Summary Start/discussion meeting "Verkenning Biowiskunde", Trippenhuis KNAW, Amsterdam

Date: Tuesday April 18, 2006, 9.30-17.00 h

Location: Het Trippenhuis KNAW, Kloveniersburgwal 29, Amsterdam

Each year the KNAW conducts a number of research foresight studies in order to shape the thinking and discussion about scientific developments in a particular field and to create the optimal conditions for the development of that particular field of science. Those conditions are created not just by the publication of a report with specific recommendations for policy in that field of science and the determination of priorities, but also by the foresight process itself. If researchers, policymakers, fund providers, users and other relevant actors are brought together for the purposes of a foresight study, then a forward-looking network is formed that can play an indispensable role in the development of a particular area of science.

Upon proposal by the Advisory Council for Mathematical Sciences, the Executive Board of The Royal Netherlands Academy of Arts and Sciences appointed the Research Foresight Committee Biomathematics (*Verkenningscommissie Biowiskunde*).

The Foresight Committee Biomathematics organized a plenary meeting on Tuesday April 18, 2006 in which the background and goals of the research foresight were presented, and where different aspects of the foresight were discussed with a broad audience of researchers in mathematics and life sciences.

Program

9.30-10.00 Welcome and coffee
10.00-10.30 Presentation Foresight Biomathematics,
Prof.dr. S.M. Verduyn Lunel (chairman Foresight Committee Biomathematics)
10.30-11.00 Teaching Biomathematics,
speaker: Prof. dr. J.J. Heijnen (TUD)
11.00-11.30 Coffee
11.30-12.15 Discussion 1 (theme: Teaching Biomathematics),
moderator: Prof.dr. J.G. Kuenen (TUD)
12.15-13.15 Lunch
13.15-13.45 Industry and Biomathematics,
speaker: Dr. E. de Brabander (Chief Technology Officer DSM)
13.45-14.30 Discussion 2 (theme: Industry and Biomathematics),
moderator: Prof.dr. J. de Vlieg (Organon and RU)
14.30-15.00 Tea
15.00-15.45 Research in Biomathematics,
speaker: Prof.dr. R. Heinrich (Humboldt University Berlin)
15.45-16.30 Discussion 3 (theme: Research in Biomathematics),
moderator: Prof.dr.ir. L.A. Peletier (UL)
16.30-17.00 Closing by Prof.dr. S.M. Verduyn Lunel
17.00 Drinks

Summary of the lectures and discussions

Presentation 'Foresight Biomathematics'

Prof.dr. Sjoerd Verduyn Lunel introduced the members of the Foresight Committee Biomathematics and outlined the work plan of the committee.

The following points were presented.

- History: 'Voorstudie Biowiskunde'.
- Foresight questions.
- Dates upcoming events (see http://www.math.vu.nl/~degunst/verkenningbiowiskunde.html).
- Invitation to participate in discussion and/or send suggestions to Committee members afterwards.

Lecture topic: 'education'

Prof.dr. Sef Heijnen is a professor of bioprocess technology at the Technische Universiteit Delft. He is closely involved with the bachelor program Life Science and Technology (LST). He is the recipient of the Akzo-Nobel Science Award 2005. His motto is: 'organisms are complex factories'.

In his lecture professor Heijnen explained that a model is more than a set of equations and he illustrated this via the following issues.

- Focus: educating bioengineering students in mathematics.
- Goal math education: linking experiments (on cell level) to theory.
- Key: simple behavior of complex systems.
- Modeling cycle biological systems: which molecules (interaction and system structure) → which processes (stochiometry, kinetics) → mass balances (equations, math. models) → experimental design (perturbations).
- Train students to understand the difference between dependent and independent variables (choice of experimenter or inherent to biological system, and the importance of pseudo-steady states in case of low concentrations. This leads to algebraic differential equations, undervalued in present education.
- Train students to understand that model identification is tricky because biochemists do not know everything and that missing interactions and/or missing molecules in the model structure cannot be avoided. On the other hand one cannot allow all possible interactions (too many).
- Mathematics needed: matrix algebra, statistics, ordinary and partial differential equations, numerical methods, stochastic modeling.

Discussion topic: 'education'

The discussion started with a few questions to the foregoing speaker and a consideration of what he deliberately left out, namely statistics, “which will always be present”, and the mathematical part of building data bases. After this the discussion turned more general. The following points were addressed.

