BIOPHYSICS and BIOSIGNALS

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SCIENTIFIC MISSION

Biological and Medical Physics in Trento

The Biophysics and Biosignals Laboratory of the Department of Physics aims to apply techniques and ideas from physics to study general principles of living systems organization and to develop novel technology platforms targeting disease mechanisms for improved diagnostics and therapy.

The Lab was established in 1975. Since then, it developed a number of teaching and research programmes within the University of Trento as well as in collaborative initiatives with the Trento Hospital, the Istituto Trentino di Cultura (now Fondazione FBK) and the CNR-IBF Istituto di Biofisica. As a result, new research and professional groups were established within such institutions giving rise to an internationally recognized local network active in the field of Biological and Medical Physics.

Current research activities in the Lab are described under the following topics:

- Cardiac Dynamics
- Bioimaging

Cardiac Dynamics

We study the function of the human heart pump as it emerges from the collective dynamics of millions of strongly interacting cells well organized in their geometrical structure and connectivity. In normal conditions the efficient pump function results from coherent cardiac contractions triggered by electrical non linear wave pulses spontaneously generated in the heart tissue itself (pacemaker) and characterized by a well organized propagation both in space and time. Instabilities produced by diseased tissue but also by dynamical heterogeneities, may, however, induce cardiac arrhythmia and fibrillation, the main cause of premature death in the developed world. In such conditions the electrical control of the heart passes from the pacemaker to dynamically generated, high-frequency self-excitation of the muscle (reentry, spiral or scroll waves). Consequently the coherence of contraction is lost and the cardiac pump function is impaired. Our research follows a multi-scale approach, spanning from the biophysics of individual cells, to cell to cell signal transmission in tissue, to the complex regulatory systems of whole cardiovascular system, and combines theoretical and experimental approaches to unravel the dynamical principles governing the operation as well as the malfunction of heart.

The principal ongoing projects are:

- Linear and non-linear modelling of cardiovascular control

Cardiovascular regulation is the result of a number of interacting adaptive non linear control processes. In order to modelling and disentangling the physiological mechanisms of this complex system is not only important to detect rhythms and interactions but also to identify driver–response relationships. Starting from the Nobel Prize C.W.J. Granger definition of causality, we asses and quantify directional interactions through the measure of causal interdependence of multivariate time series by exploiting and refining linear and non linear methods to quantify to which extent the variability of one series depends on the variability of the others. The results have been successfully applied to the analysis of both cardiovascular and brain signals to foster further physiological comprehension and the development of more potent and robust diagnostic tools.
Atrial arrhythmias mechanisms: identification and control.
The existence of re-entrant and spiral waves has been well documented in cardiac tissue during the abnormal electrical wave propagation related to certain arrhythmias. The stability of these waves depends on a number of factors including the properties of the tissue and the presence of heterogeneities. Under certain conditions, spiral waves can break up leading to irregular spatio-temporal patterns that may be responsible for cardiac fibrillation. We investigate atrial arrhythmias and in particular atrial fibrillation, the most commonly observed arrhythmia that can lead to reduced ability to undertake physical activity in mild cases to serious impairment or death in severe cases. This project aggregates an interdisciplinary team to help develop an understanding of atrial arrhythmias from a perspective of basic science.

Bioimaging
We pursue research on image acquisition, processing, and analysis of biological systems. In particular, we focus on use of novel optical and electron microscopy instrumentation combined with computational tools to enable dynamic, multi-modal, cell and tissue imaging. The main ongoing projects are:

- **Non-linear optical microscopy of cells and tissues.**
  In the optics laboratory of the biophysics group a state-of-art multi-modal microscope has been recently set up. Besides conventional fluorescence imaging, the device allows for 2-photon excitation microscopy which outperforms confocal microscopy with respect to resolution and penetration depth. Moreover photodamage of the sample is reduced to a minimum. This makes the technique perfectly suitable for in-vivo imaging of biological samples. After complete testing and characterization of the system, first experiments are focusing on functional imaging of the honey bee brain. Questions concerning information processing of olfactory signals in the brain and lateralization of brain functions will be addressed. Up to now, precise optical tomography imaging and 3D reconstructions of the brain morphology has been performed to identify the brain’s functional units. In ongoing experiments calcium-sensitive dyes are used to monitor brain activity changes which manifest themselves in variations of the calcium ion concentration. Thanks to the microscope’s subcellular resolution and a line-scan acquisition rate up to kHz, this will allow for real time observation of single neuron action potentials.

