

Biomathematics: A vision for success

Verkenningen, deel 13

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Biomathematics

A vision for success

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Ten geleide

Het is me een genoegen om het voorliggende rapport *Biomathematics: a vision for success* in uw aandacht aan te bevelen.

Het rapport vormt de weerslag van een verkenningsproces dat zich heeft afgespeeld op het grensvlak van de wiskunde met het brede terrein van de levenswetenschappen. In meerdere opzichten mag dit een geslaagde exercitie worden genoemd die een vervolg, c.q. een opvolging van de aanbevelingen, meer dan waard is.

Deze nog jonge eeuw wordt niet voor niets de eeuw van de biologie genoemd en niet voor niets staat de bevordering van onze gezondheid en de duurzaamheid van onze aarde steeds meer centraal. Tal van maatschappelijke problemen vragen hierbij met een groeiende urgentie om een antwoord, antwoorden die zoveel mogelijk gebaseerd moeten zijn op vanuit de wetenschap aangedragen kennis en inzichten.

De ontwikkelingen in de biowetenschappen gaan bijzonder snel. Van een voorheen hoofdzakelijk (noodgedwongen) beschrijvende aanpak zien we, mede door de sterk toegenomen technische mogelijkheden, een krachtige ontwikkeling naar verklarende en zelfs voorspellende methodes.

Deze ontwikkelingen maken het ook nodig dat de conceptuele basis van de levenswetenschappen wordt versterkt met verklarende modellen, adequate statistische methoden en andere kwantitatieve benaderingen. De successen in het biologisch onderzoek worden daarmee sterker dan voorheen afhankelijk van een adequate voeding vanuit de wiskunde. Wat we al veel langer gewend zijn bij takken van de natuurkunde, zal ook bij de biowetenschappen verder moeten worden bevorderd en gemeengoed moeten worden: een duurzame relatie met de wiskunde.

De verkenning Biowiskunde biedt een aantal betrokken partijen handreikingen om die opkomende relatie vorm en inhoud te geven en duurzaam te laten zijn. De tijd is er meer dan rijp voor. Het is dan ook mijn stellige overtuiging dat alle partijen, zowel in de diverse wetenschappelijke disciplines als in de maatschappij, daar veel profijt van zullen hebben.

Ook bij andere disciplines dan de levenswetenschappen zien we dat de noodzaak wordt ingezien om de contacten met de wiskunde te versterken. Vice versa vinden wiskundigen andere disciplines veel meer een inspiratiebron dan voorheen. Daarom is binnen de KNAW een project ‘computational sciences’ gestart met het oogmerk van het bevorderen van meer van dergelijke duurzame, co-evolutionaire relaties.

Kortom, ik hoop van harte dat deze verkenning de nodige opvolging in het veld zal krijgen. De Akademie zal zich hiervoor met enthousiasme en overtuiging blijven inspannen.

Robbert Dijkgraaf,
president van de KNAW

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Summary

What?

In the present report, biomathematics is taken to be that area at the interface between mathematics and the life sciences in which the main focus is on developing *mathematical* models, concepts, methods, techniques and approximations, with the aim of applying these to *specific* problems emerging from the life sciences, while at the same time maintaining a *generic* and *unifying* point of view. The life sciences considered in the present report are: *biology*, *medical sciences*, *agricultural sciences* and *pharmacology*. Although there are close links with bioinformatics, biophysics, biochemistry and bioengineering, these are *not* part of the investigation in themselves. The present report concerns mathematics *in interaction* with the life sciences.

Why?

The life sciences are gradually becoming more *quantitative*: biological systems can be successfully treated as *information systems*. Consequently, there are major challenges for mathematics at all levels with *complexity* as the keyword. The central role of mathematics is to generate hard principles and flexible techniques indispensable in mapping out the complex theoretical and experimental landscape. Current experimental and technological capabilities are high, but it is often

Samenvatting

Wat?

In dit rapport verwijst de term ‘biowiskunde’ naar het gebied op het raakvlak tussen de wiskunde en de levenswetenschappen, waarbij de focus met name ligt op het ontwikkelen van wiskundige modellen, concepten, methoden, technieken en approximaties met het doel deze toe te passen op concrete problemen uit de levenswetenschappen en tegelijkertijd een generiek en unificerend standpunt te blijven innemen. In dit rapport komen de volgende levenswetenschappen aan de orde: biologie, geneeskunde, landbouwwetenschappen en farmacologie. Hoewel er sprake is van een nauwe samenhang met bio-informatica, biofysica, biochemie en bio-engineering, maken deze als zodanig geen deel uit van de verkenning. Dit rapport richt zich op het samenspel tussen de wiskunde en de levenswetenschappen.

