AEROSPACE ENGINEERING / ARCHITECTURAL, URBAN AND INTERIOR DESIGN / ARCHITECTURE, BUILT ENVIRONMENT AND CONSTRUCTION ENGINEERING / **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 / MECHANICAL ENGINEERING / PHYSICS / PRESERVATION OF THE ARCHITECTURAL HERITAGE / STRUCTURAL, SEISMIC AND GEOTECHNICAL ENGINEERING / URBAN PLANNING, DESIGN AND POLICY

PhD Yearbook | 2022

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 in healthcare, life sciences 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 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 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 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, 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 candidate can acquire further skills to develop his/her 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. As examples, 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).
The PhD Board of professors is composed by 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, formed by 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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DESIGN AND DEVELOPMENT OF AN RF-BASED SYSTEM FOR THE REHABILITATION OF THE UPPER LIMB

Walter Baccinelli - Supervisors: Prof. Carlo Albino Frigo, Prof. Maria Bulgheroni

Acquired disabilities are one of the major challenges the healthcare systems have to face. As the aging of the population increases, the number of persons with disability, the need of resources and effective tools to take care of impaired patients continuously grow. One of the leading causes of acquired disability is represented by stroke, and one its most impacting consequences is the impairment of the upper limb. The recovery of upper limb functionalities can be maximized through rehabilitation therapy and, in particular, through occupational therapy. While several technologies to strengthen the rehabilitation process in clinics are available, the current need of healthcare costs reduction calls for new solutions to support the patients in the continuity of the rehabilitation also at home. To face such needs, a new system, RehabMe, has been designed and developed. The system guides the patients in the execution of functional exercises, built as sequences of reaching and grasping tasks to be executed with everyday objects. The exercises creation process and the monitoring of motor performance and the guidance during the execution, represent the three core functionalities provided by the system. The RFID technology has been identified as a suitable way to implement such system. The development required a deep analysis of the potentialities and the limits of the RFID technology, and their mapping to the clinical requirements identified, leading to the design of a technical solution based on passive UHF RFID. The system design and implementation required an accurate analysis of the hardware components and the characterization of the system as a whole from the electronics and the ergonomics point of view. This process required several development, testing, and refinement steps, from the choice of the system components to their integration and refinement. The process resulted in a robust hardware device based on flexible electronics, with a shape and dimensions designed to be easily wearable on the forearm without discomfort, able to wirelessly communicate with clients, with enough energy to be used for a rehabilitation session. To fully translate the technological bases to a rehabilitation system, the RehabMe software platform has been developed. The software implementation included the development of a logic and a procedure to create custom exercises using an unconstrained set of objects. The basic actions of the reach and grasp exercises (i.e., reach, grasp, move, release) have been identified, and a suitable flow for their combination with the objects identified through the tag's EPC have been developed. Beside the creation of the exercises, a logic has been set for the administration of the therapy. An intuitive multimodal interface has been created to guide the patient in the exercise, while controlling in background the hardware device. The use of the RFID technology in an unexplored field of application required also a fine adaptation of the standards to the needs of the system. The investigation of the parameters used to perform the reader-tag communication impacting the reading performance has been performed, and a custom optimal reading strategy has been created through the analysis of the best combination of parameters. The optimization of the reading strategy severely reduced the power consumption, the batteries capacity and the heating of the device, while guaranteeing the capability to collect the tag's response with a rate sufficiently high to assure the stability of the process. Home-system are required to provide the clinicians data describing the performance of the patient. RehabMe inherently provides the basic description of the therapy course in terms of number of sessions performed and their distribution over time, as well as the total time, number of tasks accomplished, number of tasks skipped. Nonetheless, more informative parameters had to be extracted, to monitor the performance progression. To avoid the overload of the system through the addition of new sensors, a totally new approach has been adopted: the properties of the RF signal used by the system to recognize the objects and guide the execution of the exercises have been used also to extract motor performance parameters. The variations of the phase of the signal, in combination with the signal's power level, have been analyzed to extract the movement time of each task as well as the distance covered and the movement's velocity. The algorithms for the measures extraction have been implemented and tested against validated systems, showing the stability of the measures in laboratory settings. The clinical testing of RehabMe was aimed at evaluating its robustness and usability, as well as at assessing its capability of tracking the patient's performance evolution. A testing protocol has been designed, in which the patients underwent the execution of a set of exercises, designed in collaboration with the clinicians, administrated through RehabMe. A first round of tests has been conducted on 10 patients using the system for 3 sessions. This round was aimed at evaluating the system stability and acceptability. The SUS results showed that the overall system was perceived as highly usable. The need of few interventions by the operator, as well as no failures reported demonstrated the quality of the RehabMe approach. The perceived easiness of use highlights the potential impact of this system, that could overcome the current limitations in the translation of the rehabilitation provision from clinics to home settings. Indeed, providing a simple yet effective tool to provide exercises based on occupational therapy could enable a wide use of the technology by the population of post-stroke patients at large. The second round of the testing was aimed at evaluating the capability of the system to monitor longitudinally the performance of the patients. The measures extracted were validated against the analysis of the video recordings taken during the sessions' execution, showing that, even if the quality of the data was lowered in real-life conditions with respect to laboratory setup, the values were robust enough to provide reliable information on the execution performance, in line with the recovery trend measured through standard clinical scales. The implementation of RehabMe demonstrated a new approach to the technology-based motor rehabilitation of the upper limb through the use of everyday objects, unconstrained movements, and a single wearable device to provide evidence-based rehabilitation therapy. The results showed the effective translation of the RFID technology to the field of motor rehabilitation through a technology adaptation and tuning approach. The field testing of the full system demonstrated that the use of RFID well fits the needs for home-based rehabilitation systems, thanks to its robustness and easiness of use, combined with evidence-based principles for the provision of rehabilitation therapy. The use of RFID technology has also been used as a mean to monitor the performance and the progression of the patients during the rehabilitation path, through the extraction of the movement's execution time and velocity. The longitudinal testing preliminary showed the capability of tracking performance using these measures as extracted by RehabMe, but the low number of patients involved does not allow to draw final conclusions. Limitations in the signal quality in real-life scenarios resulted from the clinical testing, showing that a redesign of the antenna for the improvement of signal quality is needed, and that further advancement could be obtained by the integration of more information sources for the motion description.

