja Zečević Luković, Nenad Filipović

Session F.5: 17:15-17:45 Chair: Nataša Vujnović Sedlar
Mini-Symposia 5: HOLOGRAM AND AUGMENTED REALITY BIOMECHANICAL MODELS OF A VIRTUAL BALANCE PHYSIOTHERAPIST AND COGNITIVE TRAINING GAMES

F.5.1 – *Preliminary Testing Of Augmentative Reality Games In Holobalance Solution* – Natasa Vujnovic Sedlar, Adrian Djura, Nenad Filipovic, Snezana Tomasevic Todorovic, Dinu Dragan
F.5.2 - *3D Hologram based balance physiotherapist software and hardware system* - Zarko

Milosevic, Ana Vulovic, Dalibor Nikolic, Nenad Filipovic

22217:45 - 18:15	Closing Ceremony

Book of Abstracts

Session W.1: 09:45-10:30

Mini-Symposia 4: COMPUTATIONAL AND EXPERIMENTAL PHYSIOLOGY: NOVEL POTENTIAL ANTINEOPLASTIC COMPOUNDS AND CARDIOVASCULAR SYSTEM

W.1.1 – *Sex differences of doxorubicin-induced cardiotoxicity in a model of isolated rat heart*

- Rankovic M[1], Bradic J[1], Radonjic K[1], Srejovic I[2], Zivkovic V[2], Jeremic N[1], Stojic V[3], Dimitrijevic M[4], Jakovljevic V[2,5]

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[5] Department of Human Pathology, 1st Moscow State Medical University IM Sechenov, Moscow, Russian Federation

Abstract:

Doxorubicin (DOX) is an anthracycline antibiotic, routinely used as a chemotherapeutic agent. However, a significant risk of cardiotoxicity limits its use. The aim of this study was to examine the sex differences of doxorubicin-induced cardiotoxicity on isolated rat heart according to Langendorff technique. This experimental study was conducted on 24 male and female Wistar albino rats (6 per group, 12 weeks old; bw: 200-250 g) divided into CTRL and DOX groups. DOX was dissolved in saline and administered by intraperitoneal injection at a dose of 15 mg/ kg, while control animals were injected with a comparable volume of saline. After 72 hours of DOX injection, all animals were sacrificed and cardiodynamic data were collected. We continuously measured parameters of cardiac function such as: maximum rate of pressure development in the left ventricle (dp/dt max), minimum rate of pressure development in the left ventricle (dp/dt min), systolic left ventricular pressure (SLVP), diastolic left ventricular pressure (DLVP), heart rate (HR) and coronary flow (CF). Administration of DOX significantly reduced cardiodynamic parameters in both male and female rats. The most prominent changes in male rats were observed in the dp/dt max, dp/dt min and SLVP values, whereas DLVP and CF were notably reduced in female rats ($p<0.05$). On the other hand, no major sex differences existed in HR values due to doxorubicin treatment. Results from our study could help to better understanding the impact of sex differences on doxorubicin-induced cardiotoxicity.

Keywords: doxorubicin, cardiotoxicity; cardiodynamics, isolated rat heart, Langendorff technique

W.1.2 – *The effects of chronic administration of o,o'-diethyl-(s,s–ethylenediamine-n,n'–di–2-(3-cyclohexyl) propanoate dihydrochloride and its octahedral pt(iv) complex on rat heart function: comparison with cisplatin*

- Zivkovic V[1], Smigic J[1], Sabo T[2], Vranic A[3], Krivokapic M[4], Bolevich S[5], Stojic V[6], Kocic V[7], Jakovljevic V[1,5]

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[7] Superlab Group, Belgrade, Serbia

Abstract:

The aim of the present study was to compare the cardiodynamic parameters in the isolated rat heart in animals chronically treated with cisplatin, platinum (IV) complex and its diamine ligand. Sixty Wistar albino rats (8 weeks old) were divided into five groups: three experimental and two control groups. Animals in all groups were treated with a dose of 4 mg/kg body weight once a week for 4 weeks with different substances; experimental groups received cisplatin, ligand and octahedral platinum (IV) complex, and control groups received saline and dimethyl sulfoxide. After sacrificing the animals, hearts were isolated and perfused according to the Langendorff technique at gradually increased coronary perfusion pressures (40–120 cmH2O). The following parameters of cardiac function were continuously recorded: maximum and minimum rate of change of pressure in the left ventricle, systolic and diastolic left ventricular pressure, heart rate and coronary flow. The results showed statistically significant differences between all experimental groups in maximum and minimum rate of pressure development as well as in systolic pressure of the left ventricle, whereas cisplatin, ligand and the platinum (IV) complex had effects on heart contractility without significant influences on coronary circulation. The findings of the present study could be important for a better understanding of anticancer drug cardiac side effects. Our results indicate that compared to cisplatin as a “gold standard”, novel platinum complexes and ligands do not possess fewer negative effects on the heart, indicating insufficient safety for their usage in terms of affecting cardiac function, a result that can be of great interest for further investigations.

Keywords: cisplatin, O,O’-diethyl-(S,S–ethylenediamine-N,N’–di–2-(3-cyclohexyl) propanoate dihydrochloride, platinum(IV) complex, rat, cardiodynamics

W.1.3 – *The acute effects of cisplatin and its structural analogues on cardiodynamic and coronary flow of the isolated rat heart* - Milosavljevic I[1], Novokmet S[1], Zivkovic V[2], Srejovic I[2], Nikolic Turnic T[1], Jeremic J[1], Bogojeski J[3], Bolevich S[4], Dimitrijevic M[5], Kocic V[6], Jakovljevic V[2,4]

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[6] Superlab Group, Belgrade

Abstract:

The therapeutic use of cisplatin for the treatment of solid tumours is associated with organ toxicity. Amongst those, the cardiotoxicity is an occasional but very serious and severe side effect. To prevent or reduce these negative effects, many cisplatin analogues have been synthesized and evaluated in terms of being a less toxic and more effective agent. In present study, we examined the effects of cisplatin and its three analogues in the isolated rat heart to determine whether changes in the structure of the platinum complexes (changing of carrier ligands – ethylenediamine; 1,2-diaminocyclohexane; 2,2’:6’,2’’-terpyridine) can influence their cardiotoxic effects. The results of our research indicate that the deleterious effects on heart function and CF are more pronounced with [Pt(terpy)Cl]Cl compared to the other examined complexes. This finding agrees with the known statement that introducing an aromatic ring in a drug’s structure can increase toxicity. The two other complexes had shown a less negative effect on heart function compared to cisplatin. In that sense, these findings can be of interest for a possible synthetic strategy for new platinum-based anticancer agents in terms of their carrier ligand structure, mode of coordination and valence state, which can lead to platinum-based drugs with less cardiotoxic potentials.

Keywords: cardiac function, cardiotoxicity, cisplatin, isolated-perfused heart, metal toxicity, platinum (II) complexes

Session W.2: 11:00-13:00

Mini-Symposia 6: MULTISCALE IN-SILICO MODELING OF CARDIOMYOPATHY FROM GENO TYPE TO PHENO TYPE

W.2.1 – ***Surrogate Models of Huxley Muscle Model Based on Artificial Neural Networks*** - Bogdan Milićević [1*], Lazar Vasović[1,2], Miloš Ivanović[1,2], Boban Stojanović[1,2]

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**corresponding author*

Abstract:

Analysis of biological systems based on computational experiments is often extremely computationally expensive. In order to employ Huxley-like muscle models for modeling real-life problems more efficiently, we developed surrogate models using artificial neural networks. The inputs for these surrogate models consist of muscle activation, velocity of muscle fiber shortening or lengthening, and distribution of attached myosin heads. Based on myosin heads distribution in certain time step, we aim to predict the distribution of attached myosin heads in the next time step. Using supervised learning methods, we obtained highly accurate predictions with multilayer perceptron and LSTM networks. Given activation and velocity time course, in each time step we used myosin heads distributions from the previous time step as inputs to the surrogate in the current time step. This chain-like algorithm simulates the dynamic behavior of the surrogate model, during certain time period. However, although we obtained highly accurate predictions in individual time steps, the behavior of the surrogate models in the dynamic system was poor, due to the accumulation of the prediction error during chain-like simulation. To overcome this issue, we employed reinforcement learning and neuro-evolution of augmenting topologies. The population of the neural networks together with their topology and connection weights was created and their behavior during the whole chain simulation was evaluated. Within the process of neural networks evolution, we rewarded the networks with more accurate dynamic behavior by giving them opportunity to pass their genes to the next generation.

Keywords: Huxley muscle model, surrogate, ANN, LSTM, neuro-evolution

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W.2.2 – ***Heart mechanical model based on Holzapfel experiments*** - Milos Kojic[1,2,3*], Miljan Milosevic[1,4], Bogdan Milićević[1], Vladimir Simic[1]

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Abstract:

We have formulated orthotropic material model for human heart tissue based on experimental investigation of material properties of myocardium [1]. Material model is based on Cauchy stress/stretch and shear stress/amount of shear relation curves measured experimentally under different loading conditions: biaxial extension and triaxial shear. Experimental curves with and without hysteresis are reconstructed and used in FE computational model. Computational procedure for determination of stresses from current stretches and amount of shears is implemented in the code. Incompressibility condition is retained using penalty and mixed formulation method, for both normal and axisymmetric conditions. Applicability and reliability of this sophisticated material model is tested on various examples of heart wall segments with cardiac cells (Figure 1), and in full model of heart ventricles coupled with electrophysiology of the heart. This numerical model, as addition to experiment, can provide better understanding of ventricular mechanics and can be a step forward in the improvement of medical treatment of heart diseases.

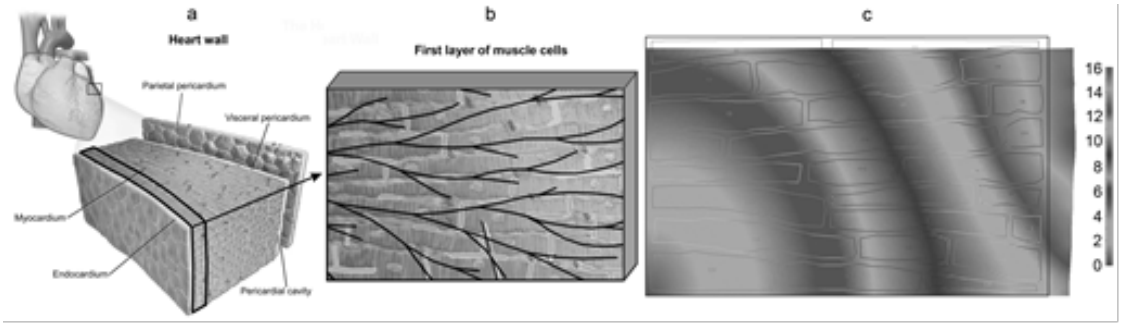

Figure 1. a) Small domain of heart wall tissue [2], b) First layer of muscle cells close to sub-endocardium, c) Field of displacements in heart tissue due to uniaxial straining.

Keywords: heart mechanics, heart material model, biaxial loading, Holzapfel experiment

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W.2.3 – *Composite smeared finite element – accuracy in electrical field* - Vladimir Geroski[1,2*], Miljan Milosevic[2], Nenad Filipovic[1], Milos Kojic[2,3,4]

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Abstract:

In this paper we present extension of the composite smeared finite element (CSFE) - a new FE for modeling drug transport in complex biological systems, to electrophysiology problems and ionic transport in heart tissue. The main advantage of the CSFE is that discrete 1D electric conduction within nervous system can be transformed into a continuum framework. The governing balance equation for electrical flow within neural fibers is defined by cable theory. This governing equation is then transformed into continuum format represented by conductivity tensor. The transported ions

change the field of electrical potential, therefore there exists a coupling between ion concentration and the electrical field. We here provide some additional details regarding the derivation of the coupling relations within the CSFE and present accuracy analysis of the element. Accuracy is tested on several simple 2D examples and basic 3D model of left ventricular of Purkinje fibers network. It was also shown that the size of the CSFE does not affect the solution, for various densities of neural network. Using this approach, we can model various complex problems in a simple form, where all necessary physical properties are included in the smeared model.

Keywords: composite smeared finite element, electrophysiology, nerve network, ionic transport, conductivity tensor

Acknowledgement: This research is supported by the Serbian Ministry of Education, Science and Technological Development (grant agreements III41007 and ON174028) and by the European Union's Horizon 2020 research and innovation programme under grant agreement No. 777204 - SILICOFCM. This article reflects only the author's view. The Commission is not responsible for any use that may be made of the information it contains.

W.2.4 – *Application of CSFE for drug delivery in liver model with tumor* - Vladimir Simic[1*], Miljan Milosevic[1], Arturas Ziemys[2], Milos Kojic[1,2,3]

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Abstract:

Recently introduced Composite Smeared Finite Element (CSFE) [1] provides a new methodology of modeling complex diffusion transport of molecules and drugs in real tissue models consisted of capillaries and tissue. Here, CSFE method is applied to 3D drug delivery model comprised of spherical tumor and surrounding liver, in order to understand parameters controlling the mass accumulation differences between tumor and surrounding liver, as well as parameters sensitivity and importance to the mass transport. We created specific models for each of the patients with given input systemic curves and experimental values (volume fraction, diffusion coefficient, etc.), and simulated diffusion process of various drug molecules, in order to estimate their apparent diffusion coefficient inside tumor, by fitting with respect to tumor experimental concentration profiles. Tumor domain was modeled without capillary presence while surrounding liver covered 20% of capillary volume. Field of correction factors, needed to improve accuracy of smeared model, is included in the model. Numerical example results matched experiments properly, verifying applicability of CSFE methodology for transport in real organs. Furthermore, this CSFE concept was used to simulate drug transport within complex 2D liver model with several domains, including tumor region inside.

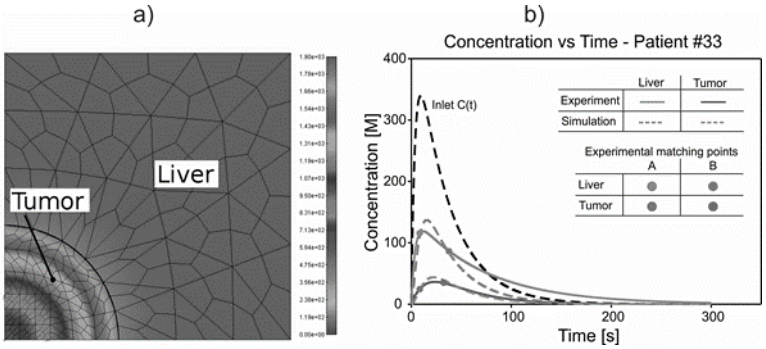

Figure 1. Concentration field within 3D drug delivery model for specific patient: a) Concentration field for 3D tumor model surrounded by liver with marked boundary (2D representation); b) Concentration vs. Time diagram for specific patient with inlet systemic curve, experimental and simulation curves that matched experimental points for both domains.

Keywords: diffusion, smeared model, composite smeared finite element, correction factors, tumors

Acknowledgement: This research is supported by the European Union's Horizon 2020 research and innovation programme under grant agreement No 777204. This article reflects only the author's view. The Commission is not responsible for any use that may be made of the information it contains. Research is also supported by the Serbian government (grant agreements III41007 and ON174028).

W.2.5 – *Tuning cooperativity of calcium activation in cardiac muscle* - Momcilo Prodanovic[1,2], Boban Stojanovic[1,3], Mladen Maric[1,3], Danica Prodanovic[1,3], Srboljub M. Mijailovich[4*]

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Abstract:

Early phase diastole and diastolic performance (filling) via resting ventricular wall tension can be affected by relaxation abnormalities. This is one of the rarely studied effects of mutations in cardiac muscle sarcomere proteins, which are often assessed from the force-pCa relations of demembraned muscle or transient twitch contractions in intact muscles. The characteristics of calcium sensitivity (pCa50) and cooperativity (Hill coefficient, nH) are assessed from force-pCa relations. Using MUSICO simulations, tightly coupled with the experiments, we managed to fine-tune calcium sensitivity and cooperativity by testing the contributions of three mechanisms to contraction and relaxation kinetics: (1) Tm azimuthal movement as a continuous flexible chain (CFC); (2) variations in cTn calcium affinity; and (3) inclusion of a super-relaxed myosin state (SRS) to reduce the number of myosins that can rebind during relaxation and modulate cooperativity between bound myosin and CFC.

