PhD Program in Bioengineering and Robotics

Curriculum: Bioengineering and Bioelectronics

Research themes

The PhD Program for the Bioengineering and Bioelectronics curriculum provides interdisciplinary training at the interface between technology and biomedicine. The general objective of the program is to form research technologists capable to deal with multidisciplinary projects and to face complex challenges at the interface between technology and life-sciences. The training to the students is delivered through the in-depth involvement into a three-year research project supplemented by specific didactic modules dealing with computational and experimental methods. The direct link with

different laboratories at both the Department of Informatics, Bioengineering, Robotics and System Engineering (DIBRIS) and the Italian Institute of Technologies (IIT) 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:

- Biomedical imaging and medical information systems
- Bioelectronics, biomedical devices and bio-sensors
- Molecular, cellular and tissueengineering
- Neuroengineering and neurotechnology
- Micro and nano-systems in medicine and biology

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 (University Department or Italian Institute of Technology – IIT) where the research activity will be developed.
International applications are encouraged and will receive logistic support with visa issues, relocation, etc.

1. ICT for data reuse and interregional exchange in chronic infective diseases

Tutor: Mauro Giacomini

Department: DIBRIS (University of Genoa)
www.dibris.unige.it

Description: DIBRIS, with infectious disease physicians, has developed the "Ligurian HIV Clinical Network" (RLH), a web tool to manage clinical data from HIV1+ patients for clinical follow-up and multicenter clinical trials and CISAI portal to manage HIV and HCV based clinical trials on a national base. At present in RLH 2843 patient from 9 hospitals are involved, with 79904 laboratory exams results recorded; in CISAI 4728 patient from 39 hospitals are involved. Possible development are:

- Fully automate data entry
- Automatic data exchange with national and international multicenter clinical trials (above all among RLH and CISAI, but also with ARCA and ICONA and others)
- Ability to use data for "on demand" clinical research, based on European guide lines (ECRIN)
- Ability to monitor resistant bacterial infection, above all for Mycobacterial infections

Using of standardized tools is required: clinical research main standard is Operational Data Model, while Healthcare Services Specification Program is the one for clinical care. In particular the Retrieve, Locate, Update Service Functional Model will be used to manage clinical data through HL7 Clinical Document Architecture, while Common Terminology Services - Release 2 will administrate the definition of semantics and syntax.
This project takes into consideration aspects interesting for: European research, Italian national health system, regional health policy.

Requirements: Direct reuse of clinical data, elements of standardization of medical information, tools for modeling web services, tools for the design and implementation of standardized services choreography according to the scheme HSSP.

Reference:
G. Cenderello, V. Tittle, A. Pasa, C. Dentone, S. Artioli, M. Setti, M. Giacomini, P. Fraccaro, C. Viscoli, G. Cassola, A. Di Biagio, A. Barbour, M. Nelson "Inpatient admissions of patients living with HIV in two European centres (UK and Italy); comparisons and contrasts" Journal of Infection, 2015, Vol. 70, Issue 6, pp. 690-694.
G. Cenderello, S, Artioli, C. Viscoli, A. Pasa, M. Giacomini, B. Giannini, C. Dentone, L. A. Nicolini, G. Cassola, A. Di Biagio "Budget impact analysis of sofosbuvir-based regimens for the treatment of HI V/HCV-coinfected patients in northern Italy: a multicenter regional simulation" ClinicoEconomics and Outcomes Research, 2016, vol. 8, pp. 15-21

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2. Modeling the impaired binocular visual system

Tutors: Silvio P. Sabatini, Agostino Gibaldi

Department:
DIBRIS, University of Genova
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Description: In binocular vision, the functional perception of the three-dimensional (3D) environment relies on the integration of motor fusion with sensory fusion, i.e. on the cooperation of binocular coordinated eye movements together with the mechanisms of stereopsis. A decorrelated binocular visual experience on the developing visual system may result in a functional impairment of the oculomotor system, such as strabismus and amblyopia [1].
The impairment of the binocular visual system is at the core of the PhD project. The main goal is to characterize and to model how sensory and motor impairments affect the normal binocular functionality and development of the visual system. The PhD student will work on two complementary tracks: a) designing biologically inspired models of the early visual system, grounded on previous research [2], to mimic different impairments; b) developing specific 3D visual and visuomotor experimental protocols to investigate binocular performance of healthy subjects and patients. Experiments will be based on 3D visual displays integrated with binocular eye tracking technologies [3].
The resulting framework, integrating neural modeling with psychophysical experimentations, will be used to investigate the computational principles of the impairments, and their impact on binocular visual processing and perception.
Expected results will concern: a) extending the comprehension of the neural mechanisms that underlie the healthy and impaired visual system, 2) developing and assessing diagnostic and therapeutic methodologies to visual impairments, 3) inspiring design principles for artificial visual systems.

