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

PhD Yearbook | 2025

Chair:
Prof. Raffaele Dellacà

DOCTORAL PROGRAM IN BIOENGINEERING

The main objective of the PhD Programme in Bioengineering is to provide candidates with high-level engineering problem-solving skills in biomedical, healthcare, and life sciences. This is achieved through intense transdisciplinary training, bridging engineering with medical and biological knowledge.

During the PhD, the candidates undertake a scientific research project addressing a complex problem at various scales, ranging from the molecular and cellular levels to living organisms and biomedical systems. They explore original methods, devices, and systems with different purposes, including expanding scientific knowledge, developing innovative diagnostic and therapeutic methods and techniques as well as improving healthcare and daily life structures and services. At the end of the programme, candidates are expected to be capable of leading innovative research and development projects in Bioengineering, proposing new methodological and technological solutions, and assessing their impact on healthcare, life sciences, and the biomedical industry.

The PhD candidates conduct their research through both theoretical and experimental activities in four major areas: biomimetic engineering and micro-nano technologies; rehabilitation engineering and technology; technologies for therapy; and 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 structured across multiple departments. Faculty members of the PhD Board belong to two departments at Politecnico di Milano: the Department of Electronics, Information, and Bioengineering (DEIB) and the Department of Chemistry, Materials, and Chemical Engineering (CMIC).

Each year, around 50 PhD candidates carry out their research in experimental laboratories at Politecnico di Milano or in collaboration with prestigious national and international universities, biomedical research centers, hospitals, and industries. At Politecnico di Milano, PhD candidates are usually developing their research in one of the following laboratories: the Laboratory of Biological Structure Mechanics, the Laboratory of movement analysis "Luigi Divieti", the Medical Informatics Laboratory, the Neuroengineering and Medical Robotics Laboratory, the Biosignals, Bioimaging and Bioinformatics Laboratory, the Biomaterials Laboratory, the Biomedical Technology Laboratory (comprising CartCas Lab, Lares Lab and TechRes Lab), the Experimental Micro and Biofluid Dynamics Laboratory, the Computational Biomechanics Laboratory, the Biocompatibility and Cell Culture Lab, and the Bioreactors Laboratory. Additionally, the Institute of Electronics, Computer and Telecommunication Engineering (IEIIT) of the National Research Council (CNR), located within DEIB, offers further research opportunities.

International research stays are a key component of PhD training. Candidates are encouraged to spend at least three months conducting research in collaboration with internationally recognized institutions, particularly abroad, in laboratories that complement and enhance their research projects. The programme already has strong collaborations with numerous national and international academic institutions, research centers, companies, and clinical partners, ensuring effective technology transfer from applied research to biomedical devices and clinical applications.
The educational syllabus includes tailored advanced courses specifically designed for Bioengineering PhD students, aimed at deepening methodological and technical expertise while also fostering essential soft skills for researchers. The programme also includes participation in the annual one-week School of the National Bioengineering Group in Bressanone-Brixen (BZ).
Additionally, the PhD Programme in Bioengineering benefits from an Advisory Board made up of distinguished experts from R&D industries, research centers, and clinical institutions. This board ensures that the programme aligns with the needs of both academia and the broader professional world.

COMPOSITION OF THE PHD BOARD

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ALIVERTI	Andrea	DEIB
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DE MOMI	Elena	DEIB
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VOTTA	Emiliano	DEIB

STRESS RESPONSE ASSESSMENT BY MULTIPARAMETRIC ANALYSIS AND WEARABLE TECHNOLOGIES

Beatrice De Marchi - Supervisor: Andrea Aliverti

According to the American Institute of Stress, stress affects one-third of the global population, with significant connections and implications on several health problems and beyond. Despite its impact, several conceptual and methodological dimensions of stress as a biomedical phenomenon remain unclear and unsettled.

Stress effects change between acute and chronic phases (**Fig. 1**) and the response to this event is expressed in very different ways among different individual people. This makes it difficult to provide a standard definition and identification procedure.

As a result, currently there is no commonly accepted definition of stress, which creates an uncertain basis to build standard stress level assessment and measurement methods.

As a response to these issues, in recent years new technological and methodological solutions have been proposed for stress research. For instance, wearable devices that can be worn directly on the body and collect large volumes of data on physiological parameters are envisioned as potential game changers in the field.