Simulations provided force-pCa relations and force transient responses where native cTnC was replaced with either cTnC L48Q or cTnC I61Q with increased or decreased Ca2+ affinity, respectively. Simulations demonstrated that proposed mechanism of changing calcium dissociation rate from mutated cTnC can achieve experimental pCa50 but cannot match observed cooperativity (nH). Adjusting myosin affinity to actin and confined persistent length (CPL) of CFC accounted for the apparent loss of cooperativity of thin filament activation for both mutants. However, in WT, predicted cooperativity was significantly lower than observed. Fine-tuning calcium dependent transition rate from SRS, provided observed nH from force-pCa relations keeping CPL values in a physiological range.

Keywords: MUSICO, thin filament regulation, cooperativity, cardiomyopathy, cTnC mutations

Acknowledgement: This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 777204.
This article reflects only the author's view. The Commission is not responsible for any use that may be made of the information it contains.

W.2.6 – *Genetic determinants of clinical phenotype in hypertrophic cardiomyopathy* - Andrej Preveden[1], Nduka Okwose[2], Maria Tafelmeier[3], Fausto Barlocco[4], Francesco Mazzarotto[4], Christopher Eggett[2], Paul Brennan[2], Lars Maier[3], Iacopo Olivotto[4], Dejana Popovic[6], Arsen Ristic[6], Aleksandar Redzek[1], Guy A MacGowan[2], Nenad Filipovic[5], Djordje G Jakovljevic[2], Lazar Velicki[1*]

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Abstract:

As a part of the international multidisciplinary SILICOFCM project developing a computational platform for in silico clinical trials of familial cardiomyopathies, the present clinical study evaluated the association between genetic mutations and clinical phenotype in patients with hypertrophic cardiomyopathy (HCM).

Genetic and clinical data were collected for 63 HCM patients, divided into two groups according to identified cardiac gene mutation i.e. group 1 myosin binding protein-C – MYBPC3 (N=48, age 49.8±14.3 years, 21% females), and group 2 β-myosin heavy chain – MYH7 (N=15, age 55.1±13.3 years, 33% females).

Family history of HCM was confirmed in 37% of patients; 41% were asymptomatic, and in 59% of patients there were dyspnea (40%), palpitations (21%), syncope (16%), fatigue (14%), and chest pain (10%). The major (clinically relevant i.e. ≥10%) differences between MYBPC3 and MYH7 carriers were identified in the following echocardiography parameters i.e. posterolateral wall thickness and intraventricular septum were 31% (10.6 vs 15.6 mm, p=0.26) and 12% (21.5 vs 25.1 mm, p=0.23) lower in MYBPC3 compared with MYH7. Left atrial volume was 10% (111.7 vs 124.5 ml, p=0.64) lower, and left ventricular end-diastolic volume was 38% (110.8 vs 69.0 ml, p=0.05) higher in MYBPC3. Left ventricular end-systolic volume was similar between MYBPC3 and MYH7 (52.6 ml vs 48.1 ml; p=0.76) as was left ventricular ejection fraction (55.6±8.2 vs 49.2±17.4, p=0.07). E/e' ratio as a measurement of diastolic dysfunction was 49% higher in MYH7 (8.8 vs 17.3; p<0.01). Also, the tricuspid annular plane systolic excursion was 19% lower in MYBPC3 compared with MYH7 (21.0 vs 25.7 mm; p=0.04).

The present study confirms that HCM patients carrying MYH7 gene mutation are presented with a more severe clinical phenotype than those with MYBPC3.

Keywords: hypertrophic cardiomyopathy, genetic mutation, myosin binding protein C, myosin heavy chain 7.

Acknowledgement: This project has received funding from the European Union's Horizon 2020 research and innovation program under grant agreement No 777204. This article reflects only the author's view. The Commission is not responsible for any use that may be made of the information it contains.

Session W.3: 14:00-15:00

Biomedical Decision Support System

W.3.1 – ***New Determinants for the Rupture Risk Assessment of the Intracranial Aneurysm*** **-** Romana Perinajová[1,2*], Merel Toussaint[1], Bob Kalkman[1], Pim van Ooij[3], Saša Kenjereš[1,2]

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Abstract:

Intracranial aneurysms cause almost 500,000 deaths in the world every year. Currently, the processes behind their genesis and rupture are not well known. New opportunities for both the treatment as well as the prevention may be found if we have a better fundamental understanding of these processes. Here we show how the combination of Magnetic Resonance Imaging (MRI) and Computational Fluid Dynamics (CFD) can provide a non-invasive alternative for studying the intracranial aneurysm.
In previous studies, it was difficult to find the precise location of rupture in an aneurysm. The aneurysm geometry of the CFD Rupture challenge from 2013 was simulated first to predict the location of a known rupture site. This rupture location was identified by combining few hemodynamic criteria: the time-averaged wall shear stress (TAWSS), the oscillatory shear index (OSI) and new criteria – the presence of vortex-saddle point structure during systole with accompanying local pressure minimum. Thanks to a parametric sensitivity study on these criteria, a critical threshold for rupture risk was proposed, which properly predicted exact rupture site for the intracranial aneurysm. By applying the same evaluation in the patient aneurysm (received from Amsterdam Medical Center), we were able to localize a possible rupture site in this case as well. Furthermore, we propose additional criterion based on the local mass transfer of oxygen in the lumen and inside arterial wall. We found that the rupture site was characterized by a continuous lack of oxygen. These results provided a first fundamental insights into origins of the aneurysm rupture.

Keywords: CFD, Intracranial aneurysm, Rupture, Risk

W.3.2 – ***Development of Virtual Angiography Protocol Combining Computer Graphics and Computational Fluid Dynamics*** **-** Hiroaki Niikura[1,2], Hiroyuki Takao[1,2,3], Soichiro Fujimura[2,3], Yuya Uchiyama [2,3*], Makoto Yamamoto[4], Yuichi Murayama[1]

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Abstract:

A cerebral aneurysm is one of the cerebrovascular diseases. We commonly perform angiography to inspect a cerebrovascular geometry. The angiography is suitable for investigating the blood flow state because of its high resolution. However, physicians use contrast media to perform angiography, and the patients have physical burdens such as being exposed to radiation. We can reduce the burden if we can make alternative methods to confirm a state of the real blood flows accurately without performing angiography. In this study, we developed a virtual angiography protocol by combining computer graphics (CG) which is superior in visualization and Computational Fluid Dynamics (CFD). We conducted CFD simulation imitating the behavior of constant media then visualization based on density with CG techniques. We compared obtained virtual angiographic images to real images and then they indicated agreement. We confirmed that the density behavior of virtual angiography was close to the behavior of real angiography. In addition, by using the virtual angiography protocol, it becomes possible to explain their blood flow status easily to the patients. For further development, we have to investigate the consistency of the virtual angiography system when we deploy endovascular devices like stents.

Keywords: Computational Fluid Dynamics (CFD), Computer Graphics (CG), Angiography

Session W.4: 15:30-16:30

Mini-Symposia 7: MULTISCALE MODELLING OF EXPERIMENTAL DATA RELATED TO BIOMATERIAL RISK ASSESSMENT (part I)

W.4.1 – ***Computational immunoprofiling predictions of immune response promiscuity to Epstein Barr Virus epitopes and oral biofilm in acute coronary syndrome -*** Mariliis Jaago[1,2], Arno Pihlak[1], Helle Sadam[1,2], Valentina Bozok[1], Oliver Nisumaa[3], Jaak Vilo[3], Pirkko Pussinen[4], Nihal Engin Vrana[5,6], Kaia Palm[1,2*]

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Abstract:

The use of biomaterials in clinical applications has increased dramatically over the past decade, as they are implemented as drug delivery vehicles, tissue repair scaffolds, and replacement elements for damaged body parts. However, introducing biomaterials to the body may include inflammation, collateral tissue damage, and thus early loss of function. Today we have no framework of identification of individuals with heightened risk for unfavourable reactions to biomaterials despite that the individuality of immune system features along with the infectious background underlying clinical diagnoses is high. Mimotope Variation Analysis (MVA), a comprehensive immunoprofiling technology based on next generation phage display enables the description of the antibody repertoire of an individual at any given time. In a clinical cohort (n=96) of persons with varying degree of coronary heart disease (stable form, or acute coronary syndrome), and background of gingivitis or periodontitis, MVA immunoprofiling revealed differential immune response against two common antigens of Epstein-Barr virus (EBV), also known as human herpesvirus 4, namely VP26 and EBNA6 across disease groups. VP26-similar regions discovered by MVA analysis were also identified in several bacterial pathogens in oral biofilms and as mimicking epitopes in certain biopolymers with potential to elicit cross-reactive immune response. Our findings support the role of the immune system in the development of the coronary artery disease and propose MVA as a technology of assessing individual's further risk against biomaterials based on the current status of their immune system.

Keywords: immunoprofiling, acute coronary syndrome, biomaterial, implant failure, risk assessment

Acknowledgement: We thank the BIIT group and team of Quretec, Llc. for IT support. Biomaterial samples kindly provided by Protip Medical. The research was funded by the institutional research grant of Protobios (nr 5.1-4/1373) and by personal research grant of KP (PRG578) from the Estonian Research Council. Protobios team was supported by EU H2020 RIA research funding (PanBioRa, EU760921).

W.4.2 – *Analysis of Focus Measure and Image Fusion of Microscopy Images -* Arban Uka[1*], Florenc Skuka[2], Latif Xeka[1], Harry Esmonde[3], Nihal Engin Vrana[4]

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Abstract:

Analysis of health condition of cellular material and the interaction of cells with different biomaterials requires the use of good and efficient image acquisition techniques. In order to mimic the behavior of a biosystem researchers employ use of microfluidic cells and these systems provide a large amount of data. The major expectation for these testing systems is to be portable and fast in acquiring high quality and processing the images. One of important aspects is to have a system that is independent for both tasks. Autofocusing is an important step that requires good control from the imaging module operator. The aim of this work is to evaluate different algorithms that quantify the focus measure metrics and determine the one that is the most efficient in terms of computational runtime and quality of the image. Fourteen different algorithms have been tested for large dataset of microscopy images (both in focus and defocused images) and the most efficient associated metric score is determined. The investigated algorithms are energy of gradient, Gaussian derivative, thresholded gradient, squared gradient, energy of Laplacian, Modified Laplacian, wavelet variance, wavelet ratio, gray-level variance, standard deviation, histogram entropy, histogram range, image curvature and spatial frequency measurement. The most reliable algorithm was chosen the one that reported the largest metric difference between any two images that were close to the best focus. The computational runtime range from the fastest to the slowest has four orders of magnitude difference. The best kernel sizes that are compatible with the inherent characteristics of a microscope image are determined. Determining the fastest algorithm is important as the microscope can be set to acquire several images of regions that are out of focus and then through image fusion all the different sections can be merged to construct a well-focused large image.

Keywords: Autofocusing, microscopy, focus measures, automated microscopy

Acknowledgement: This work received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 760921.

W.4.3 – *Mathematical simulation of biodegradable material cytotoxicity in 3D hepatocellular systems in vitro -* Alexander Makhaniok[1], Constantin-Edi Tanase[2], Amir Ghaemmaghami[2], Nihal Engin Vrana[3], Vitaly Goranov[1*]

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Abstract:

Degradation of implanted materials produces toxic byproducts that can cause cell damage and apoptosis, especially at hepatic level, where hepatocyte “take the first stab” of the circulated toxins. We elaborated own mathematical model tak-ing into account “diffusion mass transfer” to evaluate the kinetics of cell death and estimate the cytotoxicity of the biodegradation products of a degradable ma-terial by analysis of in vitro data. These model are applicable in cases when the rate of cell death is proportional to the concentration of the toxic products of bi-omaterials degradation. The model takes into account the surface area of the ma-terial under test and allows predicting the cytotoxicity of the material considering the 3D geometry of hepatocellular spheroids. We have mathematically validated spatial distribution of damaged cells inside the spheroids under the influence of different concentrations of low-toxic products that can be used for distinguishing the direct and indirect (metabolite) toxicity.

Keywords: Ascending thoracic aortic aneurysm, Inverse method, Rupture risk, Finite element

Acknowledgement: This project has received funding from the European Union’s Horizon 2020 research and innovation program under grant agreement No 760921 (PANBioRA).

W.4.4 – ***The Mathematical approach to disclose low Cytotoxicity of material from in vitro co-culture experiment -*** Ivan Siutsou[1], Lydie Ploux[2], Nihal Engin Vrana[2], Vitaly Goranov[1*]

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Abstract:

The problem of low-level (latent) toxicity uncovering is central for evaluation of new biomaterials safety. The developed method allows to estimate relevance of possible toxicity effects by comparison of growth curves in cell culture experi-ments. It naturally incorporates possible variance of initial conditions and allows it to be distinguished from real toxicity effects. We elaborated the method which includes two-parametric model of cell proliferation with parameters identifiable as basic proliferation rate r and limiting cell density c. Least squares method is used for parameters estimation. As bacterial contamination of the biomaterials and the potential interactions between biomaterials and microbiota are also important factors to analyse, such models can be also used to predict bacterial growth in the presence of biomaterials and mammalian cells for a given application.
The method was tested on the data of E. coli K12 proliferation on surfaces of os-teoblastic cells (STRO) and free surfaces of biocompatible materials (A and B). On both materials it appears that base proliferation rate are unaffected by STRO presence (A: r = 2.04±0.23 day-1 without STRO vs. r = 1.96±0.24 day-1 with STRO, B: r = 2.18±0.11 day-1 vs. r = 2.21±0.12 day-1) but limiting cell densities are reliably lowered (A: c = 0.230±0.058 μm-2 without STRO vs. c = 0.037±0.017 day-1 with STRO, B: c = 0.106±0.011 μm-2 vs. c = 0.0521±0.0076 day-1 corr.) that re-veals the ability of STRO presence to inhibit microbial proliferation is statisti-cally significant 95% (A: p = 0.9654, B: p = 0.9965).

Keywords: biomaterial cytotoxicity, statistical methods, cell culture

Acknowledgement: Funded by Horizon 2020 project # 760921 (PANBioRA).

Session W.5: 17:00-17:45

Mini-Symposia 7: MULTISCALE MODELLING OF EXPERIMENTAL DATA RELATED TO BIOMATERIAL RISK ASSESSMENT (part II)

W.5.1 – ***Convolutional Neural Networks for Fibroblast Cell Classification and Counting -*** Arban Uka[1*], Julien Barthes[2], Xhoena Polisi[1], Aleksandros Ruci[1], Albana Halili[1,3], Ali Osman Topal[1], Nihal Engin Vrana[4]

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Abstract:

Convolutional neural networks (CNN) have become a primary choice in cell classification and counting because of the large volume of data that needs a proper and fast analysis. Multimedia elements (image and video) are analyzed for the investigation of cell parameters for the biomaterial risk assessment. Here we introduce a new fibroblast cell dataset and analyze it in detail using CNN and local binary patterns (LBP). Dataset is composed of nearly 20.000 images of cells in contact with favorable and toxic biomaterials and was separated in a training, testing a validation sets. CNN parameters (number of kernels per convolutional layer, kernel size, dropout rate etc) are optimized for this specific dataset and after the training, an accuracy of 95% is achieved in determining the health condition of the cells. Large images are composed of three major components: i) nuclei, ii) cytoplasm and iii) background. LBP of these three components has been evaluated and support vector machine is used to classify the LBP values that are then used to count the cell nuclei. Counting directly the nuclei circumvents the difficulty that stems from the deformable shape of the cytoplasm and the overlap of cytoplasm of different cells. An accuracy of 93% is achieved in counting.

Keywords: biomaterial risk assessment, deep learning, cell classification, counting

Acknowledgement: This project has received funding from the European Union's Horizon 2020 research and innovation program under grant agreement No 760921 (PANBioRA).

W.5.2 – ***Coupling experimental data and numerical simulation in modelling epithelial barrier formation with A549 cancerous cell line -*** Tijana Šušteršič[1,2,3*], Milica Nikolić[1,3], Julien Barthes[4], Nihal Engin Vrana[4], Nenad Filipović[1,2,3]

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Abstract:

The overall aim of organ-on-a-chip monitoring model tissues is providing self-reporting tissue models that can either individually or as an integrated platform be used to test the biocompatibility of materials with some emphasis on materials immune-compatibility/immune-toxicity. We will focus in this abstract on coupling the experimental data with numerical simulations for the purposes of epithelial barrier formation with A549 cancerous cell line. The collected data included pictures, which have been acquired using bright field microscope at different time points: 30min, 4h, 24h, 48h and 72h, for calculation of the spreading and proliferation coefficient of A549 cell line. Developed model will provide insight into cells formation of the epithelial barrier. Calculated input parameters – characteristics of the chosen cell line: spreading and proliferation coefficients, seem appropriate and in accordance to the experimental outputs. Cells growth, migration and proliferation are modelled with a sort of extended diffusion equation. The preferred result of the simulation is time needed for formation of the barrier. This model will further become more complex in the view of getting desired outputs.