Requirements: Applicants should have a strong quantitative background (physics, engineering, computer science, applied mathematics), and a keen interest in reverse-engineering the brain. Knowledge on computational neuroscience, machine learning, image processing and programming languages (C/C++ or Python) are a plus. Experience with Graphics Processing Units (GPUs) and CUDA programming is also a plus. Successful candidates will work in an interdisciplinary environment in collaborations with engineers, neuroscientists and clinicians.

Reference:

[1] Birch, E.E. Amblyopia and binocular vision. Progress in Retinal and Eye Research, 33:67–84, 2013.

[2] Gibaldi, A., Canessa, A., Solari, F., & Sabatini, S. P. (2015). Autonomous learning of disparity–vergence behavior through distributed coding and population reward: Basic mechanisms and real-world conditioning on a robot stereo head. Robotics and Autonomous Systems, 71, 23-34.

[3] Gibaldi, A. and Vanegas, M. and Bex, P.J. and Maiello, G., Evaluation of the Tobii EyeX Eye Tracking Controller and Matlab Toolkit for Research. *Behavior Research Methods*, in press.

Contacts: silvio.sabatini@unige.it

3. Development of computational models of neuronal assemblies to understand their computational properties as a function of different network topologies

Tutor: Paolo Massobrio

Department: DIBRIS (University of Genova)
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Description: Behaviors require interaction with the environment and the contribution of different brain areas depending on the orchestrated activation of large neuronal assemblies. The present project aims at investigating how to effectively interact with neuronal systems by understating the role of the network connectivity in the computational properties of small/large/interacting neuronal networks. In particular, during the three-year research project, different computational network models will be developed and investigated, in order to: i) characterize the spontaneous activity of networks of neurons with different architectures. In particular, 2D uniform/homogeneous networks, 2D interconnected networks made up of few sub-populations (from 2 up to 4), and 3D structures will be taken into account. The observed dynamics will be investigated by checking whether particular configurations may promote phenomena like synchronization, emergence of critical phenomena, interplay between structural and functional connectivity; ii) characterize the stimulus-evoked activity induced by electrical stimulation in networks of neurons with different architectures. It will be investigated whether the evoked responses (i.e., the I/O function) can be modulated by structural connectivity.

Requirements: background in bioengineering, computational neuroscience, computer science. Attitude for problem solving. Interests in understanding/learning basic biology.

Reference:
[1] C.J. Honey, J.P. Thivierge, O. Sporns, Can structure predict function in the human brain?, Neuroimage, Vol. 52, 2010.
[2] P. Massobrio, V. Pasquale, S. Martinoia. Self-organized criticality in cortical assemblies occurs in concurrent scale-free and small-world networks. Scientific Reports, Vol. 5, 2015

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4. Sensory processing in large-scale hierarchical networks of interacting neuronal assemblies

Tutor: Paolo Massobrio, Silvio P. Sabatini

Department: DIBRIS (University of Genoa)
http://www.dibris.unige.it/en

Description: How interactions between neurons relate to tuned neural responses is a longstanding question in systems neuroscience. Feed-forward networks provide a minimal framework to study coding and decoding strategies as well as to interpret certain aspects of cortical information processing. Following this architectural paradigm, deep networks have been proposed to specialize for different perceptual tasks, for taking decisions, or planning motor acts. However, such networks rely on an over-simplification in which single nodes model homogeneous population of cells, and connections represent average interactions among populations (i.e., meta-network approach).
Starting from these premises, the proposed project aims to increase the complexity and the realism of the model by designing and analyzing the behavior of large-scale hierarchical network of interacting neuronal assemblies. Each node should be modeled as an assembly composed of excitatory and inhibitory neurons with their own dynamics.
The neurons of each assembly will respond to properties of the visual signal through their afferent receptive fields. Yet, their overall behavior will emerge from recurrent interactions, and will be ruled by network-parameters, like balance between excitation and inhibition, kind of connectivity, number of neurons of each of these assemblies.
The goal is to develop a new model and to investigate the role of specific vs. unspecific inhibition on the tuning properties of the single cells, and on the efficiency of the code provided by the emerging functionally homogeneous populations, and on their attendant adaptation capabilities. The dynamic properties of the network will be analyzed in relation with the interconnections topology, and eventually related to its sensory processing capabilities.

