UT Austin | Portugal

Workshop on

Modeling and Simulations of Cardiovascular Diseases and Cancer

November 13-15, 2017, Lisbon Academy of Sciences, Lisbon, Portugal

http://cemat.tecnico.ulisboa.pt/MSCDC2017/

Book of Abstracts

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Workshop on Modeling and Simulations of Cardiovascular Diseases and Cancer

Book of Abstracts

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Academia das Ciências de Lisboa, Portugal

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Foreword

According to the most recent statistics, cardiovascular diseases and cancer are the major causes of death in developed countries, with a significant impact in the cost and overall status of healthcare.

Understanding the fundamental mechanisms of the patho-physiology and treatment of these diseases are matters of the greatest importance around the world. This gives a key impulse to the progress in mathematical and numerical modeling of the associated complex phenomena governed by multiscale heterogeneous physical laws, integrating the knowledge of all their complex environmental, life style, ageing and genetic components into robust and fully reliable computer models and in silico settings.

To face this challenge, the emerging integrative multidisciplinary research approach that involves interactions between different disciplines such as computational sciences, mathematics, biology and medicine is therefore of major significance. The final goal is to setup patient-specific models and simulations incorporating data and measurements taken from each single patient, that will be able to predict results of medical diagnosis and therapeutic planning with reasonable accuracy and using non-invasive means.

This is a CoLab Workshop organized as an initiative of the UT Austin|Portugal Program that follows a series of events to reinforce the Portuguese competences in Computational Medicine and Biomathematics. The Workshop provides a place to exchange recent developments, discoveries and progresses in this challenging research field. The main goal is to bring together doctoral candidates, postdoctoral scientists and graduates interested in the field, giving them the opportunity to make scientific interactions and new connections with established experts in the interdisciplinary topics covered by the event, including medical researchers. Another important goal of the Workshop is to promote collaboration between members of the different areas of the UT Austin|Portugal community.

Acknowledgments

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FCT - Fundação para a Ciência e a Tecnologia

CEMAT - Center for Computational and Stochastic Mathematics, Instituto Superior Técnico

ACL - Academia das Ciências de Lisboa

Lisbon, November 13, 2017

The Organizing Committee

Adélia Sequeira
Hugo Beirão da Veiga
Helena Telles Antunes
Jorge Tiago
Marília Pires
Telma Guerra
Oualid Kafi

Program

- **Monday, November 13, 2017**

08:30 - 09:00 **Registration**

09:00 - 09:20 **Opening Session**

09:20 - 10:00 **J. Queiroz e Melo.** *Should ICD's and CRT's be reused after harvested from patients submitted to cardiac transplant?*

10:00 - 10:40 **A. Friedman.** *Mathematical modeling of combination therapy with anti-PD-1 as one of the two agents*

10:40 - 11:00 **Coffee Break**

11:00 - 11:30 **U. Ledzewidcz.** *Optimal protocols for a mathematical model for combination therapy of CML*

11:30 - 12:00 **H. Canhão.** *Three projects, three ways of collecting, retrieving and analyzing data*

12:00 - 12:30 **J. Reis.** *To be announced*

12:30 - 14:30 **Lunch**

14:30 - 15:00 **A. Veneziani.** *When the "boundary" is critical: defective/missing data for computational hemodynamics*

15:00 - 15:30 **L. Dedè.** *Numerical modeling and large-scale simulation of the cardiac electromechanics*

15:30 - 16:00 **V. Coscia.** *Pathophysiology of the venous system: Mechanisms and modeling*

16:00 - 16:30 **Coffee Break**

16:30 - 17:00 **M. Souza.** *State estimators for some epidemiological systems*

17:00 - 17:15 **G. Giantesio.** *Modeling ageing in skeletal muscle tissue*

17:15 - 17:30 **R. Fonseca-Pinto.** *Adaptive analysis in medical data processing: the Hilbert-Huang transform challenges*

20:00 **Workshop Dinner**

- **Tuesday, November 14, 2017**

09:00 - 09:40 **W. Jäger.** *Epithelial layers controlling transitions between compartments in organisms. Modelling and simulation of early stages of atherosclerosis*

09:40 - 10:10 **M. Neuss-Radu.** *Effective models for transport processes through membranes*

10:10 - 10:40 **L. Patrício/D. Neves.** *Coronary physiology and imaging–ongoing projects in CORE*

10:40 - 11:00 **Coffee Break**

11:00 - 11:30 **V. Volpert.** *Reaction-diffusion waves of blood coagulation in quiescent plasma and in flow*

11:30 - 12:00 **I. Narra Figueiredo.** *Video interpretation of wireless capsule endoscopic images with image registration*

12:00 - 12:30 **R. da Luz.** *Modeling and simulation in Oncology clinical practice*

12:30 - 14:30 **Lunch**

14:30 - 15:00 **R. Matthiesen.** *Functional regulation in lung cancer from a clinical proteomics point of view*

15:00 - 15:30 **P. Oliveira.** *A computational approach to design a restenosis criterion*

15:30 - 16:00 **J. A. Ferreira.** *Ultrasound responsive drug delivery systems: coupling wave propagation and drug diffusion*

16:00 - 16:30 **Coffee Break**

16:30 - 17:00 **L. Rosário.** *Quantitative modelling of cardiovascular physiology*

17:00 - 17:15 **G. Romanazzi.** *Biomechanical model for the simulation of colonic pit patterns*

17:15 - 17:30 **J. Felício.** *Experimental validation of medical microwave imaging for breast cancer screening*

- **Wednesday, November 3, 2017**

09:00 - 09:30 **J. L. Passos-Coelho.** *The changing landscape of Oncology*

09:30 - 09:50 **H. Telles Antunes.** *Cardiac surgery in a changing world: Avenues for clinical application of modelling and simulation solutions in cardiac surgery*

09:50 - 10:10 **S. Laranjo.** *The role of computational modelling in patients with congenital heart disease*

10:10 - 10:40 **N. El Khatib.** *Patient specific 3D numerical fluid-structure interaction model for blood flow in an atherosclerotic artery*

10:40 - 11:00 **Coffee Break**

11:00 - 11:30 **A. Fred / H. Silva.** *On and Off the person ECG data sensing and processing technology*

11:30 - 12:00 **M. Coimbra.** *Can we screen 40k children per year using DigiScope?*

12:00 - 12:30 **P. André.** *Optical fiber sensors as a non-invasive technology to the central arterial pressure assessment*

12:30 - 14:30 **Closing Session**

Lectures - Abstracts

Optical fiber sensors as a non-invasive technology to the central arterial pressure assessment

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Abstract

An important factor in the evaluation of cardiovascular risk is the control and monitoring of hypertension. In this presentation fiber optic solutions are explored in the acquisition of the pulse wave in the carotid artery, to analyze its morphology and calculate the central arterial pressure. The performance of the developed probe was compared to a commercial device in a hypertensive cohort. Invasive testes were also performed, using as reference pressure waves obtained in the lumen of the aortic artery, in the context of cardiac catheterization [1]. In clinical studies, it was obtained very strong correlation coeffcients and mean pressure differences in the range of commercial devices. It can be concluded that this solution arises as a promising low-cost alternative to the electromechanical arterial pressure devices available on the market.

