THE INTERNATIONAL CENTRE OF BIODYNAMICS

Annual Report 2010

Contents

About us

According to the Agreement between UNESCO and Romanian Government, the International Centre of Biodynamics-ICB has been established through the decision No. 1378/2000 of the Romanian Government, under the aegis of UNESCO, as a non-profit organisation of general interest and public utility to pursue graduate training, research and development initiatives in the field of Biodynamics.

ICB focuses on non invasive, real time assays and (non)linear data analysis for appraisal of biosystems or/and of their dynamics. In a multidisciplinary approach, it integrates precise measurements into detailed models (of the dynamics) of living systems, taking into account the complexity of the interaction between biological structures and measuring system.

The potential applications of these methodologies have far reaching implications for Ecology, Food industry, Bio-Medicine and Pharmaceutical industry. Some examples are: fast detection of analytes, e.g. contaminants or/and toxic compounds in liquid media, biomass monitoring etc.

Our Mission

The International Centre of Biodynamics (ICB) is a flexible, highly dynamic structure active on the national and international research areas. It initiates and coordinates research & graduate training programs in the field of Biodynamics, for development of noninvasive, sensitive and cost effective methods to analyze and control biosystems. The applicative domains span BioMedicine, Food Industry and Ecology. ICB aims to maintain a balance between fundamental and applied research.

ICB conducts and is involved in a number of collaborative national and international research projects having the following headlines:

- Characterization techniques for cellular systems, with emphasis on noninvasive, real-time monitoring
- Detection of contaminants and adulterates in food products and water (microbes, heavy metals, antibiotics & toxins)
- Biomass and cell cycle progression monitoring
- Biomedical applications - hematological assays, pre-clinical drug screening, monitoring of tissues, organs (including ischemic processes), and cell suspensions
- Monitoring & Nonlinear Analysis of the effects of external agents on the evolution of cellular systems (drugs, toxic compounds, EM radiation, etc)
- ICB aims to provide a competitive research environment supporting the (re) integration of valuable researchers and formation of new ones through the Graduate Program in Biodynamics (in collaboration with the University of Bucharest).

Important Dates in the Institute's History

November 1996: The proposal to create the International Centre of Biodynamics, ICB, was discussed at the UNESCO Centre of Membrane Science and Technology, UNSW, Sydney, Australia

April 1998: The first International Symposium on Biodynamics

October 1999: The Agreement between Romania and UNESCO to establish the ICB

December 2000: Romanian Government issued the Decision No. 1378/2000 to establish ICB

January 2001: The ICB commences its independent activities; starts AFRAMILK, the first European Research Project (under FP5) with ICB participation

March 2001: Romanian Parliament passes the low 110/2001 to ratify the Agreement between Romania and UNESCO to establish the ICB

December 2001: In Agreement with UNESCO the first Management Board of the ICB is appointed by Romanian Ministers of Education and Research

April 2004: Appointment of the first International Advisory Board of ICB

April 2005: Starts ROBIOS, the first European Project (under FP6) coordinated by ICB

April 2006: ICB activities start in the new lodging

May 2006: The International Conference Biosensing and Biodynamics: From Basics to Applications co-financed by UNESCO

September 2008: Workshop on "Biodynamics" within the Conference "DIASPORA in Romanian Research"

September 2010: Workshop "Dynamic nanosystems: from Concepts to Sensoristic Applications" within the Conference "DIASPORA in Romanian Research"

October 2010: Seminar "GE LIFE Science Day 2010 in Romania"

November 2010: Lecture – Mihaela Gheorghiu, "ICB recent results on cellular Biosensors", National Conference on Biophysics, Bucharest

Director's Message

Despite the tough economic and research environment characteristic for 2010, this Annual Report highlights with optimism and pride the accomplishments of, and challenges faced by the International Centre of Biodynamics, ICB, during 2010 and relate them with the capabilities of ICB laboratories as landmarks of future developments.

Worth emphasizing are:

- New scientific developments

✌ microscopic approach to gauge the plasmonic behavior of clustered nano-particles.

✌ dual, in situ measurement of impedance effect and secretion of ROS by renal cells challenged by calcium oxalate.

✌ development of a novel highly sensitive method and of related device for detection of pathogen microorganisms subject to two patent applications.

- Improved Human Resources

✌ Andreea Olaru Dragan has completed and successfully defended her thesis.
✌ Two other PhD students within ICB have completed their theses.
✌ Proposal ProArgus within Marie Curie International Reintegration Grants has been accepted for financial support, Dr. Alina Vasilescu, the principal investigator of this project will join ICB team starting with beginning of 2011.

- Improved Management, Marketing and Services

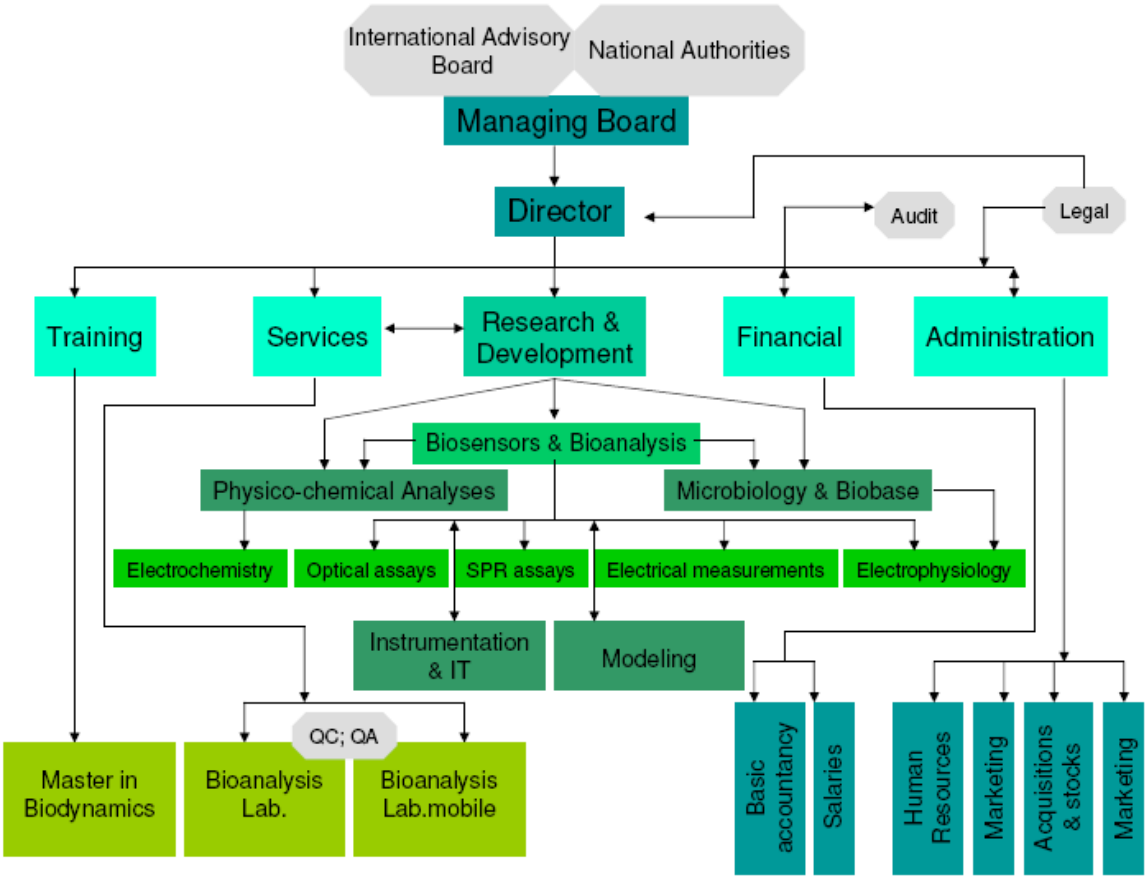
✌ Successful implementation of a project fostering ICB improved management and marketing skills financed through Structural Operational Programme.