FROM LOW FREQUENCY TO RADIO FREQUENCY: ASSESSMENT OF HUMAN EXPOSURE TO ELECTROMAGNETIC FIELDS BY DETERMINISTIC AND STOCHASTIC METHODS IN NEW AND HIGHLY VARIABLE REALISTIC EXPOSURE SCENARIOS

Marta Bonato - Supervisors: Prof. Paolo Ravazzani, Prof. Marta Parazzini

The recent years have seen a massive diffusion of man-made electromagnetic field (EMF) sources working at several frequencies, primarily thanks to the current technological innovations and the drastic changes in working and social habits. This trend seems not to stop, on the contrary, the recent deployment of 5th generation mobile networks has caused even more the diffusion of new devices and new infrastructures based on wireless communications. Although this process is relentless and contributes to bring benefits and utilities to the whole population, it is also causing an ever-increasing public concern about the possible health effects due to EMF exposure. This has induced the main International Organizations for health protection to encourage the scientific community to broaden the knowledge about the human EMF exposure assessment in order to guarantee a safe environment. With the multitude of factors that characterize more and more the realistic exposure scenarios, this also includes the necessity to investigate new methods for the quantification of this exposure variability in real environments.
To reach that goal, in the PhD dissertation the traditional computational approaches for EMF exposure assessment have been coupled also with innovative techniques derived from the stochastic dosimetry field. Indeed, computational electromagnetic techniques are mainly the most used methods for assessing the human exposure levels in body and tissues but, despite the progress in high-performance calculation, still require high computation times. For this reason, deterministic dosimetry usually assesses the exposure levels only for few specific scenarios, usually the worst-cases, providing no information about how the exposure changes in realistic and highly heterogeneous scenarios. To overcome this challenge, recently stochastic dosimetry has been proposed as a promising method to face the variability in the framework of real EMF exposure. Stochastic dosimetry uses statistical tools to obtain a surrogate model replacing the heavy numerical solver by analytical equations able to provide results very quickly. In this way, not only the variability of factors that characterize the exposure scenario can be considered, not limiting the analysis only on worst-case exposure scenarios, but it is also possible to perform a sensitivity analysis and to characterize the statistical variations of the output brought about by the variation in the inputs.
In the light of above, in this PhD dissertation two different open gaps about human EMF exposure assessment, that were worth to be further investigated, were identified, one at Low Frequency (LF) range and one at Radio Frequency (RF) range and both traditional and stochastic approaches were applied to study these issues.
The first topic in the LF range has been focused on the exposure assessment of children, i.e., the more susceptible category to EMF exposure, considering specifically power lines and domestic appliances as EMF sources. This topic has been widely studied in literature since it was found a possible correlation between the increased risk in childhood leukemia and long exposure to LF. However, the application of innovative stochastic approaches could bring an improvement of the characterization and quantification of children exposure also considering the variability of real EMF scenarios.
The second open gap was identified in the RF range exposure assessment, focusing on the recent deployment of 5G networks, which have been designed in order to meet the users' new needs such as data rate increase and low transmission latency. A new world of connectivity will then be possible, but it is also causing enormous changes in RF wireless networks, due to the involved innovation technologies (i.e. the use of mm-wave working frequencies, of MIMO antenna, of 3D beamforming techniques) and thus variations of RF human exposure levels. The 5G networks are then introducing more variability and heterogeneity in real exposure scenarios, plus this challenge is relative recent and there are still few literature studies that deals this topic. The application of deterministic methods coupled with stochastic approaches seemed then a theme that was worth to be further investigated in the framework of 5G networks and human exposure assessment.

The results showed, at both low frequency and high frequency ranges, exposure values significantly lower than the limits indicated by the International Commission on Non-Ionizing Radiation Protection (ICNIRP). Furthermore, more interestingly, the effectiveness and validity of different stochastic approaches were demonstrated. Indeed, stochastic dosimetry seems more and more a promising tool to broaden in future the knowledge on EMF exposure assessment, taking into account the increasing variability and heterogeneity that characterize the real world.
In conclusion, this dissertation provided analysis, novel stochastic methods, results and conclusions, that allowed to broaden the knowledge on human EMF exposure assessment, both at LF and at RF ranges.

ORGANS-ON-CHIP AS ADVANCED MODELS OF OSTEOARTHRITIS AND MECHANICALLY ACTIVE BODY DISTRICTS

Andrea Mainardi - Supervisors: Prof. Marco Rasponi, Prof. Ivan Martin and Prof. Andrea Barbero

