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PhD Yearbook | 2023

Chair:
Prof. Gabriele Dubini

DOCTORAL PROGRAM IN BIOENGINEERING

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, within 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 on healthcare, life sciences and biomedical industry.

During the three years of the PhD Programme, the 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, microfluidics and lab-on-a-chip systems, biomedical signal and image processing, e-health, bioinformatics, functional genomics and molecular medicine, artificial intelligence in medicine.

The PhD Programme in Bioengineering is organized with an inter-departmental structure. Faculty members of the PhD 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 (on average 20 per year) may carry out their research programs in experimental laboratories located at the Politecnico di Milano or outside, typically in biomedical research centers, hospitals and industries.

When the research is performed within the Politecnico, the PhD candidates are usually assigned to one of the following laboratories belonging to the DEIB and CMIC Departments: the Laboratory of Biological Structure Mechanics (LaBS, CMIC), the Laboratory of movement analysis "Luigi Divieti" (DEIB), the Medical Informatics Laboratory (DEIB), the Neuroengineering and Medical Robotics Laboratory (NearLab, DEIB), the Biosignals, Bioimaging and Bioinformatics Lab (B3 lab, DEIB), the Biomaterials Laboratory (CMIC), the Biomedical Technology Lab (TBMLab, DEIB), the Experimental Micro and Biofluid Dynamics (μBS Lab, DEIB), the Computational Biomechanics Lab (DEIB), the Biocompatibility and Cell Culture Lab (BioCell, CMIC), the Bioreactors Laboratory (CMIC). The Istituto di Elettronica, Ingegneria dell'Informazione e delle Telecomunicazioni (IEIIT) of the Consiglio Nazionale delle Ricerche (CNR, the Italian National Research Council), 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, for at least three months, in laboratories where the candidates can acquire further skills to develop their research work and thesis.

Collaborations that can involve PhD students are presently active with several national and international research and academic Institutions.

The involvement of companies and clinical partners very often facilitates the technological transfer of applied research into industry and clinical applications.

The educational syllabus includes *ad hoc* advanced courses specifically designed for the PhD students in Bioengineering. The syllabus also includes the School of the National Bioengineering Group, which is held yearly for one week in Bressanone-Brixen (BZ). Every year, the School is focused on a different subject. The themes in the last few years were: 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), Technologies and tools in surgery and therapy (2019), AI-enabled health care (2020), Biofabrication: An integrated bioengineering approach for the automated fabrication of biological structures for clinical and research applications (2021), Biomedical engineering for sustainable development (2022).

The PhD Board of professors is made up of highly qualified and active researchers in Bioengineering, belonging to DEIB and CMIC departments. The PhD Board is responsible of all the candidates' activities. The expertise of faculty members covers a wide spectrum of research fields. This allows a continuous updating of the PhD Programme and ensures that the PhD candidates are involved in innovative work.

The PhD Programme in Bioengineering also relies on an Advisory Board, made up of distinguished experts coming from R&D industries, research and clinical centers. The Advisory Board ensures that the goals of the PhD Programme are also aligned with the needs of non-academic world.

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WEARABLE DEVICES FOR REMOTE MONITORING AND THEIR INTEGRATION IN TELEMEDICINE PLATFORMS

Alessandra Angelucci – Supervisor: Prof. Andrea Aliverti

Telemonitoring consists in the transmission of physiological and other non-invasive data and aims at reducing hospitalisations, improving self-care, and enhancing quality of life. Wearable technologies facilitate continuous acquisitions of the data unobtrusively and in a natural setting, resulting in a complete picture of a patient's condition. With these technologies, physiological parameters can be recorded without interfering with daily life activities.

The main objective of this Thesis is to investigate telemedicine platforms for the monitoring of patients with wearables. The final goal of the work is to establish in the clinical practice reliable strategies to obtain continuous, meaningful, and high-quality data coming from multiple subjects in parallel and in real time, and to adapt the solutions to different populations. Four research studies are presented in the Thesis, following the architecture shown in the figure.

The first study is a clinical application of a commercial wearable. Preoperative assessment is crucial to prevent the risk of complications of surgical operations and is focused on functional capacity. A commercial smartwatch (Fitbit Inspire 2) was used to assess functional capacity before elective surgery and correlated with the gold standard (Six-Minute Walk Test, or 6MWT, distance). 31 patients were enrolled in the study. Patients wore the smartwatch for 7±2 days before surgery. Resting heart rate, daily steps, Heart Rate Over Steps, and a modified version of Non-Exercise Testing Cardiorespiratory Fitness (NET-F) were considered. The parameter that correlates best with the 6MWT is the NET-F ($r=0.68$, $p=0.000$), but also the other three correlated significantly. This study is a starting point for the adoption of wearable technology in the subject functional capacity evaluation.

The second study presents a continuous home telemonitoring system for chronic respiratory patients using 5G connectivity. The system featured a respiratory and activity monitor, an environmental sensor and a pulse oximeter sending the data through a 5G router to a server. Activity, respiratory and environmental data were continuously streamed and collected. The solution was tested on 18 healthy subjects during non-supervised recordings lasting at least 48 hours. Statistically significant differences were found in respiratory parameters between horizontal and vertical postures ($p<0.001$) and between vertical postures and dynamic activities ($p<0.001$); the respiratory rate (RR) showed statistically significant differences between horizontal and vertical postures ($p<0.001$).