This Thesis aims to advance the state of the art in the field of stress response assessment, by developing a multiparametric wearable acquisition platform able to acquire the main physiological signals relevant for the stress response and by providing a multifactorial analysis of stress-related features both in controlled and in real-life contexts.

The starting point for the development of the wearable acquisition platform was represented by L.I.F.E. Italia's medical-grade wearable platform called *Healer*, presenting a centralised acquisition logic and a data logger able to acquire each physiological signal with its own acquisition frequency.

The core of this wearable platform is represented by a sensorized vest (the *Healer R2*) able to acquire continuously and synchronously, among the others, two physiological signals relevant for the stress response: a 6-standard-lead ECG signal, acquired at 500 Hz by using 4 ink-based dry electrodes, and a 3-channel respiratory signal, acquired at 50 Hz from strain circumferential sensors placed at the thoracic, xiphoid, and abdominal levels.

Starting from this wearable platform, two additional physiological signals relevant to the stress response were integrated. The Galvanic Skin Response (GSR) was incorporated through the development of the so-called *GSR Thimble*, which acquires an 8 Hz GSR signal using the exosomatic method with direct current, the most used in literature for skin conductance measurements.

The photoplethysmographic (PPG) signal was integrated through the development of the *PPG Headband*, which acquires a 250 Hz signal through the use of an optical module. The added value of having both the PPG and ECG signals within the same wearable platform is the ability to apply the *time-delay* method for continuous and cuffless estimation of blood pressure (BP) values. The main advantages of the proposed wearable platform (**Fig. 2**) are that each physiological signal is acquired with its proper acquisition frequency by a common microcontroller and a data logger.

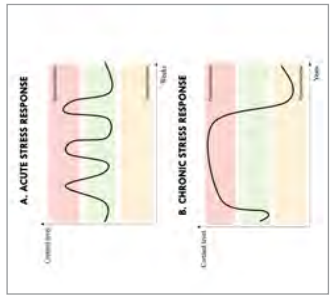

Fig. 1 - Acute (A) and chronic (B) cortisol stress response over time.

A tailored controlled-context ultra-short-term validation protocol was used to demonstrate the effectiveness of the proposed wearable platform for stress-related applications, through five rest and task-induced stress phases: *Rest*; *Low Stress*; *Moderate Stress*; *High Stress*; *Recovery*. A population of 40 healthy subjects was enrolled.

Feature extraction algorithms allowed to extract for each subject in the dataset, and for each protocol phase, stress-related features from the involved physiological signals: HRV time and frequency domain features were extracted from the ECG signal; time and amplitude related features were extracted from the three respiratory channels; tonic and phasic component features were extracted from the GSR signal; morphological features were extracted from the PPG wave.

A multifactorial statistical analysis of stress-related features was performed, in order to understand both the minimum number of physiological signals necessary for a complete stress response assessment and the different role of each signal in characterising the response itself. Statistical analyses of the extracted physiological signal features serve the dual purpose of identifying necessary physiological signals required for a comprehensive stress response analysis and discerning the distinct contributions of each signal in delineating various aspects of this response. The findings highlighted the importance of a multi-parametric approach for an accurate stress response assessment, with statistically significant features coming from all four considered physiological signals. Undoubtedly, the GSR signal can be considered the most relevant signal for assessing the stress response. Alongside GSR, the PPG signal also makes a substantial contribution.

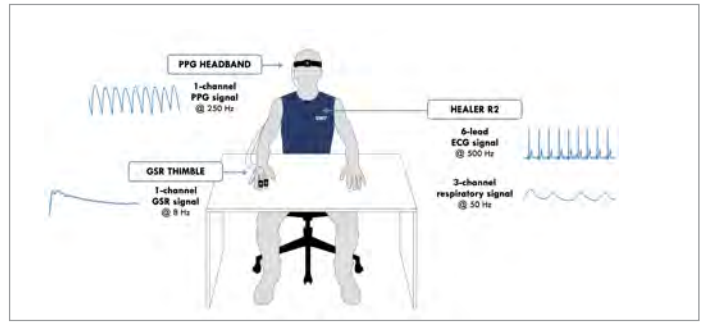

Fig. 2- The proposed wearable acquisition platform.

As a first step towards the application of the proposed wearable platform in real-life scenarios, a dedicated validation protocol was proposed to assess both the usability of the platform and the quality of the acquired physiological signals beyond controlled contexts. Based on the positive results obtained, future developments will focus on extracting stress-related features within this real-life scenario and developing stress-level classification models.

