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 tissue engineering
- 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. Diffusion tensor imaging in the developing brain: moving towards higher resolution in shorter acquisition time

Tutors: Marco Fato, Andrea Rossi

Department: DIBRIS (University of Genova), in collaboration with Advanced Neuroimaging Center, Neuroradiology Unit, IRCCS Istituto Giannina Gaslini, Genova
http://www.dibris.unige.it

Description: Interest in mapping white matter pathways in the brain has peaked with the recognition that altered brain connectivity may contribute to a variety of congenital and acquired neurologic diseases in children. Diffusion-weighted magnetic resonance imaging (MRI) can provide information related to the white matter microarchitecture noninvasively. The main challenge is to obtaining high signal-to-noise ratio (SNR) in a reasonable scan time, especially in children. Additionally, as the image size increases, the image reconstruction problem becomes more computationally demanding. The diffusion tensor is the model most commonly used to derive the orientation of the fibers within a voxel; its main technological application, tractography, is routinely used in neuroimaging studies in order to graphically depict the course of the various white matter fiber tracts. However, this model has been shown to fail in regions containing several fiber populations with distinct orientations, such as the periventricular regions where multiple fiber bundles cross with each other. A number of alternative models have been suggested, such as multiple tensor fitting, q-space, spherical deconvolution, and Q-ball imaging. However, each of these has inherent limitations. The present project aims at comparing several different diffusion tensor reconstruction models in children with brain malformations, where abnormal or aberrant fiber tracts may be found, and in preterm babies, where the physiologically absent myelination reduces the fractional anisotropy and, hence, the traceability of fiber bundles within the brain. The study will be conducted on a state-of-the-art 3 Tesla MRI scanner (Philips Ingenia 3T). We also propose to develop and implement a technique to achieve higher image resolution in order to obtain more accurate measurements of specific fiber tracts.

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

Reference: Wedeen VJ, Rosene DL, Wang R, Dai G, Mortazavi F, Hagmann P, Kaas JH, Tseng WY. The geometric structure of the brain fiber pathways. Science. 2012 Mar 30;335(6076):1628-34.

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2. Bio-inspired computational systems

Tutors: Laura Pastorino, Victor Erokhin, Sergio Martinoia

Department: DIBRIS, University of Genoa
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Institute of Materials for Electronics and Magnetism, Italian National Research Council
http://www.imem.cnr.it/

Description: There is a significant difference in the architecture of the modern computers and nervous system and brain. In computers, memory and processor are absolutely separated systems. Therefore, the information plays a passive role: it can be recorded, accessed, canceled, but it makes no influence to the processor properties. In the nervous system and brain the situation is absolutely different: the same elements are used for memorizing and processing of the information. In this case, the information plays an active role: it is not only recorded, but it varies the connections within the processor, preparing it, at a hardware level, to resolve similar problems. It is learning. The main paradigm of learning is connected to the Hebbean rule, which implies a significant role of synapses. In terms of electronic engineering, synapses can be considered as junctions, whose resistance can be varied according to the duration or frequency of their involvement into the formation of signal pathways.
Bio-inspired computational systems require the realization of two main types of elements, neurons (threshold devices) and synapses (organic memristors).
The research project is focused on the realization of bio-inspired computational systems (neural networks), able to adapt, learn and make a decision at the hardware level. This will require the realization of electronic elements, suitable to the realization of elements, allowing Hebbian type of learning of electronic circuits (electronic synapses).
Currently, organic memristors are based on the heterojunction of conducting polymers (polyaniline) with solid electrolyte (lithium salt doped polyethylene oxide). The goal of this research is to develop an alternative technology for the formation of the conducting channel and to realize organic memristors with non-standard architecture.

Requirements: Knowledge of bioengineering, electronic engineering and physics.

