PhD Program in Bioengineering and Robotics

Curriculum: Bioengineering

Research themes

Bioengineering is a discipline that integrates physical, chemical, mathematical, computational sciences and engineering principles to study biology, medicine, behavior, and health.

Bioengineering advances fundamental concepts, creates knowledge from the molecular to the organ systems levels, and develops innovative biologics, materials, processes, implants, devices, and informatics approaches for the prevention, diagnosis, and treatment of disease, for patient rehabilitation, and for improving health and well-being (NIH Working Definition of Bioengineering—July 24, 1997).

The PhD curriculum in Bioengineering implements the evolution of a long-standing tradition of the Bioengineering School of the University of Genova, characterized by a marked *experimental* and *technological* vocation, providing advanced training and research experience for graduate students interested in: *in vitro* electrophysiology, cellular mechanobiology, microscopy, tissue engineering, neural control of the movements, motor learning and neuromotor recovery, as well as neuroengineering, micro- and nano-technologies, assistive and rehabilitation technologies, integrated perceptual systems.

The research activities, mainly conducted at the Department of Informatics, Bioengineering, Robotics and System Engineering (DIBRIS), cover a variety of areas and offers potential collaborations with other departments at the University of Genova, as well as with leading national and international research institutions. This will ensure a unique scientific environment to the students to carry out international research projects.

The main research interests lie within the following broad themes:

- Neuroengineering
- Molecular and cellular engineering
- Interaction and rehabilitation engineering
- Health informatics

The training will start with plans tailored to the need and interests of each individual student and aimed at bringing all students to a common understanding of the key scientific aspects and investigation tools of the different research themes. This will be obtained also by planning exchange of students for 6 to 12 months with national and international laboratories where particularly interesting experimental techniques and/or strategic scientific approaches are well established.

The ideal candidates are students with a higher level university degree willing to be involved in multidisciplinary studies and to work in a team of scientists coming from different background but sharing common objectives. The proposed themes are presented in details in the following indicating tutors and place where the research activity will be developed.

International applicants are encouraged and will receive logistic support with visa issues, relocation, etc.

3D in vitro model of Parkinson's disease

Tutors: Laura Pastorino, Donatella Di Lisa

Tutors Affiliation: DIBRIS, University of Genova www.dibris.unige.it

Project Description: The present project aim at developing a 3D in vitro model of PD for drug screening applications. To this aim, a biopolymeric hydrogel, mimicking the main characteristics of the extracellular matrix of the brain, will be developed and used to encapsulate neuronal cells differentiated from patient induced pluripotent stem cells. The developed model will be characterized morphologically by immunostaining techniques and functionally by microelectrode arrays for the recording of the electrophysiological activity. Moreover, important intracellular parameters, such as lysosomal pH, will be monitored in real time by using silica based-microsensors. The developed platform will be used for the screening of molecules candidate to reduce alfa-synuclein agglomerates.

Requirements: Applicants are expected possess a background in bioengineering/materials science/related disciplines. Attitude for problem solving. Interests in experimental work in the lab.

References:

- Tedesco, Maria Teresa, et al. "Soft chitosan microbeads scaffold for 3D functional neuronal networks." Biomaterials 156 (2018): 159-171.
- Slanzi, Anna, et al. "In vitro models of neurodegenerative diseases." Frontiers in cell and developmental biology 8 (2020): 328.

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A computational analysis of early vision function in silico networks of LIF neurons

Tutor: Silvio P. Sabatini

Tutor Affiliation: DIBRIS, University of Genova

Project Description: One approach to understanding the implications of the initial stages of visual processing is *ideal observer analysis*, which evaluates the information available to support psychophysical discriminations at various stages of the early visual representation. Computational models of early processing typically rely on simple linear contrast-encoding assumptions, which do not account for many second-order mechanisms. Accordingly, many details remain underrated, and their implications on functional vision not fully understood. By example, let's think about asymmetries in the responses to brightness and darkness observed in the cells of ON and OFF pathways, which extend to neuronal spatial receptive fields and temporal properties. The project aims to implement neuromorphic multi-layer networks of leaky integrate and fire (LIF) neurons in cascade to a motorized event-based camera, as *artificial replicas of the early stages of an active vision system for explaining and predicting visual performance in arbitrary natural and laboratory visual tasks*. Models with be tested under multiple and varying parameters and in adaptive conditions. At functional level, the system will (1) consider the neural resources required to account for a range of linear/nonlinear early visual processes, and (2) provide the inference engines for relating the resulting visual representations to performance on psychophysical tasks. The visual performance of the resulting silicon model will be comparatively assessed with that of typical a human observer.

