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ABSTRACTS

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SESSION ABSTRACTS

A multiscale computational fluid dynamics approach to quantify mechanical stimulation within bone tissue engineering scaffolds

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Abstract (500 words max). In bone tissue engineering (BTE), mineralisation of extracellular matrix can be stimulated by using a perfusion bioreactor, in which fluid flow is used to apply a shear stress to the cells (Sikavitsas et al. 2003). However, the scaffolds used in BTE experiments usually have very complex geometries, which can result in a large variation of the wall shear stresses (WSS) sensed by cells in different locations. The aim of this study is to quantify this complex WSS distribution within irregular scaffolds using a multiscale and multiphase computational fluid dynamics (CFD) approach. The microstructural 3D geometry of a silk fibroin scaffold was determined using µCT 80 (Scanco Medical AG, Switzerland) with a nominal isotropic resolution of 10 µm. To define the permeability of the whole scaffold for the global model of the bioreactor system, we analysed nine sub-volumes from the whole scaffold. To do so, the geometries of the sub-volumes (0.5×0.5×2 mm in size) were re-constructed from the µCT dataset using MIMICS (Materialise, Belgium) (Fig. 1a), and respective fluid domains were meshed with tetrahedral elements of varying size (4 – 40 µm) depending on the local curvature. A microstructural CFD analysis was performed for each of the sub-volumes, and permeability was calculated from the prescribed fluid flow and the resultant pressure drop over the scaffold using Darcy's law. Figure. 1b shows an increased permeability in the direction of Sub-volume 4 – 1 – 6. Based on the permeability of the sub-volumes, we homogenised the whole scaffold by assigning an average permeability (4.08×10^{-10} m^2) to it. Following this, a continuum multiphase CFD model was developed (Fig. 2a), in which a flow rate of 2 mL/min was applied, and the scaffold domain was assumed as porous media with its permeability defined as above (4.08×10^{-10} m^2). From the global multiphase model, an overall pressure drop over the whole scaffold was calculated as 2.66 Pa (Fig. 2b). It was then applied as a boundary condition for the microstructural CFD models of sub-volume 6, 1 and 4, whose permeability varied distinctly. Finally, a finite volume method was used to compute the fluid velocity and WSS within the sub-scaffolds in ANSYS CFX (ANSYS Inc, USA). It was found that a higher WSS was generated within the sub-scaffolds with higher permeability (e.g. sub-volume 6 vs. sub-volume 4 in Fig 3). Based on an earlier proposed mechano-regulation theory, in which a WSS in the range of 10 – 30 mPa is assumed to induce bone tissue mineralisation (Sikavitsas et al. 2003), it can be predicted that 25.3%, 42.9% and 40.0% of the surface area of sub-volume 6, 1 and 4 were likely to mineralise, respectively (Fig 3b). This indicates that considerable non-uniform mineralisation would occur within an inhomogeneous scaffold under fluid perfusion, which is generally supported by previous experimental observation (Vetsch et al. 2016). Although respective experimental validation will be needed, we expect that the

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approach presented in this study can facilitate future BTE experiments using perfusion bioreactors by calculating optimal conditions for mineralisation within scaffolds with irregular geometries.

Keywords: computational fluid dynamics; multiscale model; Darcy's law; multiphase model

Acknowledgements

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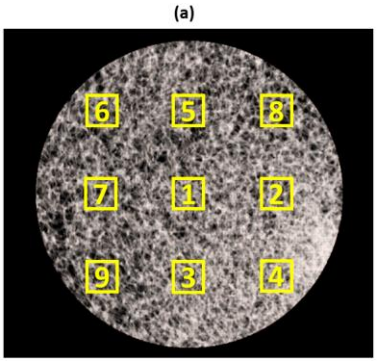

(b)

Section	Permeability/m²
1	2.5e-10
2	2.8e-10
3	3.2e-10
4	1.3e-10
5	5.5e-10
6	5.8e-10
7	5.8e-10
8	5.6e-10
9	5.9e-10

Fig. 1 (a) Locations of nine sub-sections from global scaffold; (b) local permeability of Section 1 – 9

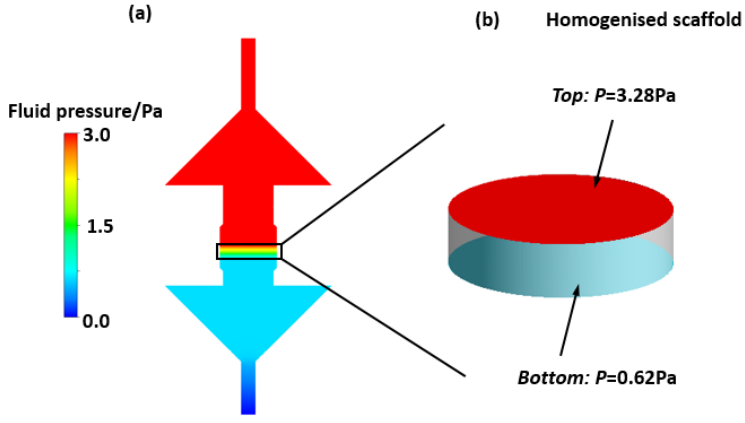

Fig. 2 (a) Fluid pressure distribution within a perfusion bioreactor systems under the applied flow rate of 2 mL/min; (b) pressure drop over the homogenised scaffold domain

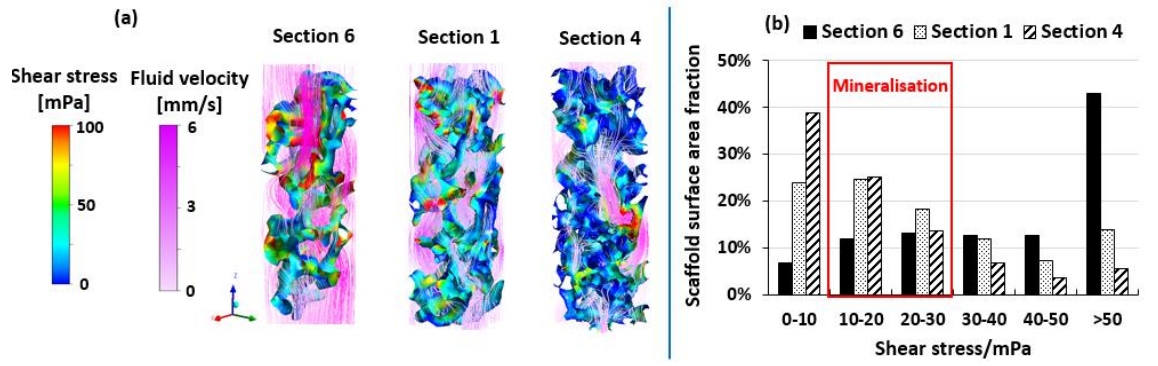

Fig. 3 (a) Wall shear stress and fluid velocity distribution within sub-scaffold 6, 1 and 4; (b) sub-scaffold surface fraction, which undergoes different ranges of wall shear stress

Finite element analysis of the remodeling of a metatarsal after head arthroplasty

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Abstract:

Nowadays, metatarsophalangeal arthroplasty for patients with severe Hallux Rigidus shows good clinical outcomes with a pain relief and a restoration of joint mobility. However, many complications or failures discredit this surgery compared to other surgeries with better outcomes, especially arthrodesis (Brewster (2010)). In a way to reduce the failure rate coupled with the procedure, we developed a subject-specific Finite Element analysis coupled with a bone remodeling law with the aim to determine the density distribution in a metatarsal after an arthroplasty. In this study, hypothesis concerning bone remodeling are the following:

- Use of a purely mechanical remodeling law developed by Weinans et al. (1992) using the strain energy as remodeling stimulus;
- Use of a metatarsal model created through a dedicated Matlab program from CT-scans of patients;
- Use of loading conditions which represent daily activities such as walking or climbing stairs;
- Use of tribological properties between bone and prosthesis close to actual conditions.

The goal of this communication is to describe the primary outcomes of bone remodeling on metatarsal bone with the description of the influence of different factors listed above on final density distribution. This study serves as a premise for the development of a reliable surgical tool with the aim at helping to prevent complications or failures of the surgery. It could allow the improvement of the design of new prostheses.

Keywords: Metatarsophalangeal arthroplasty, bone remodeling, finite element analysis

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Stem Cell Derived Osteoblasts and Osteocytes in human bone-on-chip

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Abstract: With increasing life expectancy, pathologies related to massive bone loss carry $10 billion financial burden on the U.S. healthcare system. Successful techniques to repair massive tissue regeneration or test treatment on human biological systems over long period of times can be however difficult and require the use of physiologically relevant functional materials. We propose to build *in vitro* systems where human osteocyte progenitors are seeded in a previously decellularized human bone tissue for more than fifteen months. The systems are compared to *in vitro* systems seeded with mature osteocytes. To design successful cellularized implants it is essential to quantify the relationship between *in situ* mechanical stimulation and the cell biological response at different stages of their differentiation and to characterize the ECM formed by the seeded cells. The mechanics of these systems are modeled numerically and tested experimentally in customized machines both at the tissue and cell scales.

The bone-on-chip produced after 109 days an ECM of which the strength was nearly a quarter of native bone, contained type I collagen at 256 days and was mineralized at 39 days. The cytoplasmic calcium concentrations were higher in mature osteocytes than in progenitor cells and were maintained constant under mechanical loading. The cytoplasmic calcium concentration variations seemed to adapt to the expected in vivo mechanical load at the successive stages of cell differentiation. The cells are further characterized under confocal microscopy at 547 days.

Keywords: osteocytes; bone-on-chip; MSC differentiation; bone mechanics

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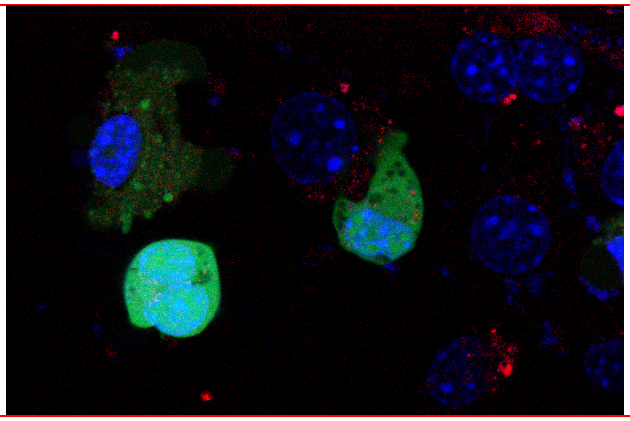

Fig. 1 Stem Cell Derived Osteocytes and Osteoblasts at 547 days in human bone-on-chip

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Multi-agent simulation for bone remodeling process: a preliminary study

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Abstract. Bone remodeling is a biological process affecting the bone density via a mechanism of cellular mechanotransduction under mechanical stimuli. A number of classical bone remodeling laws were proposed [1-2]. However, these tissue-based laws do not take the link between mechanical stimulus and bone cell dynamics into consideration. Recently, novel laws have been proposed [3-4] to achieve such important link. Finite element modeling has been used to implement these novel laws. This equation-based modeling scheme considers cell population as homogeneous. Consequently, only global behavior may be elucidated. The objective of this work was to develop a new modeling approach based on agent-based modeling and simulation (ABMS) approach for simulating the bone remodeling process integrating mechanical stimuli and cell dynamic behaviors. This modeling technique allows each bone cell and its interactive behavior with others bone cells and environmental factors to be performed. A multi-agent model of a cortical bone was created using GAMA platform (gama-platform.org/). Each agent was modeled as bone cell (osteoclast, osteoblast, and osteocyte) or biochemical factor (TGFβ, OPG/RANKL). A 3-year bone remodeling process under maximal mechanical stimuli was simulated. The evolution of bone cell populations was observed during this process. Future works related to the integration of more complex functional behaviors of bone cells. Moreover, more experimental data based on the correlation between mechanical properties and biochemical responses will be investigated. Furthermore, boundary and loading conditions will be improved based on the linking to organ- and tissue-based models.

Keywords: Multi-agent simulation; bone remodeling process

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Numerical model and experimental test bench for hemodynamic study of coronary artery: bifurcation, stent

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Abstract.

This study aimed to develop an experimental and numerical platform for improving the knowledge of hemodynamic flow disturbance due to the use of relatively rigid devices (as stents) in vessels (especially coronaries) with complex geometries (bifurcations). A regular treatment in interventional cardiology is the endovascular placement of a relatively rigid medical device to interact with the pathological tissue. The deployment of these rigid medical devices generates significant distortions of the vascular structure and modifies the hemodynamic flow [1], especially in bifurcations. The main scope of this study is to assist in planning and optimizing the surgical procedure for complex anatomical configurations with experimental measurements and robust and fast simulations. Computational fluid dynamics (CFD) models and experimental data are combined with the objective of evaluating the modification of the hemodynamic flow in a stented coronary artery.

First, a test bench (circulatory loop) was developed to visualize stent implementation and deployment and to evaluate how it disturbs the hemodynamic flow. For a more realistic configuration, experiments are performed under human-like blood flow conditions generated by a pulsatile pump. In addition, pressure pulse control is achieved using compliant and resistive elements. Pressure readings are obtained with external transducers coupled via water filled catheters. A seeded blood-mimicking fluid is used for implementing the particle image velocimetry (PIV) technique to measure flow velocity fields (Cf. Fig. 1). In this research a realistic coronary geometry with a bifurcation is studied, a transparent phantom was fabricated (polymer molding) to mimic the coronary artery shape (Cf. Fig. 2). Moreover, this experimental bench is used to confront and validate our CFD simulations. CFD [2] analysis has been recently adopted in many fields of interventional cardiology. These numerical simulations provide experimentally inaccessible quantities, as wall shear stress (WSS) and its variation during a pulse. Many studies have highlighted that an abnormal WSS could promote restenosis. In most CFD studies of stented vessels hemodynamic flow, the geometry is described using non-deformed configurations. These simulations do not consider the complex physical features, such as stent and vessel strain (and stress), which may have a major impact on the hemodynamic flow. The aim of this study is to provide more realistic simulations with pulsatile pressure and pre-strained geometry (an issue from previous tests on coronary phantoms and numerical simulations). The initial (non-strained) geometry studied in this paper was issued from a patient geometry provided by cardiologist G. Finet.

With the first results, the numerical and experimental platform seems able to provide crucial information on hemodynamic flow disturbance and the possibility of restenosis. Therefore, it points out that this experimental test bench and CFD simulations could be useful tools to compare stent designs and surgery strategies in order to identify the optimal solution for each individual's anatomy.

Keywords: hemodynamics; atherosclerosis; stent; computational fluid dynamics

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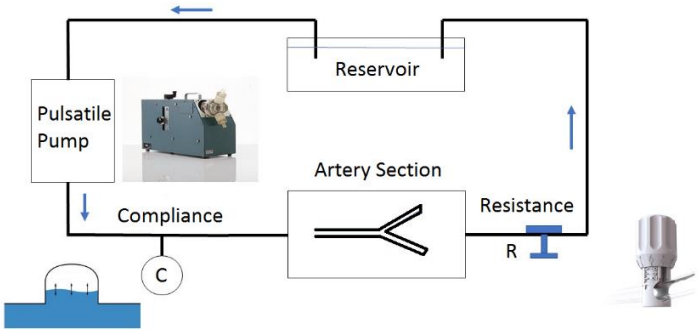

Fig. 1 Experimental test bench diagram

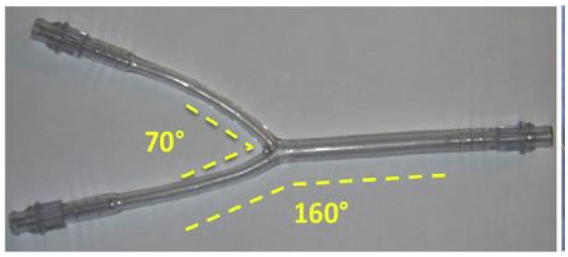

Fig. 2 Phantom of the studied coronary artery with bifurcation

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Intravascular ultrasound elasticity-palpography technique for mechanical characterization of coronary plaque anisotropy

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Abstract

Critical to the detection of vulnerable plaques (VPs) rupture is the quantification of their mechanical properties. A number of biomechanical studies have identified peak cap stress amplitude as a major key predictor of susceptibility to rupture. Estimating intraplaque stress distribution to predict plaque rupture has been a challenge. To overcome this hurdle, local strain has been measured based on intravascular ultrasound (IVUS) sequences. Once the local mechanical properties of the atherosclerotic lesion are known, intraplaque stress can be directly quantified. Therefore, on the basis of IVUS strain images, Céspedes et al. (2000) proposed an isotropic elasticity-palpography technique (E-PT). This approach was later enhanced by our group (Deleaval et al. 2013) to account for the non-concentric anatomic shape of the VPs. Despite presenting original and promising "homogenized" approaches for improving the evaluation of VP rupture, these studies did not overcome a main limitation related to the anisotropic mechanical behaviors of the arterial wall and atherosclerotic lesion.

The present biomechanical study was designed to extend the theoretical framework of the improved E-PT by considering the anisotropic mechanical properties of the arterial wall and lesion constituents. Based on the continuum mechanics theory prescribing the strain field, an anisotropic index (AI) was defined. This extended anisotropic E-PT was successfully applied to several coronary lesions of patients imaged *in vivo* with IVUS at the Lyon's Hospital of Cardiology. The robustness and performance of the new anisotropic elasticity-palpography index were investigated with respect to noise, which may affect the prediction of plaque vulnerability.

Keywords: atherosclerosis; vulnerable plaques; elastography; coronary disease; inverse problem

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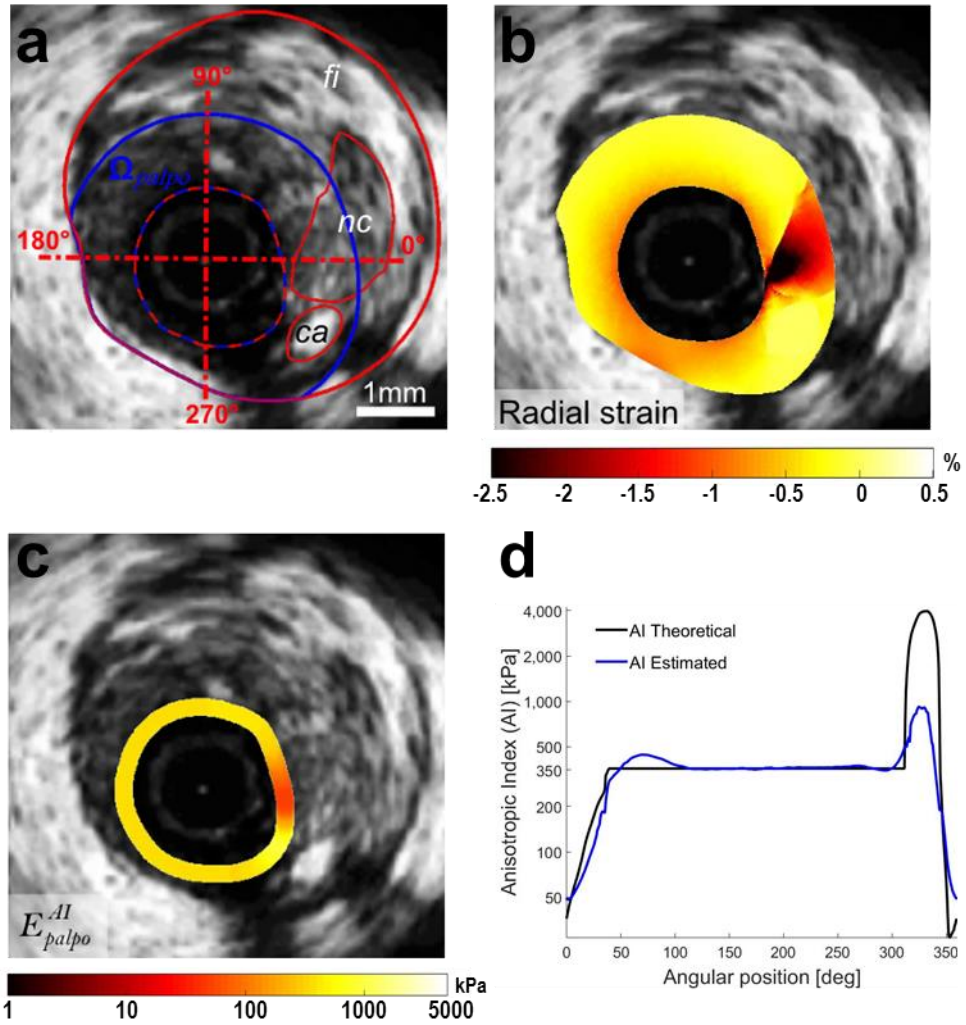

Fig. 1 Performance of the extended anisotropic elasticity-palpography technique in detecting a vulnerable plaque with a small calcified inclusion and one necrotic core. (a) Intravascular ultrasound image. (b) Simulated radial strain distribution. (c) Resulting palpogram given the value of the computed anisotropic index (AI). (d) Comparison between the computed and the exact AI.

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Recursive model identification for the evaluation of the autonomic response to exercise in Brugada syndrome

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Abstract. Brugada syndrome (BS) is a genetic disorder characterized by a distinctive electrocardiographic pattern, associated with an increased risk for sudden cardiac death (SCD) due to malignant ventricular arrhythmias. The autonomic nervous system (ANS) plays a relevant role in the pathophysiology, arrhythmogenesis and prognosis of the disease. Indeed, ventricular arrhythmias in this population tend to occur at rest and mainly at nighttime, thus being commonly related to an augmented parasympathetic tone. Furthermore, many studies have revealed an anomalous sympathetic function in BS. However, despite this connection between BS prognosis with autonomic imbalance, it remains to determine which autonomic tests and indicators are the most appropriate so as to identify those BS patients at high risk for SCD.

The cardiovascular response to exertion has been extensively studied through clinical trials and computational models. Exercise causes a sympathetic activity increase and a parasympathetic inhibition, leading to higher heart rates (HR). Conversely, post-exercise cardiodeceleration is regulated by an increase in parasympathetic activity, as well as a gradual sympathetic withdrawal. Since classical HR analysis at rest frequently fails to identify patients at risk, we hypothesize that the evaluation of HR modulation during physical stress testing may provide additional information for risk stratification in this population. Moreover, although classical markers are widely used in clinical practice to estimate sympathetic and parasympathetic levels, since computational models directly represent interactions between the ANS and the cardiovascular system (CVS), a model-based approach could provide useful knowledge to support autonomic response interpretation.

Therefore, a recursive parameter identification method is proposed and applied to a closed-loop mathematical model of the baroreflex and cardiovascular systems, in order to estimate the evolution of sympathetic and parasympathetic contributions to HR modulation during exercise. The model was evaluated with data from a BS patient, acquired during a physical stress test. The results show a close match between experimental and simulated signals (mean error = 0.85%) and the estimations of sympathetic and parasympathetic components were consistent with physiological knowledge.

In this work, we propose an original method to capture ANS dynamics in response to exertion. It is based on a recursively identified closed-loop model of the baroreflex and the cardiovascular systems, introducing: i) a subject-specific model parameter identification and ii) an estimation of the time-varying sympathetic and parasympathetic activities, by the application of a recursive evolutionary algorithm. Results demonstrate the feasibility of the model to reproduce realistic autonomic responses to non-stationary physiological conditions, such as exercise. This approach unmasks indicators capturing cardiovascular and autonomic dynamics never before studied in BS, in order to better understand the underlying mechanisms of the ANS in response to exercise that can be useful for risk stratification in this population. Current developments are focused on the application of the proposed method to a large population of BS patients with different levels of risk for SCD.

Keywords: Physiological model; Parameter identification, Brugada syndrome; Autonomic nervous system

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Mathematical models of solute transport in microcirculation: exchanges between arterioles and capillary-perfused tissue

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Abstract. Arterioles deliver solutes (gases, proteins and systemically assumed therapeuticals) to smaller blood vessels by convection. A relevant amount of solute is also delivered to the surrounding tissue by direct diffusion through the arteriolar walls [1]. The role of arterioles in solute transport cannot be analyzed separately from that of capillaries, the main site of solute exchanges with the tissue. Profound differences exist, however, between arterioles and capillaries: i) size, arteriolar diameters lay in the range 200μm to 10μm, while capillaries have mean diameter 5μm, that is under the limit of correctly representing blood as a continuum; ii) structure of the wall, arterioles have a thick muscular wall not shared by capillary (fenestrated or tighly-fissured) wall; iii) geometrical organization, arterioles tend to form tree-like structures while capillaries tend to organize into mesh-like structure; iv) distribution in the tissue, arterioles stem from larger vessels in a successive branching ordering, while capillaries are ubiquitously embedded in the tissue.

From a theoretical viewpoint, the above aspects prompt for different modeling approaches, each tailored to a specific structure. In this work, we pursue the idea of explicitly modeling arterioles and use instead homogenization techniques to describe the capillary-perfused tissue [2]. We represent the arteriolar tree as a 1D graph including several branching points and we use an upscaling algorithm to connect it with the tissue-capillary matrix. In the arteriolar tree we solve reduced balance equations for incompressible fluids representing plasma and red blood cells, respectively, and for solutes. The capillary-perfused tissue is instead modeled as a double porosity medium to describe its dual fracture/porosity structure: a fracture pore system representing the embedded capillaries and a less permeable matrix pore system representing the interstitial fluid space. Fluid flow and solute transport are studied introducing effective permeability and diffusion coefficients.

Several simulations will we presented to discuss the behavior of the above described arteriole/capillary coupled system with respect to the transport of different solutes, ranging from molecules of low to high weight.

Keywords: microvascular circulation; double porosity model; homogenization techniques; arterioles; capillary-perfused tissue

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Biomonitor: a real-time e-health app for the analysis of relevant physiological parameters using a wearable device.

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Abstract:
Aim. This work presents an e-health app (Biomonitor) for real time assessment of quantities (physiological and biomechanical) of a user wearing a wearable device. The framework of this work is the Health@Home scenario, an Italian Smart-Cities project aiming to provide a feasible and interoperable ICT solutions for a better quality of life of people at home.
Materials and Methods. The use of Biomonitor allows to measure and visualize the user's parameters, e.g. data coming from the wearable multi-parametric device, Zephyr Bioharness 3.0 (BH3), on a smartphone/tablet. The accuracy of the BH3, while the subject is doing daily activities, has already been investigated in previous works and is described in [Casaccia, 2016]. Through the proposed app, once the device has been paired (via Bluetooth), it is possible to live monitor ECG-related signals and other physiological quantities (e.g. heart rate, breathing rate, posture, peak of acceleration) and store them in databases or formatted files. The concept of the developed architecture is summarized in Fig. 1. In order to make use of such application, a smart device supporting Android 4.0.1 or later version, supporting the Bluetooth 4.0 standard at less, is required. The processing of data acquired is performed in real-time and allows the user to obtain useful information about the daily activities, together with dedicated and physiologically relevant indicators (e.g. time intervals from ECG waveform). An appropriate algorithm [Cosoli, 2015] has been implemented to calculate the ECG intervals and to find singularities when these intervals are out of range. The app has been tested in a real domestic scenario involving two adult users (a male, aged 66 and a female, aged 58). The users performed the monitoring of their ECG signals 2 times for day (sitting and standing) for a period of time of 15 days.
Results. The user can monitor if the main ECG intervals (i.e. HR, PT, etc.) are in agreement with the normal physiological ranges or if these values fall outside the ranges, in the mobile device. If this last situation happens, the system will send a notification to the appropriate service (for this particular case, the notification consists in the request to the user in performing an accurate ECG analysis in the following days). The system invites the user, with a non-stressful procedure, to make extra measurements during the day to check if the singularities are confirmed or not and eventually suggest a previously agreed procedure (i.e. calling the expert).
Conclusions. This specific function of the app provides an interesting care service for older users with cardiovascular diseases and their care assistants and doctors that can monitor in real-time the user during normal activities of daily life.
Future works. The app measures several quantities when it is associated with a wearable device and it is also possible to integrate different sensors (blood pressure meter, oximeter, body weight scale, etc.). The authors will analyzed such solutions to investigate possible scenarios and services to improve the well-being of users and the Biomonitor app.

Keywords: e-health App, real-time measurements, wearable sensors.