✌ Romanian Accreditation Association accredited the Laboratory for Bio-Analysis within ICB through the Certificate No. Li 896.

These accomplishments could not have been possible without the constant support, motivation and efforts of ICB staff and collaborators as well as of ICB Management and International Advisory Boards, that fostered the continuous increase of Centre RTD capabilities and visibility during 2010.

Thank you!

Management structure



ICB Functional Structure

- Microbiology /Electrophysiology Laboratory
- Electrochemistry Laboratory
- Microfabrication & Prototyping Laboratory
- Mobile and Fixed Bioanalysis Laboratory
- Electrical Measurements Laboratory
- (Bio) Sensors and (Bio) Surface Analyses Laboratory
- Optical Microscopy Laboratory
- Modeling and Data Analysis Laboratory
- Atomic Force Microscopy Laboratory

The Managing and Advisory Boards

The International Advisory Board, the Managing Board and the Director coordinate the activity of the International Centre of Biodynamics.

According to ICB statutes the New Board was appointed in 2009, by the International Advisory Board.

Managing Board members (alphabetical order):

Prof. Dr. Serban Panaitescu
National Centre of Programme Management

Prof. Dr. Octavian Popescu
"Babes-Bolyai" University, Cluj-Napoca

Prof. Dr. Tatiana Vassu
University of Bucharest

The members and observers of the International Advisory Board (alphabetical order):

Prof. Dr. Koji ASAMI
Institute for Chemical Research, Kyoto University, Japan

Prof. Dr. Anton ANTON,
Representative of Romanian University Research Council

Prof. Dr. Jean-Michel KAUFFMANN
Universite Libre de Bruxelles, Belgium

Prof. Dr. Maciej NALECZ
Director, Division of Basic and Engineering Sciences UNESCO –Paris, France

Director, UNESCO – CEPES

Minister of Education and Research

Representative of the European Commission, to be nominated

… and us

Eugen Gheorghiu *-2001**
ICB Director
Professor
PhD, Physicist, theoretical physics
Nonlinear Dynamics and Dielectric Modeling

Dumitru Bratu *-2001**
Engineer
Electronics
Development of Electrochemical devices

Szilveszter Gáspár *-2006**
Head of Electrochemistry Laboratory
PhD, Chemist
Novel applications of electrochemical biosensing platforms

Mihaela Gheorghiu *-2001*
Head of (Bio) Sensors and (Bio) Surface Analyses Department
Professor
PhD, Physicist
Electro - Optical Analysis of Biointerfaces

Mihai Sorin David *-2003**
PhD student
Biophysicist
Bioimpedance Measurements, Biosensor Development and Nonlinear Analysis

Dana Cucu *-2004*- sept. 2010*
Head of Microbiology & Electrophysiology Laboratory
PhD, Biologist – Physiologist
Cell Physiology

Andreea Gabriela Olaru *-2006**
PhD
Biochemist
Biosensors development with different colloidal systems

Cristina Polonschii *-2006**
PhD student Biochemist
Development of analytical methods to interrogate bio interfaces

Cezar Giubalca *-2001**
Head of the Administrative Office

Valeria Nane *-2001**
Chief Accountant
Economist

Dumitru Letea *-2007**
Mechanical Technician

Irene Marcu *-2007**
PhD student
Electrophysiology

Loredana Ioana *-2010**
Management Associate
Economist

* Date of employment at ICB

Cell Biology/Electrophysiology Laboratory

Team: Dana Cucu
Irene Marcu
Mihai Sorin David

Facilities

The equipment acquired in the past years and currently used for ongoing projects is the following:

- **T**ransepithelial **I**mpedance and **N**oise **S**ystem, TINS, set-up for simultaneous measurements of transepithelial macroscopic parameters such as: short-circuit current (I_{sc}), transepithelial conductance (G_T) and transepithelial capacitance (C_T). Moreover, the system is able to perform impedance spectroscopy measurements from which one may discriminate between the trans and para-cellular pathways.

The system is set in conjunction with the culture cell facilities that enable cultivation of different epithelial tissues. Our cell collection contains renal epithelial cells (A6, MDCK-I, MDCK-II, MDCK parental, LLC-PK1), intestinal epithelial cells (CaCo-2), epithelial cells from a cervical carcinoma (HeLa), cells derived from an adrenal medulla (PC12).

- TEVC system for the measurements of currents and conductance through ionic channels expressed in *Xenopus laevis* oocytes. The set-up allows estimation of cellular capacitance from impedance spectroscopy data. The system is connected to the injection setup (Nonoliter injector) and Pipette Puller.

Current Research

In the Cell Biology/Electrophysiology Laboratory we have developed a battery of methods to study the effects of external factors (pharmaceutical compounds or bacteria) assessing several useful parameters. The methods consider:

A. Analysis of transport and cellular permeability;
B. Toxicity studies at cellular level (changes in transport properties and cellular viability);
C. Protein studies for those compounds that did not reach preclinical studies;
D. Enhancement of a compound absorption by binding to a carrier.

The results of this research were disseminated in a paper published in Biosensors and Bioelectronics.