The objective is twofold: on the one hand, we contribute a deeper understanding of visual processes, especially about predicting how early computations may reverberate through the sensory pathways eventually contributing to functional vision. On the other hand, we contribute to a new generation of seeing machines which will bring about breakthroughs in AI systems and profound societal and economic changes.

Requirements: Applicants are expected to: (1) have a Master's degree in Bioengineering, Computer Science, Physics, Psychology or related disciplines, (2) have a keen interest in Vision Science and in Artificial Intelligence, (3) have good programming skills in at least one language (MATLAB, C/C++, Python, C#), (4) work well in group problem solving situations, (5) have intermediate communication skills (oral and written in English). Experience in neural modeling is a plus.

References:

[1] Carandini M, Demb JB, Mante V, Tolhurst DJ, Dan Y, Olshausen BA, Gallant JL, Rust NC. Do we know what the early visual system does? J Neurosci. 2005 Nov 16;25(46):10577-97. doi: 10.1523/JNEUROSCI.3726-05.2005.

[2] Farrell J. E., Jiang H., Winawer J., Brainard D. H., & Wandell B. A. (2014). Modeling visible differences: The computational observer model. SID Symposium Digest of Technical Papers, 45, 352–356. doi: 10.1002/j.2168-0159.2014.tb00095.x.

[3] Testa S, Sabatini SP, Canessa A. Active fixation as an efficient coding strategy for neuromorphic vision. Sci Rep. 2023 May 8;13(1):7445. doi: 10.1038/s41598-023-34508-x.

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Innovative collaborative neurorehabilitation systems based on virtual reality and visuo-haptic feedback

Tutor: Danilo Pani

Tutor Affiliation: Dept. of Electrical and Electronic Engineering, University of Cagliari (https://unica.it/unica/it/dip_ingelettrica.page)

Description:

Neurorehabilitation aims at motor recovery after a nervous system injury. Although robotics-based interventions have shown great potential, these solutions are still complex and expensive, which limits their widespread adoption. At the same time, low-cost systems exploiting simple bodyweight exercises, albeit adopting virtual reality (VR) and motion tracking tools, do not usually go beyond the conventional movement/task-oriented exercises.

This research aims at conceiving and test novel approaches to neurorehabilitation that can be performed also in home settings. In this context, approaches consisting of advanced visual feedback in exercises featuring VR, for the improvement of the neural control of upper-limb movements, can be deployed. In the context of the MYRTUS Horizon Europe project, such approaches also include the challenge of collaborative rehabilitation tasks in a virtual environment with limited interaction features, i.e., where the interaction among physically distant participants is only visuo-haptic.

In this research, the approach that will be studied is based on the possibility of projecting the participant in a virtual scenario characterized by physical laws, unknown to him/her, and resulting in perturbation or distortion of the mapping between the real and the virtual space, by leveraging on collaborative neuromotor or cognitive tasks with visuo-haptic interactions. The candidate should develop and test the rehabilitation approaches by including multimodal sensing features and haptic interaction devices. Immersive approaches will be primarily studied. Adaptation and retention will be assessed to understand the effect of the proposed approach. The creation of models able to explain the observed effect will be also pursued.

Requirements:

Applicants are expected to own a strong biomedical engineering background and proficiency in high-level programming. Previous experience on Matlab, C#, and Python is valuable, as well as with Unity or Unreal. Attitude to the conduction of acquisition campaigns with both impaired and unaffected people is requested, along with a good attitude at team working. The activity will be carried out at the MeDSP Lab of the University of Cagliari (medsp.it).

References:

- E. Hajissa, C. Celian, K. O. Thielbar, F. Kade, Y. A. Majeed, and J. L. Patton, “Stroke Rehabilitation with Distorted Vision Perceived as Forces,” in 2019 IEEE 16th International Conference on Rehabilitation Robotics (ICORR), 2019, pp. 644–647, doi: 10.1109/ICORR.2019.8779410.
- E. Hajissa, A. Shah and J. L. Patton, "Visual Limit-Push Training Alters Movement Variability," in IEEE Transactions on Biomedical Engineering, vol. 65, no. 10, pp. 2162-2167, Oct. 2018, doi: 10.1109/TBME.2017.2786142.