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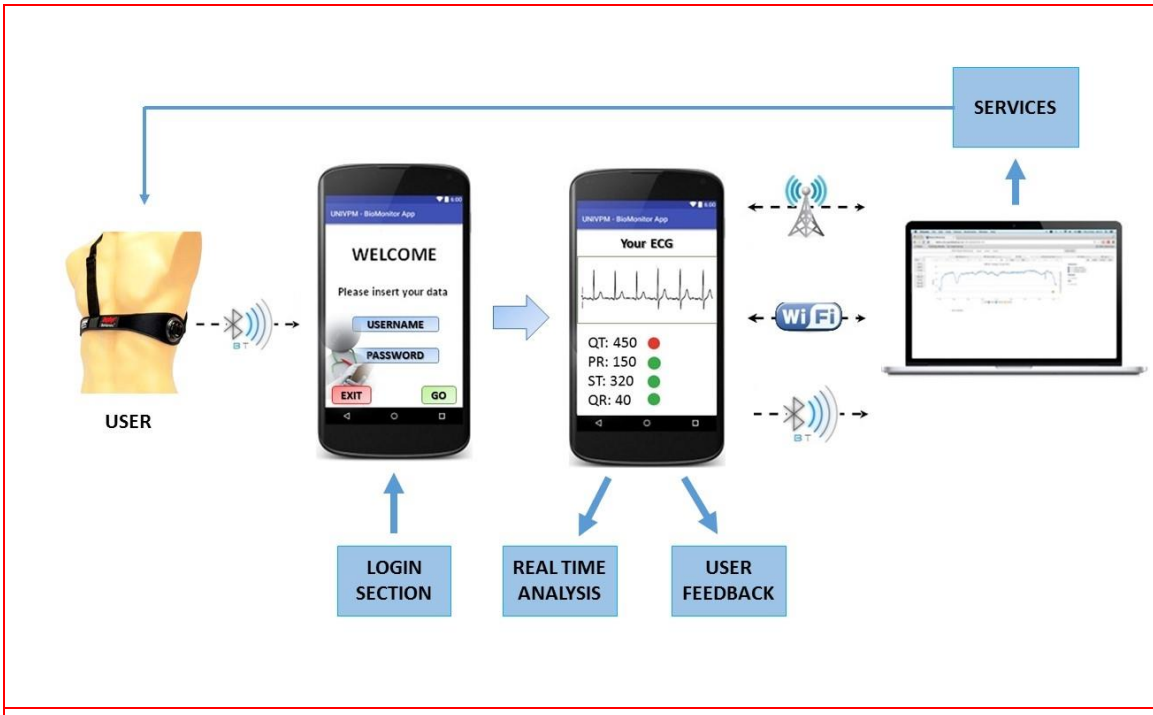

Fig. 1. Concept of the Biomonitor app

Rehabilitation at Home with real time feedback

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Abstract. This study describes a serious game for musculoskeletal rehabilitation with real-time feedback, using different types of sensors, such as the Kinect camera and inertial measurement units (IMU). Traditional rehabilitation programs require patients to perform assigned exercises at home; however, this current approach does not offer the experts objective data to analyze these home sessions. Serious games have been studied as a possible connected approach to solve this problem. Nevertheless, due to the high cost of deployment, most serious game systems use the Kinect camera to acquire the patient's motion data. This leads to a poor angle estimation due to the lack of precision in the Kinect's joint estimation. We have proposed, in the past, a fusion algorithm between Kinect and IMU sensors to estimate joint angles at a higher precision (Tannous 2016). This led us to investigate the possibility of real time data collection from several types of sensors applied to serious games. The Kinect camera gives the possibility to save joint position and angle data into text files. Using fusion between Kinect camera and IMU sensors on a specific joint will lead to a more precise data being saved in text files for offline expert analysis. Experts can specify the joints that require more precision, on which the patient will attach IMU sensors, and the real-time data saved from these joints will be the fusion outcome. For the other joints, the raw data from the Kinect will be saved.
A complete scenario starts with a clinical session, where the expert assesses the case of the patient, assigns a serious game rehabilitation session (containing exercises from six different simple movements, a football game and an object manipulation scene), and requests the placement of IMU sensors on some body parts (maximum 7 IMUs). At the beginning of a serious game session, the ID of each sensor placed on the body is provided. The sensors are auto-calibrated, and the patient can start the game. At the end of the game, joint positions and angles are saved, to be analyzed by the experts. Results will be presented to the experts in the form of angle graphs and remapping the patient's motion, as requested by medical experts following a previously conducted acceptability study (Figure 1). In the future, we will study the possibility of predicting and correcting patient movements.

Keywords: Serious Games, Musculoskeletal Rehabilitation, Real Time Computing.

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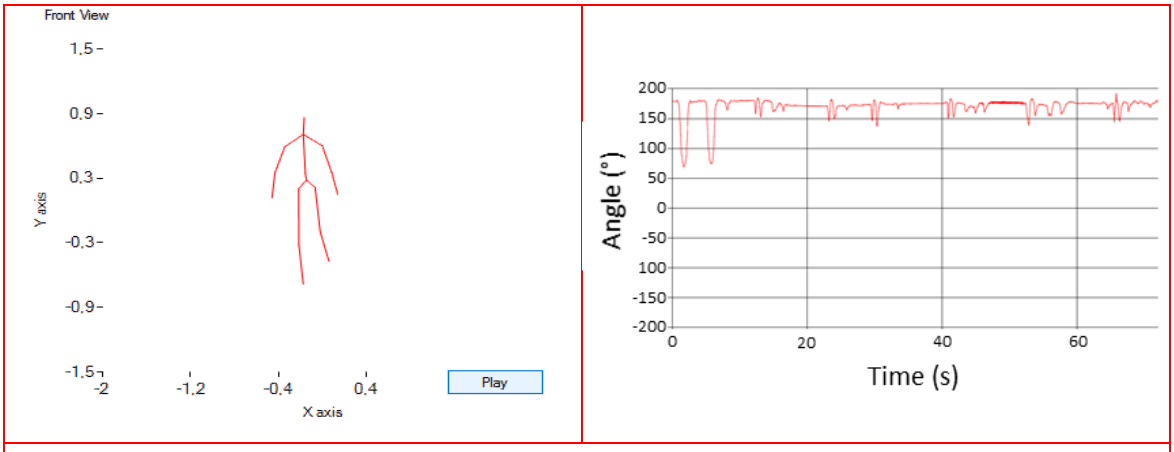

Fig. 1 Presenting exercise trial joint positon video (Left) and joint angles (Right) for experts to analyze

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AUTOMATIC AND REAL-TIME DETECTION OF CONTRACTIONS APPLYING THE NON-LINEAR CORRELATION COEFFICIENT H^2 ON ELECTROHYSTEROGRAMS

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Key words: Electrohysterogram (EHG), non-linear correlation coefficient, H^2, real-time detection of contractions

ABSTRACT

Real-time detection and characterization of contractions are of great interest in a biomedical context. Indeed, the kind, strength and frequency of contractions are crucial information that obstetricians consider to diagnose risks of preterm labor. Usually, patients are monitored with a tocodynamometer, which registers the different contraction thanks to a pressure sensor.
In this study, we investigated a different technology, the uterine electromyography, or electrohysterography (EHG). This technic is noninvasive and allows recording the electrical activity of the uterine muscle by placing electrodes on the patient's abdomen.
Herein we used 18 Ag/AgCl electrodes, 16 were placed according to a 4x4 grid under the patient's navel as recording electrodes, and 2 were placed on her hips as reference electrodes. A relevant committee validated this protocol and all patients gave their consent for the study.
We recorded thus, during about 40 minutes, on 53 pregnant women (501 contractions), 16 simultaneous EHGs for each woman, The EHGs were digitized with a sampling frequency of 200Hz. A tocography recording was realized simultaneously in order to identify the bursts of EHG activity related to uterine contractions.
In order to increase the S/N ratio, we realized some pretreatments, first a Butterworth filtering, (frequency band : 0,2 and 3Hz) [1]. Then, we computed two bipolar matrices, realizing pair-wise signal subtractions on the 4x4 EHG initial matrix according to the vertical and the horizontal axis respectively. We obtained 2x12 signals: 3x4 for the vertical, 4x3 for the horizontal bipolarization.
The non-linear correlation coefficient H^2 is a nonparametric method able to estimate the level of non-linear dependency of a signal to another. Its value varies from 0 (low correlation) to 1 (high correlation) [2]. In this study, we use a window (length: 4 seconds, step size: 2 seconds) to go through the two bipolar matrices, and compute for each window position, 36 H^2 values

between each available adjacent pair of bipolar signals. We count the H^2 values over a first threshold (T1) . Then, the positions of the window where this number is over a second threshold (T2) are considered as events (T1 and T2 being selected as the best among two sets of tested values). These events can be located outside a contraction burst (considered as "False alarms"), or inside (correctly detected as "Full" when the event matches the contraction limits or "Partial" when one or more events are detected but their limits do not match the contraction limits). We also count the "Empty" conditions (no event detected within one contraction). In this study, we obtained 80,04% (401/501) of contractions presenting events detected into their limits. Among these, 52,69% (264/501) are "Full" detections, 27,35% (137/501) are "Partial" detections, 19,96% (100/501) are "Empty" detections and 344 events are "False alarms".
These first results show the potential of the H2 parameter to detect contraction in real-time. Post treatments still need to be investigated to increase the Full detection rate, and to reduce the "False alarms" thanks to other information, such as EHG frequency content for instance.

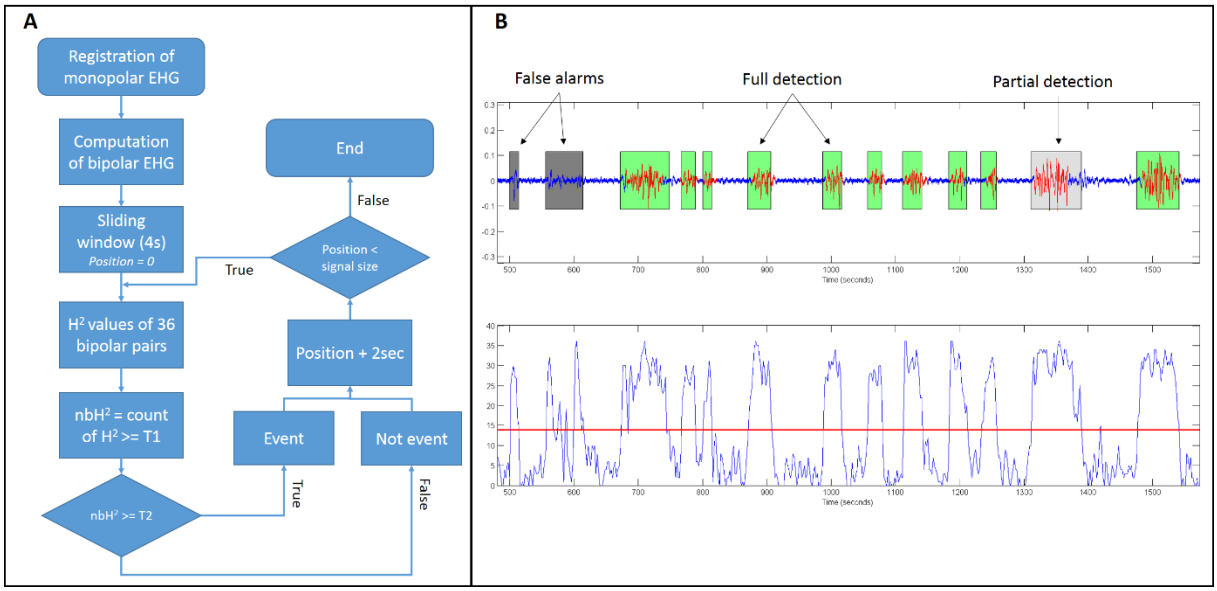

Figure 1 A) Flowchart of the algorithm. B) On top: a bipolar signal with contractions in red, and events detected by the H2 algorithm (black: false alarm, gray: partial detection, green: full detection). On bottom: counts of H^2 >T1 for each window position (blue) and threshold T2 (red)

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Data analytics oriented to personalized medicine. Use cases

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Abstract. In recent times, data analysis discipline is considerably increasing its capacity of action in several fields and sectors of society. The improvement of technology, together with a greater ability to acquire, transmit and store information, results in a wealth of information and data available (Big Data). With a view to discover the implicit knowledge from data, it is necessary the use of leading data analytics techniques, such as Machine Learning techniques.

The application of data mining techniques in Medicine offers and enormous potential for many medical areas, like for example genomics, clinical trials, epidemiology or tele-assistance. In this sense, we aim at creating value, by providing medical services that are more effective, as well as allowing both the personalization of the service itself and the optimization of available resources. Personalized medicine increases the relationship among doctors and patients, which leads to the active participation of all the agents involved. Moreover, the analysis of data applied to health eases the design of new treatments; leads to more effective clinical decision making; and provides more efficient prevention approaches.

The "Wellbeing and active aging" and "Intelligent Data Analysis" specialization areas at CTIC Technology Centre are committed to the research and development of solutions, leading to possible breakthroughs in this field. In particular, our team of experts and researchers is currently working on the following application fields:

- Analysis of the biomechanical factors that influence the human gait, through the study of the accelerations. The objective is to evaluate the quality of patient's gait after a surgical intervention and to analyze the risk of falls in elderly people. This analysis also allows the design and planning of personalized rehabilitation treatment plans and routines.

- Active surveillance of patients with bipolar disorder, through the analysis of their physical activity, using accelerometer-based solutions. Our objective is to predict and anticipate disease progress, which will allow adjusting the treatment and hence anticipating or delaying appointments with the specialist.

- Study of the main chronic diseases in order to identify and monitor the medical and social variables that directly influence them. This will facilitate patients' segmentation or stratification and allow for the deployment of action plans for those in whom the risk of worsening is greater.

To sum up, the application of analytical techniques in the description, prediction and prescription within the health sector, contributes to improve the medical care system for people and therefore, their physical and social well-being.

Keywords: Data Analysis; Personalized Medicine; Machine Learning; Human Gait; Bipolar Disorder; Chronic Diseases

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Subject-specific 3D Musculoskeletal Simulations of the Human Tibialis Anterior

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Abstract. This work aims to assess the influence of subject-specific geometry of a muscle-tendon complex (Tibialis Anterior (TA)) by comparing two geometric model variations to that of a subject-specific geometric model. With the results of this study, the predictive ability of 3D computational finite element models can be enhanced.

A biomechanical analysis of the human musculoskeletal system provides insights into the functioning of human movement, which typically cannot be obtained *in vivo*. Since validation data is very difficult or impossible to obtain experimentally, the predictive ability of such models is limited by the most simplified component in the overall model structure. Generally, the major components of a musculoskeletal biomechanical model can be grouped into the (1) geometric model of the anatomy, (2) joint kinematics and/or muscle forces which are related via the constitutive description of the individual structural components and (3) the analysis of bio-signals. A critical component in linking the kinematics and forces within a biomechanical system is the geometry of the anatomical components, for example, the computation of joint moments requires the positioning of muscle attachments relative to the joint centre. There exists, however, a large amount of anatomical variation between humans. To account for this, state of the art methods use population (statistical) modelling or scaling of bone-segments to overcome inaccuracies which arise when using a generic anatomical geometric model. These methods, while providing a trade-off between modelling effort and accuracy, may not represent the realistic internal situation of the musculoskeletal system. For example, Lenaerts et al. (Lenaerts, 2009) showed that significant differences in hip contact forces can arise when comparing scaled and subject-specific models. However, since this study represented muscles as 1D elements, subject-specific geometry of the muscles themselves was not considered.

In order to quantitatively judge the influence of subject-specific geometry on the predictive ability of a biomechanical model, a subject-specific 3D FE geometric model of the TA was developed by using a combination of MRI and DTI (diffusion tensor imaging) to define subject-specific muscle boundaries and obtain local muscle-fibre orientation. The (same) subject performed isometric contractions of the TA muscle and the resulting forces about the ankle and muscle activity were measured via a torque sensor and high density surface EMG, respectively. The EMG measurements were then used to extract muscular activation profiles, which were used to drive the active component of the constitutive model for each of the three TA FE-models. The constitutive description of the muscle-tendon complex was based on a non-linear hyperelastic constitutive muscle model developed by Röhrle et al. (Röhrle, 2016). Variations were taken on the geometric models by (1) using a publicly available data set (visible human project (VHP)) and (2) using a scaled generic geometry obtained via scaling of the VHP model to the subject's segment length. By comparing predictions such as total forces, lines of action and internal stresses within the muscle, from all three models, a quantitative influence of subject-specific geometric modelling can be obtained.

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Keywords: Muscle; skeletal; musculoskeletal; FEM; 3D; subject-specific

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Estimation of the individual muscle force by modeling of the sEMG/force relationship

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Abstract. The knowledge of the force level is highly important in clinical applications for diagnosis and treatment purposes, biomechanical studies for prosthesis control and kinesiology applications for rehabilitation purposes. However, the main problem is that the force developed by an individual skeletal muscle cannot be measured non-invasively. Therefore, it is necessary to develop an accurate way to estimate it. Furthermore, the muscle activation generates an electric phenomenon, measured at the skin using electrodes; the surface electromyogram (sEMG). In the biomechanics literature, several models of the sEMG/force relationship are provided. However, they suffer from several important limitations such as lacks of physiological realism, personalization, and representability. A recent study, presented a global analysis of this relationship in simulation (Al Harrach, 2017), where they investigated the shape of the sEMG/force relationship and the factors that governs it using High Density sEMG (HD-sEMG) and data fusion. In addition, they proposed a 3rd degree polynomial equation in order to model this relationship (Al Harrach, 2017). In this study, we propose to use this HD-sEMG/force relationship model in order to estimate the individual muscle force using optimization technique in simulation. For this purpose, we will use a fast generation cylindrical model (Carriou, 2016) for the simulation of an 8×8 HD-sEMG grid and a twitch based force model for the muscle force generation. These models are adapted to the Biceps Brachii muscle specifications. For different configuration of parameters 10 isometric isotonic contractions lasting 5s are simulated. The Root Mean Squared (RMS) value in mV representing the HD-sEMG amplitude at each contraction level is obtained by data fusion via Watershed algorithm. For the muscle force, it is averaged along the 5s plateau in order to obtain one representative value. The objective of the work is to estimate the polynomial coefficient in order to find the sEMG/force relationship equation. This subject specific equation, will allow us to estimate the individual muscle force from the RMS value obtained after data fusion. The schematic of the estimation problem is visualized in Fig. 1, where the inputs are the three RMS values in addition to other subject specific parameters and the outputs are the three polynomial coefficients. In order to estimate the polynomial coefficients, we used an optimization tool, the linear least square solver with constraints and boundaries. First, we only added the coefficients signs constraints obtained from (Al Harrach, 2017) and we computed the Normalized Root Mean Squared Error (NRMSE) between the estimated and the simulated force. We obtained an error equal to 9.54 ± 4.54 %. Then, in order to accurately estimate the coefficients of the HD-sEMG/force relationship, we added additional boundaries on the optimization procedure following the different morphological and anatomical parameters obtained from the sensitivity study presented in (Al Harrach, 2017). In this case, the new computed NRMSE is equal to 5.94 ± 2.5 %. Thus, it seems that the HD-sEMG/force relationship model is a subject specific model. Subsequently, adding personalized parameters to the energetic ones is essential for efficient force estimation process as demonstrated by simulation.

Keywords: surface electromyogram, HD-sEMG, muscle force, optimization, Biceps Brachii, high resolution sensor network.

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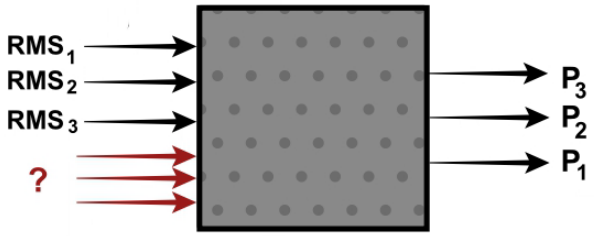

Fig. 1 Schematic of the input/output system.

Modeling the effect of mechanotransduction on the Intra Uterine Pressure

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Abstract. Preterm labor is an important public health problem as the percentage of preterm births reaches 9.6% of all births worldwide. The efficiency of uterine contraction during labor is complex and still poorly understood. It has been related mainly to two phenomena evolving during pregnancy: i) cell excitability (their ability to exhibit spontaneous bursts of action potentials, APs, inducing contraction at the pacemaker area); ii) the global synchronization of the uterus (the whole uterus contracts in 20s during labor). This study aimed to develop a multi-scale (from cell to whole organ levels), multi-physic (electrical and mechanical) model of the uterine muscle, to represent the links existing between the electrical and the mechanical behaviors of the contractile uterus. This model, based on an existing electrical model [Rihana, 2009] permitting to represent the cell excitability and the electrical diffusion in the uterine muscle (cell and tissue levels), includes now a modeling of the force generated by the uterine cells electrically active. The link between the electrical and the mechanical models is done trough the intra-cellular calcium concentration, one output of the electrical model, input to the force model. The mechanical model in turns, computes by using a viscoelastic representation of the uterine tissue, the stretching of the tissue (at the organ level) [Yochum, 2016]. This stretching, output of the mechanical model, is then input to the electrical model and activates stretch activated channels (SAC, means of the mechanotransduction process), included in the electrical model at the cell level (Fig 1.a). This multi-physic model has been developed to validate the newly raised mechanotransduction theory stating that the electrical diffusion can explain the local propagation of contractile activity, while the stretch activation mechanism process explains the global synchronization of the whole uterus. Both models have been co-simulated at the organ level, by using a surfacic mesh representing a 3D realistic pregnant uterus, obtained thanks to the Femonum project (http://femonum.telecom-paristech.fr/) that offers to the scientific community 3D fetal, uterine, organs and abdominal meshes extracted from MRI images. The effect of the mechanotransduction on the force generated by the uterine muscle (the intrauterine pressure, IUP) has been tested by co-simulating both electrical and mechanical behaviors, with or without the presence of the SAC feedback. The IUP generated by the muscle is estimated by computing the pressure at each facet of the 3D mesh and then by averaging these values over the whole organ. The effect of the mechanotransduction process is presented Fig 1.b. We notice that the co-simulation with SAC feedback generates a more important IUP than without SAC feedback. These results confirm that the mechanotransduction process improves the synchronization of the whole uterus, by activating cells that are far from the pacemaker area, faster than with the only electrical diffusion. Further work needs to be done for the development and the validation of this model mainly on the mechanical model (Finite element modeling) as well as on the SAC feedback loop (SAC number, their relation to stretching).

Keywords: Uterine model, multi-scale, multi-physic, co-simulation, mechanotransduction, synchronization.

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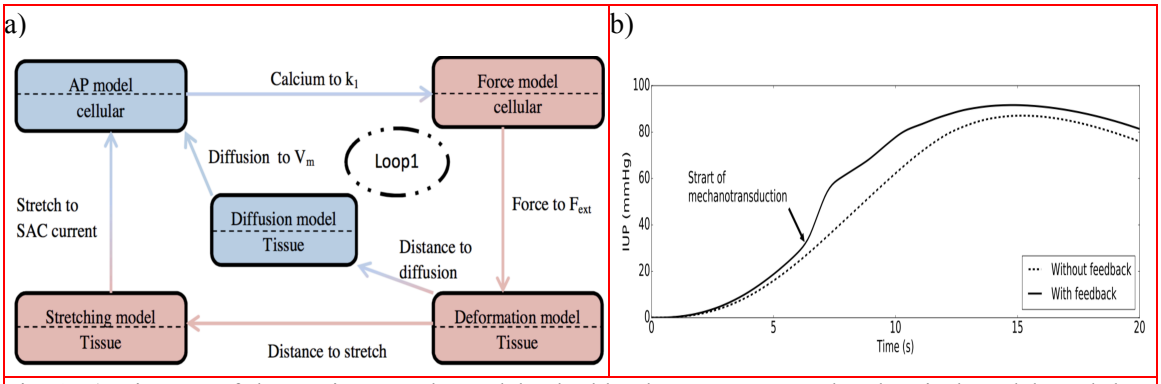

Fig. 1: a) Diagram of the uterine muscle model. The blue boxes represent the electrical models and the red boxes the mechanical ones. The AP and Force models are defined at the cellular scale while the stretching, diffusion and deformation models are defined at the tissue/organ scale. The co-simulation of the whole model is done at the tissue or organ level. Vm is the transmembrane potential output of the AP model, k1 is the phosphorylated rate of cross-bridges of Force model, SAC is the stretch activated channel and Fext is the external force applied to each cell of the deformation model; b) IUP estimated from the forces generated by the uterine cells with and without the SAC feedback. Notice at time 6s (arrow) the increase in the IUP slope, due to the appearance of the mechanotransduction effect.

Multiphysics simulations of the electro-mechano-fluidic function of patient-specific left ventricular models

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Abstract Combined electromechanical and hemodynamic computer models of the left ventricle (LV) and the aorta provide a critical pathway for analyzing the interplay between LV deformation, valvular anatomy and flow patterns. Typically, image-based kinematic models describing endocardial motion or MRI-based flow measurements in the LV outflow tract are used as an input to blood flow simulations. While such models are suitable for analyzing the hemodynamic status quo, they are limited in predicting the response to interventions that alter afterload conditions, as this approach assumes that the heartbeat itself will remain unchanged. Electro-mechano-fluidic (EMF) simulations of the LV have the potential to overcome this limitation as they allow to modify the activation sequence, tension development or preload and afterload conditions to provide the kinematics of an altered heartbeat. This comes with the price of a more challenging formulation, parameterization and computation. In this study, we report on our recent advancements in developing an automated workflow for the creation of patient-specific EMF models of the LV and the aorta that are suitable to drive blood flow simulations. Models are custom-tailored to individual patients to ensure that the in-silico simulation replicates clinical observations for a given patient. These models can be used to probe the effect of different therapeutic options and thus identify the therapy that yields the best post-treatment outcome.

Keywords: Multiphysics simulations; image-based validation studies; high-performance computing

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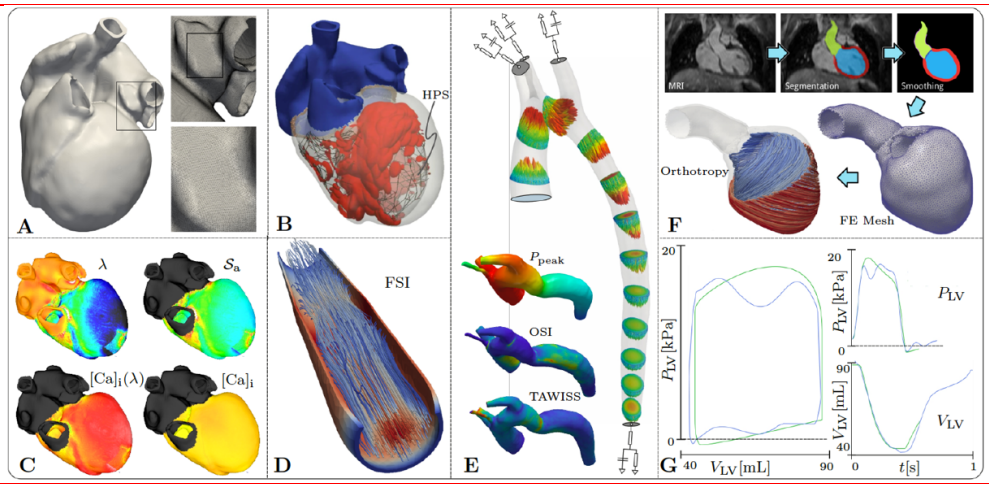

Fig. 1 Basic building blocks for constructing a FSI coupled electro-mechano-fluidic model of the LV.

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Stochastic modeling of mesenchymal 3D cell migration guided by chemotaxis

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Abstract (500 words max). The cellular migration process is an essential part of both life and development. Likewise, chemotaxis is one of the fundamental aspects of cell migration. This study aimed to develop a model to accurately predict mesenchymal 3D migration under chemotactic gradient. Based on the results of previous in vitro studies, we divided mesenchymal chemotaxis in three main stages, namely: chemosensing, dendritic protrusion dynamics and cell-matrix interactions. The numerical model was particularized for the case of fibroblast chemotaxis under PDFG-bb gradient. Fibrobasts migration was simulated embedded in two different 3D matrices – collagen and fibrin – and under several PDGF-bb concentrations. Our previous attempt (Ribeiro et al., 2017) to model chemosensing used Gillespie's stochastic simulation algorithm (SSA) which, because of its precision, turned out to be impractical. In this work we apply the tau-leaping method (Cao et al., 2006) as an approximate simulation strategy in order to speed up the process. Validation of the model results was provided through qualitative and quantitative comparison with in vitro studies.