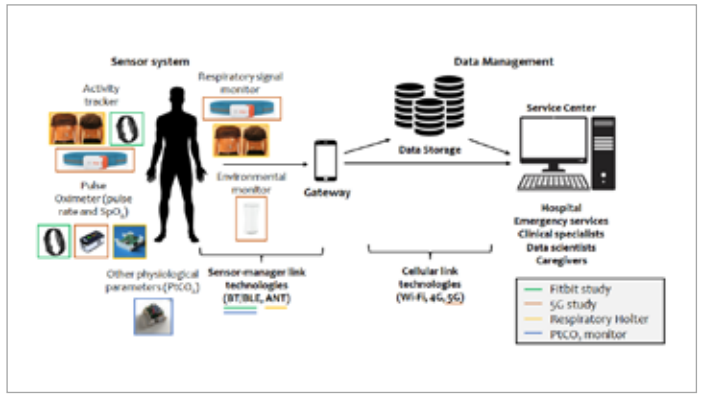

Fig. 1

The third study is a platform to monitor multiple parameters ('Respiratory Holter' in the figure) and is divided into three parts. Part A uses a wearable sensor system constituted by three IMUs to simultaneously estimate RR in static and dynamic conditions and perform human activity recognition (HAR). Two units detect chest wall breathing-related movements (on the thorax and on the abdomen); the third is the reference. All units compute the quaternions describing the subject's movement. Data from 20 healthy subjects during different postures and activities were analysed to extract RR with an algorithm based on the first component of the Principal Component Analysis (PCA). Differences between dynamic activities and static postures were detected ($p<0.05$). Data from the IMUs were used as inputs to artificial intelligence methods for HAR, with accuracies ranging from 90% to 99%. It was possible to perform simultaneous HAR and RR measurements in static and dynamic conditions with the same sensor system.
Part B proposes a method to estimate RR based on the activity. RR was assessed during standing, walking, and running in one volunteer. Data from a gold standard (K5, COSMED) and from the IMU-based system were collected. The analysis of the IMU signals exploits the first two components of the PCA to identify different movement patterns. Agreement was found between the systems. In a static posture, RR was computed from the first PCA component. During dynamic activities, RR was computed from the second PCA component, while the first PCA component was related to the stride. This finding suggests further research to develop an algorithm for respiratory signal filtering based on activity.
Part C integrates a wrist-worn pulse oximetry unit that allows to measure SpO_2 and pulse rate (PR). The four-unit system was validated on 11 healthy subjects against a Cardiopulmonary Exercise Testing machine during a rebreathing test to induce hypoxia. The instruments were compared in terms of normalized amplitude of the respiratory signal, RR, SpO_2 and PR. Good agreement between the measurement systems was found, however the wrist-worn pulse oximeter tends to underestimate SpO_2.

The fourth study presents a wearable device to monitor the partial pressure of transcutaneous CO_2 ($PtCO_2$). The electrochemical approach is the clinical practice for the measurement of $PtCO_2$. However, it presents requires the continuous calibration of the device, the remembranization of the electrodes, an infrastructure with specialized personnel, and stillness during the measurement. This study presents a wearable for $PtCO_2$ measurement with a non-dispersive infrared sensor. The device performs three main actions: first the environmental CO_2 is measured, then the skin temperature is brought to 42°C, and finally the $PtCO_2$ is measured. 16 healthy subjects were enrolled to validate the new device against a gold standard, the Sentec probe. The new PCB device proved to be capable of detecting a response to the stimulus of hypercapnia with a time delay comparable to the gold standard. Before reaching a baseline, both devices require an assessment time of minutes. The main noticeable difference is that the Sentec device goes back to the baseline once the effect of the stimulus is finished, while the new PCB device saturates. This is probably due to the lack of air recirculation, which can be solved with technical improvements. This work demonstrates the feasibility a wearable to measure $PtCO_2$ based on an optical sensor.

In conclusion, commercial systems offer opportunities to monitor different aspects of patients' health, for instance functional capacity. Despite this, there is a major need to investigate strategies for the monitoring of chronic patients, in particular those affected by respiratory diseases, and this Thesis offers solutions in this direction.

FUNCTIONAL NEAR-INFRARED SPECTROSCOPY TOWARDS A MONITORING TOOL IN NEUROREHABILITATION: SIGNAL PROCESSING AND BRAIN MAPPING METHODS

Augusto Bonilauri

Advisors: Prof. Giuseppe Baselli, Dr. Francesca Baglio, Dr. Francesca Sangiuliano Intra

Functional Near-Infrared Spectroscopy (fNIRS) represents a versatile optical imaging technique, since non-invasive and low-cost measurements of brain activity can be acquired in an ecological setting while employing a wide range of tasks. Among the promising fields for clinical applications, we find the monitoring of chronic neurological diseases. In this context, we conducted a systematic review of applications, evidencing that fNIRS is mostly employed to provide a cross-sectional characterization of clinical phenotypes. Nevertheless, current literature suggests that fNIRS can be effectively employed in longitudinal studies to monitor cerebral activity, disease progression, and assessment of intervention-based strategies.
The roadmap towards the full integration of fNIRS in clinical applications is still hindered by two major methodological issues: i) the intrinsic physiological interference over the fNIRS signal and the lack of standardized signal processing pipelines; ii) the limited spatial resolution compared to functional Magnetic Resonance Imaging (fMRI) as gold standard, hence the indirect reference of fNIRS channels to cortical anatomy.