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3D printed in vitro model of cortical brain-like tissue

Tutors: Laura Pastorino, Sergio Martinoia

Tutors Affiliation: DIBRIS, University of Genova , www.dibris.unige.it

Project Description

The cerebral cortex is characterized by its layered cellular structure, where distinct neurons are organized into vertical columns. This intricate architecture plays a pivotal role in enabling advanced cognitive functions. Nevertheless, existing tissue engineering methods fall short in reproducing these complex structures. The present project aims at developing a 3D in vitro model that mimics the laminar organization of cerebral cortical columns. Human induced pluripotent stem cells derived neural progenitors will be separately encapsulated into a layered 3D hydrogel architecture and differentiated in order to obtain cortical microtissues. The model will be characterized both from a morphological, functional and genomic point of view. The developed model will provide an innovative platform for in-depth study of the mechanisms of neurodegenerative diseases.

Requirements: Applicants are expected possess a background in bioengineering/materials science/related disciplines. Attitude for problem solving. Interests in experimental work in the lab.

References:

- Roth, Julien G., et al. "Spatially controlled construction of assembloids using bioprinting." Nature Communications 14.1 (2023): 4346.
- Slanzi, Anna, et al. "In vitro models of neurodegenerative diseases." Frontiers in cell and developmental biology 8 (2020): 328.

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Development of a computational pipeline to design RNA aptamers

Tutors: Gian Gaetano Tartaglia

Tutors affiliation: RNA Systems Biology research Group, IIT

Background. The “RNA Systems Biology” lab combines computational and experimental approaches to investigate interactions of RNA molecules in physiology and disease. We aim to discover the involvement of RNA molecules in regulatory networks controlling protein production and we are interested in understanding mechanisms whose alterations lead to aberrant aggregation.

Description. We plan to exploit the predictive power of the catRAPID algorithm for the de novo design of therapeutic/diagnostic RNA sequences. These sequences, also called RNA aptamers, bind with high affinity and selectivity to a specific target molecule through structural recognition similar to protein antibodies. In the last three years, we exploited the predictive power of our catRAPID algorithm (Armaos et al., 2021; Cirillo et al., 2017) for the de novo design of therapeutic/diagnostic RNA sequences (patent filed). These sequences, called RNA aptamers, bind with high affinity and selectivity to a specific target molecule through structural recognition similar to protein antibodies. They are promising biomedical tools and have competitive advantages over other drug classes. To date, experimental approaches such as the Systematic Evolution of Ligands by Exponential Enrichment’ (SELEX) technique stand at the basis of the high-throughput development process to obtain aptamer sequences. We are overcoming SELEX limitations: instead of libraries/reagents, a timeframe of several months and its associated high costs, catRAPID takes only a few days per target (computation time between 2 and 10 depending on the length of the molecules), therefore speeding up the aptamer design.

Using the catRAPID algorithm, in 2022 we designed RNA aptamers specific for TDP-43 and used them together with advanced microscopy techniques to follow the protein transition towards its aggregated forms (Zacco et al., 2022). We are now in the process of designing aptamers for other proteins and we would like to integrate catRAPID in a pipeline where Genetic Algorithms and Monte Carlo simulations are going to be used to refine the scoring of RNA molecules for proteins. On top, new developments of catRAPID are planned to incorporate the effects of RNA chemical modifications.

Purpose. At the end of this doctoral project, the candidate will acquire skills related to machine learning and, especially, predictions of protein-RNA interactions. Knowledge on RNA structure, protein-RNA interactions, liquid-like phase separation, liquid-to-solid phase transition will be acquired during the training.

References.

[1] Armaos, A. et al. (2021) Nucleic Acids Res.

[2] Cirillo, D. et al. (2017) Nat Meth.

[3] Zacco, E. et al. (2022). Nat Com.

Requirements. We are looking for highly motivated candidates with a degree in Physics and Engineering that are keen to work in an interdisciplinary environment. Graduated students of other disciplines may be considered. *General background*: Computational Science, Bioinformatics, Machine Learning, Physics. Fluency in Python is a must. Use of R is appreciated. Languages such as C and C++ are a plus. *Specific background*: Protein-RNA interactions, Structural Modelling, Neurodegeneration. Biochemical knowledge of polymers such as RNA and proteins is a must.

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Development of novel user experience metrics to evaluate lower and upper limbs exoskeletons for rehabilitation

Tutors: Boccardo Nicolò / Freddolini Marco

Tutors affiliation: Rehab Technologies Lab, IIT.

Background. Rehab Technologies Lab (Rehab Tech) is coordinated by Lorenzo De Michieli, who has extensive experience in the field of robotic assistive medical devices development, including prosthetics for upper-limb and lower-limb and assistive exoskeletons for upper and lower body districts.