- What is new?
    - Shift from academic to engineering type of research, which makes research more quantitative.
    - Integrated research.
    - Mathematicians are now interested in working in biology.

- What is needed?

    - Light and heavy math courses in statistics, differential equations, linear algebra for life science students.
    - To define minimum/optimal amount of mathematics for biologists and vice versa.
    - Training in art of modeling for non-mathematicians and mathematicians alike.
    - To expose students from early stage in education to *highly underdetermined models*. Although this is daily practice in research, it is not apparent in the curriculum.
    - To also make clear in education that there is a shift from academics towards engineering: teach students to *design something that works.*
    - Training in translating problems from other disciplines into own discipline.
    - Training of strong mathematicians who can understand and solve biological driven problems.
    - Learn how to talk to each other

- Other important remarks
    - There exist a few examples of biomathematics curricula; also theoretical biology curricula.
    - Role of mathematics in biology is *not* to enable working with the complex information–brute computing force can solve most problems–but to evaluate complex systems in smart way such that understanding of them can increase. Or "how to convert complexity in simplicity".
    - Biomathematics is easier to teach at master-level; in bachelor education there should be room for light *and* heavy math courses for life scientists.
    - Biologists need to be educated in mathematics and mathematicians in biology. Whole continuum from math via hybrids to biology is needed. Majority agrees, but also some comments:
- Do not miss the interface, i.e. do not just make a mix of both disciplines, but make either a dedicated separate curriculum (that might not contain traditional mathematical and biological courses), or offer a minor in the bachelor program and design a specific master program.
- Maybe more important to teach mathematics to biologists than biology to mathematicians, who just need to be good mathematicians.
    - Keyword is: *communication.*

- Problem
    - Small number of students.

<u>Lecture topic: 'industry'</u>

Dr. Ellen de Brabander is vice-president corporate technology DSM. She is a member of the European Research Advisory Board (EURAB). In 2000 she received the gold medal of the Royal Dutch Chemical Society.

The lecture consisted of two parts. In the first part Ellen de Brabander presented the new directions DSM is heading to. The researchers in DSM are teaming up with universities regarding various topics, such as, coatings, life science products, performance material and advanced personalized nutrition products. In the second part Herman Pel (DSM) stressed the need for bio-textmining, bio-statistics, bio-informatics and system biology. The following points were addressed in the lectures.

- Short overview of the ambitions of DSM in `white' biotechnology.
- Exponential growth available biological data.
- Metabolic pathways (liver cell).
- Need for integrative data analysis.

- Outsourcing of bio-expertise to universities.
- Stimulate algorithmic development.

Discussion topic: 'industry'

There are ample opportunities for mathematicians: R&D expenditure in pharmaceutical companies is growing by 20% per year. The average cost per approved drug is now $950 million and development of a drug up to its approval takes 12 years. But the number of identified New Molecular Entities (NCE) is declining by 30% per year. New techniques and methods from mathematics and statistics are needed to handle huge amounts of complex heterogeneous data sets apparent in genomics-based biology. The following specific points were raised.

- What is new?
  - Many more mathematicians are needed in life science research–this is viewpoint of a large majority.

- What is needed?
  - Communication
    - between mathematicians and applied mathematicians–a platform is missing.
    - between mathematicians and biologists.
  - More interest of the side of mathematicians.
  - Identification of challenging biology driven problems that can lead to interesting problems in mathematics of sufficient focus. This will attract good mathematicians to become involved.
  - Visibility of biomathematicians to a broader audience.

- Other important remarks
  - Would having a `clear goal' help to get more mathematicians involved? Not everyone agrees on this point, some opinions:
    - not on a too rigid goal;
    - one big goal will help sitting together with many people;
    - mathematics has universality in its domains of applications and should not loose this.

- Problem
  - A lot of biological data is not useful yet. Accurate data are essential in mathematical modeling and analysis. Bottle necks:
    - experimental design, etc.–mathematicians should help;
    - extensive routine work is required to acquire accurate and consistent data. How to fund such routine work?

Lecture topic: 'research'

Prof. dr. Reindert Heinrich heads the group in Theoretical Biophysics at Humboldt University and he is the director of the graduate program 'Dynamics and evolution of cellular and macromolecular processes'. His research interests are modeling metabolic networks and signal transduction networks and the application of nonlinear dynamics to biological systems.