Keywords: Biomedical fiber sensors, hypertension, cardiovascular monitoring.

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Cardiac surgery in a changing world: Avenues for clinical application of modelling and simulation solutions in cardiac surgery

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Abstract

Cardiovascular disease is one of the most prevalent diseases worldwide and cardiac surgery has been challenged with new and innovative ways of diagnosing and treating surgical patients. New and emerging technologies have changed the way cardiac surgeons think and radically changed therapeutic possibilities, allowing for an increasingly personalized approach and treatment.

In a data driven age, systematic analysis is needed to accomplish better and better results.

We will try to summarize recent developments in the application of simulation and modelling to clinical cardiac surgery and suggest some areas of future development.

Three projects, three ways of collecting, retrieving and analyzing data

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Abstract

Non-communicable chronic diseases are major causes of morbidity and mortality in western societies. Even though we are living longer, last years' quality of life is distinctive in different countries. In this presentation we will talk about 3 different projects and 3 different types of collecting and retrieving data. Reuma.pt (www.reuma.pt) is the national registry of rheumatic diseases, which follow more than 17,800 rheumatic patients with more than 140,000 medical appointments. Online, structured collection of data with easy data export to statistics software makes this registry a powerful research tool. EpiDoC cohort (http://cedoc.unl.pt/epidoc-unit/) is a closed population based study that follows since 2011, 10,661 adult individuals representative of the Portuguese dwelling population. These subjects were randomly selected across Mainland and Islands and act as a barometer of the population living in the community. Finally, Patient Innovation Project (https://patient-innovation.com) is an open, free, online platform that gathers and facilitates sharing of innovations and solutions developed by patients and informal caregivers. It acts like a social network, but the solutions are published only after clearance from the medical screening. 800 innovations from 50 different countries are available to help patients suffering from different diseases and disabilities.

Can we screen 40k children per year using DigiScope?

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Abstract

Ever since the invention of the stethoscope in 1816, auscultation has been an essential component of a patient's clinical examination. It is a powerful screening tool, considered the most cost-effective [1], and the most widely used method for screening heart disease [2]. It is also a hard skill to master, due to several factors associated with the nature of the collected sounds and our human ability to hear them. Relevant pathological activity is often soft, short-lived and occurs in proximity to loud, normal activity: a typical murmur is 1000 times softer than normal heart sounds and can last for as little as thirty milliseconds [3]. What if we have the ability to digitally record auscultation sounds? Could we create richer electronic health records for future reference? Would we make better diagnostics if we could ask an expert opinion from a remote specialist or from a local clinical decision support system? Could we radically improve the way we train our clinicians in the art of auscultation? This is the essential vision of the DigiScope research line: combining electronic stethoscopes with the power of modern portable computing technology to create interactive auscultation systems for telemedicine, assisted decision and teaching [4].

A ten-year long partnership has been established between the University of Porto (Instituto de Telecomunicações, CINTESIS - Faculdade de Medicina da Universidade do Porto) with the largest hospital in northeast Brazil, Real Hospital Português located in the city of Recife, Pernambuco. Throughout these years, relevant interactive auscultation technologies have been researched, developed, tested and some of them successfully transferred to the market via spin-off processes. During this talk, a summary of the most remarkable events of this partnership will be given, culminating in the empowerment of the state of Paraíba with the technological ability to screen the nearly 40k children that are born per year here.

Will the digital revolution propel one of the oldest arts in medicine for 200 more years of clinical practice? Join us in this discussion.

Keywords: Biomedical Signal Processing, Human-Computer Interaction, Auscultation, Telemedicine.

References

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Pathophysiology of the venous system: Mechanisms and modeling

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Abstract

Aim of the talk is to review some of the main mechanisms leading to the most common diseases associated with venous insufficiency, in particular in the inferior limbs, and to present modeling approaches for the related haemodynamic pictures. In particular, we discuss the fluid dynamics of the sapheno-femoral junction before and after surgery and the mechanical action of compression therapy. In both cases, we report on comparison between models'outcomes and clinical observations [1], [2].

Keywords: Mathematical modeling, Venous system, Free iron, Compression therapy.

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Numerical modeling and large-scale simulation of the cardiac electromechanics

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Abstract

Simulating the whole cardiac function represents a challenging task from the mathematical, numerical, and computational standpoints. This is mainly due to the fact that a full cardiac model should exploit the multiphysics nature of the problem, which is indeed comprised of several core models, namely electrophysiology, mechanics (both in its passive and active components), valve dynamics, and fluid dynamics. Each of these models is intrinsically complex and features a wide range of spatial and temporal scales along the heartbeat; these need to be suitably captured to correctly represent the mutual interactions of the heart components [6]. Notable examples are the study of blood flows in the heart [5, 7] and through the valves [3].

In this talk, we consider the mathematical and numerical modeling of the left ventricle by integrating state–of–the art models for the electrophysiology of the tissue, mechanical activation at the cellular level [1], and the passive mechanical response of the muscle, thus yielding a coupled electromechanical problem [4]. We consider its spatial approximation by means of the Finite Element method and we propose a fully coupled approach with an implicit scheme for its time discretization based on BDF formulas. We solve the corresponding discrete, large–scale problem by means of the GMRES method with a newly proposed physics–based preconditioner that exploits the coupling of the core models [2, 4]. We present and discuss numerical results – obtained in the high performance computing framework – for the electromechanical problem applied to patient–specific geometries of the left ventricle.

Keywords: Cardiac modeling, mathematical and numerical modeling, electromechanics, Finite Element method, preconditioning.

References

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Patient specific 3D numerical fluid-structure interaction model for blood flow in an atherosclerotic artery

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Abstract

The inflammatory process of atherosclerosis leads to the formation of an atheromatous plaque in the intima of the blood vessel. The plaque rupture may result from the interaction between the blood and the plaque. A three dimensional realistic fluid-structure interaction (FSI) model is used to perform the study. An absorbing boundary condition is imposed directly on the outflow in order to cope with the spurious reflexions due to the truncation of the computational domain. We show that the risk of plaque rupture is higher in the case of a moving wall, while in the case of a fixed wall the risk of progression of the atheromatous plaque is more important.