Keywords: tau-leaping simulation method; 3D mesenchymal migration; fibroblast; chemotaxis; platelet derived growth factor; phosphoinositide 3-kinase

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Multi-Scale Modeling of Viral Dynamics and Evolution

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Abstract. This study aims at describing the multi-scale interaction between a virus infecting a host and its defective interference particles engineered as a containment therapy.

Defective interference particle (IPs) represents a deletion mutant of a virus that cannot complete replication cycle on its own, but requires the presence of the wild type virus in the same cell. Empirically, IPs have been observed as early as 1970s and proposed as a therapeutic antiviral agent in 1980s. And yet, mathematical theory of the process is only being developed [1], and the experimental evidence for their potential efficacy is sporadic at best.

New vigor this idea acquired recently, with new studies combining fresh theoretical results and serious experimental support. The motivation behind these new general interest in IPs is to use them as viral vector agents acting against various emerging viruses, including new pathogenic polio strains, other enteroviruses, arbroviruses passed by insects (Chickengunya), displaced from their natural host reservoir to humans (Ebola), vertically transmitted to newborns from mothers (Zika), and many others. Essentially, IPs represent a form of containment therapy which is a viable alternative to the full eradication approach, especially when eradication is not possible or not practical.

Based on a recently published work [RW], here we review the existing mathematical theory of interaction between a virus and a therapeutic IP. We explain how to connect the two levels by using output (predictions) of the single-cell level as the input (initial parameters) of the multi-cellular level i.e., a cell culture or an individual host. Applying these results for both replication and genetic evolution, we demonstrate that the interaction between adjacent levels of biological organization is the key to understanding the models and helping with IP design.

Keywords: Virus; evolution; interference particle

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Computational modeling of cell migration through a degradable viscoelastic extracellular matrix

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Abstract.

Introduction
Cell migration is vital for many processes in the human body like tissue development, tissue regeneration and angiogenesis. Cells adhere to the extracellular matrix (ECM), generate protrusive and contractile forces and degrade the ECM in order to move through. Therefore, the ECM is an important regulator of cell migration. In order to get a better understanding of the role of the ECM in cell migration, we have developed a computational model of cell migration through the ECM by local ECM degradation.

Methods
A 2D computational model has been developed coupling a mechanical deformable cell model to a model describing the viscoelastic behavior and degradation of the ECM. The ECM is modelled by a method called non-inertial smoothed particle hydrodynamics (NSPH) [1]. This is a mesh-free numerical method in which, by discrete convolution with a smoothing kernel, the continuum laws of fluid and solid mechanics are implemented in a discrete way. The mesh-free character allows to simulate large deformations of the ECM and to simulate the migration of a cell through the ECM without the need of computationally expensive remeshing. The cell is modelled by a set of NSPH particles connected by line segments that capture the mechanical properties (viscoelasticity and bending rigidity) of the actin cortex as implemented before in [2]. This cell model is embedded in the ECM model. A boundary correction is applied for NSPH particles of the ECM in contact with the cell model in order to ensure correct contact mechanics between the cell and the ECM. Filopodia that apply contractile forces leading to cell migration are modelled as springs that are initially positioned in a stretched state and are attached both to a particle of the cell model and to particles of the ECM. Degradation of the ECM by the cell is modelled by local relaxation of the deviatoric stress, resulting in a fluidized material that can be pushed aside by the cell in order to move through the ECM. Altogether, this results in a model of cell migration through a viscoelastic ECM.

Results and discussion
Various simulations have been performed to validate viscoelastic NSPH with an extended boundary correction as a new method to model the ECM. The potential of this method to capture cell-ECM interactions has been demonstrated first by the migration of a rigid circular cell model through the ECM by local degradation. Next, spreading of a deformable cell in an ECM (see Fig. 1) has been modelled and compared with results from traction force microscopy. Finally, migration of a deformable cell model by contractile filopodia forces and local degradation has been simulated. This model will be used to investigate the effect of mechanical ECM properties, degradation and filopodia dynamics on cell

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migration. Altogether, data suggest that our coupled cell-ECM model can capture important features of single cell migration and cell-matrix interaction. By validation with and feedback to experiments, this model can therefore aid in unravelling the mechanisms behind cell-matrix interaction.

Keywords: smoothed particle hydrodynamics, deformable cell model, cell migration, viscoelastic extracellular matrix, degradation

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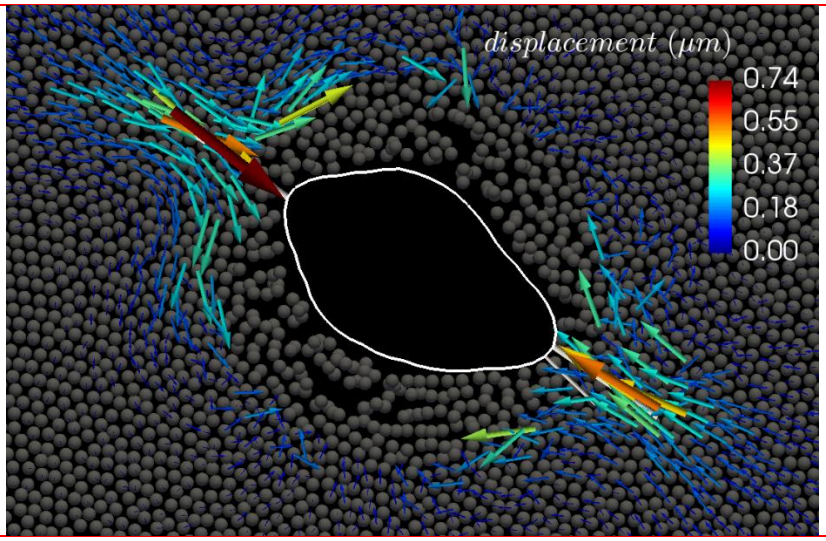

Fig. 1 Displacement field in the ECM around a deformable cell model that adheres to the ECM by contractile filopodia on opposing sides.

Model-based analysis and design of gene regulatory networks: A computational framework

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Abstract. Computational and mathematical models have significantly contributed to the rapid progress in the study of gene regulatory networks (GRN), but researchers still lack a reliable model-based framework for computer-aided analysis and design. Such tool should both reveal the relation between network structure and dynamics and find parameter values and/or constraints that enable the simulated dynamics to reproduce specific behaviors. We address these issues and propose a computational framework that facilitates network analysis or design. It follows a modeling cycle that alternates phases of hypothesis testing with parameter space refinement to ultimately propose a model network that exhibits specified behaviors with the highest probability. Hypothesis testing is grounded on an automated simulator of the qualitative dynamics of the hypothesized models (Ironi, Tran (2016)). Such a tool, called GRENS, operates in presence of incomplete knowledge of parameter values and assumes that regulation is modeled by steep sigmoid functions and incompletely known parameter values by order relations only. Given as input an ODE model of a GRN, initial conditions and parameter space, it provides *all* sound symbolic/qualitative predictions of the nonlinear and temporal multiscale dynamics in *a single run*. Each simulated trajectory is characterized by delimited ranges of parameter values and by its qualitative dynamical property, e.g., stable or cyclic solution or damped oscillations. Parameter space refinement optimizes parameter stochastic values initialized by probability distributions with large variances (Ironi, Lanzarone (2014)). It is grounded on a method that computes the probability of occurrence of each predicted trajectory, labeled by a sequence of parameter inequalities, by associating probability density functions with network parameter values. Thus, we take into account the intrinsic stochasticity of regulation by assuming that network uncertainty is expressed by fluctuations in parameter values only. The integration of the qualitative and stochastic aspects provide powerful insights to the study of GRNs because: (i) the qualitative simulation allows us to predict all possible system behaviors, and (ii) the stochastic parameters to predict the likeliness of occurrence of a specific behavior. Taken all-together, the modeling cycle becomes a process of development, ranking, and eventually choice of a network as the best one for explanation and analysis or implementation by the synthetic biologists.
The power and ease of our framework is demonstrated by working out a benchmark synthetic network to get a synthetic oscillator.

Keywords: Gene regulatory networks; nonlinear and temporal multiscale ODE models; Qualitative dynamics; stochastic parameters; Systems and Synthetic Biology.

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Blood flow numerical simulation in a realistic liver model : effect of blood pressure on the liver rigidity

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Abstract

In the context of soft tissue mechanobiology, numerical models have the advantages of providing information that will help physicians, biologists, mechanicians, surgeon and more generally all people in need of predictive tools to bridge the physiological biology and solid physics. More specifically, for mini-invasive surgery of liver tumor resection, real time augmented reality [1] provide the surgeon with a lot of information in 3D that can help him in making the right surgical decisions. The numerical models require to be computed quickly to provide pre and per-operation 3D real time data [2], while providing a high level of precision. Although parametric approaches like Proper Generalized Decomposition (PGD) Method allow a real-time response [3], they require the numerical model to integrate simplified mechanical behaviors [4]. In the context of the 3D-SURG project, we use homogenization techniques to develop a simplified mechanical model of the liver including its vascularisations and feed the Proper Generalized Decomposition.

First, geometries of the liver and its vascularisations are obtained from patients imaging data (MRI or CT scan). The mechanical properties of each material are extracted from experimental tests from non-invasive techniques. Based on these data, numerical mechanical tests, such as indentation, are applied on the different patient cases, integrating the vascularisation vessels walls and blood pressure, to identify the corresponding macroscopic mechanical behavior. Once the mechanical impact of those microstructures identified, a complete homogenized numerical model is developed providing precise deformations and displacements. Finally, a multi-layer homogenization is made to extract the numerical macroscopic homogenized material properties.

In the proposed study we will focus on the blood flow behavior in the liver vascularisations that will be later integrated in the homogenized numerical model. The overall geometry is decomposed in three parts : the incoming flow through the vena porta, the liver (considered as an equivalent porous media) and the outgoing flow through the vena cava. The three domains are coupled in the same simulation and solved for unsteady realistic flow rates.

Keywords : liver ; vascularisation ; CFD simulation

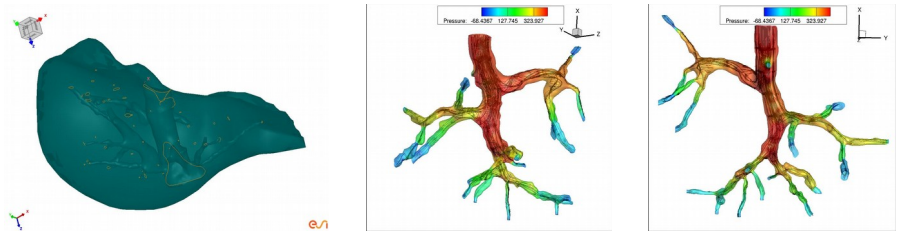

Fig. 1 : Topology of the realistic model; wall pressure and streamlines in the vena porta.

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Patient-specific numerical FSI model for bile flow simulation based on inter-disciplinary studies

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Abstract. The given study presents the results of patient-specific modelling using FSI algorithm to evaluate bile velocity and pressure distributions as well as the wall shear stress and von Mises stress distributions in the extra-hepatic biliary tree. Bile rheology in the healthy and pathological states was determined. It was confirmed that normal bile can be modeled as Newtonian fluid and lithogenic bile can be modeled as non-Newtonian fluid (Carreau fluid). The comparison between healthy bile (considered as Newtonian fluid) and lithogenic bile (considered as non-Newtonian fluid (Carreau fluid)) was made. Moreover, some cases dealing with gallstone presence influence on bile flow dynamics was also examined. Bile ducts were modeled as hyperelastic material (Mooney-Rivlin hyperelastic model). The constitutive parameters were obtained from performed inflation tests. The patient-specific biliary tree model was created using MRI and imported in FEM Commercial Package. The velocity and pressure distributions during the gallbladder emptying were presented. Velocities were found to have lower magnitude in the case of lithogenic bile, but the pressures are higher in this case. Stress state of bile ducts was also evaluated. It was shown that von Mises stress distribution is located in the cystic duct and hepatic ducts mostly; whereas, the shear stress distribution is mostly prevailing in the common hepatic duct. It is believed that duct wall shear stress can be considered as indicator of gallstones formation and von Mises stress is related to biliary pain. The developed model can be applied in the medical practice to evaluate the circumstances of surgical interventions.

Keywords: bile, biliary tree, patient-specific modeling, Mooney-Rivlin model, Carreau fluid, FSI

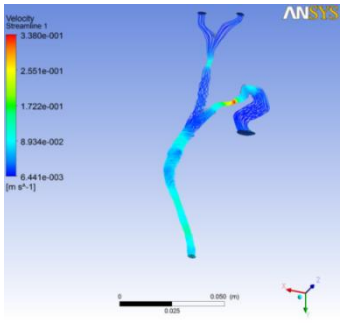

Fig. 1 Velocity distribution during the gallbladder emptying for non-Newtonian (lithogenic) bile

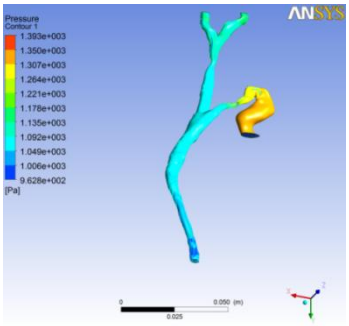

Fig. 2 Pressure distribution during the gallbladder emptying for non-Newtonian (lithogenic) bile

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Fluid-structure-interaction model of Transcatheter Aortic Valve Implantation configuration: comparison with an in-vitro study

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Abstract: Transcatheter aortic valve implantation (TAVI) is the treatment of preference for patients who are too weak or ill to undergo major surgery. Though the clinical benefit of the treatment has been demonstrated, some post procedural complications have emerged. In particular, the occurrence of silent ischemic lesions and dementia is considerably higher than with surgical valve replacements (Kahlert *et al*., 2010).
The source of these pathologies is still unclear, but a potential cause has been recently identified as haemodynamic perturbations downstream the valve (Ducci *et al*., 2013). In fact, contrary to surgical valve replacements, TAVI produces a valve-in-valve configuration which alters the flow in the aortic root, and may establish haemostatic conditions typically associated with thrombus formation.
The aim of this study is to expand these findings through a numerical model, allowing to analyse to identify the thromboembolic risk in the various regions of the fluid domain, for different configurations.
A fluid-structure-interaction (FSI) approach was chosen, in order to model the interaction of highly deformable structures with pulsatile fluid flows. The analyses were performed using the explicit finite element software LS-DYNA (LSTC, Livermore, CA, USA).
The models include the aortic root and the prosthetic valve, in an Eulerian fluid domain. Both the structure and fluid were meshed using ICEM 17.0 (ANSYS, Inc., Canonsburg, PA, USA) and then exported to LS-DYNA. An arbitrary Lagrangian–Eulerian (ALE) algorithm was used to implement the coupling between the structural and fluid elements.
The numerical results were validated versus the flow patterns measured *in vitro* with particle image velocimetry (PIV). The study confirms that the TAVI approach has a major impact on the flow pattern, leading to the formation of zones characterised by slow flow velocities which may promote pathological conditions.
Once refined, the computational model could be used to predict the haemodynamics in diseased and virtually treated conditions, providing a more appropriate tool for therapeutic planning and for the design of new improved devices.

Keywords: Fluid-structure-interaction (FSI), Transcatheter aortic valve implantation (TAVI); Arbitrary-Lagrangian-Eulerian technique (ALE); Valsalva sinus; blood stagnation

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Simulation of fractional flow reserve and plaque development in the coronary arteries

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Abstract. The objective of this work was to compare computer simulation of plaque development and Fractional Flow Reserve (FFR) with standard angiography patient data. We simulated of the plaque formation with mass transport of LDL through the wall which is coupled with the Navier-Stokes equations, the Darcy equation for model blood filtration and Kedem-Katchalsky equations. Additional three reaction-diffusion equations for the inflammatory process and lesion growth model in the intima were used. Outlet boundary conditions were prescribed as inverse resistance from the corresponding diameter. Hemodynamic FFR threshold was observed for 0.80 and 0.75. We found a good correlation between real and computed FFR results on ten patients ($p<0.005$). Computer simulation may predict plaque development and non-invasive anatomic and functional assessment of coronary stenosis for each specific patient which may be a clear benefit for patient study.

Keywords: plaque development; FFR simulation; coronary arteries

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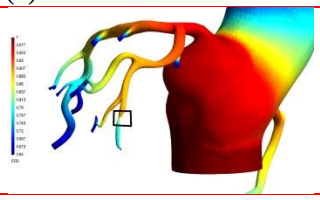

Fig. 1 Computed FFR and plaque development

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Study of the effect of partial hepatectomy on liver function through modeling of ammonia detoxification.

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Abstract

Along with the kidney, liver is one of the main detoxifying organs, with a remarkable regenerative capacity. To treat some diseases, as liver cancer or cirrhosis, the damaged part of the liver can be surgically removed. Within a few days, liver will grow back to its original weight. After surgery the liver mass is reduced which can impair its ability to detoxify the blood from ammonia. Yet ammonia concentrations in the blood above a certain threshold for too long can cause brain damage and in extreme cases death.

This study aims at studying the influence of partial hepatectomy on liver function through the study of ammonia detoxification. We have developed a multi-scale model of ammonia detoxification after partial hepatectomy, taking into account its metabolism in the cells as well as the spatial inhomogeneities within the liver. From experimental confocal images of liver tissue before and after partial hepatectomy analyzed in TiQuant [1], statistically representative functional and anatomical units of the liver, liver lobules, at different time points have been generated. Blood flow is modeled as a resistive network, taking into account the effect of red blood cells.. Using a representative liver lobule permits a precise definition of boundary conditions. This results in a large algebraic system of equations. Transport of ammonia in the blood, modeled by a 1D transport PDE, is coupled with its metabolism in the cells modeled by non-linear first order ODEs, through a passive uptake of ammonia. The metabolism model inside the hepatocytes is calibrated on healthy and drug-induced-damaged liver [2].

Ammonia levels at the liver outlet are predicted, from known input levels. This study has been done for mice and an extension to pig will be investigated.

This multi-scale model can be easily extended to any drug, marker or metabolite, as long as its metabolic pathways are known.

Keywords: tissue functional unit; ammonia metabolism simulation; sensitivity analysis; compound transport and metabolism; liver; microcirculation

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Modeling of Field Potential in Microlectrode Arrays and Applications in Safety Pharmacology.

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Abstract

The study of the electrophysiological impact of drugs, e.g. in the CiPA initiative [1], are mainly addressed by three approaches: *in vitro* patch clamp assays; *in silico* Action Potential (AP) assays; *in vitro* assays on human induced pluripotent stem cells (hiPSC-CMs). The present work investigates a 4th direction: *in silico* assays on hiPSC-CMs.

The use of microelectrode arrays (MEAs) and hiPSC-CMs allows high-throughput screening of new drugs directly on human-derived cells. But the field potential (FP) signals acquired by MEAs are difficult to analyze. We believe that an *in silico* approach can improve the practical use of FP signals. The presentation will include a demonstration of a web application of our FP analysis tool.

Method: We developed a new strategy based on a mathematical model of MEA and an inverse problem. The model consists of the bidomain partial differential equations, coupled to a system of equations representing the ionic channels. The model provides both AP and FP, and can account for cell heterogeneities and imperfect contact with electrodes. Various devices (96-well and 6-well MEAs) and ionic models (Paci *et al.* for hiPSC-CM, or classical ionic models like O'Hara-Rudy or MV) were tested. An inverse problem algorithm was used to identify parameters of the ionic models from quantities measured on the FP.

Results: By extracting three biomarkers from real FP data for various drugs, the proposed identification algorithm provided concentration-response curves for potassium, sodium and calcium channels. IC50 determined by simulation were in good agreement with literature values (2.8uM for Ivabradine, 114uM for Moxifloxacin).

Conclusion: The forward simulations provide signals qualitatively close to those experimentally observed. They give new insights into some aspects of the FP difficult to address in real experiments, like the variability of the measurements, even in absence of variability of the cells. The inverse problem allows us to estimate the conductance of some channels and to obtain dose-response curves directly from FP measurements.

Keywords: cardiac electrophysiology; safety pharmacology; hiPSC-CM; MEA;

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On a Tri-Scale Multiphase Model for the Description of Perfusion coupled to Growth Effects in Human Liver

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The human liver regulates metabolism in a complex time depending and non-linear coupled function-perfusion-mechanism. The viability of the organ is affected by a failure in the liver structure. A common chronic disease is the excessive accumulation of fat in the tissue, known as a fatty liver. The growing fat proportion has a high impact on the perfusion of blood through the liver. A central task of the human liver is the clearance of toxic metabolites which can be found in several medications. The clearance capacity of the human liver depends on an unimpaired perfusion of the blood through the vascular system and micro circulation. Since fatty liver growth influences the perfusion we claim that a fatty liver impacts the recommended dose of daily medicines.

The anatomy of the organ is characterized by a complex vascular system which changes on the different size scales from a vascular branching tree to microvessels, called sinusoids in liver lobules. To capture the interplay between fat deposition arising in the microstructure and the perfusion on the organscale it is important to couple the processes on each scale. For this we present a computational model for the human liver which is composed of three coupled submodels for the organ-, lobule- and cellscale. With the whole organ model we present the effect of growing fat vacuoles in the liver cells, which are inhomogenously distributed on organ-scale, up to the total hepatic hemodynamics.

On the organscale we use a Bernoulli approach (laminar steady state) calculating the perfusion in the branching system of the vascular tree. The vascular system starts with a single branch and subdivides into smaller vessels ending up in the portal triad - the interface of the organscale to the lobulescale. With a computation of the vascular perfusion we provide information of the blood velocity and pressure as boundary condition. The lobulescale uses a homogenized mixture model for the simulation of important functionalities in the liver lobules as presented in [2] including microperfusion, growth aspects and clearance capacity. The approach uses the extended theory of porous media (eTPM) [1] to consider the biological tissue as a multi-phase structure including the liver tissue, the fat vacuoles and the blood. On the microscale we focus on metabolic processes which take place in the liver cells.

Keywords: Tri-Scale Multiphase Model; eTPM; hepatic hemodynamics; growth; clearance

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Intra-operative quantitative estimation of liver function with indocyanine green fluorescence measurements

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Abstract (500 words max).
Liver transplantation and liver partial ablation are surgeries performed to treat liver diseases (cirrhosis, liver cancer). These surgery complications are related to a poor liver function, thus the evaluation intra-operatively of the hepatic function is an important clinical question. The liver function can be evaluated with blood sample analysis (for example by quantifying the level of bilirubin). Since the indocyanine green is a fluorescent dye exclusively removed from the blood by the liver cell, another method for liver function estimation is the indocyanine green clearance (plasma disappearance rate). However, these methods require time and therefore are not intra-operatively available. Besides, they only provide a combined information about possible perfusion/liver functions dysfunction.
In this work, we propose a framework to evaluate the liver function intra-operatively, based on a pharmacokinetics model and its parameters identification, analyzing the indocyanine green fluorescence dynamics in the liver tissue.
In [1], the measurements of liver tissue concentration of indocyanine green are fitted with a sum of two exponential functions (with two parameters) for six groups of rabbit with different treatments (colchicine, vessel occlusion…). In this work, the indocyanine green fluorescence is measured in the liver blood vessels, the liver tissue and the common bile duct, before or after liver partial ablation on pigs. The measurements enable to develop a mathematical model representing the indocyanine green processing from its removal from blood by the hepatocytes to its secretion into bile. The model focuses on a precise description of the dye processing by the liver, including the three different types of liver tissue (the sinusoids, the hepatocytes and the bile canaliculi). This model enables to precisely study the exchanges between the different liver tissues. This is a novelty compared with the previous model proposed in literature.
First, the model's outputs sensitivity to parameter is analyzed, and then the parameter estimation is performed with a population approach using Monolix software [2]. The parameters are estimated with the fluorescence measurements from pig surgeries. The link between the model's parameters and liver function is investigated. Then, the model is adapted to clinical constraints. Since more data is available during pig surgeries, the procedure is first tried out with a subset of measurements from pig surgery that would be available in the clinics. Then, a feasibility study is performed on a few measurements from patients after liver transplantation. The first results suggest that the liver surgeries impact the exchange between blood and liver cells. This new framework may provide a new estimation of the liver function(s) intra-operatively.

Keywords: Pharmacokinetics models; parameter estimation; indocyanine green; liver function estimation

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Integrated vs. multi-level/multi-scale spatial temporal modeling of ammonia detoxification after drug-induced liver damage: using modeling to guide towards a new therapy approach

Keywords: integrated modeling; compartment modeling; multiscale modeling; spatial-temporal modeling; agent-based modeling; liver damage; detoxification; model-guided experimentation; therapy

Hyperammonemia is a severe complication after drug induced liver damage, for example resulting from overdosing acetaminophen (paracetamol), and can lead to encephalopathy and dead of the patient. A set of chemical reactions identified by Häussinger (1983) and Gebhardt (1983) has become the biological consensus model for ammonia detoxification in healthy liver.
We will show how the iterative application of a pipeline consisting of confocal scanning microscopy, image analysis and modeling can be used to design predictive models of tissue regeneration and metabolism suited to guide modeling driven experimental strategies (Drasdo et. al., 2014). As an example we will present an integrated model, integrating a compartment model of ammonia detoxification and a spatial-temporal micro-architectural agent-based model of liver regeneration after drug induced liver damage, that was able to identify lack of a critical ammonia sink mechanism in the consensus reaction scheme (Schliess et. al., 2014). The finding has led to identification of a so far unrecognized ammonia sink mechanism that could be experimentally demonstrated to represent a potential therapy approach in hyperammonemia (Ghallab et. al, 2016). In a further step we redo the analysis in a full spatial temporal micro-architecture model of the smallest virtual functional micro-anatomical unit (called lobule) obtained from image analysis (Hammad et. al., 2014; Friebel et. al., 2015) whereby the detoxification reactions are executed in each individual hepatocyte. Comparison between integrated and full multiscale modeling identifies transport / reaction conditions under which critical differences between both approaches are to be expected.

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Subject-specific Shoulder Muscle Attachment Region Prediction Using Statistical Shape Models: A Validity Study

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Abstract: Subject-specific musculoskeletal models (MSKMs) can predict accurate joint and muscle biomechanics. However, assumptions made about the input model parameters make them generic and limit their clinical utility. Shoulder MSKM faces a huge challenge of subject specificity, in particular, muscle origin/insertion sites are always almost approximated. This considerably affects the muscle force and moment arm predictions and thus cannot be effectively used for pre-surgical or for rehabilitation assessments. In this study, we present a statistical shape model (SSM) based pipeline of using the SSM's ability to incorporate statistical variability for predicting subject-specific muscle regions in shoulder muscles. We also report the concurrent validity of the muscle origin/insertion region prediction on a randomly selected population of shoulder bones (scapula and humerus).

A database of dry bone samples (27 scapulae and 28 humeri) was used for building the bone SSMs using previously published IMCP-GMM pipeline [1]. The bone SSMs were then augmented with five muscle attachment (origin/insertion) regions (Subscapularis, Supraspinatus, Infraspinatus (I-S), Teres Major (T-Maj) and Teres Minor) on both the bones. For each bone surface mesh of the database in correspondence, origin/insertion regions were identified and masked by two experts using Meshlab (http://meshlab.sourceforge.net/). Inter-rater reliability for two randomly selected muscles was quantified by comparing the area of each muscle region obtained by each expert on each bone and also by quantifying dice similarity coefficient for each muscle region. The regions were represented by subset of vertices on the bone meshes and were tracked using vertex identifiers (VIDs). Using the correspondence within the database, a subset of vertices representative of each muscle was extracted and identified on mean shape of the bone SSM, by exploring the frequency of appearance of each point (VID) in the same muscle for the whole database (Fig. 1). To avoid the overlapping between muscle attachment sites, a frequency of 60% was selected to ensure the exclusivity of each VID for a single muscle region. Subject-specific muscle attachment regions were predicted using external set of bones not used in building the SSMs. An open source toolbox SCALISMO [2] was used to create and perform functions related to augmented SSMs.