This PhD work held in collaboration with IRCCS Fondazione Don Carlo Gnocchi ONLUS has two major aims: i) a methodological aim to provide insights of fNIRS signal processing and cortical mapping methods, hence improving the characterization of functional activation and integration with MRI/fMRI techniques; ii) a translational aim to demonstrate the full potential of fNIRS as viable ecological monitoring tool of brain activity in PD patients.
In all studies, we employed a continuous wave fNIRS system with 32 sources and detectors, resulting in 102 measurement channels able to cover the major frontal, motor, temporal, somatosensory and occipital areas. A block-design motor grasping paradigm was employed as functional task.
In a first study, we investigated the major steps of fNIRS signal pre-processing and analysis over 23 healthy young adults (HYA, age 28.3 ± 4.0) by comparing motion artifact (MA) reduction algorithms and their variants without employing separate artifact sensing systems, resulting in 8 different pipelines. A major focus was presented on the progressive energy relative decrease over fNIRS signals across pipeline steps (i.e., MA reduction, bandpass filtering and principal component analysis), the final SNR of estimated hemodynamic response and statistical group-level activation maps.
The energy of the pre-processed signal was reduced to values around 4% compared to initial energy, hence highlighting that fNIRS signal preprocessing is a sharp procedure that requires careful considerations prior to statistical analysis. Overall, we suggest adopting MA reduction algorithms following a channel-wise approach to prevent an invasive interpolation over MA tracts if occurring at high rates.
Notably, most of statistical differences in cortical activation across pipelines were referred to non-motor areas. This aspect can possibly lead to misleading conclusions if overlooked in translational applications, such as assessing cortical activation according to pathological conditions or supplementary areas.
Next, we applied the proposed pipeline to a clinical dataset for analyzing the cortical activity of PD patients at different stages of the disease according to Hoehn & Yahr (HY) scale. Patients derived from the baseline assessment of the SIDERA^B project performed at IRCCS Fondazione Don Carlo Gnocchi ONLUS, and they were subdivided into two groups: early PD (ePD, HY=[1; 1.5], N=13, age 63.52 ± 1.65) and moderate PD (mPD, HY=[2; 2.5; 3], N=26, age 71.68 ± 1.37). The analyses considered specific ROIs based on bilateral Brodmann Areas (BA), statistical group-level activation maps to contrast task conditions among groups and the correlation between fNIRS data and patient's clinical variables.
The ePD group had higher activation over motor and occipital areas compared to mPD, while the inverse trend was found over frontal areas. Significant correlations with the level of cognitive reserve, motor impairment, disease duration and stroop color word test were mostly found over non-motor areas.
We can conclude that PD motor impairment affects the activation level of motor areas depending on the progression of the pathology, while the recruitment of non-motor areas follows different trends of activation, which can be taken as an overall index of loss of function and neurovascular coupling impairment. Results are also in accordance with current fNIRS and fMRI/MRI literature, which suggests that non-motor areas provide a compensation mechanism to PD motor impairment.
Then, we analyzed the effects of anatomical variability when mapping fNIRS measurements onto cortical surface by proposing a novel graphical and numerical method for ex-post fNIRS to anatomical MRI integration. This method reconsidered the fNIRS sensitivity profile of 13 HYA (age 29.3 ± 4.3) to define Sensitivity-Displacement Surfaces (SDS) and the coupling between channels and cortical parcellations of interest as Area to Channel (A2Ch) sensitivity coefficients.
Results over the integral value of SDS indicate that the mapping of fNIRS data onto cortical anatomy is no more informative when considering scalp-cortex distances above its second quartile range, since confining from 55.4% up to 71.4% of the overall sensitivity profile across subject-specific and atlas-based anatomies. As well, A2Ch results evidenced that there is an intrinsic variability in channels to cortical areas coupling, especially when considering occipital and somatosensory BA compared to frontal regions.
We also proposed a surface-based approach for the ex-post fNIRS-fMRI integration and data analysis. We considered non-simultaneous fNIRS and fMRI acquisitions over 18 HYA (age 30.55 ± 4.7) to assess fNIRS vs. fMRI spatial agreement according to Dice Coefficient (DC), signal intensity and temporal correlation.
Subject-level DC values yielded fair to substantial agreement (DC range 0.36-0.62), while at group-level it increased up to 0.71. This trend was also followed by the temporal correlation of signals, since ranging from moderate (range 0.61-0.72) at subject-level to strong values (0.84-0.94) at group-level. Conversely, the signal intensity, as measured by mean z-values derived from statistical maps of activation, was higher in fMRI compared to fNIRS, both at single-subject (5.21-6.68 for fMRI vs. 2.26-3.21 for fNIRS) and group-level (4.02-5.29 for fMRI vs. 2.04-2.42 for fNIRS).
In conclusion, this work addressed the major methodological and translational issues that hinder the application of fNIRS as viable monitoring tool of neurological conditions and disease progression. We also highlighted, both in the PD study and methodological studies, the importance of a whole-head mapping to cover the entire scalp surface, as well as the need of integrating MRI and fMRI information to increase the interpretation and translation of fNIRS into clinical applications.
The work on the ex-post fNIRS-MRI integration suggested that fNIRS channels on average sense mainly cortical gyri positions, hence highlighting the importance of considering strict anatomical constraints when mapping fNIRS data onto cortical anatomy. As well, the group-level fNIRS vs. fMRI moderate to substantial spatial agreement and strong temporal correlation, despite a lower signal intensity by fNIRS, suggested that fNIRS provides reliable insights over cortical activation. In general, the proposed methodological approaches do not require major modifications of either fNIRS, MRI or fMRI experimental set-up, thus being suitable to routine clinical applications. As prospective applications of this PhD work, we find multiple fNIRS measurements as longitudinal monitoring of brain activity, while fMRI and MRI employed at predefined periods, such as pre- and post-rehabilitation stages.

VIRTUAL REALITY-BASED INTERVENTIONS FOR PULMONARY REHABILITATION

Vera Colombo - Supervisors: Prof. Andrea Aliverti, Prof. Marco Sacco

Chronic respiratory diseases represent one of the main causes of comorbidities and death worldwide. Among these, Chronic Obstructive Pulmonary Disease (COPD) is the most common. At the same time, the COVID-19 pandemic has recently brought a new clinical condition, the post-COVID syndrome, that may emerge as a chronic respiratory disease. The so-called Pulmonary Rehabilitation (PR) is a comprehensive intervention, with physical exercise as a cornerstone, proven effective in improving the health condition of patients with respiratory diseases. However, the benefits of PR usually decrease when the patients return home because they are not enough motivated to regularly carry out the prescribed activities due to their repetitiveness, the lack of direct surveillance and insufficient self-awareness. In the last decade, researchers have started investigating the potentiality of Virtual Reality (VR) to improve PR protocols. VR allows to create personalized, interactive, multisensory environments able to motivate and to monitor patients both in the clinical and in the domestic environment. Despite promising, VR is still under-explored in the field of PR. This thesis aimed at investigating whether and how VR can be applied to pulmonary rehabilitation. The main objectives were to investigate how VR could enhance PR protocols, and to verify the feasibility of integrating VR in a complete PR pathway from hospital to home.

