MECHANICAL ENGINEERING / PHYSICS / PRESERVATION OF THE ARCHITECTURAL HERITAGE / STRUCTURAL, SEISMIC AND GEOTECHNICAL ENGINEERING / URBAN PLANNING, DESIGN AND POLICY / AEROSPACE ENGINEERING / ARCHITECTURE, BUILT ENVIRONMENT AND CONSTRUCTION ENGINEERING / ARCHITECTURAL, URBAN AND INTERIOR DESIGN / **BIOENGINEERING** /DATA ANALYTICS AND DECISION SCIENCES / DESIGN / ELECTRICAL ENGINEERING / ENERGY AND NUCLEAR SCIENCE AND TECHNOLOGY / ENVIRONMENTAL AND INFRASTRUCTURE ENGINEERING / INDUSTRIAL CHEMISTRY AND CHEMICAL ENGINEERING / INFORMATION TECHNOLOGY / MANAGEMENT ENGINEERING / MATERIALS ENGINEERING / MATHEMATICAL MODELS AND METHODS IN ENGINEERING

PhD Yearbook | 2020

DOCTORAL PROGRAM IN BIOENGINEERING

Chair:
Prof. Andrea Aliverti

The main objective of the PhD Programme in Bioengineering is to prepare the PhD candidates to develop high level engineering problem-solving abilities in biomedical, healthcare and life sciences, inside research groups or in private/public industrial contexts, through a strong interdisciplinary training bridging engineering and medical/biological knowledge.

During the PhD, the candidates develop a scientific research project dealing with a complex problem which can be at different scales, from the molecular and the cellular levels to living organisms up to biomedical systems. They investigate original methods, devices, and systems with different purposes: increasing knowledge, proposing innovative methods for diagnosis and therapy as well as improving healthcare and daily life structures and services. At the end of the PhD programme, the candidate are expected to be able to carry out innovative projects and research and development in the field of Bioengineering, by proposing new methodological and technological solutions and properly evaluating the technology impact in healthcare, life science and biomedical industry.

During the three years of the program, PhD candidates perform their research through theoretical and experimental activities in four major areas: biomimetic engineering and micro-nano technologies; rehabilitation engineering and technology; technologies for therapy; physiological modelling and non-invasive diagnostics.

More specific areas include but are not limited to: molecular and cellular engineering, biomaterials, tissue engineering, bio-artificial interfaces and devices, neuro-prostheses, movement analysis, cardiovascular and respiratory system bioengineering, central nervous system signal and image processing for rehabilitation, biomechanics, computational fluid-dynamics, computer assisted surgery and radiotherapy, robotics, artificial organs, implantable devices, biomedical signal and image processing, E-Health, bioinformatics, functional genomics and molecular medicine.

The PhD Program in Bioengineering is organized with an inter-departmental structure. Faculty members of the PhD Advisory Board belong to two Departments of the Politecnico di Milano, namely DEIB (Department of Electronics, Information and Bioengineering) and CMIC (Department of Chemistry, Materials and Chemical Engineering "G. Natta").

PhD candidates (who are, in average, 20 per year) develop their PhD research programs within experimental laboratories located at the Politecnico di Milano or outside it, typically biomedical research centers, hospitals or industries. When the research is performed within the Politecnico, PhD candidates are usually assigned to one of the following laboratories belonging to the DEIB and CMIC: Laboratory of Biological Structure Mechanics (LaBS, CMIC), Laboratory of movement analysis "Luigi Divieti" (DEIB), Medical Informatics laboratory (DEIB), Neuroengineering and medical robotics Laboratory (NearLab, DEIB), Biosignals, Bioimaging and Bioinformatics Lab (B3 lab, DEIB), Biomaterials laboratory (CMIC), Biomedical Technology Lab (TBMLab, DEIB), Experimental Micro and Biofluid dynamics (μBS Lab, DEIB), Computational Biomechanics Lab (DEIB), Biocompatibility and Cell culture Lab (BioCell, CMIC), Bioreactors Laboratory (CMIC). The Istituto di Elettronica, Ingegneria dell'Informazione e delle Telecomunicazioni (IEIIT) of the Consiglio Nazionale delle Ricerche (CNR), which is located at DEIB, represents another possible option. Stage periods in distinguished research institutes in Italy and abroad are an essential feature of the PhD candidate training. The candidates are encouraged to carry out part of their research activities in contact with other research groups, preferably abroad through periods of at least three months spent in laboratories where the candidate can acquire further skills to develop his/her research work and thesis.

Collaborations that may involve the PhD students are presently active with several national and international research and academic Institutions. Very often, the involvement of companies and clinical partners facilitates the technological transfer of applied research into industry and clinical applications.

The educational offer includes *ad hoc* advanced courses specifically designed for the PhD in Bioengineering. The offer includes also the school of the National Bioengineering Group, which is held yearly for one week in Bressanone (Bz). Every year, the School is focused on different topics. As examples, the themes of the last few years have been: Neuro-informatics (2011), Biomedical devices from research to market (2012), Regenerative medicine (2013), From functional recovery to artificial organs (2014), Experimental models for development methods for 3R (2015), Bioengineering for Active ageing (2016), E-Health and digital medicine (2017), Biomedical Images (2018).

The PhD Board of professors ('PhD Board') is composed by highly qualified and active researchers in Bioengineering, belonging to DEIB and CMIC. The PhD Board is responsible of all the candidate's activities. The competencies of Faculty members cover a wide spectrum of research fields. This allows a continuous updating of the PhD program and ensures that the PhD candidates are involved in innovative work.

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The PhD Programme in Bioengineering relies also on an Advisory Board Member, formed by distinguished experts coming from R&D industries, research and clinical centers, in order to ensure that that the goals of the PhD Program are in line also with the needs of non-academic world.

