POLITECNICO DI MILANO

PhD in BIOINGEGNERIA / BIOENGINEERING - 38th cycle

PNRR_351_PUBBL_AMMIN Research Field: MODELLING PHARMACOLOGICAL TREATMENT IN ATRIAL FIBRILLATION

Monthly net income of PhDscholarship (max 36 months)
€ 1250.0 In case of a change of the welfare rates during the three-year period, the amount could be modified.

Context of the research activity	
Motivation and objectives of the research in this field	During drug development, promising therapeutic compounds are tested to evaluate their potential arrhythmic risk (risk of inducing ventricular tachycardia that can precipitate in ventricular fibrillation causing sudden cardiac death). In the case of atrial fibrillation, the interest relies on the effectiveness of the given compounds in achieving cardioversion within the first 24 hours. The most simple mechanism explaining pro-arrhythmicity involves a reduction of the rapid delayed rectifier potassium current (IKr), an important contributor to action potential repolarization. This has promote the adoption of guidelines that measure the IKr channel block and the prolongation of the QT interval in-vivo to estimate the arrhythmic risk. However, these markers are known to be insufficient to fully characterize drug-cardiotoxicity and may prevent potential safe drugs to reach the market. This research proposes the development of a framework combining in vitro studies to measure the drugs effects on each of the different types of ion channels (not only IKr) and in silico models of the organ considering the muscle structure, the cardiomyocyte electrophysiology, and its variability, to understand how these effects influence cardiac function. The main novelty of this research lays on the incorporation of fully detailed models of the organ structure and its electrophysiology for arrhythmic-risk assessment of new drugs. The framework will be applied to atrial fibrillation since it is one of the most common arrhythmic pathologies among adults to date.

Methods and techniques that will be developed and used to carry out the research	Mathematical models of the cardiomyocyte electrophysiology incorporating the effect of drugs will be developed together with populations of models to assess electrophysiological variability. Mathematical/computational models make possible to simulate with precision extreme conditions, such as high drug concentrations, and to obtain insights that are usually limited to animal experiments. A three-dimensional model of a human atria that incorporate the underlying tissue anisotropy and regional heterogeneity will be specified to incorporate electrophysiological variability. The technique of population of models will be used to incorporate electrophysiological variability in the model. In brief, hundreds of thousands of models will be generated by varying the parameters of the different ionic channels. Models will be filtered based on their stability to then be clusterized to different regions of the atrium based on the characteristics of the action potential. Clusterization will be performed based on the characteristics of the population to be studied (recently induced AF, or persistent AF). The effect of the drug will be simulated in this setting providing a more detailed insight on the anti-arrhythmic behavior of the compound. In addition, simulated measurements extracted from the biophysical model will be fed to machine learning (ML) models, with the aim of extracting mechanistic insights hidden in the data that could be otherwise ignored.
Educational objectives	The main educational objectives of the project are: - Learn the biophysical modeling of heart electrophysiology and the effect that different pharmacological influence cardiac function. - Become an expert in the regulatory process behind new cardiac drugs - Apply Machine Learning techniques to data extracted from biophysical simulations to uncover mechanistic insights associated with arrhythmogenic behavior of new drugs.
Job opportunities	After finishing the PhD, the candidate could find job opportunities at regulatory agencies, thanks to the

	familiarity with the regulatory process behind new cardiac-drugs. At the academic level, thanks to the knowledge acquired in biophysical modeling and simulation, or that pharma industry on developing advanced models of drug interactions for cardiac risk assessment.
Composition of the research group	2 Full Professors 1 Associated Professors 1 Assistant Professors 5 PhD Students
Name of the research directors	Prof. Jose Felix Rodríguez Matas

Contacts
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Additional support - Financial aid per PhD student per year (gross amount)	
Housing - Foreign Students	--
Housing - Out-of-town residents (more than 80Km out of Milano)	--

Scholarship Increase for a period abroad	
Amount monthly	625.0 €
By number of months	6

National Operational Program for Research and Innovation	
Company where the candidate will attend the stage (name and brief description)	Agenzia Italiana del Farmaco (AIFA); www.aifa.gov.it
By number of months at the company	6
Institution or company where the candidate will spend the period abroad (name and brief description)	Università Politecnica di Valencia; www.upv.es/en
By number of months abroad	6

Additional information: educational activity, teaching assistantship, computer availability, desk availability, any other information
Attinenza alla tematica prescelta del bando ex D.M. 351, artt.6-9, comma 1 Il presente progetto si colloca nell?ambito della ricerca applicata nelle pubbliche amministrazioni

ed è finalizzato a favorire maggiore efficacia, efficienza ed economicità dell?azione pubblica nel settore delle cure sanitarie. Il programma di ricerca proposto ricade nell?Area disciplinare CUN 09 ? Ingegneria industriale e dell?informazione. Esso si realizzerà in un?ottica multidisciplinare, sviluppando strumenti innovativi per la modellazione computazionale e per la valutazione dell?efficacia e della sicurezza dei nuovi trattamenti farmacologici delle aritmie cardiache, che potranno contribuire a una maggiore digitalizzazione del sistema di farmacovigilanza (?in silico clinical trials?). Il programma potrà, in particolare, contribuire all?aggiornamento delle istruzioni a carattere tecnico/applicativo, come specifiche tecniche e linee-guida applicative, in materia di farmacovigilanza, ancora basata sul Regolamento UE 1235/2010 e sulla Direttiva 2010/84/UE.

Impresa, centro di ricerca, pubblica amministrazione presso cui si svolgerà l'attività esterna
Agenzia Italiana del Farmaco (AIFA)
www.aifa.gov.it
Mesi previsti: 6
Descrizione sintetica attività:
Durante il periodo di ricerca all?AIFA il dottorando si familiarizzerà con il processo regolatorio associato alla valutazione del rischio aritmico di nuovi farmaci, e l?implementazione nella procedura di modellizzazione in-silico.

Ente, università, azienda, centro di ricerca presso cui si svolgerà il periodo di studio e ricerca all'estero
Università Politecnica di Valencia - Ingegneria industriale e dell?informazione
www.upv.es/en
Mesi previsti: 6
Descrizione sintetica attività:
Il lavoro sarà sviluppato con il Prof. Jose Maria Ferrero e la prof.ssa Beatriz Trenor. La modellizzazione farmacologica sarà stessa a diversi modelli anatomiche dell'atrio in modo di studiare l'effetto della variabilità anatomica insieme alla variabilità elettrofisiologia del trattamento farmacologico.

A shared desk and a PC will be given to the student for the time needed to carry out research. A limited budget will be available for travelling and purchases, too.