Waarom?

De levenswetenschappen worden geleidelijk steeds kwantitatiever: biologische systemen kunnen worden benaderd als informatiesystemen. Dit betekent dat de wiskunde op alle niveaus voor grote uitdagingen staat, met complexiteit als sleutelwoord. De centrale taak van de wiskunde is het genereren van harde principes en flexibele technieken die onmisbaar zijn om het complexe theoretische en experimentele landschap in kaart te brengen. De experimentele en technologische mogelijkheden zijn enorm, maar de vraag is vaak wat het best gemeten

hard to know what is best to measure and how to interpret what has been measured properly. Mathematics can provide guidance and can help to decide on the proper experimental set-up (experimental design). There is considerable momentum and consequently a sense of urgency to pick up on the multiple opportunities.

How?

During the foresight, a start-up meeting and two brainstorm meetings were held, one for senior and one for junior researchers in biomathematics. An survey via a questionnaire was carried out, both at the start-up meeting and via Internet, and interviews were held with secondary school students. Inventories were made of ongoing biomathematics research and education in The Netherlands, including contacts with industry. Moreover, several international documents were analyzed, and there was exchange of information with leading researchers in biomathematics abroad, in order to benefit from their experiences and insights. The results of these activities are *integrated* into the report.

Who?

In the 2008 strategic documents ‘*Concentratie & Dynamiek. Een strategie voor de Wiskunde*’ [4] and ‘*Masterplan Toekomst Wiskunde*’ [10], the Dutch mathematics community laid down its plans for the next decade. Central in the document are the need for interdisciplinarity, the need to recruit and train junior researchers, and the need to provide senior researchers with enough time to develop new interfaces. The document positions biomathematics as a *key area* for the future to which all these needs apply, and targets the Dutch researchers in mathematics and the life sciences as *key partners*.

Challenges and opportunities

- Biomathematics is a key interdisciplinary field, offering multiple scientific challenges and multiple benefits to society. The Netherlands is a small player on the international scene, but of high quality. Research is in the international focus of attention. Currently some 200 people in The Netherlands are active in biomathematics. Strategic activities with regard to biomathematics will

kan worden en hoe de resultaten daarvan moeten worden geïnterpreteerd. De wiskunde kan daarvoor aanknopingspunten bieden en kan helpen om besluiten te nemen over de juiste opzet van experimenten (experimenteel design). Er is sprake van een aanzienlijk momentum, zodat het gevoel bestaat dat er nu snel moet worden ingespeeld op de talloze mogelijkheden.

Hoe?

Tijdens de verkenning zijn een startbijeenkomst en twee brainstormmiddagen gehouden – één voor senior- en één voor junioronderzoekers in de biowiskunde. Er is een enquête gehouden (zowel tijdens de startbijeenkomst als via internet) en er zijn middelbare scholieren geïnterviewd. Er is een inventarisatie gemaakt van de stand van zaken rond het biowiskundig onderzoek en onderwijs in Nederland, inclusief de contacten met het bedrijfsleven. Bovendien zijn er documenten uit het buitenland geanalyseerd en heeft er een informatie-uitwisseling plaatsgevonden met gezaghebbende buitenlandse onderzoekers op het gebied van de biowiskunde, zodat van hun ervaringen en inzichten kon worden geprofiteerd. De resultaten van deze aanpak zijn geïntegreerd in het rapport.

Wie?

In 2008 heeft de Nederlandse gemeenschap van wiskundigen haar plannen voor het komende decennium uiteengezet in de strategienota's 'Concentratie & Dynamiek. Een strategie voor de Wiskunde' [4] en 'Masterplan Toekomst Wiskunde' [10]. Centraal in dit document staan de noodzaak om interdisciplinair te werk te gaan, de noodzaak om junioronderzoekers te werven en op te leiden, en de noodzaak om senioronderzoekers voldoende tijd te geven om nieuwe raakvlakken te ontwikkelen. De biowiskunde wordt gepositioneerd als een centraal gebied voor de toekomst waarop deze drievoudige noodzaak van toepassing is, en de Nederlandse onderzoekers in de wiskunde en de levenswetenschappen worden gezien als centrale partners.

Kansen en uitdagingen

- De biowiskunde is een belangrijk interdisciplinair vakgebied dat tal van wetenschappelijke uitdagingen en maatschappelijke voordelen in zich draagt. Internationaal gezien is de rol van Nederland op biowiskundig gebied bescheiden maar van hoge kwaliteit. Het onderzoek staat internationaal volop in de aandacht. In Nederland zijn momenteel ongeveer tweehonderd

give the field a higher national profile, leading to a more effective network via natural selection.