IN SILICO 3D MODELLING STRATEGIES FOR THE PATIENT-TAILORED PLANNING OF PERCUTANEOUS PROCEDURES

Alessandro Caimi

Congenital heart disease (CHD) indicates abnormalities in cardiocirculatory structures or functions present at birth. CHD is the most common cause of major congenital anomalies, representing a significant global health problem. In most cases, surgical corrections are essential for the restoration of the heart functionality but, although the survival rate to open heart surgery increases, medium and long-term post-surgical complications bring to further anatomical disfunctions.
The standard clinical approach would require subsequent open-heart surgery, inevitably increasing the development of patient co-morbidities. For this purpose, percutaneous approaches have evolved through years to extend the life span of the dysfunctional anatomy exploiting metal stent. Nevertheless, the stent inflation within complex clinical scenarios may lead to critical periprocedural complications, that cannot be predicted through standard clinical approach, except during the procedure. Therefore, a sound and comprehensive pre-procedural planning is crucial for the success of the treatment. At this aim, different engineering methodologies can be exploited for the design of patient-tailored percutaneous strategies. *In silico* approaches, if well-conditioned, can be used for the simulation of stenting procedure predicting periprocedural complications, *in vivo* strategies may study the time dependent variation of vessel geometry and distensibility from clinical pre-operative images throughout the cardiac cycle, while *in vitro* tests may be performed on deformable 3D-printed models to assess the feasibility of complex procedure.
Hence, the main objective of this Phd project consisted in the development of dedicated engineering strategies able to support interventional cardiologists in the patient-tailored planning of percutaneous procedures.
In this work three different clinical scenarios were studied.
First (Figure 1), a novel *in silico* workflow was proposed for the simulation of the percutaneous pulmonary valve implantation (PPVI) in three patient-specific anatomies characterized by obstructed right ventricular outflow tracts (RVOT). A comprehensive reproduction of the anatomy, composed of the aortic root, the RVOT, the left coronary artery and the calcific deposits were combined with a comprehensive reproduction of the devices used in the procedures. The numerical simulations proved to be able to predict the risk of coronary compression in one patient as confirmed during the sizing stage of the PPVI. Furthermore, the deployed configuration of the stent, computed by the numerical model, well matched with fluoroscopic measurements available in the catheterization laboratory (Cath Lab).

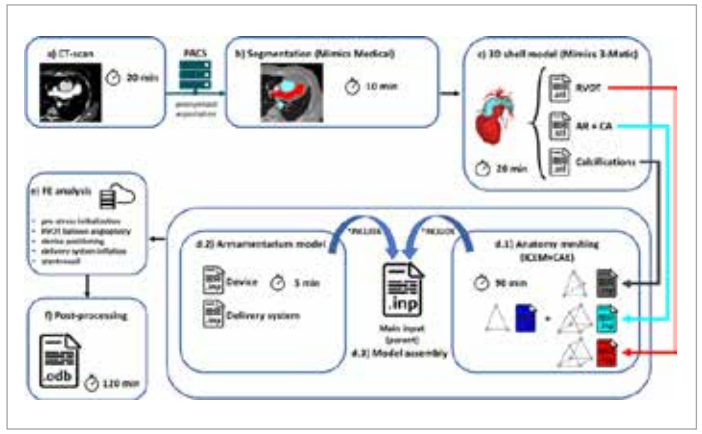

Fig. 1 - Figure 1 Workflow for the numerical simulations of PPVI procedure within patient with calcified RVOT

Second (Figure 2), two different strategies were proposed to study the planning of PPVI in patients with enlarged RVOTs. On the one hand, three-dimensional (3D) patient-tailored strategies, based on digital and physical 3D-printed models, were exploited to support PPVI in a dysfunctional native RVOT with borderline dimensions. On the other hand, a dedicated image-based framework was implemented to study the time dependent geometrical variation of enlarged RVOTs in a large cohort of patients (n=32). In both the cases, the proposed frameworks effectively assessed the anatomical determinants of RVOT dysfunction reporting borderline conditions or adverse predisposition to PPVI.

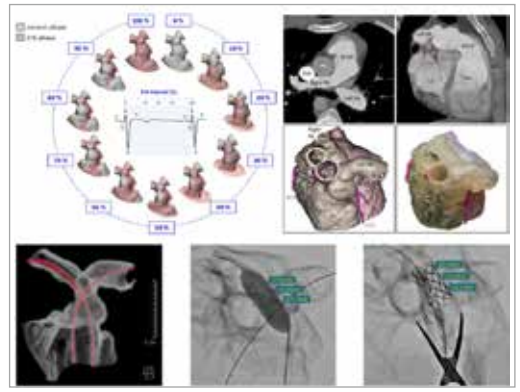

Fig. 2 - Different approaches for the pre-procedural planning in patients with dilated RVOT.

Finally (Figure 3), a finite element simulation protocol was proposed for the stenting simulation of three patient-specific native coarctations (CoA) characterized by different level of aortic stenosis and different aortic shapes. Since the CoA treatment consists in a pronounced enlargement of a stenotic region through stent deployment, a remeshing procedure was implemented in order to remove mesh distortion and preserving the information of the wall stress distribution. The FE model proved to be able to reproduce the stenting procedure within an extremely tight CoA and the reported numerical results were consistent with intraprocedural in-vivo evidences available in the Cath Lab.

The strategies designed in the current PhD project effectively support the candidate selection in complex clinical scenarios, pinpointing the impact of the stenting procedure on the anatomy and elucidating potential periprocedural complications. Moreover, the synergy between different engineering methodologies and clinical expertise may enhance the efficacy of patient-tailored planning of percutaneous procedure, shortening the operating time while improving the patient safety.

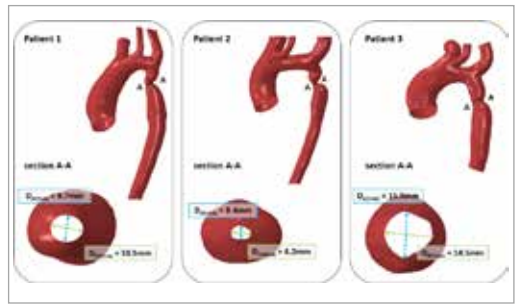

Fig. 3 - Three different CoA scenarios studied in the current work

CHARACTERIZATION OF CARDIOVASCULAR AUTONOMIC MECHANISMS DURING SHOCK RESUSCITATION FOR AN IMPROVED FUNCTIONAL HEMODYNAMIC MONITORING

Marta Carrara - Supervisors: Manuela Ferrario, Giuseppe Baselli

Circulatory shock is one of the major complication in critically ill patients with a mortality rate reaching 40%, a high-risk of second line treatments and long term physical and cognitive impairments in survivors. Currently, clinical guidelines are mainly concerned to restore homeostasis and to prevent multiple organ failure (MOF), but, despite significant improvements, clinicians are still far to have found the optimal therapy. Patients are commonly treated with fluids and vasopressors to restore a physiological blood pressure (BP), blood volume and oxygenation, thus, the benefit of the resuscitation strategies is evaluated only based upon global hemodynamic, clinical and metabolic end-points. However, the understanding of the root causes is the main issue in order to find new therapy targets, improve drugs administration, and tailor therapies to each individual patient. From this perspective, a different approach to patients monitoring is needed in critical care.

Derangements in cardiovascular (CV) control by the autonomic nervous system (ANS) typically occur during shock, but the restoration of these alterations is not commonly targeted by the clinical resuscitation protocols, although it is determinant for the return to a physiological condition of CV control.

The present thesis bases on the idea that combining the traditional mean values, as proposed by the current guidelines, with non-invasive indices of CV function and integrating them into bedside monitoring of shock patients, may be of clinical importance; the aim is to have a functional hemodynamic monitoring to predict a possible catastrophic deterioration of the patient, thus allowing clinicians to act beforehand. This hypothesis has been explored in three different datasets, including a clinical dataset of 21 severe septic shock patients and two experimental datasets consisting of pigs undergoing a protocol of septic and hemorrhagic shock and resuscitation, respectively. All the datasets were collected under the project ShockOmics. Standard and advanced mathematical indices and models were exploited to investigate the role of the ANS in CV regulation during shock and standard resuscitation. In particular, standard indices include baroreflex sensitivity (BRS), heart rate variability (HRV), and blood pressure variability (BPV); the advanced and novel approaches proposed are based on black-box mathematical models to describe the different contributions in peripheral resistance control and ventricular contractility regulation, and on the 2-element Windkessel model to investigate the characteristic time constant of the arterial tree.