Requirements: background in bioengineering, computer science, physics or related disciplines, strong interest in computational neuroscience. Attitude for problem solving. Interests in understanding/learning basic biology.

References:
A. Kumar, S. Rotter, A. Aertsen (2010). Spiking activity propagation in neuronal networks: reconciling different perspectives on neural coding. Nature Rev. Neurosci. 11:615-627.
P. Massobrio, V. Pasquale, S.Martinoia (2015). Self-organized criticality in cortical assemblies occurs in concurrent scale-free and small-worl networks. Scientific Reports 5:10578.
S.P. Sabatini (2014). Deep Representation Hierarchies for 3D Active Vision. KI - Künstliche Intelligenz, 29(1):31-40.

Contacts: paolo.massobrio@unige.it, silvio.sabatini@unige.it

5. Action-perception transfer in visual and visuo-haptic behavior

Tutor: Silvio P. Sabatini, Vittorio Sanguineti

Department: DIBRIS (University of Genoa)

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Description: We perceive the changing physical world by interacting with it and by observing the corresponding changes in our sensory inputs. The two main forms of interaction are visual (eye movements), and haptic (arm, hand and finger movements). Experiencing the sensory feedback gained from movements allows us to learn the contingencies and correlations between action events and sensory events. Although this *sensorimotor contingency* theory (O'Regan & Noë, 2001) has become a paradigmatic principle in cognitive science, a systematic derivation of its computational and theoretical constructs has not been fully attempted yet.
The proposed research aims at investigating the interplay between action and perception at different levels, ranging from (1) modelling early action-perception transfer in visual feature extraction (cf. neural coding of visual properties) and perceptual judgement processes (cf. decoding stages), to (2) experiments on bidirectional perceptual-action influence - including the development of systems and devices that integrate vision and haptics - up to (3) applications in neuromotor and cognitive rehabilitation, in which action is used to educate perception and perception is used to educate action. Implications of motor learning on perceptual capabilities and their underlying computational processes will be analyzed.

Requirements: background in bioengineering, computer science, physics or related disciplines. Attitude for problem solving. Interest in experimental work.

Reference:

O'Regan & Noë, A sensorimotor account of vision and visual consciousness. Behavioral and Brain Sci. 24:939-1031, 2001.

Hecht et al., Motor learning enhances perceptual judgement: a case for action-perception transfer. Pyschol. Research 65:3-14, 2001

Contacts: silvio.sabatini@unige.it, vittorio.sanguineti@unige.it

6. Myoelectric control to study motor learning and neuromotor rehabilitation

Tutor: Vittorio Sanguineti

Department:
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Description: The general objective of this research is to develop novel technologies for neuro-rehabilitation and new analytical tools aimed at personalization of therapy through an innovative approach, based on patient models which account for the interplay between muscular and functional levels of description (Casadio, Tamagnone, Summa, & Sanguineti, 2013). These models can be used to monitor the evolution of neuromuscular control strategies during recovery, and for the design, administration and control of robot-assisted rehabilitation exercises, highly customized and specifically targeted to the development of specific muscle activation strategies. We will specifically focus on myoelectric controllers, in which muscle activation signals (EMG) directly control devices like hand prostheses or assistive robots. Recently, myocontrollers have been used to probe motor system adaptivity (de Rugy, Loeb, & Carroll, 2012) and modularity (Berger, Gentner, Edmunds, Pai, & d'Avella, 2013), in situations in which there was no actual movement (isometric force control). We will extend this approach to more realistic scenarios - predicting muscle forces from EMG signals during actual movements. In conjunction with a robot, myoelectric control will be used to generate perturbations and/or assistive forces that are directly controlled by the user and directly account for type and modalities of his/her voluntary control. The ultimate goal will be to understand whether and how robot-generated assistive forces could be used to facilitate the reorganization of neuromuscular control. This will enable the development of novel approaches to neuromotor rehabilitation (eg stroke, multiple sclerosis) that promote not only the recovery of functions, but also a specific reorganization of neuromuscular control.