Excellent intra-class correlation coefficient (ICC) for inter-rater reliability was reported for the two muscle origin/insertion regions on scapula (I-S (ICC = 0.927) and T-Maj (ICC = 0.942)), as well as, on the humerus (I-S (ICC = 0.981) and T-Maj (ICC = 0.962)). Dice coefficient ranged from 0.821 to 0.987 indicating a high region similarity between experts. Validity of region prediction was visually confirmed by the expert in ten external scapulae and eight external humeri. Excellent concurrent validity of muscle region prediction was observed based on the mean and root mean square distance measures and also based on similarity coefficient. We assumed that bone shapes can predict muscle origin/insertions regions and the excellent concurrent validity results confirm this for five major shoulder muscles on both the bones. The SSM based MSKM pipelines seems to be a good approach however, further validations are warranted on all the muscles of the shoulder complex.

Keywords: shoulder biomechanics, muscle insertion prediction, SCALISMO, point correspondence

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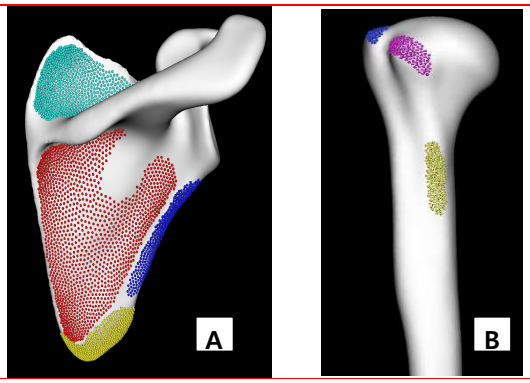

Fig. 1 Attachment regions of scapula and humerus bones. **A:** Posterior view of right scapula with the final selection of VIDs of: I-S= Infraspinatus (Red), Suprasp= Supraspinatus (Light Blue), T-Maj = Teres major (yellow), T-Min= teres minor (Dark blue). B: anterior view of right humerus with the final selection of VIDs of Subscap = subscapularis (Pink), Suprasp=Supraspinatus (Blue) and T-Maj=Teres major (yellow).

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The microscopic behavior of a Holzapfel-like model is supported only for low strain: application to mice skin

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Skin is a multi-layered composite structure, in which the most important is the dermis for the mechanical properties. The dermis is a "collagen-rich" tissue where the collagen network bathes in an extra-fibrillar matrix (proteoglycans, elastin, etc.), that induces a mechanical behavior involving structures at different scales. In this present study, a bi-axial tensile test coupled independently to a macroscopic measurement and a microscopic measurement was developed. The mechanical parameters of Holzapfel's behavior were identified from a DIC (Digital Image Correlation) displacement field measurement, and the associated affine transformation was tested from microstructural SHG (Second Harmonic Generation) measurements.

First, a biaxial test (Fig.1a) was adapted from Bancelin et al. [1]. An alternated 10% loading was imposed successively on each arm, while measuring the displacement field and the force in each arm. Then, a FEMU (Finite Element Model Updating) approach was developed in order to minimize the quadratic discrepancy between experimental measurements (force and displacement field) and numerical data. Finally, the 5 parameters which govern the of Holzapfel's behavior were identified on 6 mice: *C10* describes the non-collagenous isotropic ground material behavior, *k1* and *k2* the contributions from collagen fibers, and κ the level of fiber dispersion along the mean fiber direction α ($0 \leq \kappa \leq \frac{1}{3}$).
Identification results showed a large variability on the angle α (from *-7°* to *80°*). In addition, the distribution parameter (κ) presented always a value close to 0 that highlights a strong fiber orientation ($3.9 \pm 0.6 \ .10^{-3}$). The non-collagenous matrix (C_{10}) was always in the same range (104 ± 59 *kPa*) but seemed to be anti-correlated with the contributions from collagen fibers k_1 (55 ± 30 *kPa*) and k_2 ($25 \pm 3 \ 10^{-4}$). These results illustrated the interindividual and positionning variabilities.

Second, we observed the microstructure in 3 areas (center and 2 arms) across the loading (Fig.1b) with SHG microscopy (Second Generation Harmonic). It allowed us a local monitoring of the stretch thanks to the hair follicles and a local measurement of the collagen network distribution (Fig.1c). As presented in [1], the orientation index (OI) was computed to extract quantitative information from the fiber distributions. In practice, this index informs us on the fiber alignment along the direction of traction. Holzapfel's behavior implying an affine transformation [2], the evolution collagen network is easily calculated knowing the kinematic of the transformation and the initial distribution.
The results presented a good agreement between the affine model and the experiment. This validates the model for low local stretches whatever the observed area. Nevertheless, for stretches above 1.2, the affine assumption was not relevant.

Despite many studies of the GOH-like model, this study highlighted the limits of the affine transformation assumption. Therefore, it would be interesting to develop models in which the fibers interact at the microscopic scale to give microstructural information in simulations.

Keywords: Identification, Affine transformation, Microstructure, Holzapfel's behavior, Mice skin

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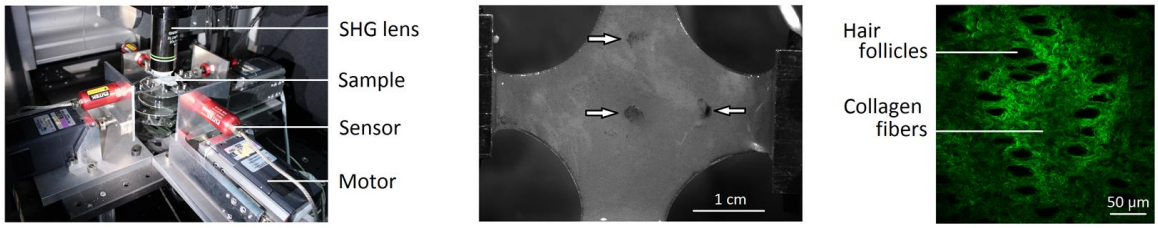

Fig. 1 a) *In-situ* custom-made device. b) Mice skin sample on which the microstructural acquisition are located. c) SHG acquisition acquired without loading.

Computational Fluid Dynamics (CFD) applied to Whole Body Cryotherapy (WBC)

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Abstract
The aim of this study is to develop a numerical model that can both predict the skin temperatures of the human body but also to accurately simulate the thermal plume that develops during a whole body cryotherapy (WBC) session. Whole Body Cryotherapy (WBC) can be considered as a therapeutic complement consisting to place the human body in a hermetic chamber, where the temperature varies from -60 ° C to -110 ° C for a short period of time (varying from 2 to 4 minutes). The objective is to stimulate the human body in order to activate natural defenses against the cold. This extreme temperature induces to the beneficiary a thermal shock thus activating biomechanical and biochemical survival reactions giving the ability to the human to perform a physiological shock. Extreme cold stimulates skin sensors, activating the Central Nervous System (CNS) response. This causes the release of endorphins, body's natural pain inhibitors and mood elevators, while the enhanced blood circulation activity decreases inflammation by clearing toxins and metabolic waste with a supply of oxygen and nutrient enriched blood to stimulate cellular regeneration. However, the self-protective mechanisms of the human body which are activated in case of prolonged exposure to extreme temperatures cannot go on forever. This is why it is essential to know precisely the thermal transfer occurring at the cutaneous surface of the patient during WBC session which is mainly due to the aeraulic and thermal conditions within the cryotherapy cabin. In practice, accurate knowledge of the patient's skin temperature variation during a WBC session will help to limit the risks inherent in such a practice while maximizing the duration of the protocol. The experimental study is based on analysis of skin surface temperatures maps to obtain boundary conditions for the numerical problem. Indeed, the skin is considered as the main organ of study, place of thermal exchanges at the interface of the body (and its internal temperature) and the environment. The CFD (Computational Fluid Dynamics) model is thus a model of anisothermal fluid mechanics where free radiation and convection contribute to thermolysis losses. The modeling of the heat transfer between the energy production (metabolism) and losses leads to determine the thermal parameters which will constitute one of the thermal limit conditions of the problem to be modeled. The various steps of development of this numerical model are presented here and constitute the aim of the paper. First numerical results are also presented and are compared to experimental ones, particularly the skin temperature maps of the human body. Effects of the human thermal plume on the average velocity and temperature distribution within the cryotherapy cabin and around human are also investigated, considering fluctuation velocity, temperature and other unsteady characteristics.

Keywords: Cryotherapy; thermal plume; CFD simulation; skin temperature; convective-radiative model

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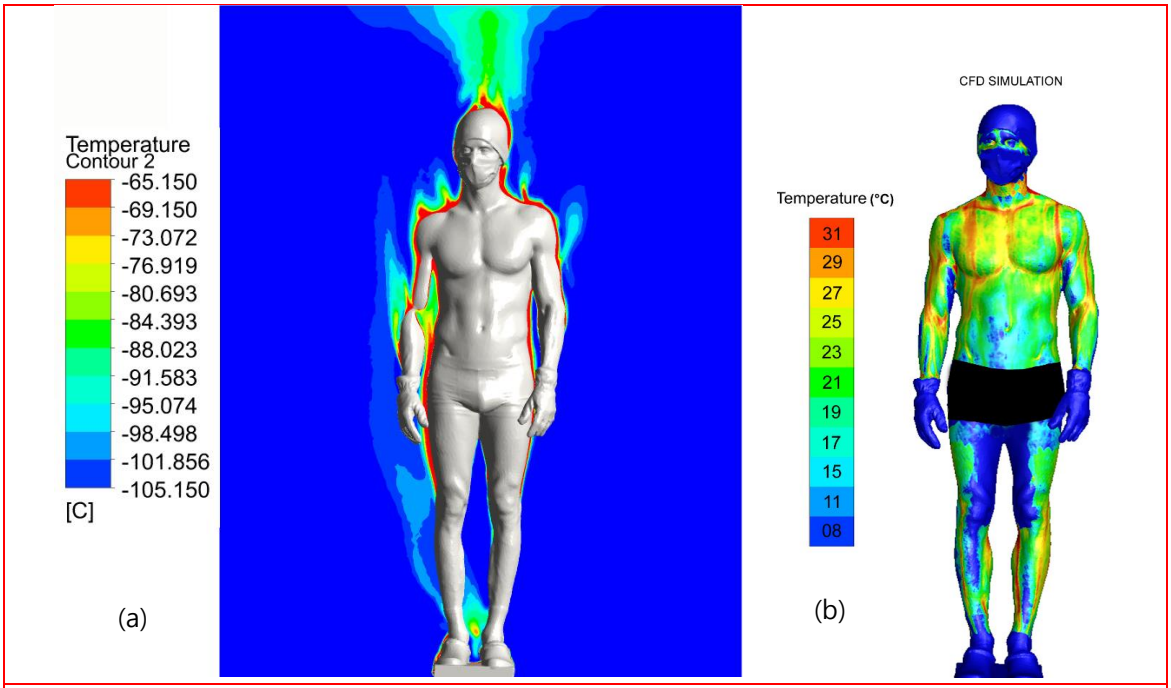

Fig. 1 Human thermal plume (a), Cutaneous temperature map (b)

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Assessment of the anisotropy of in vivo human skin: numerical simulations of multi-axial contact-free creep tests

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Abstract. Human skin is a living barrier between the outside influences and the inside of the body. It is a multi-layered complex structure composed of 4 main layers which are from the skin outer surface inward: the stratum corneum, the viable epidermis, the dermis and the hypodermis. The peculiar physiology of each layer is well adapted to its protective functions and influences the overall answer of the skin soft tissues to external loads. In particular, the dermis is a complex material made out of cells, an extra-cellular matrix, vessels and entities all bathed in a physiological fluid and structured by dense networks of collagen and elastin fibers. These networks give skin its mechanical structure not only at the dermis level but also in all other skin sub-layers. This results in layers of skin soft tissues considered as complex nonhomogeneous, anisotropic, nonlinear viscoelastic materials subjected to a prestress in vivo. Assessing quantitative and objective descriptions of these layers is a challenging issue in many chirurgical and medical domains and for every day quality of life of persons.

This paper proposes numerical simulations of multi-axial contact-free creep tests with the aim to investigate the anisotropy of the in vivo human skin materials and its consequences on the overall answer of the skin soft tissues.

The experimental tests are performed with the Waveskin® which is the contact-free indenter developed by the team of Prof. Hassan Zahouani at the LTDS (Laboratoire de Tribologie et Dynamique des Systèmes). This indenter is able to apply an air flow onto the external upper surface of the skin in vivo. During the tests, the deflection of the surface is recorded by a laser-line (length: 7 mm). It is important to notice that there exists no contact between the device and the skin before, during and after the tests. Therefore when the load is suppressed, the skin can freely come back to its natural state. Moreover this indenter is able to generate reproducible loads. Thus it is possible to generate cycles of identical loads. These cycles associated with different orientations of the laser-line (4 orientations) make it possible to perform tests equivalent to multi-axial contact-free creep tests. Following this procedure experimentations have been carried out on the volar forearm of two volunteers: a young woman and an old woman.

The 3D numerical simulations of these multi-axial contact-free creep tests are performed using the software SYSTUS®. They consider a skin specimen composed of 4 layers. Each layer simulates one of the main layers of the in vivo human skin. The key point of this paper is to consider an anisotropic behavior law to model the overall answer of the skin specimen. An inverse procedure is coupled with these simulations to characterize the mechanical parameters in different directions and investigate the influence of their different order of magnitude on the answer of the skin soft tissues. The numerical simulations provide also the stress fields in the volume of skin soft tissues. Starting from the study of these stress states, it will certainly be possible to establish a link between the physiology of the layers of skin soft tissues i.e. the fibers networks functions and the anisotropy observed at the outside skin surface and in its overall answer.

Keywords: human skin; numerical simulations; contact-free test; anisotropy; in vivo; multi-axial test

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Computational modelling of the dual action of parathyroid hormone in osteoporosis

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Abstract (500 words max). Osteoporosis is a disease characterized by long-term bone loss that occurs when bone resorption exceeds bone formation in the remodelling process. Progress has been made in the formulation of computational models of bone remodelling in order to take into account major cell-cell signalling pathways and regulatory mechanisms. Many hormones exhibit different release patterns, such as continuous or intermittent, which then modulate differential cell behaviours. In the bone literature, the most prominent example is the dual action of parathyroid hormone (PTH). It has been shown that a continuous administration of PTH leads to a catabolic effect on bone remodelling. On the other hand, daily subcutaneous injections of PTH constitute an effective anabolic treatment for osteoporosis. However, current computational models of bone remodelling are not able to distinguish between these two administration patterns. The purpose of our study was to develop a computational model of bone remodelling that takes into account the dual action of PTH. The model was built using human pharmacokinetics data, then calibrated and validated with data from postmenopausal osteoporosis (PMO).

The mechanism implemented in the model accounts for the anabolic effect of intermittent PTH on bone remodelling via the reduction of the apoptosis rate of active osteoblasts (OB). This mechanism involves the runt-related transcription factor 2 (Runx2) and the cAMP response element-binding protein (CREB). Runx2 is a mediator for the transcription of survival genes, such as B-cell lymphoma 2 (Bcl-2). The action of PTH on OB apoptosis is modeled with a system of three ODEs describing the intracellular signalling components (Runx2, CREB, and Bcl-2) as a function of PTH. Changes of Bcl-2 drive the reduction of OB apoptosis rate. This action is implemented in the model via a sigmoid E_{max} function. The effect of PTH on bone remodelling is described by coupling the intracellular model of OB apoptosis together with a bone cell population model to compute changes over time of bone cell numbers and bone matrix fraction (f_{bm}). The latter quantities can be linked to bone turnover markers (BTM) and bone mineral density (BMD). To reproduce the change over time of PTH concentration in plasma under different dosing regimens, a pharmacokinetic (PK) model has been developed.

PMO is simulated with a rate of bone loss equal to 0.65%/year. The daily PTH subcutaneous injections are reproduced using a pharmacokinetic model. The computed apoptosis rate follows the intermittent behaviour of PTH, with an overall reduction in the daily average compared to baseline. The model shows a 3% trabecular f_{bm} increase from baseline after the simulation of 2 years of treatment. This value is consistent with the BMD increase measured at the femur neck and distal radius. Simulation of 40 μg PTH injections lead to a higher f_{bm} gain compared to the 20 mg dose. These results indicate that the model is capable of reproducing a dose-dependent gain in bone volume. By coupling the intracellular signalling of OB apoptosis and the bone remodelling process, our model can simulate the anabolic effect of intermittently administrated PTH for PMO treatment.

Keywords: bone remodelling; bone mechanobiology; computational modelling; osteoporosis; pharmacokinetics; pharmacodynamics;

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SESSION ABSTRACTS

Object-oriented programming of optimized analytic neuromuscular model

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Abstract Each movement even the simplest is the result of complex interactions between several systems. The muscles responsible for the joint movement respond to a neural command controlled by the Central Nervous System. Then, muscles will generate several physical and chemical responses to this neural activation, i. e., calcium release, electrical activity and force generation. These muscle responses cannot be measured in experimental conditions without using an invasive protocol. Moreover, the interactions contributing to the muscle contraction cannot be experimentally determined. For this purpore, simulations can provide some new insights about the muscle contraction and a preliminary step before starting an experimental study. In this paper, we present the software structure of a neuro-electrical model (Carriou2016) describring the contraction of a muscle. We will point out the well suited object-oriented programming used to implement this model. Object-oriented programming is a programming concept based on macro structure containing data describing the object. Those objects can interact together through methods. Considering the complexity of the neuromuscular System of Systems (SoS) the first step before implementing the model is to clearly described the different systems and the interactions between them (see Fig. 1). Implementation of the model is made in Python programming language which is an interpreted language.
To clarify each object and method developed in the model, a documentation is written within the model to describe how to use these features. Moreover, the Application Programming Interface (API) has been specified to simplify the use of the model through human readable definition of the model's input/outputs. One of the significant advantage of the object-oriented programming is the modularity of the computing code. In fact, this code modularity allows users to easily upgrade and extend the computing code to fit new functionalities (Al Harrach2017). Once these features considered, the management of the simulation computing time is the other challenge in muscle modeling. In the proposed model, reduction of the computing time is made at three levels. Firstly, optimization has been made on the mathematical equations describing the problem where all the calculus are considered in the Fourier domain to avoid the use of the convolution operator. Then, optimization procedures available with Python (list comprehension, code profiling, optimized libraries, etc.) were implemented in the model. Finally, thanks to all these features presented above, parallel computing has been easily integrated in the model, reducing significantly the computing time of the model. To conclude, considering the object-oriented programming for modelling the complex neuromuscular system seems to be well-suited for describing its composition and interactions (Carriou2016). Thanks to these integrated features in the model, upgrading the model to new methods or studies is feasible. Thus, a wide-spread use of this model in the scientific community can be considered.

Keywords: Neuromuscular system; System of systems; Object-oriented programming; Skeletal muscle model; Parallel computing; Analytic model;

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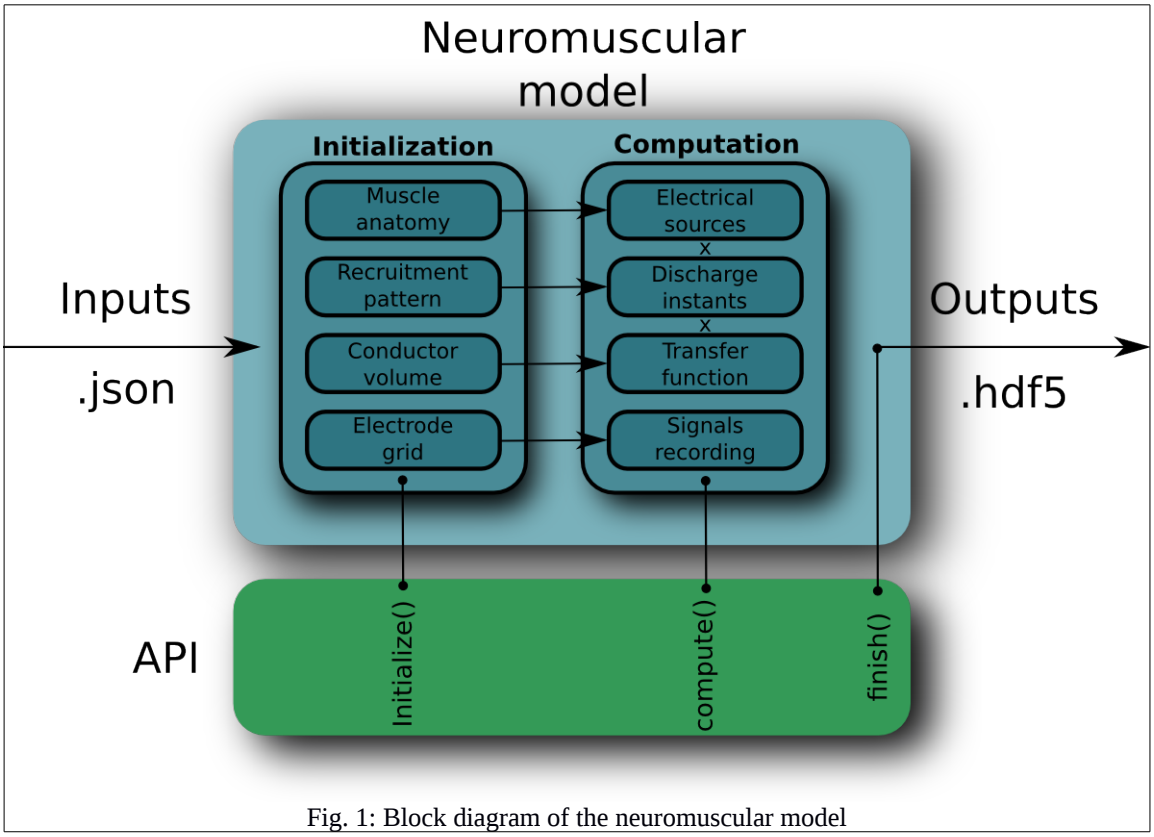

Fig. 1: Block diagram of the neuromuscular model

Modelling the adaptation of skeletal muscles in response to isometric exercise

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Abstract. Exercise-induced skeletal muscle adaptation occurs over time through changes in mechanical and neural properties of the muscle targeted by exercise. In this study, a computational model describing the adaptation of skeletal muscles in response to isometric exercise is used to investigate the neural adaptation mechanisms.

A systematic review of the experimental studies on isometric exercise was performed. The review focused on randomized controlled studies involving healthy, normal-weight, young (aged between 18-30) subjects, and studies which included the measurement of the changes in maximal voluntary contraction (MVC) of the target muscle. These criteria yielded a total of 56 experimental studies. When grouped based on the specific exercise type and the muscle group, it was seen that the highest number of studies (22) focused on isometric unilateral knee extension exercises in which the target muscle is the quadriceps femoris (QF).

Training regimes (number of repetitions, number of sets, frequency of training sessions, rest in between sets and individual contractions, length of the individual contractions, total duration of the study), profile of the subjects (gender, age, weight, height) and changes in the MVC of QF were extracted. Data on the changes in neural properties (e.g. level of activation) and cross-sectional area and/or volume of the muscle were also extracted depending on their availability. A sensitivity analysis was performed on the extracted data to investigate which parameters influence the improvement in MVC and to what extent.

The results of the sensitivity analysis provided the parameters needed for formulating the adaptation equation that describes the change in strength throughout the training period. The adaptation equation is structured as an ordinary differential equation (ODE) with respect to the exercise input. The exercise input depicts the (cumulative) number of contractions for a given exercise regime (i.e. exercise input = repetitions/set x number of sets/training session x training sessions/week x total duration of the exercise in weeks).

A one-dimensional active muscle model that generates force upon the summation of individual motor unit firings was used to compute the MVC. In the model, the motor units are distributed between type I and type II. The force is generated by convoluting the twitch response of individual motor units with their respective firing times. The firing times of individual motor units are assumed to be statistically independent. The firing rate of individual motor units, the number of recruited motor units and their synchronization rate were altered in various combinations to match the improvement in MVC that is computed from the adaptation equation for a given exercise input.

Keywords: isometric exercise; skeletal muscle mechanics; systematic review; adaptation of skeletal muscles

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Dynamic Viscoealstic Properties of a Fiber Composite Phantom for MRE

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Abstract:
Magnetic Resonance Elastography (MRE) is a non-invasive imaging technique employed to assess biological tissue properties (typically shear stiffness) by inducing the propagation of mechanical waves in the region of interest and measuring the tissue response by means of phase contrast magnetic resonance imaging [1]. The challenge in employing MRE on muscular tissue is to characterize a non-homogeneous, viscoelastic, and anisotropic material through an inverse approach able to identify regional variation of tissue viscoelastic properties from material response to harmonic mechanical loading.
Different inverse engineering techniques can be used to identify material properties either by direct local inversion of Navier's equations or by iterative methods aiming at minimizing the mismatch between the experimental results and simulation predictions. The inverse problem can be quite a formidable task for complex material behaviour involving anisotropy and viscoelasticity. The use of phantom composite materials with a-priori known mechanical properties which mimic the anisotropic frequency dependent response of skeletal muscle tissues can be a suitable strategy to set up identification methods.
In this work, we propose a finite element model able to predict the macroscopic response of the fiber-reinforced micro-composite used as a phantom material.
A regular cross-ply micro fiber layers immersed in an isotropic PVA gel matrix has been simulated by modeling a unit cell of the composite and considering the material response as that of an infinite repetition of the representative unit cell. Known viscoelastic properties in the frequency domain have been assumed for the constituents (fibers and matrix) and periodic boundary conditions have been used to replicate the behaviour of adjacent cells not included in the model.
The homogenized macroscopic constitutive model is then used to predict the response of the phantom subjected to harmonic loading. The effect of fiber density and the effect of macroscopic anisotropic material response is assessed in terms of displacement amplitude and phase angle in a frequency domain steady state dynamic finite element simulation of propagation of steady shear waves.
The model will be used in the future to design optimal mechanical properties of the phantom material to be employed in MRE experiments and set up of inverse identification approaches. This study aimed to develop a model to accurately predict the acceleration of structural systems during an earthquake. The acceleration and applied force of a structure were measured at current time step and the velocity and displacement were estimated through linear integration.

Keywords: Magnetic Resonance Elastography (MRE); Finite Element models; Steady State Dynamic

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Source localization of uterine activity using Maximum Entropy on the Mean approach

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Abstract. This study evaluates the ability of distributed source localization method to accurately estimate the location of the sources of activity, as well as their sensitivity to the spatial extent of such sources when using EHG data. We used here realistic simulations of uterine electrical activity, taking into account the 16 electrodes for recording EHG signal, and involving a realistically shaped uterus model. A Data Driven Parcellization (DDP) method [1] was used to segment the uterus surface into non-overlapping regions. Our results showed that the localization were sensitive to spatial extents of the sources (ranging from 11 cm^2 to 29 cm^2), and also to the number and size of the regions defining the model. Our analysis of the evolution of the real sources during contraction showed a nonlinear propagation of uterine electrical activity.

Keywords: Maximum Entropy on the mean; Data Driven parcellization DDP; nonlinear propagation of uterine electrical activity

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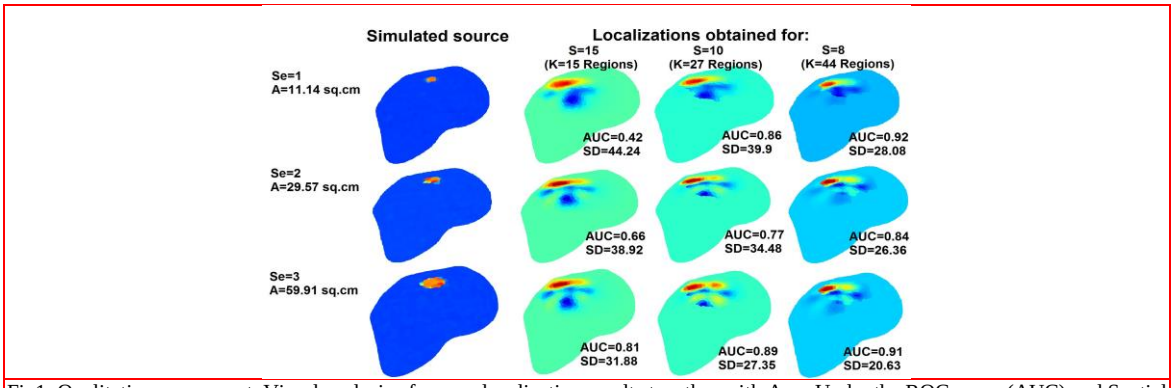

Fig1: Qualitative assessment. Visual analysis of source localization results together with Area Under the ROC curve (AUC) and Spatial Dispersion(SD) values for a simulated source of spatial extent se = 2, 3 and 4 at different spatial scale s=15, 10 and 8.

