NICPB Science Advisory Board Report

1. Overview

The Science Advisory Board met over a period of two days from September 26-27, 2016 in Tallinn to evaluate the scientific program of the National Institute of Chemical Physics and Biophysics (NICPB). The SAB members present were Professors Peter Littlewood (Chairman), Gian Giudice, Nigel Hussey, Patrick Janot, Robert Kaptein, Vera Slaveykova, and Hanna Tähti. Mart Saarma and Marten Wikström were not present but have provided written input. Evaluation involved an in depth review of the main research programs, tours of the facilities and laboratories, discussions with younger researchers and potential leaders, and a panel discussion on new initiatives and strategy.

Since the last review in 2012, there has been some considerable evolution of the programs, and the recent appointment of a new director, Urmas Nagel. The Institute is sound and well run, with a good relationship between the Staff and the Director. The NICPB is evolving a strategy and direction that will be beneficial for the Institute and for Estonia as a whole, and despite some structural and financial impediments, is performing well scientifically. There are many high quality science programs, several of international calibre, across the disciplines but including high-energy physics (HEP) and computing, quantum condensed matter physics, NMR spectroscopies, ecotoxicology, and bioenergetics. These programs increasingly make interdisciplinary links within the Institute, and some also support substantial national and international collaborations. The committee believes that there are considerable opportunities to increase the role and impact of the Institute as a major national laboratory of Estonia, as long as strategic decisions are swiftly taken and executed.

2. Key Recommendations

A National Laboratory that operates in close cooperation with universities and with industry can contribute substantially to the health and effectiveness of research networks and education, by taking on roles that are not naturally performed within the university sector. A vision for a National Science and Engineering Laboratory is naturally constructed around several features:

- the ability to operate at scale, supporting facilities, infrastructure and competences that are too large for the academic sector, and/or too early for the commercial one;
- the flexibility to bring together multidisciplinary teams to address complex problems of national importance;
- the support of major collaborative international research programs which will attract top international scientists and engineers, as well as industry partners;
- the showcasing of national science priorities, involving advanced training of researchers, outreach, and public visibility of science

The Institute is continuing to evolve in this direction. We encourage a discussion between the Institute and Government over the Institute’s role in national priorities, considering the opportunities available. We remark that:

- The High Energy Physics (HEP) group has grown substantially and has reached international prominence in a fairly short period. This provides an opportunity for Estonia to reap strong benefits from joining CERN, which would likely spark strong engagement of Estonian companies, increase the public appreciation of science, and support education in science, technology, engineering and mathematics.
- The "big data" applications of a CERN tier 2 centre have already played out into national grid infrastructure and this could be amplified in different disciplines. The connection of advanced researchers to Estonia's knowledge economy has already generated two spin-out companies.
- The Institute has an internally leading position in the science of environmental nanotoxicology and is a major resource both nationally and in Europe in an important and growing topic. Some laboratories are in need of renovation.
- The strong fundamental condensed matter physics program has developed instruments and tools, which, together with the established NMR facilities could support a substantial Estonian 'user community' from universities and in industry. Opportunities to twin with one of the four pillars of the European Magnet Lab are available that could expand this reach.
- The condensed matter program could be complemented by an applied materials effort that connected to applications and the emerging industry of "materials for energy applications" - such an effort could interact well with University programs in materials and chemical engineering;
- The Institute offers advanced training to researchers and teaching at the graduate level that could be expanded to develop human capacity in areas of national need.

To accept these opportunities requires a number of changes. The first, already mentioned, is long-term investment and a commitment to the stability of research directions over the long term. In parallel there is a need to integrate with a national strategic vision that looks outward into the societal implications of the research activity. Ambition on the part of national funding agencies and universities is required to support the continuing transformation.