Keywords: A549 cell line, epithelial barrier, numerical simulations, image analysis

Acknowledgement: This research is supported by the European Union's Horizon 2020 research and innovation programme under grant agreement No. 760921 - PANBioRA. This article reflects only the author's view. The Commission is not responsible for any use that may be made of the information it contains. This study was also funded by the grants from the Serbian Ministry of Education, Science and Technological Development III41007 and OI174028.

W.5.3 – *Computer Assisted Spheroid Formation Analysis* - Xhoena Polisi[1], Constantin-Edi Tanase[2], Arban Uka[1*], Nihal Engin Vrana[3], Amir Ghaemmaghami[2]

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Abstract:

Computer assisted techniques could enable the use of morphological characteristics of hepatic spheroids as surrogate for their response to various stimuli. The aim of this work is to develop an automatic analysis procedure able to correctly acquire all the important morphological parameters of the hepatic spheroids under steady and after stimulation conditions. Within the datasets, several issues can occur related to the non uniform illumination background and inherent limitation in counting the exact object number when two or more are adjacent. Some of the images include patterns with intensity comparable to the spheroid intensity, such as extended grooves, and they are filtered out based on their eccentricity values. Traditional methods such as Otsu threshold does not segment the spheroid images truthfully due to their energy minimization based approach. To circumvent this limitation initially background removal is applied as a preprocessing step. Filters applied for this depend on the relative size of the spheroids in order not to diminish the image quality. Therefore, we propose a guided automatic threshold value that can differ the background and the spheroids more accurately by finding the critical peak on the pixel intensity histogram. Pixel intensity histograms are composed of three modes and the local minimum after the peak at the lowest values

is the threshold value. After applying the new guided thresholding technique, watershed algorithm is used in order to determine the separating nodes between objects that are contiguous to each-other. After this step, the total area covered by the spheroids is appropriately determined for all the images. Employing the above steps; the number, area and the perimeter of the spheroids; were correctly determined.

Keywords: Spheroid culture, segmentation, guided thresholding

Acknowledgement: This project has received funding from the European Union's Horizon 2020 research and innovation program under grant agreement No 760921 (PANBioRA).

Session W.6.1: 17:45-18:30

Gene Expression Analysis and Engineering

W.6.1.1 – ***The logic of regulation design in bacterial restriction-modification systems -*** Andjela Rodic[1,2*], Bojana Blagojevic[3], Magdalena Djordjevic[3], Konstantin Severinov[4], Marko Djordjevic[1]

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Abstract:

Restriction-modification (R-M) systems are small, often plasmid-encoded, bacterial gene networks which express two enzymes: restriction enzyme (RE) cuts specific DNA sequences, while methyltransferase (MT) protects them. Their main role is to defend the cell from foreign DNA, while keeping the host's genome intact. To achieve tightly controlled expression of enzymes in a newly-inhabited bacterium, including delayed expression of RE to provide enough time for initial genome methylation, surprisingly, they resort to a number of different regulatory features, such as specialized transcription factors (C proteins), binding cooperativity, overlapping promoters, antisense RNAs, leaderless transcripts, etc. Having in mind the immune function shared by all R-M systems, we hypothesized that the design of their regulation is guided by few selected properties of R-M system expression dynamics, ensuring safe and efficient establishment in a new host. Previously, we thermodynamically modeled regulation of transcription initiation in three R-M systems exerting different C protein binding patterns, and showed that these systems design can be explained by the proposed dynamic principles. In a recent, both experimental and theoretical study of the Kpn2I R-M system, we analyzed another R-M regulatory feature: a roadblock established by C proteins, affecting the rate of transcription elongation. On this example we show that specific functional requirements are achieved in R-M systems not only by carefully choosing combinations of regulatory features, but also through fine tuning of interaction energies. Overall, regulatory features and evolutionary design principles found in R-M systems might serve as building blocks and guidelines in engineering synthetic gene circuits.

Keywords: Restriction-modification, gene expression, modeling regulation, design principles

Acknowledgement: Research was funded by the Swiss National Science Foundation (SCOPES IZ73Z0_152297), FP7 Marie Curie Reintegration Grant (PIRG08-GA-2010-276996) and the Ministry of Education, Science and Technol. Development of the Rep. of Serbia (ON173052).

W.6.1.2 – ***Effects of bacterial cell growth rate on dynamics of a natural gene circuit -*** Stefan Graovac[1,2], Andjela Rodic[1,2], Magdalena Djordjevic[3], Marko Djordjevic[2*]

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Abstract:

In vivo dynamics of protein levels in bacterial cells depends on both intracellular regulation and the relevant population dynamics. However, the population dynamics effects are often neglected, or are included through simple dilution models, that take into account only effective increase in the protein degradation rates due to cell division. In our previous work, we have shown that such dilution model cannot explain part of the data from the first available single-cell experiments on restriction-modification (R-M) system establishment in a naïve bacterial host. To assess importance of the population dynamics effects on this example, we included in the model an interplay of cell and plasmid division rates and showed that this is necessary in order to explain the experimental data. From the point of methodology, and to deal with a significant increase in the dimensionality of the parameter space, we proposed a novel "mean-field like" iterative approach to resolve the problem of effective coupling due to plasmid dynamics, which allows estimating the population dynamics parameters from the observed dynamics of only one molecular species. We next proceed by incorporating the full set of effects related with changing the cell growth parameters (changes in RNA polymerase concentration, cell volume, gene copy number, etc.), in the model of R-M regulation and establishment dynamics. Using this framework, we established which system dynamical properties remain robust with respect to changes in cell growth rate, and which system regulatory features are responsible for this robustness.

Keywords: cell growth rate, population dynamics, restriction-modification systems, computational modeling, gene expression regulation

W.6.1.3 – *A simple criteria for predicting direction of CRISPR array: applications to investigating non-canonical CRISPR/Cas functions -* Ognjen Milicevic[1,2,*], Bojan Bozic[3], Jelena Guzina[3], Marko Djordjevic[3]

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Abstract:

CRISPR/Cas protects bacteria from invasion by foreign DNA (e.g. by bacteriophages). It is also becoming increasingly clear that CRISPR/Cas has an important function in the regulation of endogenous bacterial genes (non-canonical CRISPR/Cas functions). In recent work, we provided computational evidence that CRISPR/Cas system in E. coli has dominantly non-canonical function, which leads to a question of how widespread such non-canonical functions are in other bacteria. To address this, one has to be able to probe, on a large scale, interactions of CRISPR spacers with sequences in the host genome and derived mRNAs. However, to achieve this it is necessary to know direction of CRISPR spacers, which is standardly predicted through CRISPRDirection method, which in general provides predictions for up to 70% arrays, with this number dropping to as little as 20% for Type II-B CRISPR/Cas systems where non-canonical functions were experimentally found; due to this, a simplified Potential direction method (implemented through CRISPR Finder) was developed. We here propose a novel simple criterium for determining CRISPR array direction, based on the direction of associated Cas genes (CasDirection). We show that CasDirection gives comparable accuracy to CRISPRDirection, and a few times higher accuracy compared to Potential Direction while being able to provide a prediction for an array of any CRISPR/Cas type. We further use CasDirection to investigate non-canonical functions in Type II-B systems, where, in distinction to E. coli, we find large heterogeneity, with mixed preferences of both individual arrays, and spacers within these arrays, towards canonical and non-canonical functions.

Keywords: CRISPR/Cas, protein-nucleic acid interactions, non-canonical CRISPR functions, CRISPR array direction, bioinformatics

Acknowledgement: This work is supported in part by project OI173052 by Serbian Ministry of Education, Science and Technological development of Republic of Serbia.

Session W.6.2: 17:45-18:30

Mini-Symposia 3: RISK ASSESSMENT IN CARDIOVASCULAR DISEASES

W.6.2.1 – ***The role of magnetic resonance imaging in the assessment of biological activity of intraluminal thrombus and proteolytic processes in abdominal aortic aneurysm -*** Milos Sladojevic[1,2], Zeljka Stanojevic[3], Igor Koncar[1,2], Petar Zlatanovic[2], Sasenka Vidicevic[3], Jelena Tosic[3], Aleksandra Isakovic[3], Miroslav Markovic[1,2], Lazar Davidovic[1,2]

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Abstract:

The aim of this study was to determine whether magnetic resonance imaging can be used to assess the biological activity of intraluminal thrombus (ILT) and proteolytic processes of the abdominal aortic aneurysm (AAA) wall.
Using magnetic resonance imaging, fifty patients with asymptomatic infrarenal abdominal aortic aneurysm were analyzed at the maximum aneurysm diameter on T1w images in the arterial phase after contrast administration. Relative intraluminal thrombus signal intensity (relative ILT SI) was determined as the ratio between intraluminal thrombus and psoas muscle signal intensity. During surgery, the full-thickness of the intraluminal thrombus and the adjacent part of the aneurysm wall were harvested at the maximal diameter for biochemical analyses. The concentration of matrix metalloproteinase-9 and neutrophil elastase were analyzed in harvested ILT and the concentration of collagen type III, elastin, and proteoglycans was analyzed in harvested aneurysm walls. The patient group was divided into two equal subgroups based on relative ILT SI median value (0.93). We analyzed differences in demographic, clinical and laboratory parameters between patients with detected low and high relative ILT SI values (less than 0.93 and equal to or greater than 0.93, respectively).
Subgroups were homogenous according to age, body mass index, gender, and prevalence of males. Prevalence of coronary artery disease was significantly higher in patients with low relative ILT SI than in patients with high relative ILT SI (40% and 4%, respectively). Additionally, among patients with low relative ILT SI prevalence of antiplatelet therapy was higher than in patients with high relative ILT SI (64% vs 32%). Significantly lower elastin concentrations in AAA wall (p=0,047) and a higher concentration of neutrophil elastase in ILT (p=0,028) were observed in patients with high relative ILT SI.
Our findings indicate a potential novel usage of magnetic resonance imaging to predict the concentration of thrombus proteolytic enzymes and the extracellular matrix content of the aneurysm wall, thus providing additional information towards the risk for potential aneurysm ruptures.

W.6.2.2 – ***Identification and assessment of the impact of preoperative mortality predictors within the formulation and validation of outcome prediction models for patients operated on for a ruptured abdominal aortic aneurysm – a study design -*** Ivan Tomić2, Miroslav Marković1,2, Igor Končar1,2, Miloš Sladojević2, Perica Mutavdžić2, Lazar Davidović1,2

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Abstract:

In an effort to predict the outcome of surgical treatment of a ruptured abdominal aneurysm (RAAA), many surgeons calculate using different outcome prediction models. Despite the relatively large

number of publications concerning the validation of these models, there is currently no solid evidence that they can be used with absolute accuracy when it comes to predicting treatment outcomes.
Creating a new statistical model for predicting outcome (mortality) in the early postoperative period (up to 7 days) and in the distant postoperative period (up to 30 days) based on previously identified preoperative mortality predictors, as well as validation of the created model and comparison of the sensitivity of the created outcome prediction model with the two most commonly used outcome prediction models so far - Hardman Index and Glasgow Aneurysm Score.
The study will be conducted over a one-year period by analyzing prospectively collected data for operated patients for RAAA from 2009 to 2019. The respondents will be randomly divided into two groups. The training group of 500 respondents will be used to formulate models for predicting outcomes. The test group of 200 respondents will be used to validate the models formed. Using multiple logistic regression analysis in the training group, the most influential preoperative predictors of mortality will be identified and models will be formed to predict mortality. The regression equations, that is, the models obtained in the training group, will be used to predict mortality for the postoperative period of 7 and 30 days in the test group. The test group will calculate postoperative mortality using existing scoring systems. Comparison of sensitivity, specificity and number of correctly classified patients between models and existing scoring systems will be performed.

Keywords: cell growth rate, population dynamics, restriction-modification systems, computational modeling, gene expression regulation

W.6.2.3 – ***Validation of Taxinomisis stratification tool through observational multicentre clinical trial -*** P. Mutavdzic[1], N. Tiemerman, J. Pelisek[2], D.P.V de Kleijn[5], G.J. de Borst[5], HH. Eckstein2, V. Obach[4], V. Riambau[5], D. Palombo[6], F. Montecucco[7], F. Sigala[8], L. Davidovic[9], D. Fotiadis[10], I. Koncar[9]

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Abstract:

Taxinomisis trial is part of the Taxinomisis project. The concept of the Taxinomisis project is to stratify carotid artery disease relying on new modern data corresponding to contemporary patients and adjust such stratification through prospective clinical trial. Initial step of the project is characterization of symptomatic and asymptomatic carotid atherosclerotic plaque lesions, identification of risk and susceptibility factors through the exploitation of longitudinal cohort data and multiomics and disintegration of carotid artery disease phenotypes into endotypes through joint modeling of multipleomics datasets and systems medicine approaches. Finally such stratification model will be validated and adjusted in the Taxinomisis clinical trial.
Aim of the trial is to validate TAXINOMISIS system for risk stratification of carotid artery stenotic disease. Primary endpoints are stroke, transitory ischemic attack or retinal symptom while secondary endpoints are MRI silent brain lesions and carotid plaque progression.
Patient with moderate to severe extracranial, both asymptomatic and symptomatic, carotid artery stenosis will be enrolled in the prospective observational multicentre trial in five European (Athens, Barcelona, Belgrade, Genoa, Munich and Utrecht) vascular centres. Inclusion will last from 31.3.2018 – 01.06.2019. Patients with short life expectancy, high potential of stroke from other cause or patients

with complex and tandem carotid lesions will be excluded from the trial.
Included patients will be examined clinically, basic laboratory exam will be performed and part of blood specimen will be stored and assessed later. Carotid plaque will be analyzed by means of duplex and MRI image while brain lesions will be detected on brain MRI.
Treatment strategy will be dependent on Good Clinical Practice GCP guidelines and let independently to institutional multidisciplinary panelist board. In patients treated with CEA carotid plaque will be stored and assessed for future analysis. In respect to allocated therapy patients will follow different follow up protocols.
Patients that underwent intervention (CEA or CAS) will be followed by clinical examination and carotid duplex on 12, 24 and 36 month. If there is coexisting contralateral carotid stenosis greater than 50% and not requiring interventional treatment (CEA or CAS), patient should cross in optimal medical therapy group.
Patients not subjected to intervention (or in whom one carotid has been treated with CAS or CEA and contralateral has stenosis is greater than 50%) will be followed with carotid duplex (at 12, 24 and 36 months) and MRI imaging of carotid tree from aortic arch up to the circle of Willis after 12 and 36 months.
Trial plans to recruit 270 patients distributed in participating centers based on individual capabilities of each center. The diagnostic performance of the new risk model, and its accuracy to discriminate high versus low risk cases for cerebrovascular complications from carotid artery disease will be evaluated using Receiver Operating Characteristic (ROC) curve analysis. The accuracy (discriminative ability) of the model will be assessed by measuring the Area under the ROC curve (AUC). An AUC 0.80 and 90% CI, for the sensitivity of prediction model of 80% with marginal error of 10%, will be targeted.
Trial will terminate after finalizing 36 months of follow up for included patients at June 2022.

Acknowledgement: This research is supported by the European Union's Horizon 2020 research and innovation programme under grant agreement No. 755320 - "TAXINOMISIS".". This article reflects only the authors' view. The Commission is not responsible for any use that may be made of the information it contains.

Session T.1: 09:30-11:00

Computational Modeling

T.1.1 – ***Mathematical modeling of the passive mechanical properties of human fascia*** - Miglena Kirilova-Doneva[1,2*], Dessislava Pashkouleva[2], Stoyan Stoytchev[2]

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Abstract:

The modeling of a long-term variability of mechanical properties of fascia will help to improve the mathematical models of the abdominal wall. The purpose of this study was to present a constitutive model of fascia suitable for finite element analysis of surgical procedures using strain energy function (SEF) for quasi-elastic materials.
The samples obtained from human fascia were divided in tree age groups. Group A - up to 60 (mean age 52.5±6 yrs., 27 samples), group B - between 61-80 years (mean age 70.4±5.2 yrs., 22 samples) and group C- between 81-90 years (mean age 83.2±2 yrs., 37 samples). Tensile test was applied to fascia specimens cut along and parallel to fibers. From the stress - stretch ratio curves the age-related changes in the mechanical properties of human fascia were assessed based on the results for secant modulus at 5% strain, maximum stress and maximum stretch. The results indicated an increase in the secant modulus at both directions according to age. There is no clear trend for the long-term behavior of the maximum stress.
The obtained stress-strain ratio curves were approximated with non-linear constitutive models of Mooney-Rivlin, Yeoh and Demiray. A Neo-Hookean SEF was also applied. A good agreement between theoretical and experimental results was obtained for all SEF except the Neo-Hookean model. The results can be used in the numerical simulation of an abdominal wall.