Associated project: Expression and Function of Tight Junction proteins-a study in experimental models and in patients with dementia

Summary

Dementias are among the most frequent diseases of aged population and are characterized by a general cognitive and biological decline together with a decrease in quality of life of patients and their families. Current treatments for dementia are only symptomatic and all patients finally enter an inevitable worsening course with premature death. Our project proposes a search for new scientific data, relevant for the pathogenic mechanisms of dementias (both degenerative and vascular), which could establish new targets for pharmacological treatment. The blood-brain barrier (BBB) is a unique structure of the human body, with high selectivity and special regulation. The BBB suffer important alterations in both Alzheimer's disease and vascular dementia. Formed by protein complexes with partially unknown functions, the tight junctions (TJs) hold the key of BBB integrity, which is important since the normal function of the central nervous system depends on it. In this project we plan to explore the expression of the TJs constitutive proteins within the brain tissue and to compare it with expression in other tissue types. We also want to setup experimental models in order to study the function of these proteins in physiological conditions. To reach our aims, we propose a partnership which guarantees access to patients with dementia and to a brain bank, combined with basic neuroscience laboratory workup, targeting an investigation of both morphological and functional properties of TJs proteins. These new scientific data could generate an impact for the current pathogenic scenario of dementia and for the way we understand passage of drugs to the central nervous system, at the level of BBB.

Electrochemistry Laboratory

Team: Szilveszter Gáspár
Cristina Polonschii
Mihai Sorin David

Facilities

The resources of the laboratory include the following equipments: VSP modular potentiostat/ galvanostat (from Bio-Logic S.A., France), CellTest multi-channel potentiostat/ galvanostat (from Solartron Analytical, UK), Nanoband Explorer II anodic stripping voltammetry-based heavy metal analyzer (from TraceDetect, USA), 797 VA Computrance PC controlled system for voltammetry (from Metrohm AG, Switzerland), trinocular stereo microscope (from World Precision Instruments, USA) equipped with a Coolpix 995 digital camera (from Nikon, Japan), EG-40 micropipette beveller (from Narishige, Japan), and 3D micropositioner (HS6 from World Precision Instruments, USA).

Current Research and associated projects

Development of amperometric biosensors, and the use of such sensors to observe how cells are reacting to certain chemical stimulus, remained in the focus of our research during 2010. As a step forward, we started using electrochemical impedance spectroscopy (EIS) to observe changes in cell adherence. Changes in the adherence (to the substrate and to the neighboring cells) and the release of superoxide were simultaneously recorded from A6 renal cells exposed to calcium oxalate using EIS and cytochrome c-based amperometric biosensors, respectively. The obtained results were included in a manuscript submitted to Analytica Chimica Acta in December 2010. The manuscript highlights the advantages of simultaneously and continuously observing several cellular processes and is the continuation of another paper that has been published in the March 2010 issue of Biosensors and Bioelectronics [1].

(1) Gaspar, S.; Niculite, C.; Cucu, D.; Marcu, I. *Biosensors and Bioelectronics* **2010**, *25*, 1729-1734.

Microfabrication & Prototyping Laboratory

Team: Mihai Sorin David
Dumitru Bratu
Dumitru Letea

Facilites

CNC Shape Cutting Machine-2000 series 8 direction mill (from Sherline Products, USA), P6700 Spin coater (from Specialty Coating Systems, USA), lathe and rectifier lathe. Physical Vacuum Deposition PVD 75, Kurt J Lesker, US, Modular design configured to suit a variety of thin film deposition applications, typically for research and development or small batch production.

Current Applications

The 2000-series 8-direction mill is used for developing user defined parts and accessories from holders and test fixtures to measurement cells (static and flow through), with sizes down to tens of microns. In addition to the side-to-side rotary tilt movement, the column base offers a center pivot lock that allows the ram to be moved both in and out as well as swung from side to side. In/out travel is 5.50" and side-to-side motion is up to 90° of movement either way. These four movements are in addition to the standard mill's X-, Y-, Z-axis travel and headstock rotation movement. When used with accessories like the tilting angle table and rotary table, the machining possibilities of the mill are virtually unlimited. Mill Axis Travels: X=8.65" (220 mm)*, Y=5" (127 mm), Z=6.25" (159 mm), Maximum travel speed set into the EMC software is 22 inches/min.

PVD 75* is a three-target sputtering system with a turbomolecular pumping system, two RF targets and a DC target, for thin film deposition.

***Physical Vapor Deposition-PVD 75**

PVD 75 standard platform comprises as major modules: PVD process chamber, 210 l/s speed control compound turbo pump, dry roughing pump, 3 thermal evaporation source assembly with water cooled high current feed-through (for sequential deposition),

film thickness control, Recipe Driven Computer Control.

PVD 75 thermal evaporator from KJ Lesker is currently used for manufacture of different configuration of electrodes and for different applications requiring precise deposition of several layers of materials. For example: SPR – we manufacture SPR chips by depositing 2 nm of Chromium/Titanium and 50 nm of Gold; Magnetic SPR – we prepare metallic "sandwiches" comprising of Chromium, Cobalt and Gold; Electrode passivation – we deposit thin layer of insulating materials (e.g. SiO).

Additional facilities: Spin coating machine within glove box, laminar flow hood for specific surface functionalization, ultrasonic processors and UV ozone cleaning system. The spin coater is used for controlled deposition of thin polymer layers on solid substrates for specific applications including electrode preparation for impedance measurements, investigation of cell adhesion to various materials, controlled local electrical insulation for electrode design, customized PCB boards, optical coupling for SPR measurements

Mobile and Fixed Bioanalysis Laboratory

Team: Mihaela Gheorghiu
Szilveszter Gaspar
Andreea Gabriela Olaru
Mihai Sorin David
Cristina Polonschii

Facilities

Anodic Stripping Voltammeter Nanoband Explorer II (from Tracedetect U.S.A) Dual system EIS/SPR (ICB patent), Glomax Luminometer 20/20 (from Promega U.S.A), pHmeter and conductometer (from WTW Germany), portable UV-VIS Spectrophotometer Nova 60A (from Merck, Germany), Mobile autolaboratory equipped with working areas, separate access and electrical connections.