There are a number of models for the management of a national laboratory as part of a differentiated academic and research system, though in all cases crosstalk and good relations are necessary. The Institute has considerable autonomy, but in the current form operates as an entirely soft-money organisation dependent on short-term funding via external grant income, which is not a tenable situation for a national laboratory that aspires to intellectual leadership as well as supporting permanent facilities for the benefit of the nation. There needs to be developed a different financial model that allows for seed funding of new activities, long-term support of excellence, and support of large-scale facilities for the university and commercial sector.

A number of junior researchers have joined the institution, but that number should be increased to match expected retirements, and those younger researchers should rapidly be brought into PI status and then into leadership roles within the Institute. Bringing in independent young researchers will require the allocation of start-up resources and salaries outside the currently funded programs, and is necessary in order to maintain the intellectual foundation and ensure a flow of new ideas and programs. A partial remedy, that will also beneficially increase the flow of students and postdocs, is to pursue joint appointments with universities. In turn, strong programs at NICPB will benefit the universities, providing better interdisciplinary links to the naturally discipline-based institutions.

3. Reports on main research programs

The panel recommended on its last review that on an annual basis the research programs provide an informational report on their activities, which might include:

- number of doctoral and postdoctoral students, and other research personnel;
- research grants;
- publication activity;
- research collaborations with national universities, international partners and with industry.

The presentations given to us included this information, which was very helpful. In the following sections, we provide brief reviews of the main research programs.

Laboratory of High-Energy and Computational Physics

The high energy group in NICPB started in 2003, mostly under the initiative of Martti Raidal. The group started research activity both in the theoretical and experimental areas and became an independent Laboratory in 2011. In these years the group has grown steadily, both in terms of size and scientific output. It has now achieved an excellent international reputation and scientific recognition. This extraordinary success is largely the merit of the scientific brilliance, energy, and dedication of Martti Raidal, on the theoretical side, and Mario Kadastik, on the experimental side.

The theory group has been active in particle physics phenomenology (collider and Higgs physics, neutrinos, model building at the electroweak scale) and in cosmology (leptogenesis, dark matter, inflationary models), obtaining results of high international visibility and impact. Studies made by the NICPB group on the Higgs properties and interpretations of LHC results are some of the most cited in the field. The group has also become well known for original attempts to address the naturalness problem of the Higgs. Recently, a new branch in statistical physics was started in NICPB. Although it is too early to assess its impact, early indications are positive. The scope of its research is quite broad and the publication record is good.

The NICPB now represents the Republic of Estonia at CERN, and has the mandate to coordinate research and training activities of Estonian Universities at CERN. Mario Kadastik, recently nominated deputy director of NICPB, performs this coordination task. The CERN summer student and high-school teacher programs have a special impact on Estonian educational system. These programs give the opportunity to about 6-7 students and 10 teachers a year to have a unique experience in a leading European laboratory.

The NICPB is also a member of the CMS collaboration, one of the two multi-purpose experiments operating at the Large Hadron Collider (LHC). Mario Kadastik leads the still-developing group of experimental physicists participating in the CMS data analysis, which today consists of three experienced researchers and two post-docs, who train a number of PhD, MSc, and BSc students. The topics of interest in the group are related to in-depth studies of the Higgs boson and the top quark, the two heaviest and least known particles of the Standard Model for particle physics.

To enable this activity, the institute has developed a potent datacenter for high-performance computing. The computing center has about 6600 job slots, but also has about 1.25PB of usable disk space that is used both for local data as well as buffering of central and group space. The datacenter is effectively 100% for CMS use, though researchers in other topics have used it locally as well. The short-term strategy is to make it available also for the rest of Estonia according to needs. The platform will therefore be enhanced towards a nation-wide research Cloud architecture. It is worth mentioning that the NICPB is already very active on this front, as one of the leading companies creating Cloud architectures has developed from NICPB former scientists. Finally, Mario Kadastik represents Estonia at the EGI Council, allowing the NICPB to actively take part in policy making for Grid and Cloud future in Europe.

