SUBMISSION FORM OF PROPOSALS FOR DOCTORAL RESEARCH PROJECTS

Objective of the Doctoral Programme in Health Sciences and Technologies

The objective of the new interdepartmental Doctoral Programme in Health Sciences and Technologies is to train the next generation of leaders in industrial, clinical, and academic research. Our goal is to develop an organic research programme at the interface between engineering and medicine, which is inspired by the quantitative and integrative approach of physical sciences, and by the latest development in biomedical research, drive the development and clinical translation of disruptive health technologies.
The doctoral training programme will prepare students in conducting research which:
- Extend the comprehension of how human physiology and pathology work in term of physical and chemical mechanisms, and how these mechanisms respond when perturbed by external factors such as therapies, changes in life style, and environmental factors;
- Develop new technologies that by leveraging on this mechanistic understanding pursue a wide spectrum of applications relevant to human health, including prevention, diagnosis, prognosis, treatment, and rehabilitation.

Procedural aspects on the submission of proposals for doctoral research projects

Every year the PhD process will start with the submission of proposals for doctoral research projects. Each proposal must be submitted jointly by two supervisors, one providing the clinical expertise, the other the technological expertise. The Project Selection Committee will select a number of projects that is three times the number of available scholarships and should be distributed in similar proportion between medical-led or technology-led proposals. The resulting list of projects will be included in the call for student applications that the Executive Committee will compile soon after. Each student, depending on their degree, will be able to apply only for a sub-set of projects; among them each student will be allowed to select three projects, and name them in order of preference; however, in some cases it might not be possible to satisfy all requests, and some students might be offered a research project different from those they selected.

Doctoral training program

In order to be admitted to the selection, a student needs a five-year higher education degree, which includes at least one module for each of the following disciplines: mathematics, physics, computer science, biology, physiology, and anatomy.

Max number of proposals for each member of the Academic Board: 3 (three)
Max number of selected projects for each member of the Academic Board: 2 (two)
Max number of selected projects for 2019: 12 (twelve)

Title of the project

New Insights on Atrial Fibrillation from Imaging and Computational Modelling

Student's degree (you can choose more than one, if needed)

Yes/Not	Cultural area
No	Medicine, biology, or related disciplines
Yes	Engineering, physics, mathematics, computer science, chemistry, materials science or related disciplines

Student's skills (you can fill more than one field, if needed)

Cultural area	Skills
Medicine, biology, or related disciplines	Cardiac physiology, Cardiac imaging
Engineering, physics, mathematics, computer science, chemistry, materials science or related disciplines	Biomedical Engineering, Computational Modelling, Image/Signal Processing, Matlab Programming

Tutors (2, from different cultural areas and with at least 1 from the Academic Board)

Cultural area	Name & Surname	Department
Medicine, biology, or related disciplines	Igor Diemberger	DIMES
Engineering, physics, mathematics, computer science, chemistry, materials science or related disciplines	Cristiana Corsi	DEI

Research project

	Synthetic description
Summary (max 1000 chars)	Atrial fibrillation (AF) is the most common arrhythmia, causing substantial morbidity and mortality. AF is often treated with catheter ablation, but the mechanisms underlying the arrhythmia are incompletely understood and ablation success rates remain low. Recent observations promise to lead to better outcomes: a) atrial fibrosis correlates with the ablation responsiveness b) AF is maintained by electrical rotors and targeting their suppression improves the success rates. However, the lack of a rigorous mechanistic framework of AF pathophysiology limits the values of those studies, which are still debated. This project aims to provide such a framework by exploiting advanced biomedical engineering concepts. AF mechanisms will be first analysed in AF patient data, acquired with state-of-the-art instrumentation. Measured data will be integrated within a multi-scale personalized computational model of the atrium. providing an in-silico environment for personalized ablation planning. Key in the project will be the synergy between state-of-the-art expertise in the fields of medical imaging, computational modelling and clinical electrophysiology.
Objectives (max 1000 chars + max 5 relevant references)	This project aims to elucidate role and relationship between fibrosis and re-entries on the pathophysiology of AF. The relationship will be first analysed on experimental data available from cutting-edge instrumentation for real-time monitoring of atrial activation. Measured data will be integrated within a multi-scale patient-specific computational atrial model that will seek to establish a mechanistic connection between fibrosis and rotors and will constitute an in-silico environment for ablation planning. Ultimately, all developed solutions will aim at the improved clinical decision making and treatment planning for the AF patient condition.
Rationale and scientific background y (max 2000 chars+ max 5 relevant references)	AF is often treated with catheter ablation since trials question the efficacy of pharmacological strategies. Since early AF episodes are triggered by localized ectopy from the pulmonary veins (PVs), standard ablation involves PVs isolation. Nevertheless, once initiated, AF induces alterations in the substrate (atrial remodelling) in a way that causes the typical gradual worsening to persistent and permanent forms. Remodelled tissue promotes chaotic electrical activation patterns that sustain AF even after ectopic sources are isolated. Unfortunately, the knowledge of these mechanisms is very limited. Hence, the practice consists in the incremental ablation of the substrate until termination of AF. This might lead to excessive atrial tissue destruction and consequent loss of cardiac function. Altogether, current success rates in these patients are still low (~50%). Two recent observations promise to improve ablation strategies success rates. The first shows that fibrosis in the LA directly correlates to non-responsiveness to ablation. As such, the new indicator is useful for patient stratification. The second study hypothesizes that AF is sustained by localized stable reentrant waves (rotors) whose ablation. showed a 38.5% to 77.8% improvement in the 3 years follow-up over PV isolation. Unfortunately, both studies still represent independent experimental observations from single centres that strongly require further verification. Moreover, the lack of a solid mechanistic framework of AF deprives those experimental studies of strong theoretical fundaments. Computational modelling is a bioengineering technique that may provide such framework. Recently, patient-specific models of AF have been developed and proved in silico that fibrotic tissue promotes the formation of electrical re-entries. Establishing such a connection between pre-operative (fibrosis) and intra-operative (rotors) features is key in the purpose of optimal procedure