Keywords: atherosclerosis, fluid-structure interaction, blood flow, WSS.

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Experimental validation of medical microwave imaging for breast cancer screening

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Abstract

Breast cancer is the second most common type of cancer in Europe and the cancer with most incidence on women [1]. Yet, the detection of breast cancer in an early-stage highly increases the chances of surviving, as well as it decreases the morbidity of tumor treatments, leading to better quality of life of tumor survivors. However, screening breast cancer in mass populations is extremely challenging.

The primary technique used for breast cancer screening is the mammography exam [1]. Despite having very good resolution, it uses ionizing radiation, which is hazardous for health. In fact, there is an established limit for the amount of ionizing radiation a person can be exposed to per year. In case of positive detection of potential carcinomas, the patients are forwarded to further exams, which generally include ultrasound and/or Magnetic Resonance Imaging (MRI). Although these exams offer quite good detection rates, they are time consuming or expensive, thus not appropriate for mass population screening.

Within this framework, new technologies are emerging as alternatives to mammography. One of these is Microwave Imaging (MWI), which is revealing promising results. Unlike X-rays, it uses much lower frequencies (approximately between 1 GHz and 30 GHz) at which there are no known damages in tissues. Nevertheless, as a consequence of using larger wavelengths, microwaves do not achieve the same resolution as X-rays.

MWI involves illuminating the breast with microwave (MW) energy radiated by antennas distributed around the breast. Literature reports sufficient dielectric contrast between healthy and malignant breast tissues [2], which encourages the use of microwaves. Indeed, the dielectric contrast causes the MW energy to be scattered and picked up by the same antennas. Based on these echoes, it is

possible to use strategies to reconstruct the reflectivity map of breast tissues, therefore identifying the tumor. Yet, as any recent technology, MWI involves great investment in research and development, until the concept is experimentally proven and ready for clinical trials, especially in the Medicine field.
At Instituto de Telecomunicações, Lisbon, we are developing and experimentally validating a prototype aiming at the early detection of breast cancer based on MWI. We envisioned the patient would lie on prone posture with the breast inserted in a cavity embedded in the examination bed. This posture reduces the influence of the chest movement due to the respiration and gives easy access to the breast [3]. To this end, we use an anthropomorphic breast model that resembles the examination posture [4]. Moreover, the breast tissues were mimicked by appropriate liquids [5].
The irregular shape of the realistic breast poses a significant challenge in MWI; however most experimental works found in the literature assume regular-shaped breast models. Also, we use a cylindrical antenna configuration around the breast, since it is easily adjustable to any breast size and avoids the use of complex mechanical parts. Lastly, our experimental prototype does not require immersing the breast in any coupling medium, unlike the majority of published works. We reckon this will make the exam more comfortable to the patient without sacrificing the overall imaging performance.
The demonstrator has been assembled and tested in our facilities. The results obtained in our experiments show very good precision, since the tumor was correctly detected. These results show the potential of MWI in breast cancer screening that may serve as an alternative to mammography, thus avoiding the use of hazardous radiation.

Keywords: Antennas for medical imaging, breast cancer screening, experimental validation, microwave imaging.

References

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Ultrasound responsive drug delivery systems: coupling wave propagation and drug diffusion

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Abstract

Stimuli responsive drug delivery systems (SRDDS) have been the object of intense laboratory and clinical research in different disease scenarios, such as cancer [4]. SRDDS aim to avoid the drawbacks of the traditional drug administration systems and controlled drug delivery systems. In medical applications, the drug is transported to the target tissue, using nanocarriers or by implanting the device directly in contact with the target tissue. In both cases, a stimulus is used to disrupt the drug reservoir, in general composed by a polymeric matrix where the drug is entrapped, and physiological barriers and force or enhance the drug release and its absorption. Promising results have been reported in the literature [1].

A set of complex phenomena are involved in the drug release that occurs in the polymeric matrix and target tissue: solvent absorption, swelling, biodegradation, dissolution, diffusion, active transport and stimulus propagation. We observe that the literature on mathematical modelling of drug release from SRDDS is fragmented and very few models (taking into account few phenomena) have been proposed. To the best of our knowledge, no mathematical models combining significant phenomena for the enhanced drug release were published [2],[3].

In this talk, we are mainly interested in SRDDS based on ultrasound stimulus. The behaviour of ultrasound propagation is described by a general telegraph equation whose coefficients and reaction term are specified in function of the particular application (polymer and target tissue). Ultrasound induces an

active drug transport through the polymeric matrix onto the target tissue. The drug release and drug absorption are then described by convection-diffusion reaction equation that is coupled with the telegraph equation for the stimulus. In this work this system is studied from analytical and numerical point of view.

Keywords: Ultrasound, wave equation, drug concentration, convection-diffusion equation.

References

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Video interpretation of wireless capsule endoscopic images with image registration

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Abstract

Wireless Capsule Endoscopy (WCE) is a relatively recent medical technique used for the visualisation of the interior of the small bowel by gastroenterologists [1, 2]. The capsule is a very small device, consisting of a miniaturised camera, a light source and a wireless circuit for the acquisition and transmission of signals. In a WCE exam, the capsule is ingested by the patient, and it produces a video, containing thousands of images, that should be carefully viewed and interpreted by medical experts. A fast interpretation of the video is then of utmost importance, as well as, the correct identification of abnormalities in the images and, subsequently, their precise location in the small bowel relative to some known physiological landmark (the intestine moves due to the peristaltic movement, and the exact location of the capsule, that is propelled by peristalsis inside the body, is unknown).

In this talk we explain how an image registration approach can be a valuable auxiliary medical tool for WCE video interpretation. This tool enables an overall, and extremely quick, analysis of the entire WCE video and, interestingly, it also provides an indication of the speed of the capsule, which is of course an important information towards capsule location.

In short, this tool is a curve, computed by our algorithm with given WCE video sequences. It represents the degree of similarity between consecutive frames in a WCE video of the small bowel of a patient. This curve is obtained

by using an appropriate mixed multiscale affine and elastic image registration approach, that detects both rigid-like and non-rigid like deformations, due respectively to the rigid-like WCE movement and the elastic deformation of the small bowel generated by the gastrointestinal peristaltic movement.