Requirements: Master's degree in Bioengineering or equivalent; Expertise in computer programming (C++, matlab), biomedical signal processing, data analysis

References:
Berger, D. J., Gentner, R., Edmunds, T., Pai, D. K., & d'Avella, A. (2013). Differences in adaptation rates after virtual surgeries provide direct evidence for modularity. *J Neurosci, 33*(30), 12384-12394. doi: 10.1523/JNEUROSCI.0122-13.2013
Casadio, M., Tamagnone, I., Summa, S., & Sanguineti, V. (2013). Neuromotor recovery from stroke: computational models at central, functional, and muscle synergy level. *Front Comput Neurosci, 7*, 97. doi: 10.3389/fncom.2013.00097
de Rugy, A., Loeb, G. E., & Carroll, T. J. (2012). Virtual biomechanics: a new method for online reconstruction of force from EMG recordings. *J Neurophysiol, 108*(12), 3333-3341. doi: 10.1152/jn.00714.2012

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7. Polysaccharide Hydrogels for 3D Functional Neuronal Networks

Tutors: Laura Pastorino, Sergio Martinoia

Department:
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Description: Hydrogels have been extensively used in various biomedical fields such as drug delivery and biosensing. More recently the ability to engineer the size, shape and chemical properties of biologically relevant hydrogels has generated new opportunities in addressing challenges in mimicking the 3D native cellular microenvironment.
The proposed theme of research concerns the development and characterization of tunable biomimetic scaffolds. In this respect, polysaccharide microbeads will be fabricated, by an air-dynamically driven encapsulator, and then the developed microbeads will be functionalized and self-assembled into a 3D microporous scaffold for neuronal cultures. The developed 3D neuronal cultures will be deeply characterized by means of different microscopies, mechanical testing, immunofluorescence and electrophysiological techniques. The possibility of encapsulating into the microbeads active molecules for chemical stimulation will be also investigated. The network dynamics of the 3D cultures will be compared to those of 2D cultures.

Requirements: background in bioengineering, materials science, chemistry, physics or related disciplines. Attitude for problem solving. Interests in experimental work in the lab.

Reference:
Frega M., Tedesco M., Massobrio P., Pesce M., and Martinoia S., Network dynamics of 3D engineered neuronal cultures: a new experimental model for in-vitro electrophysiology, Scientific Reports, 4, 5489, doi:10.1038/srep05489 (2014)

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8. Novel targeted drug formulations for infections in cystic fibrosis

Tutors: Laura Pastorino

Department: DIBRIS (University of Genova)
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Description: Chronic pulmonary infections by Pseudomonas aeruginosa are characteristic of cystic fibrosis (CF) patients, representing a limiting-life factor, currently treated by antibiotics. However, the efficacy of such treatment protocols is limited by the overproduction of a viscous and highly complex mucus in CF patients, which limits drug bioavailability and targeting at the site of infection. As a consequence, the administration of high drug concentrations is required, which results at the end in systemic side effects. Currently, the main challenge in the therapy of CF-associated infections is then related to the engineering of targeted and more efficient drug formulations.
The proposed theme of research concerns the development and characterization of nano-in-micro drug formulations displaying properties suitable for pulmonary administration and able to overcome the mucus barrier. To this aim the nanoparticles should display dimensions and chemical properties tailored to pass through the mucus layer, reaching thus target bacteria. Since the nano-dimension is not suitable for inhalable formulations, the nanoparticles should be loaded into microcontainers specifically designed for efficient pulmonary delivery, displaying also a mucolytic activity in order to facilitate nanoparticle penetration into the mucus layer.

Requirements: background in bioengineering, materials science, chemistry, physics or related disciplines. Attitude for problem solving. Interests in experimental work in the lab.

Reference: Klinger-Strobel, M., Lautenschläger, C., Fischer, D., Mainz, J. G., Bruns, T., Tuchscherr, L., & Makarewicz, O. (2015). Aspects of pulmonary drug delivery strategies for infections in cystic fibrosis–where do we stand?. *Expert opinion on drug delivery*, 12(8), 1351-1374.
Pastorino, L., Erokhina, S., & Erokhin, V. (2013). Smart nanoengineered polymeric capsules as ideal pharmaceutical carriers. *Current Organic Chemistry*, 17(1), 58-64.