Current Status

The accreditation for Bioanalysis Laboratory and Mobile Bioanalysis Laboratory as third party laboratories has been finally completed, RENAR (Romanian Accreditation Association) issuing the Certificate of Accreditation L896, in October 2010. The accreditation procedure respects the ISO/IEC 17025:2005 clauses which specify the general requirements for the competence to carry out analysis (tests) and/or calibrations, including sampling. Reference standard ISO/IEC 17025:2005 is world wide used by laboratories in developing their management system for quality, administrative and technical operations performed using standard methods, non-standard methods, and laboratory-developed methods. High precision techniques such Surface Plasmon Resonance, Impedance Spectroscopy, Luminometry or Anodic Stripping Voltammetry and classical methods (UV-VIS Spectroscopy, pX-metry) are used to make primary characterization and to check the level of contaminants, for food and water samples.

Electrical Measurements Laboratory

Team: Eugen Gheorghiu
Mihai Sorin David
Cristina Polonschii
Andreea Gabriela Olaru

Facilities

Impedance analyzer Agilent 4294A (from Agilent Technologies, USA), Impedance / gain phase Analyzer Solartron; 1470 E Cell Test System(both from Solatron Analytical, U.K), Digital Oscilloscope TDS 3052 (from Tektronix SA-France), Signal generators, Phasemeter, Spectral Analyzer HP 3585; 8 channel low frequency impedance spectrometer (designed and produced in ICB);

Dedicated working lab and current utilities (purified air, ultra pure water, Faraday and thermostated chambers, 4 point electrode configurations and wide range of surface electrodes – circular and/or interdigitated, compatible with complementary optical assays).

Current Research and associated projects

- CHARPAN - Charged Particle Nanotech (FP6) •(Ro)NANOINT - Controlling the interaction between human and bacterial cells with nanostructured surfaces. Strategies for achievement "Intelligent" biosurfaces.

Investigation of lipid film formation in view of lipid sensors development - mimics for actual biological membranes.

Investigation of the dynamics of electrical parameters of cellular platforms in relation to engineered interfaces (with attractive/repulsive chemical and morphological features),

Investigation of the dynamics of electrical parameters of cellular platforms in relation to chemical and biological stressors (heavy metals, pathogen cells).

Monitoring cell cycle progression on non/synchronized cell suspensions – an on line system for electro-optical evaluation of yeast cell suspensions has been developed.

Evaluation of functionalization protocols (deposition of thin polymeric layers, biorecognition compounds or ligand – e.g. thiol layers). – Development of a multi channel dual SPR impedance set-up.

(Bio) Sensors and (Bio) Surface Analyses Laboratory

Team: Mihaela Gheorghiu
Mihai Sorin David
Cristina Polonschii
Dumitru Bratu

Facilities

-Biacore 3000 system (from Biacore AG Sweden)

-Dual spectrometer EIS/SPR (ICB patent),

-3 channel Spreeta Modules, Contact Angle Meter CAM 100(from KSV, Finland).

-Dedicated working lab and current utilities (purified air / N2, chemical hood and ultra pure water, thermo stated chambers)

-Advanced set-up for monitoring the dynamics of aquatic species and the quality of growth environment.

Additional facilities: variable angle specular module + Thermo Evolution 600 UV-VIS Spectrofotometer, AFM module NanoWizzard II, JPK, Germany, Multimode readers Promega / Turner.

Current Research and associated projects

The design of novel (bio) sensing interfaces (for selectively recognition of the analyte of interest, from low molecular compounds to cells, and for providing a concentration-dependent phenomenon that is easy to translate into useful analytical signal) towards a new generation of analytical tools. These analytical tools will extend our ability of detecting compounds of interest:

- in very low concentrations,
- in complex samples without prior separation,
- in small sample volumes (microliters) or exotic environments (such as cellular sub compartments), and
- in a timely manner. Traditional analytical approaches are very often lacking such abilities.

The integration of complementary analytical tools (SPR, electrochemistry) with micro technologies (fluidics, electronics) for the development of portable, sensitive solutions for real time detection of target analytes.

The team is involved in the developing of the following national and international projects

- BIOSADN – Development of biosensors based on nucleic acids for the evaluation and monitoring of some toxic agents with applications in bioterrorism
- ACVACONTROL – Assessment of the behavior (dynamics) of aquatic species with economic value to improve of the activities related to aquaculture and water quality survey
- (Ro)NANOMAGMA & FP7 NanoMagma NANOstructured active MAGnetoplasmonic MAterials

Accomplishments:

- 1 paper on a novel functionalization concept totaling already 8 citations;
- 1 invited lecture "Cellular Biosensors: towards a unitary, integrated (nano-bio) analytical platform" Romanian Biophysics Conference, November 2010,
- 2 invited book chapters:
  - M. Gheorghiu*, C. Polonschii, S. David, A. Olaru, E. Gheorghiu, SPR Bioanalytical platform to appraise the interaction between antimicrobial peptides and lipid membranes, In Optical Nano- and Microsystems for Bioanalytics, Series Chemo and Biosensors, **Springer** in press
  - S. Andreescu, M. Gheorghiu*, R. E. Ozel, K. Wallace, Methodologies for Toxicity Monitoring and Nanotechnology Risk Assessment book chapter in **ACS** books series "Biotechnology and Nanotechnology Risk Assessment" in press.

Novel functionalization concept

C. Polonschii, S. Tombelli, S. David, M. Mascini, M. Gheorghiu*, A novel low-cost and easy to develop functionalization platform. Case study: aptamer based detection of thrombin by surface plasmon resonance, *Talanta* 80 (2010) 2157–2164

A novel low-cost platform to assess biomolecular interactions was investigated using surface plasmon resonance and an aptamer-based assay for thrombin detection. Gold SPR surface functionalized with a carboxylated cross-linked BSA film (cBSA) and commercially available carboxymethylated dextran chip (CM5) were used as immobilization platforms for the thrombin binding aptamer. The high end commercial instrument Biacore 3000 and a custom made FIA set-up involving TI Spreeta sensor (TSPR2K23) were used to assess different concentrations of thrombin within the range 0.1–150nM both in buffer and in a complex matrix (plasma) using the obtained aptasensors. Based on data derived from both CM5 and

cBSA platforms, the cBSA aptasensor exhibited good selectivity, stability and regeneration ability, both in buffer and in complex matrices (plasma), comparable with CM5.

Optical Microscopy Laboratory

Team: Mihaela Gheorghiu
Mihai Sorin David
Andreea Dragan

Facilities

Zeiss Total Internal Reflection Microscope (TIRFM), Zeiss AxioObserver Z1, fully motorized with xyz nm resolution, equipped with EMCCD ANDOR IXon DU-885K camera, with facilities for epifluorescence, laser (3 line Ar) and white light TIRF, and various contrast methods (Ph, DIC) and for cell cultivation (OkoLab controlled environmental cage); Extended image processing facilities (AxioVision, Andor IQ and Andor IQ Tracker); dedicated chambers for combined (optical and electric) assays.; Additional filter sets 02, 09, 14.

