New FOM Programme:

Title:

Biomolecular Physics

Program manager:

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Program advisory committee:

Prof. Dr. C. Dekker (Delft Technological University)
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Objectives:

The objective of the programme is to deepen our understanding of the physical workings of bio-macromolecules and their aggregates. Within its scope are both the properties of single, isolated biomolecules as well as their aggregates formed either by spontaneous or driven processes up to the scale of the cell. The first aim of the programme is progress towards a fundamental understanding of the physical function of biomolecules, viewed as nanometer sized dynamic machines. The second aim is to explore the possible uses of bio-macromolecules in the development of novel nanoscale hybrid devices. The programme will serve as a focus for the existing and emerging research community in the Netherlands in this expanding field.

Background and relevance:

The life sciences are undergoing rapid development with more and more focus on the microscopic details of life, exemplified by the genomics revolution. This development is also putting demands on the physics community. On the one hand more and more physical techniques are employed in the study of biological systems, on the other hand a detailed physical understanding of biological systems is becoming conceivable which poses new and challenging problems. The physics of bio-macromolecules is focused on a quantitative understanding of their dynamic function and behaviour in a cellular context and is based on knowledge of their chemical structure and interactions. At the same time the molecular processes of life, optimized by evolution, can be studied with a view towards the development of novel nano- or micronscale technical devices with tailored properties with for applications also outside the biological or biomedical domain. The physical study of these systems requires input from several disciplines. The present programme therefore follows naturally from complimentary proposals that originated within the Condensed Matter and Statistical Physics communities of FOM.

Programme description:

Physical properties of single biomolecules

Bio-macromolecules such as proteins or nucleic acids are complex structures with complex functions. The details of their functioning are often impossible to study with at the level of statistical ensembles. New techniques such as scanning probe microscopy (SPM), optical tweezers (OT), and the use of nanofabricated structures have opened the way to measure down to the level of single molecules. This allows measuring a wide range of the intrinsic, not-ensemble-averaged, properties such as the structural, elastic, and electrical characteristics of biomolecules. Force and electric spectroscopy may be carried out at local spots along biomolecules. Well-known examples are the use of SPM or OT to measure the forces needed to stretch, or even "unzip" a DNA molecule, which can be done to an accuracy approaching the separating of single bonds, or the use of OT to manipulate motor proteins such as myosin or kinesin. The same approach will allow us to gain a better understanding of the supercoiling of DNA, protein folding, and other dynamic processes. Local SPM probes will also be essential to elucidate the electronic properties of single bioelectronic elements such as a photosynthetic centre, an ion channel, etc., by resolving the local charge transfer both spatially and spectroscopically. Nanostructures fabricated in silicon or other inorganic materials can be employed to study and manipulate the local ordering of biomolecules, as well as their dynamics in confined geometries with well-defined dimensions. It will also be exciting to explore hybrid bio-inorganic structures where biomolecules are employed to build new devices with sophisticated functional properties on nanometer scales that could be useful in- and outside the biological environment. DNA, for example, might be used as a template to establish electric or magnetic wires and junctions, which may provide a rational approach to build molecular electronics.

Dynamics

A microscopic understanding of living systems begins with molecules, prominently proteins and nucleic acids, and it extends to the higher levels of organization, structures built by many molecules and systems of interacting molecules. Exploring physical as opposed to (bio)chemical aspects of such systems implies looking at detailed dynamics, forces, elastic properties, pattern formations, in other words the actual workings of the microscopic molecular machines, beyond the first step of determining their consistence and structure. Biological materials have on the one hand interesting and specifically adapted passive mechanical properties. Examples are the meticulously regulated cytoskeletal protein polymer structures guaranteeing the stability and flexibility of cells. On the other hand, many biomolecules are in the truest sense of the word microscopic engines, converting chemical energy into physical work, for example enzymes performing active conformational changes to manipulate their substrates. This is true for most enzymes, but is particularly striking for "mechanoenzymes" such as myosin in muscle cells, kinesins and dyneins in many intracellular transport processes and a variety of DNA manipulating enzymes. Another source of force and motion generation are (nonequilibrium) polymerization processes involving filaments or membranes. Many of these elements together drive highly complex processes such as cell division or cell locomotion. The focus of this subtheme of the program is the understanding of such active dynamic processes from the level of the single molecule to that of larger assemblies up to the whole cell. Typically these dynamics occur on the μs to second time scale and can be studied by single molecule and various microscopy techniques. Precise quantitative experimental results form then a basis for theoretical and numerical modelling using established as well as developing new concepts in statistical physics and (soft) condensed matter physics.

