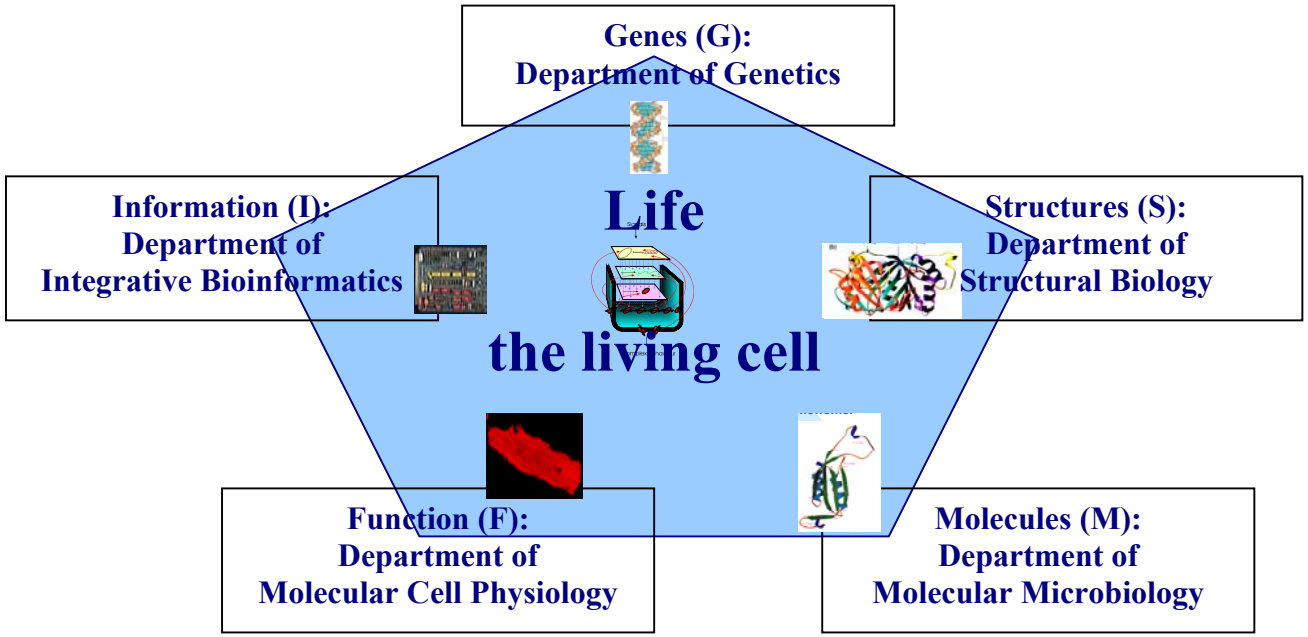
The Institute of Molecular Cell Biology:

From Molecule to Cell



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Mission

1. The Institute of Molecular Cell Biology (IMC) strives to elucidate how the integration of molecular structure, function, and behavior can lead to a functional living cell. Subjects under elucidation range from the structural dynamics of domains within macromolecules and subunits of macromolecular assemblies, through the integration of pathways and organelles, to the interactions of a cell with its immediate environment. The integration generates new functional properties through the nonlinear, dynamic and spatial nature of the interactions between biological macromolecules.

The IMC wishes to determine how:

(i) dynamic interactions of functional units create new functional properties that cannot be attributed to the properties of individual parts;

(ii) perturbations of molecular structures and their interactions cause malfunction and disease,

(iii) subtle interference might lead to more effective therapies of multifactorial disease;

(iv) optimization of the integration may improve the safety, efficiency and reliability of biological production methods.

2. The IMC strives to generate excellent human potential for the above and its applications, by engaging in excellent teaching of Molecular and Integrative Cell Biology and its many supporting disciplines.

Vision

The institute's research is based upon the finding that life requires the dynamic changes and interactions of quite a number of biomolecules. Partly by genetic programming, partly by self-organization, partly by pre-specification, partly by external factors, physical and chemical processes become life processes. In many scientific disciplines any of these categories of phenomena are studied independently of one another. The key vision of the Institute is that above all individuality it is the integration of these phenomena that matters most for the function and malfunction of living organisms. It is a web of vertical and horizontal paths of interactions that define the smallest unit of life, the cell. An example of such a vertical path is the connection of events leading from the genome through the transcriptome, the proteome and the

metabolome to cell function. Another example is the horizontal path corresponding to the entry, translation, amplification and the ultimate conversion of a signal. In particular the multifactorial, multigenic diseases, which constitute the main threats to human health, result out of malfunction during such complex interactions.