The clinical patients were followed during the first 48 hours of therapy after development of septic shock (time point T0) and they were analyzed at T1, within 16 h from T0, when the inflammatory cascade has been just activated, and at T2, within 48 h after T0. SOFA score, an index typically used in critical care to assess organ function, was used to classify patients into two groups according to their responsiveness to early therapy: responder patients (n=14) consisted in patients with a positive response to initial treatment, i.e. an improving SOFA score between T1 and T2; non-responders consisted in patients who still had an elevated SOFA score at T2. Our results highlighted a sympathetic activation in response to fluids and vasopressors only in responder patients, who significantly improved their organ function, although all patients reached an adequate mean BP. Moreover, non-responder patients received a higher dosage of vasopressors and fluids with respect to responders. Thus, common mean targets routinely used to guide hemodynamic optimization and fluid therapy in acute shock patients, such as mean BP, are not sufficient alone to explain the evolution of patient's organ dysfunction. Variability indices and baroreflex trend can add information to individual vital signs and can help in understanding the responsiveness to the combination of sympathomimetic drugs and fluid therapy.

Such considerations are at the basis of the animal experiments, where we aimed at verifying the previous findings in a more controlled condition, avoiding possible confounding factors.

The septic shock animals were studied at baseline, after the development of polymicrobial septic shock, and after administration of fluids and noradrenaline.

We proposed a new black-box autoregressive model to investigate the autonomic control of ventricular contractility. The two mechanisms of interest are the baroreflex-mediated control of ventricular contractility and the force-frequency autoregulation mechanism. Ventricular contractility was indirectly measured by computing the index dP/dt max from left ventricular pressure. Moreover, we adopted a 2-element Windkessel model to estimate the characteristic time constant τ of the arterial tree, which takes into account both the resistive and the elastic properties of the vessels. This computation was performed at different sites along the arterial tree, such as in the central aorta, in the radial and in the femoral artery. Independent estimates of total arterial compliance (AC) and total peripheral resistance (TPR) were also performed. Finally, we assessed similar indices, as in the clinical study, to characterize the CV autonomic dysfunction. Our results highlighted an autonomic-mediated increase in ventricular contractility during shock which was not restored after resuscitation. Moreover, a severe vascular disarray was induced by septic shock, as appeared by a decreased time constant, AC and TPR, and a peripheral vascular decoupling phenomenon, i.e. an inversion of the physiological pulse pressure amplification. Finally, ANS dysfunction was described by reduced BRS, BPV, and HRV. This compromised condition was not resolved by administration of fluids and noradrenaline, although global hemodynamic markers were restored. To conclude, a condition of CV inefficiency, vascular dysfunction and autonomic disarray was triggered by septic shock, and it was not resolved after resuscitation. The ANS-related indices, the vascular properties measures, and the ventricular contractility model were able to highlight and track this inefficient condition, and, thus, they could be useful to evaluate the effectiveness of treatments, combined with standard clinical measures.

The hemorrhagic shock pigs were studied at baseline, after massive blood withdrawal, after fluids and noradrenaline administration, and after shed blood reinfusion. We were interested in verifying if there are common hemodynamic patterns in septic and hemorrhagic shock, and, for this purpose, we applied similar analyses as in the previous studies, to evaluate the trend of autonomic indices. Our results highlighted that after resuscitation with fluids and noradrenaline, mean BP reached the target value, but all the CV indices were not fully restored, hinting at a partial recovery of the autonomic mechanisms. Only after shed blood was reinfused, all the indices returned to the baseline level. The trends of autonomic indices obtained in hemorrhagic shock animals showed similarities to those observed in septic shock, highlighting how the ANS is similarly elicited and how it plays an important role in the recovery.

In conclusion, both septic and hemorrhagic shock studies showed how the resuscitation maneuvers were able to restore global hemodynamic variables, but this was not accompanied to a recover of a physiological homeostatic condition, as highlighted by the CV indices and models. The shock subject may be considered resuscitated according to clinical guidelines, but the combined information derived from autonomic CV indices may reveal a persistent autonomic disarray, that, if not appropriately treated, could lead to development of MOF, CV collapse and death. Clinical protocols should give importance to the trends of these indices, in order to make a step further in the optimization and personalization of the therapy.