Furthermore, part of this Thesis targeted the ethics of wearables for stress by applying an ethical framework based on the normative principles of bioethics (beneficence, non-maleficence, autonomy, justice). This led to innovative results that fill in the gap of current discussions on wearable technology and stress.

A NOVEL APPROACH FOR AQUATIC GAIT ANALYSIS USING WEARABLE INERTIAL AND HYDRODYNAMIC PRESSURE SENSORS

Cecilia Monoli - Supervisors: Jeffrey A. Tuhtan, Manuela Galli, Alessandro Colombo

Aquatic physical therapy is crucial for rehabilitation due to water's unique properties of buoyancy, hydrostatic pressure, and resistance. Traditional motion analysis techniques, such as optoelectronic systems and infrared cameras, struggle underwater because of electrical and imaging limitations, while portable IMU devices, with their compact and waterproof design, offer a promising alternative. However, our understanding of the impact of aquatic physical therapy on quality of life and motor skills remains limited, underscoring the need for water-specific technologies and methodologies.

This Ph.D. thesis addresses these gaps by developing, testing, and validating a novel method to measure aquatic motion using wearable inertial and hydrodynamic pressure sensors. The research is structured around four research objectives (RO).

A comprehensive literature review (RO1) established the state-of-the-art in aquatic motion analysis with an emphasis on wearable technologies. Using a PRISMA workflow, the review revealed that the most common methods for aquatic motion analysis include dynamometers, force plates, and motion capture systems. Analysis of the 23 (out of 572) papers that used wearable devices for aquatic motion analysis uncovered four primary gaps: (1) lack of standardized clinical protocols for aquatic motion analysis; (2) insufficient whole-body coverage using IMU devices; (3) absence of longitudinal studies monitored by wearable devices; and (4) the over reliance on land-based measurement and assessment methods. RO1 highlighted a significant deficit in evidence-based approaches and water-specific protocols.

To overcome these issues, RO2 focused on developing and validating a method based on Inertial Measurement Unit (IMU) sensors for both overground and aquatic motion analysis. An initial proof-of-concept study compared an IMU prototype against an optoelectronic system (Vicon-460) and a marker-based motion-capture system (Sony Alpha A5000 and Kinovea software), both on land and in water. Two sensors were placed on the shank and thigh of the right leg, near the center of mass, to analyze gait and estimate knee joint kinematics, demonstrating strong reliability and portability ($r > 0.8$ on land, 93% accuracy in water).

An improved version of the sensors, integrating inertial and pressure sensors (PIMU), was later tested against an optoelectronic system (BTS Bioengineering) to evaluate temporal gait and knee joint parameters. Sixteen healthy young adults participated (9 F/7M). Using the Outwalk protocol, with 3 PIMU sensors placed on the right lower limb (thigh, shank, and foot, Figure 1), gait analysis achieved a root-mean-square error for stride of ~3% of the gait cycle.

The sensors were further applied in a clinical trial to compare walking gait on land and in water (RO3). Subjects (same participants of RO2, following the same testing procedure) performed 10 walking tests, which revealed greater variability in gait parameters in water (coefficient of variation 60.57%) compared to land (31.02%). A pilot study on backward aquatic walking further confirmed the flexibility and reliability of the PIMU sensors, though the parameters' variability suggests that standard kinematic parameters may not fully capture underwater motion.

RO4 focused on exploring the lateral hydrodynamic pressure on the lower extremities (Figure 2) during aquatic gait to provide deeper insight into the interaction between the body and the water. During the stance phase, up to approximately 40% of the cycle, near-zero z-scored pressure was recorded at all sensor locations. Around mid-stance (40%), the pressure on the shank began to decrease as the contralateral leg swung and the leg moved upward, while the pressures on the thigh and foot remained relatively constant until 50% of the cycle, corresponding to the heel-off phase. After 50%, as the limb moved closer to the water surface during the swing phase, the pressure decreased – with the most marked reduction at the foot, moderate changes at the shank, and minimal changes at the thigh. In the final phase of the gait cycle (80-100%), pressure steadily increased as the leg moved away from the water surface in anticipation of heel strike. Notably, the variation of hydrodynamic pressure at the foot (39.65%) was comparable to that measured for the knee angle on land (31.20%), suggesting that hydrodynamic pressure could serve as a reliable metric for describing aquatic walking by capturing the interaction between the submerged body and the surrounding fluid.