Contacts: laura.pastorino@unige.it

9. Organic transistor for novel neuro-electronic interfaces

Tutors: Sergio Martinoia, Annalisa Bonfiglio,

Department: DIBRIS (University of Genova), DIEE (University of Cagliari),
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http://dipartimenti.unica.it/ingegneriaelettricaedelettronica

Description: Organic Field Effect Transistors (OFETs) and Organic ElectroChemical Transistors (OECTs) have gained in recent years a considerable interest in the scientific community because of their potential in several fields of application related to the detection of biological species and samples that need to be measured with high precision, fast, reliable and possibly low-cost methods.
The proposed theme of research concerns the development of arrays of these devices for the detection of the electrophysiological and metabolic activity in neuronal networks. The organic transistors transduction principle is that of a charge detector sensing both the quasi static variation induced on the surface of the sensor by the pH variations and the rapid charge variations induced by the cell electrical activity. In this project we aim to exploit both capabilities for developing an integrated and novel neuro-electronic interface. We plan to optimize the design of the transducer and of the array to be coupled to the neuronal system (i.e., neuronal cultures) and to investigate possible further development for in-vivo applications.

Requirements: background in bioengineering, electronic engineering, physics or related disciplines. Attitude for problem solving. Interests in experimental work in the lab.

Reference:
Spanu A., Lai S., Cosseddu P., Tedesco M., Martinoia S., Bonfiglio A., An organic transistor-based system for reference-less electrophysiological monitoring of excitable cells, Scientific Reports 5, 8807, doi:10.1038/srep08807, (2015).

Contacts: annalisa@diee.unica.it; sergio.martinoia@unige.it

10. Functional and structural connectivity: from neurons to brain networks

Tutor: Sergio Martinoia, Gabriele Arnulfo

Department: DIBRIS (University of Genova)
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Description: We are interested in investigating how computational properties emerge in neuronal populations and how information processing and transmission is related to the topological properties of neuronal networks. The nature of representation depend on the structure of the neuronal networks in terms of connectivity, size and topology, and it is further constrained by the dynamics of the system and on networks and microcircuits that are activated. In this project we propose to develop a systematic experimental and theoretical approach to focus on the interplay between structure and dynamics. For this aim, we will make use of in-vitro models constituted by neuronal networks coupled to innovative high-density devices and advanced analysis tools to characterize and interpret the experimental data. This approach will be also complemented by translating this concept into brain networks by analyzing in-vivo measurements from human patients during neurosurgery and by investigating functional connectivity by means of non-invasive measurements (high-density EEG). These techniques will be then applied to specific pathologies (e.g. epilepsy)

Requirements: background in bioengineering, physics, computational neuroscience, computer science. Attitude for problem solving. Interests in understanding/learning basic biology.

References:

Poli D., Pastore V.P., Martinoia S., and Massobrio P., From functional to structural connectivity using partial correlation in neuronal assemblies, ***J. Neural Eng.***, 13, doi:10.1088/1741-2560/13/2/026023, (2016).

Poli D., Pastore V.P., Massobrio P., Functional connectivity in in-vitro neuronal assemblies, Front. In Neural Circuits, doi: 10.3389/fncir.2015.00057, (2015)

Contacts: sergio.martinoia@unige.it

11. Do single neurons need to sleep and why? Investigating the functional significance of local sleep in humans

Tutors: Maura Casadio, Maria Felice Ghilardi
Department: DIBRIS, University of Genoa
http://www.dibris.unige.it

The city college of New York
https://www.ccny.cuny.edu/

Description: Prompted by the finding in rodents that local sleep, assessed with OFF period detection in multiunit recordings, is accompanied by slow activity in the local EEG1, we will establish if local sleep also occurs in humans and if it is related to intense learning involving circumscribed cortex areas. Preliminary results in humans show, as in rodents, a progressive increase of slow activity (2-9Hz) detected with high-density EEG in cortical areas heavily involved in learning. To further characterize these effects, we will use a motor learning task that relies on sensorimotor-parietal areas and a visual sequence learning task with prominent working memory component relying on frontal and occipitotemporal areas. In Aim 1, we will verify if intense training in each task results in EEG local, regionally-specific slow activity occurrence. In Aim 2, we will test if: intense training leads to specific impairment in performance tests involving the same brain areas; errors are associated with local EEG slow activity in specific areas and at specific times, depending on the task. In Aim 3, we will test if local EEG slow activity in wake is due to intense synaptic plasticity (tiredness), like sleep, or instead is merely fatigue due to intense activity. We will also establish if a nap, rather than just rest, is necessary and sufficient to counteract local EEG slowing and tiredness. If successful, these studies will open new ways to investigate the causes of neuropsychiatric diseases.