BRAIN FUNCTIONAL INTERACTIONS: QUANTITATIVE EVALUATION IN PHYSIOLOGICAL AND PATHOLOGICAL CONDITIONS

Stefania Coelli - Supervisor: Anna Maria Bianchi

Background: The study of the brain functional interactions is fundamental to understand the mechanisms generating neurophysiological functions and pathological conditions. The complexity of the human brain and of its functional interaction patterns are still not fully comprehended and further investigations are needed.
Electroencephalography (EEG) is particularly suited to grasp the dynamics of the mutable brain functional organization, by directly measuring the neural correlates with high temporal resolution. Moreover, the invasive intracerebral EEG, providing multi-channel recordings from cortical areas and deep structures, adds the possibility of an even more direct exploration of the functional and dysfunctional patterns of interactions at different time and spatial scales, finding its principal application in the study of brain network disorders, such as epilepsy.
From a functional point of view, epilepsy is described as a network disorder in which altered brain rhythms, abnormal neural interactions, complex functional connectivity and dynamics play a fundamental role for the rising of epileptic seizures and their propagation.
Objectives: In this context, the present PhD dissertation addresses three complementary aspects of the study of cerebral interactions taking advantage of both invasive and non-invasive EEG: functional network interactions, rhythms synchronization and waves propagation. The studies presented in this thesis aim at the identification and development of analysis methods to describe and provide quantitative measures of the EEG functional interactions in physiological and pathological conditions.
Study 1: A new time-frequency adaptation of a functional clustering approach exploiting the Tononi's Cluster Index (CI) is presented aiming at developing a data-driven tool for the investigation of the functional patterns of electroencephalographic activity at different time and frequency scales. The proposed method is then employed to prove that the sleep stages exert a specific influence on the epileptiform activity.
The whole study was carried out on a set of Stereo-electroencephalographic recordings of seven patients affected by Focal Cortical Dysplasia Type II (FCD-II) with Sleep Hypermotor Epilepsy (SHE).
The developed algorithm comprises the construction of a time-frequency framework by means of the discrete wavelet transformation (DWT) providing a representation of the SEEG signals in the delta, theta, alpha, beta and gamma frequency ranges.
On the decomposed signals, the computation of the CI on different time-intervals and the evaluation of the probability for each element (i.e., SEEG lead) to be part of the most significant functional cluster (FC) provide a representation of the interaction patterns throughout the considered time slot (interictal in REM and N-REM, Pre-ictal and Ictal) at different frequency. For each patient, 20 SEEG leads were selected by an expert neurophysiologist and divided in three groups: leads positioned inside the epileptogenic zone (EZL); leads early (EIL) and late (LIL) involved in the seizure propagation.
Results showed the predominant role of the dysplasia in the epileptic system organization detecting a higher probability to be part of FCs for the contacts located inside the epileptogenic zone than the other ones in all the time periods, confirming that the lesion in FCD Type II behaves like a highly integrated FC with a peculiar pattern of activity.
In conclusion, in this study we proposed an alternative method for the exploration of the frequency-dependent functional connectivity changes due to both physiological and pathological conditions.
Study 2: The non-linear brain-rhythms interaction issue is addressed by examining the EEG response to a visual stimulation protocol in a group of healthy subjects and patients affected by photosensitive epilepsy (PSE), using higher order spectral analysis. The aims of the study were i) to test the hypothesis that the visual stimulation elicits a non-linear behavior of the cortex in the form of quadratic phase coupling (QPC) between brain oscillations; ii) to characterize the rhythms interactions in terms of bicoherence and iii) to identify possible clinically valuable different characteristics in PS subjects and healthy controls.
The analysis was carried out on a data-set of scalp EEG acquired during a visual stimulation protocol obtained by means of a full field square wave reversing checkerboard (black/white) on a screen at three different stimulation frequencies: block I at 7.5 Hz, block II at 15 Hz and block III at 24 Hz. The artefacts free and Laplacian spatially filtered signals were analyzed in baseline (B), stimulation (S) and recovery (R) sections.
Results in the spectral domain showed that most of the subjects presented a response to the flickering stimulation, localized at the occipital regions, where peaks in the power spectrum related to the driving frequency and its harmonics and sub-harmonic components were enhanced. The behavior was the same in the two groups, showing an increase of the power associated to the stimulation-related frequencies with respect to both the baseline and recovery sections. This was prominent in the parietal and occipital region. We also confirmed that the visual rhythmic stimulation has a desynchronizing effect of the occipital alpha oscillations in both the analyzed populations. This effect was present also on the central area for the PS subjects only.
At rest, the main bicoherence peak was related to the alpha rhythm.
A significant difference between the subjects' groups during stimulations periods over the central region was found with a higher bicoherence values for controls. An ordered bicoherence pattern in the bi-frequency plane during stimulation was associated with a decrease of significant bicoherence in the alpha range. Sharp peaks emerged in the stimulation periods suggesting that the energy of the harmonic was partially due to a non-linear cortical modulation within the visual cortex.
From a physiological point of view, the study confirmed the non-linear behavior of the cortex in response to rhythmic visual stimulation, while the bicoherence was shown useful for the investigation of the interactions between stimulus-related frequency components.
Study 3: A new method to study the traveling of brain waves within cortical structures is proposed. The main focus was the feasibility of the adaptation of the cortical traveling wave analysis (CTWA) method to a SEEG framework and the extraction of useful measures to describe the epileptic network.
The implemented procedure was composed of two main sections: the propagation analysis in the SEEG sensors space and the CTWA analysis applied in the space of the reconstructed cortical sources. To test the feasibility of the method, the procedure was applied on simulations and to SEEG data acquired in three patients during their pre-surgical exploration. For each subject the identification of a common propagation pattern in the SEEG space and the CTWA, for interictal epileptic spikes propagating within the cortex, were performed.
For each event, descriptive measures were extracted: number of computed cortical streams (or trajectories), size of the involved surface areas, mean propagation pathlength and mean duration of the longest trajectories. Furthermore, the most involved areas and the principal propagation directions were derived.
Conclusion: This dissertation proposes innovative tools for the research on brain functional interactions with application in the study of epilepsy. The included works explored different fundamental aspects of the topic, analyzing physio-pathological mechanisms under different perspectives.

SIMULATIONS OF CEREBELLAR NETWORKS TOWARDS UNDERSTANDING OF PATHOLOGIES, LINKING COMPLEX NEURONAL MODELS TO BEHAVIOUR

Alice Geminiani

Brain simulation is suggested as a crucial tool to understand brain (dys)functioning, based on two key elements: (i) *multiscale integration* of elements in the same computational model; (ii) *data-model-theory integration* to increase the reliability of models and predictions.
In the current PhD project, the challenge of developing computational models of brain circuits to investigate their functioning and the impact of lesions, was applied to the cerebellum. Advancing previous bioinspired cerebellar models, we aimed at developing and testing a multiscale model of the cerebellum able to reproduce and explain not only the neural bases of cerebellum-driven motor learning but also the alterations leading to pathological conditions, eventually suggesting possible compensatory mechanisms and treatments.
Spiking Neural Networks (SNNs) were chosen, in order to build a multiscale tool, ensuring the best compromise between computational load and biological plausibility. They were embedded into closed-loop simulations of motor behaviors, investigating how neural mechanisms lead to motor (dys)function. To develop and test realistic cerebellar SNNs and reliable simulations, we followed the *decomposition-reconstruction cycle* approach.
We proceeded from cerebellar system models to update of model elements at multiple spatial scales, in a continuous comparison with experimental reference data and theory. Reconstructed system models were exploited to investigate the relationship between components of the cerebellar circuit across scales, eventually generating cerebellum-driven motor (mis)behaviors, and the underlying mechanisms of cerebellar pathologies. We simulated alterations associated to cerebellar diseases applying localized damages in network model and evaluating the consequent modifications at different scales. We evaluated the possible mechanisms compensating for lesions, predicting and suggesting hypotheses on the underlying causes of emerging misbehaviors.
As reference cerebellum-driven protocol for closed-loop sensorimotor simulations, we chose Eye Blink Classical Conditioning (EBCC).
Simulations of cerebellar pathologies: a proof of concept
The starting point was a proof of concept model of cerebellar pathologies based on a bioinspired SNN, demonstrating the potential of multiscale models to investigate the underlying neural mechanisms of diseases. In all simulated cases, the model was able to reproduce the partial and delayed conditioning typical of the pathologies and allowed to shed light on the underlying neural mechanisms causing the alterations. The findings indicated that an intact cerebellar cortex functionality is required to accelerate learning. However, the model suggested that cortical lesions can be partially compensated by nuclear plasticity mechanisms, on a longer timescale. Starting from these promising results, based on new experimental evidence, we proceeded through a systematic update of model elements at different scales to increase the predictive power of simulations.
Simplified neuron models for Spiking Neural Networks
In a first decomposition of the system model, we aimed at summarizing complex single neuron dynamics in simplified point neuron models to be embedded into SNNs, evaluating the impact at the higher scales. Focusing on the cerebellar Golgi cell, we designed a new point neuron from the Generalized Leaky Integrate and Fire family, E-GLIF. The model was optimized through a multi-objective gradient-based algorithm, towards desired input-output relationships. The neuron was then validated against *in vitro* experimental data, proving able to generate the full set of Golgi cell responses – autorhythm, adaptation, bursting, phase reset, intrinsic self-sustained oscillations and resonance – with a single set of parameters, depending only on the input stimulus. The E-GLIF neuron model and optimization framework developed were then extended to the other main cells in the olivocerebellar circuit, providing a full set of tuned neurons (including interneurons) with cell-specific specific electroresponsive phenotypes.
The olivocerebellar circuit: modelling network dynamics
Then, we reorganized the SNN connectivity to obtain a geometrically-organized architecture, where the connectivity generates well-defined olivo-cerebellar modules, including interneurons among the neural populations. We applied the model to evaluate how single neuron dynamics and network topology contribute to encoding of EBCC sensorimotor signals in the cerebellum, showing that single neuron dynamics and connectivity are fundamental for realistic signal encoding and for generating complex spiking dynamics also at network level.
Simulations of cortical damages in a multiscale model of EBCC
Consecutive model reconstructions described in above paragraphs showed how the update and validation of cerebellar model elements, based on novel experimental evidence, can lead to more realistic simulations of mechanisms at multiple scales. We finally focused on plasticity, and then reconstructed a cerebellar network, integrating the other updated elements with a new plasticity rule in the molecular layer. We challenged the model in simulations of EBCC, investigating the complex balance of underlying neural mechanisms, while addressing open issues raised in that could not be evaluated there. As experimental reference, we used a multiscale dataset from mice experiments. The model was challenged in reproducing associative motor learning deficits in case of localized damages in the cerebellar cortex.
The outcome of simulations with the updated model suggested that single neuron complex dynamics and distributed synaptic plasticity in the cerebellar cortex (Purkinje and molecular layer) and in the nuclei, are both fundamental for motor behaviors. This interaction of mechanisms at multiple scales is crucial in case of localized lesions, where redundancy can be translated into tolerance or compensation of damages, allowing a partial recovery of functions.

