Strategic Research Programmes of the NICPB for 2013 – 2020

Estonian Research Infrastructures Roadmap 2010 is a long-term (10-20 years) planning instrument of Estonian science infrastructure. The NICPB co-ordinates as the leading partner (partners University of Tartu (TU) and the Tallinn University of Technology (TUT) roadmap objects „Estonian Magnet Laboratory“ (EML) and „Estonian participation in CERN“. The Institute participates as a major partner together with the TUT in consortiums „Estonian Scientific Computing Infrastructure“ (ETAIS, lead by TU) and Estonian Beamline at MaX-IV Synchrotron Radiation Source“ (ESSource, lead by TU).

The Institute’s strategic research programmes are directly linked to the goals and priorities of both Framework 7 and Horizon 2020 and stem from the key recommendations of the Institute’s International Science Advisory Board (SAB) of July 28, 2012.

1. High Energy Physics and Theoretical Physics

The most important open questions in contemporary elementary particle physics are the origin of mass and the physical mechanisms determining the state of the Universe (including Dark Matter and Energy). This program includes both theoretical work and numerous international experiments in particle physics and cosmology. The strategy of the Institute is to be involved in both: in the development of new theories and in their experimental testing in forthcoming experiments.

1.1 Experimental High Energy Physics

In the experimental side NICPB is a member of the CMS collaboration of the forthcoming Large Hadron Collider at CERN. NICPB is the coordinator of Estonian scientists and summer students at CERN. As a spin-off of the experimental particle physics program, a distributed computing concept Grid is under development and NICPB participates in it in both levels - Estonian and European level.

The Institute houses a Tier-2 computing centre, which is one of the biggest computing centres for the CMS experiment in Europe.

1.2 Theoretical Particle Physics

The direction of the theoretical work in NICPB is phenomenological, and relies on availability of experimental data. Experimental neutrino physics and cosmology are currently and in the near future under fast development. This motivates the NICPB group work in developing neutrino mass models and connecting them to experimental data. The neutrino masses might be directly connected to the expansion of the Universe shortly after the Big Bang. A fundamental problem in understanding the genesis and existence of the Universe is the emergence of asymmetric matter, or why there are ten orders of magnitude more matter than antimatter. One explanation goes through the leptogenesis, and NICPB participates in this work. Another priority of the NICPB group is the connection of the inflation of the Universe to the elementary particle theory.

2. Physics of Condensed Matter and Material Science

Modern physics of condensed phases and material science focuses on substances with novel electric, magnetic, optical and thermal properties. The functionality of those compounds is highly unpredictable either due to strong electron correlation (magnetism, ferroelectricity, charge order etc) or due to extremely complicated structure (huge unit cells of intermetals and oxides, composites), and more often, due to both reasons.

The current Programme offers three approaches to facilitate better understanding of the complex quantum matter and its design – better synthesis and control, state-of-the-art experimental (analytical) techniques and novel theoretical methods.

2.1 New Spin Materials

Spin is a fundamental property of an elementary particle that is described properly only by laws of quantum mechanics. Despite the deep quantum nature spin has practical implications in material science. Nuclear magnetic resonance uses nuclear spin as a local probe of structure and dynamics of materials at the atomic level. Permanent magnets and giant magnetoresistive effects are caused by coherent action of many electron spins. Even more, in multiferroics it is possible to reorient the spins with electric field. This reduces the amount of Joule heating of write operations in magnetic memories. Magneto-electric interaction between spin and polarization waves in multiferroics is a cornerstone for new THz devices. Spin plays an important role in pairing of charge carriers in high-T_c superconductors. The driving force of the exploration of quantum phase transitions in materials with strong electron correlations and Bose-Einstein condensation of magnons (spin waves) has been superconductivity and magnetism. Among strongly correlated electron materials the heavy fermion systems have been the source of unconventional superconductivity, novel magnetism and hidden order.

The research programme on new spin materials aims at studying fundamental physical phenomena in materials that may have high-tech applications. Spin materials are studied with nuclear magnetic resonance, THz and Raman spectroscopy methods, all contributing to the understanding of structure and structure-function relationship. The quantum nature of material properties requires application of high magnetic fields and low temperatures.

2.2 Investigation of Structure, Dynamics and Properties at Different Magnetic Field Strengths and at Various Temperatures

NMR spectroscopy is based on high-precision measurement of nuclear spin energy levels in a magnetic field. Fine structure of the spectra depends on local interactions, generated by chemical bond and other nuclei. Different magnetic field strength and various temperatures allow for increased sensitivity and/or to alter the states and functionality of the sample at hand.