Reference: Electrochemical model of the polyaniline based organic memristive device, Demin, V. A. and Erokhin, V. V. and Kashkarov, P. K. and Kovalchuk, M. V., Journal of Applied Physics, 116, 064507 (2014)

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3. 2D and 3D neuronal networks coupled to microtransducer arrays for the development of in-vitro neurotoxicity tests

Tutor: Sergio Martinoia

Department: DIBRIS (University of Genova)
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Description: We are interested, in general, in investigating how computational properties emerge in 2D and 3D neuronal populations and how information processing and transmission is related to the topological properties of neuronal networks. In this project we propose to develop a systematic and controlled experimental approach for investigating the dynamics of 2D and 3D neuronal networks coupled to innovative high-density devices by means of advanced analysis tools. We plan to extensively characterize and compare 2D and 3D neuronal cultures by means of electrical and chemical stimulation. In addition we will also characterize the 3D structure by means of optical (confocal) microscopy and immunofluorescence techniques. Within this framework we seek at developing a new in-vitro and automated system for neurotoxicity tests. In the last part of the project we foresee to challenge our experimental models with chemical substances and to study the electrophysiological response with respect to specific parameters (biomarkers).

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

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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4. 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)
http://www.dibris.unige.it

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: C.J. Honey, J.P. Thivierge, O. Sporns, Can structure predict function in the human brain?, Neuroimage, 52 766-776.

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5. Representing peripersonal space through sensorimotor likelihoods

Tutors: Silvio P. Sabatini, Fabio Solari

Department: DIBRIS (University of Genova)
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Description: While there is a growing evidence that the space immediately around the body (i.e., the *peripersonal space*) is coded in a distributed way across several coexisting reference frames, our knowledge of how different representations are aligned, adapt, and interact is still in its infancy. Where, when, and how does the brain implement the internal models underlying the sensorimotor transformations that guide both our actions and perceptions? Is the encoding of sensory information static, or does it change dynamically as the action unfolds? Looking for answers to these questions should help understanding how an agent should use sensing and proprioception-like signals dynamically to build sensorimotor representations of peripersonal space and self-calibrate.
Within the research framework developed in the PSPC lab at DIBRIS (see www.eyeshots.it), the activity will focus on the design of theoretical models by converting computational approaches from engineering into cortical-like models of implicit representations of the peripersonal space. Such implicit representations, besides advancing experimental predictions about neuronal activity, are expected to drive learning of meaningful interactions with the environment thus achieving fluid multi-dimensional motor control in the presence of multiple sensory channels, and with minimal *a priori* knowledge.

Requirements: background in bioengineering, computer science, physics or related disciplines, strong interest in computational neuroscience.

Reference: Antonelli M., Gibaldi A., Beuth F., Duran A.J., Canessa A., Chessa M., Solari F., del Pobil A.P., Hamker F., Chinellato E. and Sabatini S.P. (in press) *A hierarchical system for a distributed representation of the peripersonal space of a humanoid robot*. IEEE Trans. on Autonomous Mental Development.

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6. Bidirectional body-machine interfaces

Tutors: Maura Casadio, Ferdinando A. Mussa-Ivaldi

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

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.*

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

Tutors: Annalisa Barla, Alessandro Verri

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

Description: Genomics is a relatively new scientific discipline, evolved 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.
Data made available by new 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).
Indeed, 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 investigating statistical learning methods customized for genomics sequencing data, focusing in particular on the so-called "matrix recovery" problem to deal with incomplete or unavailable measures and on the parallelization of statistical methods that do not yet scale on such huge dimensionality.