Osteoarthritis (OA) is a degenerative joint disease particularly affecting load bearing articulations such as knees and hips and one of the most prevalent musculoskeletal pathologies. Knee OA alone is estimated to affect roughly 10% of men and 13% of women over the age of 60.
OA pathological alterations include cartilage degradation, chondrocyte assumption of a hypertrophic phenotype, vascular invasion and increased mineral content of calcified cartilage, and subchondral bone sclerosis and hypomineralization. The whole osteochondral unit (OCU) is affected.
Despite its diffusion, a successful OA treatment is still missing. Existing therapeutic choices are palliatives aimed at relieving symptoms rather than reversing the degenerative processes. This lack is associated, at least in part, with the absence of relevant preclinical OA models to better understand the pathological triggering factors and screen putative therapeutic solutions. The generation of representative OA models is however challenging given the difficulty of representing the multitude of tissues involved, as well as the natural mechanically active joint environment.
There is a case, in particular, for introducing a mechanical active environment in OA models since, while no consensus is present regarding OA origin, a clear correlation between the pathology and mechanical risk factors such as trauma, joint misalignment, and obesity has been demonstrated.
The necessity for more relevant preclinical models extends however beyond OA as indicated by the low efficiency of pharmacological innovation in general. The development of a new drug is estimated to require $ 2.8 billion and a time comprised between 10 and 15 years. Moreover, only 10% of compounds considered in phase I clinical trials reach the market. Organs-on-chip (OoCs) are microfluidic based devices aiming at recapitulating organ and tissue level functions in vitro. Allowing an increased control over the experimental environment, OoCs are gaining increasing consensus as disease analogues. Modelling pathologies affecting mechanically active body districts, such as the musculoskeletal apparatus or the myocardium remains however an open challenge.
In this framework, the present PhD work aimed, focusing in particular on OA, at exploiting OoCs principles and microfabrication techniques, together with tissue engineering, to develop disease relevant models of mechanically active tissues.
The final aim was subdivided into five subsections, each intended at delivering a specific technological or biological advancement.

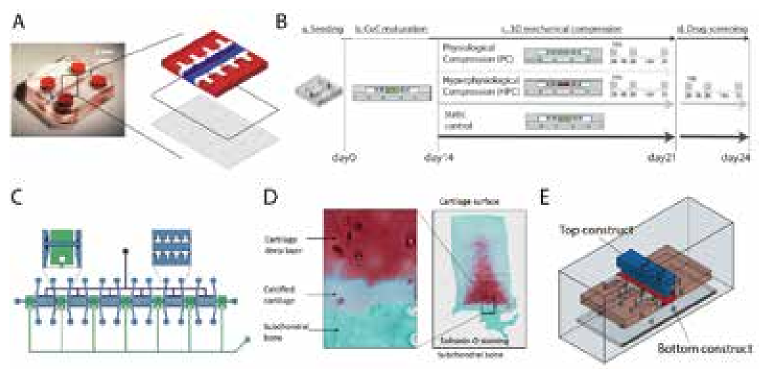

Fig. 1
Microfluidic-based osteoarthritis models. A Picture and schematization of the cartilage on chip model. The 3D cell laden hydrogel is represented in blue. B Timeline of the cartilage on chip model establishment and exploitation: from tissue maturation to drug screenings. C Mid-throughput mechanically active device layout. D Safranin-O staining of an OA osteochondral biopsy highlighting the tissues organization. E Biphasic joint-on-chip model. The two cellular constructs are represented in blue and red respectively

i) A mechanically active OoC platform capable of providing 3D constructs with physiological or hyperphysiological compression levels was designed (Fig. 1A), functionally validated, and exploited to achieve a healthy cartilage on chip (CoC) model rich in cartilage extracellular matrix constituents (e.g. collagen type II and aggrecan). OA traits were induced in this CoC model through the sole application of hyperphysiological compression. Specifically, the imbalance of catabolic and anabolic processes, the increased inflammatory state, and the hypertrophic phenotype characterizing cartilage in OA could be recapitulated. The model was also exploited to evaluate the response to known and innovative anti OA compounds (Fig. 1B).
ii) The adoption of OoCs as testing systems in drug screening campaigns depends on the achievement of a satisfactory experimental throughput. A platform capable of subjecting multiple independent 3D constructs to cyclical mechanical stimulation was engineered and functionally validated. Appropriately designed valves positioned between the different culture chambers allowed to inject multiple compartments with a single operation while assuring their independence during the culture period (Fig. 1C). The device was adopted to apply cyclical strain to cardiomyocytes-fibroblasts co-cultures, recapitulating some traits of cardiac fibrosis. The platform was then modified to make it suitable for the study of OA, shifting its mechanical stimulation from the stretching to the compression of hosted tissues.
iii) Cartilage and bone are examples of tissues with a hierarchical organization. During OA the whole OCU is affected leading to alterations in the mechanical properties of these tissues. A direct assessment of the mechanical, compositional and morphological alterations of the different OCU tissues of OA patients was performed. Indentation type atomic force microscopy (IT-AFM) was adopted to study OCU tissues mechanical properties at an OoC relevant sub-micrometre scale and differentiating between hyaline cartilage zones, calcified cartilage, and subchondral layers.
iv) While the whole OCU is affected by OA, most in vitro models are limited to the study of cartilage. Modelling physiologically relevant mechanical stimulation in other OCU layers remains a challenge.
To fill this gap, a new OoC platform enabling the provision of well-defined and discrete levels of mechanical compression to directly interfaced superimposed 3D microconstructs was engineered. A new microfluidic concept, the Vertical Capillary burst Valve (VBV) was introduced (Fig. 1 E). The VBV consents the vertical superimposition of two 3D cell-laden hydrogels and the spatially precise modulation of the strain field experienced upon compression by these two tissues which exhibit distinct levels of mechanotransduction signalling. The platform was then exploited to demonstrate that the loading response of cartilage-like constructs is modulated by local perturbations in the composition of acellular subchondral layers.
v) Finally, the culture conditions to obtain cellular microconstructs recapitulating multiple OCU layers were investigated. Primary human articular chondrocytes (hACs) and mesenchymal stromal cells (MSCs) were differentiated, respectively, in hyaline cartilage and calcified cartilage. A biphasic microconstruct integrating the two tissues was then achieved through a specifically designed OoC platform allowing a direct interface between two adjacent cell-laden hydrogels. The model was further integrated with a vascular compartment used to preliminary assess how endothelial cells influence MSCs differentiation. Lastly, providing spatially discrete mechanical compression to the obtained biphasic constructs, a preliminary evaluation of the effect of loading was performed.