- Biomathematics can boast an impressive list of past achievements, both nationally and internationally. It is expected that quantitative approaches to problems in the life sciences will continue to repay in formulating and guiding experiments, in managing and interpreting data, and in understanding the behavior of complex biological systems. Biomathematics has a unique capability of building bridges between the descriptions of biological systems at different aggregation levels. The final challenge is the end-to-end scientific data management.
- New instruments and new measurement techniques, coupled with a computational infrastructure, provide a flood of data. However, it is hard to filter out what is relevant. This offers challenges for the mathematics community to help building a framework for formulation, comprehension, prediction and synthesis.
- Education is important if mathematics and the life sciences are to be successful in meeting the above challenges. With the discourse in the life sciences becoming more quantitative, mathematicians and life scientists need to understand each other's perspectives and – to some extent – each other's methods. Educational programs need to prepare a sufficient number of students to work at key interfaces. Developing a contingent of trained individuals is urgent.
- The current challenges in the life sciences are at the center of attention because of their consequences for national health and economy. Key examples are: aging populations, progressive diseases, personalized medicine, biological food production, and sustainability.
- There is major concern about the vulnerability of biomathematics within funding programs, due to the prevailing selection schemes.

To meet the above challenges and opportunities, six recommendations are offered, falling into four categories: *research*, *education*, *human capital*, and *valorization*. Each recommendation is addressed to a specific set of organizations and is presented after a brief sketch of the relevant background.

biowiskundigen actief. Dankzij strategische activiteiten rond de biowiskunde zal het vakgebied zich internationaal beter kunnen profileren, waardoor via natuurlijke selectie een effectiever netwerk zal ontstaan.

- In binnen- en buitenland kan de biowiskunde bogen op een indrukwekkende reeks successen. Kwantitatieve benaderingen van problemen in de levenswetenschappen zullen naar verwachting vruchten blijven afwerpen bij het formuleren en begeleiden van experimenten, het beheren en interpreteren van gegevens en het doorgronden van het gedrag van complexe biologische systemen. De biowiskunde is bij uitstek in staat om een brug te slaan tussen de beschrijvingen van biologische systemen op verschillende aggregatieniveaus. De uiteindelijke uitdaging is om te komen tot ‘end-to-end’-beheer van wetenschappelijke gegevens.
- De combinatie van nieuwe instrumenten, nieuwe meettechnieken en een computationele infrastructuur levert een overvloed aan data op. De kunst is om daaruit te filteren wat relevant is. Dit is een uitdaging voor het veld om mee te bouwen aan een kader voor formulering, begrip, voorspelling en synthese.
- De wiskunde en de levenswetenschappen kunnen aan deze uitdagingen alleen het hoofd bieden als het onderwijs daarin de juiste rol vervult. Nu de levenswetenschappen meer kwantitatief georiënteerd worden, moeten wiskundigen en levenswetenschappers inzicht hebben in elkaars gezichtspunten en – tot op zekere hoogte – elkaars methoden. Het onderwijs moet voldoende studenten afleveren die op belangrijke raakvlakken kunnen worden ingezet. Er is dringend behoefte aan een nieuwe generatie goed opgeleide mensen.
- De huidige uitdagingen in de levenswetenschappen staan in het centrum van de aandacht vanwege de gevolgen die zij hebben voor de volksgezondheid en de economie. Voorbeelden zijn de vergrijzing, progressieve ziekten, medicijnen op maat, biologische voedselproductie en duurzaamheid.
- Een punt van zorg is de kwetsbare positie die de biowiskunde inneemt in financieringsprogramma’s als gevolg van de meest gehanteerde selectieprocedures.

Er worden zes aanbevelingen gedaan om te kunnen inspelen op de bovengenoemde kansen en uitdagingen, verdeeld over vier categorieën: onderzoek, onderwijs, human capital en valorisatie. Elke aanbeveling is bestemd voor een specifieke groep organisaties en wordt voorafgegaan door een korte achtergrondschets.

Recommendations

RESEARCH

Background:

- It is necessary to strengthen the biomathematics community by creating new research kernels led by promising researchers in biomathematics.
- It is better to stimulate biomathematics research broadly than to push for a few hot topics. The mathematics cluster ‘Nonlinear Dynamics of Natural Systems’ (= one of three academic research clusters funded by OCW) can take a leading role in developing the national research agenda in biomathematics.
- It is necessary to create more opportunities for biomathematics research within larger funding schemes such as the FES (= Fonds Economische Structuurversterking) rounds and NGI (= Netherlands Genomics Initiative), in order to more effectively facilitate the long-term collaboration between mathematicians and life scientists required to develop the basic research tools for the future. More attention is needed for research with a long-term horizon, where mathematics can offer its greatest strength.
- Bioinformatics, biophysics, biochemistry and bioengineering offer valuable bridges between mathematics and the life sciences. For instance, currently about 30 percent of Dutch physics is concerned with ‘living matter’. During the past 10 years a number of core questions in biophysics have filtered out, which offers excellent opportunities for mathematics to hitch-hike.