Keywords: fascia, long-term mechanical properties, mathematical modeling

T.1.2 – ***Numerical modeling and simulations of magnetic drug delivery for the lung cancer therapy*** - S. Kenjereš[1,2,*], P. Bakker[1]

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Abstract:

In the present work, we investigate the concept of the targeted delivery of a super-paramagnetic pharmaceutical drug aerosols in an anatomically realistic geometry of the human upper and central respiratory system. In our computer simulations, we combine the transitional Reynolds-Averaged Navier-Stokes (RANS) and the wall-resolved Large Eddy Simulation (LES) methods for the air phase with the Lagrangian approach for the particulate (aerosol) phase. We validated simulations against recently obtained 3D magnetic resonance velocimetry (MRV) measurements performed in identical geometry with a water as a working fluid. Both approaches produced good agreement with experiments, and the transitional RANS approach is selected for the multi-phase simulations of

aerosols transport, because of significantly lower computational costs.
The local and total deposition efficiency are calculated for different classes of pharmaceutical particles, without and with a super-paramagnetic core (the shell-core particles). For the latter, an external magnetic field is imposed. The source of the imposed magnetic field was placed in the proximity of the first bronchial bifurcation, such that the highest gradients are generated at locations affected by cancer. Various forms of the spatial distribution of the imposed static magnetic field are investigated.
We demonstrated that both total- and local-depositions of aerosols at targeted locations can be significantly increased by an applied magnetization force. This finding confirms the possible potential for further advancement of the magnetic drug targeting (MDT) technique for more efficient treatments of lung cancer.

Keywords: magnetic drug targeting, lung cancer, CFD, Lagrangian particle tracking, LES

T.1.3 – ***Evaluation of Methods for POD Basis Interpolation on Grassmann Manifolds for Simulations of Complex Hyperelastic Structures*** - Orestis Friderikos[1*], Mayra Mora[2], Emmanuel Baranger[1], David Neron[1]

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Abstract:

Modeling of the mitral valve hyperelastic structure including different types of interactions between its components is a challenging task due to geometric non-linearity, constitutive equations of increasing complexity and contact. To this end, solution of these problems are generally obtained using High Performance Computing (HPC) clusters. Moreover, in many cases, like in patient specific modeling, it is often desirable to estimate the system's response according to changes of various input parameters in near real time. As mentioned above, this issue cannot be carried out for lack of today's computing resources. To address these issues, Reduced-Order Models (ROM), i.e., Proper Orthogonal Decomposition (POD), can be used to decrease complexity and solve parametrized problems in hyperelasticity. In particular, the procedure starts by a learning state during which the problem is solved for some given values of parameters. The simulation "snapshots" are then compressed using the POD method to generate a ROM that is expected to resemble the dynamics of its high-fidelity counterpart. Interpolation of the reduced order POD bases is performed on Grassmann manifolds, its tangent space at a reference point and the computation of geodesic paths on this manifold. An approach which combines separate interpolations of the spatial and time basis on Grassmann manifolds to generate the interpolated snapshot matrix is compared with classical POD methodology. The dependency of the reference point selection on the accuracy is investigated using different interpolation schemes. Results concerning the accuracy and computational cost of the various methods are discussed.

T.1.4 – ***A multi-agent system of the cell membrane: auto-assembly and particle/ion interaction*** - Víctor A. Acosta Santamaría[1*], Tien-Tuan Dao[1], Karim El-Kirat[1]

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Abstract:

Skeletal muscles comprise multiple individual muscle fibers that are stimulated by motor neurons. The muscle excitation-contraction coupling occurs at the nanoscale of a hierarchical multiscale structure. This complex process relates to multi-physical phenomena's (e.g. muscle contraction mechanics, physiochemical evolution, voltage dynamics, thermodynamics). In this context, the present study aims to develop and evaluate a multi-agent system of the cell membrane and its interactive factors, analyzing the substance exchange through the neuromuscular junction (chemical-mechanical coupling behavior) using system of systems approach. The complex behaviors at the nanoscale can be handled in different sub-systems: (i) Across the synaptic cleft, the neuromuscular junction connects the distal motor nerve ending with the sacrolema membrane. The junction involves acetylcholine neurotransmitters/receptors that process the initial electrical impulses into chemical signals that result in a localized depolarization (ligand-gated ion channels). (ii) The voltage-gated channels govern the muscle action potential (self-propagating depolarization). The regulation of the electrochemical gradient across the membrane is achieved by ions fluxes (Na+ and K+). (iii) In the transverse tubular system, the action potential stimulates the L-type calcium channels that release Ca2+ from the sarcoplasmic reticulum through ryanodine receptors. (iv) Finally, for striated muscles, the cytosolic calcium stimulates different signaling pathways that drive and regulate the contraction process. The chemical signals are converted into a mechanical signal on the actin filaments. All these sub-systems are modeled and integrated into a simulation system of the auto-assembly and particle/ion interaction at cell membrane level. As an application, the proposed model is used in the simulation of facial muscles contraction.

Keywords: Multi-agent system, Cell membrane, Substance exchange

Acknowledgement: This work was carried out and funded in the framework of the Labex MS2T. It was supported by the French Government, through the program "Investments for the future" managed by the National Agency for Research (Reference ANR-11-IDEX-0004-02).

T.1.5 – *Deterministic and stochastic parameter analysis of the bone cell population model* -
Julijana Simonović[1,2*], Thomas E. Woolley[3]

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Abstract:

Mathematical models are a great way of cementing biological verbal models. Specifically, they can provide causative mechanisms linking inputs and outputs and illuminating underlying assumptions that determine a biological system's dynamics. Further, they offer a means of predicting new outcomes, as well as highlighting the most sensitive modelled components, resulting in the construction of new experimental hypotheses and reducing experimental waste. This study represents a deterministic and stochastic analysis of bone cell population model. We explore this system through its homogeneous coupled ordinary nonlinear differential equations of generalized S-System type as well as through its probabilistic analogue, to investigate whether the model can capture the essential autocrine, paracrine and synergistic characteristics of bone cell communication processes, both in targeted and random remodeling processes. Continuum deterministic models assume that the simulated populations are large enough that a continuum approximation is valid. However, in the bone creation-degradation application, which these equations describe, cell population numbers often fall below 10 cells. Thus, the stochastic description is more appropriate. Critically, we see dynamics that are often present in the deterministic equation, which are used to

explain a variety of observed experimental dynamics, do not occur in the stochastic model. Additionally, we are in a good position to comment and put insights onto parameter ranges according to the constraints from the specific bone multicellular unit (BMU) activity cycle detected in the histopathological screening and 3D in-vitro experiments. Thus, we are able to correlate the biological reality that these equations.

Keywords: bone remodeling, bone cell population model, S-System type, stochastic vs. deterministic computational modeling

Acknowledgement: These results are part of research on project MMoBEER (Nov. 2017-Nov. 2019) that has received funding from the European Union's H2020 MGA MSCA-IF-2016 under grant agreement No. 752793.

Session T.2: 12:00-13:00

Computational Modeling

T.2.1 – *Endothelium resolving simulations of wall shear-stress dependent mass transfer of LDL in arteries* - S. Kenjereš[1,2,*], J.P. van der Krieke[1], C. Li[1]

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Abstract:

In the present study, we investigate blood flow and mass transfer of the low-density lipoprotein (LDL) in a simplified axisymmetric geometry with a mathematically well-defined narrowing (stenosis), which mimics a diseased human coronary artery. The interior of the arterial wall is represented as a porous media containing multi-layered structures of different thickness. This multi-layered structure includes anatomically realistic sub-layers: endothelium, intima, internal elastic layer (IEL), media and adventitia. The coupling between the blood flow and mass transfer of LDL in the lumen (interior of artery) and arterial wall is established through a multi-pore model at the lumen/endothelium interface.
This multi-pore model takes into consideration three different contributions for transport of LDL: (i) normal and (ii) leaky junctions of endothelial cells, as well as their vesicular pathway (iii). A comprehensive mathematical model, which is based on solving the set of PDEs for conservation of mass, momentum, and concentration, is completed by introducing the wall shear-stress (WSS) dependent transport properties of the arterial wall.
Several variants of the model are evaluated, including the constant and wall shear-stress dependent transport properties of the endothelium, as well as different representation of the arterial wall internal structure. The response of the model on changing the transmural pressure (to simulate hypertension effects) and geometrical shapes of the stenosis (to mimic the various stages of atherosclerosis development) is also presented.
It is shown that the present model can predict the levels of LDL inside the arterial wall in good agreement with experimental studies in pressurized rabbit aorta under similar conditions.
The model is recommended for future simulations of LDL accumulation in the patient-specific cardiovascular system conditions.

Keywords: LDL, blood flow, mass transfer, arterial wall, atherosclerosis

T.2.2 – *Optimization of Parameters for 3D-Bioprinting Scaffold Production – Blood Vessel Bioengineering* - Marko N. Živanović[1,2 *], Dalibor D. Nikolić[2,3], Nenad D. Filipović[2]

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Abstract:

3D bioprinting is new age technology for printing of complex human tissue models, i.e. structures that could mimic or even replace parts of organs or organs in whole. Such tissue engineering field is nowadays recognized to possess high potential in human curing and fast treating of patients in personalized medicine sense. 3D bioprinting approach is interconnected with many scientific fields, such as engineering, mathematics, biology, and medicine.
Production of bypasses for replacement of affected blood vessels is hot topic in regenerative medicine and tissue engineering. While the polymer-based commercial bypasses are commonly used in medicine, the production of patient-personalized bypass derived from his/her own stem cells is attracting great attention among many groups of researchers. Although several groups worldwide succeeded to produce artificial blood vessel with in vivo application, there are many obstacles to be solved at this moment.
This paper is focused on optimization of chemical and physical parameters for 3D bioprinting of scaffolds that are used for stem cell seeding prior to production of artificial blood vessel. We used a series of bio-acceptable polymers and bioprinted scaffolds were tested on different mechanical parameter conditions. The most convenient solutions of polymers were used for producing the scaffolds on which stem cells were seeded prior to produce blood vessel-structures.

Keywords: 3D bioprinting, Bypass, Scaffolds, Blood vessel

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Session T.3.1: 14:00-16:00

Biomechanics (part I)

T.3.1.1 – ***Technical approach to CFD streamlines calculation in 3D alveolar models*** - Danko Milasinovic[1,2*], Igor Saveljic[2,5], Frank Henry[3], Akira Tsuda[4], Nenad Filipovic[2,5]

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Abstract:

In an effort to better understand how inhaled particles deposit in the respiratory region of the lung, we computed streamlines in various 3D moving-wall models of alveoli in the proximal region of the pulmonary acinus. We used a number of different techniques to define the model surface, prescribe adequate boundary conditions, and perform finite element numerical simulations. The resulting vector velocity fields were used to compute streamlines at various times within the breathing cycle. The resulting streamlines confirm the existence of regions of recirculating flow in the alveoli. Using 2D axisymmetric models, we have previously shown that recirculating flow in an expanding alveolus requires the existence of a saddle point near the proximal wall of the alveolus. The importance of the occurrence of a saddle point is that it is a necessary condition for chaotic, or convective, mixing. Convective mixing has been shown to enhance the rate at which particles deposit in the lung. The current calculations offer more evidence of the existence of convective mixing in the lung. In future studies, the 3D moving-wall model will be used to compute particle deposition in the respiratory region of the lung. Although the techniques used in this study were employed to study alveolar flow, the same methods can be used to investigate a variety of fluid flow systems.

Keywords: CFD analysis, alveoli, streamlines calculation, finite element method

Acknowledgement: The research has been carried out with the support of the Ministry of Education, Science and Technological Development, Republic of Serbia with project OI174028.

T.3.1.2 – ***Investigation on Effect of Pulsation Condition Involved in Recanalization of Coil Embolized Aneurysms*** - Takumi Ishii[1,2*], Hiroyuki Takao[1,2,3], Soichiro Fujimura[1,2], Yuya Uchiyama [1,2], Hiroshi Ono[1,2], Takuma Okudaira[1,2], Toshihiro Ishibashi[3], Katharina Otani[3,4], Koji Fukudome[5], Yuichi Murayama[3], Makoto Yamamoto[5]

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Abstract:

Although a prediction of aneurysmal recanalization has been attempted using CFD (Computational Fluid Dynamics), the effect of pulsation has not been clearly investigated. In this study, the difference in the prediction ability of recanalization models with and without considering pulsation was investigated. We identified 30 middle cerebral artery (MCA) aneurysms (7 recanalized, 23 stable) and 42 internal carotid artery (ICA) aneurysms (8 recanalized, 34 stable). The coil shapes were reproduced using a virtual coiling technique. CFD simulations were performed under non-pulsatile (steady) and pulsatile (unsteady) flow condition. We performed multivariate logistic regression analysis to develop recanalization models under steady and unsteady flow conditions and compared their sensitivity, specificity, and area under the curve (AUC). As a result, for MCA cases, the model under steady simulation included only the predictor of inflow area on the neck surface before and after coil embolization (sensitivity 1.00, specificity 0.57, AUC 0.80). In contrast, the model under unsteady simulation included both the inflow area and inflow velocity entering the aneurysmal sac (sensitivity 0.86, specificity 0.91, AUC 0.93). On the other hand, for ICA cases, both the steady and unsteady simulations gave models that included elevated pressure region on the neck surface and coil packing density (steady: sensitivity 0.88, specificity 0.76, AUC 0.83; unsteady: sensitivity 0.88, specificity 0.76, AUC 0.84). In conclusion, we obtained different statistical measures of the performance for with and without considering pulsation only in MCA cases. Unsteady flow condition can improve the prediction ability of recanalization models.

Keywords: Coil embolization, Recanalization, CFD, Boundary condition

T.3.1.3 – *Different hemodynamic metrics induce growth and remodeling of patient-specific ascending thoracic aortas* - S. Jamaleddin Mousavi[1*], Raja Jayendiran[1], Solmaz Farzaneh[1], Stéphane Avril[1]

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Abstract:

Growth and remodeling (G&R) are fundamental mechanobiological processes in normal tissue development and in various pathological conditions. It is suggested that G&R in tissues may be mediated by mechanical stresses to maintain the homeostatic state whilst a failure of reaching homeostasis may result in pathologies. For example, cardiac hypertrophy and normal cardiac growth develop in response to increased hemodynamic loading and altered systolic and diastolic wall stresses. In addition, it is proved that relative residence time (RRT) along with wall shear stress (WSS) can also associate to arterial wall G&R by trigger of wall elastin degradation. This adaptation ability of soft tissues is related to the existence of a mechanical homeostasis across multiple length and time scales in the vasculature. At the tissue scale, this manifests through continuous mass changes of the components of the extracellular matrix (ECM) such as collagen, elastin and

proteoglycans. The problems can become extremely challenging in the case of ascending thoracic aortic aneurysms (ATAA) evolution due to the simulateneous and region specific evolution of geometry, material properties, and hemodynamic loads. Therefore, in this work, we fully coupled a continuum finite-element CMT-based G&R model of arterial wall with CFD analyses to study the effects of the different hemodynamic metrics, such as helicity, WSS, time averaged WSS (TAWSS), oscillatory shear index (OSI) or RRT, on aortic G\&R. Two novelties can be highlighted in our work: application of CMT-based models to patient-specific geometries and integration of layer-specific properties (media and adventitia). The model is applied on 8 patients including 3 healthy patients and 5 suffering from unbounded dilatation of the ATAA.

Keywords: Ascending Thoracic Aortic Aneurysm, CFD, relative residence time, Growth and Remodeling

Acknowledgement: The authors are grateful to the European Research Council for grant ERC-2014-CoG BIOLOCHANICS.

T.3.1.4 – *Numerical simulations of blood flow patterns in the patient-specific left ventricle model with dynamic valves* - Fei Xu[1*], Sasa Kenjeres[1]

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Abstract:

The left ventricle is one of the chambers in the human heart. It is connected with the aorta by the aortic valve and the left atrium by the mitral valve. The left ventricle is responsible for pumping the blood through the aortic valve into aorta and then to the whole body. Hence it is the most important heart chamber. Besides, in the left ventricle the blood flow has the most complex pattern and pressure variation during cardiac cycles.
With series of images from measurements (MRI and PIV) and the RBF (radial basis functions) method, a cost-effective image (CT and/or MRI) based numerical simulation technique has been developed for the blood flow simulation in realistic patient-specific ventricles.
The numerically calculated velocity components and the vortex structure have been compared with available PIV as well as MRI measurements at characteristic time instants during a cardiac cycle. Obtained results are in a good agreement with experimental data. Furthermore, the vorticity as well as the velocity components have been compared between different simulation approaches (i.e. Direct Numerical, Large Eddy and Detached Eddy Simulation; DNS, LES and DES respectively) at specific locations. Additionally, the energy spectra of the velocity time series at characteristic monitoring locations within the left ventricle have been analyzed to identify the turbulent/laminar regions in the flow field.
In conclusion, the obtained results provided detailed insights into energetics of the instantaneous flow features of the left ventricle model. The presented method can be applied for future analysis with the patient-specific geometries.