GENERATION OF ADVANCED MUSCULOSKELETAL TISSUE MODELS BY INTEGRATING BIOFABRICATION AND COMPUTATIONAL TECHNIQUES

Valerio Luca Mainardi - Supervisors: Prof. Gabriele Dubini, Prof. Matteo Moretti, Prof. Chiara Arrigoni

The engineerization of human tissues is a very complicated process involving several steps that are strictly connected. However, to be able to study specific mechanisms of physiological and/or pathological processes, it is necessary to develop models that replicate the structural and functional properties of involved tissues. The strong crosstalk occurring among musculoskeletal tissues should be considered and the integration of multiple biological components in the same device should be achieved in order to realize reliable models.
In this work, biofabrication and computational simulation techniques have been combined to optimize some phases of the whole process towards the development of advanced musculoskeletal tissue models.
One possible approach of biofabrication of biological constructs consists in seeding cells on three-dimensional (3D) scaffolds that support cell proliferation and extracellular matrix (ECM) formation during the tissue development. In this case, cell seeding outcome influences all the subsequent phases. Thus, it is clear the crucial role of this step in the whole process. In chapter 2 an easy and effective approach to improve the efficiency of cell seeding performed using dynamic systems is presented. Specifically, extrusion-based 3D printing technology was applied to produce 3D scaffolds made of polymeric fibers that are characterized by a non-circular cross-sectional shape. These multilobed scaffolds were tested using an oscillating perfusion bioreactor and the number of adhered cells was compared using scaffolds characterized by standard cylindrical fibers as control. Computational fluid dynamic (CFD) simulations were performed to analyze the influence of multilobed fiber geometry on two different aspects: first, the path followed by cells flowing through the scaffold fibers was assessed to understand how the fiber shape modifies the cell trajectories; secondly, the distribution of fluid velocity and shear stress on scaffold fibers was evaluated to analyze their effect on adhered cells. The proposed multilobed approach resulted in a higher seeding efficiency on multilobed fiber scaffolds compared to circular fiber scaffolds due to a combination of fluid dynamic parameters that increased the number of cells reaching regions of the fibers more suitable for cell adhesion. As a consequence, the obtained results suggest that the reciprocal influence of geometrical and fluid dynamic features and their combined effect on cell trajectories should be considered to improve the dynamic seeding efficiency when designing scaffold architecture.
The growth and differentiation of several cell types are strongly dependent on environmental stimulation induced by fluid flow and/or mechanical stimuli. Thus, several types of bioreactors have been developed aiming at recreating the physiological stimulation required to obtain proper tissue maturation.
In chapter 3 the influence of fluid dynamic stimulation on bone tissue maturation is evaluated. Specifically, an extrusion-based bioprinting technology was applied to produce alginate and gelatin constructs embedding human mesenchymal stem cells (hMSCs). Bioprinted constructs were dynamically cultured using a perfusion bioreactor. The effect of flow-induced mechanical stimulation was assessed through CFD simulations, performed to evaluate the distribution of shear stress, fluid velocity and hydrostatic pressure on construct fibers. Obtained results demonstrate that stimulating the developing constructs with adequate stimuli can improve the level of tissue maturation and promote the development of bone substitutes suitable for clinical applications.
A strategy based on biofabrication to address the integration of multiple tissues is presented in chapter 4, where a novel mesoscale perfusable device was designed as a tool for the 3D bioprinting of a multi-tissue construct. Specifically, a muscle-tendon-bone interface model with a physiological architecture was bioprinted ensuring a structural and functional connection between the tissues. The optimization of the perfusable device allowed the stimulation of the bioprinted tissues with distinctive culturing conditions that can be adapted to the specific needs of involved tissues.
Only recently, the need of multi-tissue models is being considered with the proper attention taking into account all the aspects involved in the engineerization of human tissues, such as architectural, structural and functional connection and proper fluid dynamic and/or mechanical stimulation of involved tissues. In this regard, the work presented in this thesis represents an important contribution towards the development of advanced models for the study of all those physio-pathological mechanisms that involve multiple tissues.

IMPROVING RESPIRATORY SUPPORT OF PRETERM NEWBORNS BY BEDSIDE CHARACTERIZATION OF LUNG MECHANICS AND RESPIRATORY CONTROL

Valeria Ottaviani - Supervisors: Prof. Raffaele L. Dellacà, Prof. Emanuela Zannin

Preterm birth is defined as the birth before the 37th week of gestation. In infants born preterm, the last stages of lung development occur under very different conditions than in the intra-uterine environment, making them prone to develop respiratory system pathologies requiring respiratory support. Since even a few breaths of aggressive mechanical ventilation may alter the physiological development of the preterm lung, the selection of the best-suited ventilation strategy is crucial from the first minute of life. In recent years, non-invasive respiratory support modes have gained popularity in the Neonatal Intensive Care Units (NICU) to avoid endotracheal intubation and reduce ventilation-induced lung injury. Unfortunately, achieving good patient-ventilation interaction during non-invasive ventilation is challenging. In clinical practice, the main respiratory parameter used to monitor infants receiving non-invasive respiratory support is the peripheral oxygen saturation (SpO_2), or the fraction of inspired oxygen (FiO_2) needed to keep SpO_2 in the target range. However, an inadequate gas exchange may be due to several different factors. Therefore, the possibility to monitor other parameters would be valuable to guide and personalize the respiratory support strategy, including respiratory system mechanics, asynchronies, respiratory muscle activity (and fatigue), and central control of breathing.