Description. The candidate will contribute to developing assessment strategies on lower and upper limbs exoskeleton to evaluate patient’s user experience when exoskeletons are used as rehabilitation devices in the context of the IIT-INAIL project ClinicExo.

To develop a specific methodology for assessing the user experience of exoskeleton devices in rehabilitation, the first step is to evaluate state-of-art methodologies by understanding pro and cons and adapt them to the context of this project. Technical development will help in improving the human-device interaction therefore promoting user experience. This will help to develop novel user experience metrics derived from correlations between human-machine system movements and physiological measurements. These metrics would quantify the user's actual effort during usage, motor performance, mental and cognitive load.

This comprehensive assessment framework can optimize exoskeleton device design and usability for improved rehabilitation outcomes.

To this end, the Candidate will benefit from a lively network of collaborations with hospitals and research institutions. This project requires broad expertise in biomechanics (i.e. motion capture system, EMG signals, GSR equipment) and a demonstrated expertise in biomedical engineering and attitude to interact with patients. The ideal candidate should hold a degree in Biomedical Engineering or related disciplines, be a highly motivated and creative individual who wants to work in a dynamic, multi-disciplinary research environment. Former lab experience and previous technical and scientific results will be highly considered.

Requirements. Background in Bioengineering; proficient programming skills: experience with Matlab/Simulink, C and/or Python for data analysis. Experience with human acquisitions with EMG and/or motion capture system. Experience in clinical environment will be taken in high account.

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Activity of Daily Living in Multiple Sclerosis: A Technological Assessment

Tutors: Andrea Tacchino, Maura Casadio

Tutors Affiliation: Scientific Research Area, Italian Multiple Sclerosis Foundation, www.aism.it; DIBRIS, University of Genoa, www.unige.it

Project Description

Multiple sclerosis (MS) is a chronic autoimmune inflammatory disease of the central nervous system (CNS). MS is characterized by a wide range of symptoms including muscle weakness, spasticity, fatigue, cognitive impairments, mobility difficulties, and vision problems, which usually have enormous long-term impacts on almost every aspect of the lives of people with MS and their families.

Rehabilitation is fundamental for preventing complications of MS and improving the individual's independence [Gil-Gonzales et al. 2020; Goverover et al. 2009]. It improves mobility, cognition, fatigue, occupation, communication, and social integration. In clinical practice, these domains are usually assessed through objective tools such as Patient Reported Outcomes or performance tests. However, these methods have several limitations, such as poor sensitivity to mild impairment and to small specific changes. In the last decade, technological solutions have been introduced to objectively quantify clinical disorders in domains relevant to people with MS as assessment of balance, walking, fatigue, sleep and upper limb functions [Bradshaw MJ et al. 2017].

Less attention has been dedicated to the quantitative assessment of activities of daily living (ADLs) through technological solutions, such as non-intrusive environmental or wearable sensors, home-testing biomarker-sensing devices, immersive virtual reality devices, and assistive robots that can operate in everyday life situations [Chitnis et al. 2019]. These technological solutions will allow investigating in ecological contexts two important aspects of our neural control that have received limited attention and are often compromised by MS: bimanual control and the simultaneous control of motion and forces. These technologies and the related methods will also provide the therapist with objective performance measures, providing indications for improving the rehabilitative approach and finally the effectiveness of an intervention. In this context, the therapist would help people with MS to increase participation in ADLs by making their performance easier.

The aims of the project are: 1) based on clinical knowledge, developing an integrated system of wearable sensors, home-testing biomarker-sensing devices, and assistive robots to quantitatively assess the performance of people with MS in ADLs; 2) identifying digital biomarkers of performances in ADLs to be used in the prediction of disease evolution in MS.

Requirements: administration of performance tests; ability to use sensors and technological devices.

References:

- Gil-González Irene et al. BMJ Open. 2020, doi: 10.1136/bmjopen-2020-041249.
- Goverover Yael et al. Rehabil Psychol. 2009, doi: 10.1037/a0014556.
- Bradshaw Michael J et al. Neurol Clin Pract., doi: 10.1212/CPJ.0000000000000382.
- Chitnis Tanuja et al. NPJ Digit Med. 2019, doi: 10.1038/s41746-019-0197-7.