First, the Virtual Park, a semi-immersive system for endurance training, was developed; it provides a VR experience simulating a bicycle ride in a park, implementing a configurable exercise protocol. In the first study, nine elderly (age = 69 ± 7.94) with either COPD or bronchial asthma, performed a 20-minute cycling session. We obtained excellent usability (SUS = 87.5 ± 12.61 out of 100) and high acceptability (TAM = 6.1 ± 0.21 out of 7 points). The second study addressed the feasibility of a multisession in-hospital endurance training program based on the Virtual Park. Fourteen patients with mild/moderate COPD (age = 71± 6.9 yrs.) participated to the study. The adherence ratio (96.78 %) demonstrated the feasibility and safety of the intervention for a daily use in the clinical centre. All participants considered the VR experience exciting and interesting, and showed high engagement (SFSS-pre = 4.66 ± 0.22, SFSS-post = 4.40 ± 0.36 out of 5 points). The motivation in doing exercise with VR remained high over the 3 weeks of training, suggesting that a long-term motivation is possible. Most participants reported that being immersed in the virtual environment has distracted them from the physical task and, therefore, from the related feeling of fatigue.

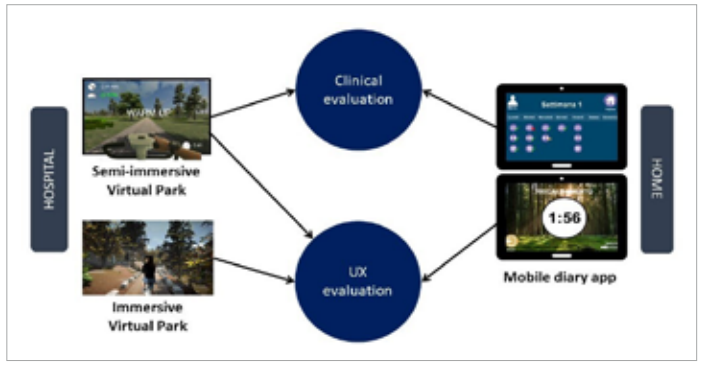

Fig.1 - A scheme summarizing the main VR solutions discussed in this thesis classified according to the context of use (hospital / home) and the evaluation performed (clinical / user experience).

To explore this further, a second activity aimed at evaluating the effects of VR on exercise tolerance focusing on the impact of the level of immersion - i.e., the virtual environment was displayed through a head-mounted-display - and interaction - i.e., an entertaining task is added to the main physical task. Thirty healthy young adults (age = 26.20 ± 4.85 yrs.) participated in a within-subjects study, consisting in cycling in four experimental conditions (control, non-immersive, immersive, immersive + interactive) at light/moderate intensity (HR = 62.71 % of their maximum heart rate). Perceived exertion was not directly mediated by any factors of VR. However, adding an entertaining task to the immersive experience made participants cycle faster and make more physical effort, showing a breathing rate of 26.38 ± 5.29 BPM, significantly higher than during other conditions. Moreover, participants enjoyed the immersive experience more, despite slight, though acceptable, cybersickness symptoms.

The next step, therefore, consisted in developing an immersive cycling system that could be used by respiratory patients. The immersive Virtual Park was developed to meet the rehabilitation needs of post-COVID patients. Ten individuals with post-COVID participated in the study (age = 56.60 ± 5.93 yrs.). Usability and acceptability were promising (TAM = 5.50 ± 0.83); all participants recognized the value of the system perceiving it as useful. The task proposed was overall enjoyable and able to engage patients, who reported a good level of flow (SFSS = 3.6 ± 1.05 points). We did not encounter acceptability issues; some participants reported slight symptoms, mainly discomfort and sweating, which were likely due to the physical demand required by the exercise. Further longitudinal studies are needed to strengthen our outcomes, reduce the side effects, and improve the motivational aspect.

In parallel to applications for the clinical setting, part of my work was dedicated to tele-rehabilitation. More specifically, I have developed a mobile app that works as a training diary for supporting the patients in continuing rehabilitation at home through physical training, cognitive stimulation and an educational program. Ten patients with COPD (age = 71 ± 7.39 yrs.) used the app at home for three months with encouraging results in terms of treatment's adherence and satisfaction. The majority of patients (70%) used the app as planned, considering it motivating and helpful for continuity of care in daily life.

Finally, the last part of my work focused more on the clinical perspective. A hybrid (hospital + home) intervention based on VR has been defined and tested with twelve patients (age = 70.92 ± 7.85 yrs.). Our study, although with limitations, suggested that VR-based interventions provide similar outcomes to that of traditional ones. Exercise capacity improved after the in-patient rehabilitation period resulting in a 42.50 m increase in the 6MWT. Dyspnoea, assessed through the BDI/TDI, significantly decreased between the beginning and the end of the in-hospital period. The COPD impact was reduced by 4.42 points, and the gained benefit has been maintained after the 3 months at home (CAT_1 = 6.09, CAT_2 = 5.83). In-hospital period was crucial for achieving clinical improvements that could be maintained while at home thanks to the gained motivation and self-awareness.

In conclusion, the results of this work are promising and improved the current knowledge on the use of VR for respiratory patients. Although some limitations, our studies allowed us outlining potential areas of interest and future research opportunities that, once fulfilled, will lead to the implementation of more personalized and technologically advanced PR models.