Aanbevelingen

ONDERZOEK

Achtergrond:

- De biowiskunde-gemeenschap moet worden versterkt door nieuwe onderzoekskernen te creëren. Deze moeten worden geleid door veelbelovende biowiskundige onderzoekers.
- Het is beter het biowiskunde-onderzoek breed te stimuleren dan zich in te spannen voor enkele ‘hot topics’. Het wiskundecluster ‘Nonlinear Dynamics of Natural Systems’ (een van de drie door OCW gesubsidieerde onderzoeksclusters) kan een voortrekkersrol spelen bij het ontwikkelen van de nationale onderzoeksagenda voor de biowiskunde.
- Het biowiskunde-onderzoek moet meer kansen krijgen binnen grotere subsidieprogramma’s, zoals de FES-rondes (Fonds Economische Structuurversterking) en het NGI (Netherlands Genomics Initiative). Dat moet leiden tot de structurele samenwerking tussen wiskundigen en levenswetenschappers die nodig is om de basale research tools voor de toekomst te ontwikkelen. Er is meer aandacht nodig voor onderzoek met een lange horizon, waar de wiskunde juist het meest kan betekenen.
- Bio-informatica, biofysica, biochemie en bio-engineering vormen belangrijke schakels tussen de wiskunde en de levenswetenschappen. Een voorbeeld is dat ongeveer 30 procent van het fysisch onderzoek in Nederland betrekking heeft op ‘levende materie’. De afgelopen tien jaar is in de biofysica een aantal kernvragen komen bovendrijven, die voor de wiskunde uitstekende kansen bieden om mee te liften.

Recommendation 1: NWO, Universities, CWI

Support research in biomathematics by starting up a *Priority Program Biomathematics*. This program should have two tracks, one to stimulate new research kernels, and one to fund a number of smaller innovative projects with appropriate flexibility, proper incubation period ('mass after focus' instead of 'mass and focus') and growth capability. The program should be led by an international panel and result in a national platform for all activities in biomathematics. The universities are expected to take *flanking initiatives* to consolidate this platform. Funding should come from the 'NWO-Gebiedsbesturen' EW and ALW. The past NWO-programs '*Landelijk Samenwerkingsverband Mathematische Fysica*', '*Niet-Lineaire Systemen*' and '*Fysische Biologie*' serve as guiding examples.

Recommendation 2: NWO, FOM, STW, ZonMw, EZ

Offer funding for *white projects*, i.e. projects not within a predefined program structure, but rather based on ideas by talented people with a track record, who are offered support on the basis of bottom-up suggestions. Projects with a calculated risk and with a long-term horizon are welcome, and should be judged by international peers. Funding should come from within larger funding schemes such as the FES rounds and NGI.

EDUCATION

Background:

- It is of vital importance that young researchers are attracted to the field of biomathematics. This can be achieved by organizing msc courses at a national level. MasterMath, the national program of mathematics courses at the msc level, can serve as the proper vehicle. This program is expected to develop into the Dutch Graduate School of Mathematics. A few universities can take the lead.
- Service teaching in biomathematics should be developed nationwide, with modules being prepared jointly, and where possible borrowed from institutions abroad. Service teaching should involve people from all the participating disciplines.

Aanbeveling 1: NWO, universiteiten, CWI

Ondersteun het biowiskunde-onderzoek door een Prioriteitenprogramma Biowiskunde op te zetten. Dit zou een twee-sporen-programma moeten zijn: enerzijds gericht op het stimuleren van nieuwe onderzoekskernen, anderzijds op het financieren van een aantal kleinere innovatieve projecten met de nodige flexibiliteit, de juiste incubatietijd ('massa na focus' in plaats van 'massa en focus') en groeipotentie. Het programma moet worden aangestuurd door een internationaal panel en moet uitmonden in een nationaal platform voor alles wat er in de biowiskunde gebeurt. Verwacht wordt dat de universiteiten flankerende initiatieven nemen om dit platform te consolideren. De financiering moet komen van de NWO-gebiedsbesturen EW en ALW. De eerdere NWO-programma's Landelijk Samenwerkingsverband Mathematische Fysica, Niet-Lineaire Systemen en Fysische Biologie kunnen als voorbeeld dienen.