	planning. Nonetheless, a clear verification of the models' prediction against experimental measurements of electrical activation is still missing. This is partly due to the unsuitability of the equipment used for measuring dynamic AF events as rotors. Moreover, model creation is highly operator dependent. These facts limit the clinical interest of existing tools.
Preliminary results if existing (max 1000 chars+ max 5 relevant references)	A preliminary version of an in-silico test framework for rotor ablation has been developed at DEI-UniBo. Few EGMs acquired by multielectrode catheter have been analyzed. What we found is that the distance between the catheter and the atrial wall as well as the inter spacing between the electrodes affect the reliability of rotor detection substantially. This activity resulted in several conference proceedings publication and in two journal articles (A computational framework to benchmark basket catheter guided ablation in atrial fibrillation, Front. Physiol., 21 September 2018 | https://doi.org/10.3389/fphys.2018.01251; Towards a repository of synthetic electrograms for atrial activation detection in atrial fibrillation, Comput Biol Med. 2018;1(101):229-235. doi: 10.1016/j.compbiomed.2018.09.001). A second study used computational fluid dynamics to stratify the risk of stroke in atrial fibrillation patients. Hereto, a personalization pipeline for the CFD simulations was developed and studied on AF patients. The initial findings showed that the chaotic contraction pattern in AF favors blood stagnation in the left atrium which, in turns, might generate blood clots and therefore stroke. This activity resulted in several proceeding papers, one paper in international journal (The impact of left atrial appendage morphology on stroke risk assessment in atrial fibrillation: a computational fluid dynamics study, Front. Physiol., 22 January 2019 | https://doi.org/10.3389/fphys.2018.0193;) and one paper under review (A computational fluid dynamics approach for personalized stroke risk assessment in atrial fibrillation, Journal of Biomechanical Engineering – minor revision required).
Research project including methodology (max 5000 chars)	The key of the project is the multidisciplinary integration of leading expertise in the fields of medical imaging, biophysical modelling and clinical electrophysiology, provided by the different tutors and department involved. Moreover, the PhD candidate will have high exposure on clinical and industrial sectors. The project will take strong advantage of an existing joint collaboration between the different groups involved (at DEI and DIMES) and the company Boston Scientific (BSc), Natick, MA. Thanks to the latter, state-of-the-art instrumentation in the field of interventional electrophysiology (multielectrode catheters) is employed by the clinicians of the Cardiology Unit at DIMES to map atrial activity and guide the intervention. Unlike standard EAM, which creates static snapshots of atrial activation by interpolating punctual measurements obtained sequentially (hence unaligned in time) from a single transducer operated within the atrial cavity, multielectrode catheters provide intracardiac electrogram (ECG) traces in real time and simultaneously from several locations. As demonstrated by the FIRM study (S. M. Narayan et al., JACC, 2014) basket catheters (a specific type of multielectrode catheter) are intrinsically better suited to map transitory AF events as the rotors. The introduction of this promising technology in the clinical practice is still at its early stage. Hence, industrial exposure is also high. Ultimately, intracardiac electrograms (EGMs) will be available for analysis from a cohort of AF patients together with: MR Angiography (MRA) scans, late-enhanced MRI (LE-MRI) scans and blood test exams. All data will come from the treatment plan predefined for the patients and no acquisition will be performed prospectively for this study. All data will be anonymized before being transferred to the PhD candidate. The first objective is to examine the relationship between fibrosis and electrical re-entries from experimental data (EGMs from 64 intracardiac electrodes already available and EGMs from other mapping catheters characterized by different resolution and atrial surface coverage will be used in the project). Hereto, a framework will be optimized to interpolate the available EGMs on the 3D patient-specific atrial anatomy obtained from MRA. The model will include personalized fibrosis distribution measured from LE-MRI. Catheter's tips position will be tracked from the intracardiac mapping system in use in the electrophysiology unit. The development of the mapping framework will require advanced image processing knowledge to perform image segmentation, multi-modal image registration and interpolation. Particular care will go to minimizing