Using NMR as an **analytical tool** in chemistry, biology and solid state physics forms an essential part of the program. Structural analyses and control of syntheses of enantiomers, diastereoisomers and other sophisticated molecules is addressed as an issue of basic chemistry. The goal of the molecular biology part is to determine protein mobility and interactions, regarding also quantum- and tunnelling effects, and also to develop studies on membrane and transport proteins (Cf also Bioenergetics). High accuracy cell metabolite measurement will be used for malignancy diagnostics in collaboration with central hospital.

In solid state physics the programme is strongly coupled and quintessential to both the spin materials programme (see above) and to the energy materials' programme (see below). Towards that end super fast rotation techniques at extreme temperatures will be developed. High resolution and sensitive measurements at temperatures ranging from 10°K (new spin materials) up to 1200°K (energy materials) open qualitatively new possibilities for detailed study of the structure and dynamics of molecular interactions and facilitate the development of new technological materials.

2.3 Energy materials

Research of energy materials is of utmost importance to the energy production and storing in the next generation fuel cells, Li-ion batteries and supercapacitors. The programme focuses on

solid oxide fuel cells making use of our unique capacity and competences to do optical, electrochemical impedance, thermogravimetric measurements of those compounds, to say nothing about solid state NMR studies at extremely low (10°K) and high (1200°K) temperatures.

We are also active in the development of commercially usable SOFC elements with our commercial partner Elcogen Ltd.

3. Macromolecular interactions

3.1 Molecular System Bioenergetics

Molecular System Bioenergetics approach is aimed to study intracellular structural interactions in the regulation of energy metabolism in healthy cells as well as in pathology. System Biology paradigm assumes the description of complicated biological system through the study of relatively independent subsystems; describing their structure, function and interactions between them.

In the case of cardiac muscle cell bioenergetics the approach requires the kinetic co-functioning description of the system comprising of respiratory chain, ATP sythasome in the mitochondrial inner membrane (including ATP synthase, adenosine-nucleotide translocase and phosphate transporters), mitochondrial creatine kinase, porine channel in the mitochondrial outer membrane (through which the metabolites are exchanged to cytosol) and protein factors modulating the channel, one of which is assumed to be tubulin heterodimer.

Alterations of intracellular structural interactions and formation of mature energy metabolism during postnatal development is an ideal model to study highly organised intracellular systems, where the bioenergetic regulation of cells varies according to their structure. Changes in the cell bioenergetics are one of the first signs of the cell pathology; therefore the studies of the bioenergetics of the malignant cells are of great importance.

The program gives us theoretical background to understand the bioenergetics of healthy muscle cells, as well as cellular pathologies like ischemia, heart failure, myocardial infarction, neurodegenerative diseases, bioenergetic mechanisms of cancer, and mechanisms of reperfusion injury.

3.2 Interactions of Biomolecules

Cellular processes and their regulation are based on recognition, binding and co-operation of bioactive molecules, and are determined by fundamental interactions in a very special cellular medium that is highly crowded with biomolecules. These basic interactions tend to yield non-traditional and unexpected manifestations.

The aim of the research is to understand the interactions and to give their predictable description combining experimental studies with corresponding theoretical modelling of processes based on structural data.

Basic principles of molecular recognition and complex formation are studied in systems: protein-protein, protein-DNA, protein-cell membrane, protein-bioactive peptide, and protein low molecular ligands.

Our focus in these studies is finding and isolating new catalytic, gene regulating, diagnostic and pharmacological active substances from different natural sources and the overall biochemical characterization of these substances.

The results of the studies have fundamental character as they clarify the mechanism of molecular recognition between proteins and other signalling molecules in normal and

pathological processes. The practical importance of the investigations is based on the potential role of the new unique proteins in understanding and resolving of contemporary health problems such as cancer, neurodegenerative, heart and blood diseases. The knowledge of the structure - function relationships of biomolecules is necessary in medicine and in pharmacology for designing new drugs and diagnostics and these data are helpful for synthesis of new bioactive substances.

3.3 Two-photon Absorption (2PA) in Biomolecules

Two-photon fluorescence microscopy is becoming one of the standard and most informative methods in biological research because it facilitates increased spatial resolution and increased depth of tissue penetration. These useful attributes occur due to special physical properties of two-photon absorption (2PA) phenomena, which include quadratic dependence of the excitation probability on instantaneous photon flux density, and which also allow using near-infrared wavelengths to excite visible fluorescence.