Advancing previous cerebellar SNNs, we here developed the first computational model of the cerebellum, where motor behaviour is generated by the interaction of single neuron, plasticity and network mechanisms, bridging the gap across scales. The model was able to explain the underlying mechanisms of associative motor learning, in physiological conditions and in case of localized lesions, with potential future applications for accelerated medicine.
At the same time, the results opened a series of interesting issues on the future of cerebellar theory. Thanks to the multiscale realism of the model, we put the bases to the investigation of additional cerebellar mechanisms that are currently debated, e.g. the role of intrinsic plasticity and long-term potentiation in associative motor learning, or the differentiated learning mechanisms across cerebellar modules in more complex cerebellum-driven paradigms. In addition, the work developed within this thesis paves the way to a new generation of bottom-up models of the cerebellar circuit resulting from a theory-driven simplification of detailed models. The obtained results prove the high potential of computational modelling in investigating brain functions, its underlying mechanisms and the neural bases of pathological conditions, provided that system models are built from the integration of multiscale realistic elements and a continuous interaction between experiments, models and theory.
A further future challenge includes moving from spiking representations to mean-field rate-based models, in order to investigate long-range network connectivity properties and using the model to explain mean field data. Finally, referring to animal experiments was mandatory in the current work to validate the models at multiple scales. Indeed, validation requires multimodal neural data that can hardly be collected in humans. However, explaining human misbehaviors is the eventual aim of the current project, paving the way to applications of *in silico* models of pathologies for supporting clinical decisions.

THE SCIENTIFIC AND TECHNOLOGICAL INSIGHTS NEEDED TO DESIGN NITINOL MEDICAL DEVICES

Carlo Guala - Advisors: Gabriele Angelo Dubini, Lorenza Petrini

Nitinol is recognized today as a material of choice for medical implants and devices, due to its unique mechanical properties and excellent biocompatibility. In particular nitinol has become the best candidate material for manufacturing self-expanding peripheral stents, heart valve frames, endovascular grafts and many other cardiovascular devices (annuloplasty rings, catheter components, guidewires, etc.). Heart valve disease and peripheral artery disease are the pathologies where nitinol has found the main fields of application within cardiovascular devices.

This work is aimed at giving the insights needed to design nitinol cardiovascular devices. In particular, both scientific and technological details are analyzed, including the key factors for raw material choice, the equipment needed for manufacturing and testing the devices, the design features and process history role and the criticalities to be faced out in raw material and device testing. Along this purpose, the experience done by the author is presented: building up a complete prototyping laboratory, the design choices and process strategy made for producing the specimens and the stents used for material and device characterization, the study undergone on the raw material in order to understand its role on the performances of the final device.

Firstly, a brief introduction to anatomy and pathology of cardiovascular system is presented, focusing on heart valve disease and peripheral artery disease. An overview of cardiovascular devices and nitinol properties is also given, in order to show how this material has the peculiar features needed to address the clinical challenges. The nitinol tube fabrication techniques are illustrated, explaining pros and cons of some choices.

The manufacturing steps and equipment needed to obtain nitinol devices are then described and detailed. For each technology an evaluation of the state of the art is carried out and the pros and cons of the different opportunities available are analyzed. Furthermore, it is reported the experience done in the *Medtronic Invatec* company where a complete nitinol prototyping laboratory was built up (see Figure 1), explaining the technical choices adopted and the technical / cost compromises faced out in a real-world environment.

Material characterization and device characterization are crucial steps during nitinol device design. The importance of using the correct specimen geometry for the specific characterization is a key factor during material characterization; for this reason it is analyzed the geometry (discussing pros and cons) of the different specimens commonly used for mechanical characterization, explaining their limitations and the choices that led to identify the specimens used in this work (see Figure 2). The thermo-mechanical characterization (see also Figure 2) undergone is then reported, highlighting how this is needed to gather the correct values of the material constitutive model. The role of design features and design choices is hence discussed as a key factor for nitinol stents performances, as well the process strategy (mainly shape setting) to be adopted on stents. This is the reason why, after a material characterization, it is however very important to test the final device (vascular stent or heart valve frame) with dedicated methods. The design choices and the shape setting strategy adopted on the stents manufactured are detailed, focusing on radial force determination and crush resistance tests undergone on these stents, since they are key performance features of both implant phase (when the device is released from the delivery system) and the long term interaction with the implant site (vessel wall for vascular stents or valve annulus for heart valve frames). Finally, the role of the raw material choice on nitinol device performances is analyzed, since the manufacturing techniques of ingot and nitinol tube have a critical impact on the level of inclusions and the level of cold work found in the material used to process the device. In particular, an *ad hoc* study has been performed with the specific purpose of investigating the impact of different raw material properties (strongly dependent from cycles of cold working and annealing and thus from grain size distribution along the wall thickness of the Nitinol tube) on radial forces and thermo-mechanical properties achieved by the final stent. Some studies have been performed to address this question on cold worked Nitinol wires and their findings show that time and temperature of heat treatment and the amount of prior cold work all influence the material response. However, no studies have been ever performed on tubes and on how the different levels of initial cold working influence the thermal and mechanical properties of the final device.