Strategy

The Institute's strategy is tripartite:

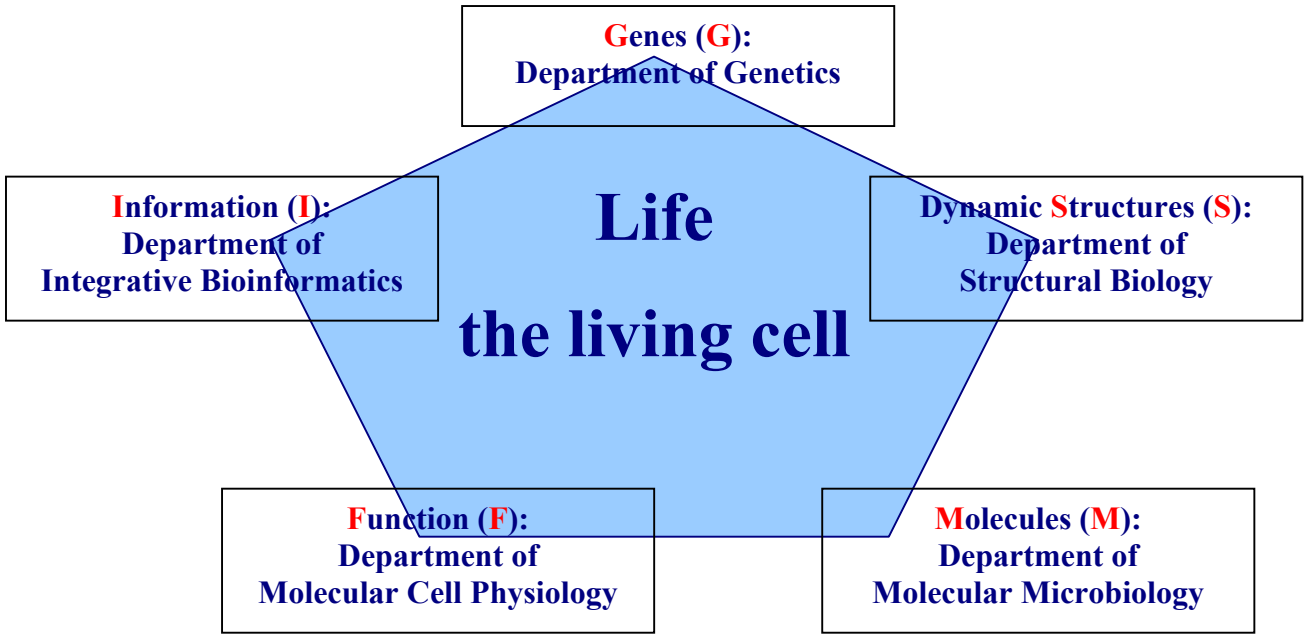
- **Current research activities**: A solid basis has been (and is being) created by well established research projects of the institute's core groups. These groups engage in research at key positions of the molecular and integrative biology of the living cell.
- **New research lines**, often interdisciplinary, are promoted. These are identified as connections of hitherto successful points of research, aiming at essential functions of the living cell, at the understanding of integration, and at the relevance of the research for human health and technology.
- **Advanced teaching**: Human capital for the area of molecular and integrative cell biology is created. This is achieved by a strong contribution to teaching in bachelor programs of the University and in innovative MSc and PhD programs of the institute itself, in collaboration with similarly focused national and international institutes. The human capital is that of advanced researchers, of science policy makers, and of medically or biotechnologically oriented experts.