Aanbeveling 2: NWO, FOM, STW, ZonMw, EZ

Verstrek financiering voor 'white projects', d.w.z. projecten die niet binnen een vaste programmastructuur vallen maar berusten op ideeën van ervaren, getalenteerde onderzoekers, die ondersteuning krijgen op basis van bottom-upsuggesties. Projecten met een gecalculeerd risico en met een lange horizon zijn welkom en moeten door een internationale peergroup worden beoordeeld. De financiering moet komen uit grotere programma's zoals de FES-rondes en het NGI.

ONDERWIJS

Achtergrond:

- Het is essentieel om jonge onderzoekers naar de biowiskunde te trekken, bijvoorbeeld door op landelijk niveau msc-opleidingen te organiseren. Hiervoor kan gebruik worden gemaakt van MasterMath, het landelijke programma van wiskundeopleidingen op msc-niveau. Dit programma zal zich naar verwachting ontwikkelen tot een Dutch Graduate School of Mathematics. Enkele universiteiten kunnen hierin het voortouw nemen.
- Op landelijk niveau moet worden gewerkt aan service-onderwijs in de biowiskunde, waarbij modules gezamenlijk worden ontwikkeld en zo mogelijk overgenomen van instellingen in het buitenland. Bij het service-onderwijs moeten mensen uit alle deelnemende disciplines zijn betrokken.

Recommendation 3: Universities, VSNU, OCW

Offer *integrated curricula* at three levels: BSc (generate interest, provide basic training), MSc (increase focus, address mathematical and biological concepts), PhD (go for depth, offer catching-up courses for graduate students with insufficient background). Develop leading threads through the curricula, offering minors at interfaces. Stimulate *joint preparation of teaching material* (advantage: in the present-day setting the result of joint preparation is effectively state of the art). Interest may be expected also from bioinformatics, biophysics, biochemistry and bioengineering students.

Recommendation 4: Universities, VSNU, OCW, Industry

Develop an *Honours Program* in biomathematics for a select group of students, with input by leading researchers from abroad, who visit for short periods, and with special attention for topics of broad societal interest. Develop *propaganda material* that can be used to recruit high school students and change their prevailing image of biomathematics.

HUMAN CAPITAL

Background:

- Biomathematicians are in high demand. They bridge two languages and two cultures, being either mathematicians with biological know-how or biologists with a thorough mathematical training and orientation. In view of this demand, there is a need to develop a contingent of young researchers.

Recommendation 5: Universities, Industry, CWI, TNO

Combine forces to create a *biomathematics community* with a common agenda, a portal function and a matchmaking capability. Try to capture the attention of senior players from bordering areas. Even a few percent of their time is valuable when setting up a national framework.

Aanbeveling 3: Universiteiten, VSNU, OCW

Bied samenhangende curricula aan op drie niveaus: BSc (belangstelling wekken, basisopleiding), MSc (meer focus, ingaan op wiskundige en biologische concepten) en PhD (diepgang, inhaalcurssussen voor afgestudeerden met onvoldoende achtergrondkennis). Ontwikkel leidraden door de curricula, en bied bijvakken aan op de raakvlakken. Stimuleer gezamenlijke ontwikkeling van lesmateriaal (voordeel: in de huidige setting is het resultaat daarvan feitelijk state-of-the-art). Er is ook belangstelling te verwachten van studenten bio-informatica, biofysica, biochemie en bio-engineering.

Aanbeveling 4: Universiteiten, VSNU, OCW, bedrijfsleven

Ontwikkel een honours-programma in de biowiskunde voor een selecte groep studenten met input van bezoekende buitenlandse toponderzoekers en met speciale aandacht voor thema's van algemeen maatschappelijk belang. Ontwikkel propagandamateriaal om middelbare scholieren te interesseren en een genuanceerder beeld van de biowiskunde te geven.

HUMAN CAPITAL

Achtergrond:

- Er is veel vraag naar biowiskundigen. Omdat het ofwel gaat om wiskundigen met biologische kennis ofwel om biologen met een gedegen wiskundige opleiding en oriëntatie, overbruggen zij twee talen en twee culturen. Gezien deze sterke vraag moet er een nieuwe generatie jonge onderzoekers worden opgeleid.

Aanbeveling 5: Universiteiten, bedrijfsleven, CWI, TNO

Bundel de krachten om te komen tot een biowiskunde-gemeenschap met een gezamenlijke agenda, een portaalfunctie en het vermogen om de juiste 'matches' te maken. Probeer de aandacht van gezaghebbende wetenschappers uit aangrenzende vakgebieden te trekken. Zelfs een paar procent van hun tijd is al waardevol bij het opzetten van een nationaal kader.

VALORIZATION

Background:

- Industry plays a key role at both the initial and the final stages of research at the interface between mathematics and the life sciences. It is necessary to create better opportunities for academic research institutes to benefit from this role.