The aim of this Ph.D. project was to improve the management of non-invasive ventilation in preterm infants. Specific objectives of this Ph.D. project included i) the development of novel tools for the assessment of different aspects of the respiratory function in preterm newborns receiving non-invasive respiratory ventilation, which may help disentangle the complexities of the pathophysiological mechanisms resulting in inadequate gas exchange, ii) the definition of criteria for surfactant administration based on the direct assessment of lung volume recruitment; iii) the assessment of the short-term physiological effects of a non-invasive ventilation strategy synchronized with and proportional to the neural breathing activity. The Ph.D. project lasted 4 years during which:

1) Pressure and volume accuracy delivered by mechanical ventilators currently employed in NICUs were evaluated;
2) The measurement of lung mechanics was included into a commercial ventilator already available at the bedside;
3) An in-depth video-based method based on structured infrared light was developed to monitor preterm breathing pattern inside the incubator;
4) A system based on a sensorized transesophageal catheter was developed to evaluate respiratory drive at birth with the simultaneous monitoring of lung mechanics;
5) A compact device able to acquire and store data from a mechanical ventilator continuously without interfering with clinical practice was developed, to perform offline analysis to evaluate the variability of breathing pattern by the analysis of long time series correlation properties.

These tools have been evaluated in-vitro, on animal models, and in in-vivo feasibility studies, then they have been employed to monitor infants' respiratory systems condition during two clinical studies.

During our studies, we found that pressure, flow, and volume signals measured by the ventilator may be inaccurate in case of incorrect maintenance of the ventilator. We found clinically significant errors in estimating the delivered tidal volume, which is critical during volume-target ventilation and that could become even more challenging during non-invasive respiratory support.

A compact system based on not-expensive RGB-D cameras has been developed and validated in-vitro to add to standard breathing parameters monitoring thoraco-abdominal movement evaluation that could show respiratory asynchronies. Measurements using the developed system were feasible in preterm infants receiving non-invasive respiratory support in a research setting. Further development is needed before this system can be used as a clinical tool, including the automatic selection of ribcage and abdominal points, the possibility to perform real-time analysis, and the field of view occlusion artefacts removal.

Lung mechanics is another important parameter to monitor during respiratory support and guide treatment. Lung mechanics were successfully measured in infants receiving invasive respiratory support. It is currently integrated into a commercial mechanical ventilator, and therefore, it is already a clinical tool available at the bedside. Respiratory system reactance has been successfully used during an observational study to define a threshold value that, combined with clinical criteria, may identify infants requiring surfactant or prolonged respiratory support.

The diaphragm's electrical activity provides a direct estimation of the infants' respiratory drive and can be accurately measured using a nasogastric tube with electrodes. This measurement is integrated into a commercial mechanical ventilator to deliver a ventilation mode synchronized and proportional to the infant's respiratory drive. Such ventilatory mode demonstrated lower inspiratory pressures and lower effort to generate the same tidal volumes, with a better patient-machine synchronization as compared to a synchronized intermittent mandatory ventilation. The combination of electrical diaphragmatic activity and lung mechanics can be very informative also to monitor the breathing effort of the patient and the respiratory control mechanisms used to establish an adequate functional residual capacity at birth or to dynamically maintain it during spontaneous breathing. The developed device based on sensorized catheter that allowed the evaluation of patient-machine synchronization during spontaneous breathing demonstrated to be reliable during a preclinical study and was successfully combined with lung mechanics evaluation performed by a self-made blower-based resuscitator achieving a more comprehensive understanding of mechanisms that regulate respiratory control after birth. The system has to be firstly tested during preclinical study and then transferred to the clinical setting.

The presence of breathing pattern variability indicates a mature respiratory control respiratory pattern demonstrated to enhance ventilation in heterogeneous lung. We proposed a method to acquire and study this variability based on Detrended Fluctuation Analysis (DFA), not much explored in the respiratory field yet, with a focus on the definition of an optimal period for the early change detection due to clinical intervention, with a first example of long-time monitoring on a patient without interfering with clinical practice.

In conclusion, these studies confirmed the feasibility of the methods developed during this Ph.D. project in preterm infants receiving non-invasive respiratory support allowing a more comprehensive understanding of the condition of their respiratory systems. Two studies were performed using the developed tools in a clinical environment.

The first one allowed the identification of a respiratory system reactance value that can be used in combination with clinical criteria for a more individualize surfactant administration and for the identification of preterm infants at high risk of prolonged respiratory support needs.

The second study compared the effect of two different ventilation modes on infants' breathing pattern, showing that an assisted proportional ventilation mode leads to lower pressure and effort to reach comparable volumes with less asynchrony breaths, with respect to a standard synchronized intermittent mandatory ventilation mode. Other studies are necessary to further validate the proposed tools and demonstrate the added value of including these tools in daily clinical routine.

SUPRASPINAL LOCOMOTOR NETWORK DERANGEMENTS: A MULTIMODAL APPROACH

Chiara Palmisano - Supervisors: Prof. Carlo Albino Frigo, Prof, Isaias Ioanni Ugo

The overarching goal of my research activities was to investigate the pathophysiological alterations of the supraspinal locomotor network at gait initiation (GI) in subjects with Parkinson's Disease (PD) and Progressive Supranuclear Palsy (PSP). My experimental work relied on a multimodal approach combining clinical, biomechanical, neuroimaging, and neurophysiological data, carried out in the context of a Joint-PhD between the Politecnico di Milano and the Julius-Maximilians-Universität Würzburg (Germany).

Gait and balance disorders are a major problem for patients with movement disorders and their caregivers, especially as related to falls and poor quality and quantity of life. Effective treatments for gait disturbances are lacking, probably as our understanding of the supraspinal locomotor network is still limited. My PhD studies aimed at expanding our knowledge of the supraspinal locomotor network and in particular the contribution of the basal ganglia to the control of locomotion, fostering the development of effective therapeutic strategies for gait in patients with movement disorders.