Despite the significant contributions of this work to aquatic motion analysis, limitations remain. The study involved a small sample of healthy young adults, used a fixed-depth pool, relied on single-limb sensor placement, and focused on planar knee motion. Future research should expand to include diverse aquatic exercises, pathological populations, bilateral sensor setups, refined processing algorithms, and subjective assessments of comfort and fatigue.

This dissertation ultimately addresses the limited availability of wearable monitoring methods for aquatic motion analysis and the predominant reliance on land-based parameters. By introducing new insights and methodologies—particularly the use of hydrodynamic pressure on the lower extremities as a novel metric—it advances our understanding of aquatic locomotion. The developed wearable inertial technology, combined with hydrodynamic pressure measurements, has proven to be a versatile and reproducible method for aquatic gait analysis. This work offers a more nuanced understanding of how water influences movement and holds potential to inform the development of future aquatic rehabilitation protocols.

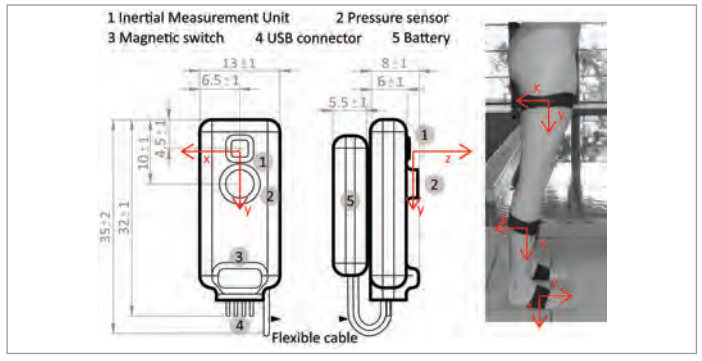

Fig. 1

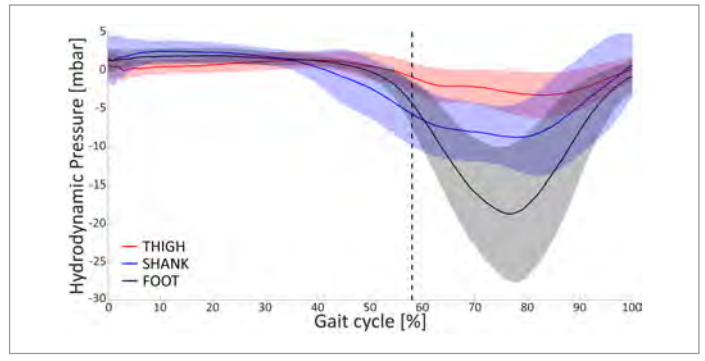

Fig. 2

TARGETED APPROACHES TO PROMOTE REPAIR AND REGENERATION IN EPITHELIAL LUNG DISEASES

Camilla Predella - Supervisors: Silvia Farè, Nicolino Valerio Dorrello

Respiratory diseases are a major global health issue, with a 38.9% increase in prevalence since 1990. Over 4 million of patients die annually worldwide. Key diseases include asthma, COPD, acute lower respiratory tract infections, lung cancer, and tuberculosis, collectively affecting over 1 billion people. A spectrum of end-stage lung disease, including cystic fibrosis, surfactant deficiencies, and acute respiratory distress syndrome (ARDS), frequently target the lung epithelium, necessitating lung transplantation as a primary definitive treatment. Lung transplantation faces challenges like low survival rates and organ shortages, with a five-year survival rate of 55% and high mortality rates while awaiting transplantation. One alternative solution can be cell therapy to treat the disease *in situ* and avoid the need of transplantation.
In the field of bioengineering and regenerative medicine in pulmonology, the studies outlined in this thesis for the first time showed that targeted approaches, in which only the dysfunctional cells or the whole epithelium of a specific region are removed and replaced with therapeutic cells *in vivo*, try to re-establish alveolar homeostasis to halt or reverse an injury or the disease progression. This thesis work has the potential to significantly advance our understanding of lung repair and regeneration and to develop new modalities for treating lung disease. The thesis investigates two distinct approaches, each using a different animal model, within the main scope of designing conditioning strategies to support lung repair *in situ* though endogenous or exogenous cells.

In Vivo De-Epithelialization in a Rat Model: Regional de-epithelialization (**Fig. 1**) was achieved using a mild detergent solution, selectively removing only about 20% of the lower left lung lobe's epithelium without causing respiratory distress or significant mortality *in vivo* in a rat model. This treatment led to extensive epithelial cell proliferation and complete recovery of the alveolar epithelium by day 10, facilitated by endogenous lung progenitors.