Fig. 1 - Overview of nitinol prototyping laboratory. On the left: salt bath equipment and fluidized bed for shape setting (thermal treatment), chemical etching and electropolishing equipment under chemical hood for post-processing and surface finishing treatments. On the right: Nd:YAG laser cutting equipment with nitinol tube availability.

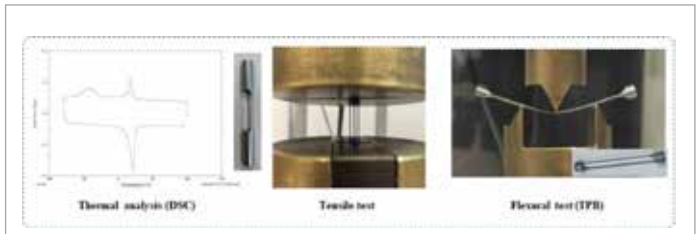

Fig. 2 - Material thermo-mechanical characterization to be performed on nitinol material. From left to right: thermogram obtained by thermal analysis with Differential Scanning Calorimeter test, ad hoc three-pillar specimen developed in this work for material characterization, uniaxial tensile test set-up developed for three-pillar specimen, flexural test (Three Point Bending) set-up developed for two-pillar specimen (shown bottom right).

ADAPTIVE CONTROL OF SERIAL REDUNDANT ROBOTS FOR MINIMALLY INVASIVE SURGERY

Su Hang - Supervisors: Giancarlo Ferrigno, Elena De Momi

Research on surgical robots has produced impressive progress in the past decade. The number of operating rooms equipped with surgical robots for Minimally Invasive Surgery is growing faster and faster because of the benefits like higher surgical precision, increased range of motion, improved dexterity, and so on. However, the current state of commercial surgical robotics, like the da Vinci Surgical System, is specialized designed and expensive, which limits their popularization and application. The general serial industrial robots have achieved significant advancements in terms of accuracy and safety, which have potential in the surgical robots area. Notably, their capacity to operate in an uncertain environment with Human-robot interaction has shown prominent benefits over the latest decades. It becomes a promising theme to introduce the general serial robot in the surgical robotics research field, where Human and Robots physically interact (Physical Human-robot Interaction-pHRI) is impossible to be avoided or prevented. This work is an effort on investigating and implementing adaptive control methodologies to introduce the serial robot for Robot-assisted Minimally Invasive Surgery. To this end, research actives, such as human-like redundancy resolution, Remote Center of Motion, and manipulability optimization, etc., have been investigated on a redundant serial robot in this thesis to improve the operations in terms of safety, accuracy, cognitive load, and surgeon fatigue. Furthermore, accurate target tracking with constraint and haptic feedback is achieved to improve its feasibility. All the proposed methodologies have been implemented and validated using the KUKA Light Weight Robot LWR4 + on a 3-D printed patient phantom. The validation results showed that the effectiveness and feasibility of the proposed algorithms in terms of accuracy, a remote center of motion constraint, and manipulability. This work includes experimental demonstrations of the proposed methods. It has been proven here that adaptive control of the surgical robot according to challenges, can lead to better surgical outcomes.

Fig. 1 - Teleoperated minimally invasive surgical scenario

AN *IN SILICO* EVALUATION OF CARDIOVASCULAR DEVICES BY FLUID-STRUCTURE INTERACTION SIMULATIONS

Giulia Luraghi

Supervisors: Francesco Migliavacca, Jose Felix Rodriguez Matas

Computational analysis has become one of the most widely used tools to investigate the behavior of cardiovascular devices and to understand their interaction with the anatomical domain. In particular, heart valves modeling involves structural and fluid dynamic aspects, which need to be both considered and coupled. For this reason, fluid-structure interaction (FSI) numerical analysis is required.

*The **aim of this thesis** is to verify and validate the application of the FSI methodology to the modelling of heart valves and to apply the analysis on two different cardiovascular devices, namely percutaneous aortic valves and ventricles of a total artificial heart.*

Different FSI algorithms have been considered and validation studies with a coupled *in vitro /in silico* approach were carried out. The deep knowledge of these methods has allowed a thorough investigation of a total artificial heart and of a transcatheter aortic valve implantation procedure.

*The **main hypothesis** is to prove the necessity to implement an FSI methodology to model cardiovascular devices and its impact on clinical decisions and interventional planning.*

Chapter 1 provides an overview of the theoretical foundation of the research, including the numerical coupling algorithms and kinematics approaches for FSI modelling.

In particular, FSI methods in cardiovascular applications and the specific algorithms adopted in this thesis are pointed out.

The First part of the thesis focuses on the Verification & Validation (V&V) in order to demonstrate the reliability of the FSI modeling.

Chapter 2 presents a verification study of key modelling considerations for the FSI simulations of heart valve in vivo performance. The selection of the appropriate type of finite element for the model is the first and fundamental step to achieve accurate simulations and results of key importance to this work. In particular, the convergence analysis of the mesh on both the structure and fluid domains, the influence of the element typology, formulation and damping factor in an idealized three-leaflets valve model loaded with physiological pressure conditions is investigated. The best shell and 3D continuum element formulations are individualized and the damping coefficient sensitivity analysis is defined as necessary phase in heart valve modeling.

In *Chapter 3*, a validation study of the FSI methodology to capture scenarios of heart valves close to reality is presented. In collaboration with the Department of Chemical Engineering and Biotechnology, University of Cambridge (Cambridge, UK), this part of the thesis concerns numerical models of a new bio-inspired polymeric heart valve. A hydrodynamic pulsatile test is replicated with both structural finite element and FSI simulations. The importance of this study rests on the qualitative and quantitative validation of the *in silico* models using experimental data. The FSI simulations are shown to provide a much closer agreement with experimental results than structural simulations in terms of leaflets' kinematics.

In the Second part of the thesis the methodological aspects learned from the V&V studies are applied to a real cardiovascular device: the Carmat Total Artificial Heart (CARMAT SA, Velizy-Villacoublay, France).

Chapter 4 is focused on the development of a numerical methodology to evaluate the hemodynamics inside the left pumping chamber of the Carmat device. Deformable membrane and valves are modeled and blood and oil phases are simulated on opposing sides of the membrane. The modeling workflow combines FSI simulations based on a fixed fluid-grid method with CFD analysis that accounts for the kinematics of the valves and membrane by means of a dynamic mesh technique. This application to the Carmat Total Artificial Heart provides consistent results with those from previous clinical studies and demonstrates the efficacy of the numerical workflow in calculating local hemodynamics quantities in the presence of complex moving boundaries. The resulting hemodynamics is used to evaluate the blood damage associated with the device.