Requirements: background in bioengineering, computer science, physics or related disciplines
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8. Integration of health-related services into platforms for active ageing

Tutors: Danilo Pani, Luigi Raffo

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

Description: The conception of systems for social inclusion, active ageing and independent living is a complex task, requiring a multidisciplinary approach aimed at the development of acceptable solutions for the elderly. Compared to other systems, the target users present peculiar needs, primarily due to the digital divide problem and to low computer literacy. Furthermore, the inclusion of health services has a certain psychological impact, because of the contrasting needs of monitoring and assistance and the desire of both independency and self-confidence. Regulatory issues in the field of medical devices also need to be carefully taken into account.
The research activity is part of the international AAL project HEREiAM - *An interoperable platform for self care, social networking and managing of daily activities at home* coordinated by University of Cagliari http://www.hereiamproject.org/, where an Android-based system for the digital television is envisioned to provide services fostering independent living of older adults. The proposed research theme concerns the conception, development and evaluation of tele-health services, including both software and hardware components, possibly implemented as medical devices, embedded in the HEREiAM platform.

Requirements: background in bioengineering and/or electronic engineering. Attitude for problem solving. Interests in experimental work.

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9. Bi-directional Electronic Interfaces with the Human Peripheral Nervous System

Tutors: Massimo Barbaro, Paolo Meloni

Department: DIEE (University of Cagliari)
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Description: The human upper limb and hand are versatile organs capable to reach and grasp heavy or delicate objects and to perform highly complex manipulations on the basis of fine motor control and precise sensory feedback. Limb amputation implies the loss of part of the limb and also the truncation of the nerves that provide the limb with sensory and motor innervation. The restoration of these sensorimotor functions after upper limb amputation is particularly challenging. A key element for such restoration is the development and use of suitable interfaces for online bridging the user's nervous system and the external prosthesis. Within such research framework, several tasks are needed: development of a proper recording/stimulation integrated device, development of a wireless transcutaneous link for data communication and power transfer, safe and hermetic packaging of the embedded electronics, development of an implantable digital processing platform. Key features will be low-power/low-noise capabilities, medium-large effective resolution, long-lasting batteries compatible with year-long implantation.

Reference: Sci. Transl. Med., 6 November 2013: Vol. 5, Issue 210, p. 210rv2

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10. Organic Bioelectronics

Tutors: Annalisa Bonfiglio

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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.
Several examples of OFET- and OECT-related sensors and biosensors have been presented with a variety of working principles, as, for instance, Ion Sensitive OFETs (ISOFETs), Electrolyte-Gated OFETs (EGOFETs), OTFTs, OECTs.
In a transistor, the channel current is normally modulated by varying the voltage applied across the dielectric layer between gate and source (taken as the reference terminal), i.e. any charge variation on the gate side is able to induce, by capacitive coupling across the gate dielectric, a current variation in the channel. Thus, a transistor is in fact a charge sensor and any bio- or chemo-reaction which implies or induces a charge variation on the gate could be in principle detected with this device.
The proposed theme of research concerns the development of these devices and, in particular, the specialization of these structures towards the detection of physical variables (as for instance temperature and/or strain) by means of piezo- and piroelectric materials at the interface between the device sensitive area the surrounding environment. Applications in the field of robotics, wearable monitoring systems, multimodal sensing will be addressed.

Requirements: background in bioengineering, electronic engineering, physics or related disciplines. Attitude for problem solving. Interests in experimental work in the lab.
Reference: M. Demelas, S. Lai, A. Spanu, S. Martinoia, P. Cosseddu, M. Barbaro, A. Bonfiglio "Charge sensing by Organic Charge-Modulated Field Effect Transistors: application to the detection of bio-related effects", Journal of Material Chemistry B, 2013, published online 16.05.13, DOI: 10.1039/C3TB20237B

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11. Organic transistor for novel neuro-electronic interfaces

Tutors: Annalisa Bonfiglio, Sergio Martinoia

Department: DIEE (University of Cagliari), DIBRIS (University of Genova)
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http://www.dibris.unige.it

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).