The Laboratory has produced many students who have successfully continued their research abroad, but who may come back to Estonia in the future bringing experience and new knowledge into the country. The high-energy group is also attracting high-level postdocs. With a wise use of EU resources, it was possible for the Laboratory to attract foreign visitor scientists, who helped to increase the international visibility of NICPB and strengthen its ties with other institutions. Overall, there is no doubt that the group has been one of the most brilliant examples of scientific success in Estonia achieving, in about a decade of constant growth, of putting Tallinn on the world map of high-energy physics.

Recommendations

Because the CMS group historically grew out of the theory and phenomenology group of Martti Raidal, all efforts have been solely on the CMS data analysis so far. In addition, the group resources are generally based on time-limited grants, which do not give the long-term visibility necessary to develop a sustained and strategic hardware activity in particle physics experiments, with usually span over several decades.

It would be beneficial to the institute to balance the analysis effort with competencies in hardware and longer-term research and development. The institute is currently in talks with the track trigger development of the CMS detector upgrade for the high-luminosity phase of the LHC. This strategy should not be limited to only LHC or CMS; a participation in the long-term vision for both new experiments and future colliders would be more than welcome, in both theory and experiments, making it a viable curriculum in the local universities.

The Laboratory of High Energy and Computational physics offers a unique opportunity that should be fully exploited by NICPB and by Estonia. This could be done at the academic level, with a more intense collaboration with the University system. Members of NICPB could participate more actively in teaching graduate or advanced courses, making the Institute more visible for University students. Also at the level of the local community, the visibility of NICPB could be enhanced by various scientific outreach activities for schools and interested citizens.

Laboratory of Physics of Condensed Matter and Material Science

This laboratory (also referred to as the Chemical Physics laboratory) runs the largest infrastructure of the institute, including several NMR instruments, THz and FIR spectrometers, vibrating sample magnetometers and an emerging atomic force microscope set-up. They also have a suite of cryostats giving access to several decades in temperature, all backed by the in-house helium liquefier. Collectively, these instruments allow the group to explore magnetism and magnetic interactions over an extremely large phase space along the three principal axes of frequency, temperature and magnetic field.

Their research programme covers multiferroicity, frustrated magnetism, correlated electron physics and the physics of endofullerenes, all subject areas that are closely aligned with the experimental techniques that they employ in house (in combination with experiments at large-scale international facilities elsewhere). The group have published a number of papers in high-impact journals, such as *Nature Physics*, *Nature Communications*, *PNAS* and *PRL* over the past 4-5 years. As such, their international visibility is strong.

Recommendations

For such a large group of researchers (18 in total), the number of PhD students is low. This may reflect a general lack of awareness of the national physics undergraduates of the opportunities in condensed matter physics available within Estonia and the committee would like to see a strategy for increasing this awareness in the coming years, e.g. through committed graduate courses in partnership with the Universities.

Another potential area of weakness is possible over-reliance on samples from collaborators around the world. This strategy may have worked until now, but there is a potential risk that the group's experimental tools will be reproduced elsewhere and their ability to gain access to the best samples will be compromised. We recommend that the Institute investigate the possibility to attract a solid-state chemist to the Laboratory who could synthesize magnetic materials of interest. It would be an advantage if this individual possesses the know-how to synthesize new materials, but that is not an absolute requirement. Indeed, other world-leading condensed matter institutes have successful in-house programs that produce high quality samples of known (as opposed to new) materials.

Looking ahead at the bigger picture, it is strongly recommended that the Laboratory explore ways to offer their equipment and expertise within a facility-type capacity, both within Estonia and possibly further afield. This way, it may be easier to justify funding requests for additional large-scale infrastructure, such as the next upgrade to their NMR suite. It is noted that the previous plan to secure national funding to enlarge operations and join the European Magnet Laboratory (EMFL) was unsuccessful. However, a new call for Twinning with Horizon-2020 will be launched in May 2017 with a funding ceiling of 1M€. This is something that could be pursued in partnership with the EMFL.