BOTTOM-UP STUDY ON THE IMPLICATIONS OF CELLULAR HETEROGENEITY IN THE MECHANISMS OF ATRIAL FIBRILLATION

Jordan Elliott - Supervisor: José Félix Rodríguez Matas
Co-Supervisor: Luca Mainardi

Advancing technologies have been key to furthering this understanding of physiology and is being increasingly relied upon in medical research.
Using mathematical models to represent the mechanisms and behaviours of a biological system on multiple scales, it is possible to further the understanding of how a pathophysiological condition begins, adapts, progresses and potentially could be reversed. In-silico modelling enables detailed exploration and prediction of the impact of disease progression, as well as interaction and effects of pharmacological intervention or use of medical devices. In-silico modelling can be useful in understanding the mechanisms of atrial fibrillation and can provide information that is otherwise unobtainable.
With the increased reliance on in-silico modelling in the medical field, it is imperative that the models be an accurate representation of behaviour of the system, tissue or organ they model. Typically, whole-atria studies in atrial fibrillation use regional homogeneity to reduce the complexity of the models with the assumption that it does not compromise the results.
This however has never been confirmed to be true. The impact of cell-to-cell heterogeneity has not been established in healthy atrial behaviour, let alone under physiological conditions.
Using in-silico modelling, the overall aim of this thesis is to challenge the assumption that cellular heterogeneity in the atria has a negligible impact on the overall electrophysiological behaviour in the atria. Starting with single cellular simulations and gradually progressing to whole-atria simulations in sinus rhythm, during atrial arrhythmias and in response to pharmacological cardioversion, this thesis presents the impact of cellular heterogeneity on electrophysiological atrial behaviour.

Method:
Using the Monte Carlo sampling method, a population of 200,000 unique action potentials was created by varying 9 maximum channel conductances by a range of –100% to +200% of the standard value. This created a non-biased population that can be calibrated purely on the characteristics of the action potential morphology, without first assuming limitations or characteristics of the channel conductances.
Using published data, 5 biomarkers (RMP, APA, APD20, APD50, APD90) were used to define regional action potential characteristics. The 200,000 action potential models were clustered based on these criteria. To simulate AF remodelling in the cells in the context of the population of models approach, two methods were used and evaluated using published experimental data.
The atrial model was then divided into ten anatomical regions with different conductance and fibre orientations. Each node of the atrial model was assigned an action potential model from the regional population created.
A regionally homogeneous atrial model was created for comparison, using the mean action potential model for each regional population of models.
The atrial models were simulated under sinus rhythmic conditions and in response to rapid pacing from 5 separate ectopic locations. Simulations producing a re-entry were continued to analyse the nature of the re-entry and the impact of three antiarrhythmic agents at varying concentrations.

Results:
High order sensitivity analysis showed the relationships between channel conductances and biomarkers was highly non-linear, indicating a significant interplay between different ionic currents and the AP morphological markers. In this regard, clustering action potentials into atrial regions based on biomarker classification maintained the highly non-linear relationships between channel conductance and biomarkers.
Directly applying percentage changes to individual channel conductances for AF remodelling imposes an a priori imprinting in the ionic conductances that could result in action potentials outside of the physiological ranges.
Ordinary linear regression results showed differences in non-linear relationships between biomarkers and channel conductances across regions and between cellular models. This supports the suggestion that the impact of AF remodelling differs between atrial regions.
No significant difference was observed in activation time as a result of heterogeneity. Cellular heterogeneity impacted the repolarization of atrial regions to varying degrees.
Electrotonic coupling is unable to completely remove variability and results in changes in repolarization across the heterogeneous atria compared with the regionally homogeneous atria. Results also showed regional boundaries have a strong impact on variability despite electrotonic coupling.
Results also showed that the boundary impact extends beyond regional boundaries and can cause a change in the AP morphology and therefore cellular behaviour.
In response to rapid pacing, results showed that in some instances, cellular heterogeneity can act in a way that increases re-entrant susceptibility, but in other instances, provides protection against re-entry. Susceptibility to re-entry is therefore impacted by localised electrophysiological heterogeneity, rather than entirely on anatomical features.
Heterogeneity in the AF remodelled atria showed both an increased vulnerable window in most locations compared with homogeneous models, and a different re-entry path due to heterogeneity. This showed that heterogeneity impacts both the susceptibility to re-entry and the mechanisms of re-entries. Cellular heterogeneity therefore has a significant impact on re-entrant characteristics and cannot be ignored when undertaking research.
Results showed that cellular heterogeneity has insignificant impacts on the changes in the re-entry frequency for each of the antiarrhythmic agents. Conversely, significant differences were observed in the ability to terminate the re-entry. The heterogeneity enabled the termination of the re-entry in response to flecainide at 2.5x EFTPC, whereas the re-entry was not terminated in the regionally homogeneous atria.
Conclusion:
This study showed the importance of tailoring the AF remodelling to individual regions. For both remodelling methods, it was clear that the non-linear relationships between channel conductances and biomarkers varied between atrial regions.
This study confirmed that cellular heterogeneity does not significantly influence the activation across the atria. Whereas the general assumption is that the electrotonic coupling completely masks any impact of cellular heterogeneity in the tissue, this study proves that whereas electrotonic coupling does significantly reduce variability across atrial tissue, it does not irradicate it. Consequently, the assumption that cell-to-cell heterogeneity can be ignored when modelling the atria, is an oversimplification of the atria in-silico and can result in drastically different results.
This study confirms that the combined impact of cellular heterogeneity on a regional and cellular level, electrotonic coupling and tissue anisotropy significantly influences the action potential morphology and variability in the atria for both the healthy and AF remodelled atria. Furthermore, this study goes on to prove that this combination significantly influences the susceptibility to re-entrant behaviour, re-entrant mechanisms, and the capability for pharmacological cardioversion to terminate the re-entry.
Overall, this study confirms that the impact of cell-to-cell heterogeneity is significant on the whole-atrial and therefore should not be ignored. This is most significant in the repolarization across the atria and has significant implications in the initiation, maintenance and termination of arrhythmic behaviour. To this effect, it is important to consider this when modelling the AF remodelled atria, rather than taking a regionally uniform approach.