Recommendation 6: Universities, STW, CWI, EZ, Industry, MKB, RIVM, UMCs

Stimulate biomathematics research between universities, spin-off companies and industry via a *voucher system*. Organize *internships* for students, aiming for long-term acquaintance rather than immediate knowledge transfer. Organize a yearly ‘*Study Group Mathematics and Biology*’, along the same lines as the successful ‘*Study Group Mathematics and Industry*’. Facilitate meetings of small research groups to act as *docking stations*.

VALORISATIE

Achtergrond:

- Zowel in de begin- als in de eindfase van onderzoek op het raakvlak tussen de wiskunde en de levenswetenschappen speelt het bedrijfsleven een sleutelrol. Om daarvan te kunnen profiteren, moeten er betere kansen worden gecreëerd voor academische onderzoeksinstituten.

Aanbeveling 6: Universiteiten, STW, CWI, EZ, bedrijfsleven, MKB, RIVM, UMC's

Stimuleer samenwerking in het biowiskunde-onderzoek tussen universiteiten, spin-off-bedrijven en de industrie via een vouchersysteem. Organiseer stages voor studenten, die meer gericht zijn op langdurige contacten dan op onmiddellijke kennisoverdracht. Organiseer een jaarlijkse Studiegroep Wiskunde en Biologie volgens hetzelfde stramien als de succesvolle 'Studiegroep Wiskunde met de Industrie'. Faciliteer bijeenkomsten van kleine onderzoeksgroepen om als 'docking stations' te fungeren.

Foreword

The Biomathematics Research Foresight Committee was installed on July 1, 2005, by the Executive Board of the Royal Netherlands Academy of Arts and Sciences (KNAW), as a result of a preliminary investigation on behalf of the Advisory Council of Mathematics (ARW). The Foresight Committee was asked to conduct a scientific research foresight in the area of biomathematics. In the present report biomathematics is taken to encompass those areas of *mathematics* that, on the one hand, contribute to the mathematical formulation and study of questions in the *life sciences* and, on the other hand, are motivated and encouraged by models that are developed and experiments that are carried out within the life sciences. Phrased differently, biomathematics is that area at the interface between mathematics and the life sciences in which the main focus is on developing mathematical models, concepts, methods, techniques and approximations, with the aim of applying these to concrete problems coming from the life sciences, while at the same time pursuing a generic and unifying point of view.

The life science areas that are considered in the present report are: *biology*, *medical sciences*, *agricultural sciences* and *pharmacology*. Although there is a close link with bioinformatics, biophysics, biochemistry, and bioengineering, these were not part of the investigation in themselves. The report is written primarily from the point of view of mathematics interacting with the life sciences. Statistics is considered to be part of mathematics.

The Foresight Committee was asked to shed light on the following questions:

- Which global scientific trends can be observed in biomathematics research?
I.e., what are the dominant programmatic or thematic trends, also according

to reports published abroad?

- What role does biomathematics play in society?
- What is the demand for and supply of biomathematics research in The Netherlands and how is biomathematics research financed?
- Which niches and opportunities are open to Dutch biomathematics in international terms, and what are the related priority research themes?
- Which prospects are there for national and international collaboration in the field?
- Which financing or organisational measures would give biomathematics research good prospects for development?
- What can be said about higher education in this field?
- Which job prospects do talented young biomathematics researchers have?

The outcome of the foresight study, carried out over the period September 2005 – December 2007 and laid down in the present report, considers these questions in an integrated manner and puts forward a series of recommendations for researchers, universities, intermediary research institutes, funding organisations, government authorities, and the business and industrial community.

During the foresight, a start-up meeting and two brainstorm meetings were held, one for senior and one for junior researchers in biomathematics. An inquiry via a questionnaire was performed, both at the start-up meeting and via Internet, and interviews were held with secondary school students. Inventories were made of ongoing biomathematics research and education in The Netherlands, including contacts with industry. Moreover, several international documents were studied, and there was exchange of information with leading researchers in biomathematics abroad, so that benefit could be taken from their experiences and insights. The opinions expressed at the various meetings, as well as the results of the questionnaires, the interviews and the inventories, are integrated into the observations and recommendations made in the report.

The present foresight is the first strategic study conducted in The Netherlands in the area of biomathematics. Currently some 200 people in The Netherlands are active in biomathematics. This group has been identified, and the first steps have been taken towards building a community, lining up opinions about how the field is best developed and supported, and listing the most urgent needs for the near future. The current position of biomathematics in The Netherlands is

vulnerable and a delicate balance needs to be struck between bottom-up flexibility and top-down control. The hope is that the foresight study contributes towards a better understanding of the catalyzing role mathematics can play in the life sciences. Much remains to be discovered still.