I focused my attention on one of the most common motor transitions in daily living, GI. It combines a preparatory (i.e., the Anticipatory Postural Adjustments [APA]) and execution phase (the stepping) and allows the study of movement scaling and timing as an expression of muscular synergies, which follow precise and online feedback information processing and integration into established feedforward patterns of motor control. GI is particularly interesting and a relevant paradigm to address balance and gait impairments in patients with movement disorders as it is associated with *Freezing of Gait* (FoG) and high risk of falls. FoG is a peculiar gait derangement characterized by a sudden and episodic inability to produce effective stepping, causing falls, mobility restrictions, poor quality of life, and increased morbidity and mortality. Between 50-70% of PD patients have FoG and/or falls after a disease duration of 10 years, only partially and inconsistently improved by dopaminergic treatment and Deep Brain Stimulation (DBS). Treatment-induced worsening has been also observed under certain conditions.

Despite several studies aimed at identifying the biomechanical alterations of GI in PD, results are controversial. The influence of confounding factors (i.e., anthropometric measurements, initial stance condition, medication condition and cues) on motor performance has consistently been neglected and may constitute the grounds for the poor agreement on the topic in the scientific literature. The first step of my work was the design of a novel approach to record and analyze GI, minimizing the influence of confounding factors on outcome variables without influencing subjects' motor performance. The experimental setup and pipeline for the data analyses designed in my PhD studies might provide useful guidelines for further studies on the GI assessment of both healthy subjects and patients.

In the study of GI, neuroimaging data were a fundamental contribution, as they opened an observational window on brain region dysfunctions allowing the connection between the altered motor resultants and their primary cause (i.e., neurodegeneration of specific areas). By applying a multimodal approach that combines biomechanical assessments and neuroimaging investigations, my work unveiled the essential contribution of striatal dopamine to GI in patients with PD. Results in patients with PSP further supported the fundamental role of the striatum in GI execution, revealing correlations between the metabolic intake of the left caudate nucleus with several GI measurements. My analyses also unveiled the interplay of additional brain areas in the motor control of GI, namely the Thalamus, the Supplementary Motor Area (SMA), and the Cingulate cortex.

Involvement of cortical areas was also suggested by the analysis of GI in patients with PD and FoG. Indeed, I found major alterations in the preparatory phase of GI in these patients, possibly resulting from FoG-related deficits of the SMA. Changes in the weight shifting preceding the stepping phase were also particularly important in PD patients with FoG, thus suggesting specific difficulties in the integration of somatosensory information at a cortical level. Of note, all patients with PD showed preserved movement timing of GI, perhaps indicating preserved and compensatory activity of the cerebellum. Postural abnormalities (i.e., increased trunk and thigh flexion) showed no relationship with GI, ruling out an adaptation of the motor pattern to the altered postural condition.

In a group of PD patients implanted with DBS, I further explored the pathophysiological functioning of the locomotor network by analysing the activity of the Subthalamic Nucleus (STN) during static and dynamic balance control (i.e., standing and walking). For this study, I used novel DBS devices capable of delivering stimulation and simultaneously recording Local Field Potentials (LFP) of the implanted nucleus months and years after surgery. I showed a gait-related frequency shift in the STN activity of PD patients, possibly conveying cortical (feedforward) and cerebellar (feedback) information to mesencephalic locomotor areas. Based on this result, I identified for each patient a Maximally Informative Frequency (MIF) whose power changes can reliably classify standing and walking conditions. The MIF is a promising input signal for new DBS devices that can monitor LFP power modulations to timely adjust the stimulation delivery based on the ongoing motor task (e.g., gait) performed by the patient (adaptive DBS).

These new DBS sensing devices would allow to study patients in ecological and domestic settings. Still, precise laboratory evaluations remain necessary and an essential part of neurophysiological studies of the supraspinal locomotor network. It is therefore critical to develop new and more reliable setups for objective multimodal recordings of gait disturbances. Only in this way we will be able to describe the exact and distinctive pathophysiological derangements of each symptom (e.g., FoG) in the context of a more general network disorder, and then use this information for proper restorative neuromodulatory therapies. With this aim, during my PhD years I supervised a student for a Master thesis at the Politecnico di Milano for the validation of a fully immersive experimental virtual reality (VR) setup developed to study gait modulation. In collaboration with the colleagues of the Department of the Human-Computer Interaction of the University of Würzburg, we created a VR environment with a virtual agent (VA) programmed to cross the trajectory of the patient in a standardized manner. This consistently induced a modulation of gait speed or its interruption and reprise, which are, together with GI, the most likely context for the occurrence of FoG and falls. Preliminary recordings were very promising: the VR setup was able to induce gait *freezing* episodes otherwise not present in real-life gait.

Altogether my achievements allowed to define the role of different cortical and subcortical brain areas in locomotor control, paving the way for a better understanding of the pathophysiological dynamics of the supraspinal locomotor network and the development of tailored therapies for gait disturbances and falls prevention in PD and related disorders.

We are just at the beginning of a fantastic new journey in the field of neuroscience and neuromodulation that will lead to fundamental discoveries about the human brain and to improve the quality of life for many patients with motor disorders.

TOWARDS THE DEVELOPMENT OF PHYSIOLOGICAL MODELS FOR EMOTION AND STRESS ASSESSMENT

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In the last decades, there has been a growing interest in evaluating stress and emotions using physiological signals. Stress and emotion recognition have promising applications in several fields, including health, human-machine interaction, and marketing. In particular, there is strong evidence that high levels of chronic stress and negative emotions may severely affect life quality, facilitating burnout and increasing cardiovascular risk. Therefore, monitoring personal stress and emotional state is essential to promote healthier lifestyles and reduce abrupt performance drops in critical work environments (e.g., hospitals). Physiological signals, such as electroencephalography (EEG), electrocardiography (ECG), and photoplethysmography (PPG), are envisaged as means for the objective assessment of individuals' stress levels and emotions.