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Data-based parametric modeling of human liver anatomy for patient-specific real-time deformable models in computational surgery

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In this study a parametric Finite Element (FE) model of the human liver is built accounting for anatomical variability from patient to patient. An explicit parametric solution is computed at once for the whole "family" of anatomical shapes with prescribed loads and material properties using Proper Generalized Decomposition (PGD), allowing real-time computation.

The shapes of human livers were reconstructed from 712 Magnetic Resonance Images acquired at IRCAD (Institut de Recherche contre les Cancers de l'Appareil Digestif, Strasbourg). All the shapes were registered to a template liver. Non-rigid registration was performed using Iterative Closest Point with Thin Plate Spline parametrization. Several dimensionality reductions techniques were applied, in a comparative way, to find the intrinsic coordinates ζ_i describing a lower dimensional manifold of the liver geometries. These include Principal Component Analysis (PCA), kernel Principal Component Analysis (k-PCA), Locally Linear Embedding (LLE) and t-distributed Stochastic Neighbor Embedding (t-SNE). Finally, the livers biomechanical behavior was taken into account using a quasi-static hyper-elastic material model and PGD was used to compute numerical solutions for displacement fields $\boldsymbol{u}$ under prescribed loads as an explicit function of the shape parameters ζ_i.

Based on the quality of segmentation, only 678 segmented liver shapes were retained for the study. The correspondence process gave good results to fit the majority of the livers. Since the database contains a large variety of anatomical shapes, we observed that linear dimensionality reduction techniques like PCA are unable to find low dimensional representations for the whole family of shapes. On the other hand, nonlinear techniques like (k-PCA, LLE, t-SNE) are more suitable to produce low dimensional mappings in terms of reduced shape parameters ζ_i. A nonlinear greedy algorithm is used to compute a reduced order representation.

The main advantage of generating an explicit solution $\boldsymbol{u}(\boldsymbol{x}, \boldsymbol{\zeta}, p_2, \dots, p_D)$ (with $\boldsymbol{x}$ the space coordinate, $\boldsymbol{\zeta}$ the shape-parameter coordinate and $(p_2, \dots, p_D)$ additional coordinates that are introduced to parametrize loads and material properties), is that a fully customizable deformable organ model is readily available without the need to go through mesh generation, boundary conditions assignment and FE solution all over again for each patient. Since the solution is pre-computed offline, visualization of particular load-material-shape combination can be done practically in real time. The model can be thought of as a fully customizable virtual deformable twin of the patient's liver.

Keywords: human liver; statistical shape model; dimensionality reduction; model order reduction

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Real-time surgical simulation by Proper Generalized Decomposition techniques

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Abstract. The real-time computer-based simulation of surgery has proven to be an appealing alternative to traditional surgical simulators. Amongst other advantages, computer-based simulators provide considerable savings on time and maintenance costs, and allow trainees to practice their surgical skills in a safe environment as often as necessary. However, in spite of the current computer capabilities, computational surgery continues to be a challenging field of research. One of its major issues is the high speed at which complex problems in continuum mechanics have to be solved so that haptic interfaces can render a realistic sense of touch (generally, feedback rates of 500–1 000 Hz are required).

The work here presented introduces some novel numerical methods for the interactive simulation of two usual surgical procedures: cutting and tearing of soft tissues. The common framework of these two methods is the use of the Proper Generalized Decomposition (PGD) for the generation of computational vademecums (Chinesta et al. 2013), i. e. general meta-solutions of parametric high-dimensional problems that can be evaluated at feedback rates compatible with haptic environments.

In the case of cutting, computational vademecums are used jointly with XFEM-based techniques, and the computing workload is distributed into an off-line and an on-line stage. During the off-line stage, both a computational vademecum for any position of a load and the displacements produced by a set of cuts are pre-computed for the organ under consideration. Thus, during the on-line stage, the pre-computed results are properly combined together to obtain in real-time the response to the actions driven by the user (Quesada et al. 2016). Concerning tearing, a computational vademecum is obtained from a parametric equation based on continuum damage mechanics. The complexity of the model is reduced by Proper Orthogonal Decomposition (POD) techniques, and the vademecum is incorporated into an explicit incremental formulation that can be viewed as a sort of time integrator.

By way of example, the cutting method is applied to the simulation of a corneal refractive surgical procedure known as radial keratotomy (Fig. 1), whereas the tearing method focuses on the simulation of laparoscopic cholecystectomy (i. e. the removal of the gallbladder) (Fig. 2). In both cases, the implemented methods show excellent performances in terms of feedback rates, and produce very realistic simulations from the visual and haptic point of view.

Keywords: Proper Generalized Decomposition; computational vademecums; computational surgery; surgical simulation; real-time computing; cutting of soft tissues; tearing of soft tissues; XFEM; POD; continuum damage mechanics

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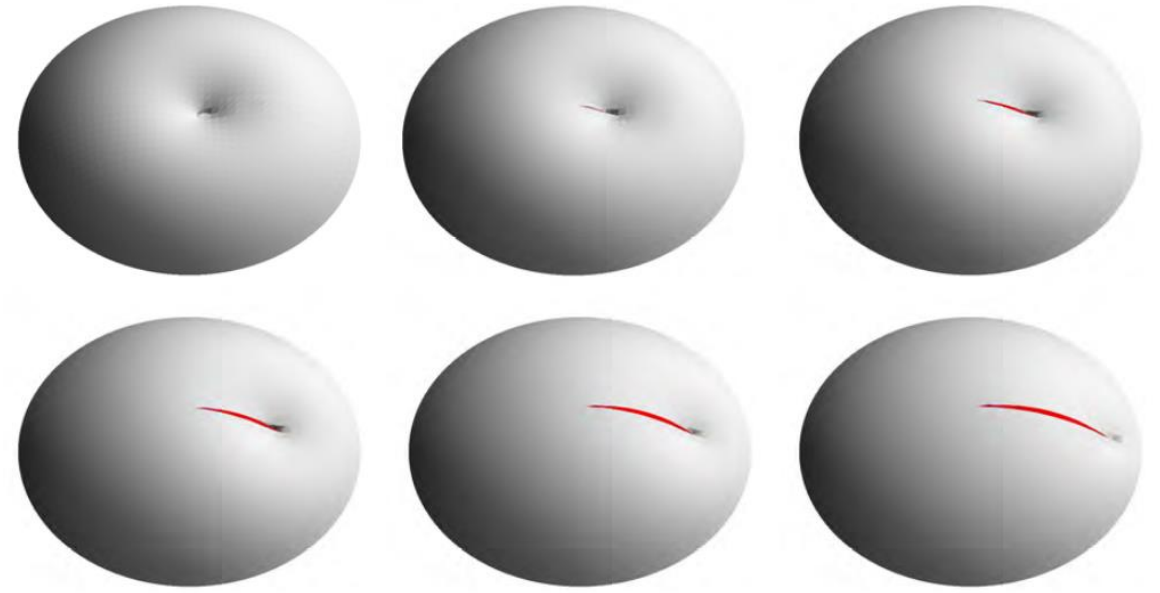

Fig. 1 Radial cutting procedure in a rendered model of the cornea. The interior of the cut has been colored in red, and its amplitude has been artificially increased by 100 times to make it visible.

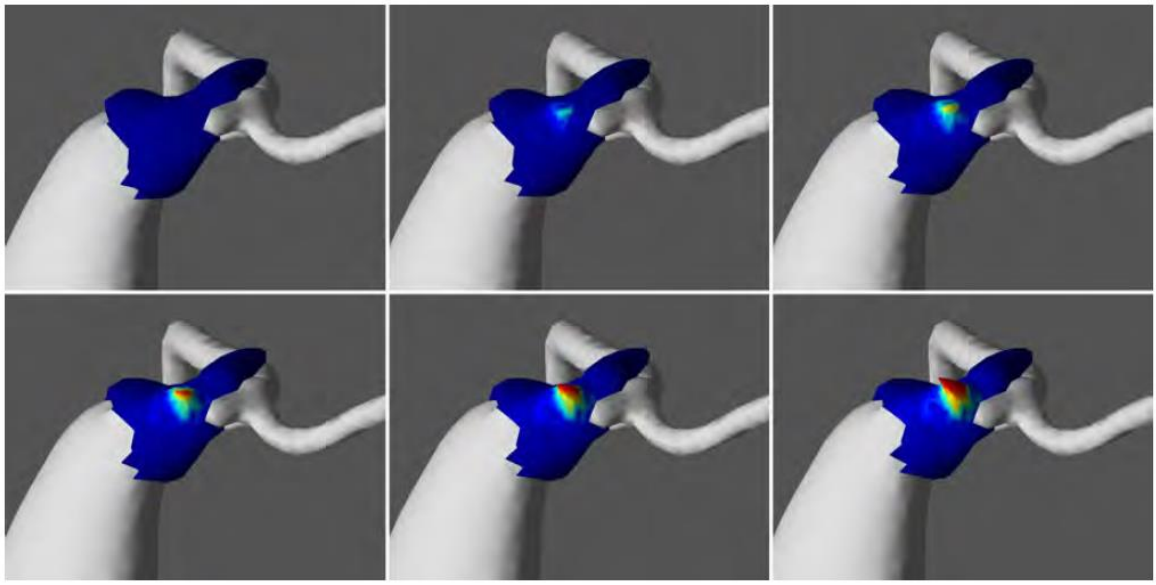

Fig. 2 Damage sequence of the removal of fatty tissue when it is pulled upwards from the gallbladder. Blue represents undamaged parts, while red represents full damage.

Blood flow triple-imaging

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Abstract The study of blood flow in the great thoracic arteries is closely related to the ventricular contractile force of the heart and therefore a quantitative assessment of flow can provide information about cardiac function and indicate potential development of vascular diseases [1].
Flow-sensitive four-dimensional Magnetic Resonance Imaging (4D MRI) has increasingly been utilised to characterise patients' blood flow in the clinical environment. Nevertheless, spatial and temporal resolution are still limited to achieve a detailed assessment of the hemodynamics.
Computational fluid dynamics (CFD) is a powerful tool that has potential to expand these information and, integrated with experimentally-obtained velocityfield , enable to derive the pressure fields. However, the accuracy of the computed flow parameters is necessarily limited by the resolution of the 4D MRI.
Hence, in order to adopt MRI-derived CFD models as reliable clinical tools, it is essential to understand and quantify the potential errors associated with the approach [2].
This study is aimed at identifying the limitations of this methodology by comparing the flow parameters obtained from 4D MRI and MRI-derived CFD with those measured for the same setup from plane Particle Image Velocimetry (2D PIV). This experimental technique enables high spatial-temporal resolution, but limitedly to 2D planes of *in vitro* transparent models.
The study was performed on an idealised-simplified model of the human aortic arch. The flow patterns were studied with MRI and PIV, and used as boundary conditions for equivalent numerical models, analysed using Ansys CFX.
This study enlightens the main strengths and limitations of 4D MRI flow reconstructions both, as a stand alone clinical approach and in combination with CFD. This is a much needed step towards the implementation of experimentally based numerical techniques in the clinical arena.

Keywords: Blood flow; Magnetic Resonance Imaging (MRI); Computational Fluid Dynamic (CFD); Particle Imaging Velocimetry (PIV); Cardiovascular diseases.

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Evaluating *in vivo* dynamic ankle kinematics in children with spastic equinus due to cerebral palsy: A feasibility study

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Abstract: Spastic equinus is the most common deformity due to cerebral palsy which exhibits limited ankle dorsiflexion leading to abnormal gait. Surgical treatment is the best-known technique, but indicates up to 48% recurrence surgery rate, making it imperative to look for solutions. Being a dynamic phenomenon, understanding of ankle joint mechanics of equinus deformity should be done in dynamic setting. This study demonstrates a feasibility of using a combined approach of using dynamic magnetic resonance imaging (MRI) sequence and a robust image processing technique to evaluate *in vivo* ankle mechanics in children with equinus deformity.

So far, two cohorts (control and equinus) with five children each (age between 7 to 14 years) have participated in this study approved by local ethical board and after signing the informed consent by both the parents. For the MRI protocol (3T Philips Achieva scanner), each child went through a static and a dynamic part. For dynamic imaging, subjects were positioned supine, knee in full extension and ankle placed in a custom-made MRI-compatible fixture (Fig 1). A real-time dynamic MRI acquisition sequence was used to acquire dynamic images of ankle joint complex in sagittal plane (FOV 200 x 150mm; pixel = 1.28 x 1.6mm; TE = 2.4ms; TR = 4.7ms; slice thickness = 6 or 7mm). For this, subjects moved their ankle from maximum platar-flexion to maximum dorsi-flexion and back, while acquiring the images in 16 time frames (6 planes each) in 18 seconds. For static imaging, ankle was placed in an 8-channel knee coil and high-resolution (0.29mm X 0.29mm X 1.0mm) images were acquired using a 3D gradient recall echo sequence.

Static images from five healthy controls were used to build surface meshes of ankle joint bones (tibia, talus and calcaneus) in Amira (FEI, Hillsboro, V 5.4.3). Bone kinematics was determined by registering the high-resolution bone surface mesh with sparse dynamic bone outlines using Iterative Closest Point Robust (ICPr) algorithm [1]. However, the feasibility of the kinematic determination method was evaluated by using a set of synthetic data generated from high-resolution data, applying known transformation to synthetic data, and gradually making the synthetic data sparse to the extent that represented the dynamic MRI data. The accuracy of the method was determined by comparing the registration kinematics with known transformation.

For all the three bones, fitting error remained within ±1mm and ±1° from 24 synthetic data planes till 7 planes and overall, using 5 sparse planes in all the bones resulted in lowest-error – lowest-sparse-plane combination. More evaluations are warranted to reduce the error further. Thus, it is feasible to use the combination of ICPr post-processing and dynamic MRI protocol for determining the ankle bone kinematics. Furthermore, evaluations in Equinus cohort are also necessary to understand the validity of this technique. Sensitivity of the post-processing algorithm will also be evaluated to check its feasibility for use in equinus cohort. Current work is involving quantification of ankle bone kinematics using the ICPr and dynamic image data for comparing the kinematics between control and equinus groups.

Keywords: Ankle biomechanics, rigid registration, robust ICP, dynamic MRI

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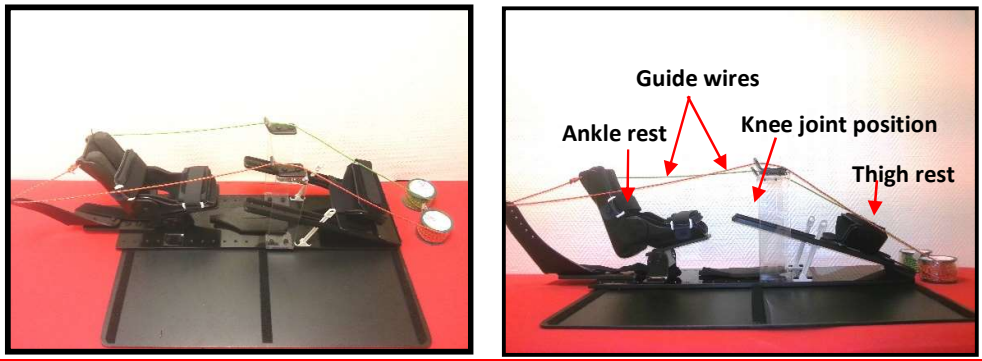

Fig. 1: MRI scanner compatible fixture to control dynamic ankle motion inside the 3T Philips Achieva scanner. For active motions, the fixture was used to make sure that the knee angle is maintained at full extension during the ankle motion and for passive motion, fixture was used to move the ankle using the guide wires.

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A computational data science framework for personalised bone health prognosis

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Abstract (500 words max). Personalised bone health prognosis uses computer simulations to predict medical outcomes months, years and even decades before the actual event and would allow, e.g., simulating the effects of treatment options virtually in patients. Some mathematical and computational models describing biological processes and mechanical properties of bone health already exist, but to model the effects of treatments on bone mechanical competence, they still need to be merged and basic biological mechanisms discovered and incorporated [Christen et al., 2014]. Also, novel modelling theories are needed as most biological models rely on parameter and input values that are usually not known and cannot be measured, not in animal models and certainly not in patients. The advancement in patient big data acquisition emerges to provide input for computer simulations potentially enabling personalised bone health prognosis. We here present a computational data science framework [Ohs et al., 2016] that combines biological and mechanical models as well as integrates patient big data for personalised bone health prognosis. We provide a first prototype of bone loss associated with adolescent idiopathic scoliosis (AIS) – a three-dimensional spinal deformity during pubertal growth without clear aetiology and pathogenesis. We test the hypothesis that this bone loss is due to reduced physical activity and use patient-specific vitamin D and parathyroid hormone (PTH) levels as they were speculated to be altered in AIS.

The computational data science framework consists of a cellular automaton to represent medical images, Boolean networks to represent molecular profiles, and micro-finite element (micro-FE) analysis to calculate mechanical tissue loading (Fig. 1). Each cell of the cellular automaton contains a Boolean network and thus molecular and cellular interactions are modelled in each voxel of the medical image. This allows to simulate molecular and cellular effects in the Boolean network and through the coupling with the cellular automaton also their effects on the phenotype. The cellular automaton is incrementally updated over time accounting for local biological and mechanical stimuli as determined by the Boolean network and micro-FE analysis, respectively. Updates are computed on the graphics processing unit (GPU). In the AIS prototype, high-resolution peripheral quantitative computed tomography images of the distal tibia, physical activity levels, and circulating vitamin D and PTH levels were integrated.

Personalised bone health prognosis of an AIS patient with normal physical activity and patient-specific vitamin D and PTH levels showed minor changes in bone mass whereas the prognosis with reduced physical activity of the same patient led to reduced bone mass (Fig. 1). This indicates that indeed physical activity plays an important role in AIS associated bone loss and that at least some mechanical regulation of bone cells is occurring in AIS patients. Our computational data science framework thus allows integrating patient big data, especially imaging, molecular, hormonal, and physical activity data to study complex trait diseases and perform personalised bone health prognosis. It couples biological and mechanical models by implementing a Boolean network into each cell of a cellular automaton. Furthermore, it makes use of the available patient big data and with that personalises prognosis.

Keywords: Personalised bone health prognosis; patient big data; cellular automata; Boolean networks; high-resolution peripheral quantitative computed tomography; adolescent idiopathic scoliosis.

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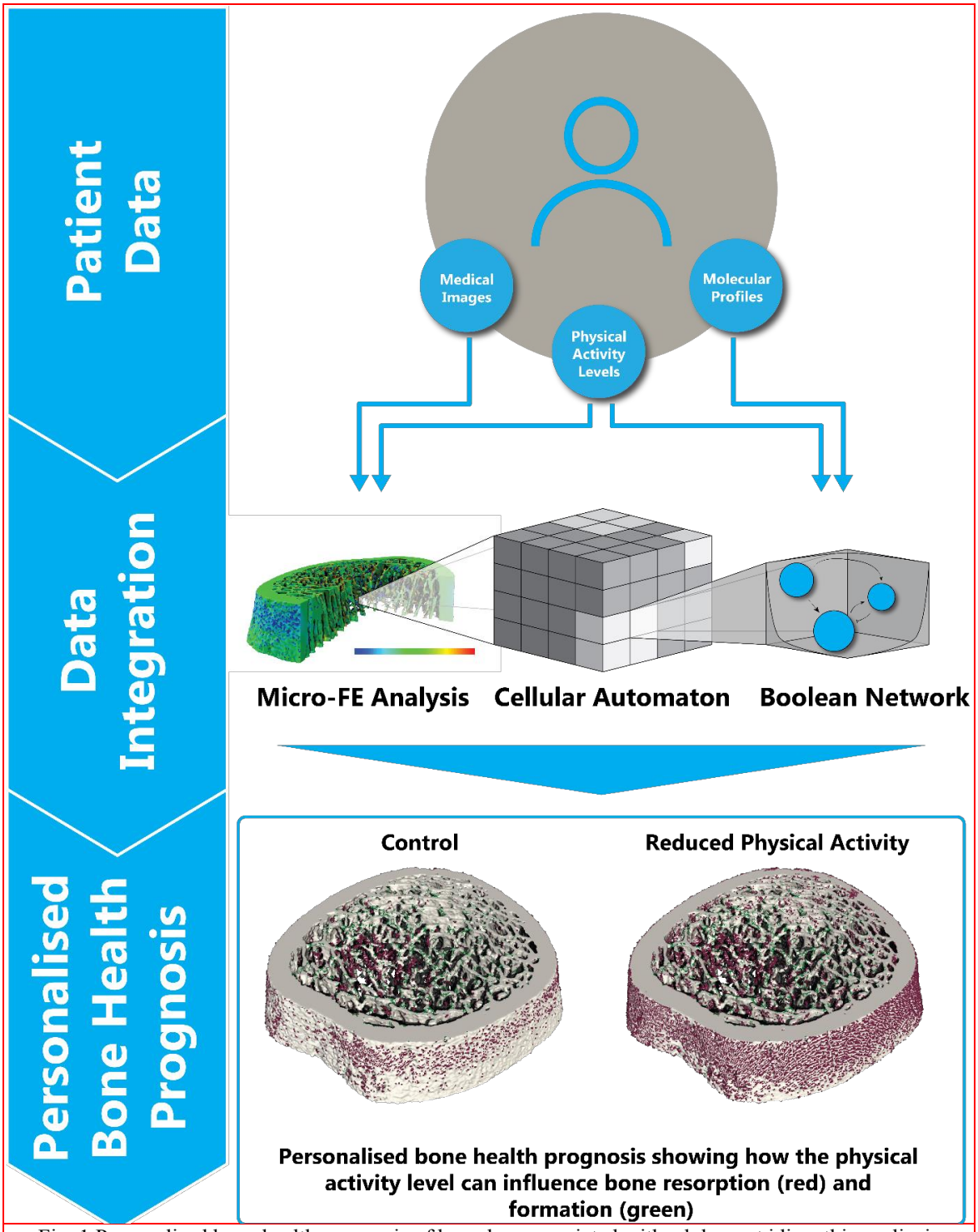

Fig. 1 Personalised bone health prognosis of bone loss associated with adolescent idiopathic scoliosis integrating patient big data including medical images, physical activity levels, and molecular profiles.

In silico modelling of cell-topography induced migration

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Introduction

Topographical cues have been shown to influence cell fate dramatically. This phenomenon opens new opportunities to design the interaction between biomaterials and biological tissues in a predictable manner. We have previously established a high throughput screening platform of surface topography (the TopoChip) and have demonstrated that surface topography significantly affects cell shape and cell proliferation [1]. Interestingly, the migratory behavior of the cells is also highly affected by the surface topography. However, a complete understanding of the mechanisms underlying topography-induced cell behavior, and more specifically cell migration, is lacking. In this study, we hypothesize that the topography-induced cell shape influences the spatiotemporal distribution of molecules involved in key mechanotransduction pathways.

Materials and Methods

28 diverse surface topographies were imprinted in polystyrene surfaces and used as a culture substrate for bone marrow-derived human mesenchymal stromal cells (hMSCs). The migration was assessed by 24 hours of observation using a Life Cell Imaging Microscope. CellProfiler and R were used to perform image analysis and data processing. Realistic cell shapes were imported in VirtualCell to calculate the dynamics of the phosphoinositides (PIs) and Rho family GTPases, based on the computational model of Marée et al [2].

Results and discussion

The 28 surfaces showed a variety of cell migration responses. The general trend was that topographical surfaces affected both the speed and direction of migration. In order to investigate how the initial polarization, and subsequent migration was influenced by the topography-induced cell shapes, the computational model of Marée et al. was used to calculate the spatiotemporal dynamics of key mechanotransduction components (Figure 1). The preliminary results of the calculations indicate that topography-induced cell shapes highly affect cell polarization, although further validation is necessary.

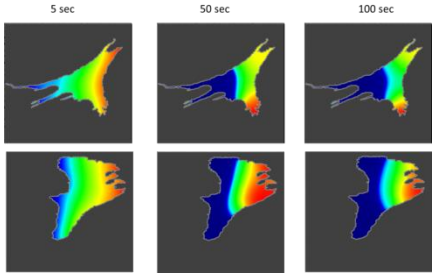

Figure 1: Distribution of active Cdc42 as a function of time and space in realistic topography-induced cell shapes.

Conclusion

The results of this study indicate that topographical surfaces influence cell migration. Future work will focus on model validation through various *in silico* and *in vitro* perturbation tests.

Keywords: *in silico* modelling; migration; topography

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Acknowledgements

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From CT images to non-homogeneous Timoshenko beams: a computational biomechanics approach

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Abstract

3D Finite Element models are undoubtedly the golden standard in computational biomechanics. However, as a rule, they pose severe challenges in terms of computational power needed for model generation and for solving the corresponding systems of equations. This renders them cumbersome, particularly when the target should be a real-life, real-time use of such models in the clinical practice.

As a remedy, we here present a CT-image-to-short sandwich beam conversion technique. The theory of shear-compliant beams is derived from the principle of virtual power, so as to account also for inhomogeneous mechanical property distributions across the beam cross sections. It is then applied to CT images of a human vertebra, whereby the attenuation coefficients are converted into elastic properties according to a recently developed method coupling X-ray physics and micromechanics [Blanchard et al, 2016]. Solution of the corresponding boundary value problem for bending, transverse, and axial loading of the beam is based on the 2D stress function proposed by Kourtis [Kourtis et al, 2009]. The corresponding results show decent fit with those obtained from classical 3D FE approach, with decreased calculation and model building times.

Keywords: computed tomography; inhomogeneous material; Timoshenko beam theory; Finite Element

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Fiber reorientation in carotid arteries under tension-inflation mechanical loading.

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Abstract. Soft biological tissues, made of variously organized collagen and elastin networks, exhibit a highly nonlinear anisotropic behavior with the ability to sustain large reversible strains. The latter originates in a load-induced progressive morphological rearrangement of the fibers, as shown by recent experimental mechanical tests performed on soft tissues and coupled to multiphoton microscopy. However, the mechanisms driving these geometrical rearrangements remain unclear: do the fibers follow the matrix deformation, or do other mechanisms exist that allow them to rotate independently from the matrix? We here analyze morphological changes of the microstructure of carotid arteries under mechanical biaxial loadings, and investigate the underlying microscopic mechanisms governing fiber reorientation.
Samples of rabbit carotid arteries were prepared into cylindrical segments for tension-inflation testing. The samples were imaged under different load configurations: either axial stretching under imposed internal pressure, or increasing pressure under imposed axial stretch; in each case, the microstructure was analyzed in terms of local angular density of the adventitial collagen network. This analysis enabled to compare observed fiber reorientation with affine reorientation amplitudes (see Fig. 1).
Adventitial collagen bundles show under axial stretch a remarkable capacity to realign in the direction of the load, resulting in larger rotations than the ones predicted by the affine assumption. On the contrary, the bundles show a very limited realignment under inflation, with noticeably lower rotations than the ones predicted by the affine assumption. As a second step, we propose a multiscale mechanical model of the arterial wall, based on Eshelbian micromechanics [1], introducing another mechanism of fiber reorientation, and test its ability in predicting both fiber orientations and mechanical response.

Keywords: multiphoton microscopy, multiscale model, collagen bundles, crimping

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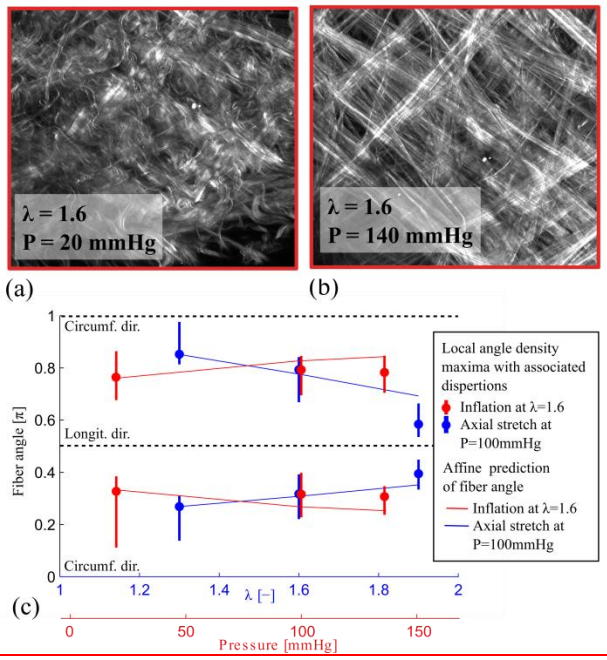

Fig. 1 (a) adventitial collagen bundles under low pressure; (b) under high pressure; (c) fiber reorientation analysis

Finite element study:- Locus of Axis of Rotation of T11-T12 and T12-L1 Segments under different loading configurations

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Abstract In human, the thoracolumbar junction (TLJ) is a transitional region where the normal kyphotic thoracic region shifts to the normal lordotic lumbar region; the coronally oriented facet joints of the thoracic region transform to the sagitally oriented facet joints of the lumbar; and the relatively immobile thoracic region changes to the relatively mobile lumbar region. The different anatomical characteristics at the functional spinal units (FSUs) of T11-T12 and T12-L1 provide an opportunity to study the associations between pathoanatomical changes in these two levels. Hence, it is of interest to investigate the biomechanical responses of the spinal motion segments T11-T12 and T12-L1, which possess the transitional vertebra T12, to determine whether the biomechanical kinematic properties reflect these anatomical changes between these FSUs. The movement of a FSU is dependent upon several parameters, namely its complex geometry, facet articulations and material characteristics of the ligamentous tissues, intervertebral discs, and upon the applied load vectors.