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Robotic rehabilitation in severe acquired brain injuries: a tailored multidimensional approach

Tutors: Pietro Balbi, Maura Casadio

Tutors Affiliation: Fondazione Don Carlo Gnocchi ONLUS, IRCCS, www.dongnocchi.it; DIBRIS, University of Genoa, www.unige.it

Project Description

Multiple sensory, motor, cognitive and behavioral deficits result from severe Acquired Brain Injuries (ABIs). Thus, a multidisciplinary intensive personalized rehabilitation approach is required to deal with the complexity of the patients' disabilities, aimed at obtaining favorable outcomes and acceptable social and familial reintegration.

In these patients, upper limb functional deficits greatly impair the ability of motor control and planning, yet the current rehabilitation strategies are seldom able to improve the patients' functional abilities, particularly regarding the reaching and grasping movements, which in turn improve daily life activities [2].

Nowadays, the adoption of robotic devices alongside the pathway of functional recovery resulted in favorable outcomes for upper limb motor deficits [3].

Preliminary results demonstrated the feasibility and efficacy of a multidimensional robotic rehabilitation treatment, besides a conventional rehabilitation cycle, on upper limbs motor deficits in ABI patients in a post-acute phase [4].

The aims of the project are: 1) to extend and confirm the preliminary results on the feasibility and efficacy of the robotic devices used in the rehabilitation treatment of ABI patients' upper limb motor control; 2) to identify clinical and cognitive biomarkers able to select the most responding subjects to the treatment, to personalize the treatment and make the procedure tailored.

Requirements: ability to use technological devices and on administering clinical and performance tests.

References:

[1] Allison Capizzi, Jean Woo, Monica Verduzco-Gutierrez. Traumatic Brain Injury: An Overview of Epidemiology, Pathophysiology, and Medical Management. Med Clin North Am. 2020; 104(2): 213-238.

[2] Sandeep K Subramanian, Melinda K Fountain, Ashley F Hood, Monica Verduzco-Gutierrez. Upper Limb Motor Improvement after Traumatic Brain Injury: Systematic Review of Interventions. Nurorehabil Neural Repair. 2022 Jan;36(1):17-37.

[3] Iris Jako, Alexander Kollreider, Marco Germanotta, Filippo Benetti, Arianna Cruciani, Luca Padua, Irene Aprile. Robotic and Sensor Technology for Upper Limb Rehabilitation. PMR. 2018; 10(9 Suppl 2): S189-S197.

[4] C. Tramonti, B. Gnetti, S. Callegari, B. Grassi, P. Gemignani, P. Balbi, M. Germanotta, I. Aprile. Gravi cerebrolesioni acquisite e riabilitazione robotica degli arti superiori: approccio multidimensionale personalizzato in fase post-acuta. 51° Congresso Nazionale SIMFER, 12-15 ottobre 2023, Bologna, Italy.

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Development of "Organ-on-Chip" semi-automatic platforms using pumping systems and robotics

Tutors: Maurizio Aiello[1], Silvia Scaglione[1], Marco Fato[2]

Tutors Affiliation: (1) React4life SpA (www.react4life.com), (2) DIBRIS (University of Genova)

Project Description

The project is about novel organ on chip to be used for drug testing and human disease modeling in vitro. This project includes a period of study and research divided into three phases, in which the candidate, supported by academic and company tutors, will achieve the following objectives:

(I) development and testing of new pumping solutions able to manage 12-24 independent lines of OOC for high-throughput purposes, to maintain a controlled laminar flow connecting multiple organs (1) having flexible distance between them, to manage a new fluid flow pumping system for cell circulation (2). Different types of pumping can be tested including syringe, peristaltic, pressure pumps.

(ii) development and testing of new OOC solutions with micro/macro braiding to manage different technical needs (flows, flow rates, different volumes); in this phase there is also a careful analysis and testing of the components (e.g. pipes, connectors)

(iii) software development to realize the user interface of the pumping system, computational fluid dynamics modeling, CAD modeling of the OOC, as well as software (e.g. phython) and electronics (integration, firmware) skills for mechanical and electronic interface of the pump.

Requirements: Degree in Engineering, Maths, Physics or similar.

References:

1. Fedi, A.,Vitale, C. Fato, M.,Scaglione, S. “A Human Ovarian Tumor & Liver Organ-on-Chip for Simultaneous and More Predictive Toxo-Efficacy Assays” Bioengineering, 2023, 10(2), 270
2. Marrella A, Varani G., Aiello M., Vaccari I., Vitale C., Mojzisek M., Degrassi C., Scaglione S. “3D fluid-dynamic ovarian cancer model resembling systemic drug administration for efficacy assay” ALTEX 2021; 38(1), pp 082-094.

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