In the process, valuable input and assistance was obtained from many colleagues. In addition, constructive comments on a preliminary version of the report were received from a number of people. This is gratefully acknowledged. The Foresight Committee has come to realize that biomathematics in The Netherlands is a fast growing research area that is carried by an enthusiastic group of excellent researchers many of whom are still young. The Foresight Committee is confident that with the right stimulus, care and patience, as outlined in the recommendations listed at the beginning of the report, biomathematics can develop into a full-fledged field with a bright future and a capability to offer ‘a vision for success’. A successful future for Dutch biomathematics is well within reach.

Sjoerd Verduyn Lunel (chair)

Mathisca de Gunst (secretary)

1. Introduction

In the present report, biomathematics is taken to encompass those areas of mathematics that, on the one hand, contribute to the mathematical formulation and study of questions in the life sciences and, on the other hand, are motivated and encouraged by models that are developed and experiments that are carried out within the life sciences. Phrased differently, biomathematics is that area at the interface between mathematics and the life sciences in which the main focus is on developing *mathematical* models, concepts, methods, techniques and approximations, with the aim of applying these to *concrete* problems coming from the life sciences, while at the same time pursuing a *generic* and *unifying* point of view. The life science areas that are considered in the report are: *biology*, *medical sciences*, *agricultural sciences* and *pharmacology*. The report is written primarily from the point of view of mathematics *in interaction* with the life sciences, rather than mathematics *from within* the life sciences. Statistics is considered to be part of mathematics.

Although there is a close link with bioinformatics (the distinction between biomathematics and bioinformatics is not always clear), bioinformatics in itself was not part of the investigation. The same holds for biophysics and bioengineering. For example, research that concerns the statistical analysis of life science data was taken into account, but research on data mining aspects was not. Similarly, computational modeling in the life sciences was included only if it has a mathematical component according to the definition given above.

1.1 The importance of biomathematics

The sequencing of the human genome and the enormous progress of new technology in, for example, nuclear magnetic resonance, mass spectrometry and brain imaging, has resulted in a large amount of novel experimental research. This, together with the simultaneous developments in computational power, allows the scientific community to search for answers to questions in the life sciences that are much more complex than could be handled before. Mathematicians can play an important role. Their contribution is *indispensible* in providing a solid basis for translating complex biological systems into useful mathematical models, and for designing appropriate methods and tools for the analysis of novel types of complex data sets. In order to interpret and understand the experimental results in coherence, and to optimize the experimental design, it becomes more and more important to have a fruitful and rich *interaction* between theory and experiment, with special emphasis on qualitative and quantitative analysis. It is a challenging task to align experiment and theory, and to influence the experimental design. Many societal benefits can be expected from biomathematics, for example, regarding aging, personalized medicine, prediction of progressive diseases, and efficient food production.

1.1.1 Complexity

Biological networks and pathways, such as the nervous system, the immune system and the signaling pathways, are high-level building blocks from the life sciences. An important feature of these biological systems is that they exhibit *complexity at multiple spatial and temporal scales*. Biological scales range from molecules, cells and organisms to populations and communities, whereas time scales range from 10^{-9} seconds at the molecular level to 10^9 seconds at the level of a whole organism. Nodes that form a biological network are quite sensitive to their surroundings and to their interactions with other nodes, leading to non-local effects. For example, isolated cells in a nutrient solution may stay alive, but often lose many of their specialized functions when operating in a network. Tissues and organs are the next level of biological complexity. Again, even homogeneous organs, such as the liver, function in a systematic coordinated manner far different from the isolated behavior of the cells that constitute them, and a whole organism cannot be fully understood by understanding the organs and the cellular parts separately. A further level of biological complexity arises at the level of populations, for example, the spread of infectious diseases and the behavior of ecosystems.

1.1.2 New opportunities

While scientists have been studying biological systems at these various scales for many years, successfully applying mathematical methods and techniques, the recent technological achievements in the life sciences have created many new opportunities for biomathematicians. Indeed, the currently available techniques have resulted in vast quantities of descriptive information at various sublevels for biological systems, and the task is to turn this information into useful information about the overall function and behavior of the system. This is a defying problem, because complexity and interrelationships of the different levels of integration typically lead to multi-scale models, in which a small event on a given spatial or temporal scale has a large effect on other scales. Such multi-scale problems naturally occur in the mathematical modeling of spatially distributed interacting processes, like cell-to-cell interaction arising in chemotaxis, neuronal networks, and individual and collective cell movement. The feature of these multi-scale models is that they include both *deterministic* (continuous and discrete) and *stochastic* elements. Their hybrid nature complicates the analysis of the dynamic behavior of such models, because available theoretical results have mainly concentrated on equations of a single type, such as systems of reaction diffusion equations or Navier-Stokes equations to model fluid flows. These results cannot readily be applied to the hybrid setting that arises in multi-scale problems. The analysis of biologically motivated multi-scale models *challenges* the current methods and techniques in mathematics.