Keywords: Computational fluid dynamics (CFD), left ventricle, vortex structure, Direct Numerical Simulation (DNS), Large Eddy Simulation (LES), Detached Eddy Simulation (DES)

T.3.1.5 – *Effect of hip implant surface modification on shear stress distribution* - Aleksandra Vulović[1,2,3*], Nenad Filipović[1,2,3]

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Abstract:

Hip replacement surgery is one of the most common procedures in the world. Annually, more than 1 million hip replacement surgeries are performed worldwide, while it is anticipated that this number will double in the next decade. After the damaged or worn out hip joint is replaced with the artificial hip joint, bone healing process starts. In order to ensure the long and proper function of the artificial joint, the connection between the bone and the inserted implant should be as strong as possible. However, if the established connection is not strong enough, the implant starts to loosen. Experimental studies have indicated that implants with a rough surface form a stronger connection with a bone. The goal of this paper was to numerically analyze different spherical shapes on the implant surface. The results obtained numerically are considered to be a very helpful addition to the experimental studies. Numerical analysis of the implant surfaces has been performed using the Finite Element Method. The obtained results include distribution of the shear stress on the implant surface. This type of stress is important for this study because in order to promote bone ingrowth, the shear stress should be minimized. Our study considered the interaction between cortical bone and implant with rough surface. Material properties and boundary conditions were adapted from literature.

Keywords: hip implant, implant surface, finite element analysis

Acknowledgement: This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No. 760921 - PANBioRA. This article reflects only the author's view. The Commission is not responsible for any use that may be made of the information it contains. The research has also been carried out with the support of the Ministry of Education, Science and Technological Development, Republic of Serbia with projects III41007 and OI174028.

Session T.3.2: 14:00-16:00

InSilc Workshop

T.3.2.1 – ***In-silico module to model transient three-dimensional drug delivery in subject-specific geometries of stented arteries: physics-based simulation of controlled release and tissue retention*** - Farhad Rikhtegar Nezami[1*], Abraham R. Tzafriri[2], Elazer R. Edelman[1,3]

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Abstract:

Drug-eluting stents (DES) are the mainstay therapy for obstructive arterial disease, yet further innovation is hampered by cost and lack of experimental techniques. In silico models offer flexible and readily available tools to address these issues, enabling determination of the spatio-temporal variation of bound/unbound drug concentration in the arterial wall not achievable through animal models or human trials.

We developed and verified a drug-delivery module to study pharmacokinetics and pharmacodynamics in emerging endovascular implants. To extend the realism of existing computational models we here consider controlled transient release of drug from the coating (including the burst phase), flow-mediated convection of drug, realistic diffusion inside the porous tissue, and binding process (including different receptors and their saturation). Sirolimus was assumed to be loaded on abluminal face of emerging bioresorbable scaffolds and released in a porous artery via plasma infiltration and diffusion. Binding and unbinding to extracellular matrix cells (ECM) and specific receptors (SR) were also included. An innovative reduced-order analytical model of pharmacokinetics was developed to approximate the realistic release profile and validated by experimental measurements conducted by device manufacturers. We confined the enormously costly simulation of drug distribution via an innovative set-up that solves the transient transport equations only during the early distribution phase, while only solving for the equilibrium distribution under a prescribed unit flux during the retention phase - and accounting for time dependence via multiplication by the time instantaneous value of the flux. Our results highlight that physico-chemical characteristics of depleted drug play a critical role in drug dynamics. This module is an invaluable tool to design and develop emerging devices and contribute to regulatory oversight and evaluation of clinical performance.

Keywords: Drug delivery, diffusion, binding, controlled release, in silico modeling

Acknowledgement: We acknowledge European Union's Horizon 2020 research and innovation program (grant agreement no 777119) and NIH R01 909.

T.3.2.2 – ***The Impact of Various Bioresorbable Scaffold Designs on Hemodynamics*** - Imane Tarrahi[1], Monika Colombo[3], Eline M.J. Hartman[1], Maria Natalia Tovar Forero[2], Ryo Torii[5]; Claudio Chiastra[3,4], Joost Daemen[2]; Frank J.H. Gijsen[1]

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Abstract:

Bioresorbable scaffold (BRS) regions exposed to flow-recirculation, low time-averaged wall shear stress (TAWSS) and high oscillatory shear index (OSI), develop increased neo-intima tissue. We investigated hemodynamic features in 4 different BRSs.
Fantom (strut height (SH) = 125μm), Fantom Encore (SH = 98μm), Absorb (SH = 157μm) and Magmaris (SH = 150μm) BRSs were deployed in phantom tubes and imaged with microCT. Both 2D and 3D geometrical scaffold models were reconstructed. Computational fluid dynamics (CFD) was performed to compute TAWSS and OSI.
Thicker struts had larger recirculation zones and lower TAWSS in 2D. Absorb had the largest recirculation zone and lowest TAWSS (240μm and -0.18 Pa), followed by Magmaris (170μm and -0.15 Pa), Fantom (140μm and -0.14 Pa) and Fantom Encore (100μm and -0.13 Pa). Besides strut size, stent design played a dominant role in 3D. The highest percentage area adverse TAWSS (<0.5 Pa) and OSI (>0.2) were found for Fantom (56% and 30%) and Absorb (53% and 33%), followed by Fantom Encore (30% and 25%). Magmaris had the smallest areas (25% and 20%), due to a small footprint and rounded struts.
Due to stent design both Fantom Encore and Magmaris showed smaller TAWSS and OSI than Fantom and Absorb. This study quantifies which scaffold features are most important to reduce long-term restenosis.

Keywords: bioresorbable scaffolds, stent design, wall shear stress, computational fluid dynamics

Acknowledgement: This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 777119.

T.3.2.3 – *Myocardial perfusion modelling for predicting the clinical significance of side-branch occlusions in virtual in-silico trials* - Toni Lassila[1*], Ali Sarrami-Foroushani[1], Nishant Ravikumar[1], Andres Diaz-Pinto[1], Alejandro F. Frangi[1]

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Abstract:

This work has been developed in the framework of the European project InSilc, that aims to develop an in-silico clinical trial platform for designing, developing and assessing drug-eluting bioresorbable vascular scaffold (BVS). Coronary artery bifurcation lesions are frequent and should form part of the virtual study cohort in in-silico trials for new endovascular devices. A serious complication arising in roughly 10% of patients with bifurcation lesions is side-branch occlusion, which may be exacerbated when using bioresorbable vascular scaffolds with thicker struts than found in standard metallic stents. Comprehensive modelling tools are required to predict the significance of side-branch occlusion. We detail the construction of a patient-specific computational model for: i) the main coronary artery branches from coronary CT angiograms, ii) the simulation of coronary flow in the main and side-branches using lumped-parameter models, and iii) a 3-D myocardial perfusion model based on treating perfusion as a porous media flow problem. By coupling the coronary flow model to the Myocardial Perfusion Module, we are able to provide quantitative estimates of myocardial perfusion. Within the InSilc platform, the objective is to predict post-operative summed difference perfusion scores, which have been shown to predict increased risk for major adverse cardiac events (MACE) in clinical trials, and can be used as a surrogate end-point for MACE.

Keywords: In-silico clinical trial, computational fluid dynamics, myocardial perfusion

Acknowledgement: This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 777119.

T.3.2.4 – *In-silico clinical trial: development of computational models predicting degradation of bioresorbable stents in patient specific coronary arteries* - Katarzyna Polak-Kraśna[1], Constantino Fiuza[1], William Ronan[1], Ted Vaughan[1*]

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Abstract:

This study is part of a multiphysics modelling framework developed within European project In Silico Clinical Trials for the Design and Evaluation of Bioabsorbable Vascular Scaffolds (InSilc). The framework aims at developing a platform for computational clinical trials for evaluation and design of existing and new vascular stents for coronary arteries. Using multiscale and multiphysics approach, the framework predicts stent behaviour during deployment in patient-specific image-reconstructed artery in a short term and in a long term during stent life and degradation. The platform consists of modules aiming at predicting stent deployment behaviour, fluid dynamics, drug-delivery, and degradation. This work's focus is bioresorbable stent degradation model development.
Bioresorbable stents offer distinct advantages over permanent stents including reduced risk of thrombosis and in-stent restenosis. One of the major challenges in the implementation of bioresorbable medical implants is having reliable predictions of the physical and mechanical changes that take place during degradation of resorbable materials and implants. Reliable predictions of device behaviour requires both (i) detailed experimental characterisation of physical and mechanical behaviour and (ii) sophisticated computational models that can account for underlying mechanisms of material degradation to provide robust predictions of behaviour throughout the lifetime of the device.
In this study we developed a highly flexible predictive framework with the capacity to predict the behaviour of a wide-range of polymer-based materials/devices undergoing degradation. We performed an accelerated degradation study on medical grade PLLA and bioresorbable stents. The polymer degradation models were shown to capture observed experimental behaviour of PLLA material. The material models were implemented on a device level within the InSilc platform and compared against device-level experimental data. Our results clearly highlight the importance of understanding the degradation behaviour and accurate description of material models for stent modelling applications.

Keywords: In-silico clinical trial, finite element models, bioresorbable vascular scaffold, coronary artery, polymer degradation

Acknowledgement: This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 777119.

T.3.2.5 – *In-silico clinical trial: development of computational models for virtual deployment of vascular scaffolds in patient specific coronary arteries* - Lorenza Petrini[1], Luca Antonini[2], Lorenzo Mandelli[2], Francesco Migliavacca[2], Gabriele Dubini[2], Giancarlo Pennati[2*]

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Abstract:

This work has been developed in the framework of the European project InSilc, that aims to develop an in-silico clinical trial platform for designing, developing and assessing drug-eluting bioresorbable vascular scaffold (BVS). The platform is based on multiphysic and multiscale computational models to investigate the behavior of drug-eluting BVSs and to predict their interaction with a stenotic coronary artery, in the short and medium/long term. In particular, the research developed at the Politecnico di Milano is devoted to accurately describe the stent deployment in patient-specific image-reconstructed vessels and predict short term clinical endpoints. The developed approach includes a preliminary (offline) step where the finite-element (FE) models of various delivery systems, consisting in a specific stent crimped onto the corresponding folded balloon, are generated, calibrated and experimentally validated; the second step is carried out using the platform (online) and deals with the simulation of the whole clinical procedure, coupling the FE models previously generated to a virtual patient-specific coronary artery. All the treatment procedures are described as a proper combination of a few in silico steps (positioning, inflation, deployment). The total number of steps ranges between two (simple angioplasty) to about 20 (treatment of complex coronary bifurcation). The numerical strategies adopted in order to obtain a compromise between realism and accuracy of results, numerical robustness and computational effort will be described during the presentation, as well as the experimental experiences designed for validating the computational results.

Keywords: In-silico clinical trial, finite element models, drug-eluting bioresorbable vascular scaffold, coronary artery

Acknowledgement: This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 777119.

T.3.2.6 – *The development of a cloud-based in-silico clinical trial platform* - Peter Mortier[1*], Reinjan Ergo[1], Dries Desmet[1], Nic Debusschere[1], Bjorn Kristinsson[1]

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Abstract:

This work has been developed in the framework of the European project InSilc, that aims to develop an in-silico clinical trial platform for designing, developing and assessing drug-eluting bioresorbable vascular scaffold (BVS). FEops is responsible for the development of the cloud platform, that links all the different technical modules and that allows end-users to set-up, monitor and assess in-silico clinical trials. More specifically, users are able to define a virtual population that will be studied in a 'virtual clinical trial' by filtering and selecting a subgroup of the full database of patient models that is available. Next, they are able to set up and launch an experiment, by selecting one or more modules that will be applied to this virtual population. A workflow manager has been implemented that handles the tasks related to this experiment. Those tasks can involve manual processing or could be fully automated. Once all tasks related the specific experiment are completed, the user is able to access and analyse all simulation results, for example by using the online 3D viewer that has been developed. Proven technologies are used to develop this platform (Django, vue.js, three.js, Heroku and Amazon Web Services) in combination with state-of-art development techniques.

Keywords: In-silico clinical trial, cloud platform

Acknowledgement: This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 777119" programme under grant

agreement No 777119.

T.3.2.7 – *3d Reconstruction tool of coronary arteries, plaque morphology and "virtual" population* - Karanasiou, G.S.[1], Sakelarios A. I[1], Kyriakidis S.[1], Pleouras D.[1], Fotiadis, D.I.[1,2]

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Abstract:

Atherosclerotic plaque growth is a chronic disease which contributes to high mortality rates in Europe and worldwide. To treat atherosclerosis, bioresorbable vascular scaffolds (BVSs) are among the most common treatment options. InSilc is an in silico platform that allows the utilisation of multiscale models for informing the ends users on the BVS performance. In order this to be achieved, virtual patients are provided with virtual stents and the results are evaluated in terms of the models expected outputs. For the creation of the virtual population, among other, the following tools are employed: (i) the 3D reconstruction and plaque characterisation tool, (ii) a multi-level numerical model of atherosclerosis.

The 3D reconstruction tool allows the 3D reconstruction of the arterial tree (inner, outer wall) and the plaque components (calcified and non-calcified). Depending on the imaging modality (CT, IVUS, IVUS-VH, OCT/ fused with angiography) different algorithms and methods are employed. The output of the 3D reconstruction and plaque characterisation tool is then used by the plaque growth model to create 3D patient specific geometries with diverse types of atherosclerosis. Further to this, the inclusion of hypertension and diabetes in the plaque growth models enables the enrichment of the virtual population database with arterial anatomies with diabetes, hypertension or even their combination.

In brief, diabetes main effect is the increase of the average blood glucose concentration, which in turn results in the decrease of the endothelial nitric oxide production rate by affecting several biologic pathways. Nitric oxide is a signaling molecule regulating the endothelial flow rates, and any abnormal alteration leads to endothelial dysfunction, the major culprit of atherosclerosis. The atherosclerotic model with the diabetes considers the modeling of blood flow in lumen and of species transport and reactions in the arterial wall. The considered factors include: (i) LDL, (ii) HDL, (iii) oxidized LDL, (iv) monocytes, (v) macrophages, (vi) cytokines, (vii) smooth muscle cells (contractile & synthetic), and (viii) collagen. As far as hypertension is concerned, it affects the LDL, HDL and plasma fluxes through the endothelium, which are also parameters of the plaque growth model.

Currently, the models of plaque growth which incorporate comorbidities are in the process of validation. Specifically, data from 60 patients have been used for the validation of the plaque growth model with hypertension, while the plaque growth model with diabetes has been so far validated with data from 7 patients.

Keywords: In-silico clinical trial, 3d Reconstruction

Acknowledgement: This work is supported by the InSilc project that has received funding from the European Union's Horizon 2020 research and innovation program under grant agreement No 777119.

T.3.2.8 – *The InSilc Project and the regulatory roadmap* - Karanasiou, G.S.[1], Fotiadis, D.I.[2]

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Information Systems, University of Ioannina, GR 45110, Ioannina, Greece.

Abstract:

Atherosclerosis, the major disease process of Coronary Artery Disease, is a result of the growth of atherosclerotic plaques inside the coronary arteries. Currently, one of the available treatment approaches concerns the implantation of Bioresorbable Vascular Scaffolds (BVS). BVS provide adequate mechanical support, drug delivery and complete resorption. InSilc is an in silico clinical trial platform that simulates the short and medium/long term BVS performance through the utilisation of biological and biomedical knowledge and integration with advanced modelling approaches. To accomplish this, different module are developed: (i) Mechanical Module, for reproducing the standard mechanical tests performed by the Stent Industry, (ii) 3D Reconstruction and plaque characterisation tool, for creating the 3D reconstruction of the arterial tree, (iii) Deployment Module, for simulating BVS mechanical performance after expansion and interaction with arterial wall, (iv) Fluid Dynamics Module, for providing flow dynamics variables in the micro/macro environment, (v) Myocardial perfusion Module, for capturing ischemia and revascularization in the myocardium, (vi) Degradation Module, for predicting degradation phenomena.
InSilc platform enables the different users: (i) to test the BVS using state-of-the-art in silico models and resources (user: Stent Industry), (ii) to design more effective clinical studies (user: Clinical Research Organisation) design for achieving statistically sound study endpoints with the minimum number of patients. (iii) to evaluate the BVS performance prior implantation and select the best scaffold/process (user: Interventional cardiologist), (iv) to test different models for research only purposes and through the platform available data and modules register a model/computational resource as a "under validation" model (user: Researcher). In parallel to the research and technological objectives, the facilitation of the definition of a regulatory framework towards the successful application of InSilc complementary to the real clinical trials is of utmost importance. Towards this direction, well design steps and processes are followed so as to address the regulatory and ethical issues and follow the new emerging standards.