In *Chapter 5*, a validation of the kinematics of the deformable structures of the total artificial heart during its physiological working condition is presented. *In vitro* experimental tests are performed at San Raffaele Hospital, Milan, Italy to characterize the left chamber using a CT Scanner. An FSI simulation is then performed to replicate the *in vitro* test and it provides a close correlation to the observed membrane deformations during a cardiac cycle. Physiological working conditions for both the left and the right chambers are then replicated with the aim to generate a strong numerical methodology to study the washout capability of the device coupled with the fluid dynamics evaluation. Evaluation of contrast injection and distribution of contrast blood reveals that the contrast is found primarily in low-velocity and stagnation regions.

The Third part of the thesis presents a second clinical application related to Transcatheter Aortic Valve Implantation (TAVI-Figure 1); these works are in collaboration with the Humanitas University (Milan, Italy).

In *Chapter 6*, the FSI method is used to replicate the pathological condition of seven patients who underwent TAVI, suffering from aortic stenosis. The innovative aspects regarding the FSI methodology are the use of patient-specific anatomy and boundary conditions. The importance to develop realistic and accurate FSI patient-specific models and how the quality of the clinical data affects the simulation results are assessed. In particular, the impact of the CT-images resolution and pressure data used to set the FSI patient-specific models is qualitative and quantitative analysed. The segmentation and reconstruction phases result to be carefully performed not to alterate the numerical results and they result key steps in the development of viable and robust *in silico* medical diagnostic tools.

In *Chapter 7*, two patients who underwent the implantation of an aortic percutaneous valve but with different outcomes are studied with FSI simulations. The implemented numerical workflow is able to model the crimping of the complete device, the implantation phase as well as the valve working conditions during two cardiac cycles. The simulation of the contact interaction between the device and the hyperelastic anisotropic aorta is extremely challenging from a computational viewpoint. The numerical model confirms the post-procedure diagnosis of mild and moderate paravalvular leakage. Moreover, the final release configuration of the device and the velocity field are compared with postoperative CT scans and Doppler tracings showing a good qualitative and quantitative correlation.

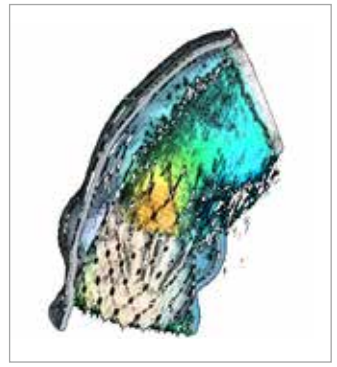

Fig. 1 - *In silico* Transcatheter Aortic Valve Implantation

RESPIRATORY MOTION MODELING IN PARTICLE THERAPY

Giorgia Meschini - Advisors: Marco Riboldi, Guido Baroni

In particle therapy, organ motion causes tumor position and radiological path length uncertainties, thus preventing the effective use of the geometrical selectivity of particle beams. Image guidance is crucial to plan and verify the quality of the treatment, and with the support offered by four-dimensional (4D) imaging modalities also respiratory motion can be described and quantified. Indeed, 4D imaging allows to define a patient-specific model of respiratory motion, establishing a correspondence between changes of the irradiated anatomo-pathological structures and a respiratory surrogate signal. However, irregularities and intra-/inter-fraction variability usually affect breathing motion and are not adequately described by conventional 4D Computed Tomography (4DCT). Therefore, there is the clinical need for (i) improved description of respiratory motion variability, (ii) strategies to manage irregular breathing motion in case of inadequate or lacking imaging data, and (iii) accurate prediction of the impact of irregular breathing motion on the dose distribution.
Different respiratory motion modeling approaches were investigated and proposed as tools for both the geometrical quantification of respiratory motion and the evaluation of related dose variations, aiming at granting treatment quality in presence of regular and irregular breathing motion. First of all, the work focused on maximizing the potentialities of 4D imaging for estimating geometrical changes caused by variable respiratory motion. The 4D Magnetic Resonance Imaging (4DMRI) was investigated for capturing variable breathing motion, and an approach for virtual 4DCT generation from 4DMRI was implemented in order to evaluate dose changes due to breathing motion variability in carbon ion therapy. Furthermore, a mathematical modeling technique was validated for the estimation of respiratory phases not captured by 4D imaging in presence of intra- and inter-fraction variability. Also methods for the evaluation of radiological path length changes induced by breathing motion were investigated, allowing to evaluate the dosimetric impact of respiration. A method for the improved definition of the internal target volume was tested, and a model to estimate physical and RBE-weighted dose variations in case of irregular breathing motion during carbon ion therapy was validated.
The investigated respiratory motion modeling techniques are put forward as tools to support the treatment planning of moving tumors in particle therapy, allowing to test the robustness against breathing motion variability and giving the opportunity to simulate irregular and unimaged respiratory motion.

ENGINEERED MICROSCALE STRATEGIES FOR CARDIOMYOCYTE MATURATION AND CONTRACTILITY ASSESSMENT

Daniela Cruz-Moreira - Supervisors: Marco Rasponi, Alberto Redaelli

Cardiovascular disease (CVD) has long been recognised as worldwide leading cause of morbidity and mortality. This consciousness of CVD prevalence sets a fast pace for the deeper understanding on heart development and disease progression that ultimately lead to the development of new therapies. However, clinical studies still face several limitations regarding accuracy and cost-effectiveness of preclinical trials, largely due to the limited ability to model human cardiac physiology in vitro. Human induced pluripotent stem cells technology holds the potential to improve upon traditional cell culture and animal-based methods. However, cell immaturity remains an open issue in modelling cardiac disease.

The present PhD Thesis aimed to engineer microscale platforms for the maturation and advanced functional assessment of cardiomyocytes in vitro. By tailoring relevant mechanotransductional cues, the ultimate goal is the generation of physiologically relevant cardiac models.

A heart-on-chip platform to assess the influence of culture media perfusion on 3D engineered cardiac tissue maturation will be first presented. Microfluidic platforms engineered to apply relevant mechanical forces to cell cultures have proven to regulate cell phenotyping, cell-cell interactions and tissue functionality. The peristaltic perfusion system integrated on the platform represents an attractive alternative to traditional bulky electronic off-chip fluid handling systems (e.g. peristaltic pumps and syringe pumps) as it is compact and compatible with typical humidified cell culture incubators. The microfluidic valves integrated in the system are sequentially controlled to finely define the flow rate. This platform was used to study different flow rates and consequently different shear stress effect on neonatal rat cardiomyocyte microtissue functionality and maturation.

Furthermore, a new technology allowing for the first time the measurement of electrical field potential within microfluidic 3D platforms was developed. This platform was designed to directly extract electrophysiological signals during culture. The developed system represents a powerful pre-clinical cardiac model to screen the cardiotoxic effects of new compounds. The platform design builds upon our previously published beating heart-on-chip, a platform able to condition 3D cell laden hydrogels through a combination of biochemical and mechanical (10% uniaxial strain at 1Hz) stimulations. The electrophysiological measurement was made possible by the inclusion of guide channels dedicated to the positioning of stainless steel electrodes. The effects of compounds known to alter the cardiac electrical activity were evaluated by the variations in the field potential morphology induced after incremental administration of the drug.