Biomolecular aggregates and assemblies

Biological macromolecules often assemble either spontaneously or through active processes into aggregates whose function depends on the collective behaviour of the molecules involved. These aggregates are sometimes well described by bulk properties. An example is the cytoskeleton that can in some cases be viewed as entangled network of semi-flexible polymers. The mechanical properties of such networks, especially in interaction with bounding surfaces formed by lipid membranes are important for understanding the mechanical properties of cells. The micro-rheological properties of such networks can e.g. be studied by studying the response of colloidal probes introduced into the network to externally imposed oscillations. As the cytoskeleton is highly inhomogeneous, due to the internal structuring of the cell, and dynamic, due to the processes that rearrange it dramatically throughout the cell cycle, there are challenging problems in trying to understand structure and function of these networks.
Microtubules, one of the main components of the cytoskeleton, are often actively assembled into functional aggregates. The most striking of these is the mitotic spindle, the mechanical scaffold used to separate the duplicated chromosomes during the division of eukaryotic cells. At present it still an open question how the mitotic spindle is formed and how it operates as a force-producing or force-directing machine. This is an example of a class of problems that involve the spatial arrangement of dynamical biopolymers under the influence of targeted nucleation, spatial constraints and possibly the interaction of motor proteins. These systems pose challenges both for in vitro experimentation and statistical mechanical theory.
Finally, there is increasing evidence that cells exploit the slow dynamics of collective processes involving the transport and assembly/disassembly of protein aggregates to construct spatio-temporal clocks that serve to establish geometrical markers for other processes in the cell. This is a new and highly exciting area of research open to quantitative experiments and theoretical modeling.
The last two examples both fall under the general heading of systems consisting of many interacting components with energy dissipation, i.e. out of equilibrium, a novel field of fundamental research in its own right.

Relation to other FOM Programmes:

The proposed programme is timely coming at a point where the FOM/ALW programme "Physical Biology" has seeded several new research nuclei in the field and has fostered collaboration between the physical and biological communities. This has created the conditions where we can now initiate a program that focuses on the exploration of the physical properties of bio-molecular systems in their own right. This focus, however, by no means excludes the participation of biologists and (bio)chemists in the programme, but simply emphasizes physical properties of biomolecular systems as the primary research interest.

Although touching the subject area of the FOM programme "Structure, function and flow of soft materials" at the level of bio-molecular assemblies and aggregates, it distinguishes itself in its more exclusive focus on the functional properties and dynamics of the aggregates and the constraints imposed by the finite size of the cellular domain. In contrast to the FOM programme under development "Physics for Medical Technology" its primary focus will be the fundamental understanding and, moreover, it will be limited to structures and processes at the cellular level. Although single molecule detection techniques are expected to play a mayor role in the research field of the programme, their further development is not a primary goal. The programme will therefore be complementary to the more technology driven efforts in the programme "Single-molecule detection and nano-optics".

Aims and scope

The program Biomolecular Phyisics aims to fund novel research on the physical properties of individual biomolecules and biomolecular aggregates and assemblies and their interaction with the external environment. The research in question need not be motivated by a biological question, but does need to explore properties unique to the biomolecules in question. At the single molecule level the focus is on functional or dynamical properties. The development of single molecule detection techniques or molecular structure determination e.g. falls outside of this scope. The upper length scale of aggregation we consider is the one pertinent to the size of the living cell viz. $\leq \sim 10$ μm. This rules out the study of supercellular biomaterials like bone as well as other macroscopic properties of biomolecular materials.

Program operation and budget

The programme will run for 6 years. It has a total budget of 3,63 M€ (= 8 Mf). It will fund projects through two open calls for proposals; one at the start of the program and one two years into the program. To allow for a broad coverage of the subject area and to provide opportunities for new groups to enter the field, individual projects will be limited to the scale of a "FOM Projectruimte" proposal. This scheme allows the funding of 4-5 projects per funding round.

To be eligible for consideration proposals need to meet the following requirements:

- The applicant(s) must either have a permanent position at a Dutch university or a publicly funded research institute, or have a tenure-track position at one of these institutions funded by the NWO “Vidi” program or equivalent. Applicants from any of discipline relevant to the program may apply.
- The proposal must fit into the aims and scope of the program (see above).
- The total budget of the proposal must not exceed 450 k€. For proposals above 300 k€ the additional rules as specified in the HANDWIJZER FOM-PROJECTRUIMTE 2002 will apply.

The scientific merit of the proposals will be evaluated by a panel of scientists working outside the Netherlands. The selection of this panel is in the hands of the program committee. The panel will physically convene for a single day session per funding round. On this day an opportunity will be given to the applicants (or a subset selected beforehand by the panel on the basis of the proposals) to briefly present their proposals orally and answer questions from the panel. The panel will then produce a ranking of the proposals. This ranking will then be used as-is by the program committee to fund the projects in order of priority, within the allotted budget per funding round. In case that a project in the first funding round falls partly within the cut-off mandated by the budget, the program committee may if the quality of the proposal as established by the evaluation panel warrants this “borrow” the missing amount from the second funding round. Coherence within the program will be fostered by regular participation of the funded groups in the bi-monthly biophysics meetings currently held at the KNAW.

Budget summary:

In the table below we have assumed that the projects funds of each funding round are equally distributed over a period of 4 years.

Year	2002	2003	2004	2005	2006	2007	Total
Projects	450,0	450,0	900,0	900,0	450,0	450,0	3600,0
Panel cost	5,0		5,0				10,0
Program support	4,5	4,5	4,5	4,5	4,5	4,5	27,0
Total	459,5	454,5	909,5	904,5	454,5	454,5	3637,0