There is however at least one more unique physical property of 2PA that can and should be exploited to obtain important novel information, especially in order to address numerous critical questions regarding structure and function of biopolymers. Namely, because 2PA constitutes a higher-order interaction between light and molecular chromophore, the probability of this process depends not only on transition dipole moments between different molecular energy levels, but also depends on the value of permanent electric dipole moments of the same chromophore, which itself varies as a function of local electric field. Recently it was shown that quantitative measurement of 2PA cross section in biological chromophores such as fluorescent proteins can be used to determine accurate value of the corresponding dipole moment difference parameter, and thus determine the strength and direction of the local electric field acting inside 3-nm diameter barrel protein. This type of novel physical measurement is uniquely valuable because it allows to begin shedding light on the very fundamental, but still largely unknown properties of local electrostatic interactions in- and between biopolymers on nanometre scale.

The purpose of the research work in this area is two-fold. The **first goal** is to continue developing physical principles of local electric field sensing by two-photon spectroscopy and microscopy. This is addressed by investigating 2PA properties in broad range of different fluorescent as well as non-fluorescent biomolecular constructs and probes, in order to create and characterize novel type of molecular multi-photon optical sensors that are specially designed to detect and quantify local electric fields. Improving accuracy and reliability of 2PA data, as well as improving acquisition speed, optimizing wavelength range, integration with existing microscope systems etc. are examples of numerous critical technical issues that also need to be addressed. The **second** and at this time a more distant goal is to initiate R&D level work on specialized hardware and software that, in combination with the specialized 2PA-optimized molecular probes can be used by other researches' for a broad range of biomolecular investigations.

The utmost **purpose** of this strategic research direction is to develop new experimental methods and physical instruments or tools that will allow us and other researchers worldwide to understand how biopolymers perform their most amazing complex functions, and perhaps how man-made technology could augment or mimic these functions. All this will ultimately allow us better understand physical principles of life itself.

4. Environmental Toxicology and Chemistry

Research of environmentally hazardous materials – toxic substances that are released by human activity and are harmful to ecosystems as well as to people – is a field that involves

biology, physics, chemistry, material science and healthcare. An interdisciplinary institution such as NICPB is therefore highly suitable for the successful development of this field of research and environmental studies continue to be one of the central research strategies of NICPB.

The research in environmental toxicology in NICPB, especially the studies of environmental hazards of metal oxide nanoparticles initiated in 2004 are groundbreaking in the world as reflected in the number of citations as well as in the successful participation in the FP6 and FP7 projects of the European Union.

The strategic goal of the environmental toxicology program is to elucidate the hazard of (industrial) chemicals that are already in the environment or that have the potential to end up there. This goal will be approached by answering the following questions: is it toxic, to whom and how toxic, why toxic and how to assess the toxicity comprehensively and cost-effectively. According to the chemicals regulation in the European Union (REACH) all chemical substances produced in excess of 1 tonne per year (estimated number exceeds 100 000) have to be characterized in terms of toxicity. It is a considerable burden for the European chemical industry (including Estonian chemical industry), since the responsibility of assessments lies on the manufacturer.

A new class of chemicals – synthetic nanoparticles (particles with at least one dimension less than 100 nm) – are already produced in large scale in a variety of compositions, shapes and sizes. Compared to conventional materials, the nanosize particles have novel properties, exploitation of which may lead to breakthroughs is many technologies starting from energy production and ending with medicine. However, the novel properties may also lead to adverse effects for man and the environment.

One direction of the strategic program of environmental toxicology is development of test systems that enable efficient assessment of biological effects of chemicals and nanomaterials. Attention is focused mostly on in vitro tests that allow the assessment of adverse effects and toxicity mechanisms of chemicals and nanoparticles using fast, high-throughput systems. As a rule, the toxicity of chemicals is related to adverse effects on cell membranes and processes of basal metabolism, which can be predicted reliably using in vitro assays (including tests with e.g., bacteria, protozoa and invertebrates). Quantitative Structure-Activity Relationships (QSARs) are widely used for the prediction of chemical toxicity, but only beginning to emerge for nanoparticles as the latter are considerably more difficult to model compared to conventional chemicals.

A prerequisite of toxicity is the contact between the toxic substance and the organism. Another important factor of toxicity is bioavailability: ability of a chemical substance to cross the biological membrane and enter the cell/organism. The mobility of pollutants in the environment (sorption, desorption, solubility, complexation etc.) is being studied in the NICPB. In addition to previously developed environmental chemistry approach the NICPB now possesses the expertise in environmental toxicology that has been used and will continue to be used for the environmental hazard assessment of pollution originating from the oil-shale industry and energy production. The earlier research initiated by NICPB scientists led to the reclassification of one of the most important pollution flows of the oil-shale industry – fresh semi coke - as hazardous waste in 2003, resulting in the change of its deposition according to the rules of the European Union. The current strategic program also aims to develop a method for the separation of hazardous substances from the oil-shale solid waste and explore the possibilities of its large scale reuse. An independent field of work is the study of environmental aspects of the dictyonema shale (rich in e.g., uranium, molybdenum and vanadium) as well as other oil shales.