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12. Telomerase activity detection by organic electronic biosensor

Tutors: Massimo Barbaro

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

Description: The activity will be part of project AMBROSIA – *Pl**a**tfor**m** for **b**io-elect**r**onic detecti**o**n of expres**si**on of telomer**a**se*.
AMBROSIA aims at developing a technology for rapid and real-time assessment of telomerase activity by the electronic measure of telomeres elongation.
Telomeres are the structures that protect chromosome ends from both recombination and degradation; they progressively shorten in replicating cells, thus their length represents a "biological clock" that determines cell senescence. Telomerase is able to avoid telomere shortening by synthesizing the addition of further hexanucleotide repeats in telomeric DNA. Elevated expression of telomerase is a key hallmark of human cancer and an indication of malignancy, while its reduced activity has been demonstrated in neurodegenerative diseases. Inhibition of telomerase is one of the most promising strategies for blocking the replication of cancer cells, while its re-activation has been shown to address amyotrophic lateral sclerosis. Telomerase is selectively expressed in very low natural abundance and the assays currently used have problems of speed, accuracy and reproducibility. AMBROSIA proposes overcoming these problems by developing reliable electronic systems based on the integration of biodevices realized in different technologies (CMOS, organic), microfluidic flow cells and appropriate surface chemistry.
The proposed theme of research concerns the conception, study and development of the electronic organic biosensor.

Requirements: background in electronic engineering and bioengineering. Attitude for problem solving. Interests in experimental work. Expertise in organic devices realization and DNA electronic detection.

Reference: Lai S., Demelas M., Casula G., Cosseddu P., Barbaro M., Bonfiglio A., "Ultralow voltage, OTFT-based sensor for label-free DNA detection", (2013) Advanced Materials, 25 (1), pp. 103-107.

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13. Mechanobiology of cancer tissue engineering

Tutors: Roberto Raiteri, Silvia Scaglione

Department: DIBRIS (University of Genova) http://www.dibris.unige.it **; Institute of Electronics, Computer and Telecommunication Engineering (CNR)** http://www.ehw.ieiit.cnr.it

Description: Cancer maturation and progression is associated to metastasis, a multi-stage process in which the malignant cells comprising the primary tumor spread and colonize distant organs. The steps characterizing metastasis initiation and progression are characterized by various and heterogeneous biological processes that are challenging to incorporate in current models of cancer research.
The aim of this PhD project is to develop and characterize a 3D model of cancer tissue (e.g. breast cancer) using scaffolds based on ECM-like hydrogels Both aggressive metastatic cells and non-malignant cells will be used in order to optimize the optimal cellular composition to reconstruct the native cancerous environment. Hydrogels show peculiar mechanical and topographical properties, and can be functionalized to promote enzymatic degradation and cell migration, this triggering the metastatic potential of the cells in contact with them. Moreover, they allow to generate versatile 3D configurations. In particular, the effects of the mechanical stimuli/properties from the environment on metastasis will be investigated, together with the mechanical properties of cancer cells, with particular reference to cytoskeleton stiffness changes in the transition from healthy to malignant and during tumor progression. It has been highlighted, in fact, (i) that cell stiffness decreases in cells with higher malignancy and metastatic potential, (ii) that tumors with high invasive potentials have a stiffer extra-cellular environment, and (iii) that cancerous cells present increased acto-myosin cortex contractility as compared to corresponding healthy cells, thus significantly changing cytoskeleton properties. While several genetic mutations or chemical processes characteristics of metastasis have been identified, the contribution of the mechanical properties of cells and their environment in this process is yet unclear. This project will allow to further decouple the importance of the underlying signaling pathways and possibly formulate new routes for cancer treatment.

Requirements: background in one or more of the following fields: bioengineering, materials science, physics, biomechanics. Attitude to experimental work. Interest in understanding/learning basic biology.