Accordingly, this study aimed to use a validated FE models of thoracolumbar junctional T11-T12 and T12-L1 functional spinal units (FSUs) validated under physiological loading modes: flexion, extension, lateral bending and axial rotation, and to compare the kinematics in terms of the locations and loci of instantaneous axes of rotation (IARs).

Figure 1. shows T12-L1 FE model and Figure 2. shows one validation study on the biomechanical responses of T11-T12 and T12-L1 under flexion/extensions. Figures 3., 4. show the locus of axis of rotation of T11-T12 and T12-L1 models under two loading configurations of flexion/extension and axial rotation, respectively.

The locations and loci of T12-L1 differ greatly from those of T11-T12. In sagittal plane, the locations and loci of the IARs were located below the intervertebral disc for T11-T12, situated in the intervertebral disc for T12-L1. In transverse plane, they fell in the medio-anterior region of the movable vertebra T11 for the T11-T12, and located near the cortical shell of the upper vertebra T12 for T12-L1. It is known that the anatomic geometrical structure of a FSU defines it motion and related biomechanical responses. Hence, some differences in anatomical features of the two FSUs may account for the variation in loci. At level T11-T12, the facet articulation is essentially oriented in the coronal plane; while in the T12-L1 segment, the facet joint surfaces are sagitally aligned. For the intervertebral disc, at T11-T12, the anterior height is slightly larger than the posterior height; whereas, at T12-L1, the anterior height is greater than the posterior height, which results a lordotic angle. These different orientations of the facets and the geometry of interveterbral discs may demonstrate the difference in loci at the two levels.

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These findings offer an insight to better understanding the kinematics of the human thoracolumbar spine; provide clinically relevant information for the evaluation of spinal stability and implant devices functionality, and the biomechanical load effect on spinal deformity.

Keywords: thoracolumbar junction; finite element; axis of rotation, functional spinal unit

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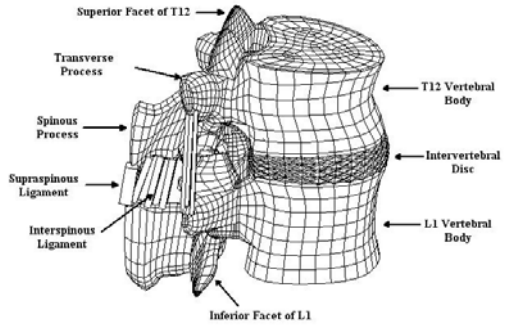


Fig. 1 FE model of T12-L1

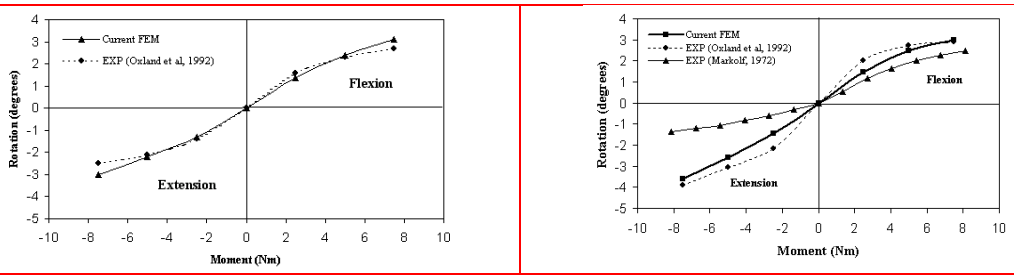
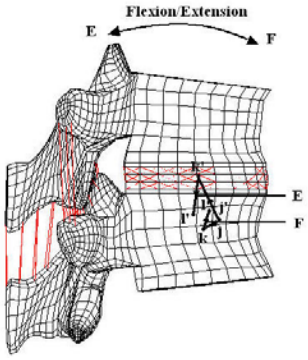


Fig.2 Angular motion of T11-T12 and T12-L1



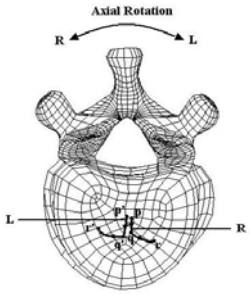
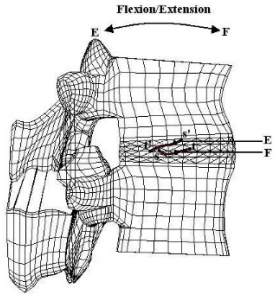


Fig. 3 T11-T11 Locus of axis of rotation under F/E and A Rotation



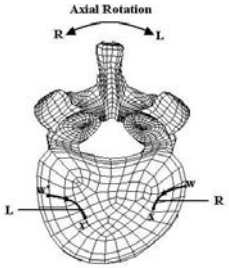


Fig. 4 T12-L1 Locus of axis of rotation under F/E and A Rotation

The use of 3D *in-vitro* intervertebral disc bulge in the validation of specimen-specific finite element models.

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Abstract. Back pain is the greatest single source of disability worldwide, with the degeneration of the intervertebral disc (IVD) being the main cause [Hoy *et al*, 2014]. *In-silico* models of the IVD are a promising preclinical testing instrument for the development of new interventions but require robust validation. The aim of this study was to develop a method for evaluating the agreement of specimen-specific *in-silico* models of the IVD against 3D *in-vitro* measurements of disc bulge under load. The method was used to investigate the application of non-linear and linear mechanical properties of the IVD.

Fresh sub-adult bovine caudal osteodiscs (n = 4) were dissected, isolating the IVD from other tissues and leaving approximately 15 mm of vertebral bone at each end. Forty glass fiducial markers were placed on the surface of the IVD (five markers distributed axially at every 45°). The specimens were CT-scanned (XtremeCT, Scanco Medical AG, Switzerland) at a resolution of 82 µm and compressed axially using a customised rig designed to fit within the CT imaging chamber. The specimens were imaged at three stages: before loading, and after 1 mm and 2 mm of applied axial compression.

Finite element models were generated using a specimen-specific approach, based on the geometry captured from the unloaded CT scans. The images were segmented to isolate bone, soft tissues, individual glass fiducial markers and the cement endcaps, in ScanIP v7.0 (Synopsys, Mountain View, USA). The IVD was modelled using linear [Kumaresan, *et al*., 1999] and non-linear elastic mechanical properties previously derived for an independent set of bovine IVD specimens. Images of the compressed IVD were aligned to the unloaded ones and the *in-vitro* local disc bulge was measured as the radial displacement of the markers. The corresponding *in-silico* measurements were compared with the *in-vitro* ones using concordance correlation coefficients (CCC).

A good agreement was observed between the *in-vitro* measured bulge and the *in-silico* predicted bulge using the linear elastic (CCC= 0.67) and non-linear elastic material properties (CCC=0.63) with an applied displacement of 1 mm (Figure 1.a). Only three models converged for the linear models (CCC=0.60, n=3) at 2 mm (Figure 1.b), whilst all models converged for the non-linear models (CCC=0.63, n=4).

The methodology developed in this study allowed the specimen-specific comparison of local deformation across the tissue of interest with corresponding points on individual *in-vitro* specimens. This provides a more robust method of validation than assessment of only global measures. The study demonstrated that the use of both linear and non-linear elastic material models resulted in good agreement between *in-silico* vs *in-vitro* IVD bulge at low strain levels, but the linear models struggled to converge at higher levels of strain. The methods developed could now be used to

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calibrate the material properties for different tissues types (e.g. different levels of degeneration), potentially by combined with load-displacement behavior to enrich the level of validation. These models could be further used in the assessment of interventions such as nucleotomy and new therapies that aim to repair the structural integrity of the disc.

Keywords: spine biomechanics; microCT scan; specimen-specific models; experimental validation

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Fig 1.a

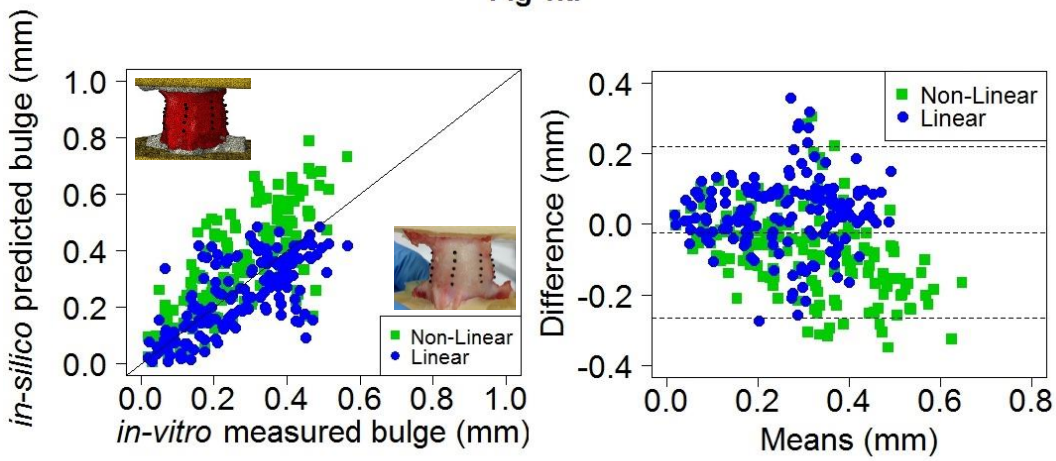

Fig. 1.b

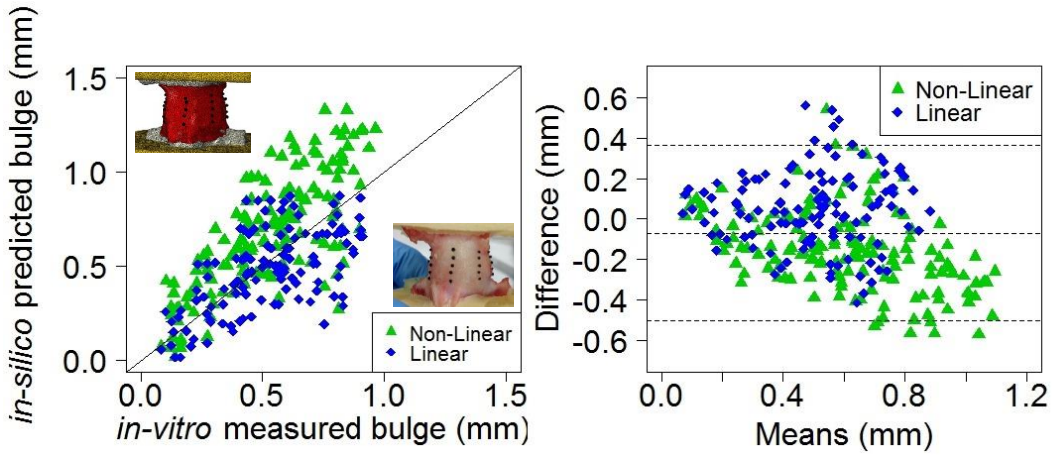

Figure 1: Bland-Altman plot of the *in-silico* vs *in-vitro* measured IVD bulge for 1.a)1 mm nominal axial compression (n=4), 1.b) 2 mm nominal axial compression (Linear elastic n=3, Non-linear elastic n=4).

On measuring pre-strain and functional extrafibrillar behaviour of the annulus fibrosus to reverse-engineer its fibrous behaviour

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Abstract.
Material parameters for *in-silico* models of the intervertebral disc are often derived from experimental data of tissue tested *in-vitro*, e.g. the behaviour of the extrafibrillar matrix (EFM) in the annulus fibrosus has been derived from mechanical tests performed on small tissue samples loaded perpendicular to the fibre direction. This approach has the disadvantage that the collected data does not account for the *in-situ* pre-strain to which the tissue is submitted.
The first aim of this study was to measure the *in-situ* pre-strain of the annulus of bovine intervertebral discs and define a functional elastic modulus for the EFM. The second aim was to reverse-engineer non-linear material properties for the fibrous part of the annulus tissue.
Fresh bovine caudal discs (N=8) were dissected from juvenile animals and prepared to isolate the disc from any other tissues. The annulus was freed from the central nucleus pulposus with a circumferential cut in the inner annulus. A radial cut through the annulus was performed at a random location and the disc was left free to open for between 20 and 25 minutes, after which high resolution photographs were taken (Fig 1a). Angular opening of the annulus, φ, was measured in imageJ and hoop pre-strains derived as $\varepsilon_h = \varphi/(2\pi - \varphi)$.
A linear fit was performed on EFM tensile data (N=3) obtained from single lamellar testing of similar tissue [Monaco et al., 2016]. A linear regression between strain values corresponding to ε_h and the strain at maximal stress was used to define a functional linear modulus (Fig 1b).
Finally, finite element models of caudal bovine osteodiscs (disc surrounded by two half vertebrae, N=6) were built from micro-CT images (Fig 1c) of specimens tested *in-vitro* [Sikora et al., 2016]. Material behaviour for the bone was based on the greyscale of the underlying image. The nucleus was assumed to be a Mooney-Rivlin incompressible material. The annulus non-linearity was captured with a Holzapfel exponential model assuming two fibre orientations. The linear modulus derived in the first part of the study was used for the EFM, and compressibility was that of water. Loading scenario replicated *in-vitro* axial compression, and direct calibration of the fibre components was performed (http://dx.doi.org/10.5281/zenodo.49565), minimising for each sample the RMS error between the *in-vitro* and *in-silico* load/displacement data.
Hoop pre-strains were measured as 19± 4 %. The EFM linear modulus was 1.3± 0.3 MPa, with a concordance coefficient of at least 0.98. The EFM was thus assumed to behave linearly when *in situ*. The exponential behaviour of the annulus fibres, derived with RMS errors under 15%, was described with two parameters of 2.3± 0.6 MPa and 6.9± 3.0.
This study showed that using the linear elastic modulus derived from small sample mechanical testing is equivalent to assuming the annulus is under pre-strain *in-situ*. Using such a value in the calibration of finite element models allowed us to reduce the number of parameters to reverse-engineer while being sure the other parameters are representative of the actual EFM behaviour.

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[d] Prof., E-mail: R.K.Wilcox@leeds.ac.uk

Keywords: intervertebral disc, annulus fibrosus, pre-strain, reverse engineering

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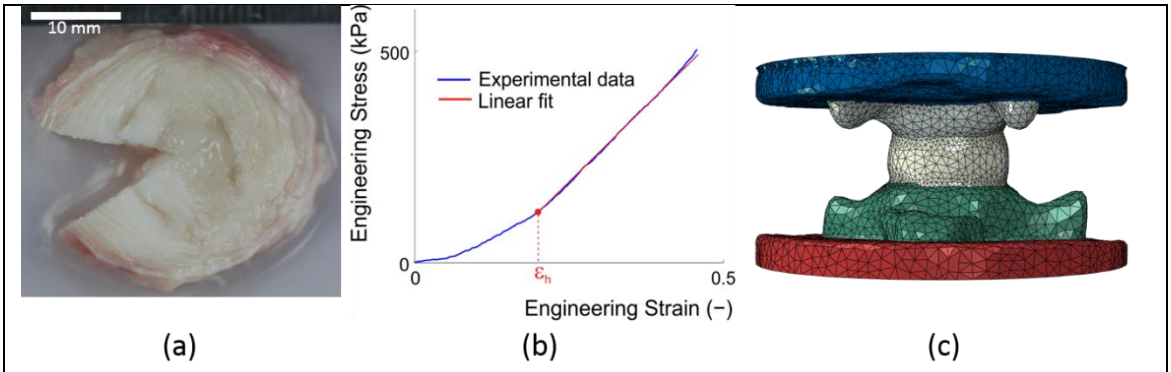

Fig. 1 (a) typical opening of the AF ; (b) typical stress-strain behaviour of the EFM, with linear fit ; (c) Finite Element model of bone-disc-bone sample

Material-driven mesh derived from medical images. A case study on patient-specific modeling of the lumbar spine

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Abstract. This work presents a methodology for patient-specific finite element modeling which takes both individualized geometry and material properties of biological structures into consideration. In this study, the mesh is driven by personalized material knowledge which is extracted from advanced medical imaging. Additionally, a user-friendly program including image processing, material-driven meshing and material properties assignment, named C3M "Computed Material-driven Mesh Model", has been developed to generate efficiently subject-specific FE models derived from medical images. This process is applied to generate a patient specific FE model of lumbar spine based on both MRI and CT images.

Keywords: patient specific finite element model; material-driven meshing; medical images; lumbar spine

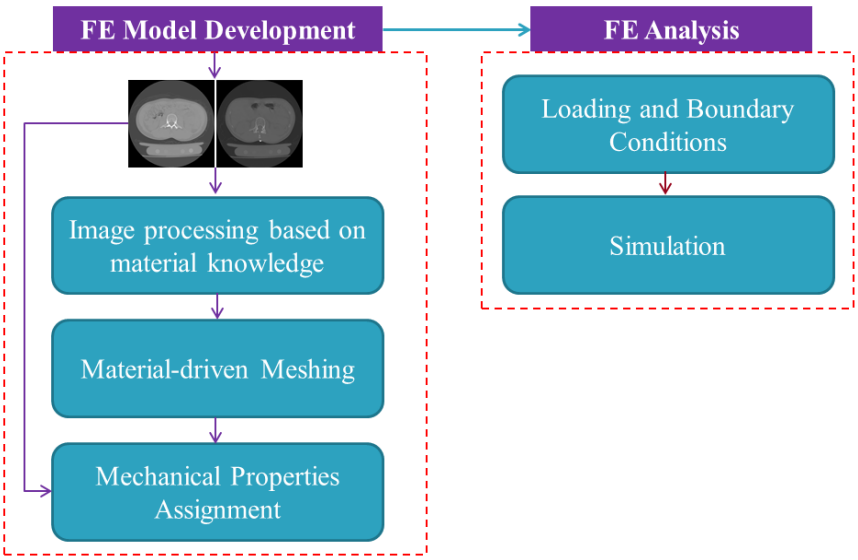

Fig. 1 Modeling workflow.

An alternative tonometric results analysis for measuring intraocular pressure – A computational approach

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Abstract. Intraocular pressure (IOP) is the main tool used for the diagnosis of ocular pathologies such as glaucoma, which is one of main diseases causing blindness in the world. There exist a variety of devices for the IOP measurement, most of them calibrated against the Goldmann Applanation Tonometer. Tonometry is based on the Imbert-Fick law, which establishes that the pressure in the interior of a flexible sphere having thin walls can be approximated by knowing the required force to flatten a given area of the sphere. However, not only the assumption of infinite thin wall is not valid considering the corneal radius-to-thickness ratio, but also the influence of several corneal parameters such as external curvature radius (ECR), central corneal thickness (CCT), and corneal modulus of elasticity (E) are not considered. In this study, a series of computational simulations of ocular tonometry are performed, and a new protocol for measuring IOP, based on the results that can be extracted from conventional tonometry, is proposed and validated. Finite Element simulations were performed to evaluate the interaction between the cornea and a rigid element used as the tonometer. Simulations were performed for different combinations of actual IOP and E. In addition to tonometric pressure, displacements of six reference points over the cornea were obtained from the simulations. These results along with actual IOP, E, initial CCT and CCR were subjected to a principal components analysis (PCA) allowing a dimensional reduction to a vectorial space using two main PCA components. This new representation exhibited a distinguishable behavior for each actual IOP and E. Based on this PCA analysis, a simple methodology is proposed to estimate the IOP and the instantaneous E of the cornea. The methodology can be summarized in the following steps: 1) Generation of a database of simulation results subjected to PCA considering different corneal geometries, intraocular pressures, and corneal mechanical properties; 2) In the ophthalmologist office and for the specific patient, perform tonometric measurement and determination of the displacements of the reference points of the patient cornea; 3) Calculate the corresponding values for the two main principal components 4) Interpolate within the generated database between constant pressure and constant elastic modulus data to estimate the actual IOP and instantaneous E. The proposed methodology was validated by randomly selecting 7 pairs of IOP and E for which tonometric simulations were performed, the corresponding results for these 7 simulations represent the data that would be taken at the ophthalmologist office. Then, using a previously created database, and following the proposed methodology, an estimation of the IOP and corneal instantaneous E were obtained with a maximum error of 2% for E and 4% for IOP.

Keywords: Intraocular Pressure; Computational Simulation; Tonometry; Glaucoma

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Modeling fiber interface with stochastic cross-bridges

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Abstract. Biological organisms make extensive use of fiber networks for structural integrity across multiple length scales, be it soft tissues such as skin or tendon at the tissue level, or cytoskeleton at the cellular level. In this study, we develop a stochastic fiber network model, where the mechanical response of interacting fibers is given by stochastic attachment and detachment of springlike cross-bridges. The motivation behind such a model lies in the natural variability of fiber network microstructure, giving rise to interspecimen variability and the possibility of biological restructuration during mechanical loading, both features which can be apprehended in a probabilistic framework.

In this model, rigid filaments are mechanically coupled via parallel springs possessing on one hand a stochastic attachment rate, dependent on the distance to binding sites on the filaments and on the other hand a stochastic detachment rate, dependent on local mechanical load, see Fig. 1 (a). A natural inspiration for this system can be found in collagen-based fiber networks, where stiff collagen fibers interact in the midst of a compliant proteoglycan matrix.

The law describing the detachment rate is derived from Kramers theory for the escape of a particle from a potential well in the presence of thermal fluctuations. The shape of the potential is used here as a proxy for the strength of the cross-bridge binding mechanism. The result is an exponentially load-dependent detachment rate, commonly called Bell's law[1][2]. The attachment rate takes into account the probabilistic diffusion-like spreading of unbound cross-bridges due to thermal fluctuations as well as the distance to the neighboring binding sites.

Once the time-dependent attachment and detachment rate are prescribed, we use an iterative Monte Carlo algorithm to solve the 1-dimensional problem of sliding filaments with an arbitrary number of cross-bridges and periodical binding sites for the cross-bridges. The response exhibits two features separated in time scales as shown in Fig. 1 (b). For long time scales, a stable steady-state force appears, akin to viscous drag, but which depends non-monotonously on the sliding speed v, as shown in Fig. 1 (c). This shows that an optimal sliding speed exists with respect to maximal adhesion between fibers.

At short time scales, avalanche-like fluctuation patterns due to cascading detachment events are observed, which persist throughout the steady state.

Our model thus shows that applying stochastic attachment/detachment events can cause the emergence of viscous non-linear behavior from purely linear mechanical elements. Since the parameters of the model are a representation of the actual microstructure of the fiber network, the groundwork is laid for these parameters to be extracted from experiments. These would put real constraints on the model and once validated, the model could then estimate the effect of parameter modifications such as in biological experiments or pathologies.

Keywords: stochastic modeling; fiber networks; soft tissues; Monte Carlo simulation

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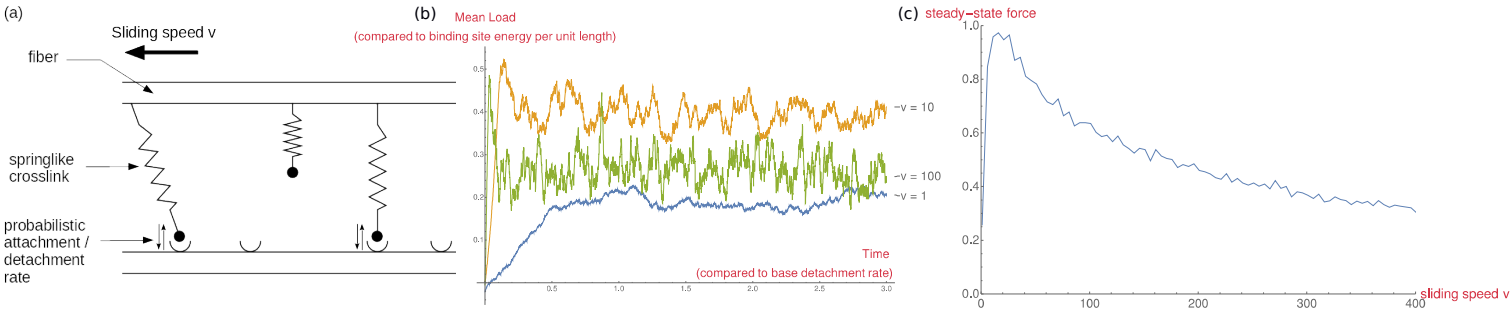

Fig. 1: Stochastic sliding fiber model. (a) Schematic of the model. (b) Simulation of the force as a function of time for different sliding speeds (c) Plot of steady-state force as a function of sliding speed v exhibiting a maximum of the adhesion force

An optimized parameter identification of soft biological tissue through finite element analysis and biaxial tensile tests: application on abdominal porcine skin

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Abstract. To contribute to a numerical model of high bio-fidelity for deformable biological structures, parameter identification for the mechanical behavior law of soft tissue is essential. Today, numerical simulations allow complex nonlinear behavior laws to be identified, by fitting the simulation results to experimental data measured on specimen. In this presented work, we propose an optimized identification procedure of soft biological tissue, through finite element analysis and biaxial tensile tests. The method was tested by identifying an abdominal porcine skin specimen for isotropic hyperelastic behavior laws (second-order polynomial form), which validates its feasibility and practicability. In future work, this methodology could be extrapolated on human soft tissues.

Keywords: Parameter identification, Finite element, Biaxial tensile test, Porcine skin, Hyperelastic material

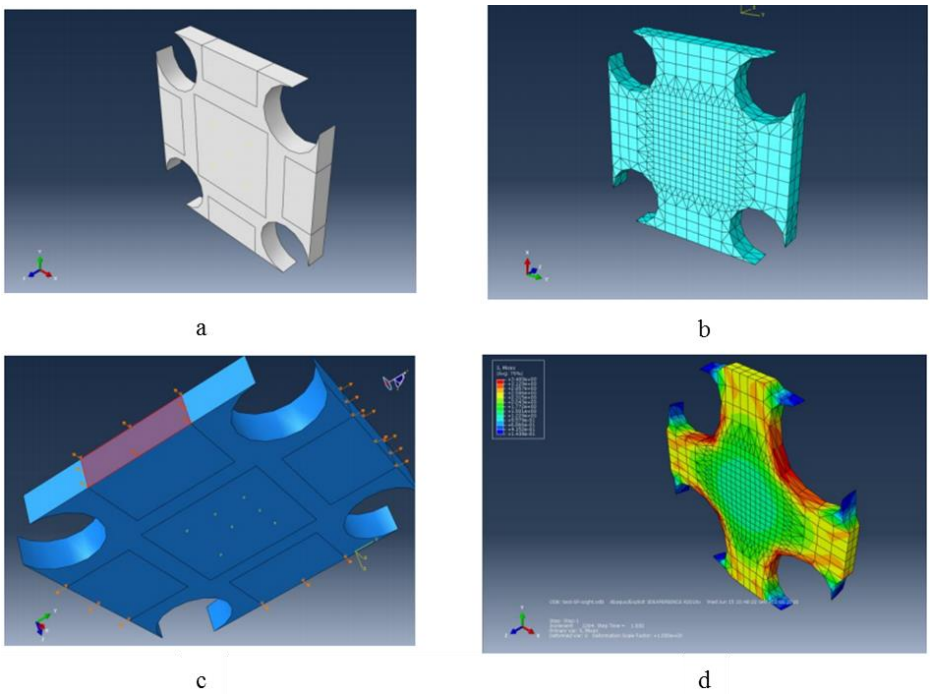

Fig. 1 Numerical modeling and simulation of the specimen undergoing biaxial tensile test.