Current research activities

The institute wishes to approach the challenge of understanding the living cell strategically. The pentagon below depicts the living cell as the aim in the center, and the following intellectual and methodological perspectives at the corners:

- **G**enes: The department of Genetics (**G**)
- **I**nformation: The department of Integrative Bioinformatics (*i.s.n.*) (**I**)

- **S**tructures: The department of Structural Biology (**S**)
- **M**olecules: The department of Molecular Microbiology (**M**)
- **F**unction: The department of Molecular Cell Physiology (**F**)



Genes:

The inherited information that secures the consistency of living organisms resides in the DNA and is organized in genes. Changes in function are caused by changes in the DNA sequence, either through mutagenesis, or much more frequently through exchange of genetic information, *e.g.* when genetic information is recombined during the production of offspring. Biological functions often depend on more than a single gene. It is of great interest to understand the genetic origin of polygenic traits, which also constitute an important aspect of the multifactorial diseases that

plague our society. The interaction between many different gene products expressed in different cell-types in higher organisms ultimately controls development. Multifactorial disorders are often due to changes in genes that are involved in development. Developmental genetics is the main research topic at the department of genetics. A second important issue with respect to developmental genetics is that the set of genes that encode a biological function does not determine that function on its own. Genes need to be expressed, and the level of expression is subject to regulation that is in turn determined by the basic genetic programming of the organism, by its environment, and by many other genes. This phenomenon is called epigenetics, and it is also a major issue at the department of genetics (G) of the IMC.
The department of Genetics does not only study the gene in terms of the development of the organism but also in terms of the effects that combinations of genes have on individual cell functions, e.g. their control of intracellular pH and of lipid metabolism. Here there are connections with the departments of structural biology (S), which studies proton pumps, and the department of Molecular Cell Physiology (F) which studies the functioning of metabolic pathways. The epigenetics topic is related to topics such as the structure and dynamics of (prokaryotic) chromatin and control of gene expression that are studied in the department of molecular cell physiology (F).

Information:

The basic function of genes is to provide the information for the (primary) structure and physical chemical properties of proteins. The connection between genetics and function is direct only to the extent that function can be deduced from sequence. To a significant extent such a deduction (calculation) is impossible. Yet, thanks to the developments in genomics, some aspects of function can be calculated, or at least, guessed in a sophisticated manner. Bioinformatics has been key in this. Based on the comparison of DNA sequences and on the association of those sequences to functions, this discipline has boosted biology and molecular medicine. At present, mainstream bioinformatics tends to be limited to the use of sequence information and its annotations. The IMC feels that more can be gained if physical chemical information is also added, and if the information is put to 'live', *i.e.* formatted in terms of an *in silico* replica (mathematical model) of a given biological object. Extracting knowledge from large amounts of already existing data is the focus of the Department of Integrative Bioinformatics (I). This department is presently in development under the leadership of Prof Heringa. The department will bear many connections with the other departments but at present the connections are particularly strong with the department F.

Structure:

Understanding the path *from molecules to life* requires thorough understanding of structures at the molecular level. Moreover, important for function is the four-dimensional structure, *i.e*. how the 3-D structure can evolve in time during catalytic action. Although the DNA sequence determines the amino-acid sequence and indirectly the 3-D structure of the cellular machinery (the proteins), dynamical changes are often

brought about by intra- or intermolecular interactions. The department for structural biology (S) of the IMC focuses on the structure of biological molecules with an emphasis on these dynamic aspects. Although research dedicated to this goal is fundamental in nature, it leads to substantial inroads into the level of applications. One example is the smallest known rotary biological motor, F_0F_1 ATPase. This enzyme, regarded as a paradigm for rotary energy conversion in biology, is presently discussed as a probably universal nano-engine suitable to drive all kinds of *nanotechnological* devices. A second IMC department (F) studies the function of the F_0F_1 ATPase at the cell physiological level in bacteria and in human cardiomyocytes and endothelial cells. The dynamic structures of ATP hydrolyzing proteins are also important for the protein exporting machinery studied in departments M and S and for the DNA gyrase studied in department F of the IMC.

Molecules:

Life does not yet begin with motile molecules however. Life also has to obtain and maintain its structure, with topology constituting a prime aspect of the organization of living cells. A simple model for this issue is the pathways that ensure that membrane and extracellular proteins are brought to where they should be. Part of the department Molecular Microbiology (M) of the IMC focuses on protein transport across the plasma membrane of bacteria. Since these functions are crucial for bacterial function, their better understanding offers potential for the discovery of new antibiotics. Besides that, however, better understanding of these transport processes and eventually gaining the ability to control and optimize them should greatly benefit the biomedical industry when using microbial cells to produce important molecular medicines. Indeed, there is a growing trend towards the utilization of living cells in the production of compounds; transport processes. Intelligent regulation is central in such applications. Department S also has a major activity in protein export mechanisms. Department F developed a research paradigm that links nucleoid structure, DNA structure, transcription, translation, and translocation in the bacterium *E. coli* and which provides for a strong connection between the three departments. Department F and S both work on intelligent regulation.