-NIKON Eclipse 400 microscope with epiflourescence system and CCD camera for data acquisition.

Dedicated working area endowed with individual air filtration and purification units, anti-vibration tables and special illumination conditions.

Additional facilities:

spectrophotometer Evolution 600, Thermo, with variable angle specular reflectance accessory and thermostated carrousel.

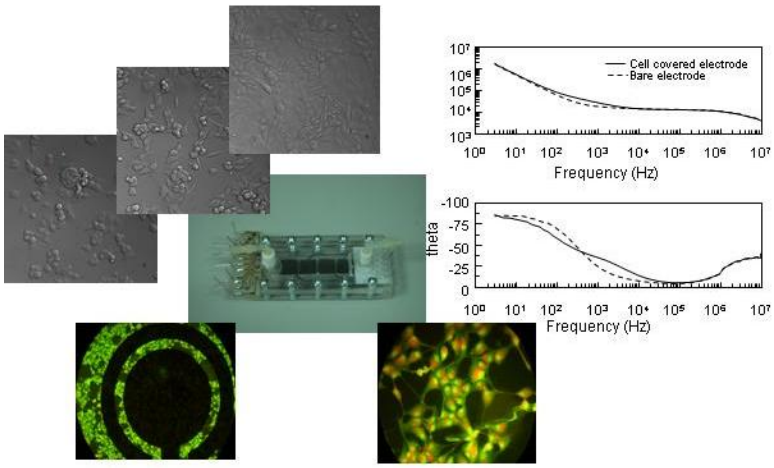
- GloMax 20/20 Multimode reader, Promega, with 2 injectors and UV and Blue fluorescence modules.

-Compatible AFM module fully integrable with advanced optical assessment.

Current Research and associated projects

Dual electro-optical measurements based on dedicated flow cells with optimized electrode configurations.

Time lapse assessment of the dynamics of cells (morphology, attachment and metabolism) and cell organelles (pH, ions, morphology) in response to external stimuli and engineered bio-interfaces cues; membrane processes in normal and pathologic conditions; manipulation and characterization of natural and synthetic lipid environments (including cholesterol). ATP & Cytotoxicity assays; Intracellular Ca^{2+};



Investigation of giant liposomes and their interaction with pore forming compounds.

- DEMENTJUNCTION - Expression and function of the tight junction proteins – a study on experimental models and dementia diagnosed patients
- PROPETHAD – Advanced research concerning medical applications of nuclear technologies (partnership with IFIN -HH)

1 Invited book chapter: S. Andreescu, M. Gheorghiu*, R. E. Ozel, K. Wallace, Methodologies for Toxicity Monitoring and Nanotechnology Risk Assessment book chapter in **ACS** books series "Biotechnology and Nanotechnology Risk Assessment" in press.

Modeling and Data Analysis Laboratory

Team: Eugen Gheorghiu
Titus Sandu
Cristina Polonschii

Current research and associated projects

We are currently developing fast, efficient methods to calculate the dielectric behavior of multi-shelled biological cells of arbitrary shape. These methods are based on the integral equation for the polarization charge induced on the dielectric interfaces. The integral equation is solved for two cases. The first case considers no free charge. The problem is broken in smaller problems which are generated by the integral operators at each interface. The solution spaces generated by the simpler problems will be used to generate the solution for multi-shelled structures. The second case adds free charge.

Current Research and associated projects

1. Dielectric modeling and nonlinear time series analysis

Strong emphasis is placed on both experimental and theoretical aspects regarding:

- Development of new, portable impedance spectrometers;
- Development of microscopic models of dielectric behavior of non spherical cells (focusing on yeasts, red blood cells, and gap junction connected cells). A quantitative approach providing shape evolution of budding yeasts during the cell cycle, consistent with experimental findings, is available.
- Nonlinear complex fitting algorithms related to microscopic and phenomenological models (e.g., Havriliak-Negami).
- Time series analysis of dielectric data yielding quantitative measures of the system dynamics (revealing changes in the tissue structure and function and the invariants of the cell cycle)

The title of our main project is: "Dielectric modeling of biological cells and hetero-structures with fast and efficient algorithms for boundary integral method" .

Accomplishments

T. Sandu, D. Vrinceanu, E. Gheorghiu "Surface Plasmon Resonances of Clustered Nanoparticles" accepted in *Plasmonics*

Linear clusters made by tightly connecting two or more metallic nanoparticles have new types of surface plasmon resonances as compared with isolated nanoparticles. These new resonances are sensitive to the size of the junction and to the number of interconnected particles and are described by eigenmodes of a boundary integral equation. This formulation allows effective separation of geometric and shape contribution from electric properties of the constituents. Results for particles covered by a thin shell are also provided highlighting ultrasensitive sensing applications. The present analysis sheds a new light on the interpretation of recent experiments

Sandu T, Vrinceanu D, Gheorghiu E. *Linear Dielectric Response of Clustered Living Cells,* Physical Review E, 81, 2, 0219131-11, (2010)

Summary: The dielectric behavior of a linear cluster of two or more living cells connected by tight junctions is analyzed using a spectral method. The polarizability of this system is obtained as an expansion over the eigenmodes of the linear response operator, showing a clear separation of geometry from electric parameters. The eigenmode with the second largest eigenvalue dominates the expansion as the junction between particles tightens, but only when the applied field is aligned with the cluster axis. This effect explains a distinct low-frequency relaxation observed in the impedance spectrum of a suspension of linear clusters

Atomic Force Microscopy Laboratory

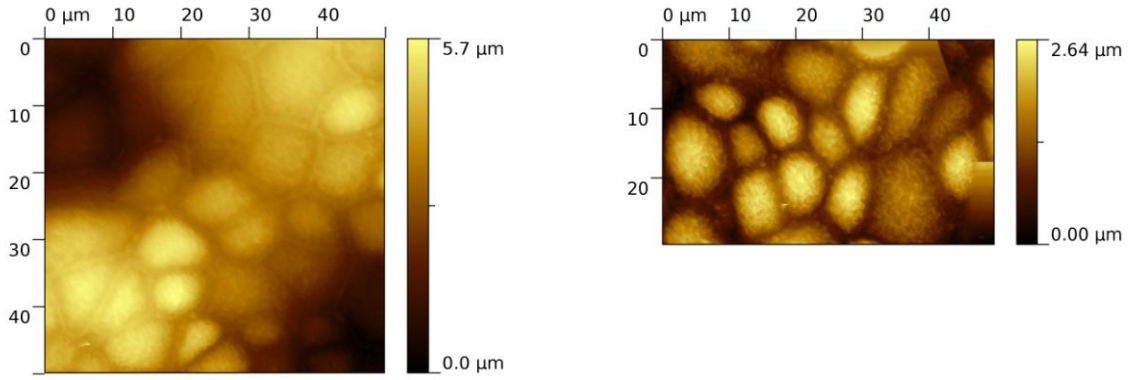
Team: Szilveszter Gáspár
Mihai Sorin David

Facilities

The major piece of equipment of the laboratory is a NanoWizard® II Atomic Force Microscope JPK AG (Berlin, Germany).