Mechanical barrier function of in vivo human skin stratum corneum: viscoelastic numerical simulations incorporating damage

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Abstract. The stratum corneum is the first barrier protecting the human body against external mechanical, biological, chemical and thermal influences. It is one of the sub-layers of the human skin. It is composed of hard dead keratinized cells: the corneocytes held together by lipid mortar with less than 10% water. This structure gives the stratum corneum its strong mechanical resistance. However, during everyday life, the stratum corneum appears to be endangered by the repeated contact with clothes and other soft or hard tissues. These frictions may result in a damaging process for the stratum corneum and may modify the overall answer of the human skin to external influences. Nowadays, the question of the evolutions of these answers of skin layers is of prime importance when speaking of quality of life all along the life of a person (baby till old persons) as well as for clinical purposes (surgical dressings) and cosmetic researches (care cream dressings).

This study proposes numerical simulations to investigate the influence of the state of the stratum corneum (intact or damaged) on its mechanical barrier function.

Experimental contact-free creep tests and friction tests are performed in vivo on volunteers.

Then 3D numerical simulations of these tests are carried out using the finite element method. For these numerical simulations, skin is seen as a stratified medium with two layers: the stratum corneum and a second layer simulating the remaining sub-layers of skin soft tissues. The stratum corneum is specifically modeled with its own viscoelastic behavior law incorporating damage. The second layer is supposed to be described by a Zener non-linear viscoelastic law. This coupled "experimentations-numerical simulations" method results in:

- the determination of the mechanical parameters of the undamaged skin soft-layers ;
- the numerical follow of the progressive mechanical damaging process of the stratum corneum ;
- the determination of the mechanical parameters of the damaged skin soft-layers.

Comparison of these different states gives insights on the evolutions of the mechanical parameters of the stratum corneum when subjected to friction. Now it is well admitted that there is a direct link between the mechanical state and the physiology of the human skin in vivo. Therefore, the changes in mechanical parameters highlight the coupled changes in the physiology of the stratum corneum and the associated changes in its mechanical resistance.

Keywords: human skin in vivo; numerical simulations; viscoelastic behavior; damage; experimental tests

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Development of novel tools based on patient specific models for guidance and education and orthognathic surgery.

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Abstract

Dentofacial deformities consist of discrepancy between facial bones, mainly the upper and lower jaws resulting in prognathism, retrognathism or asymmetry. Such deformities are possibly unsightly and can disturb the psychological and social balance. They can cause difficulties in chewing, talking, and ultimately lead to the loss of teeth. In the USA, 17 million individuals (aged 12 to 50 years, in 2006) have dentofacial deformities severe enough to warrant surgical correction. Such correction consists of orthognathic surgery, a subspecialty of maxillofacial surgery, which restores facial harmony and dental occlusion through bone section, reposition and fixation.

In our routine practice of orthognathic surgery, we face the limitations of conventional tools such as two-dimensional radiographs and dental casts and the lack of intraoperative assistance. These limitations occur at every step of the surgical workflow:

- Planning: designing the procedure and making the optimal surgical choices
- Simulation: validating the planning according to the simulated outcome and delivering appropriate information to the patient
- Navigation: providing the surgeon with relevant intraoperative assistance.

If computer science has provided satisfactory solutions for planning, yet simulation and navigation appear improvable.

The aim of our research was to provide novel tools to improve these issues.

Therefore, we first developed a semi-automated segmentation pipeline allowing accurate and time-efficient patient-specific 3D modeling from CT scans. From this virtual model, we achieved the prerequisite surgical planning consisting in mathematically "converting" the surgical cutting plane, as well as specifying and quantifying the displacement of facial bone segments. This planning step was achieved using surface meshes and transformation

matrices. To do so, we had to choose a set of anatomically relevant points in order to define cutting plane and axis of both rotation and translation. Once the cutting plane was defined, the mesh could be cut into two separate sub-meshes. Then, points and axes were defined in order to apply bone movements.

Further, we developed a software program meant to simulate the alterations of facial soft tissues resulting from the surgical displacement of underlying bone segments. This step required volume meshes, which were processed from segmented DICOM images of patients' CT-Scans. We used the TetGen® library in order to generate volume meshes.
We also used the Bullet® mechanical engine and a mass-spring model in order to simulate soft tissue deformation.
We evaluated our simulation software through the comparison of the simulation outcome with the ground truth consisting of surface meshes extracted from postoperative CT-Scans.
Evaluation showed promising results, since accuracy was below 1 mm. Such accuracy and the refreshing speed can allow our simulation to be used in real-time applications requiring to being realistic.
Therefore, such software could be used in clinical routine for patient communication, and surgeon validation of the planned operative procedure.

In order to provide a complete software suite dedicated to orthognathic surgery, we also developed and evaluated a real-time navigation system based on minimally-invasive electromagnetic tracking, featuring a novel user-friendly interface.

We believe that our developments could provide significant improvement for patient optimal care.

Keywords: orthognathic surgery, computer-assisted surgery, simulation, mass-spring model, navigation.

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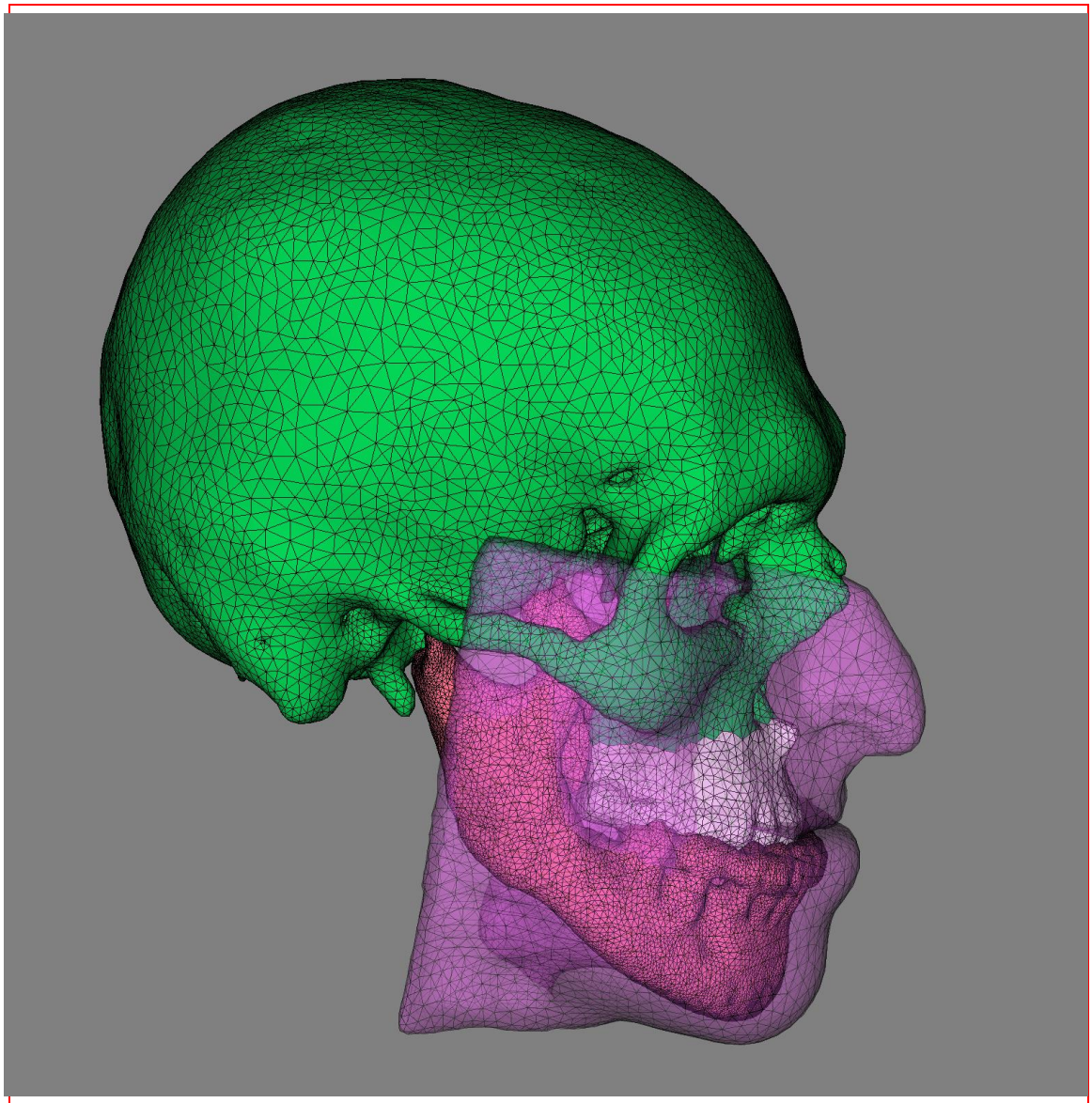

Fig. 1 Surface bone meshes of the upper facial skeleton (green), the maxillary segment (white) after section and the attachment of the simulated soft tissue layer volume mesh (pink) (right lateral view).

Analysis of the influence of a four-implant retained bridge on the stress state in mandibular bone

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Abstract. The study deals with full dental prosthetic reconstruction on four implants ("All-on-four"). The aim is to compare the stress state in the mandibular bone between a non-restored mandible and a restored mandible. A finite element model (Abaqus®) of an edentulous mandible with a fully customized denture screwed onto four implants is established. Two anterior axial implants are placed in the right and left canine areas with another two posterior tilted implants. Three distinct phases of mastication are modelled: maximum intercuspation (ICP), incisal clench (INC) and unilateral molar clench (only the right molar clench RMOL is considered). In the bare mandible, the maximum stresses are found near the right tilted implant location during RMOL. Otherwise, the stresses are the highest during ICP, in comparison to the INC and RMOL stages: this seems to be logical, as ICP stage corresponds to the phase of the mastication where both jaws are completely tightened. In the restored mandible, during ICP, the decrease of the stresses is explained by the fact that the greatest stresses are supported by the framework. The slight rise of stresses during INC is the result of two separate mechanisms inducing opposite effects on the stresses: the stiffening of the mandible caused by the framework and the deformation process of the framework, significantly different between INC and ICP. The major differences between the non-restored and the restored mandibles arise during RMOL. They concern the working side's implants: the stresses decrease (about 65 %) near the tilted implant and increase (about 200 %) near the axial implant, which behaves as an essential component to transfer the twisting movement as a bending and translation movement for the rest of the lower jaw. This stress deviation could explain some of the therapeutic failures concerning implants loosening in the "All-on-four" technique.

Keywords: dental prostheses; bone/implant interface; finite element modeling

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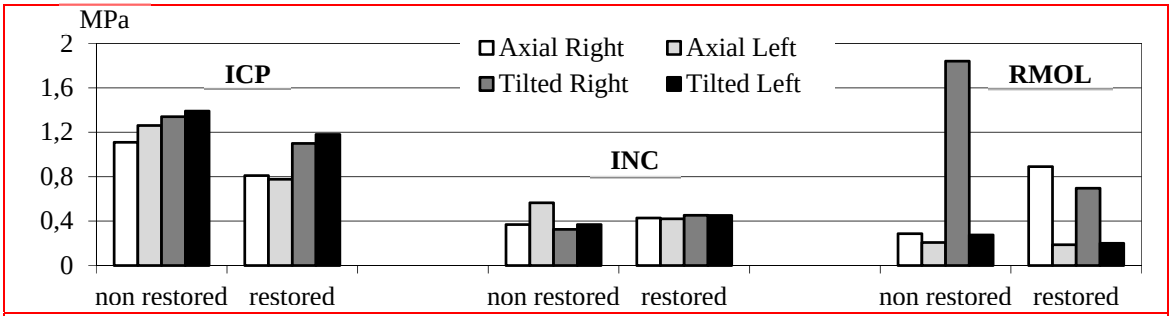

Fig. 1 Von Mises stresses at the 4 bone/implant interfaces in the bare mandible and in the restored mandible.

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Skeletal Muscle Coordination for Facial Mimic Simulation

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Abstract. Skeletal muscle coordination is a fundamental mechanism for human locomotion function. The understanding of this complex mechanism leads to better diagnosis and treatment of musculoskeletal disorders. Rigid body modeling has been commonly used to simulate this complex phenomenon. Surface electromyography (sEMG) has been used for elucidating the skeletal muscle synergies. However, the validation of these outcomes as well as their integration into numerical models requires further investigations. Moreover, sEMG allows only electrical behavior of muscle coordination to be characterized. Medical imaging has been usually used for morphological characterization of skeletal muscles. Recently, magnetic resonance imaging has been used for extracting the activation behavior of the single facial muscle leading to drive the finite element simulation with subject specific information. The objective of this work was to use MRI technique to characterize the activation behavior of three facial muscles and then simulate their coordination mechanism using a subject specific finite element model. MRI data of lower head of a healthy subject were acquired. A subject specific finite element model was developed. This model includes skin, skull, fatty tissues and three pairs of facial mimic muscles (Zygomaticus Major (ZM), Levator Labii Superioris (LLS), Levator Anguli Oris (LAO)) derived directly from medical images. Transversely-isotropic, hyperelastic, quasi-incompressible behavior law was implemented for facial muscles. Hyperelastic behavior law was assigned to subcutaneous soft tissues. Skin envelop was model as linear elastic material. Appropriate loading and boundary conditions were applied. The interaction between muscle and surrounding soft tissues was defined as tie constraint. The simulation to produce the pronunciation of the sound [o] was performed using Abaqus/Explicit solver v6.12-3 (Dassault Systèmes©, France). FE simulations of the cumulative coordination between three pairs of facial mimic muscles (ZM, LLS, and LAO) were illustrated in Fig. 1. The comparison of numerical displacement amplitude of skin envelop with MRI-based measurement showed a good agreement with a relative deviation of 15% when all three muscles are involved. Simulation of facial mimic with three muscle coordination behavior was performed in a subject specific manner. By comparison with experimental measurements, it is shown that the involvement of more relevant muscles indeed improve the simulation results. In future work, the model will be completed by adding more muscles. Moreover, subject-specific data on material properties of biological tissues will be acquired through experiments, in expectation of increasing the bio-fidelity of this subject-specific model.

Keywords: muscle coordination; facial mimics; finite element simulation; MRI

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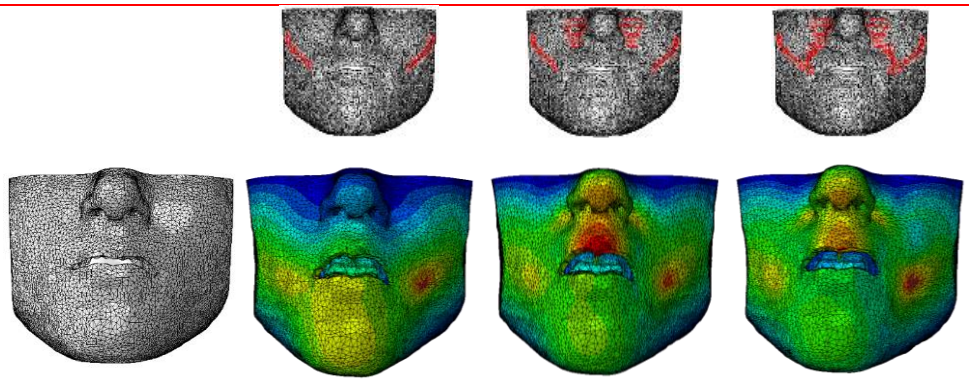

Fig. 1 Simulation of pronunciation of sound [o]: (from left to right) neutral position; ZM involved; ZM+LLS involved; ZM+LLS+LAO involved.

Biomechanics of Biomimetic and Bioinspired Systems

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Abstract. Mimicking Nature becomes very popular in technology, however the approaches used for bio-imitation are not clearly defined especially in bioengineering and biomedical science. Most of the time, these scientific fields apply imitation principles but the biomechanical evaluation is lacking. There are three main approaches to mimic biological systems: biomimicry, biomimetics and bioinspiration. But most importantly, the biological system must be understood, especially regarding the pivotal question of the structure-function-property relationships. In this task, the complexity of biological entities often requires a simplification that can be achieved with the biomimetic approach. Once the fundamental biological principles are understood, they can be mimicked through the bioinspiration approach to conceive cutting-edge technologies.

Keywords: Biomimicry, biomimetics, bioinspiration, biomechanics.

Data-driven and human-inspired design of a scalable lower extremity exoskeleton

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Abstract. Exoskeleton has been developed for improving the human performance or for recovering disabled functions of musculoskeletal patients. Generic prototypes have been designed, manufactured, and evaluated. Current limitations relate to the inaccurate fitting process and loss of patient specificity. The objective of this work is to develop a data-driven and human-inspired design of a scalable lower extremity exoskeleton. Anthropometric data were used to create an initial exoskeleton model and then a scaling process was developed to fit this model into a patient specific geometry derived from medical imaging. Inverse dynamics was used to estimate the real torque profile of the patient and additional torques needed when wearing the exoskeleton. Design parameters were identified using a mathematical model. This study allows the exoskeleton design to be performed using available multimodal data leading to optimize the design parameters. Moreover, simulation-based verification allows expected functions of the exoskeleton to be virtually tested and improved.

Keywords: Data-driven and human-inspired design; CAD model; scalable lower extremity exoskeleton.

Fig. 1 Illustration of the developed scalable lower extremity exoskeleton model

AFM to decipher biological surface properties.

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Cell surface does not only serve to delimit compartments but it also plays pivotal roles in cellular adhesion, signalling, communication, transport, mechanosensing etc. To study these properties, atomic force microscopy (AFM) is a particularly adapted tool as it allows to decipher surface topography at nanoscale resolution and in physiological conditions. In the last two decades, AFM has constantly evolved and now offers wealth of new opportunities in biology. Here, we will give an overview to show how AFM - much more than an imaging technique - can help addressing pertinent biological questions. First, a brief description of the set-up and the immobilization process used to image cells will be presented. Then, we will explain how AFM-based force measurements can give insights in cell surface remodelling during growth or incubation with drugs, in cell adhesion or in cell mechanics. For each modality, concrete examples will be given to illustrate that AFM can be used at various spatio-temporal scales, ranging from the nanometer, to the single-molecule and the single-cell levels and with a millisecond resolution.

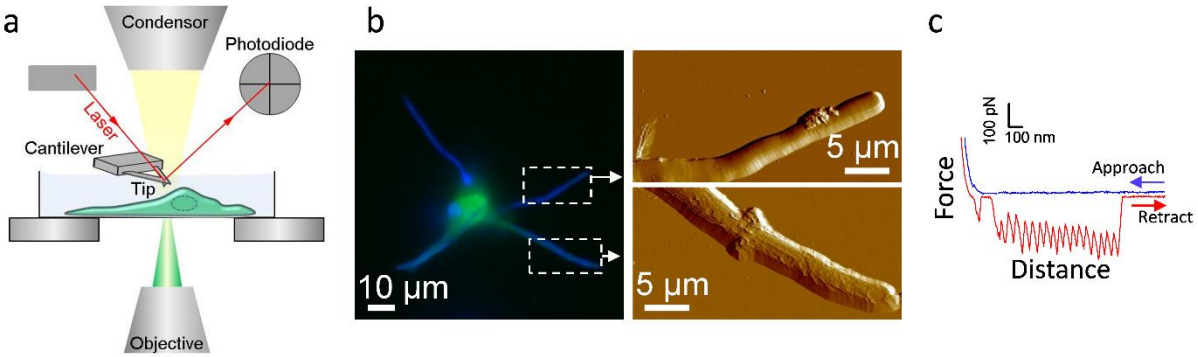

Figure 1. (a) Schematic of the AFM set-up combined to optical/fluorescence microscopy. (b) Example of correlative fluorescence (left) – AFM (right) imaging of macrophages interacting with pathogenic yeast. (c) Typical force-distance curve displaying the indentation of the tip in the sample on the approach curve (blue) and the adhesion signature with multiple peaks on the retract curve (red).

How to probe biological forces by AFM.

Audrey Beaussart

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Atomic force microscopy (AFM) is now established as an advanced tool to detect, localise and manipulate biological samples with high precision and high speed. In the force indentation mode, the mechanical properties of cells (Young modulus and osmotic pressure) can be determined in distinct spots of the surface with a lateral resolution in the nanometer range. Being a surface technique, AFM has been recently combined to fluorescence methods to correlate surface and intracellular events. AFM can also be used as a detection technique for specific biomolecules. To do so, AFM tips are functionalized with ligands to decipher the distribution of the corresponding receptors at the cell surface. In addition to the localisation of individual molecules, the force-distance curves obtained in this force spectroscopy mode allow to decipher their mechanical properties as they unfold under external load. Finally, the newly developed single-cell force spectroscopy modality allows to understand the adhesion of a whole cell to abiotic substrates or to other cells. Through relevant examples, recent biophysics breakthroughs obtained via these different AFM modes will be presented.

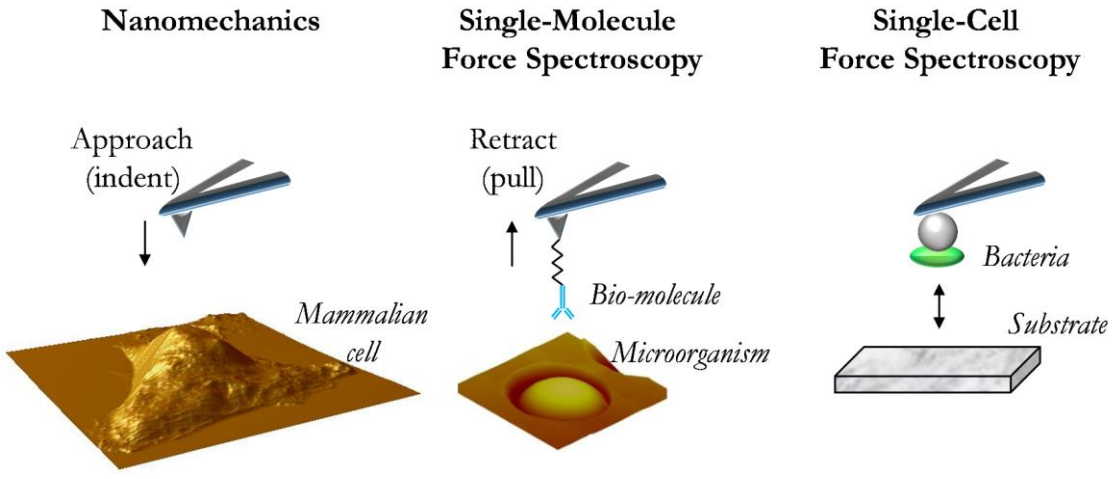

Figure 1. Principle of forces measurements by AFM. For nanomechanics, bare AFM tips are used as nanoindentors to obtain the mechanical properties of the cell. In Single-Molecule Force Spectroscopy mode, AFM tips are functionalized with biomolecules to specifically detect, localize and manipulate individual receptors on living cells. In Single-Cell Force Spectroscopy, an individual living bacteria is attached to the AFM cantilever to probe the interaction of the whole cell toward abiotic substrates or other cells.

September 8th 2017

SESSION ABSTRACTS

A minimal multi-scale approach for cell migration modelisation

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Abstract (500 words max). This study aimed to develop a model to accurately predict cell crawling migration. Cell migration plays a key role in many physiological processes, such as embryogenesis, wound repair, or metastasis formation. Cell migration is the result of a complex activity. It involves many different time and space scales, which makes it difficult to understand. Our goal is to build a minimal model of cell trajectories, which includes the different scales involved in cell migration.

We are interested in cell crawling for cells located on a 2D adhesive plane. A recent study [1] has highlighted a universal process through which the structures responsible for migration reinforce cell polarisation, which favours a ballistic displacement. This positive loop passes through a molecular marker, which is transported by the cell cytoskeleton. Its inhomogeneous distribution characterises a polarised state.

In this talk I shall present a deterministic model for unicellular migration. In a first step, I shall describe our approach, which is inspired from [1], that allows describing the internal structures linked to migration as an active fluid. In this approach, the active character appears through boundary terms, which makes its original. Then, we shall see that the marker concentration obeys to a non-linear and non-local convection-diffusion equation, where the convection field corresponds to the fluid advection field. Finally, the marker distribution on the domain boundary exerts a feedback loop on the fluid.

From the mathematical viewpoint, it is possible to study the 1D model [2]: global existence or apparition of a singularity in finite time, non-trivial steady states, long-time convergence. Some numerical simulations in 2D will be presented in rigid domain and also in deformable domain.

Keywords: complex and multiscale processes; active fluid, biofluid, cell migration; CFD simulation; free boundary problem; surface tension

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Computational Fluid Dynamic Analysis of the Left Atrial Appendage to Predict Thrombosis Risk

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Abstract Thromboembolic events, mainly caused by atrial fibrillation (AF), affect 1-2% of the population. More than 90% of the left atrial thrombi responsible for these originate in the left atrial appendage (LAA), a trabeculated finger-like projection about 2-4 cm long departing from the main body of the left atrium (LA). Current treatment to prevent thromboembolic event is oral anticoagulation, surgical LAA exclusion or percutaneous LAA occlusion. However, the role played by the appendage morphology in the clotting mechanism is still poorly understood. This sac can vary substantially from patient to patient, in terms of structure and number of lobes, and is typically classified into four groups, characterised based on their shape: "chicken wing", "cactus", "windsock" and "cauliflower" [1]. The aim of this work is to analyse the hemodynamic behaviour in all four LAA morphologies, to identify potential relationships between the different shapes and the risk of thrombotic events.

Computerized tomography (CT) images from four healthy subjects were acquired at University College London Hospital (London, UK) and segmented to derive the 3D anatomical shape of LAA and LA. The 3D structures were meshed in Ansys-ICEM (ANSYS, Inc.), with *10 prism layers* in proximity of the walls and *tetra elements* elsewhere (average size ~ 0.3 mm). Computational Fluid Dynamic (CFD) analyses based on patient-specific anatomies were implemented in Ansys CFX (ANSYS, Inc.) for all four cases. An opening boundary condition was set at the mitral valve outlet, where a velocity profile derived from the flow measured by Rabbah *et al.* [2] was imposed. Transient simulations were carried out to perform four cardiac cycles, to allow the flow to fully develop. The time step was set to 5×10^{-4}. A turbulence model was used and blood was considered as non-Newtonian, using a Casson model. Residence time in the different LAA regions was estimated introducing a virtual contrast agent in the computational models; the remaining contrast agent normalised volume in the LAA at the end of every cardiac cycle was monitored throughout the simulation.

CFD results indicate that both velocity and shear strain rate decrease along the LAA, from the orifice to the extremities, at each instant in the cardiac cycle, thus making the LAA edge regions more prone to fluid stagnation, and therefore to thrombosis formation. Moreover, CFD analyses allowed to identify the different flow dynamics produced by the four LAA shapes. The largest normalised volume of contrast agent (Fig. 1) was obtained for the cauliflower shape (4.7%), and the smallest for the chicken wing LAA (2.1%). This suggests that the latter is expected to be associated with a lower risk of thrombosis, confirming the reports in the literature [1].

These computational models could be translated into clinical practice to support clinicians in the stratification of patients under high risk of thrombus formation, towards personalised patient care.

Keywords: Left Atrial Appendage (LAA); CFD simulation; Thrombosis risk; LAA morphologies.

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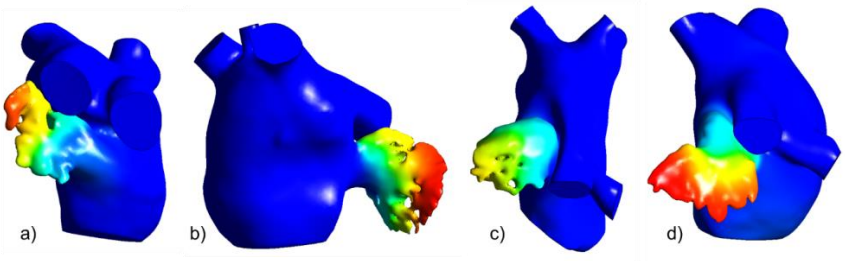

Fig. 1 Colour map representing the CFD simulation results in terms of different contrast agent concentration at the end of the fourth cardiac cycle for all the 4 LAA shapes: a) chicken wing, b) cactus, c) windsock, d) cauliflower

Reduced-order model of the deformation of elastic microcapsules in flow

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Abstract. The objective of this work is the development of reduced-order models for liquid-filled elastic microcapsules in flow. These models must allow not only to predict the deformation (i.e. the *shapes*) of the capsules when they flow in straight or bifurcated square-section channels, but also to characterize their mechanical properties. The microcapsules considered in this work are spherical particles ranging from 1 μm to 1000 μm, composed of a thin deformable elastic membrane of solid biocompatible material, which are filled with liquid. Although this kind of capsules can be commonly found in nature (eggs, cells), they have aroused considerable interest since they can be artificially produced for a large number of industrial applications. Some examples include the local delivery of therapeutic drugs in the pharmacological industry, or the masking and protection of certain substances in the chemical and cosmetic industries.