As shown in [3, 4] the advantage of using this curve as an auxiliary medical tool for a quick and efficient video inspection is threefold. Firstly, it permits a global and fast interpretation of the video, since it clearly divides the video frames into two main classes: consecutive frames with similar content, which correspond to low values in the curve, and consecutive frames displaying abrupt changes in the image content, which are depicted by peaks, i.e. high values, in the curve. Secondly, it is also a rough indicator of the speed of the capsule. A very low value of this curve indicates that the image content does not change in the corresponding pair of consecutive frames, and therefore the capsule is almost still or rotates/moves slowly, because it is capturing the same scene. On the other hand, a high value in the curve indicates abrupt scene changes in the two consecutive frames, therefore the image content is changing, and consequently the capsule should have moved, or the background has changed dramatically due to peristalsis. Finally, it can also be used to search quickly for abnormalities, as for instance bleeding.

Keywords: Elastic and parametric image registration, Multiscale representation, Wireless capsule endoscope.

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Adaptive analysis in medical data processing: the Hilbert-Huang transform challenges

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Abstract

Mathematical methods have historically assumed a central role in classical Signal Processing theory, carrying the robustness of the formal demonstration techniques to the methodologies, which start in some cases by empirical rules with good results in practice. Despite the solid Mathematical foundation, there are assumptions regarding the signal and the system itself that, if not considered, can lead to biased information, incomplete results or results without physical meaning. When faced with real data, usually we are dealing with the transient nature of the physical phenomena itself, and also to the finite span of captured data (which may be shorter than the longest time scale that describes the phenomena).

Signal stationarity and system linearity must be regarded as an exception instead of a rule in real data signal processing (in particular in biomedical data in which the non-stationarity property is highly present). Hence, a new paradigm of signal processing has emerged since the early nineties of the last century, changing the imposed *a priori* knowledge of the basis functions (*i.e.* sinusoidal functions or more recently wavelet functions). This adaptive analysis approach is based on the idea of choosing the methodology independently of the data to be processed.

To address the issue of non-linearity and non-stationarity, Huang and his coworkers in 1998 proposed a new approach to obtain the basis functions, extracted from the signal, in terms of a numerical procedure (shifting algorithm) known as Empirical Mode Decomposition (EMD)[1]. As result of this decomposition, the signal is separated into components (modes), producing a set of orthogonal basis functions (Implicit Mode Functions-IMF) derived from the signal in an adaptive manner. EMD is the first stage in the Hilbert-Huang Transform (HHT) methodology, obtained by applying the Hilbert transform to each IMF previously achieved by EMD. This second step is known by Hilbert Spectral Analysis (HSA), and the outcome of HHT is a time-frequency representation of the signal. HHT has been applied in different fields of science

such as fluid dynamics in ocean engineering, financial applications and system identification among many others [2][3]. By its own characteristics, biomedical signals are suited to HHT analysis and have been successfully applied to the study of a broad range of biomedical related problems. The EMD extension to 2 dimensions (BEMD) has been also used to image processing, in particular in the feature extraction to be used in Machine Learning algorithms [4].

In this talk, the HHT state-of-the-art will be presented, pointing the main steps in the recently proposed solutions for some identified drawbacks in the technique.The main goal is to increase the awareness of the Mathematical community for the open problems regarding the EMD decomposition. In order to illustrate the HHT performance, recent results from our group will be presented regarding the assessment of the homeostatic control in chronic dysfunction of the Autonomic Nervous System-ANS (as is the case in T2 diabetes rat model [5]) and also some examples of the clinical potential of using HHT in acute care management and clinical decision with patients.

Keywords: Adaptive Analysis, Hilbert-Huang Transform, Sympathovagal Balance.

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On and Off the person ECG data sensing and processing technology

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Abstract

In the era of the IoT, associated with the growth of technological innovation in the field of ubiquitous computing, sensors are nowadays at the core of wearables and applications aiming at wellbeing and fitness. Continuous monitoring of physiological signals has become a reality, with the generalization of self-tracking and wearable devices, such as wrist bands, smart watches, and smartphones, mostly focused on quantifying physical activity.

Concerning heart-related activity, the most common technology is based on pulse photoplethysmography (PPG), a simple and low-cost optical technique that can be used to detect blood volume changes, from which the instantaneous heart rate can be determined. While many commercial systems exist exploring this modality, the reliability of the provided measurements, most often in terms of average heart rates in (unspecified) temporal windows, is dubious, which poses the question of how precise and useful they actually are. Independent evaluation of some of these devices, namely the popular brands Fitbit and Samsung Gear smart watches, lead to disappointing results. Hence, adoption of a particular device for clinical purposes requires critical validation.

In a different perspective, a new paradigm entitled off-the-person acquisition that consists of embedding health and self-tracking technology on everyday-life objects, complements the on-the-person wearable paradigm with more advanced sensors, such as Electrocardiography (ECG), and Galvanic Skin Resistance (GSR). Built upon authors' work on low cost systems for physiological measurements [1], such devices provide clinical grade recording of ECG signals [2][3]. Furthermore, ECG signals, measuring heart's electrical activity and assessing both rhythmic and morphological patterns of activity, provide a much richer plethora of information. In our work, exploration of this signal is three-fold: person identification/authentication [4], emotion assessment [5], and health monitoring [6]. This paves the way to personalized health frameworks.

The richness of information acquired by these sensors can additionally be complemented by other sources of context and temporal information, in a continuous monitoring framework. Besides cardiac conditions, it has been shown that patterns of ECG temporal evolution correlate with other health conditions. In particular, epileptic seizures can be predicted with about 30 minutes anticipation by monitoring ECG patterns in the temporal domain. By applying supervised and unsupervised learning techniques to these physiological data, tracking trends and individual time evolution patterns of cardiac activity, it is expected that preventive health scenarios, in addition to personalized diagnosis and treatment, may provide significant impact on health and wellbeing. Current work thus provides a step forward towards personalized continuous health monitoring, prevention and treatment.