However, emotion and stress evaluation through physiological signals requires the definition of robust models to relate the individual's physiological response to the experienced emotions or stress level. Moreover, their monitoring in daily life requires the adoption of wearable devices that can accurately measure the signals of interest. This Ph.D. dissertation aims to evaluate the physiological response to different emotions and stress levels, select the most sensitive features to stress and emotional variations, and develop physiological models for emotion recognition.

In a first study, we applied linear mixed-effects regression models (LMM) to select the most valuable EEG features to predict valence and arousal responses from a set of emotional pictures. Pictures were selected from the International Affective Picture System (IAPS) and presented to a sample of healthy adults. Our feature selection procedure based on LMM proved accurate for choosing EEG indices that show higher explanatory power of valence and arousal scores. We confirmed the importance of frontal-theta power and frontal-alpha asymmetry for the assessment of the valence dimension and the major role of delta and theta rhythms in evaluating perceived arousal. Moreover, since we opted for mixed-effects models, we could separate individual-level (i.e., related to each participant's characteristics) from population-level effects (shared among participants). Our final valence and arousal models achieved notable values of conditional R-squared ($R^2_c \geq$ 0.839) but poor marginal ones (0.004 $\leq R^2_m \leq$ 0.021), indicating that most of the model likelihood was explained by individual-level effects and pointing out the high subjectivity of the elicited physiological response. Different standardization techniques can be used to improve the generalizability of these models and increase their applicability in emotion recognition applications.

In a second study, we compared three algorithms for quantifying respiratory sinus arrhythmia (RSA), a well-known marker of vagal activity, to select the most sensitive to stress variations. Among the tested algorithms, the Porges' one and the univariate autoregressive (AR) approach derive the RSA from heart rate variability (HRV). In contrast, the bivariate AR analysis exploits both HRV and respiratory signals to automatically detect cardio-respiratory interactions and estimate the RSA based on the individual's respiratory frequency. The comparison was conducted in a sample of healthy preschoolers undergoing a validated stressful procedure, which allowed us to evaluate the performance of the different methods in a more natural context, given the spontaneous behavior of children. Our results showed that bivariate methods produce significant improvements to stress detection. The average RSA variation measured between the least and the most stressful protocol phases significantly differed among the methods (Porges: -17.5%; univariate AR: -18.3%; bivariate AR: -23.7%), indicating the bivariate AR approach as the most sensitive to the induced stress variations. Thus, bivariate methods can provide more accurate measures of stress, especially in more natural contexts, when respiratory rate changes are more likely, and the choice of a predefined breathing frequency range is unfeasible.

In a third study, we analyzed HRV patterns during the elicitation of the so-called *flow* state, a highly functional condition linked to increased motivation, effort, and perseverance. Our principal aim was to select time-, frequency-domain, and non-linear HRV features predictive of this particular cognitive and emotional experience. Maximizing flow in work environments can improve productivity, shield from burnout, and sustain coping with job-related stress, which explains the recent growing interest in HRV features that may act as markers of flow intensity. In our study, the flow state was elicited through arithmetical tasks of optimal difficulties. The HRV features extracted during these tasks were compared with those computed during the administration of suboptimal difficulty tasks (i.e., too easy or too hard). Our analyses revealed HRV features that might be more promising markers of flow. Specifically, some non-linear HRV indices, namely SD2 and the approximate entropy (AppEn), were found to vary significantly with the intensity of perceived flow. Interestingly, the variations of AppEn were found independent of time, suggesting this could be a robust marker of the flow experience for long monitoring sessions. Among time-domain features, the average, standard deviation, and root mean square of successive differences (RMSSD) of the RR intervals were found to significantly discriminate the too easy from the optimal difficulty task (i.e., the one that elicited the highest flow).

Finally, we assessed some currently available wearable devices to be employed for stress and emotion monitoring. Our aim in this direction was twofold. First, we compared several HRV features extracted from an ECG-shirt and a PPG-wristband with those derived from a standard ECG. Second, since many wearable devices rely on low-sampling rate PPG for heart rate measurement, we investigated the efficacy of various PPG interpolation strategies on the accuracy of the extracted HRV at different sampling rates. Concerning the former objective, we highlighted current limitations on the use of PPG-wristbands for stress monitoring. Specifically, our analyses confirmed the accuracy of the HRV measures provided by the ECG-shirt, which were highly comparable with those extracted from the reference ECG. On the contrary, PPG-derived inter-beat intervals (IBIs) and HRV indices significantly differed from the reference. The largest deviations were observed with participants staying in an upright position, as partially expected due to the reduced skin adhesion of the PPG sensor. However, the percentage of missing beats was considerable (higher than 16%) even during protocol phases where participants were seated, and the contact between sensor and skin was maximized. Concerning the second objective, our study supported the efficacy of spline and parabola interpolations to improve the accuracy of the HRV extracted from low-sampling rate PPG. Specifically, we showed the importance of interpolating PPG signals sampled at 32 Hz or lower rates to improve HRV estimates.

In conclusion, the present Ph.D. thesis provides the following main contributions to the development of models for the evaluation of stress and emotions: (1) it shows the added value of applying mixed-effects modeling strategies to EEG-based emotion recognition; (2) it substantiates the higher reliability as stress markers of bivariate RSA measures compared to univariate ones; (3) it reveals several HRV indices, especially non-linear ones, highly sensitive to variations of the flow experience; (4) it highlights current limitations of using PPG signal for HRV assessment and proves the efficacy of different interpolation strategies to compensate for the discretization error introduced by low PPG sampling rates.