Keywords: In-silico clinical trial, roadmap

Acknowledgement: This work is supported by the InSilc project that has received funding from the European Union’s Horizon 2020 research and innovation program under grant agreement No 777119.

Session T.4: 17:00-18:45

Mini-Symposia 2: APPLIED COMPUTATIONAL CHEMISTRY (part I)

T.4.1 – *Role of atomic and molecular non-observable properties in the understanding and description of real observables of the chemical systems* - Ivan Juranić

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Abstract:

Chemical species can be characterized by various observable features: mass, enthalpy of formation, charge, dipole moment, magnetic susceptibility, etc. On the other hand, the understanding of chemical and physical behavior is usually based on specific non-observable features: electronegativity, partial atomic charges, atomic and molecular orbitals, etc. Non-observable features have no physical unit and are not amenable to experimental measurements. The values ascribed to them are strongly dependent on the definition(s). For example, we use various electronegativity scales: Pauling's, Mulliken's, Alfred-Rochov's, and other. They are based on different theoretical assumptions, and produce (significantly) different numerical values. On the other hand, all scales follow similar general trend, indicating that the values reflect some intrinsic chemical property.
Situation with partial charges is even more complicated, because more than 30 different scales are known, and can be divided in four classes, based on method for defining them. Partial atomic charges were tested as a reliable method for the calculation of the observable properties of molecules.
Density functional theory is quantum-chemical method for accurate calculation of electron density distribution. It relies on basic idea of quantum chemistry that all molecular properties stem from the distribution of electron density in molecule. It justifies the use of partial atomic charges in molecule reflecting distribution of electron density. Specificity of DFT method is inclusion of electron correlation in the calculation of electron distribution in molecule. Besides DFT, many semiempirical methods implicitly include electron correlation in the calculations of electron density. They offer quick computation methodology for calculation of partial atomic charges. We shall present the results obtained for assessment of pH values for acids and bases.

Keywords: Non-observable properties, partial atomic charges, characterization of molecules

T.4.2 – *The interaction of protonated octopamine and norepinephrine whit β1-adrenergic receptor: Molecular docking and dynamical simulation* - Zoran Marković[1,2], Žiko Milanović[2*], Dušan Dimić[3], Jasmina Dimitrić Marković[3], Marijana Stanojević-Pirković[4]

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Abstract:

In this study, were examined the interactions between the protonated neurotransmitters: octopamine (4-(2-amino-1-hydroxyethyl)phenol) and norepinephrine (4-[(1R)-2-amino-1-hydroxyethyl]benzene-1,2-diol) with the (β1) Beta-1 adrenergic receptor (β1AR) belonging to the G-protein coupled receptor group. The investigation was carried out on physiological pH=7.4. It was estimated that both compounds exist in protonated form in water at physiological pH. The optimization of protonated structures of octopamine and norepinephrine- was performed in the Gaussian09 program package at B3LYP-D3BJ/6–311++G(d,p) level of teory without any geometrical constraints. The molecular docking method was used to predict the best binding mode of the investigated compounds with the β1AR receptor. It was found that both protonated neurotransmitters established similar interactions with amino acid residues of receptor, such as: salt bridges, conventional hydrogen bonds, π-σ and T-shaped π-π interactions. The most stable structures obtained by molecular docking simulation, were used as the starting structures for molecular dynamic (MD) simulation whit total time of 10ns. The results obtained by using molecular dynamics are in good agreement with those obtained by using molecular docking. The Root Mean Square Deviation (RMSD) values of β1AR and β1AR–octopamine (β1AR-O) complex, as well as of β1AR and β1AR–norepinephrine (β1AR-N) complex achieved equilibration after 4000 ps. Based on analysis of Root Mean Square Fluctuation (RMSF) values, it was found that the amino acids at the binding sites remained rigid during the simulation of the investigated protein β1AR and the corresponding β1AR-ligand complexes.

Keywords: molecular docking, molecular dynamic, neurotransmitters, octopamine, norepinephrine

Acknowledgement: The authors are grateful to the Ministry of Education, Science and Technological Development of the Republic of Serbia (Projects Nos. OI172015 and OI172040) for financial support.

T.4.3 – ***The PCET-RRC mechanism in the reaction of ferulic acid with •OH free radicals*** - Ana Amić[1*], Dejan Milenković[2]

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Abstract:

In this report we investigated ability of ferulic acid (FA) to scavenge •OH free radicals via here proposed Proton Coupled Electron Transfer□Radical-Radical Coupling (PCET-RRC) mechanism. FA is a notable constituent of a diet rich in fruits and vegetables and an abundant colon catabolite of various (poly)phenolic compounds. As highly bioavailable it may appear in systemic circulation in sufficient concentrations to efficiently scavenge excess of intracellular free radical species and thus may help in suppressing oxidative stress conditions. Thermodynamic and kinetic of •OH free radical scavenging by FA were studied at M06-2X/6-311++G(d,p) level of theory in gas-phase using Gaussian 09 program package. Features of the SOMO orbital of the ferulic acid phenoxyl group□•OH free radical transition state, and QTAIM charge of the transferring H atom (qH), indicate PCET mechanism as operative pathway in scavenging of single •OH free radical specie. In addition, ability of resulting ferulic acid phenoxyl radical to scavenge another •OH free radical via RRC was considered. RRC occurs on two potential energy surfaces, the phenomenon known as two-state reactivity. RRC begins with separate reactants in doublet state which forms reactant complex in triplet state, and via spin crossing point terminates in singlet state product. For both PCET and RRC pathways reaction rates were evaluated using TheRate program. It should be noted that the final product of proposed PCET-RCC mechanism is 5-hydroxyferulic acid. It is already known that catechol moiety of this acid is able to scavenge another two •OH free radicals via formal HAT mechanism. It hich significantly contributes to overall antioxidant potency of FA.

Keywords: ferulic acid, hydroxyl radical, PCET, radical-radical coupling, DFT

T.4.4 – *A combined experimental and theoretical study on vibrational spectra of 3-(1-(m-toluidino)ethylidene)-chroman-2,4-dione* - Zoran Marković[1,2], Dejan Milenković[2*], Edina Avdović[3] , Srećko Trifunović[3], Jelena Đorović[2]

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Abstract:

The vibrational spectroscopic analysis of the new synthetized coumarine-derived ligand 3-(1-(m-toluidino)ethylidene)-chroman-2,4-dione was carried out using infrared (IR) spectroscopy, in the range 4000 to 400 cm-1, respectively. A combined theoretical and experimental study on vibrational spectra of investigated molecule was employed. The geometry of examined compound, optimized in gas-phase, was used for calculation of the IR frequencies. Assignments of the experimentally obtained normal vibrational modes were done by the density functional calculation using the B3LYP-D3BJ functional in combination with the 6-311+G(d,p) basis set implemented in the Gaussian 09 package. Assignation of theoretical peaks was done with FCART version 7.0 Program Package, based on the Potential Energy Distribution Analysis (PED). The most intesive bands in the IR spectrum appering in high frequency region (4000–2000 cm-1) includes different modes of stretching N–H and C–H vibrations. Low frequency region (1800–500 cm-1) involves modes of ν(C=O), ν(C-C), ν(C–H (methyl)), and δ(HCH) vibrations. The bands between 1500 and 1000 cm-1 characterized follow modes of ν(C–C (ring), C–O, NC) and δ(HCH, HCC, HCC (ring), HCO and HOC)) vibrations. Spectral assignment based on the best fit comparison between experimentally and theoretically calculated IR spectra match quite well, with scaling factor of 0.9670 and coefficient correlation (R) of 0.9998. This correlation point out that B3LYP-D3BJ provide very good agreement between the experimental and simulated vibrational spectra, suggesting correct mode assignments. The applicability of selected functional (B3LYP-D3BJ) was proven for this type of molecules.

Keywords: Coumarine-derived ligand, IR spectra, DFT, FCART, PED

Acknowledgement: The authors are grateful to the Ministry of Education, Science and Technological Development of the Republic of Serbia (Projects Nos. OI172015, OI172016, and OI174028) for financial support.

T.4.5 – *An experimental and theoretical study of the reactivity of selected catecholamines and their precursors towards ascorbyl radical* - Dušan Dimić[1], Đura Nakarada[1], Miloš Mojović[1], Zoran Marković[2], Jasmina Dimitrić-Marković[1*]

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Abstract:

Ascorbyl radical is a product of the antiradical activity of ascorbic acid, which acts as an antioxidant or prooxidant in reaction with reactive oxygen species and in the presence of different enzymes and catalysts. Because of its unique EPR spectrum, ascorbyl radical is used as a marker of oxidative stress. In this contribution, the reactivities of norepinephrine, octopamine, 3,4-dihydroxyphenylacetic acid (DOPAC), homovanillic acid (HVA) and vanillylmandelic acid (VMA) towards ascorbyl radical were investigated experimentally by EPR spectroscopy. The measured reduction was 35 % for norepinephrine, 34% for DOPAC, 27 % for VMA and HVA, and 23 % for octopamine. The reactivity is correlated with the structural parameters and the importance of catechol moiety was proven. The most probable mechanism of antiradical activity was determined based on the thermodynamic parameters, calculated at M06-2X/6-311++G(d,p) level of theory. It was shown that in polar and non-polar media, the dominant mechanism is Hydrogen Atom Transfer (HAT). The other two investigated mechanisms, namely Single Electron Transfer followed by Proton Transfer (SET-PT) and Sequential Proton Loss - Electron Transfer (SPLET) have high values of thermodynamic parameters for the first step. Good correlation between experimental and theoretical parameters was achieved. This result proves that ascorbyl radical can possibly react with important biological molecules, like neurotransmitters and their metabolites, and further reduce them to respective radicals.

Keywords: EPR, ascorbyl radical, catecholamines, antiradical activity (five keywords maximum)

Acknowledgement: The Authors acknowledge the Ministry of Education, Science and Technological Development of the Republic of Serbia for the financial support through Grants no. 172040, 172015 and 41005.

T.4.6 – *Graph theory based model for the enthalpy of formation of benzenoid hydrocarbons* -
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Abstract:

Dependence of the enthalpy of formation (ΔHf) of catacondensed benzenoid hydrocarbons (CBHs) on structural features was examined. To elucidate influence of the molecular size (expressed through the number of hexagons, h), number of bay regions (expressed through the number of bays (B), number of coves (C), and the number of fjords (F)), and the molecular branching (expressed through the number of the A3-type hexagons, hA3) on ΔHf, a simple mathematical model was developed. ΔHf values obtained from the PM7 calculations for 1221 randomly chosen CBHs were used as learning set for constructing the model. Multiple linear regression was achieved by using the corresponding spectral moments up to M12. Fortunately, the dependence of these spectral moments on molecular structure of CBHs has already been determined. Agreement between the experimental and calculated ΔHf is satisfactory, with an average relative error of 4.4 %.
It was found that the major part of ΔHf is determined by h, where ΔHf increases with increasing h. Subtle variations in the value of ΔHf is explained by other structural features of a molecule. ΔHf decreases with increasing B, C, F and hA3. Because the effects of bay regions and A3-type hexagons are being overshadowed, two series of isomers with h = 20 were constructed to determine the influence of hA3 on ΔHf. It turned out that the molecules having molecular branching, compared to unbranched molecules, possess larger ΔHf values. This is the first study that connects ΔHf of CBHs with structural features that can be straightforwardly obtained.

Keywords: polycyclic aromatic compounds, thermochemical quantity, mathematical model, structural features

Acknowledgement: The authors thank the support of the Ministry of Education, Science and

Technological Development of the Republic of Serbia (Project Nos. 172016 and 174033).

T.4.7 – *Antioxidative properties of usnic acid and its interaction with tyrosyl-DNK phosphodiesterase 1* - Zoran Marković[1,2], Jelena Đorović[2*], Nedeljko Manojlović[3], Marijana Stanojević-Pirković[3], Svetlana Jeremić[1]

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Abstract:

In plant kingdom lichen phenolics represent unique substances, which possess numerous applications. One of the most explored compound from this group is usnic acid, which is isolated from Usnea or Ramalina species of lichens. Nowadays, usnic acid is commercially offered, and as a pure compound it has been articulated into creams, toothpaste, mouthwash, deodorants, antibiotic ointments and sunscreen products. This study aimed to investigate antioxidative properties of usnic acid, as well as its interaction with tyrosyl-DNK phosphodiesterase 1(TDP1). Antioxidative properties are estimated on the basis of the Density Functional Theory (DFT) calculations. For this propose, full optimization of parent molecule of usnic acid and corresponding radical cation, radicals and anions was done at M05-2X/6-311++G(d,p) level of theory. The CPCM solvation model was applied to approximate the influence of water. Obtained results indicate single electron transfer followed by the proton transfer as thermodynamically most unfavorable mechanism of antioxidant action. The lowest values were achieved for proton affinity, and that pointed out sequential proton loss electron transfer mechanism as dominant antioxidative mechanism. The second part of this study is the examination of the interaction between usnic acid and TDP1, which is an enzyme responsible for repairing the protein-DNA bond in the cells. In order to perform molecular docking simulation AutoDock 4.0 software was used. Analysis of obtained data specifies interactions with Asn162, Leu168, Gly182, Tyr167 and Ser485 as the most significant. Further, the molecular dynamic simulations was performed using NAMD software. It is noticed that similar interactions are obtained.

Keywords: usnic acid, TDP1, molecular docking

Acknowledgement: This work was partially supported by the Ministry of Science and Technological Development of the Republic of Serbia (Grants no. 174028 and 172015).

Session F.1: 09:00-11:00

Biomechanics (part II)

F.1.1 – ***Hemodynamic Investigation on Growth of Unruptured Cerebral Aneurysms During Follow-up Term*** - Takuma Okudaira[1,2], Hiroyuki Takao[1,2,3], Soichiro Fujimura[1,2*], Yuya Uchiyama[1,2], Hiroshi Ono[1,2], Takumi Ishii[1,2], Toshihiro Ishibashi[3], Katharina Otani[3,4], Koji Fukudome[5], Yuichi Murayama[3], Makoto Yamamoto[5]

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Abstract:

A cerebral aneurysm is a cerebrovascular disease in which weakened areas of cerebral arteries become dilated. When a cerebral aneurysm ruptures, it causes subarachnoid hemorrhage. The rupture risk for cerebral aneurysms is considered to increase for larger aneurysms, therefore, surgical treatments should be prioritized on aneurysms that will grow large. If it were possible to predict whether an aneurysm will grow or not, it would greatly aid treatment planning for patients with cerebral aneurysms. In this study, we used 15 hemodynamic parameters estimated from computational fluid dynamics (CFD) and investigated parameters closely related to aneurysm growth. Patient-specific geometries of aneurysms located on the middle cerebral artery (MCA: 16 growth, 15 non-growth cases) and the internal carotid artery (ICA: 10 growth, 21 non-growth cases) were reconstructed from computed tomography angiography images. By defining growth rate based on the volume increase rate before and after follow-up term, the cases were classified into growth and non-growth cases. A CFD simulation under steady flow conditions was performed on all cases and the hemodynamic parameters were compared statistically between the growth and non-growth groups. For MCA cases, the growth cases had statistically significant higher pressure values ($p=0.01$). For ICA cases, the non-growth cases had significantly lower pressure values ($p=0.02$) and higher compressive strengths ($p=0.02$) on the aneurysm walls. The present results from CFD analysis reveal that pressure and compressive strengths acting on the aneurysm walls are related to aneurysm growth. With further research, prediction of aneurysm growth may become possible, optimizing aneurysm treatment planning.

Keywords: Cerebral aneurysm, Aneurysm growth, Computational fluid dynamics, Hemodynamics

F.1.2 – ***Numerical analysis and virtual surgery for acute aortic dissection*** - Igor Saveljic[1,2,*], Lazar Velicki[3], Dalibor Nikolic[2], Nenad Filipovic[1]

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Abstract:

The aorta, as the largest blood vessel in the man, is continuously exposed to high blood pressure and shear forces. Aortic dissection is a very serious condition which leads to cleavage of the inner layer of the aortic wall, and further fragmentation. The mortality rate in untreated dissection was 75% in the first two weeks. Hemodynamic properties of blood flow through the newly created false lumen, and its dominance over the true lumen, has a significant impact on the outcome of the surgery and the patient's life. The main method used in this paper is the finite element method (FEM). Pressure and wall shear stress distribution in nodes of finite elements are determined by specific points of the pulsatile blood flow. These results give a clear picture of the relationship of true and false lumen. Virtual operations, as well as numerical methods for solving fields of physical quantities obtained model, gives a clear picture how the operation affects the flow through the branches affected dissection. The patient used in this paper had an aortic dissection of type I according to DeBakey. Results are presented for the case before and after the virtual surgery.