Requirements: Knowledge of Neuroscience, Biomedical Engineering, Physiology

Reference:
Vyazovskiy VV, Olcese U, Hanlon EC, Nir Y, Cirelli C, Tononi G. Local sleep in awake rats. Nature 2011;472(7344):443-7.

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12. Bidirectional body-machine interfaces

Tutors: Maura Casadio, Ferdinando A. Mussa-Ivaldi

Department: DIBRIS (University of Genova)
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Description: Stroke survivors face the dual problem of regaining independence in everyday tasks and recovering motor abilities. Body-machine interfaces (BMIs) address the former problem and compliant robots the latter. This project aims at developing adaptive/smart tools, based on combining BMI and robotic technologies for helping stroke survivors to recover functions of the upper body by exploiting/enhancing their residual capabilities.
The rationale is to integrate interface and robot technologies with the ultimate goal of overcoming stereotypical compensatory strategies in favor of a gradual and continuous functional reorganization of upper body movements. This reorganization will be obtained by continuously adapting the interface to the subject's physiological/psychological changes, including recovery, and progress of the illness.
The work is organized in three general objectives:

(i) TO TRANSLATE BODY-DERIVED SIGNALS onto BMI commands, encoding subjects' state, impairment and residual abilities.
(ii) TO DESIGN AND IMPLEMENT ADAPTIVE BMIs for rehabilitation, based on the individual characteristic of each subject.
(iii) TO ENCODE FEEDBACK INFORMATION of the subject's state of motion and interaction with the environment.

If successful, this research will generate the knowledge necessary for developing a new class of customized interfaces based on the users' evolving abilities. These interfaces will provide their users with both assistance and rehabilitation under a unified framework.

Reference:
Sensory motor remapping of space in human-machine interfaces. *Mussa-Ivaldi FA, Casadio M, Danziger ZC, Mosier KM, Scheidt RA. Prog Brain Res. 2011; 191:45-64.*

Contacts: maura.casadio@unige.it

13. Mechanobiology of arrhythmia

Tutors: Roberto Raiteri

Department: DIBRIS (University of Genova)
www.dibris.unige.it

Description: The project aims at investigating mechanical properties of cells that are associated with disease or dysfunction. This would allow a better understanding of the mechanisms of pathogenesis or dysfunction progression, as well as novel disease treatment strategies. The candidate will focus on the relation of cytoskeleton structure and function of cardiac muscle cells with arrhythmia, a set of heart dysfunctions that can cause sudden cardiac arrest and stroke, the two main causes of death in the world (http://www.who.int/mediacentre/factsheets/fs310/en/). The study will be conducted experimentally at the single cell level by integrating different techniques, including atomic force microscopy, optical microscopy, and electrophysiology recording. The candidate is expected to develop new *in vitro* methods for the electromechanical characterization of cardiac myocites, focusing on the role of the cytoskeleton in the so-called Mechano-Electrical-Feedback (MEF).

Requirements: The ideal candidate holds a Master degree in experimental bioengineering/biophysics, has some experience in electrophysiology and/or scanning probe microscopy on cells, and is interested in the development of new experimental set-ups.

Reference:
J.P. Kerr *et al.* "Detyrosinated microtubules modulate mechanotransduction in heart and skeletal muscle" *Nature Communications* 6: 8526 (2015) doi:10.1038/ncomms9526

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14. Development of an acoustic stimulation technology of genetically modified cells

Tutors: Michael Pusch, Roberto Raiteri

Department:
Biophysics Institute (CNR) (www.ibf.cnr.it) and DIBRIS (University of Genova) http://www.dibris.unige.it

Description: The project aims at developing a novel strategy capable to modulate remotely and non-invasively the electrical activity of genetically modified heart and nervous cells *in vitro*, by using acoustic waves. Neurons and or cardiac myofibres will be genetically modified to over-express the recently identified mechanically activated *Piezo* ion channels. The sensitivity of these cells to direct contact stimulation and to remote acoustic stimulation shall be characterized in terms of the electrical and mechanical response as well as intracellular Ca^{2+} dynamics using micro- and nano-electrode recordings, Ca^{2+} imaging and atomic force microscopy. The necessary technology to perform direct and remote acoustic stimulation combined with electrical/mechanical and Ca^{2+} dynamic readout will be developed and used to obtain a biophysical characterization of the mechano-response of the genetically modified cells (initially in simpler cell lines) at the molecular, cellular, and network level in order to prove the concept, get a better understanding of the *Piezo* channels working properties, and find optimal stimulation parameters for low-intensity, selective, and non-invasive stimulation. This technology could lead in the long term to the development of a novel class of neuroprosthetic cardiac stimulation devices.