ERGONOMICS OF OCCUPATIONAL EXOSKELETONS: EVOLVING DESIGN AND ASSESSMENT METHODOLOGIES OF PHYSICAL ATTACHMENTS

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Work related Muskoskeletal disorders (WMSDs) undermine safety and wellness of workers and companies productivity. Annually, there is a growing impact of WMSDs due to the ageing working class, that is more related likely to develop a WMSD for working longer in physical wearing tasks (e.g. manual material handling, over-head assembly and un-ergonomic static postures). Ergonomics guidelines are a mitigation strategy to reduce the risk of injury and often results in limitations of weights or task frequencies. Industrial automation is a viable solution to address the problem and relieve the strain from the workers. However, unstructured workplaces, high costs, failsafe plans to ensure continuous availability of the services and social consequences do not encourage investing in high-level automation. Occupational wearable robots rise as a feasible alternative solution to address WMSDs. Wearable assistive robots, or exoskeletons, can be regarded as a parallel kinematic chain secured to the biological kinematic chain (limbs and articulations) of the users. The scope of an exoskeleton is to unload biological joints from physical overload (or stress) resulting from repetitive and un-ergonomic tasks.

Nevertheless, adoption from the end-users (workers) is low. A key factor to improve acceptability is to improve ergonomics of the wearable assistive robots designed for industrial tasks (hereinafter referred to as occupational exoskeletons (OEs)). Exoskeletons' ergonomic can be affected by these factors: (i) efficiency and modalities of assistive force delivery, (ii) body segments where assistance is unloaded and (iii) hindrance to users' movements. All these three effects are mostly part of the physical attachments' domain. Here, we refer as physical attachments to any cuffs, braces, garments or harnesses that secure exoskeletons to user's limbs. The state-of-the-art physical attachments relies on design from orthotic devices, protective or sport equipment. However, those designs can fail to satisfy both freedom of movement and a secure fit on all movements. Therefore, OEs may not deliver assistance forces efficiently or comfortably while permitting complete freedom of movement to their users. To this end, the overall aim of my thesis is to investigate the influence of physical attachment's design on an OE's physical ergonomics, as a matter of physical comfort and force transmission efficiency, through kinematic and kinetic simulations and experimental approach.

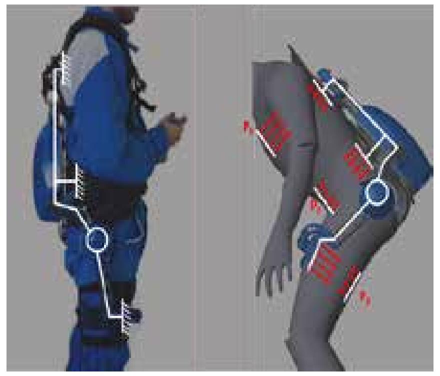

Fig. 1
On the left, the XoTrunk OE worn by the user with an overlapping simplified mechanical representation. On the right, the exhange of forces and pressures over the body.

The practical investigation of force transmission efficiency focused on the effects and sources of un-ergonomic and unpredictable forces F_{unergo} and torques T_{unergo} at the attachments. Indeed, any unpredictable and unwanted force or torque created as a reaction to mechanical constraints may lower transmission efficiency by: (i) induced drifts from the ideal body anchor area and (ii) elastic or plastic deformations of the attachments. As mechanical constraints are mainly correlated to human body dimensions and shapes variability, a Human in the loop (HIL) simulation approach was developed and experimentally assessed, to account inter and intra subject variability. Simulations were run imposing the body area that are the best suited to bear the exoskeleton's assistance, varying body measurements and postures. Qualitative and quantitative results from kinematic simulations indicate the influence of different anthropometrics and different movements on exoskeleton performance, showing a correlation between simualted Funergo and Tunergo when any of the OE's joint is saturated. Kinematic simulation of XoTrunk, a trunk OE fully developed at Istituto Italiano di Tecnologia (IIT), joints configuration showed saturation of one of the joints up to the 90% of one the movements due to *Boundary* singularities.

The *Boundaries* singularities occur when a kinematic chain is stretching outside its working space, entailing that the exoskeleton is not well suited to follow all users' movements for any body dimension of a subject in working-age population. Kinetostatic simulation and the experimental data show that up to 20% of the nominal assistive force is dissipated because of forces F_{unergo} and torques T_{unergo} .

My work also consisted in the ergonomic design process and realization of braces for XoTrunk, using a User-Centered Design (UCD) approach to guide developments aiming to promote exoskeleton's acceptance. Prototyping phases are of a paramount importance to experimentally assess the models developed and, then, to improve the design through experimental validation. Custom metrics and subjective tools, based on state-of-the-art guidelines for surveys in the wearable devices field, were developed and then validated through formative evaluation tests to meet the requirements of unambiguity, good wording and correct score system. Custom metrics and surveys were essential to measure the users' subjective comfort of physical attachments. The surveys, once validated, has been administered to subjects in an experimental campaign to test the effects on comfort of a proper *static fit*. The regulations (e.g. webbings glides and buckles) to achieve *static fit* were defined on a minimum set of anthropometric measurements to match subject and exoskeleton

Fig. 2
Images from one of the field test in food processing plant. The OE was used in the warehouse section of the company. The custom surveys collected subjective effects regarding physical ergonomic of our XoTrunk.

dimensions. During experimental tests, survey items determined the influence of such regulations on physical ergonomics. Results showed, in descriptive statistics, that all the male and female subjects experienced an improvement of physical ergonomics dimensions of *Perceived pressure*, *Attachment stability* and *Freedom of movement*. Those three dimension are related to the concept of *static fit* for a wearable device: the alignment between dimensions of the human and the wearable device in one or a small number of predefined posture.

All the developed simulations and survey tools are tested on different prototypes of the attachments for a back-support exoskeleton in the scope of the sponsored project IIT-INAIL "Sistemi Cibernetici Collaborativi". Indeed, this project supported the further developments of active occupational exoskeletons to address the problem of work related muskoskeletal disorders at the lower-back and at the shoulders. In addition, experimental campaign were run as pilot field application with several companies involving different stakeholders (i.e. RSPP, companie's managerial boards and employees) to promote exoskeletons as new tools for enhancing workers' safety and wellness.