STATISTICAL MODELLING AND STATISTICAL LEARNING FRAMEWORKS FOR ADVANCED MONITORING IN THE INTENSIVE CARE UNIT

Maximiliano Mollura - Supervisor: Prof. Riccardo Barbieri

Recent technological advancements have led to an increasing number of devices and sensors able to continuously collect data and information regarding the patient's state. However, the main drawback of having so much information available is mainly related to the complexity for the clinicians to deal with such overwhelmingly large amount of data contemporaneously.
Nowadays, Artificial Intelligence (AI) proved the ability to deal with (and also benefit from) such a large amount of data in many different fields of science and its potential was also recognized in medicine as well. Some exemplary applications in the ICU are the prediction of patients' risk and length of stay, patient readmission, identification of sepsis and sepsis phenotypes, the prediction of circulatory failure, and the identification of optimal treatment strategies.
However, despite the extremely high potential of AI applications, some significant challenges in translating AI-based solutions to clinical practice arise, like the need to deal with both technical and practical issues, where some examples are: the presence of biases in data usually collected retrospectively, the presence of noise and corruption, the difficulty in using these algorithms for making decisions that eventually would improve patient outcomes, and the need for a physiological interpretation of the decisions recommended by an AI system. Therefore, a more appropriate exploitation of the collected signals can help overcoming some of the presented issues.
This work highlights important methodological and clinical considerations from three major specific research aims from different clinical contexts. Aim 1 is devoted to the handling and processing of information from large clinical databases. Aim 2 describes the characterization of the physiologic response of ICU patients monitoring through advanced modelling of the cardiovascular system, and Aim 3 focuses on researching the fusion of AI tools and physiology-related indices.
Each research aim is focused on different clinical scenarios referred to as "Studies". Aim 1 proposes the application of a competing risk extended cox proportional hazard model to characterize the importance of dead space monitoring in patients undergoing mechanical ventilation due to COVID (Aim 1 - Study 1), and the application of a reinforcement learning approach for optimal fluid and vasopressor interventions (Aim 1 - Study 2). Research Aim 2 focuses on the application of statistical physiological modelling frameworks in order to assess the physiological changes induced by the administration of fluids (Aim 2 - Study 1), and to characterize the dynamic evolution of physiological parameters in patients with heart failure (Aim 2 - Study 2). Research Aim 3 proposes the combination of statistical learning and physiological modelling frameworks in the context of sepsis (Aim 3 - Study 1) and septic shock prediction (Aim 3 - Study 2). The results of this work yield specific important considerations for each specific research aim, which can be summarized as follows:

A novel study design is able to process information from large electronic health records.
Study 1 in Aim 1, about COVID-19 monitoring, has showed the development and application of a novel and effective study design able to process information from large clinical health records which allow for the application of advanced statistical learning tool like the proposed "extended competing risks Cox proportional hazards model" to highlight the role of different features in time-varying clinical settings. From a more clinical perspective, the proposed methodology shows the association between the dead space fraction and the outcome of patients affected by COVID-19 undergoing mechanical ventilation, when correcting for several confounding factors. Methodologically, the results point at the importance of a proper approach to summarize and process data from large electronic health which permit the application of advanced statistical methods which also deals with the dynamic variations of patients' vital signs.

Advanced statistical learning tools deal with the dynamic nature of ICU patients, thus improving patient monitoring and optimizing treatments.
Study 2 Aim 1 showed the application of a Reinforcement Learning approach for optimal fluids and vasopressors administration. In particular, the study investigates the best strategies to deal with the large set of available clinical variables, which highlights the importance of feature selection and dimensionality reduction procedures. Results show that a proper management of the feature space improves the results of such powerful statistical learning tools for the estimation of optimal treatment strategies. The application of a reinforcement learning pipeline shows a great ability to improve clinical practice by giving the possibility to explore the effectiveness and key role of a reduced set of cardiovascular variables that showed the ability to improve the existing model performances. This result paves the way to the possibility of developing continuous models that, by simply monitoring patients' vital signs, can optimally recommend patients treatments.

Statistical modelling of the cardiovascular system characterizes patients' response to interventions and predicts the risk of heart failure.
The second part of this research has focused on the exploration of some of the most advanced approaches to model the cardiovascular system by proper processing of the continuously recorded vital signs at the patients' bedside. The proposed modelling approach allows for the assessment of underlying physiological mechanisms describing the activity of the autonomic nervous system and its regulation of the cardiovascular system. The derived indices show different responses to fluid administration, as shown in Study 1 Aim 2. When stratifying the population according to patients' outcomes, the indices estimated from statistical modelling hold the potential for assessing patients' response to interventions.
Study 2 in Aim 2 has evidenced that different dynamic variations of autonomic indices are observed in patients being tested for heart failure. Therefore, this result suggests that the inclusion in the clinical practice of indices from statistical modelling of the cardiovascular system can be extremely informative because of their correlation with biomarkers of heart failure.

Physiology-informed statistical learning tools boost septic shock prediction and sepsis identification, and provide physiology-based explainable models.
The approach followed to evaluate solutions for sepsis prediction and identification is based on the assessment of a general methodology aimed at fusing both frameworks in order to develop AI-based and physiology-informed algorithms that can support clinicians in their decision-making processes. The studies proposed in Aim 3 show that it was possible to identify physiological indices able to predict acute clinical events like septic shock (study 1), and identify the presence of severe infections at the patients' admission (study 2).The proposed algorithms, which also include clinical information, mainly rely on indices extracted from patients' vital signs, thus allowing for the possibility to investigate the model decision rules and link them with physiology.