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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. ICT for standardized and secure clinical data management

Tutors: Mauro Giacomini

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

Description: Nowadays, the necessity for an EHR to store all relevant healthcare information related to a person's lifetime to support treatment continuity, education and research is increasing. An efficient EHR system must be integrated within an architectural context designed to satisfy the needs of all actors involved in this information management by adding and integrating new functionalities to existing solutions, financed by previous investments. The Service Oriented Architecture (SOA) paradigm provides a good approach to promote the easy integration and alignment of a new and existing solution into a cohesive architecture. DIBRIS has designed a SOA based solution, following the indications and standards provided by Healthcare Services Specification Program (HSSP) to completely support interoperability in healthcare, which can represent suitable candidate of this infrastructural context.
This project aims to study ICT solutions able to be integrated within this architecture, requiring fewer changes possible, to design a complex solution that must guaranty security in terms of:

- Access control
- Auditability
- Clinical and administrative data cryptography.

Security is a fundamental requirement to allow healthcare solutions to be approved by national and international Ethics Committees, which represent the patient's right to data privacy. This aspect is necessary to allow solutions to be adopted in daily clinical practice.

Requirements: background in bioengineering/computer engineering/electronic engineering, deep knowledge on SOA, infrastructural architectures, security, software programming, medical informatics standards and attitude in problem solving.

Reference: R. Gazzarata, F. Vergari, T. Salmon Cinotti and M. Giacomini "A standardized SOA for clinical data interchange in a cardiac telemonitoring environment" IEEE Journal of Biomedical and Health Informatics, 2014, vol. 18 n. 6, pp. 1764 – 1774, http://dx.doi.org/10.1109/JBHI.2014.2334372

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16. Community detection in biomolecular networks

Tutors: Stefano Rovetta

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

Description: Inferring groups of interacting proteins or genes with biological significance is a main trend of the current bioinformatics research, as this task can help in revealing the functionality and the relevance of specific macromolecular assemblies or even in discovering possible macromolecules affecting a specific biological process. Protein and gene interaction networks can be modeled similarly to social interaction networks, so that these biologically significant groups correspond to communities. Reliable algorithms able to discover such communities may increase knowledge about biological functions at a molecular level, and may support drug discovery and enhance disease treatments even in earlier stages. This project is aimed at the development of effective tools for community detection in biological networks using methods of network and graph theories, machine learning, and computational intelligence. For instance, a significant application goal, important for cancer biomarker research, is a better understanding of the role of miRNAs, a novel class of non-coding RNA able to modulate the expression of their "target" genes. The available algorithms, mostly based on structural information, are still not able to provide a biological enrichment of their results, that can instead be obtained from the proposed analysis.

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

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17. Interaction of NPs with biomembranes

Tutors: Silvia Dante, Alberto Diaspro

Department: Nanophysics (IIT)
http://www.iit.it/en/research/departments/nanophysics.html

Description: Nanoparticles (NPs), and in particular ultrafine structures with a size from 10 to 100 nm, are increasingly employed for a great variety of biomedical applications, including drug delivery, imaging, cancer treatment and gene therapy. One of the crucial aspects of using NPs is their unknown toxicity. Manufactured NPs, are indeed potentially capable of inducing defects in cell membranes such as physical disruptions, formation of holes, thinned regions, and can therefore compromise the correct cellular machinery. Since the cytoplasmic membrane is the first place where NPs-cell interactions can occur, the investigation of how NPs may influence biological membranes is essential for understanding potential cytotoxic effects of NPs. Recently, it has been shown that NPs may directly interact with lipid bilayer membranes, affecting thereby their stability; additionally, formation of ion-selective pores in lipid bilayer as a consequence of NP interaction with membranes has recently been reported. However, the mechanism of how NPs interact with lipid bilayer remains unclear. The aim of this project is to clarify these mechanisms at the nanoscale and as a function of model membrane composition and NPs size, shape and surface charge; several techniques will be employed ranging from advanced AFM, correlative imaging techniques, and spectroscopic methods. Synchrotron radiation and neutron scattering are also proposed as structural methods of investigations, upon beam time assignment at Large Scale Facilities.

Requirements Candidate should have a M.D. Biotechnology, Bioengineering, Chemistry, Physics.