Function:

Perhaps the closest to life itself, is the cell function studied by the Department of Molecular Cell Physiology (F). Here the perspective is that of a hierarchy of processes at various organization levels in the cell, which *together* organize and execute cell function. The department studies these aspects in bacterial and yeast cells, where the coordinate behavior of metabolic, signal transduction and gene-expression pathways are examined. The interest also extends to heart cells and endothelial cells, as well as to deranged cells obtained from tumors. Amazing coordination of the pathways and networks is observed, with most processes being controlled by many factors at the same time in highly sophisticated manners. The results leave little space for amazement about why we are so unsuccessful at curing most diseases of the modern world. At the same time, they offer entirely new strategies of going after the origins and potential cures for, or managements of, such diseases.

Unexpected steps in and features of parasites are found to be the best targets for drugs against them. The department engages in quantitative studies of cell function, ranging from molecular genetics to time resolved confocal microscopy of live cells, and employing mathematical tools to deal with the complexity of the topic. In similar ways the department of Genetics (G) works on metabolic pathways effecting the control of intracellular pH, whilst the departments F and S share much interest in biological energetics, and departments I and F in concepts underlying control, regulation and organization.

New research lines

As compared to the present situation, the institute will establish the following optimizations:

(i) establishment of new research lines focusing on integrative cell biology with medical biology and health science aspects

(ii) integration of new and existing research projects into larger research lines that span important aspects of the living cell

These optimizations are subject of an upcoming Institute Symposium and Discussions of an Institute committee, and will lead to a detailed recommendation in the summer of 2004.

(i) establishment of new research lines:

The intended kind of research necessitates cooperation and indeed the integration of different disciplines of modern Life Sciences and the application of a huge variety of methods. A key role in the research process will be taken by the rather new disciplines of Integrative Bioinformatics, Integrative Genomics and Molecular Systems Biology. On the one hand the IMC already has key aspects of these disciplines in house and works towards obtaining an even more complete basis. On the other hand, the IMC will serve as a nucleation point for many trans-institute research programs, which will connect the IMC to other institutes with additional required expertise. This is necessary because of the wide spectra of disciplines that are important for Integrative Cell Biology. The IMC aspires to become a hub in a web of similarly directed, excellent international institutes in modern cell biology.

Special emphasis will lie on what is sometimes called bio-complexity, describing situations where a sum of nonlinear interactions between biological molecules and between these molecules and their dynamic environment, causes behavior that could not be reached by any part alone. With this research, the IMC takes a central position within the VU "*profileringsgebied 'de weg van molecuul naar leven [focal plane: the path*

from molecule to life]". In addition the IMC is active in more applied research, as illustrated below. In many if not all of the fields currently covered by IMC groups, research has created a scientific landscape of isolated islands of detailed and meticulous information. New disciplines, such as Systems Biology and Integrative Bioinformatics, strive to establish connections between these islands, *i.e.* to understand observations that cannot be explained by studying the isolated islands alone. The IMC intends to make extensive use of these new disciplines at all levels of complexity, also aiming at increasing the efficiency of our current research by the establishment of iterative cycles of experimentation and modeling. The living cell for instance depends on the integration of many more than 300 molecular processes. Its understanding therefore requires the simultaneous processing of many times 300 pieces of information. Integrative bioinformatics is thus a crucial aspect of the IMC, which in turn renders the IMC one of the clearest theatres of the subject "*levenswetenschappen en informatica"* [*lifes sciences and informatics*] in the *VU ster* [Free University' star; the Universities research landscape].