Finally, a 2D microscale strategy to measure force generate by cardiomyocytes derived from human induced pluripotent stem cells (hiPSC-CM) will be presented. Nuclear lamina gene lamin A/C (LMNA) mutations cause a heterogeneous group of disorders, known as laminopathies, characterized by a spectrum of clinically distinct phenotypes (e.g. dilated cardiomyopathy and arrhythmia) whose molecular mechanisms still need clarification. Traction force microscopy (TFM) is a method used to evaluate the force generated by single cardiomyocytes by measuring the displacement of the surrounding substrate. In this technique, force calculation is made by video-optical recordings and takes into account the elastic properties of the substrate to which the cells adhere. The substrate was optimized to be suitable for both the imaging system and iPS cells. The forces computed were presented on a heat map of the cell and the total force was calculated considering the different regions.

In sum, this dissertation focus on the role of biophysical stimuli in driving maturation of cardiomyocytes, as well as the development of new methodologies for the readout of functional characterization. Combining these technological advancements leverage the utility of cardiac in vitro models in predicting drug cardiotoxicity with high biological fidelity and its application to clinical studies.

DEVELOPMENT OF TISSUE CULTURE SYSTEMS FOR BIOMECHANICAL CONDITIONING OF SMALL-CALIBER ARTERIAL VESSELS

Simona Seminati - Advisor: Monica Soncini

Co-advisors: Gianfranco Beniamino Fiore, Marco Piola

Cardiovascular diseases (CVDs) are the leading cause of death in the world. Within the scenario of CVDs, atherosclerosis plays a key role, as it is responsible for myocardial infarction, stroke, and vascular diseases.
Atherosclerosis is a complex multi-factorial phenomenon, characterized by a chronic inflammatory process of the arterial wall. The first event that occurs is the accumulation of cholesterol containing low-density lipoproteins in the *intima* with subsequent activation of the endothelium. Eventually, the inflammatory activation may induce plaque rupture and thrombus formation, leading to acute manifestation of the disease.
Traditionally, two approaches have been used to study the mechanisms involved in the atherosclerosis and to evaluate the effectiveness of therapies or devices: *in vitro* and *in vivo* models.
In vitro methods are well-established, easy to perform, relatively not expensive, suitable to investigate cell-cell interactions and cell migration and allow to study isolated and controlled stimuli. On the other hand, they lack of biological realism and often the behaviour of cultured cells can be very different from their behaviour *in vivo*. *In vivo* models, instead, provide a complex environment and the possibility to induce more realistic pathological conditions. They are still unavoidable for testing hypothesis addressed by *in vitro* models and pharmacological treatments. But the use of animals is very expensive, and, technically, animal studies may fail to represent human diseases. Moreover, the scientific community insists on the reduce, replacement and refinement (3 Rs) in the use of animals for experiments. *Ex vivo* models can bridge the gap between *in vitro* and *in vivo* models, because they permit to isolate and investigate specific stimuli, but without losing the complexity of the tissue. In addition, with *ex vivo* models the bias induced by the use of animal tissue can be overcame. These approaches do not claim at substituting *in vitro* and *in vivo* models. But, instead, they yearn for supporting traditional approaches.
Given this, the goal of this doctoral thesis was to design and develop three innovative *ex vivo* methods aiming at investigating different aspects related to the atherosclerotic process.
Firstly, we developed an innovative model for studying the cellular and molecular mechanisms involved in the spreading of thrombosis. The culture system consisted in a parallel-plate optically accessible chamber for culturing human arterial slices exposed to a controlled blood flow. Computational studies were used to verify that the arterial slices in the chamber were stimulated with a shear rate of 500 s^{-1}. The functional evaluation of the system proved it to be compliant with standard laboratory procedures and microscopy techniques (*i.e.*, confocal microscopy). The design of the chamber and the protocol of the experiments were optimized to avoid the formation of unspecific thrombi. The system could be used for culturing arterial slices with and without atherosclerotic plaques to assess the nature of vascular components involved in thrombus formation. The project was carried out in collaboration with the Cardiovascular Research Area of IRCSS Ospedale San Raffaele.
Then, it was designed an *ex vivo* culture system for translating in *ex vivo* models procedures that have been typically employed for studying thrombosis *in vivo*. For example, the ferric-chloride induced thrombosis, that, as far as we know, has been studied only with animal models.
The bioreactor was designed and developed to culture whole vessels with different diameters and lengths under fluid-dynamic controlled conditions. It was manufactured a preliminary prototype. The functional evaluation of the bioreactor showed that it was suitable for culturing human vessels, but the manipulation of the samples proved to be harmful for the vessel itself. Therefore, starting from the strengths of this bioreactor, a second advanced prototype was developed. An innovative way to mount the vessels within the system was designed and tested with porcine coronaries. The *ex vivo* platform was realized exploiting additive manufacturing. The hydraulic characterization of the system proved that it was capable of inducing a controlled fluid dynamic status on the vessel. Preliminary experiments with porcine coronaries were performed to assess the viability of the tissue cultured within the system. Results proved that the structure of the vessel was generally preserved and viability guaranteed. In perspective, the system could be used to induce the disease to the vessel and to study the cellular pathways involved. This platform, in fact, could provide a reproducible and well controlled model of vessel damage and it is suitable for investigating the effects of pharmacological treatments. The preliminary validation of the system was performed in collaboration with the Cardiovascular Research Area of IRCSS Ospedale San Raffaele.
Finally, it was designed a tissue-engineered model for studying atherosclerosis-related angiogenesis. Tissue-engineered inspired models permit to maintain the complexity of *in vivo* structures, but controlling cellular composition. As a proof of concept, we cultivated adventitial progenitor cells on tubular electrospun scaffolds under fluid-dynamic conditions to evaluate the angiogenic effects of hypoxia. In atherosclerosis, in fact, an unstable angiogenesis is an important trigger for the vulnerability of the atherosclerotic plaque and the induction of a physiological stable angiogenesis could be addressed as a therapeutic target. The scaffolds proved to have mechanical properties comparable to native vessels. Moreover, functionality tests showed that the composition of the scaffolds guarantee a good viability of cells. The model is suitable for performing these studies, but, before exploiting its potentiality, technical problems must be solved. In fact, one main drawback of tissue-engineered models is related to the necessity to adapt traditional analysis protocols, such as q-PCR and ELISA, to these innovative approaches. The study was entirely performed at the School of Translational Health Science of the University of Bristol, during a six-months period sponsored by the Erasmus Plus Traineeship.
In the present Ph.D. thesis technical novelties were achieved. The platforms presented could be therefore used for establishing biological novelties and therapies effectiveness in the field of atherosclerosis.