Requirements: The ideal candidate holds a Master degree in experimental bioengineering/biophysics, has some knowledge in electrophysiology and possibly in cell and molecular biology, and is interested in the development of new experimental set-ups.

Reference:
Coste B, Mathur J, Schmidt M, Earley TJ, Ranade S, Petrus MJ, Dubin AE, Patapoutian A. 'Piezo1 and Piezo2 are essential components of distinct mechanically activated cation channels', Science, 2010, 330:55-60

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15. Machine Learning methods for big data in biology and medicine

Tutor: Annalisa Barla, Alessandro Verri

Department: DIBRIS (University of Genova)
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Description: Genomics evolved dramatically in the recent past as technology improvements allowed for sequencing of DNA at decreasing costs. This powerful technological revolution shifted the paradigm of biology and medicine to address questions at a genome-wide scale.
In this context, high-dimensional data from sequencing technologies pose complex problems from the viewpoint of understanding the real structure underlying the biological/medical phenomenon under study (i.e. finding explanatory genes for a given disease) and new computational methods are needed to deal with: (a) ever increasing dimensionality, (b) discrete nature of the measures, (c) high correlation among measured molecular variables, (d) incompleteness of measures, (e) sparseness of the underlying model and (f) computational limits of existing methods and algorithms.
This research project aims at designing and implementing a robust, unbiased and reproducible pipeline of statistical learning methods that "bet on sparsity" to find interpretable models for complex and multifactorial diseases. In particular, a great effort will be made to deal with the problem of integrating different data types and with the available domain knowledge.

Requirements: background in bioengineering, computer science, physics or related disciplines

References:
Hastie, Trevor, Robert Tibshirani, and Martin Wainwright. Statistical learning with sparsity: the lasso and generalizations. CRC Press, 2015.

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16. Towards label free super resolved microscopy by means of a differential polarization light scattering approach.

Tutor: Alberto Diaspro
Department:
Molecular Microscopy and Spectroscopy, Nanophysics, Istituto Italiano di Tecnologia
https://www.iit.it/research/lines/molecular-microscopy-and-spectroscopy

Description: Super resolved fluorescence microscopy demonstrates how the optical microscope can be pushed towards unlimited spatial resolution. Recently, polarization and scattering aspects have been developed with the aim of performing high-resolution optical microscopy without the need of labelling: label free approaches. More specifically, polarization control in pumping and probing light-matter interactions is gaining an increased interest (1). Considering biological objects acting as phase elements it is possible to decipher their structural characteristics by means of differential polarization light scattering measurements. Differential polarization light scattering microscopes (2), following the demonstration of the ability in monitoring ultra-structural motifs of biological macromolecules like chromatin-DNA (3), can be designed and optimized taking advantage of the current available technologies in optics, electronics and light sources.
This project aims to design and to implement a differential polarization light scattering microscope with the ambitious target of producing super resolved dynamic images of macromolecular architectures in vitro and in situ.

Requirements: The candidates should preferably have a background in bioengineering, optics, physics or related disciplines and experience in programming. Enthusiasm and interdisciplinary attitude are important requisites.

References:
Oldenbourg, R. 2016. A new view on polarization microscopy. Nature. 381: 811–812.
Diaspro, A., M. Bertolotto, L. Vergani, and C. Nicolini. 1991. Polarized light scattering of nucleosomes and polynucleosomes-in situ and in vitro studies. IEEE Trans. Biomed. Eng. 38: 670–678.
Finzi, L., L. Ulibarri, and C. Bustamante. 1991. Differential polarization imaging. V. Numerical aperture effects and the contribution of preferential scattering and absorption to the circular dichroism images. 59: 1183–1193.

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17. Imaging beyond the diffraction and the diffusion limits: super-resolved photoacoustic microscopy.