In his lecture professor Heinrich stressed the essential role mathematics is playing in modeling the dynamics and analyzing the structure of complex cellular processes. Flux balance analysis and network analysis through differential equations are important tools in the analysis of metabolic networks (glycolysis in red blood cells) and in the modeling and analysis of signal transduction pathways (Wnt-signaling-pathway in organ formation, limb development and tumor biology). The role of time scales–structure such as network topology and kinetic properties, leads to dynamics on a scale of days to hundred years; whereas physical constraints and biological function lead to structure on a scale of million to billion years–in these problems generate several mathematical challenges. The following points were addressed.

- Metabolic pathways
- Signal transduction pathways
- DNA-repair mechanisms
- Intra-cellular traffic
- Cell-to-cell communication
- Large scale structural analysis
- *Challenge:* Is it possible to explain the structural design of metabolic pathways from optimization?

<u>Discussion topic: 'research'</u>

Research in biomathematics is a collaboration and often data driven, not mathematicians solving the biologists' problems. A lot of talking is involved. In some cases crude mathematical models suffice *initially* for modeling complex biological systems in setting up cooperation between researchers in bioscience and mathematics. In other cases deep mathematical modeling is needed from the start.

There are several examples of successful cooperation, often small scale research. So far quite often the 'biomath-expert' has a physics background, rather than being a ' real mathematician'. However, examples in other fields (in mechanical engineering, shell theory, elasticity and bucking) show that an enormous progress was realized after the investment was made to involve mathematicians as well. For instance, the important new methods in nonlinear analysis used in these applications, were developed by mathematicians. The following issues were considered.

- What is new?
  - Last century mathematics developed based on applied mathematics stemming from engineering. Now applied mathematicians should do this work themselves. Then new mathematics follows.
  - There are many new challenges for mathematicians in the life sciences. For instance, the biomedical field is wide open for modeling of complex biomolecular and supracellular systems, in particular: metabolic networks, signal transduction networks and (emerging) gene networks.
  - Part of the challenge is to combine different time scales, length scales, submodels having different detail, etc.

- What is needed?
  - Focusing on *mathematical sciences*, rather than solely on mathematicians.
  - New developments in mathematics for modeling in biosciences; not everyone agrees, but majority does.
  - Internal communication on national scale and regular meetings of Dutch scientists involved in bio-modeling.
  - A platform for mathematicians interested in applications in the life sciences.

- Other important remarks
  - Funding issues
    - Complaint: difficult to get funding for interdisciplinary projects. This is not a shared opinion: "this simply requires a different type of grant writing; if picked up, excellent chances for funding".
    - NWO is more open now for mathematics-physics-biology type of programs: e.g. in ZonMW Top program, Computational Life Sciences program; new Strategic Plan NWO focuses explicitly on such combinations of expertise (e.g. focus on systems biology and brain and cognition)

    - Suggestion made: reconsider funding criteria (e.g. NWO and STW): make transfer of knowledge from one field to another fundable as well as the experimental research needed to validate mathematical models (integrative research).
  - In the US there exist small conglomerates of scientists (NIH-funded research-resource centers) that generate generic modeling approaches for a variety of complex biological systems.
  - The CMSB, SysBioNL and Epidemics initiatives bring together Dutch bio(medical) groups and math expertise: aim is initiate iterative cycle of experiment → computational model → prediction → experiment → better model → etc. in biological and biomedical research in NL.
  - The Biorange project has been very successful. A network was established and much new collaboration has emerged. This kind of projects should be stimulated for biomathematics.
  - Starting in the late nineties NWO (ALW + FOM) has specifically and quite successfully stimulated synergy between biology and physics; for creating mathematics-biology momentum we may learn from this; learning curve for scientists from both disciplines.

- Problem
  - Biomathematicians are not visible: scattered small groups; people do not know where to go for what.

The Foresight Committee Biomathematics:

Prof.dr. R. van Driel
Prof.dr. C.M. van Duijn
Dr. M.C.M. de Gunst - *secretary*
Prof.dr. W.Th.F. den Hollander
Prof.dr. M.C.M. van Loosdrecht
Prof.dr.ir. R. Rabbinge
Prof.dr. S.M. Verduyn Lunel - *chair*
Prof.dr. J.G. Verwer
Prof.dr. J. de Vlieg

For more information on the Foresight Biomathematics (in Dutch):
http://www.knaw.nl/cfdata/verkenningen/uitvoering.cfm?verkenning=37