Keywords: Personalized health monitoring, preventive healthcare, pervasive ECG monitoring

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Mathematical modeling of combination therapy with anti-PD-1 as one of the two agents

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Abstract

Effective T cells kill cancer cells, but they are inhibited by checkpoints, such as PD-1. When its ligand PD-L1 combines with membrane protein PD-1 on the T cell, the T cell activity is blocked. Recently several anti-PD-1 drugs have been approved by FDA, and they offer exciting opportunities in cancer therapy. In this talk we first consider a combination therapy of cancer, with one drug, a vaccine, which activates dendritic cells, so that they induce more T cells to infiltrate the tumor, and another drug, a checkpoint inhibitor anti-PD-1, which enables the T cells to remain active against the cancer cells. To address the question of synergy between the two drugs, we develop a mathematical model, by a system of partial differential equations, which includes dendritic and cancer cells, $CD4^+$ and $CD8^+$ T cells, IL-12 and IL-2, CM-CSF produced by the vaccine, and a T cell checkpoint inhibitor associated with PD-1. We use the model to explore the efficacy of the two drugs, separately and in combination, and compare the simulations with data from mouse experiments. We next introduce the concept of synergy between the drugs and develop a synergy map which suggests in what proportion to administer the drugs in order to achieve the maximum efficacy.

In the second example we consider anti-PD-1 with BRAF inhibitor. In this case we find that the two drugs can be antagonistic in some ranges. This suggests that clinical trials with combination therapy should carefully consider the relative amounts of the two drugs before advancing to the next phase in the trial.

This is joint work with MBI postdoctoral fellow Xinlan Lai.

Modeling ageing in skeletal muscle tissue

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Abstract

One of the important changes associated with human ageing is the so called *sarcopenia*, which is defined as the progressive loss of skeletal muscle mass and strength. According to [2], this syndrome affects more than 50 millions people today and it will affect more than 200 millions in the next 40 years. There is still no generally accepted test for its diagnosis and many efforts are made nowadays by the medical community to better understand this syndrome. Having this in mind, a mathematical model of sarcopenic muscle can be a valuable resource.

Skeletal muscle tissue is one of the main components of the human body. The muscular fibres are organized in fascicles, containing a concatenation of millions of sarcomers, which are the fundamental unit of the muscle which produces force and movement (i.e. *activation*). Connective tissue, which is essentially isotropic, fills the spaces among the fibres.

Focusing our attention only on steady properties, we model the skeletal muscle tissue as a continuum hyperelastic material [5]. The alignment of the muscular fibers and the high water content of the tissue suggest the assumptions of transverse isotropy and incompressibility. In the model that we propose, there are two main constitutive prescriptions: one for the hyperelastic energy when the tissue is not activated (*passive energy*) and one for the activation. Moreover, in order to describe sarcopenia, the loss of performance and the loss of mass are obtained by two different methods.

As far as the passive part is concerned, we assume an exponential stress response of the material, which is customary in biological tissues [3].

Coming to the activation, we follow the *active strain* approach [1], where the extra energy produced by the activation mechanism is encoded in a multiplicative decomposition of the deformation gradient in an elastic and an active part.

In addition, the loss of activation is represented by a damage parameter d which reduces the active part of the stress by a given percentage; while the loss

of mass is encoded in the model by a further multiplicative decomposition of the deformation gradient, where a parameter g measures the fraction of muscle fibers which are not active anymore [4].

Finally, we present some numerical results. We show that the experimental data of [6] on the passive and active stress-strain curves, obtained *in vivo* from a tetanized *tibialis anterior* of a rat, can be well reproduced by our model in the healthy case. Moreover, we discuss the behaviour of aged tissue when g and d increase.

Keywords: Hyperelasticity, activation, ageing, active strain, biomechanics.

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Epithelial layers controlling transitions between compartments in organisms. Modelling and simulation of early stages of atherosclerosis

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Abstract

Epithelial cells are regulators of barrier function and immune homeostasis. Layers of these cells are controlling the transitions between different compartments of organisms, the exchange of chemical substances, of ions, of fluids, of cells. They are track switches of signalling and regulators coupling processes in different compartments. On cellular level membranes and envelopes are playing a similar role.

In this lecture the endothelial layer, an epithelium that lines the interior surface of blood and lymphatic vessels, will be in the focus of mathematical modelling and simulation. In particular the dynamics of the arterial endothelium separating the lumen and the intima is investigated in the early stage of atherosclerosis or inflammation. Here the evolution of the permeability to substances like LDL, to cytokines, to cells like leukocytes, in particular to monocytes, is modelled and simulated. The blood flow in the vessel is coupled with the filtration flow through the intima, considered as porous elastic medium, with the endothelial layer as separating interface. This investigation is intended as a step to a more comprehensive model for the formation of plagues, a process running on a different time scale.

The research of the last years showed the great importance of the epithelial layers in parts of organisms controlling transitions and the coupling of processes in different compartments. In an outlining overview on different subsystems of the human body, we are demonstrating that similar questions and tasks in mathematical modelling and simulation of model systems are arising and posing challenges for future research. Examples of subsystems, where processes highly important for health are taking place and epithelia play an important role, are the digestive system or the oral system. This lecture is based on joint research with Telma Fortes, Maria Neuss-Radu and Adélia Sequeira and a joint manuscript (in preparation for publication): "Mathematical Modelling of the Early Stage of Atherosclerosis" (2017).

The role of computational modelling in patients with congenital heart disease

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Abstract

Interest in the application of engineering methods to problems in congenital heart disease (CHD) has gained increased popularity over the past decade. Computational fluid dynamics (CFD) is a technique of determining fluid flow by numerically solving its equations of motion. It has been a critical and invaluable tool in discovery, prediction, and validation of a wide variety of natural and artificial phenomena. In cardiovascular disease, CFD has been used to understand the contribution of flow disturbances to the evolution of atherosclerosis and risk factors for growth and rupture of aneurysms.

Increasingly, computational modelling and numerical simulations are used to help plan complex surgical and interventional cardiovascular procedures in children and young adults with CHD. It may aid in improving our understanding of the pathophysiology and mechanism of cardiovascular disease, in elucidating measures to treat these diseases, and in surgical planning [1].

From its origins, more than 30 years ago, surgical planning with analysis of flow hemodynamics and energy loss/efficiency has helped design and implement many modifications to existing techniques. The use of computational simulation to examine a broad range of congenital heart disease, including patients with single ventricle physiology and the associated surgical approaches ([2]-[8]), those with aortic coarctation ([9]-[14]), bicuspid aortic valve, Kawasaki disease [15], tetralogy of Fallot [16] or with double outlet right ventricle [17], as well as the effects of pacemaker implantation on vascular occlusion, or delineation of the biomechanical effects of implanted medical devices is now routinely appearing

in clinical journals within all paediatric cardiovascular subspecialties. Interventional planning is equally intriguing. Stent diameter, length, and location can be modelled preprocedurally, with finite element as well as CFD simulations performed to determine an ideal outcome [18],[19].

