HEAL ITALIA – SPOKE 2 – WP 2 – TASK 2.3
TASK 2.3: DIGITAL TWINS FOR COMPUTATIONAL MODELING AND PERSONALIZED INTERVENTION

Progetto di Ricerca e Piano di Attività

"Digital twins for personalized interventions: applications to Cardiac electrophysiology, Stroke risk assessment and Polycystic kidney disease"

Project

Digital twin solutions are an innovative approach for the prediction of disease diagnosis, personalized intervention, and precision treatments using computational modeling and simulations of complex physiological systems. The proposed project will address some of the open methodological issues in the field (multiscale and multiphysics integration of computational models; algorithm optimization to reach real-time or close to real-time simulations; reliable understanding and description of the genotype-phenotype relationships to fully exploit a personalized medicine approach; integration of mechanistic, biophysical, statistical and population models; uncertainty quantification) and will ultimately lead to the development of a Digital Twin for specific target organs or a specific target pathology. It will have as input patient-specific data, including biosignals as well as images. Patient-specific simulations based on mechanistic models will be applied to anatomical and functional patient information. Simulation output will possibly support: *i)* diagnosis; *ii)* drug safety and efficacy assessment; *iii)* therapy planning; and *iv*) risk stratification.
At least two out of three specific applications will be addressed: Cardiac electrophysiology, Stroke risk assessment and Polycystic kidney disease.

<u>Cardiac electrophysiology</u>

For more than 50 years, computational modeling of cardiac cellular electrophysiology has been shown to be beneficial in identifying the drivers of cardiac arrhythmias at the cellular scale. By employing the perfect control and observability of in silico models, the key determinants of arrhythmogenesis can be identified and managed.

Numerous in silico cardiomyocyte models for a wide range of species have been developed and used to evaluate the pro- and antiarrhythmic effects of pharmacological interventions. Cardiac electrophysiology is a quantitative science based on well-established physical principles and with large amounts of experimental data. Existing cardiomyocyte models have been constructed based on the available experimental data when the models were developed, and they have been useful to address the specific research questions that they were intended to answer.

There is a growing interest in more personalized modelling approaches that accommodate inter-individual heterogeneities to unravel patient-specific mechanisms and develop tailored therapy of cardiac arrhythmias. Additional personalization based on genetic, cellular (e.g., induced pluripotent stem-cell-derived cardiomyocytes, biomarkers and electrolytes) and functional (e.g., electrocardiogram [ECG] and electrophysiological mapping data), as well as integration with emerging machine-learning approaches based on the large amounts of cardiovascular data that are being generated, may help to realize the vision of the 'digital twin' that can be used to improve patient care. Validation of model-based care in clinical trials and instructions on appropriate use will be essential for clinical adoption.

For this reason, some computational models will be proposed to enlighten the mechanisms behind different (patho)-physiological conditions and contribute to the personalized modelling described above.

Stroke risk assessment

The project aims to present a digital twin of the atria. In this specific project the clinical scenario involves atrial fibrillation patients since AF is one of the major causes of cardioembolic events due to the high possibility of thrombus formation linked to the risk of stroke. Its genesis and evolution involve many mechanisms and there are comorbidity conditions (congestive heart failure, hypertension, diabetes mellitus, obesity, alcohol consumption and obstructive sleep apnea) that promote its occurrence and maintenance. In clinics, the thrombus generation risk is evaluated considering empirical factors such as the CHA_2DS_2VASc. Therefore, this project is driven by the need to satisfy the lack of quantitative indices by developing a new quantitative parameter able to stratify stroke risk on a patient specific basis.

Polycystic kidney disease

The project aims to present a digital twin of the kidney in patients affected by ADPKD. This pathology is characterized by a progressive growth and development of cysts in the kidneys, which cause an increase of kidney volume associated with renal failure, arterial hypertension, abdominal pain, episodes of rupture of hemorrhagic cysts with macrohematuria, nephrolithiasis and worsening of the patient's quality of life. Furthermore, ADPKD is a systemic pathology associated with multiple extra-renal manifestations including the development of cysts in other organs such as the liver and the formation of cerebral aneurysms. Continuous advances in genetics have contributed to a better understanding of the pathogenesis of this disease and have suggested new treatment strategies to inhibit or delay the formation and expansion of renal cysts. The administration of such treatments is based on an imaging-based classification of ADPKD patients requiring an accurate instrumental approach: in this scenario, radiological imaging techniques have become an important tool for the diagnosis, prognosis and monitoring of the evolution of ADPKD both in patients on specific and conservative therapy. Although KV is currently considered the best prognostic biomarker for the evaluation of the degree of renal failure, it may not always be so accurate, such as in patients with few cysts but large or in patients with renal atrophy secondary to vascular or urinary tract obstruction. Therefore, this project is driven by the need to satisfy the lack of additional quantitative indices able to better characterize the disease and its prognosis on a patient specific basis.

Activities

Cardiac electrophysiology

- To develop an atrioventricular nodal (AVN) cell and tissue model for mice, and eventually translate it into human.
- To develop a computational model for the sinoatrial node tissue to investigate physiological and pathological pacemaking conditions.
- To use and develop different computational cardiac cell models to investigate pathological conditions (e.g., Brugada syndrome, HCM patients, genetic mutations, or drug effects)

Stroke risk assessment

- Reproduce fluid dynamic behavior of the atrial chambers throughout the cardiac cycle by performing CFD simulations with realistic boundary and initial conditions.

- By using the simulation results from the previous step, extract the velocity field within the atria and use it to implement a thrombogenic risk score, to stratify stroke risk.

Polycystic kidney disease

- Assess the potential contribution of cyst volume for patient's risk classification and possible therapeutic choice.
- Assess the potential contribution of tensor MRI to optimize ADPKD patients' classification and prognosis.