Current Research and associated projects

Our AFM instrument has the necessary features to work with biological samples (i.e. soft samples in liquid), and it is most often used to observe small cellular structures (e.g. tight junctions, microvilli, etc.) or surface immobilized proteins. For example, it was used to observe morphological changes in A6 renal cells during their growth [1] or exposure to Cd. When exposed to Cd, the morphology of A6 cells is changed. As shown in the height images below, the tight junctions are most significantly affected (i.e. they disappear).



Height images of A6 cells, before (left) and after (right) exposure to Cd.

AFM obviously remains a useful tool for materials sciences as well. Surface features and thickness of polymeric, metallic, or metal oxide films (prepared or not within the institute) are often revealed using the AFM.

(1) Gaspar, S.; Niculite, C.; Cucu, D.; Marcu, I. *Biosensors and Bioelectronics* **2010**, *25*, 1729-1734.

International projects

ONGOING

"**NANOMAGMA**" - NANOstructured active MAGnetoplasmonic MAterials"

Funded under 7th FWP (Seventh Framework Programme)

Contract no.: 214107 /2008

The purpose of this project is to study, develop and implement a new concept of nanostructured materials formed by combining components and activity plasmon and magneto-optical (MO).

ACCOMPLISHED

- „CHARPAN" – „CHARged PArticle Nanotech"
- „ROBIOS"- Strengthening ROmanian Research and Training Capacities in BIOSensing and Related Areas"
- „Effective Biosensing Platform for Rapid Detection of Environmental Pollutants", NATO Reintegration Grant, Grantee: PhD. Szilveszter Gaspar, Supervisor PhD. Eugen Gheorghiu
- Role of membrane organization and dynamics on cell behavior and response to external stimuli; Romania -Flanders Bilateral Agreement

Partners: Prof. Dr. Paul Steels, Faculty of Medicine, Limburgs Universitair Centrum; Prof. Dr. Marc de Broe, Faculty of Medical Sciences, University Hospital Antwerpen; Prof. Dr. Maria Luiza Flonta, Faculty of Biology, University of Bucharest.

- Novel Impedimetric Affinity Biosensors (IAB) for toxicological applications exploiting E.Coli membrane protein LamB - Romania-Flanders bilateral agreement

Partners: Prof. Dr. Wim de Coen, Universitaet Antwerpen; Dr. Wim Lauyren, IMEC Belgium; Prof. Dr.Patrik Wagner, Limburg Universitair Cetrum

- Development of an Impedance Assay for Immunocapture - Brancusi Romania - France bilateral agreement

Partners: Prof. Dr. J.-L. Marty, Universite de Perpignan; Prof. Dr. C. Grommidh, Universite de Montpellier

- Towards the development of a rapid portable immunoassay device for the detection of Microorganisms and Toxins in Food industry & Ecology - COBASE Grant Program 2001

Partner: Prof. O. Sadik, Dept. of Chemistry, State University, New York, Binghamton

- Impedance Spectroscopy of biological membranes: modeling the epithelial tissues and the dielectric dispersion of the plasma membrane; Romania-Flanders bilateral agreement 2001-2003

Partners: Prof. Dr. W. Van Driessche, Catholic University, Leuven; Prof. Dr. P. Steels, LUC; Prof. Dr. G. Borghs, IMEC, Belgium

- Biomonitoring quantitative evaluation of biological systems, Romanian-German Bilateral Agreement reference number RUM 003-98

Partner: Prof. Dr. E. Gersing, Anaesthesiology Clinic, Georg-August University, Goettingen, Germany

- AFRAMILK -Antifraud impedimetric and ultrasonic control system to detect fraud (adulteration) of milk GRD1-2000-25801, within the 5th Framework Program of the European Commission 2001-2004

Partners: Institute for Bioprocess - and Analysis Methods, Germany; Centre for Molecular Electronics, Durham University, UK; SECAD S.A., France; RIKILT, State Institute for Quality Control of Agricultural Products, Holland; MEVGAL DAIRY PRODUCT INDUSTRY S.A., Greece

- Fluid Rheology – Application to biology and medicine, financed by the World Bank

Coordinator: Bucharest Politehnic University (UPB), Faculty of Energetics

Partners: Gastroentherology Clinic Fundeni Hospital – Bucharest; Institute of non-newtonian fluid mechanics, Univ. of Wales –U.K; Material Science Department, T.U. Darmstadt – Germany; Chemical Engineering Department, Universidad de Huelva, Spain.

National projects

ONGOING

Financing period	Project title and managing/partnership status
2009 – 2011	RO- NANOstructured active magneto-plasmonics Materials Principal Project Coordinator: ICB
2010 – 2011	Improvement of Management and Marketing abilities within the International Centre of Biodynamics - Structural Funds, Economic Competitiveness Improvement, Axis 2.2.4
2010 – 2012	Advanced research for transforming waste (fat of ostrich) in a product with high economic value – Structural Funds, Economic Competitiveness Improvement, Axis 2.1.1 Partenership with SC SURAKI SRL