In conclusion, this thesis shows that an elaborate combination of statistical learning and modelling frameworks in the Intensive Care Unit can provide a valuable analytic and possibly clinically effective paradigm, which would result in: the improvement in patient monitoring, the boost of model performances, the increase in trustworthiness and explainability of data-driven models thanks to physiological information, and the potential to build medical equipment which can continuously monitor patients while actively optimize the delivered treatment.

IN-SILICO COMPARISON OF INNOVATIVE SPINAL FIXATION TECHNIQUES UNDER APPROPRIATE LOADING CONDITIONS

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Spine and pelvis are very important and complex structures able to provide structural support and flexibility to the human body. However, they can undergo several pathologies commonly associated with ageing such as adult scoliosis, high-grade spondylolisthesis, and sagittal imbalance, changing the physiological curvature of the spine. There are different surgical techniques that could be used in order to restore a physiological condition of the spine in select cases, such as spinal fixation and osteotomies. Despite the general good results obtained with standard treatments, postoperative complications and failures such as pseudoarthrosis, breaking and loosening of implants, sacroiliac joints pain, sagittal imbalance and so on, are very frequent. Nowadays, several in-vitro and in-silico studies are performed in order to understand and overcome the biomechanical complications and explore novel techniques and implants. However, a simplified loading scenario consisting of pure moments (sometimes in combination with follower load) is applied to the spine instead of realistic loading conditions, consisting of muscle forces, with potential major consequences on the numerical predictions.

The aim of this project was to determine whether a simplified loading scenario (pure moments) is appropriate for the investigation of spinal fixation with respect to realistic loading conditions (muscle forces), and to use the most appropriate loads to study novel fixation techniques (also a multi-rod construct) by means of innovative implants with or without a L5 pedicle subtraction osteotomy.

In the first part of this thesis, a comparison between simplified and realistic loading conditions is presented. Three standard spinal fixation techniques (lumbar, sacrolumbar and sacropelvic with S2 alar-iliac screws fixations) were implemented in a finite element model and subjected either to pure moments of 7.5 Nm (simplified loading conditions) or to muscle forces derived from a musculoskeletal simulation (realistic loading conditions). After the validation of the intact model under both loading conditions against two in-vitro studies and the validation of the instrumented musculoskeletal models against an in-vivo study, a comparison between these two loading conditions in terms of stresses in the implants was performed for each instrumented model. For the lumbar and the sacrolumbar model, simplified loading conditions were not sufficient to produce accurate results as those of realistic loading conditions, in particular for the posterior rods. For the sacropelvic model with S2 alar-iliac screws, instead, the results obtained with simplified loading conditions were very similar to those found with realistic loading conditions. Therefore, appropriate loading conditions for the lumbar and sacrolumbar fixation models were realistic loading conditions, while for the sacropelvic fixation model simplified loading conditions were sufficient.

In the second part of this thesis, the use of a novel porous fusion/fixation implant to enhance sacropelvic fixation was explored with respect to a standard sacropelvic fixation technique. After the validation of the intact model, four spinal fixation techniques with novel implant were created and compared under appropriate loading conditions (simplified loading conditions). One of these models represented a standard sacropelvic fixation technique with S2 alar-iliac screws and was used as baseline. The validation of the intact model was performed against two in-vitro studies. The novel implant resulted in a similar stability of L5-S1 and SIJ motions with respect to the standard techniques, as well as a reduced risk of screws failure and in a similar risk of rod failure. The novel implant seems therefore effective in protecting the pedicle screws from excessive loading.

In the third part of this thesis, the use of the novel porous fusion/fixation implant to enhance sacropelvic fixation and multi-rod construct was explored when also a L5 pedicle subtraction osteotomy was performed. The intact finite element model validated in the second part of this thesis was used as starting model for this part of the thesis. Three spinal fixation techniques with novel implants were created from the intact model after resection at L5 level and compared under appropriate loading conditions (simplified loading conditions). One of these models represented the multi-rod construct with four rods. Another model (thoracolumbar fixation with S1 pedicle screws) was used as baseline.

The sacropelvic fixation with the novel implant resulted in an increase of the stability of L4-S1 and SIJ motions, a reduced risk of screws failure, and an increased risk of rod failure with respect to spinal technique without sacropelvic fixation. Using four rods (multi-rod construct) resulted in a slightly increase of the stability of L4-S1 and SIJ motions, a similar risk of screw failure, and a relevant decreased risk of rod failure with respect to other techniques with two rods.

According to this, the novel implant demonstrated a good behavior for the stability of the spine and for screws also when a L5 pedicle subtraction osteotomy was performed, but not for the posterior rods. Sacropelvic fixation with the novel implants needed to be combined with multi-rod construct in order to have a protective effect on the posterior rods, especially when a L5 pedicle subtraction osteotomy was performed. Clinical evaluation should be performed to confirm the applicability of results to patient outcomes.