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Description: Optical microscopy has been revolutionized by the introduction of new super-resolved techniques able to achieve spatial resolution beyond the diffraction limit. These techniques promise to be the methods of choice for many applications, but so far they failed in such applications that need deep imaging, such as tissues of in-vivo imaging. As light travels in a tissue, scattering events cause the photons to lose their original propagation direction and thus their ability to be focused. As a matter of fact, the penetration deep, both of conventional and super-resolved optical microscopy, is restricted by the so-called diffusion limit, which is approximately 1 mm in the skin. In parallel to the introduction of super-resolved microscopy, photo-acoustic microscopy (PAM) has shown its ability to provide penetration beyond the optical diffusion limit while maintain the diffraction resolution limit. In PAM, molecules absorb light from a short-pulsed laser beam. The absorbed photon energy is partially or completely converted into heat, which induces wideband ultrasound waves that propagate in tissue. These ultrasound waves are detected by ultrasonic transducers to form an image that maps the original optical energy deposition in the sample. In the acoustic detection phase, the ultrasound waves undergo only weak scattering in tissue, which enables imaging at depths beyond the diffusion limit.
Aims of this doctoral project will be the introduction of the super-resolved basic principles in the frame of PAM. The final goal will be the implementation of a microscope system able to overcome simultaneously the diffraction and the diffusion limit for tissue imaging. Different non-linearity response of the absorption phenomena will be explored towards the realization of this novel architecture.

Requirements: The candidates should have a background in engineering or related disciplines and experience in programming. Enthusiasm, an interdisciplinary attitude, and a strong team spirit in an interdisciplinary environment are a must.

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18. Combining time-resolved spectroscopy with super-resolved microscopy.

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Description: Fluorescence microscopy has gained importance in a lot of different fields of biomedical research. There is hardly any application field nowadays where the fluorescence microscope does not play a role for the identification, visualization and particularly for quantitative measurements of biological structures and processes. Furthermore, new methods, generally referred as super-resolved techniques, have overcome one the fundamental limitation of fluorescence microscopy, namely the diffraction barrier, which was limiting its spatial resolution to few hundreds of nanometer.
A substantial part of these super-resolved methods is based on point scanning architectures, such as STED or RESOLFT microscopy. These architectures potentially allow combining super-resolved methods with the most important fluorescent spectroscopy methods, such as the time-resolved analysis, spectral analysis and polarization analysis. This combination may open new important correlative analysis for studies molecular interactions at the nanosmeter scale level.
Main goal of the project will be the realization of a multi-dimensional super-resolved microscope, which can provide new insights into the fundamental mechanisms underlying the processes of many diseases.

Requirements: The candidates should have a background in physics or related disciplines and experience in programming. Enthusiasm, an interdisciplinary attitude, and a strong team spirit in an interdisciplinary environment are a must.

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19. Computational Intelligence Methods for Eye Movements Analysis in Patients with Neurodegenerative Diseases.

Tutor: Francesco Masulli e Stefano Rovetta

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Description: Eye tracking provides promising practical, non-invasive biomarkers of cognitive impairment in patients with neurodegenerative diseases.
The performance of saccadic eye movements is easily quantifiable. The study of eye movements allows us to gather information about various brain and motor functions, and is used to identify the neuronal networks affected in neurodegenerative diseases. There is some experimental evidence that this type of analysis can be used as a prognostic tool for detection of cognitive impairment in an early phase, even before more evident signs have developed.
The PhD student will be involved in a research project involving the CNS (Paris), the Regional Reference Center for Down's Syndrome (DS) of E.O. Ospedali Galliera (Genoa) and DIBRIS. The aim of the scientific collaboration is to conduct a longitudinal study of patients with Down's Syndrome (DS), which are subject to premature aging. The aim of the study is to monitor cognitive changes in the progression of dementia in these patients.
To this end, the student will conduct one or more campaigns of experiments by recording and studying saccadic and pursuit eye movements in a group of 200 patients with DS. The research will then include a modeling phase, and the development of computational intelligence algorithms for the analysis of eye movement data, with the aims of studying the relation between the results of the batch of test oculomotor markers with the "Dementia Questionnaire for Persons with Mental Retardation" (DMR) test on all subjects and selecting the oculomotor markers most important in dementia. Groups of subjects with dementia and subjects who will develop dementia in later years will be identified, and an 'oculomotor' prognostic tool for prediction (or early detection) of the inset of dementia in DS subjects will be designed.

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