- **Microstructures at tissue-biomaterial interface**
  The interaction of tissues with biomaterials and medical devices deserves a crucial importance in a large variety of medical technologies: from implanted sensors and prosthesis to drug delivery systems; from pacemaker leads to dialysis machines. The tissue-biomaterial interface is the location of a number of dynamic biochemical processes and reactions with intracardiac electrical recordings) and accurate modelling can be applied to provide fundamental new insights into the mechanisms and dynamics of atrial fibrillation and to improve risk assessment and therapeutic technologies.
physiological consequences that are now recognized to be decisive for success or failure of the medical procedure. Moreover, the role of interface is even more important when dealing with tissue-engineered products and the success of many emerging biotechnologies depends upon the ability to tune cell function for mimicking in-vivo conditions. Patterning biomaterial surfaces with topographical and chemical features at the micro- and nano-scale provides for engineering the tissue-biomaterial interface thus allowing the selective control of specific cell response in-vivo. The ongoing project addresses this challenging issue by characterizing explanted human prostheses and perimplantar tissues. The study, in collaboration with the Department of Medicine Laboratory at Trento Hospital, combines clinical methods (microbiology, histology and immunohistochemistry) with advanced imaging techniques (SEM, ESEM, AFM, and Confocal Optical Microscopy).

HIGHLIGHTS

1. MULTIMODAL IMAGE INTEGRATION FOR UNDERSTANDING ATRIAL FIBRILLATION MECHANISMS AND PLANNING THE TREATMENT

State of the art
Atrial fibrillation (AF), the most common arrhythmia, is frequently disabling and its management remains challenging. In the last few years its underlying mechanisms have been thoroughly investigated in the clinical setting via a range of continually evolving techniques of cardiac-excitation mapping. Basically the maps are constructed by recording the electrical activity from a number of sites within the atrial chambers. Electrical recording is accomplished through catheters with embedded electrodes threaded, via the systemic vascular tree, directly into the cardiac chambers. Images of the heart’s electroanatomy and electrophysiology (electroanatomical maps) are then produced by complementing the recording system with techniques that include an endocardial analog of the Global Positioning System. We have learned that localized anomalous sources of high frequency electrical activity (local foci) may act as initiating triggers for the AF, while its maintenance is sustained by multiple reentrant wavelets. Therefore an effective treatment is based on the catheter-delivered radio-frequency energy (ablation) to eliminate the initiating triggers that are significantly clustered within the pulmonary veins and further improved by additional lesions performed on the atrial body. The precise location of the ablation lines is still a matter of debate, mostly due to the still incomplete understanding of the mechanisms underlying the arrhythmia. Several studies have suggested that the morphology of atrial electrograms could provide significant indications about the location of critical sites involved in AF maintenance. In particular the presence of...
complex fractionated atrial electrograms has been correlated to a well defined electrophysiological substrate and thus proposed as a marker of additional target sites for ablations. To this purpose a number of quantitative methods have been devised to characterize the complexity/organization of atrial endocardial signals [1-4]. Among them, the morphological approach proposed in [3], which quantified the regularity of single electrograms as the presence of activation waveforms with stable morphology (wave-similarity analysis), has been proved to be the more effective in a multiparameter comparison study [4]. This approach evidenced the existence of spatio-temporal patterns during atrial fibrillation, characterized by organization levels correlated to the different anatomic locations [5] and progressively deteriorating with time [6]. However the construction of accurate wave-similarity maps was limited by the available scarce anatomical detail obtained from the electroanatomical mapping systems, whereas there is a need for highly-resolved anatomical reconstruction to effectively correlate the electrophysiological substrate with precise anatomical landmarks.

Our contribution
A pre-procedural imaging obtained with Multi-detector Computed Tomography (MDCT) or Magnetic Resonance (RM) tomography may offer the required anatomical resolution [7]. We developed specific segmentation techniques [8] and we obtain highly-resolved three-dimensional (3D) anatomical reconstructions of the atrial chambers. Furthermore, as proposed in a recent study [9], we were able to automatically integrate these anatomic reconstructions with electrical/functional maps that, complemented with a biophysical modelling, significantly improve the elucidation of the arrhythmia mechanisms [10]. Moreover the clinical feasibility of the image integration approach in ablative treatment of AF has been documented [11,12].

Registration and fusion of activation map of left atrial flutter occurring after atrial fibrillation ablation showing the reentrant pattern around the pulmonary vein ablative line. (from Heart Rhythm 5: 163-164, 2008)

Conclusions
Even though AF has been formerly described as a totally disorganized arrhythmia, in recent year a growing number of evidences, based on experimental/clinical observations and sophisticated signal processing methods, has strongly suggested the presence of an underlying order in its activation pattern. Our work on tomographic image segmentation and multimodal integration of anatomical, electrical and functional maps gave a valuable contribution to such advancement in the understanding of the arrhythmia mechanism by proving the presence of patterns of spatio-temporal organization as well as anatomical locations and/or periods of highly irregular and fragmented activity. The preliminary clinical applications to the AF treatment [11,12] and to other cardiac chamber diseases [13] encouraged the hope that the new insights will be translated into improved therapeutic approaches.

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Invited lecture at the Medical Physics and Engineering World Congress (Munchen, September 2009).

References