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18. A new experimental approach towards the characterization of unrevealed neurodegenerative mechanisms in Alzheimer's disease. AFM-STED correlative nanoscopy.

Tutors: Claudio Canale, Fabrizio Chiti, Alberto Diaspro.

Department: Nanophysics (IIT)
http://www.iit.it/en/research/departments/nanophysics.html

Description: The strict correlation between neurodegeneration in Alzheimer's disease and interaction of cell with misfolded protein aggregates is confirmed by several evidences. Nowadays the toxicity of oligomers rather than monomers and fibrils is well established, as well as the key role that is played by the interaction between amyloid peptides and cell membrane. In spite of this, the exact mechanism that drives neuronal failed is still an open question. In the last years we studied the interaction between lipid membranes and Amyloid Beta (Aβ) protein on model system with different degrees of complexity [1,2]. The Atomic force microscope (AFM) have been employed to this purpose, taking advantage of its ability to work in liquid environment and in controlled conditions, providing high resolution imaging capability and local mechanical characterization. On the other hand, the lack of chemical specificity represents one of the main limits of the AFM, especially working on highly inhomogeneous samples. Super-resolution techniques are able to investigate molecular systems, working on labeled samples. The coupling between these techniques will open the way to a new class of analysis [3]. Membrane-protein interaction will be initially investigated working on complex model systems, but having the capability to discriminate the diverse components of the sample by fluorescence imaging at high resolution. The aim of this project is to go deeper in the investigation between amyloid oligomers correlating the information derived by the two techniques: membrane structure and local mechanical properties (AFM) and the high resolution chemical imaging (STED).
The analysis will be initially carried out on HypF-N oligomers, a model protein that is not amyloidogenic *in vivo,* but that *in vitro* can form amyloid aggregates that displayed high level of cytotoxicity [4]. The results will be compared with those obtained studying the behavior of Aβ oligomers.

References:
1. Canale, C.; Seghezza, S.; Vilasi, S.; Carrotta, R.; Bulone, D.; Diaspro, A.; San Biagio, P. L.; Dante, S. *Biophys. Chem.* **2013**, *182*, 23–29.
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3. Harke, B.; Varghese Chacko, J.; Haschke, H.; Canale, C.; Diaspro A. Optical Nanoscopy 2012, 1,3
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19. Improving penetration depth in Two-photon Optical Nanoscopy.

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Department: Nanophysics (IIT)
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Description: In STED microscopy, fluorescence emanating from the periphery of the focused excitation beam is suppressed by a second properly shaped beam that depletes the excited state population through stimulated emission. This effectively narrows fluorescent molecule signature, the point spread function (PSF) of the microscope, to permit super-resolved images to be acquired. The Optical Nanoscopy theme is related to the development of an original class of two-photon excitation–stimulated emission depletion (2PE-STED) optical microscope. This imaging technique will be extended to the bioimaging of thick samples at nanoscale resolution in all the three dimensions, for key applications to tracking of molecular events in living cells towards the study of degenerative processes like neuro-diseases, tumor progression and nanoparticle toxic effects on biological systems. Therefore, since the image quality of a microscope is often degraded by wavefront aberrations induced by the specimen, we will improve the resolution and signal of 2PE-STED nanoscopy by adaptive wavefront correction based on sensing the wavefront of backscattered light and wavefront control by a spatial light modulator.