	the level of user interaction. The strict collaboration with the Biomedical Imaging group of UNIBO will be key for the PhD candidate to receive support and feedback in this phase. The second step is to integrate the processed measurement data within a multi-scale patient-specific computational atrial model. The model will integrate ground-breaking concepts in terms of electrophysiological modelling at single cell and organ level. The required competences will be developed by the PhD candidate as part of the research training. Standard cell models will be improved to account for patient-specific extracellular electrolyte concentrations measured from the blood tests, as recommended in previous computational studies (S. Severi et al., Philos Trans A Math Phys Eng Sci. 2009). Electrical activation will be personalized by adjusting the conduction velocity in relation to the measured P-wave duration at sinus rhythm. Tissue properties will be adjusted regionally to reflect the known electrophysiological heterogeneities in the human atrium and to account for the presence of fibrosis and scars. Anisotropy in propagation will be regulated by a personalized model of atrial fibres. Given personalized geometry and fibrosis distribution as input, the model will output a patient-specific electrical activation map. The model will be tuned to match the best possible the predicted activation to the experimental measurement available from the basket catheter. The optimization will involve the free parameters of the model, i.e. the ones for which personalized experimental measurements won't be available; essentially, the ion channels conductances of the cell model. The parameters will be progressively varied to account for pathological alterations due to AF induced electrical remodelling. Ultimately, the tuned model will be tested as an *in-silico* environment for ablation planning. Scars will be simulated as regions with zero conductivity.
Innovation potential (scientific and/or technological) (max 1000 chars)	***Clinical and Industrial Innovation:*** The developed computational framework will **1)** allow an improved and more intuitive and objective visualization of the catheter's output, **2)** verify the role of stable rotors as key features of AF, which is still matter of dispute5, **3)** allow the evaluation *in vivo* of the connection between reentries and fibrosis in humans. ***Basic Research*: 1)** The patient-specific model will seek a mechanistic connection between fibrosis and rotors using experimental electrophysiological measurements as ground truth. It will be primarily investigated whether patient-specific location and extent of fibrosis can predict existence and location of stable re-entrant circuits. **2)** The model will be used as an *in-silico* test environment for ablation strategies. With the supervision of the clinician the new FIRM protocol will be contrasted against textbook ablation patterns. The feasibility of the tool will be evaluated retrospectively by simulating the ablation procedures performed on the patients. The validity of this last study will be performed on the follow-up data available before the end of the project.
Expected results and applications to human pathology and therapy (max 1000 chars)	Ablation of AF is becoming the standard of care for all symptomatic patients. After the recent results of the CASTLE-AF trial (NCT00643188, N Engl J Med. 2018), showing a reduction in overall death and hospitalization in patients with heart failure (HF) and AF vs. medical therapy, this approach to AF treatment will certainly increase, especially in HF patients. However, the latter subset of patients more frequently needs additional lesions beyond PVI isolation (>50% of the CASTLE-AF patients) increasing complexity and potential risks of the procedure. Identification of specific targets for AF ablation could positively impact by improving the success rate of the ablation procedure while reducing both acute complications (perforations/thromboembolism) and the amount of tissue loosing mechanical contribution secondary to electrical disconnection and induced fibrosis. A further application of this approach could better explain the interaction of the hybrid approaches to AF ablation, characterized by use of antiarrhythmic drugs coupled with AF ablation, and possibly lead to identification of patients that would improve more through a similar approach.

Available resources for the project

	Synthetic description
Research environment (labs involved,	Computational Physiopathology Unit and Biomedical Imaging Group Department of Electrical, Electronic and Information Engineering "Guglielmo

background, and location)	Marconi", University of Bologna, Cesena Cardiology Unit, DIMES, University of Bologna, Bologna
Main equipment (facilities and location)	Proper computational tools and workspace – Cesena/Bologna Clinical Electrophysiology Intervention facilities, Cardiology Unit, DIMES, University of Bologna, Bologna
Additional funding (title, amount, start date, duration)	

International collaborations for the project (also in view of the Student's secondment)

	Project	**Location and team**
#1	Ongoing joint collaboration on Computational Cardiology and student secondments for master thesis	Computational Cardiovascular Science Team, Department of Computer Science, University of Oxford Blanca Rodriguez
#2	"Patient-specific computational modeling of the atrium under pathological conditions: understanding arrhythmogenesis in dialysis and atrial fibrillation for improved prevention and therapy" MIUR-DAAD Joint Mobility Program, 2016-2017;	Karlsruhe Institute of Technology, Karlsruhe, Germany Olaf Doessel, Axel Loewe
#3	Ongoing joint collaboration on patient specific models' development and student secondments for master thesis	UPMC University Pierre et Marie Curie, and LiB Laboratoire d'Imagerie Biomedicale, Paris, France Nadjia Kachenoura
#4	Ongoing joint collaboration on computational fluid dynamics simulations using patient specific models in AF	EPFL – École polytechnique fédérale de Lausanne Alfio Quarteroni, Luca Dedè