Over the last 15 years, considerable improvements were made in these calculations owing to (1) better resolution of magnetic resonance imaging, (2) improved computing power, and (3) the use of real patient data to configure the anatomy. Close collaboration between the clinicians and biomedical engineers is paramount to accurate representations and modelling. Despite the intensity of the work involved, surgical planning with computational modelling offers unique insights and tremendous potential for the care of patients with CHD, ultimately each patient's interventional procedure can be planned and analyzed preoperatively on the basis of their patient-specific characteristics to ensure optimal long-term outcomes.

In this presentation, we will review the techniques and principal finding of computational fluid dynamics studies as applied to a few representative forms of congenital heart disease.

Keywords: Hemodynamics, Computer modeling, Congenital heart disease.

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Optimal protocols for a mathematical model for combination therapy of CML

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Abstract

In the talk we introduce a mathematical model for the treatment of chronic myeloid leukemia (CML) which was developed in collaboration with Helen Moore from the pharmaceutical company Bristol-Myers Squibb. The goal is to create a minimally parameterized model which would still capture the effects of combination of tyrosine kinase inhibitors and immuno-modulatory therapies; these are introduced in the model as controls. The pharmacodynamics of the drugs is modelled using Michaelis-Menten terms and since the model focuses on the long term therapies drug dosages are identified with their concentrations. We first analyze the problem as a dynamical system in the case when these concentrations are constant. We show how increasing levels of therapies affect the equilibrium solutions and their stability. In particular, we illustrate how, depending on the parameter values, the model is able to replicate chronic, accelerated and blast phases typical of the disease. The model is then analyzed as an optimal control problem with the aim to minimize an objective functional that takes into account the tumor burden and the total pharmacologically relevant quantities which measure side effects of the drugs given. We first pursue this analysis for control sets that are intervals, i.e., allow arbitrary dosing regimens within certain limits, but also compute the best-in class solutions when a limited range of dosages and timing changes are specified a priori, a common limitation in the practical administration of drug schedules. We show that excellent approximations of optimal protocols can be achieved even within such limited scheduling options. We will also discuss challenges and computational limitations arising in searching for optimal long horizon treatments which are of particular interest for pharmaceutical companies in the case of CML.

Keywords: Mathematical model, chronic myeloid leukemia, combination therapy, optimal control

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Modeling and simulation in Oncology clinical practice

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Abstract

The incidence and prevalence of cancer is expected to increase in the next few decades. Incidence will increase mainly as a consequence of aging of the general population, with smaller contributions from environmental and genetic factors. On the other hand, the increase in prevalence will be the product of a better understanding of the biological behavior of the disease, better and earlier diagnosis and newer, more efficacious, treatments, that lead to increased survival. The increment in survival means that patients will live longer with the disease, as cure is still not a realistic goal for a large percentage of those affected.

This expected increase in the number of patients is met with an enormous quantity of new technologies, both diagnostic and therapeutic, that add up to the complexity of the multidisciplinary decision-making process. The increasing understanding of the underlying mechanisms of cell proliferation, cell invasion and cancer dynamics; the continuously growing number of drugs that target specific molecules or genetic mutations that are only present in a small number of patients; the development of new immunotherapy treatments and the need for new biomarkers that help us predict response to treatment and/or toxicity; personalized, precision or individualized treatments; drug development and pharma-economic analysis under new pharmacometrics methodologies; patient and disease pathways; clinics operations. These are all areas where mathematical modeling and simulation have been very helpful, if not essential, for success.

But more is needed if we are to face the challenges of the coming years. The areas where new developments are required by the oncology clinical community and the ones in which our department can help in the multi-institutional cooperation will be discussed.

Functional regulation in lung cancer from a clinical proteomics point of view

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Abstract

There is an unmet need for an algorithm that allows distinction between mesothelioma, benign changes, viral infections and separating mesotheliomas from other types of epithelial and connective tissue tumors such as for example adenocarcinomas. We foresee that research on lung cancer diagnosis potentially can result in minimizing invasive testing and better classify patient with respect to treatment options at an early stage. Early stage detection is associated with improved patient outcome. To this end, we are working on a proteogenomics based strategy to analyze exosomes from bronchoalveolar lavage (BAL) and pleural effusion. In our recent study applying mass spectrometry on BAL samples [1] three interesting observations were made which suggests that this proposed project will be successful: 1) we found a remarkable overlap in significantly regulated proteins found in BAL with the significantly regulated marker obtained when comparing lung cancer tissue and patient matched normal tissue, 2) we found that the proximity of the extracted BAL seems to affect sensitivity of lung cancer detection and 3) based on the expression level of the identified proteins we concluded that BAL is highly enriched in exosomes. We have now preliminary data based on exosome isolation that confirms that exosomes in BAL have a similar abundance level as exosomes in plasma. Furthermore, our recent preliminary proteomics data from BAL exosomes strongly indicate improved classification potential of exosome proteins. Finally, latest results obtained on computational functional analysis of the data will be presented.

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Should ICD's and CRT's be reused after harvested from patients submitted to cardiac transplant?

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Abstract

Over the last 10 years, heart failure patients are offered multiple treatments to delay the time for the cardiac transplantation. Some of these treatments are therapeutic, other prophylactic, to reduce the risk of sudden death.

This is the reason for implanting ICD's and or CRT's devices in most patients. Often the period of time from implant to the transplant is very short, only a few months. Actually some of the ICD's have full charge battery because they have never fired. As such at the time of the transplant surgery, these devices are explanted and discarded as litter.

The main reason is that at the law determines that all single use medical devices that are implantable should be discarded after its first use. This law is the rule in Europe and America.

There is sufficient evidence that such determination is a non-sense in many circumstances, as the clinical setting we describe.

We will present clinical evidence, biological data, ethical arguments and financial reasons to support our concept that there is the need to reformulate this legal concept.

A major impact in health care sustainability will be achieved while keeping patient care quality at the same level.

Effective models for transport processes through membranes

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Abstract

In this presentation, we develop multiscale methods for the derivation and analysis of effective models in environments containing membranes. At the microscopic level, where membranes are modeled as thin heterogeneous layers, the model consists of nonlinear reaction-diffusion equations within each subdomain. At the macroscopic level, membranes are reduced to interfaces, and effective transmission conditions and/or effective equations at these interfaces are derived. It turns out that the form of the effective laws at the interface depends on the scaling of the microscopic system as well as of the type of microscopic transmission conditions imposed at the bulk-layer interface. For the derivation of macroscopic (effective) models, we first generalize the concept of weak and strong two-scale convergence to flat membranes with periodic structure. This allows to derive cell-problems, which approximate at zeroth order the processes in the membrane. For the derivation of effective transmission conditions at the interfaces, we define test-functions of boundary-layer type, adapted to dimension reduction. In case of curved membranes, we introduce the notions of locally periodic functions on manifolds and thin layers and two-scale convergence with respect to charts.