As proof of concept, the de-epithelialization model was used to study the engraftment of human therapeutical cells, exogenous distal lung epithelial progenitors (DLEPs). Patchy areas with engraftment of human alveolar epithelium were achieved in several rats and shown to significantly reduce lung injury scores in treated rats respect to control, indicating effective lung repair.
The regional de-epithelialization of the distal lung led to significant advancements in lung bioengineering, developing an optimal environment that both induce cellular proliferation and activation and allow engraftment of exogenous therapeutical cells for repairing the lung. This study introduced an innovative approach to addressing lung epithelial diseases by focusing on lung de-epithelialization offering a platform to investigate the mechanisms to promote lung repair, potentially reducing fibrotic complications, morbidity, mortality, and the need for lung transplants in patients.

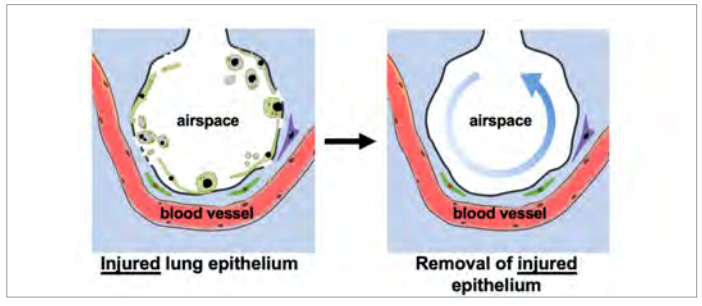

Fig.1 - Schematics of the de-epithelialization approach.

Targeted Removal and Replacement of Defective ATII Cells in Sftpc-/- Mouse Model: This approach is linked to repair and regeneration of lungs affected by a genetic defect of alveolar type II cells (ATII) cells. When these ATII cells are injured or diseased, the alveoli cannot function properly and therefore they cannot deliver sufficient oxygen to the bloodstream or remove CO_2, causing respiratory symptoms. A novel fusion protein, DT388-SPA, was engineered by combining surfactant protein (SP) A, which is secreted and taken up by ATII cells with the active domain of diphtheria toxin (DT388). DT388SPA was designed to selectively ablate defective ATII cells, enabling the introduction of healthy cells. As such, SPA acts as a "Trojan Horse" to deliver the toxin (DT388) into ATII cells, where it induces apoptosis. DT388-SPA demonstrated high specificity for ATII cells *in vitro* and *in vivo*, significantly reducing defective ATII cells and facilitating engraftment of healthy ATII cells, improving lung function and repair. Moreover, testing on human lung samples confirmed the efficacy and specificity of DT388-SPA, supporting its potential for clinical application as conditioning method for cell therapy.

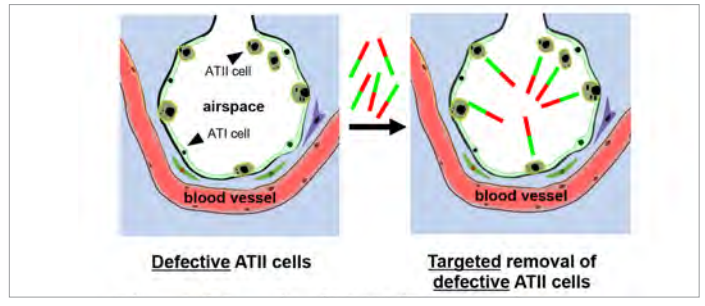

Fig.2 - Schematics of DT388-SPA approach.

This second part of the thesis created a novel strategy to treat lung disease especially where a single injured/defective cell type i mainly responsible for the disease phenotype, is identified: ATII cells in this case. This technology could also be adapted to replace other lung cell types where specific cell membrane "targets" are identified.

This thesis presents innovative approaches for lung disease treatment, focusing on *in situ* lung repair and regeneration. The de-epithelialization strategy and DT388-SPA technology show promise in reducing the need for lung transplants by directly repairing damaged lungs. Future research should focus on optimizing conditioning methods, integrating emerging technologies, and translating these therapies into clinical practice, by scaling this technology to large animal models, closer to human physiology. Collaborative efforts are crucial for advancing these innovative strategies and bringing transformative therapies to patients with respiratory diseases.