Keywords: Aortic dissection, numerical simulation, virtual surgery

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F.1.3 – *Simulation and experimental validation of pulsatile flow in a compliant tube* - Jiří Jagoš[1*], Darina Jašíková[2], Michal Knotek[2], Jiří Burša[1,3]

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Abstract:

Interaction of a Newtonian liquid with a straight hyperelastic tube was simulated. Fluid and solid equations were solved separately – iterated within each time step to obtain an implicit solution. The solid phase solution was based on FEM while FVM was used for the liquid phase. Geometry, material properties and boundary conditions were set according to the validation experiment described below: Young modulus of 4 MPa, tube diameter and wall thickness 22,5 mm and 2,3 mm, respectively. The pressure was changing between 50kPa and 210 kPa, which induced radial displacements on the order of millimeters. The calculated distribution of velocities was validated by comparison with experimental results. In the experiment, flow in a Tygon tube was investigated; water was used as Newtonian liquid and its periodic pulsatile flow was generated using a membrane pump with a frequency of 1 Hz (according to human heart). The velocity distribution in several (deformed) cross sections was measured using Particle Image Velocimetry method and evaluated in 10 time steps over the pulse period. These velocity distributions and radial displacements were compared with the corresponding results of the computational model. After this validation other credible results can be obtained from numerical simulation, for example pressure or wall shear stress distributions along the inner surface of the tube. The model is intended for future application for Newtonian liquid with a higher viscosity (water glycerin solution mimicking the viscosity of blood under large shear strain

rates), as well as for non-Newtonian (Bingham) liquids (compounds of a Newtonian liquid with solid particles).

Keywords: Fluid-structure interaction, velocity distribution, viscosity, moving mesh domain, pulsatile flow

Acknowledgement: This work was supported by Czech Science Foundation project No. GA 17-19444S.

F.1.4 – *Advanced modelling approach of carotid artery atherosclerosis* - Smiljana Djorovic[1,2*], Igor Saveljic[1,2], Nenad Filipovic[1,2]

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Abstract:

With a fast progression of computational methods and medical imaging techniques, the advanced simulations of carotid arteries can be approached aiming to address different medical conditions and support the clinical practice. Within this context, the main purpose of this study was to computationally model the biological and mechanical processes related to the plaque initiation and progression, as well as to predict plaque regions and mechanisms which are prone to atherosclerosis development within the carotid artery.

We have focused on the patient-specific model and application of finite element analysis which enables investigation of the parameters associated with plaque development. The LDL transport in the lumen of the vessel and through its arterial tissue was coupled with Kedem-Katchalsky equations. Navier–Stokes equations, and continuity equation of incompressible fluid were used for 3D blood flow. Darcy`s Law was used to model mass transfer across the wall of the vessel. Convective diffusion reactive equations were used for modeling mass transfer in the wall. Partial differential equations were used for solving the inflammatory process.

After performed the 3D simulation of plaque progression, baseline and follow-up time periods were observed. The results have shown that sites with lower shear stress values were correlated with the sites of plaque accumulation and progression. This approach will be further improved and used for risk stratification models, by detecting the parameters of unstable and stable carotid plaques related to the risk of stroke, which is objective of our future studies.

Keywords: Carotid artery, plaque progression, finite element analysis

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F.1.5 – *Combining numerical methods with parametric optimization of stent design* - Dalibor Nikolic[2*], Igor Saveljic[1,2], Marija Gacic[2], Nenad Filipovic[1]

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Abstract:

Endovascular prosthesis - stents are used as a solution for treating many health disorders and diseases. Their major application is found in treating cardio-vascular diseases. One of the problems in stent implantation is a process called in stent restenosis (ISR). In the pre-stent era, the occurrence of restenosis ranged between 32-55% of all angioplasties, and in bare-metal stent (BMS) era this range dropped to 17-41%. Many factors have influence on this phenomenon. Some studies show that in stent restenosis, strut shape and thickness have significant impact, especially if the stent is implanted in the small arteries. For better stent geometry modelling, in this paper authors suggested novel approach – combining numerical simulation with parametric optimization on the existing stent design. Using novel optimization approach system generate a several possibility of new stent designs based on some existing design. On this easy way old design is very much improved. New design has the same distribution of strain but significantly smaller strut cross section. This is huge advantage because this stent will produce less in-stent restenosis in patient and decries number of complications.

Keywords: stent, parametric optimization, stent design, FEA, finite element analysis, endovascular prosthesis

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F.1.6 – *In silico stent deployment using finite element method and contact algorithm* - Velibor Isailovic[1,2,*], Milos Kojic[2,3,4], Dalibor Nikolic[1,2], Nenad Filipovic[1,2]

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Abstract:

The cardiovascular diseases are one of most serious health problems today. One of most common disease is occurrence of atherosclerotic plaque in coronary arteries. The formation of plaque leads to the narrowing of the cross section of the blood vessels, and thus to a decrease in blood flow through the artery. The stent deployment is technique that addresses these issues. Using that technique, medical doctors can implant stent inside narrowed blood vessel to increase blood flow. In this way is possible to allow blood flow as it was before the occurrence of plaque and significantly improve the patient's health. Development of stents, in terms of different applied materials and different geometries, is very expensive and requires a large number of experiments. In order to reduce the number of experiments and reduce the cost of development of new stents, it is possible to make virtual experiments (in silico), using numerical methods. Numerical methods, such as finite element method with applying of contact algorithm, can be used to appropriately simulate real stent behavior.

This approach has multiple benefits: it is very easy to implement different stent materials using a proper material model; geometry of the stent can be modified easily; different load tests can be performed with minor changes in models, etc. Beside mentioned advantages, in silico experiments allow to get a look inside the process of stent implantation. This paper shows numerical approach in stent testing and development.

Keywords: Stent deployment, Finite element method, Contact problems
Acknowledgement: This research was supported by the Ministry of Education, Science and Technological Development through project ON174028 and European projects HORIZON2020 689068 SMARTool and HORIZON2020 777119 InSilc.

Session F.2: 11:30-12:30

Mini-Symposia 1: ARTIFICIAL INTELLIGENCE AND MACHINE LEARNING IN BIOENGINEERING

F.2.1 – *Deep Learning for the Prediction of Lower Limb Muscle Forces* - Tien-Tuan Dao[1,*], Marie-Christine Ho Ba Tho[1]

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Abstract:

The knowledge of skeletal muscle forces during dynamic movements leads to a better understanding of musculoskeletal disease etiology and allows appropriate surgical procedures or rehabilitation programs to be assigned for a specific patient. Current musculoskeletal simulation has modeling assumptions and high computational cost. The objective of the present study was to explore the ability of a recurrent neural network to predict the lower limb muscle forces from joint kinematics and kinetics data. Training and external validation datasets were constructed from two musculoskeletal models. A series-parallel architecture of the nonlinear autoregressive with external (Exogenous) input (NARX-S) neural network model was used to predict the forces of nine muscles from joint kinematics (angles) and kinetics (moments) data. Internal and external validations showed that the best force prediction was noted for soleus muscle with correlation coefficients of 0.9. Good predicted force patterns were also observed for psoas, rectus femoris, gastrocnemius, tibialis anterior muscles. Bad correlation coefficients of force predictions were found for remaining muscles (hamstring, gluteus maximus, vastus lateralis, biceps femoris). This present study showed that skeletal muscle forces could be estimated using an artificial intelligence (AI) approach with a good accuracy level from joint kinematics and kinetics data. Thus, real-time muscle force tracking becomes feasible and of great interest for clinical decision support.

Keywords: Deep learning, artificial intelligence, nonlinear autoregressive neural network, muscle force prediction, time-series data

Acknowledgement: This work was carried out in the framework of the Labex MS2T, which is funded by the French Government.

F.2.2 – *Pre-term birth prediction using EHG for home remote monitoring* - Alessandro Galassi[1], Dan Istrate[1*], Catherine Marque[1], Charles Muszynski[2]

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Abstract:

In this communication, we propose an automatic prediction system allowing to predict high probability of birth in 1-2 weeks from the EHG measurement. Preterm birth is the first cause of perinatal morbidity and mortality. Despite continuous clinical routines improvements, the preterm rate remains steady. In order to avoid long hospitalization for pregnant women we propose an embedded system which acquires and processes EHG signals.

We have already proposed a detection and recognition system for intrauterine contractions using directly the EHG signal from a matrix of 16 electrodes. Presently, we have applied different filtering methods for the signal pre-processing in order to increase the prediction performances. Since, the measurements must be made at home, the decrease of computation power is an important constraint. In this work, we compare the results of the preterm birth prediction algorithm using a filtering step and with only the raw signals. The filtering step is applied directly on the raw signals or only on the automatically detected contractions in order to reduce computation time. Two types of filtering are evaluated separately or combined: Canonical Correlation Analysis (CCA) and Empirical Mode Decomposition (EMD). The EMD decomposes a signal into a collection of oscillatory modes, called IMFs, which represent fast to slow oscillations in the signal. The CCA is a blind source separation method which assume that the observed multichannel signals reflect a linear combination of several sources which are associated with underlying physiological processes, artifacts, and noise. The global classification results are compared between filtered and not filtered signals.

Keywords: GMM, signal preprocessing, preterm birth prediction, CCA, EMD

F.2.3 – ***Deep Learning based approach for assessment of Primary Sjögren's Syndrome from salivary gland ultrasonography images*** - Milos Radovic[1*], Arso Vukicevic[2*], Alen Zabotti[3], Vera Milic[4], Salvatore De Vita[3], Nenad Filipovic[2]

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Abstract:

Salivary gland ultrasonography (SGUS) has shown a good potential for diagnosing Primary Sjögren's syndrome (pSS). However, existing scoring procedures (based on the manual analysis and grading of images) need further improvements before being established as standardized diagnostic tools. In this study we developed a deep learning based approach for fast and accurate segmentation of salivary glands extended with the scoring of pSS. Total 471 SGUS images were annotated in terms of semantic segmentation and de Vita scoring system. The dataset has been augmented using standard technique (rotation, flip, random crop) and used for training of a deep learning method for semantic segmentation and classification. Our model achieved 0.935 intersection over union (IoU) for segmentation of salivary glands and 0.854 accuracy for classification of pSS stage on validation images. With further increase of the HarmonicSS cohort and improvements and validation of methods for computer aided diagnosis of pSS, SGUS could be established as the effective tool for noninvasive assessment of pSS with the final goal to supplement or replace current invasive tests.

Keywords: Deep Learning, Semantic Segmentation, Classification, Primary Sjögren's Syndrome

Acknowledgement: Research supported by the Serbian government (grant agreements III41007 and ON174028) and EU Horizon 2020 RIA programme (HarmonicSS, grant 731944).

Session F.3: 14:30-16:15

Mini-Symposia 2: APPLIED COMPUTATIONAL CHEMISTRY (part II)

F.3.1 – ***Combined 3D-QSAR modeling, molecular dynamics and molecular docking studies in rational drug design of novel 5-HT2A antagonists*** - Milica Radan[1], Mirjana Antonijevic[1], Teodora Djikic[1], Dusan Ruzic[1] and Katarina Nikolic[1*]

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Abstract:

Serotonin 5-HT2A receptors are widely distributed in the human brain where they play a key role in many physiological functions. Numerous neurological disorders caused by 5-HT2A malfunction have made it a very attractive target. Therefore, analysis of 3D-structure of the pharmacophore as well as binding kinetics of 5-HT2A antagonists would be beneficial for future rational drug design. Three-dimensional quantitative structure-activity relationship (3D-QSAR) study was combined with molecular docking and molecular dynamic (MD) simulation in order to find crucial structural features responsible for high binding affinity and selectivity of 5-HT2A antagonists. This study was performed on wide range of structurally diverse antagonists that were divided into three different clusters: clozapine, ziprasidone, and CHEMBL240876 derivates. We have used 50ns MD simulations to obtain inactive, antagonist-bound, conformations of each cluster representative. Subsequently, these conformations were used as templates for docking studies in order to find virtually bioactive conformations of examined compounds. Selected virtually bioactive conformations were used for generation of specific molecular descriptors (Grid Independent Descriptors- GRIND) and 3D-QSAR model building. The 3D-QSAR approach was used to identify the most important structural determinants responsible for the antagonistic activity and to propose structural modifications for novel antagonists of serotonin 5-HT2A receptors. Furthermore, diverse internal and external validation methods were applied. Obtained statistical parameters indicated the reliability and good predictive potential of the created model. Following these findings we have identified differences and similarities in the binding mode and pharmacophores of structurally diverse 5-HT2A antagonists as well as conformational changes they provoke.

Keywords: 3D-QSAR, molecular docking, MD simulation, pharmacophore, antagonists of serotonin 5-HT2A receptors

F.3.2 – ***Vibrational spectroscopy study of coumarine-derived ligand 3-(1-(o-toluidino)ethylidene)-chroman-2,4-dione: A combined theoretical and experimental investigation*** - Zoran S. Marković[1,2], Edina H.Avdović[3*], Žiko B. Milanović[2], Dejan Milenković[2], Svetlana Jeremić[1], Srećko R.Trifunović[3]

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Abstract:

In order to investigate of vibrational spectra of new coumarine-coumarin derivative compound 3-(1-(o-toluidino)ethylidene)-chroman-2,4-dione, the combined experimental and theoretical study was carried out. Density functional calculations (B3LYP-D3BJ/6-311+G(d,p) level of theory) were performed with the aim to support the molecular structure and the spectroscopic characteristics of the investigated compound. To predict the IR spectra, the geometry optimized in gas-phase was used. The vibrational modes of investigated compound were assigned on the basis of the PED (Potential Energy Distribution) analysis using the FCART version 7.0 software. The scaling factor, with the value of 0.9670, was determined for IR spectrum by the least square method. The most distinct bands in the IR spectrum of investigated compound, appearing in the high frequency region (4000–2000 cm−1), were assigned to different modes of =CH and C–H vibrations. In the low frequency region (1800-500 cm-1) there are mostly weak bands assigned modes to ν(C=O), ν(C-C), ν(C–H (methyl)) vibrations. Below 1500 cm-1 there are ν(C–C (ring), C–O, NC) and δ(HCH, HCC, HCC (ring), HCO and HOC)) vibrations. The results show that there is a linear dependence between the experimental and the calculated wavenumbers. The quality of this linear correlation is evaluated by means the correlation coefficient (R). The R values for this compound is 0.9995. On the basis of these facts, it can be concluded that B3LYP-D3BJ provide very good agreement between the experimental and simulated vibrational spectra, indicating that the proposed level of theory is suitable for examining the geometry of similar compounds.

Keywords: Coumarine-derived, infrared spectroscopy, DFT, PED, assignation

Acknowledgement: The authors are grateful to the Ministry of Education, Science and Technological Development of the Republic of Serbia (Projects Nos. OI172015, OI172016, and OI174028) for financial support. This work was further supported by the Ministry of Education, Science, Research and Sport of the Slovak Republic (Project VEGA No. 1/0598/14).

F.3.3 – *Computational Cation Complexation by Cryptands* - Ralph Puchta[1,2,3,4*]

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Abstract:

Although supramolecular chemistry is traditionally an experimental science, driven by serendipity and unexpected findings, the application of quantum chemical methods has proven to be a valuable tool to rationalize results and gain deeper insights. Computational chemistry, often dealing with one isolated (supra)molecule is an outstanding possibility to investigate molecular systems unhampered by solvent molecules, neighboring effects or counter ions.

This lecture will report our results of the last years, mainly based on density functional theory (DFT) calculations, on selective cation complexation by organic cryptands and their corresponding metallo topomers. These studies allow us to compare different types of cryptands, predicte the favored and selected metal cations and understand the individual molecular mechanism to host the cations as good as possible.

While this approach is fascinating for supramolecular and computational chemists, it is additionally an excellent possibility to include high school students into a scientific project. The chemistry can be

understood based on the topics taught in school and own investigations can be done at the computer with out any harm or danger.