ACCOMPLISHED

Financing period	Project title and managing/partnership status
2006-2008	LIPTUM -Role of Membrane Lipids on the response of Tumoral Cells to Cytostatic Treatment Principal Project Coordinator ICB
2006-2008	NANOINT - Controlling the interaction between human and bacterial cells with nanostructured surfaces. Strategies for achievement "Intelligent" biosurfaces Principal Project Coordinator ICB
2006-2008	AQUACONTROL – Assessment of the behavior (dynamics) of aquatic species with economic value to improve of the activities related to aquaculture and water quality survey Principal Project Coordinator ICB
2007-2008	Dual Optical-Electrochemical platform for the simultaneous Intra-and Extracellular monitoring of reactive Oxygen Species Principal Project Coordinator ICB
2006-2008	Diaprogendo - The diagnostic and prognostic relevance of the endomicroscopic aspect of microvasculature in upper digestive premalign or malign lesions; Partnership with Fundeni Clinic Institute
2005-2008	APOCAD - The effect of cadmium on biomembranes. Implication in apoptosis Principal Project Coordinator ICB
2006-2008	NICKEL - Regulation of the epithelial na+ channel (ENaC) by the extracellular allergen Ni2+. effects on keratinocyte differentiation Principal Project Coordinator ICB
2006-2008	Mathematical modeling of Ca^{2+} oscillations induced by pathogen bacteria in renal cells Principal Project Coordinator ICB
2006-2008	ANTIOX–Cellular and subcellular effects of natural antioxidants in normal and pathological conditions Partnership with University of Medicine and Pharmacy “Carol Davilla”
2006-2007	AQUALAB–Mobile laboratory for water analysis (microbiological control, metal contamination) according with European directives Principal Project Coordinator ICB
2006-2007	VINOK - Method to evaluate the quality and safety of wine products – fast detection of highly risk mycotoxins (Ochratoxin A) Principal Project Coordinator ICB
2005-2007	PROMEBIOS- Promoting Romanian Participation In European Research Programs In Biosensing Principal Project Coordinator ICB
2004-2006	Monitoring system of water quality from the distribution pipes: detection of pathogen microorganisms using biosensors Principal Project Coordinator ICB
2004-2006	Developing the invention "Rapid High Accuracy Impedance Measurement Method in AC" to HACCP in dairy industry Principal Project Coordinator ICB
2007-2010	Dielectric modeling of biological cells and heterostructures with fast and efficient algorithms for boundary integral method Principal Project Coordinator ICB

2007-2010	DEMENTJUNCTION - Expression and function of the tight junction proteins – a study in experimental models and dementia diagnosed patients Partnership with "Victor Babes" National R&D Institute
2007-2010	BIOSADN – Development of biosensors based on nucleic acids for the evaluation and monitoring of some toxic agents with applications in bioterrorism Partnership with Faculty of Chemistry, University of Bucharest
2007-2010	PROPETHAD – Advanced Research towards medical applications of nuclear technologies Partnership with "Horia Hulubei" National Institute of Physics and Nuclear Engineering

Visibility actions

- Lecture – Eugen Gheorghiu, "Nanotechnology support for novel bio-analytical systems; expertise of the International Centre of Biodynamics: results, fields of application and opportunities for collaboration", Symposium "*10 years of nanoscience and nanotechnolgy*", Romanian Academy, February 2010

- Invited Lecture – Eugen Gheorghiu, "Quantitative Assessment of the Interaction between Antimicrobial Peptides and Lipid Membranes; Analytical and Theoretical Challenges" Third Cristofor I. Simionescu Symposium *Frontiers in Macromolecular and Supramolecular Science",* Iasi, June 2010

- Exploratory Workshop on "Dynamic NanoSystems: from Concepts to Sensing Applications", organized and hosted by ICB during 22-23 September 2010, in the framework of the Conference meant to foster new collaborative bridges with scientific Diaspora

- Biodynamics - Dedicated stand at SCIENCE SHOW Bucharest within the European event : RESEARCHERS NIGHT, September 2010

- Lecture – Mihaela Gheorghiu, "ICB recent results on cellular Biosensors", National Conference on Biophysics, Bucharest, November 2010

Development of New Proposals

FP7

Marie Curie International Reintegration Grants

- Proposal full title: "*Protein aggregation – a quantitative assessment*"

Applicant: Dr. Alina Vasilescu
Proposal acronym: ProArgus
Evaluation Result: Successful

- Proposal full title: *ADVANCED NANOTECHNOLOGY FOR PERSONALIZED TARGETED THERAPY USING MOLECULAR AND PHYSICAL CONTROLLED MACROMOLECULES TRANSPORT VIA THE BLOOD BRAIN BARRIER*

Proposal acronym: ViaBBB
Type of funding scheme: Large-scale integrating Collaborative Projects
Work programme: NMP.2011.1.2-2: New targeted therapy using nanotechnology for transport of macromolecules across biological barriers- two-stage project.
Name of the coordinating person: Prof. Moshe Hadani
Evaluation Result: Green Light for the second stage

Marie Curie Initial Training Networks

- Proposal full title: "DYNAMIC INTERACTIVE NANOSYSTEMS"

Proposal acronym: Dynano
Type of funding scheme: Marie Curie Training Network
Name of the coordinating person: Prof. Mihai Barboiu
Evaluation Result: Pending

ERC Starting Independent Researcher Grant
Principal Investigator: Szilveszter Gaspar, PhD.

- Proposal full title: "*Monitoring the extracellular space with catalytic self-propelled nanomotors*"

Proposal acronym: EXTRACELL
Proposal duration: 60 months
Evaluation Result: Pending

Our profile in relation with FP7

Type: Company Expertise

Title: Novel optical - electrochemical analysis platforms for monitoring in the biomedical, environmental, and food quality and safety field.

Details:

The activities of our Centre focus on:
-identification and study of (bio) recognition events (enzyme - substrate, antibody - antigen, other affinity interactions, whole cells - different compounds of pharmaceutical or environmental relevance) which can form the heart of novel analytical tools.

-development of novel analytical platforms based on: (bio)recognition events, microfabricated transducer systems, microfluidics, and multiple detection principles (such as Impedance Spectroscopy, Surface Plasmon Resonance, Total Internal Reflection Fluorescence microscopy, Amperometry, etc.).

-use of the developed instrumentation, micro devices, detection principles, and assay formats to solve specific problems in the biomedical, environmental, and food quality and safety field.

- among more specific interests: pharmaco-kinetic studies for active pharmaceutical ingredients using artificial membranes and electro-optical/sensing platforms; characterization of drug-liposome interactions based on SPR measurements in order to establish passive transport properties of drugs.

Programs: FP7-JRC , FP7-IDEAS , FP7-COOPERATION , FP7-CAPACITIES , FP7-PEOPLE , FP7-KBBE , FP7-HEALTH , FP7-NMP , FP7-ENVIRONMENT , FP7-REGIONAL , FP7-SECURITY , FP7-INCO.