Parts of the presented results are obtained jointly with Markus Gahn (University of Heidelberg) and Willi Jäger (University of Heidelberg).

Keywords: Thin heterogeneous layers, weak and strong two-scale convergence with respect to charts, effective equations at curved membranes.

A computational approach to design a restenosis criterion

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Abstract

The use of Drug Eluting Stents (DES) has been an important advancement in the treatment of in-stent restenosis. However despite all the progress made in DES procedures the rate of restenosis remains relatively high. Mathematical modeling and numerical simulation can play an important role in identifying zones with higher risk of restenosis. The local delivery of a therapeutic agent, from a biodegradable stent implanted in a coronary artery, is mathematically modeled and numerically simulated. The aim of the approach is to give a contribution to locate future restenosis in patients who received a DES, particularly to understand why restenosis is more frequent near calcified plaques, malapposed struts and in the case of underexpanded stents. Extensive computational results lead to the design of a restenosis criterion.

Joint work with J.Ferreira, Jahed Naghipoor, Lino Gonçalves,Timon Rabcuz.

The changing landscape of Oncology

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Abstract

The incidence of cancer and the proportion of deaths due to cancer will increase in the next decades. These changes do not reflect loss of understanding of the biology of the disease or lack of treatment advances in the field. Instead, these epidemiologic changes are a consequence of the increase in life expectancy and cancer is a disease of aging.

To add on this expected increase in cancer incidence, improvements on the comprehension of cancer biology and better treatment results, have also lead to increase in cancer survival. Cancer is increasingly a chronic disease with prolonged survival, if not curable at diagnosis. According to the American Cancer Society between 1987-1989 the 5-year overall survival of cancer at all sites was 55% and improved to 68% in the years 2004-2010. Thus the number of cancer survivors and patients living with cancer is also increasing, accounting for 14 million people in the USA.

Major challenges have happened in the field of Oncology both in drug development and patient care. Patient physician relationship has changed with an increasing involvement and dependency on technology. New imaging modalities, EMR (electronic medical records), remote outpatient medical consultations and clinical data collection away from medical facilities and sent electronically are some examples. In the area of drug development, drugs are now designed to fit and modulate a specific biologic target with new drugs requiring testing in clinical trials coming at a faster speed than patient recruitment into clinical trials is possible. Clinical trial design moving from large disease-specific studies, to small "basket trials" designed to recruit a limited number of patients with different cancer types but that share a common biologic handicap. Enormous amounts of genomic and proteomic data to be analyzed impacting on clinical decisions before thorough clinical trial validation. Germline genetic fingerprint within easy reach and at low cost without clear knowledge of the contribution of each genetic change to disease/cancer risk with difficult ethical implications. Need for validation of large but limited clinical trial data in enormous general population data bases. Incorporation of PROMs (Patient Related Outcome Measures), stressing patient's quality of life, into the more objective and traditional measures of cancer treatment efficacy based on tumor shrinkage and

prolongation of patient survival. These are some of the challenges we are already dealing with in Oncology for which improvements in technology are critical to consolidate the advances in cancer biology and treatment.

Coronary physiology and imaging-ongoing projects in CORE

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Abstract

Cardiovascular disease can be manifested in several ways. Coronary artery disease (CAD), for instance, may be diagnosed in a stable phase or in an acute coronary syndrome. For each situation, the best treatment option may be different and in the past few years several tools have been developed to aid in diagnosis and optimize personalized treatment. Regarding CAD, two areas deserve further explanation: coronary physiology tests and intracoronary imaging, both of which are subject of active research worldwide and also in our centre in Évora, in a collaboration between the Hospital do Espírito Santo - Évora, the University of Évora and the Instituto Superior Técnico.

Coronary physiology tests refers to a group of invasive techniques based on pressure or flow measurements, mostly used to evaluate the true importance of a given coronary stenosis that appears intermediate on angiography. Most of these indices are pressure-based, have been improved over time and have now a great body of clinical evidence ? generically, patients are better treated when decisions are based on coronary physiology. Every technique has its advantages and disadvantages. We are developing a software which can integrate all relevant pressure-based index in an easy-to-use way and incorporates a new algorithm to evaluate pressure wave contour (rather than the absolute pressure itself) and automatically analyze contrast hyperemia, which has the potential of being more informative and reproducible than the classic methods.

Intracoronary imaging consists mainly in two complimentary techniques: IVUS (IntraVasular Ultra-Sound) and OCT (Optical Coherence Tomography). Again, both have their advantages and disadvantages. OCT has the lead in what regards imaging definition, making possible to obtain detailed pictures of atherosclerotic plaques, stents and even make precise 3D reconstructions. We have a large database of OCT pictures from real patients, with a lot of

data to analyze. We are starting a project to develop OCT picture analysis, with automatic border detection, quantitative and qualitative analysis and 3D reconstruction.

Besides CAD, there are many other pathologies very relevant in cardiology, and currently very hot in the world of research. The scientific advances enabled the possibility of implanting heart valves (mostly aortic) without the need of an open surgery -TAVI (Transcatheter Aortic Valve Implantation). The indications for this technique are increasing, as new, safer and easier-to-use devices are developed. The long term results, however, have not yet been fully appreciated. There are great controversies regarding the hemodynamic profiles created by different devices/techniques and late clinical outcome. It is also our objective to conduct a project directed to this theme, which encompasses Computed Tomography 3D reconstruction and flow distribution analysis and respective correlation to clinical outcome.

All our projects are underway but not only they are in a young phase of development, but they are also generating other potential projects. For these reasons we welcome and challenge the interested audience to get in touch with us if there is an interest in knowing better our group and projects and to collaborate with us.

Biomechanical model for the simulation of colonic pit patterns

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Abstract

The colonic epithelium is formed by thousands of small cavities, called crypts and the extremely tiny pits, in the mucosa of the colon, are the crypt orifices. In normal crypts, the pits are roundish and grouped in a regular pattern. However in aberrant crypts, the shape and pattern of the correspondent orifices have different forms, as for example, star-like, elliptical, sulcus-like, branch-like, tubular, or roundish but smaller than the typical size [1]. The normal crypts are small tubular glands, containing different types of cells, that obey to a programmed cell mechanism in such a way that colonic cells renew themselves continuously each five-six days, in humans. The aberrant crypts occur as a consequence of an abnormal behavior of this programmed cell mechanism, inside the crypts, and are thought to be the precursors of colon cancer [2].