Keywords: selective ion complexation, cryptand, DFT-study

F.3.4 – *Scavenger capacity of the 1,2,4-trihydroxyxanthone toward hydroxyl, hydroperoxyl and methylperoxyl radicals* - Zoran Marković[1,2], Sanida Šemović[1], Žiko Milanović[2], Ana Amić[3], Svetlana Jeremić[1*]

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Abstract:

Some xanthone derivatives isolated from plants possess antifungal, antimicrobial, antioxidative and cytotoxic activities. Therefore, products manufactured from plants that contain xanthones are used as botanical dietary supplements. The operative mechanism of antioxidative action of 1,2,4-trihydroxyxanthone is investigated in this contribution. For this purpose, M06-2X/6-311++G(d,p) method is used. Antioxidative capacity of investigated xanthone is determined in benzene and water as mediums. It is found that, among three possible radicals that this xanthone can generate, the most stable is the one obtained by homolytic cleavage of O-H group in position 4. It was found that HAT (Hydrogen Atom Transfer) is the only operative mechanism for xanthone in benzene. On the other hand, the most favorable mechanism in water is SPLET (Sequential Proton Loss Electron Transfer). It should be emphasized that SET-PT (Single-Electron Transfer followed by Proton Transfer) is not plausible mechanistic pathway in both solvents. Antioxidants express their scavenger capacity in the presence of free radicals. Therefore here is examined scavenger capacity of 1,2,4-trihydroxyxanthone toward HO●, HOO● and CH3OO● radicals. It is found that the investigated xanthone is able to deactivate free radicals via competitive HAT and SPLET mechanisms. The observed reactivity of the xanthone toward free radicals decreases following the order: HO● ≫ HOO● > CH3OO●. It should be pointed out that reactivity of the xanthone to selected free radicals slightly increases with an increase in solvent polarity.

Keywords: 1,2,4-trihydroxyxanthone, hydroxyl radical, hydroperoxyl radical, methylperoxyl radical, DFT

Acknowledgement: This work was supported by the Ministry of Science of the Republic of Serbia (Projects No. 172015 and 174028), and by The Foundation of the Croatian Academy of Sciences and Arts (Project No. 10-102/244-1-2016).

F.3.5 – *Experimental and theoretical study of structure and antioxidant activity of some N'-benzylidene-3,4,5-trihydroxybenzohydrazides* - Vladimir P. Petrović[1], Vesna Milovanović[1*], Dušica Simijonović[1], Zorica D. Petrović[1], Zoran Marković[2,3]

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Abstract:

Set of N'-benzylidene-3,4,5-trihydroxybenzohydrazides was synthetized starting from 3,4,5-trihydroxybenzohydrazide and corresponding aromatic aldehydes. Compounds were characterized using experimental and theoretical tools. Namely, experimentally acquired vibrational and UV-Vis spectra were compared to the simulated ones. Gas-phase optimized structure at B3LYP-D3BJ/6-311+G(d,p) level of theory was used for the assignment of IR bands. On the other hand, TD-DFT was employed to simulate UV-Vis spectra. Very good agreement was achieved between experimental and simulated spectra. In the case of IR spectra, the scaling factor was determined by the least square method. All compounds were screened for their antioxidant activity. In vitro DPPH test was used for experimental screening. In addition, antioxidant activity was estimated using thermodinamical approach. It was found that there is very good agreement between experimental and theoretical results. Based on the obtained results, N'-benzylidene-3,4,5-trihydroxybenzohydrazides can be considered as potent antioxidant compounds.

Keywords: N'-benzylidene-3,4,5-trihydroxybenzohydrazides, Structural characterization, DFT/TD-DFT, antioxidant activity

Acknowledgement: The authors are grateful to the Ministry of Education, Science and Technological Development of the Republic of Serbia (Projects No. OI172016) for financial support.

F.3.6 – ***Influence of circadian function on the dynamical states of the hypothalamic-pituitary-adrenal axis*** - Milorad M. Anđelković[1*], Ana D. Stanojević[1], Željko D. Čupić[2], Ana Z. Ivanović-Šašić[2], Ljiljana Z. Kolar-Anić[1,2]

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Abstract:

The hypothalamic-pituitary-adrenal (HPA) axis exhibits complex oscillatory dynamics with ultradian oscillations superimposed on circadian ones. The ultradian dynamics is described by nonlinear five-dimensional stoichiometric model (cholesterol, corticotropin-releasing hormone (CRH), adrenocorticotripic hormone (ACTH), cortisol and aldosterone), whereas circadian oscillations was simulated by the influence of artificial circadian oscillations on the rate of CRH production. Although the significant results were obtained indicating importance of the interaction between two cycles, more realistic circadian function was desirable. For this purpose, we use here another model of circadian activity published in Tyson et al. 1999.
Bifurcation diagrams with mentioned circadian function were constructed and results were compared with previously published ones, obtained by simple periodic forcing. Modelling the HPA axis in vicinity of a supercritical Andronov-Hopf bifurcation suggests that the dynamical system retains vital properties enabling gradual adaptation to external perturbations. Hence, our model of ultradian dynamics combined with circadian function published by Tyson et al. 1999 could even better simulate various kinds of phenomena, including variations in circadian activity and long term adaptations.

Keywords: Nonlinear dynamics, HPA system, Circadian function, Andronov-Hopf bifurcation

Acknowledgement: This work was partially supported by the Ministry for Education, Science and Technological Development of the Republic of Serbia (Grants 172015 and 45001).

F.3.7 – *On the thermodynamics of the radical scavenging activity of 3,4-dihydroxybenzohydrazide derivatives* - Denisa Cagardová[1], Vladimír Lukeš[1], Erik Klein[1*], Vladimir Petrović[2], Zoran Marković[3]

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Abstract:

Recently, new 3,4-dihydroxybenzohydrazide derivatives were synthesized. Due to the presence of phenolic OH groups in these compounds, they may show considerable radical scavenging activity. In this ongoing work, we are investigating the reaction enthalpies related to the three mechanisms of primary antioxidant action for 3,4-dihydroxybenzohydrazide and its derivatives using Density Functional Theory (DFT). Our preliminary results indicate thermodynamic preference of Hydrogen Atom Transfer (HAT) mechanism in non-polar environment, while in aqueous solution, Sequential Proton-Loss Electron-Transfer (SPLET) should dominate. Methoxy substituent(s) placed in the ortho-position(s) to OH group of 4-hydroxybenzylidene unit of studied compounds affect homolytic O–H bond cleavage in all studied environments. Contrary to non-polar environment, these substitution(s) do not show a significant effect on the heterolytic O–H bond cleavage in aqueous solution.

Keywords: Hydrogen Atom Transfer, Sequential Proton-Loss Electron-Transfer, DFT

Acknowledgement: This work was supported by the Slovak Grant Agency (VEGA 1/0416/17) and by the Slovak Research and Development Agency under the contract no. SK-SRB-18-0016. This work was partially supported by the Ministry of Science and Technological Development of the Republic of Serbia (Grant no 172015), and bilateral project Serbia-Slovakia 2019-2020 (Grant no 337-00-107/2019-09/10).

Session F.4: 16:15-17:15

Signal Processing

F.4.1 – *Shape characterization of the gonarthrosis in the X-ray images* - Suzana Petrovic Savic[1], Branko Ristic[2,3], Aleksandar Matic[2,3], Nikola Prodanovic[2,3], Goran Devedzic[1*]

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Abstract:

Gonarthrosis is a degenerative disease of the knee joint that involves damage of the articular cartilage, formation of the osteophytes and reactive changes in the synovial membrane and in the synovial liquid. Location of the initial change in the knee joint is unknown, i. e. initial change can occur anywhere. Diagnosis of the gonarthrosis is based on the use of the clinical and radiological methods. In this study, X – ray images were used. Resolution and dimensions of the X – ray images can vary and influence precision in their reading and analysis. Taking into account a possible complexity of images, it is necessary to perform a few processing steps in order to obtain measurable information. In order to eliminate imperfections of images, a non-linear median filter is used for image filtering. The segmentation of the characteristic regions in the image is done by using active contour segmentation which is based on the curve flow, curvature and contour of the desired region. Therefore, the quantification of the obtained information is necessary in order to perform precise classification of the gonarthrosis grade. Quantification of the segmented regions was carried out by measuring space between femur and tibia and by comparing it with measured space between femur and tibia in healthy persons. The precise diagnosis of this disease is of great importance to preserve objectivity during decision making, for further treatment and to facilitate the performance of everyday activities of the patients.

Keywords: Gonarthrosis, Shape, Characterization, Segmentation

F.4.2 – *Evaluation of social and cognitive load stress detection using speech-derived features* - Giorgos Giannakakis[1*], Nikolaos Stefanakis[2,3], Angelos Ilias[2], Panagiotis Simos[1,4]

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Abstract:

Psychological stress detection is an active research domain which gains ground in the research community. Speech can be employed towards this goal considering that it is a non-invasive method permitting user convenience, being a parameter that affects per se the stress level. An experiment

protocol was established including a population consisting of 58 healthy participants in which different stressors were presented. The paper focus is on social stress (interview stressor) and cognitive load originated stress (Stroop Color Word and PASAT Test stressors). An automatic method was employed for detecting voiced segments in the recordings. Speech-derived features were then extracted from these segments including pitch (f0), glottal flow features (NAQ, QOQ, H1-H2, PSP, etc), peak slope, Mel-frequency Cepstral Coefficients, harmonic model and phase distortion means (HMPDM) and deviations (HMPDD) leading to a feature matrix of 73 features. Feature selection was performed using the minimum Redundancy Maximum Relevance (mRMR) algorithm selecting the top-ranked features. The selected features' subset was evaluated in terms of its ability to discriminate between stress and no-stress state. Preliminary evaluation results, using a 10-fold cross-validation technique on utterance basis with KNN, Generalized Linear Model (GLM), Naïve Bayes (NVB), Linear Discriminant Analysis (LDA) and Support Vector Machines (SVM) classifiers led to a best achieved classification accuracy of 84.4% for the interview stressor and of 80.3% for the cognitive load stressor.

Keywords: stress detection, speech, fundamental frequency, Mel-frequency Cepstral Coefficients, classification

Acknowledgement: This study was partially supported by the Greek State Scholarships Foundation (IKY) scholarship programme and co-financed by the action entitled "Reinforcement of Postdoctoral Researchers", in the framework of the Operational Programme "Human Resources Development Program, Education and Lifelong Learning" of the NSRF 2014 – 2020 (Grant No: 2016-050-0503-7047).

F.4.3 – *Medical Image Processing using Xilinx System Generator* - Tijana Šušteršič[1,2,3*], Vladimir Milovanović[1], Vesna Ranković[1], Nenad Filipović[1,2,3], Aleksandar Peulić[4]

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Abstract:

Although software versions of different image processing techniques are suitable for general-purpose use, in order to meet the real time applications, an image processing technique needs to be implemented in hardware. FPGAs have many benefits in applications that include digital signal acquisition, but also processing of large data, especially in real time. Mainly due to the ever-decreasing cost and re-configurability, FPGAs have also found its place in digital signal processing (DSP), now replacing ASICs in that area. Xilinx System Generator is a tool from Xilinx that enables the Mathworks Simulink models to be adapted for FPGA design. For comparative study on several levels in edge detection, CT image of a brain with a tumor is used. Performance of gradient based edge detectors - Robert, Prewitt and Sobel was compared. Even from just visual analysis of results, it can be seen that Prewitt and Sobel methods give better results than Robert method. In contrast, the calculation of Robert operator is simpler in comparison to the other operators and occupies less resource, since only adder-subtractor logic is enough to detect the edges. As the implemented algorithms could be part of more complex systems for tumor detection, the design architecture used in this paper can be extended to be used in very complex real time image processing techniques.

Keywords: FPGA, Xilinx System Generator, brain tumor, edge detection

Acknowledgement: This study is supported by the grants from the Serbian Ministry of Education, Science and Technological Development III41007 and OI174028.

F.4.4 – *Correlation of the Lumbar and Cervical Lordosis with Spinal Inclination in Children with Idiopathic Scoliosis Optically Diagnosed* - Saša Ćuković[1*], Wolfgang Birkfellner[2], Michele Fiorentino[3], Tanja Zečević Luković[4], Nenad Filipović[1]

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Abstract:

In this paper we presented a non-invasive computational solution for optical 3D diagnosis of adolescent idiopathic scoliosis (AIS), and analysis of lordotic and kyphotic postural indicators of dorsal surface and their correlations in sagittal plane. We conducted a retrospective analysis of 372 subjects (141 males and 231 females) with major thoracic AIS who were optically scanned using a 3D optical digitizer in four years period (2012-2015). We evaluated dorsal parameters using ScolioSIM1.0 module of ScolioMedIS information system and processed them statistically, with the primary aim of studying correlations between trunk inclination and imbalance with lumbar and cervical lordosis and thoracic kyphosis. We generated correlation coefficients between parameters Lumbar_Flexion_mm, Trunk_Inclination_deg, Trunk_Inclination_mm, Kyphotic_Angle_deg, Cervical_Flexion_mm. We found an interesting high correlation between parameters Lumbar_Flexion_mm and Trunk_Inclination_deg (-0.708, 95% confidence interval). The clinical relevance of the proposed research and results are high as these parameters describe hyper or hypo tonic posture of AIS patients and they can contribute to better definition of range of sagittal modifiers in a new 3D classification of AIS. We demonstrated that our radiation-free imaging technique enables a reliable 3D visualization of deformity and detection of subtle postural changes in a large cohort group.

Keywords: Idiopathic Scoliosis, Optical Diagnosis, Spinal Inclination, Lordosis and Kyphosis

Acknowledgement: Presented research is supported by the Swiss-SERI-SGES grant [2017.0024] and by the Serbian Ministry of Science grant III-41007.

Session F.5: 17:15-17:45

Mini-Symposia 5: HOLOGRAM AND AUGMENTED REALITY BIOMECHANICAL MODELS OF A VIRTUAL BALANCE PHYSIOTHERAPIST AND COGNITIVE TRAINING GAMES

F.5.1 – ***Preliminary testing of augmentative reality games in holobalance solution*** - Natasa Vujnovic Sedlar[1*], Adrian Djura[1], Nenad Filipovic[2], Snezana Tomasevic Todorovic[1,3], Dinu Dragan[1,4]

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Abstract:

Since the percentage of older people in the population is growing worldwide the balance disorders represent a growing public health concern due to the association with falls and fall-related injuries. The development of personalized technology-based coaching solution could accelerate the new disruptive innovation elements into the vestibular treatment, by implementing the newest research results and addressing the needs of medical professionals and patients during the balance disorders management. In this work, Holobalance solution is presented as that kind of solution, designed to support new forms of accessible user interaction, based on holograms and augmented reality games. Incorporated augmented reality games are organized to provoke cognitive functions of patients and also stimulate their physical activities. One of the main aspects of the developed game is motivation elements for the patients incorporated as key design factors from the entertainment video game world. The games are a collections of cognitive mini-games targeting special vestibular exercises and cognitive skills. They are, primarily, targeting elderly players, over 65. A preliminary testing was conducted focusing on the game experience, the usability of games for vestibular exercises, and the specific users' observations and remarks. The implemented study has managed to provide interesting insights into the games design taking in account restrictions of equipment, technology, environment and patients' abilities.

Keywords: balance disorders, vestibular treatment, augmented reality games

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F.5.2 – ***3D Hologram based balance physiotherapist software and hardware system*** - Zarko Milosevic[1,2], Ana Vulovic[2], Dalibor Nikolic[1,2], Nenad Filipovic[1,2]

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Abstract:

In the HOLOBALANCE project we have developed the 3D hologram-based balance physiotherapist tool which contains of software and hardware system. It gives patients opportunity to receive

personalized exercise instructions as well as feedback through virtual coach. There are two versions: the smartphone where user wears head mounted adapter to keep a smartphone at a set location on the head of the user and 3D HoloBox where highly efficient holographic foil and high lumen projector are used to create best possible 3D experience without using any type of device on the patient side for presentations purposes. The sensors are attached to patient in both cases.
Version 1.0 of the software is installed on the smartphone, where user wears a head mounted adapter to keep the smartphone at a set location on the head of the user. The head mounted adapter allows the user to see images generated from the smartphone screen as holograms.
Version 2.0 uses 3D HoloBox. It is a hologram box, using highly efficient holographic foil and high lumen projector to create the best possible 3D experience without using any type of device on the patient side for presentation purposes. Sensors have to be attached to the patient in both cases.
REST APIs have been used as the communication protocol between BPH and Edge computer in both directions in a stateless manner. Interface of this kind allows BPH to receive feedback regarding exercise evaluation in real-time and provides interoperability.
This is first time of hologram based exercises for balance physiotherapist software and hardware system which opens a new avenue for future interactive tool at patient home or hospital.

Figure 1. Example of exercise on hologram: bending and returning to upright position

Keywords: hologram, 3D HoloBox, virtual coach, balance physiotherapist software and hardware system

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