The (International) Master Program in Biodynamics

Duration: 2 years: 4 semesters: for teaching, laboratories and demonstrations

ON HOLD

Program Objectives

This post-graduate course aims to provide insights into the ways detailed information concerning the physics and chemistry of specific biological structures and processes can be cast into novel models improving our understanding of the integrated dynamics of such systems, fostering development of new types of measuring methods applicable in Ecology (e.g., waste water re-use, assessment of water quality, detection of pathogens in water, advanced technologies for risk assessment, treatment plants), as well as in Biomedical and Food industry, areas that are in great need for both highly specialized workforce and knowledge.

The main objective of the post-graduate program in Biodynamics is to provide advanced training for participants willing to engage in and develop activities in the interdisciplinary realm between biology, engineering, physics, chemistry and dynamical systems, preparing them for research, teaching and last but not least for industry.

Designed to provide the trainees (e.g., biologists, chemists, engineers, physicists,.) with knowledge and skills (principles, experimental set-ups and data analysis methods) to understand and apply advanced methods for bio sensor development and bio-analysis, the program curriculum includes:

- Modern methods in biosensing and bio-analysis;
- Training in non-invasive assessment of (bio) interfaces;
- Investigation of bio-systems using electrical & electrochemical and optical (Surface Plasmon Resonance and Fluorescence Microscopy, including Total Internal Reflection-TIRF) methods
- Advanced training in cell biology and physiology;

- Development of specific instrumentation and techniques for process modelling and (experimental) data analysis;
- An introduction to the theory of Complex Systems;
- Background tutorials for biologists, chemists, physicists and engineers interested in the development and usage of new instrumentation and devices for specific applications in Ecology (e.g., waste water re-use, assessment of water quality & pathogens in water, advanced technologies for risk assessment, treatment plants), as well as in Biomedical and Food industry.

The program is meant as a platform for demonstration and dissemination of recent achievements in areas related to its curriculum. Based on their choice and background, the trainees are concentrating on specific aspects (e.g., sensor preparation, instrumental aspects and modelling and data analysis) in the form of target oriented mini-research projects and participate to conferences and mini-symposia.

Emergent Applications fostered by the International Center of Biodynamics

1. Sensors and biosensors

Developing of some rapid, sensitive, cost effective detection platforms to determine low concentration compounds and for kinetic analysis.

In this context, surface plasmon resonance (SPR) based biosensors represent attractive solutions in environmental monitoring and for quality-control, due to their sensitivity, miniaturization amenability and wide range of detectable compounds.

Since 2006, the SPR technology is available within ICB Biosensors Laboratory through Biacore 3000 equipment (Biacore AB, Sweden), unique in Eastern Europe and operated by specialized personnel.

The analysis methods already implemented allow:

- identification of drugs residues in some food products (e.g. presence of antibiotics in milk);
- detection of drugs and hormones, present even in low concentrations in food products;
- multianalytes detection (mixture of compounds e.g. with toxicogen potential)

SPR-based techniques enable real time, label-free assessment of the interaction between an analyte (e.g. chemicals, DNA, RNA, proteins) and a covalently immobilized specific ligand, simultaneously with a high sensitivity in determination of concentrations and kinetic dates, and also the possible integration with other analysis and fluidic techniques (FIA) or with approaches like Lab-On-a Chip.

In recent years, biosensors based on cells and tissues have been intensively used for identification and characterization of toxic compounds in water and determination of their cytotoxicity. Such cellular sensors could potentially replace/complement traditional methods of analysis such as mass spectrometry, high performance liquid chromatography or ELISA rapid tests, and also biological tests – intensively used for cytotoxicity detection or cell viability after exposure to harmful substances.

In this respect, ICB has developed cellular platforms for assessment of cytotoxicity of water samples. Including specific electrochemical instrumentation (impedance spectrometer, potentiostat) and a detection unit based on electrochemical sensors, electrical components and fluidic elements to maintain the temperature at 37°C, and applying a previously validated measurement method, multiple cell parameters can be potentially determined.

Several advantages of ICB sensing platform are:

1.) Portability;

2.) Reduced analysis time;

3.) Ability to assess the effect of contaminant mixtures, and from economic point of view, the necessity to use small volumes of reagents, reducing consumption of cells and amount of valuable reagents used, decreasing significantly the costs of operation.

The analytical platform is versatile, so it can provide relevant information not only for water monitoring activities, but also in chemical or pharmaceutical industry, efficiently responding to the Romanian and European socio-economic needs regarding the environmental quality control and / or biosensing applications in other specified domains.

1. **ICB Mobile Laboratory of Bioanalysis** (MLB), accredited by RENAR is designed as a testing laboratory compliant to the provisions of European directives and national legislation on water quality. It is based on the assimilation and development of top of the art new analysis methods, high performance equipments and instrumentation.

Several physico-chemical and microbiological analyses of water samples from different sources (potable and non-drinking, surface and underground water) could be performed for a set of standard parameters such as:

- total microbiological content and specific microbiological content (e.g., E.coli)
- determination of heavy metals (Pb, Hg, Cd, Cu, As, Zn)
- determination of pH and conductivity.

These types of analyses are requested both by public authorities for surveillance processes of water suppliers, and also by producers, to fulfill the obligations derived from the provisions of water quality directives, allowing in the same time a rapid intervention of the responsible factors. The test results performed by the Mobile Bioanalysis Laboratory provide the necessary information in environmental monitoring and water quality control.

The advantages of the applied methods (low cost, accuracy, low response time, portability) are responding to the performances required by the on-line and in field applications, thus the laboratory could be a real partner for the specialized agencies and profile companies for performing the analyses and quality monitoring on short or medium term.

2. Measurement and control systems for optimization of aquaculture activities An issue of real interest facing both our country and other European countries is represented by the strong demand for automated systems that will lead to optimization of aquaculture activity through increasing productivity and reducing costs. Systems already on the market do not optimize feeding process as a function of fish behavior, which is one of the causes that generate many losses both in terms of quantity and quality of food (about 30% of the costs of aquaculture operations).

Taking into consideration these trends and the promising results obtained by ICB in research and experimental studies undertaken in this direction, some of the most important applications developed in this field are as follows:

- support system of automation and optimization of feeding
- pilot system for non-invasive , multichannel assessment of behavior (dynamics) of aquatic species
- integrated, remote monitoring system for water (aquatic environment) quality control able to activate a specific system based on biosensors whenever the behavior of aquatic species deviates from a normal pattern;
- (non) linear - analysis method which provides a set of quantitative measures, characteristic of the behavior of species with high economic value (e.g., sturgeons, carps) in relation to actual environmental conditions (including feeding conditions).

Relevant publications

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