In the biomedical field that is envisioned in the *VU ster* [*Free University star*] as *"gezondheid en ziekte"* [health and disease] molecular cell biology fulfills an ever-increasing role. Cancer may serve as an example. Whereas molecular geneticists and physicians have been focusing on the 'single' oncogenes correlating with the occurrence of cancer types, the IMC will try to understand how failure of various factors to integrate optimally can lead to neoplastic growth. Obviously, such studies rely on insights in the fields of developmental biology and regulatory networks, which are currently actively pursued within the institute. Similarly, the reciprocal interactions between viral or microbial parasites and human cells are the subject of IMC studies. Where physicians and epidemiologists were needed to confine the spreading of SARS and AIDS and to care for patients, it will be left to medical biologists, such as those in the IMC, to actually find cures. Here intense examination of how these viruses and microorganisms manage to integrate with human host cells ("bigenomics") will be crucial. The IMC's intention to establish a research line under the heading "Integrating and dynamic genomes, relevant to infection processes and cancer" reflects the high priority given to this field.

Implementation of these innovations requires substantial changes in the research activities of the institute. The IMC will support this process by the allocation of 5 Ph D studentships, to be financed out of faculty SOC. The IMC will use these positions as incentives for groups that are actually developing new research projects along the lines sketched above. The projects they propose should meet the criteria that on the basis of the output generated during the first phase, they will be able to continue on the basis of external financing.

(ii) integration of research lines

In order to catalyze the lines of research that the institute intends to pursue, a new organizational scheme will be introduced: Besides the traditional departments, *research projects* will be organized in *task groups*, clustered according to the institute's major lines of research. These task group projects preferably consist of cooperation of more than one department of the institute.

Advanced teaching: new human capital

The Institute's Master's programs: Cell Biology and Systems Biology/Biomolecular Integration

The IMC has its own fully-accredited MSc program, called **Biomolecular Sciences**. This master program provides an excellent basis for subsequent PhD projects in many areas of cell biology, biochemistry, systems biology and molecular biology. It also trains students for subsequent careers in Consulting, Politics and Management, in the sense that it provides a rock solid basis of molecular and cell biological knowledge, an insight in the value of experimentally obtainable information as decision factor, and an insight in principles of (molecular) sociology.
The Institute's Master program has two variants, *i.e*. Cell Biology and Systems Biology/Biomolecular Integration.

Cell Biology.

The standard curriculum is called **Cell Biology**. It focuses on the biology of the living cell and is geared to the usual bachelor in biology and medical biology. This curriculum offers differentiations with various emphases, ranging from the more fundamental Molecular Cell Biology to Biomedical applications. It is offered in collaboration with groups from the Free University Medical Centre (VUMC).

Systems Biology / Biomolecular Integration

The other variant is called the **topmaster** on **Biomolecular Integration/ Systems Biology** (starting 2004) and is among the 6 master curricula supported by the Free University Amsterdam (VUA) to be of high quality both in terms of entry level of the students and in terms of teaching and exit level. This topmaster is a joint program of the Faculty of Earth and Life Sciences (FELS/FALW) and the Faculty of Exact Sciences (FES/FEW) of the Free University (VUA). It has a strong international orientation. The student's reward is an MSc degree of international acclaim and a correspondingly strong candidacy for local and international PhD studentships and science management functions. The topmaster (*cf*. www.systembiology.net/topmaster) is multidisciplinary, ranging from mathematics, through physics and chemistry to biology and medical biology, all with the aim of *together* understanding the living cell and its diseases.

Participation in General Masters' Biology and Biomedical Sciences

For students in Biology who have a more general interest the IMC teaches a trajectory of a wider variety of topics related to Molecular Cell Biology. This is done in the context of the Master's Biology. For students focusing on Medical Biology, the IMC teaches a trajectory in the masters General Biomedical Sciences with a medical focus and with components offered in collaboration with the medical school of the Free University.

Other teaching

Besides being one of the most active ALW institutes with respect to bachelor teaching, the institute participates in the teaching program of the graduate school BioCentrum Amsterdam.

Organization

The institute is part of the Faculty of Earth and Life Sciences of the Free University Amsterdam (FALW-VUA). It is organized as described in its bylaws. In short it has:

- A board consisting of the heads of the departments, with a director and an adjunct director
- A manager
- A communications committee, which organizes Institute seminars, symposia and workshops
- A teaching committee organizing the Master programs, together with the director of the School for Biology and Biomedical Sciences and the coordinators of the two Institute Master's programs.
- A research committee, organizing and reorganizing the institute's research themes.