NMR spectroscopy

NMR at NICPB has a strong tradition, and while part of the Chemical Physics Laboratory we have preferred to call out specific actions. The technique is used in several research projects in materials science, organic chemistry, and biology. In particular, the special MAS probes developed at the institute attract users from Estonia and abroad, which leads to several collaborations. A range of NMR spectrometers up to 800 MHz is available for solid state and high-resolution NMR. An in-house helium liquefier is important for maintenance of these spectrometers. Unique features include the possibility to work at extremely low temperatures under magic angle spinning conditions.

Recommendations: a National high-field NMR facility

The 800 MHz instrument is still the largest in Estonia, but it is now 11 years old. In order to maintain the traditional high level of modern equipment in NMR it is necessary to consider the purchase of a 900 or 950 MHz spectrometer. The ISAB believes that this should be done in the context of establishing a National high-field NMR facility for users in Estonia. This would also enhance the status of NICPB as a truly national laboratory. For this plan to be successful several steps need to be taken:

- It is important to establish an in-house research program in structural biology as this would provide a strong argument for a high- field NMR machine.
- It is necessary to consult potential users, both from academia and from industry.
- Set up a consortium with these users and prepare a Roadmap for nation-wide investments in NMR, not only at NICPB but also at other sites in Estonia.
- Based on the Roadmap apply for funding at the appropriate funding agency.

Laboratory of Bioenergetics

This assessment is based on the NICPB Status Report September 2016, and on the scientific literature cited therein, as well as in the curriculum vitae of the six listed members of the Laboratory.

The Laboratory has a long research history in the field of cellular bioenergetics, and was built around the renowned work of Professor Valdur Saks in this field. The current programme is very demanding, and the following topics are listed

- compartmentation of adenine nucleotides
- functional coupling and direct transfer of metabolite substrates from enzyme to enzyme in multi-enzyme complexes (in the network of mitochondrial kinases
- compartmentalized systems of oxidative phosphorylation and intracellular energy transfer in cardiac and cancer cells in vivo
- functional and molecular characterization of the proteins responsible for a control over intracellular localization of mitochondria in vivo
- determination of energy fluxes via different phosphotransfer pathways, mechanisms of injury of energy metabolism in mitochondria of tumor cells
- metabolic control analysis

According to the Report, the future plans of the Laboratory include continued work in the following fields of bioenergetics: muscle bioenergetics, cancer bioenergetics and stem cells bioenergetics.

Recommendations

In their “general comments” the Laboratory considers that the work group is too small. This view is definitely correct, but only when put in relation to the extremely extensive and wide work plan presented. The committee is concerned that this plan is far too wide and extensive to be realized in any reasonable way with the resources at hand. Perhaps this problem is also the reason for the relatively meagre publication record of the Laboratory, which in the recent years contains few original research papers but topical review articles (as such quite interesting) and conference abstracts. We have a very high regard for the importance of most of the listed research subjects, but would sincerely urge the Laboratory to focus its research considerably, and have the six member researchers actively attack different but related aspects of a common research subject. Only in this way would the Laboratory be able to produce important scientific output on a high international level, which must be set as the common goal for the years to come.

If this suggestion is accepted the key question becomes the choice of research subject. A good choice may be one where either muscle or cancer bioenergetics is studied by metabolic control analysis (metabolomics), making use of the NICPB's NMR expertise as well as by the expertise previously acquired on metabolic control. This research could have some practical goal e.g. comparative studies of bioenergetics of cancer cells and adult stem-cell derived cells could be beneficial for the development of new drug candidates.