Reference: Bianchini, P., B. Harke, S. Galiani, G. Vicidomini, and A. Diaspro. (2012) Single-wavelength two-photon excitation-stimulated emission depletion (SW2PE-STED) superresolution imaging. Proceedings of the National Academy of Sciences. 109: 6390–6393

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20. Zebrafish larvae as a model system for studying nanomaterial's toxicity

Tutors: Marta d'Amora, Alberto Diaspro

Department: Nanophysics (IIT)
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Description: It has been estimated that over 10% of all objects surroundings humans will involve nanotechnology. However, very little is known on the impact that products incorporating nanotechnology, could have on human health and environment. Within this framework, nanotoxicology studies is undergoing on different model systems, involving both embryos and adult organisms.
Zebrafish has a remarkable similarity in the molecular signaling processes, cellular structure, anatomy and physiology to other higher order vertebrates, making it an excellent vertebrate model organism. Recently zebrafish has been shown to be a useful animal model for assessing toxicity and pharmacological effects of numerous compounds with a focus on the developmental effects and to obtain nanotoxicity information at the whole animal level [1]. The overlying objective of this proposed research is to study the effects of different nanomaterials in zebrafish during the development with particular reference to those relating to the nervous system. The assessment of these potential effects will be carried out through a multi-level investigation, which includes the analysis of behavioral anomalies, brain malformations and molecular response. The cellular answer to the stress will be investigated using combined approaches, ranging from cellular and molecular biology techniques to the most advanced fluorescence imaging methods.

Requirements: Background in cellular and molecular biology or related disciplines with interest in multidisciplinary studies such as nanotechnology.

Reference: [1] V.E. Fako and D.Y. Furgeson, Zebrafish as a correlative and predictive model for assessing biomaterial nanotoxicity. *Adv Drug Deliv Rev*, (2009) 61:478-486, .

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21. Nanoporous alumina for chemotherapy drug delivery

Tutors: Marco Salerno, Alberto Diaspro

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Description: The project will aim at developing nanoporous substrates for drug delivery of pharmaceutical molecules for cancer therapy. Chemotherapy could be delivered in situ at the affected organ tissue by implants consisting of anodic porous alumina (APA) [1] or titania (APT) chip coatings, which should provide sustained release of the previously loaded drug (e.g. cisplatin or paclitaxel, curcumin or asparaginase, or functional nanoparticles). The controlled release will be obtained by sealing the APA carrier with spin-coated films of resorbable polymers already used in orthopedical applications, such as PLLA/PLGA. By tuning the film composition and thickness, the proper elution profile will be designed, by progressive dissolution of the sealing. The goal is reaching a time period of at least 4 weeks with levels of at least 10-5 mg/day. The device will be particularly promising for permanent implants against bone tumor. In the last part of the project, in vivo animal models will eventually be explored, to confirm efficacy of the device.

Requirements: MSc in Chemistry / Physics / Materials Science. Base knowledge of Raman/SERS spectroscopy and advanced imaging (FE-SEM, AFM) will be a necessary prerequisite. Background in electrochemistry (APA/APT synthesis), pharmaceutical drugs and/or biosensor principles, and/or cell culture techniques will be a plus.

Reference: Chiara Toccafondi et al., Multifunctional substrates of thin porous alumina for cell. Biosensors, J Mater Sci: Mater Med 2014

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22. Computational Intelligence and Health and Wellbeing Support

Tutors: Francesco Masulli

Department: DIBRIS (University of Genova)
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Description: In the last few years, in the electronic consumer market many low cost sensing devices have become available, including activity-tracking wristbands with accelerometers and monitoring of heart rate, skin conductance and temperature; motion and gesture trackers; eye trackers; and wireless brain activity trackers employing few selected eeg channels. Those sensing devices, possibly integrated with standard computer and mobile phones and tablets, make possible the development of individual health and wellbeing supports, including monitoring of the health state of fragile people, sleep analysis, and serious games for cognitive and physical rehabilitation. The development of new innovative Computational Intelligence techniques (Neural Networks, Evolutionary Computation and Fuzzy Logic) for supervised and unsupervised analysis of the masses of sensor data potentially available is one of the main challenging tasks of this activity. The project will be carried out in the framework of collaborations with clinical partners, with the aim of improving the health assistance and the wellbeing, and to reduce the costs of medical care.

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

Reference: Anguera J, et al, Video game training enhances cognitive control in older adults. Nature. 2013 Sep 5;501(7465):97-101.

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