The different patterns of colonic pits can be visualised by clinicians in real time, during a colonoscopy exam, by using an appropriate enhancement technique that involves the direct application of certain dyes in the colon. Moreover, it is also well known that there is a correlation between histopathology and distinct pit patterns.

The goal of this talk is to describe a biomechanical model representing the colonic pit and its surrounding material, and simultaneously, to simulate the

evolution of the colonic pit pattern in time, when there is a disruption of the healthy cell mechanism. It is adopted the two-dimensional crypt geometry introduced in [3], which enables a representation of a three-dimensional crypt in a two dimensional setting, in such a way that it emulates a top view of the crypt and its orifice, as in a clinician's visualisation during a colonoscopy exam.

The biomechanical model couples the cell dynamics occurring inside the crypt with the mechanical behaviour of the material surrounding the crypt orifice. This material around the crypt is considered to be visco-elastic. By using numerical simulations, we show that when a modification of the programmed cell mechanism is implemented, the irregular and abnormal colonic pit patterns, described before, are retrieved.

Keywords: Cells dynamics, visco-elasticity, colonoscopy, aberrant crypts.

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Quantitative modelling of cardiovascular physiology

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Abstract

The short term regulation of cardiovascular function is accomplished by the autonomic nervous system reflexes. This physiologic function has been described in terms of arterial blood pressure and heart rate control.

We developed a computational software to analyze left ventricle pressure and volume measurements simultaneously, which enables the extraction of left ventricle and arterial physiologic assessment, including mechanical energies and efficiency. This analytical tool was used to analyse instantaneous and dynamic hemodynamic changes in vivo in rabbits during acute cardiovascular perturbations produced by the stimulation of autonomic reflexes, for instance arterial baroreflex, carotid chemoreflex and cardiac chemoreflex.

This analysis revealed the impact of autonomic regulation on cardiovascular energetics and efficiency.

Keywords: Cardiovascular reflexes, Ventriculo-arterial coupling, Cardiac efficiency.

State estimators for some epidemiological systems

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Abstract

We consider a class of epidemiological models that includes most well-known dynamics for directly transmitted diseases, and some reduced models for indirectly transmitted diseases. We then propose a simple observer that can be applied to models in this class. The error analysis of this observer leads to a non-autonomous error equation, and a new bound for fundamental matrices is also presented. We analyse and implement this observer in two examples: the classical SIR model, and a reduced Bailey-Dietz model for vector-borne diseases. In both cases we obtain arbitrary exponential convergence of the observer. For the latter model, we also applied the observer to recover the number of susceptible using dengue infection data from a district in the city of Rio de Janeiro

When the "boundary" is critical: defective/missing data for computational hemodynamics

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Abstract

The pathway of computational hemodynamics from being a proof-of-concept research tool to a clinical-routine support is not complete, but we are not so far. Multiple challenges need to be addressed for the dream to come true. We mention particularly (i) the efficiency of solvers for large volume of patients; (ii) the reliability of simulations in patient-specific settings.

Form the clinical standpoint, the most important factors in a numerical simulation are the geometry and the boundary conditions. Imaging devices and image processing tools are currently at an excellent quality level to provide accurate morphological reconstructions of patient-specific computational domains. The numerical treatment of patient-specific boundary conditions, on the contrary, is much more troublesome . The challenges come from the fact that we have several diverse scenarios in clinical settings and the identification of standard data-retrieval procedures to be used to generate boundary conditions for numerical simulations is not easy. Most importantly, available data are almost invariably not enough to make the mathematical problems to solve well-posed. Arbitrary assumptions need to be postulated to complete defective (or even totally missing) data. In this arbitrariness, we can loose reliability of the simulations for clinical purposes. After empirical approaches exploited in the biomedical engineering literature, it is evident the mathematically sound approaches for filling the gap may provide reliable solutions. However, the trade-off between computational costs and efficiency is still to be found.

In this talk, we will give a general overview of possible approaches for prescribing boundary conditions in defective/missing data scenarios, suffering from the "image-legacy problem" (= doctors store many nice images, they do not record corresponding boundary data, so we need to run simulations on real

geometries with no data). In this context, we introduced also the so-called "geometrical multiscale" approach [1]. We address possible practical approaches to fit within clinical timelines working on real cases for aortic pathologies and coronary disease simulations [2, 3]. As the definition of a general standard "boundary-condition protocol" is currently out of reach, this talk will just outlines possible practical solutions.

We also address open challenges for setting up efficient numerical solvers that may run in small facilities, reasonably available to hospitals and healthcare institutions for the clinical routine. Special solvers designed for incompressible fluids in pipe-like domains - based on the so-called Hierarchical Model Reduction approach - will be recalled.

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Keywords: Computational hemodynamics, boundary conditions, data-driven simulations, computational diagnostics.

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Reaction-diffusion waves of blood coagulation in quiescent plasma and in flow

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Abstract

One of the main characteristics of blood coagulation is the speed of clot growth. In the current work we consider a mathematical model of the coagulation cascade and study existence, stability and speed of propagation of the reaction-diffusion waves of blood coagulation [1]. We also develop a simplified one-equation model that reflects the main features of the thrombin wave propagation. For this equation we estimate the wave speed analytically. The resulting formulas provide a good approximation for the speed of wave propagation in a more complex model as well as for the experimental data.

Vessel occlusion is a perturbation of blood flow inside a blood vessel because of the fibrin clot formation. As a result, blood circulation in the vessel can be slowed down or even stopped. This can provoke the risk of cardiovascular events. In order to explore this phenomenon, we used a previously developed mathematical model of blood clotting to describe the concentrations of blood factors with a reaction-diffusion system of equations [2]. The Navier-Stokes equations were used to model blood flow, and we treated the clot as a porous medium. We identify the conditions of partial or complete occlusion in a small vessel depending on various physical and physiological parameters. In particular, we were interested in the conditions on blood flow and diameter of the wounded area. The existence of a critical flow velocity separating the regimes of partial and complete occlusion was demonstrated through the mathematical investigation of a simplified model of thrombin wave propagation in Poiseuille flow. We observed different regimes of vessel occlusion depending on the model parameters both for the numerical simulations and in the theoretical study. Then, we compared the rate of clot growth in flow obtained in the simulations with experimental data. Both of them showed the existence of different regimes of clot growth depending on the velocity of blood flow.

Keywords: Blood coagulation, reaction-diffusion equations, blood flow, vessel occlusion.

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