The characterization of the mechanical properties of the membrane of the microcapsules in flow (which mainly consists in finding the surface elastic shear modulus G_s, and the area-dilation modulus K_s) is a challenging task because of the reduced size of the particles. Through inverse analysis it is possible to infer the membrane mechanical properties by comparing experimental results of capsules flowing in microfluidic channels with the deformations predicted by numerical models (Hu et al. 2013). Existing models accurately solve the strongly coupled fluid-structure interactions (Barthès-Biesel 2016), but require long computational times to determine the capsule deformed shapes (Figure 1a) for different values of the input parameters: the capillary number Ca, ratio of the viscous to elastic forces, and the capsule-to-tube size ratio a/l. We propose to use model order reduction techniques to predict the capsule deformation and drastically reduce the computation time.

A Proper Orthogonal Decomposition (POD) is applied on a set of solutions provided by the Hu et al. (2013) numerical model. They correspond to the three-dimensional shapes taken at steady-state by microcapsules flowing in square-section microchannels, when varying the parameters of the problem: the capillary number Ca and the size ratio a/l. POD allows to reduce the dimensionality of the problem and, therefore, its computational complexity. The resulting set of reduced observations lies on a manifold of low intrinsic dimension, and different algorithms have been used to predict and reconstruct the shapes of the microcapsules for any value of the input parameters. A good agreement was obtained on the capsule shape reconstructions (Figure 1b) with impressive gains in computation time (at least 3000 times faster).

Keywords: microcapsules in flow, reduced-order models, Proper Orthogonal Decomposition

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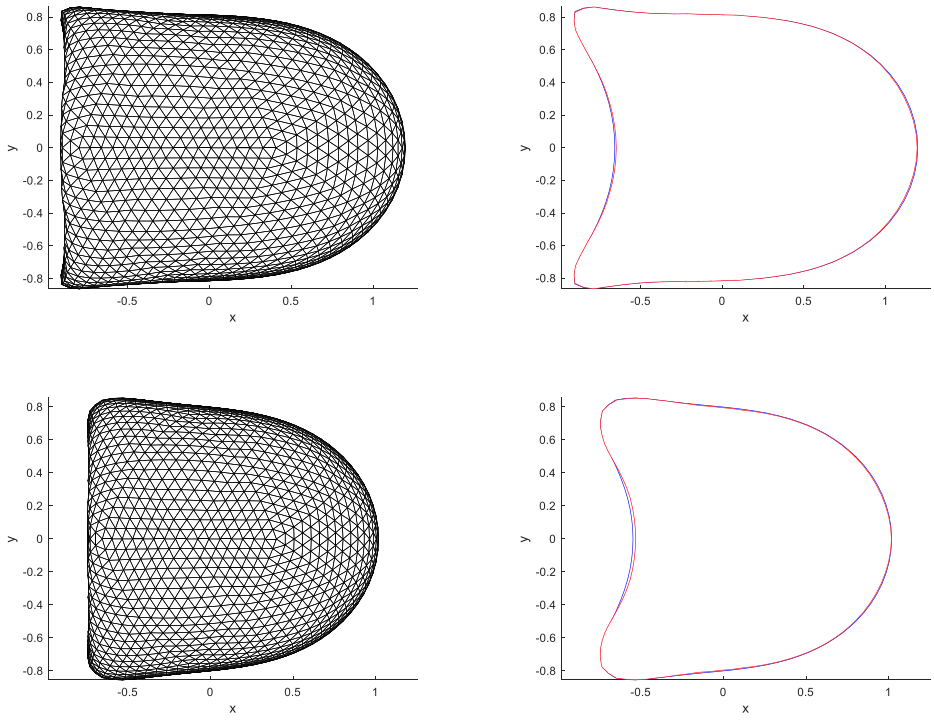

(a) (b)

Fig. 1: (a) 3D shapes of elastic microcapsules flowing in a square-section microchannel (top: Ca = 0.06, a/l = 0.98; bottom: Ca = 0.05, a/l = 0.9). (b) Comparison of the capsule cross-sections predicted by the fully coupled numerical simulation (blue line) and by the reduced-order model (red line) within the mid-plane of the channel, for the microcapsules in (a).

Optimizing the Performance of Drug-Eluting Stents: Simulations and Experiments

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Abstract. Despite the undisputed success of drug-eluting stents (DES), there is a persistent risk of serious complications including in-stent restenosis, late stent thrombosis, and stent fracture. Mechanical stresses within the arterial wall induced by stent implantation contribute to the incidence of restenosis; therefore, it is desirable to target stent designs that minimize these stresses. DES thrombosis is primarily attributable to delayed endothelialization because the drugs used in DES inhibit endothelial cell proliferation and migration; thus, there is a need for designing appropriate DES drug release strategies that minimize drug concentration at the endothelium. Finally, the likelihood of occurrence of DES fracture increases with the push towards thinner stent struts that reduce arterial wall injury upon stent deployment and perturb the flow field minimally. In light of the above, DES design involves a myriad of competing considerations and hence calls for multi-variable optimization. The goal of the present study is to optimize DES strut dimensions and drug release dynamics so as to meet the following set of specific objectives: 1) deliver efficacious but sub-toxic drug loads to the arterial wall in order to effectively control restenosis, 2) have minimal drug concentration at the endothelial surface in order to allow rapid stent endothelialization, 3) disturb the flow field minimally, 4) provide mechanically stable stent struts to avoid fracture given the loads to which the stent is subjected, and 5) induce minimal stresses in the arterial wall. A multi-physics computational model is developed that describes drug release from DES, drug convective and diffusive transport as well as drug reaction within the arterial wall, mechanical stresses within both the stent and a hyperelastic arterial wall, and the flow field within the arterial lumen. The model is subsequently used to optimize stent strut dimensions and drug release dynamics in order to meet the objectives described above. The optimization is performed using a gradient-free approach based on the surrogate management framework. The optimization results demonstrate that drug release dynamics depend strongly on the type of drug used and that optimal strut dimensions need to strike a balance between the effect on lumenal blood flow and on transmural stresses. In order to be able to experimentally test the predictions of the DES optimization studies, we have developed an *in vitro* coronary artery model which consists of an annular collagen hydrogel within which smooth muscle cells are embedded and whose lumenal surface is lined with endothelial cells. Endothelial wound healing as well as smooth muscle cell migration after stenting are monitored and quantified in the *in vitro* artery. Moreover, particle image velocimetry is used to measure the flow field within this artificial artery and to quantify the wall shear stress both within and outside the stented zone.

Keywords: stents; optimization; drug transport; endothelial cells; experimental validation

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Characterization of Early Avian Great Vessel Morphogenesis through Multiscale Modeling

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Abstract

The outflow tract consists of the vessels blood must pass through in order to exit the heart. During early development, a uniform tube and 3rd, 4th and 6th pharyngeal arch artery (PAA) pairs mature to form the aorta, pulmonary artery, and their branches. In the event outflow vessel maturation does not proceed as planned, congenital heart defects emerge. Remodeling of the primitive paired arch arteries into the great vessels of the circulation involves a delicate sequence of events yet to be fully elucidated. The PAA network experiences substantial local growth, which calls for quantitative analysis and correlation to changing hemodynamics and biological parameters. While early studies examined the cellular composition of the arches, examination of their local hemodynamics is relatively recent. Here, we work to establish natural variations in PAA morphology and local hemodynamics during a critical window of development. We quantify day 3, day 4, and day 5 PAA morphogenesis and the relationship between geometrical and hemodynamic changes across days and arches. Our population based approach allows us to establish the robustness of geometric and hemodynamic norms. Our findings show distinct population-based shape characteristics associated with stage of development that affect functional parameters and correlate with movement of the outflow tract relative to the arch arteries.

Briefly, Fertile White Leghorn chicken eggs were incubated for three, four, and five days at 37.5°C. Outflow tract velocity and that of the three paired pharyngeal arch arteries were measured using B-mode guided Doppler Ultrasound. Embryos were then preserved and sent to undergo nano-computed tomography scans. Embryo-specific 3D geometries of the day 3, day 4, and day 5 PAAs were generated. 0D circuit representations (or lumped models) of arch artery hemodynamics, in the form of a system of ordinary differential equations, were also created for each day's orientation and geometry. These circuits were adapted from Yoshigi et al's (2000) single compartment 0D model. This 0D model was used to tune the RCR (or Windkessel) outlet boundary conditions associated with full 3D finite element simulations. Multiscale CFD simulations were conducted through FELiScE (http://felisce.gforge.inria.fr).

Overall pressure increased dramatically between days (Fig. 1), while wall shear stress maintained the same global level. Vessel geometries were shown to differ from the presumed circular phenotype. Vessel cross-sectional area (CSA) and shape were shown to play a large role in the functionality of a vessel. CSA has been shown to correlate with flow distribution (Wang, 2009), with the "dominant" arch possessing the largest diameter and greatest percentage of flow over one cardiac cycle.

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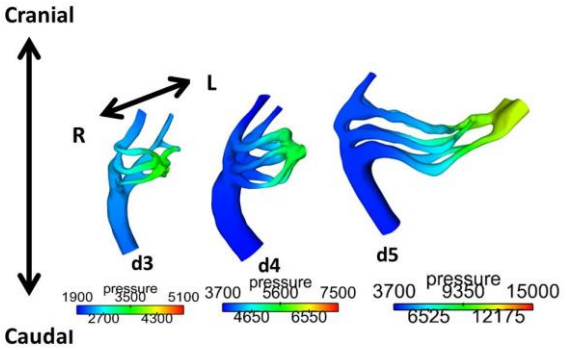

Figure 1: Pressure distributions [dynes/cm^2] for a day 3 day 4 and day 5 geometry with arrows to i ndicate notations

Through correlation of hemodynamic and geometric parameters, we identified a strong correlation between segment morphogenesis and flow that appears to be independent of PAA origin. Information obtained from a detailed subject specific population study can prove to be particularly useful when assessing the effects of abnormal flow patterning and arch artery morphology on downstream circulation. In addition to serving as improved boundary conditions, lumped parameter representations of vessel morphology provide another means of quantifying the hemodynamic properties of the vessels themselves and understanding growth across the days.

Keywords: chick embryo; morphogenesis; great vessels; CFD simulations; 3D-0D; subject- specific

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MATHEMATICAL MODELLING AND SIMULATION OF DRUG DIFFUSION IN THE BLOOD FLOW: A FLUID-PARTICLE INTERACTION

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Abstract. Currently, there are several drug delivery systems that intend to dissolve atherosclerotic plaque using non-invasive methods such as High-Density Lipoprotein (HDL) administration, anti-inflammatory agents, among others. For this purpose, different mathematical models have been formulated in order to understand the mechanisms controlling drug release in the bloodstream, which are predominantly controlled by diffusional mass transport. Whereas several studies have concentrated on understanding only the biochemical process, there is a lack of models which are able to show the fluid-particle interaction over the atherosclerotic plaque on the micro-scale.

The aim of this work is to develop a mathematical model to describe the diffusion process of a drug released across of blood flow like a way to dilutes low-density lipoproteins(LDLs), which are located in vascular membrane, including variables such as diffusion coefficient of particles, time of dispersion, density and viscosity of the substances, initial concentration injected, arterial area where the damage was developed, among others. Kinetic was assumed to a behavior of slow and controlled release. The numerical process couples the Finite Difference Method (FDM) and a Particle-Based Technique were employed. The diffusion process is modelled by FDM and the particles as drug delivery agents are modelled by Molecular Dynamic method.

The results have shown that concentration of drug approaches to a value along of vessel. In conclusion, the research allowed to evaluate the behavior of dilution of drug across blood flow to value the effectiveness of substance that

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reach be deposited in the affected arterial region.

Keywords: Drug delivery, modelling and simulation, atherosclerosis, diffusional mass transport.

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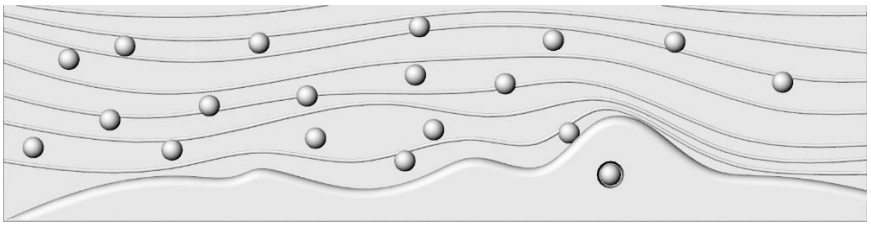

Fig. 1 Schematic model of diffusion process in atherosclerotic vessel.

Motion of a spherical capsule flowing in a branched tube with finite inertia

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Abstract (500 words max). A capsule is a liquid droplet enclosed by a thin membrane which can resist shear deformation. Capsules are widely found in nature in the forms of red blood cells (RBCs), eggs, …, but artificial capsules also have a vast range of applications in food, cosmetic, biomedical and pharmaceutical industries. In many situations, capsules are suspended in a fluid and flow through a complicated network of tubes or channels. Central to these flows is the path selection of capsules at bifurcations.

We computationally study the transient motion of an initially spherical capsule flowing through a right-angled tube bifurcation, composed of tubes having the same diameter (figure 1a). The capsule motion and deformation is simulated using a three-dimensional immersed-boundary lattice Boltzmann method. The capsule is modelled as a liquid droplet enclosed by a hyperelastic membrane following the Skalak et al. (1973) law. The fluids inside and outside the capsule are assumed to have identical viscosity and density. We mainly focus on path selection of the capsule at the bifurcation as a function of the parameters of the problem: the flow split ratio, the background flow Reynolds number Re, the capsule-to-tube size ratio a/R and the capillary number Ca, which compares the viscous fluid force acting on the capsule to the membrane elastic force. For fixed physical properties of the capsule and of the tube flow, the ratio Ca/Re is constant. Two size ratios are considered: a/R = 0.2 and 0.4. At low Re, the capsule favours the branch which receives most flow. Inertia significantly affects the background flow in the branched tube. As a consequence, at equal flow split, a capsule tends to flow straight into the main branch as Re is increased. Under significant inertial effects, the capsule can flow into the downstream main tube even when it receives much less flow than the side branch. Increasing Ca promotes cross-stream migration of the capsule towards the side branch. The results are summarized in a phase diagram (Figure 1b), showing that the critical flow split ratio for which the capsule flows into the side branch increases with Re and depends on the size ratio and Ca/Re when the inertial forces are no longer negligible. This could be due to the bending of the fluid separation line (in section S_c) towards the side branch, as shown in figure 1c for q = 0.5.

The present results suggest that the trajectory of a capsule in a branched tube can be controlled by adjusting a range of parameters such as the capsule size, membrane elasticity, tube flow rate. One potential application of the results is to guide the development of microfluidic device, using a bifurcation geometry, to separate capsules from a suspension, enrich capsule suspension or sort deformable microparticles with different size or membrane elasticity.

Keywords: capsule/cell dynamics; fluid-structure interactions; branched channel; lattice Boltzmann method; finite element method

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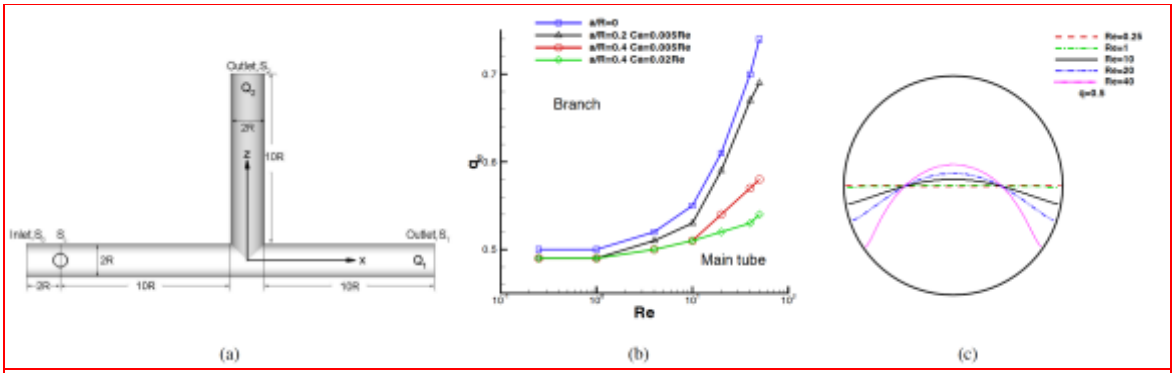

Fig. 1 (a) Geometry of a branched tube; (b) Phase diagram: critical branch flow ratio q_c as a function of the flow Reynolds number varying the capsule size and membrane shear elasticity; (c) Unperturbed flow separation lines in the cross-section S_c for q = 0.5 at different Reynolds numbers. The fluid elements above the separation line enter the side branch and those below the line remain in the main tube.

Physiology of single ventricle circulation: basic hydraulics explains basic complications.

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Abstract. Congenital heart diseases (CHD) result from heart and/or major blood vessels defects arising in early pregnancy and are the most common congenital malformations, with an overall incidence of about 1 out of 100 live births. In particular, CHD with hypoplastic left or right ventricles (i.e. with single ventricle-SV-physiology) affect about 2 out of 1000 live birth. In these CDH with SV, the only treatment option is a palliative surgical procedure, which is usually staged, with the aim of restoring the normal physiology without anatomical repair of the CHD (i.e.a separation between oxygenated and deoxigenated circulation as complete as possible). The final stage is a single circuit (Fontan circulation), with the SV pumping blood through the systemic and pulmonary trees connected in series via the total cavo-pulmonary connection (TCPC).
Despite most of these so called Fontan patients have a good quality of life and reach adulthood, nevertheless a large number of complications may arise, leading to late Fontan failure. When this is caused by ventricular failure, heart transplantation is the only available option for survival.
There is large consensus among clinicians in considering abnormally high venous blood pressure in TCPC as the leading cause of complications, but the basic haemodynamic factors driving that occurrence are not clear enough yet (Gewillig and Brown, 2016).
The present contribution is aimed to highlight the fundamental physiological elements at the basis of venous hypertension by comparing behavior of pressure grade lines in double (*dvc*) and single (*svc*) ventricle circulation, respectively. The cardiovascular system is described by the simplified circuit depicted in Figure 1, according to the lumped parameter modeling methodology here adopted (Ursino, 1998). Only main functional elements are considered, with compliance and resistance effects assigned to large vessels (Ao, Cve, PuA and PuVe) and to systemic (SR) and pulmonary (PR) microvasculature, respectively. Cardiac atria are modelled as passive chambers in which pressure variations occur according to volume changes within the chamber, while in ventricles also the activation of myofibers is considered; finally, a resistance effect is assigned to heart valves during their opening phase. Boundary conditions are assigned in the systemic ventricle, with prescribed physiological pressure wave. Initial pressure is also given in large vessels. Model calibration and validation have been performed according to literature data. Instantaneous pressure

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grade line along the *dvc* and *svc* circuit has been extracted from simulation results, in order to have a clear and immediate perspective on the effect of any specific functional compartment on the instantaneous pressure behavior. Steady flow simulations revealed that in the absence of pulmonary heart (right ventricle) pumping action, physiological pressure can be maintained in TCPC only for unattainable low pressure in the systemic heart. Pulsatile flow simulation confirmed that result, showing that the leading factor of abnormally high pressures in TCPC is the limited capability of the single ventricle to express a sufficiently strong suction effect. This finding might open new possibilities in designing surgical or technical solutions able to mitigate the early and long term complications of Fontan circulation.

Keywords: single ventricle; Fontan operation; lumped parameters model; pulmonary hypertension; ventricular suction.

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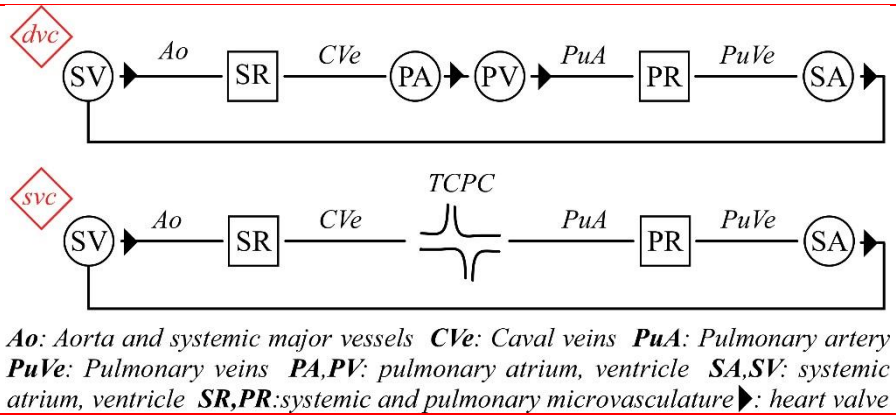

Fig. 1 Functional elements in the lumped parameter models describing cardiovascular double (*dvc*) and single (*svc*) ventricle circulation.

Impact of the viscosity contrast on dynamics, rheology and partitioning of red blood cells in the microcirculatory system

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Abstract. I will present a numerical approach to simulate the dynamics of fluid-filled soft particles (vesicles, capsules and blood cells). The flow is computed using the lattice Boltzmann method and the fluid-particle two-way coupling is achieved using the immersed boundary method. The viscosity contrast (defined as the ratio of the internal to the external viscosities) is included using a geometrical algorithm that detects if a fluid node is either located inside or outside a particle [1]. I will present recent studies where the impact of the viscosity contrast has been addressed, for example, dynamics [2], rheology [3] and partitioning of red blood cells at the level of bifurcations in the microcirculatory system [4].

Keywords: hemodynamics; microcirculation; fluid-structure interaction; red blood cells; rheology

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A Coaxial coupled model of cerebral flows: Blood and Cerebrospinal Fluid

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Abstract (500 words max). This study aimed to develop a one dimensional (1D) model to simulate the Cerebrospinal Fluid (CSF) flows in the cerebral sub-arachnoid spaces, and its coupling with the entire cerebral blood flow vascular network. The model consist in a network of coaxial tubes: the interior network represents the cerebral vasculature from the carotid and vertebral arteries to the sinuses and jugular veins (Zagzoule, 1986), and the coaxial exterior tubes the sub arachnoid spaces where the CSF flows. By integrating the mass and momentum flow conservation equations over the tubes cross-sections, we obtain a 1D coupled coaxial model of the blood and CSF flows. Our model takes into account the viscosity of the fluids (Cathalifaud, 2015), and assumes compliant boundary conditions for the coaxial compartment. Given the input pressure signal at the carotid and vertebral arteries, we therefore obtained an induced CSF flow, as shown in Figure 1. Results depends on the confinement of the coaxial compartment and the compliances of the boundary conditions, and well compared to measured CSF flows of the literature (between 2 and 5 cm^3/s). We also investigate the coupling effect of the CSF on the blood flows, especially on the cerebral autoregulation characteristic time. We show that it strongly depends on the confinement of the coaxial compartment.

Keywords: CSF flow, 1D model, cerebral blood flow, cerebral autoregulation

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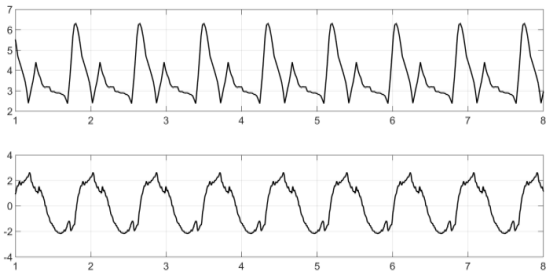

Fig. 1 (up) Flow rate in cm^3/s in a carotid artery; (down) Induced LCS flow rate in cm^3/s

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Motion of freely spheroidal particle near a wall.

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Abstract (500 words max).

The near-wall motion of particles suspended in viscous fluid has important biological and engineering applications. The increasing interest in this problem can be linked to the diverse natural and industrial applications where particulate flows are encountered [1]. Examples include micro-vascular fluid mechanics (e.g. dynamics of a red blood cells in a vein) and suspension rheology as it pertains to the design and testing of suspension products, such as personal care items (e.g. cosmetics, toothpaste). Efficient control of the flow of particles is critical to natural resource development, or in the food industry, the removal and transport of bacteria in the tubes of production lines is a problem of importance for public health, which is the focus of this work.

The flow dynamics of rigid spheroids in the presence of a bounding wall are computed. The conditions of interest include both prolate (ellipsoidal) and oblate (platelet) spheroids suspended at low concentrations in viscous, non-inertial flows. Compared to the flow of spherical particles under these same conditions, spheroids exhibit a much larger range of motions [2]. For example, spherical particles do not migrate across streamlines when suspended in a flowing fluid unless they are acted upon by an external force, even if near a bounding wall. Our results provide a more complete picture of the dynamics over a wide range of aspect ratios and orientation, spanning oblate as well as prolate spheroids.

Keywords: Spheroids, Particles, Dynamics, Boundary Element Methods

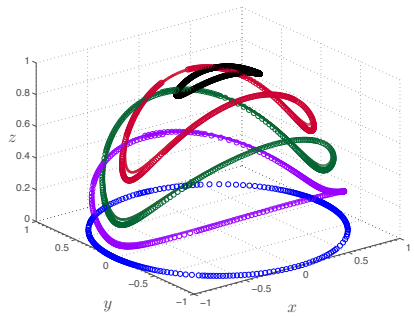

Fig. 1 Computer simulation of spheroid orbits for different initial azimuthal angles.

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Can an aortic phantom correctly reproduce the aortic arch physiology?

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Abstract. Studies on cardiovascular diseases are more and more based on in-vitro analysis aimed at reproducing physio/pathological conditions in specific anatomical districts. One of the questions raised by the spread of these models is how much such phantoms can effectively describe the physiology of the aorta. The capability of these models can be enhanced mainly in two way: the first one consists in the adoption of a more detailed geometry of the vessel; the second one is focused on correctly modelling the biomechanics of the vessel wall (Caballero and Laín, 2013).
The realistic representation of the anatomy can be satisfactorily solved thanks to in-vivo imaging acquisition; in this case, the geometry refinement is limited only by the resolution of the MRI or CT-Scan acquisitions and by the computational cost required to post-process the large amount of collected data. Otherwise, the reliable modelling of biomechanics and fluid dynamics is still an open question because of the complex physical mechanisms involved. Indeed, phantoms of aortic arch are usually made by either rigid material (e.g. plexiglass) or elastic material (e.g. rubber-like polymers); i.e. some features of aorta's dynamics might be not suitably reproduced.
The goal of this study is to analyze the hemodynamics of the aortic arch by refining the constitutive model, in order to preliminary quantify the approximations that can affect phantoms. FSI numerical simulations were run by implementing three different constitutive models of an idealized aortic arch. The first model assumed rigid wall and hence it solved the standard CFD scheme. The second model considered hyperelastic isotropic material, i.e. it mimicked the behavior of rubber-like polymers. Finally, the third model represented the observed real aorta's anisotropy introducing oriented fibers bundles which are embedded in an isotropic matrix, i.e. it mimicked the effect of elastin fibers in the aorta's wall (Gasser et al., 2006).
Preliminary simulations were carried out in order to calibrate the constitutive models parameters; specifically, the parameters were evaluated by fitting numerical stress-strain curve with the experimental data of one-dimensional tensile stress of aorta's porcine tissues. Moreover, compliance analysis was performed to determine proper wall thickness for both elastic models. In all simulations the same boundary conditions are fixed. In the inlet we applied a quasi-physiological flow, while at the outlet a constant pressure ranging between 80 and 100 mmHg was set. The synthetic pulsatile flow had flat profile, period T = 1 s, systolic fraction equal to 35 % of the cycle, and took into account the retrograde flow. The peak flow was chosen so that the stroke volume was 60 ml. The testing fluid was Newtonian with the same density and viscosity of blood.
Stress and strain fields of the solid domain and pressure and velocity fields of the fluid domain were compared for the adopted mechanical models. Results highlight that differences up to 15% can emerge in the solid domain depending on the adopted elastic model, while the fluid field solution seems to be less influenced by walls rheology at least from the global point of view. However, it must be pointed out that the importance of the material model and connected results is strictly related to the specific application investigated.

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Keywords: CFD simulation; FSI simulation; aortic arch; aortic phantom.

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