Laboratory of Environmental Toxicology

Environmental toxicology and chemistry is one of the leading research directions, as well as one of the scientifically and societally most visible activities in the NICPB. The head of the laboratory and the leader of the research group of environmental toxicology is Academy Professor Dr. Anne Kahru. The laboratory is among the best worldwide in the nanoecotoxicology domain. The group is young and dynamic, it attracts the highest number of PhD students in the NICPB. The research group consists of 9 senior scientists (PhDs) and 8 PhD students. Three PhDs are currently as post-docs in high-level foreign laboratories. They may also add new ideas and techniques to for the use of the group, when returning back. The education of young scientists is thus well organized. The laboratory hosts 1 institutional research grant and 3 personal research grants. The laboratory is a partner in the NICPB Centre of Excellence, in the Estonian Scientific Infrastructure Roadmap Object NAMUR+, and it has a research contract grant from the Ministry of Environment to review the current limit values of air pollutants.

Especially the evaluation of toxicity of nanoparticles has created high-level research with many international contacts. Since 2004 the laboratory has been among the first ones in the area of toxicology of metal oxide nanoparticles. The number of publications during the past 10 years is more than 100, mostly in the nanotoxicology domain with average citation numbers over 30/paper. Dr. A. Kahru and Dr. A. Ivask are among the 1% top cited authors in area of Environment/Ecology and A. Kahru in addition in the area of Pharmacology/Toxicology. For a small group in a small field these citation numbers indicate both the relevance of the research subject and the high scientific level of the publications. The group has participated in the FP6 and FP7 projects of the European Union. In addition to international connections, the research program of Dr. Kahru and her group is very well connected to the national strategies on the environmental safety research, which has been realized in several Estonian Science Foundation projects.

The team of Dr. Kahru has developed novel *in vitro* methods for the evaluation of the toxicity of chemicals/nanomaterials and also studied the mechanisms of the toxic actions of chemicals/nanomaterials. Especially the role of reactive oxygen species and genotoxic effects has been studied in different environmentally relevant organisms: algae, bacteria, protozoa and crustaceans. Based on the research on toxic mechanisms the most sensitive targets of the toxic action have been elucidated. Determination of the physicochemical properties of NPs (Zn, Cd, Ag, Cu, etc.) is part of the studies, as well as evaluation of the biological availability of the particles.

The development of *in vitro* test methods in ecotoxicology is urgently needed since, according to the chemical legislation in EU (REACH, Registration, Evaluation and Authorisation of Chemicals) the safety of more than 30 000 chemicals should be evaluated in a very short time frame (before 2018). To implement this task, the *in vitro* methods are in a central position. Also the directive on the use of experimental animals in EU (2010/63/EU) favours the use of *in vitro* methods instead of experimental animals whenever possible. Dr. Kahru`s group has provided new data on the QSARs e.g. to ECHA (European Chemical Agency), and generated web-based databases including toxicological information on REACH-relevant chemicals (in Russian Language).

The current guidelines (EU, OECD) do not provide specific test methods for nanoparticles. Many test methods developed by Dr. Kahru´s group are very promising *in vitro* tests in ecotoxicology, and could be submitted into the validation process of EURL- ECVAM (European Reference Lab in the European Centre for Validation of Alternative Methods), which is needed before the acceptance to the regulatory use. The industry producing nanoparticles for different purposes is constantly increasing which increases the risks that the particles are released into the environment.

Recommendations

To maintain and further develop the research lines an update of the research infrastructure and equipment (microscopes, incubators) is necessary e.g. via involvement in Roadmap NAMUR+. Part of the laboratory is located in the basement (e.g. laboratory for oil shale extraction; organism culture lab). These laboratories are sub-standard. In toxicological studies all additional external contaminations should be avoided and for the cell and organism cultures a stable environment is needed, controlled e.g. in terms of temperature, lighting and moisture. As a working environment these rooms might be also unhealthy. Space should be found somewhere else. Thus, the laboratory needs renovations.

The SAB strongly recommends support for the group to continue its research on the present lines. The studies on nanoparticle toxic mechanisms and development of sensitive tests for *in vitro* environmental toxicology are important both nationally and internationally.

Peter Littlewood, as chair of the Scientific Advisory Board

20th November 2016