ASSESSING STRESSORS AND ELECTROMECHANICAL CARDIAC DECONDITIONING INDUCED BY SPACEFLIGHT ANALOGUES BY NOVEL BIOMARKERS

Sarah Solbiati - Supervisor: Prof. Enrico Gianluca Caiani

Prolonged exposure to microgravity induces multiple adaptive changes in almost all physiological systems, possibly compromising crew health and mission success. In particular, it affects the cardiovascular system and its regulatory mechanisms, leading to altered blood volume distribution, impaired myocardial properties, vascular remodelling, and increased ventricular repolarization heterogeneity. This, in turn, increases the risk of arrhythmia when a gravity field is restored. Gravity also serves as a cue for the circadian timing system, providing regular alternation between upright (1 G on the head-to-foot axis) and recumbent (0 G on the head-to-foot axis) positions. The combination of these effects influences the neural mechanisms involved in dynamic cardiovascular regulation.
As humanity prepares for Low Earth Orbit missions and a return to the Moon, it is essential to better characterize and understand the effects of spaceflight on the cardiovascular system. Due to the limited possibilities of conducting in-flight research, ground-based analogues are used to reproduce and study the effects of spaceflight on the human body. Head-Down Tilt (HDT) Bed Rest is a well-established ground-based space analogue model for simulating the effects of microgravity on human physiology. It is also a valuable tool for testing measures to prevent or counteract microgravity-induced pathophysiological adaptations. In bed rest studies, healthy subjects lie on a bed for 5 to 60 days, preceded by a period of acclimatization and followed by a recovery period inside the bed rest facility.
The main purpose of this thesis is to increase our understanding of cardiovascular deconditioning caused by prolonged exposure to simulated microgravity. This includes developing methods for identifying novel biomarkers capable of characterizing and predicting the extent of induced deconditioning.
Initially, the deconditioning of cardiac electrical activity induced by microgravity, simulated by bed rest studies, was evaluated. Specifically, heart rate variability (HRV) and cardiac circadian rhythms of heart rate and ventricular repolarization, were studied in a large population of subjects undergoing head-down bed rest for different durations (5 to 60 days). Alterations of HRV indices were observed, including a trend of reduced time-domain and frequency-domain variability, decreased HRV complexity, and lengthened RR and QT intervals during HDT. This was reflected in a dampened amplitude of circadian oscillations of RR and QT intervals, which affected relevant HR regulation functions in response to the restoration of the gravity field at bed rest discontinuation. This led to impaired ability to compensate for the re-established gravitational condition as a consequence of the HDT, with shortened RR and QT intervals, impaired autonomic regulation, postponed circadian acrophase, and increased amplitude of circadian oscillations of the QT interval at bed rest conclusion, all indicators of a potential increase in arrhythmogenic risk. Additionally, prolonged exposure to microgravity produced changes in the temporal and morphological characteristics of ventricular repolarization and in its relationship with heart rate, eliciting a possible increased risk of developing life-threatening cardiac arrhythmias in predisposed subjects. Major changes were observed both at the beginning of the HDT and after bed rest discontinuation. In particular, a trend of dependence with HDT duration was observed, where longer HDT produced greater deconditioning upon gravity restoration.
Cardiovascular deconditioning developed during spaceflight additionally translates into reduced exercise capacity and increased orthostatic intolerance. The Head-Up Tilt test is used to study the response to postural changes in order to evaluate the level of microgravity-induced orthostatic intolerance. Similarly, a maximal exercise (VO2max) test is used to assess astronauts' post-flight performance. Variations of orthostatic tolerance and VO2max levels in astronauts have been analysed and quantified in literature with respect to their relationship with spaceflight duration. However, in the context of space research, no study has yet proposed prediction models aiming at estimating orthostatic tolerance and VO2max in a non-invasive way using ECG data only, prior to the exposure to a stress stimulus. Accordingly, machine learning approaches are developed to predict Orthostatic Tolerance Time (OTT) and VO2max levels based on features computed from beat-to-beat and trend time series extracted from 12-lead 24-hour Holter ECG recorded immediately before the day of OT and VO2max tests. Obtained results demonstrated the possibility to predict OTT based only on one Holter ECG acquisition performed the day before tilt test, with accuracy values of a-posteriori classifications of the predictions considered acceptable when compared with current techniques. Similarly, prediction of the VO2max was shown to be possible using Holter 24-h ECG data. The most interesting and accurate results were obtained when considering the estimated changes in VO2max in respect to its baseline value, before the beginning of the bed rest, also including the corresponding basal Holter 24-h data.
Cardiac activity is typically assessed through its electrical counterpart (i.e., ECG), while evaluating its mechanical counterpart traditionally requires the use of more complex and less portable analysis systems (i.e., imaging). Recent technological advances have led to the creation of wearable devices that integrate MEMS, specifically embedding inertial sensors such as accelerometers and gyroscopes. When positioned in contact with the chest, these miniaturized elements can sense the subtle vibrations in response to cardiac mechanical activity, resulting in the so-called seismocardiographic (SCG) signal. The aim of this work was to provide a robust method for extracting novel biomarkers of cardiac mechanical activity from SCG signals. This approach was first applied to study cardiac mechanical deconditioning caused by microgravity, simulated by long-duration HDT bed rest, by analysing short SCG acquisitions performed during a controlled breathing protocol. The study showed the possibility of capturing the changes induced by cardiovascular deconditioning in cardiac electromechanical activity through biomarkers that are relevant to both ultra-short-term variability of RR and novel morphological features extracted from the SCG signal. In particular, reduced peak-to-peak amplitude and slope were observed, possibly reflecting changes in contractile properties and stroke volume observed during HDT. Afterwards, the presented approach was applied to 24-hour SCG recordings obtained from normal volunteers. Obtained results constitute the first attempt to provide day and night normality ranges of the computed biomarkers in a normal population, providing evidence of the possibility of combining the more traditional evaluation of cardiac electrical activity by the ECG with the mechanical activity of the heart from the SCG, also evaluating their circadian changes, outside of the clinical setting using new wearable, user-friendly and non-invasive devices.
In conclusion, this work represents the largest attempt to identify and predict cardiovascular deconditioning resulting from microgravity exposure, exploiting traditional techniques as well as implementing innovative methods to assess novel and non-invasive physiological biomarkers of induced deconditioning. This appears particularly important as manned space exploration is now at a turning point, with NASA expecting to land the next person on the Moon by 2024, leading towards permanent human presence in cislunar space and preparing for crewed missions to Mars.