1.1.3 Example

To give an example, a fundamental question in the life sciences is how from a single cell after fertilization a complex organism emerges. After a transient phase of cell division, a complex process involving cell-cell interaction leads to cell differentiation, adaptation and selection, which in turn results in a living organism. One of the most central issues is the understanding of the *emergence of structure and form* from the almost uniform mass of dividing cells that constitutes the early embryo. Although genes play a key role, genetics does not tell us everything about the mechanisms that bring together the constituent parts in a coherent pattern. A coherent pattern often results from the response of individual cells to a spatial pattern of chemicals called morphogens: molecules that move through a tissue by diffusion or other means, and regulate gene expression in a concentration-dependent manner. While there are many variations on how this so-called process of morphogenesis works in different organisms, it is striking how conserved the basic processes are across the phyla. The most widely used models

to study morphogenesis are based on reaction-diffusion theory, and propose that a chemical pre-pattern is first set up due to a system of reacting and diffusing chemicals, and that cells respond to this pre-pattern by differentiating accordingly. Such patterns, known as Turing structures, were first identified in chemical systems. Surprisingly, these same processes are involved in cell differentiation and various diseases such as cancer. This unity and conservation of the basic processes provide the rationale for building and studying various mathematical models of these basic processes. Mathematical insight in these models can have a wide-ranging impact across the spectrum of normal and pathological development.

This is just one illustration of the importance of careful, quantifiable and mechanism-based theory for studying problems in the life sciences. Many more could be provided.

1.1.4 Integrated approach

It is nowadays relatively easy to collect large amounts of data, to engage in empirical curve fitting, or to produce complex simulations that reproduce desired behavior. However, the grand challenge is an *integrative approach*, in which one can combine and make effective the information that is obtained from molecular biology, genomic research, physiology, ecology, etc., on the one hand, and the mathematical modeling of basic processes and well-founded data analysis on the other hand. An integrative approach, combining the relevant disciplines with a strong mathematics component, will allow for a leap forward in the understanding of living organisms. Such an integrative multidisciplinary approach will have a significant impact on many areas of science and technology, including pharmacology, medicine, plant science, food microbiology and environmental science.

1.2 The interface between mathematics and life sciences

Mathematics has long been intertwined with the life sciences, but an explosive *synergy* has manifested itself in the past decades, which is enriching both fields. In the coming decades mathematics will benefit increasingly from its involvement with the life sciences, just as it has done with physics in past centuries. Conversely, through mathematics the life sciences will become more quantitative and science-based, relying on powerful analytical and computational methods to model the complexity of biological systems. The interface between mathematics and the life sciences extends across a range of biological problems and across all the major areas of mathematical research.

1.2.1 Historical examples

The history of applications of mathematics to the life sciences is full of unexpected reciprocal influences.

Populations and statistics

The work of the mathematician R.A. Fisher helped to establish the field of population dynamics. His work demonstrated that statistics is a natural tool for modeling populations. In turn, the availability of biological data led Fisher to revolutionize the field of statistics. In the past decade modern developments in genomics have revived interest in the original work of Fisher and others in statistical genetics. This has led to the development of many new statistical tools in this area, and new and highly challenging statistical research questions keep arising in this field.

Ion channels and differential equations

Another important historical example is the mathematical description of the evolution of ionic currents through ion selective channels by means of a system of four coupled ordinary differential equations with highly nonlinear terms, identified by Hodgkin and Huxley in the 1950's. One of the remarkable aspects of their work, which lies at the basis of the modern day membrane electrophysiology, is that models were developed without an understanding of the underlying molecular mechanism. It took almost thirty years of intensive subsequent research to formulate a realistic cartoon, in terms of nonlinear partial differential equations, of the mechanisms underlying the ionic currents. The ramifications of Hodgkin and Huxley's formalism continue until today. For example, their work led to the mathematical understanding of excitability in nonlinear partial differential equations, which turned out to be of an exceptionally general applicability. It is this excitability over a spatially extended biological network that allows for robust signaling over great distances, providing the basis for communication and control of many fundamental biological processes.

Biological sequences, dynamic programming, and statistics

Nowadays, the availability of sequences of entire genomes is increasing rapidly and mathematical methods are essential at all stages of the analysis of these sequences. For example, in order to compare two genomes, a local alignment of the corresponding sequences is necessary. Methods from dynamic programming have been used by Smith and Waterman in the 1980's in order to successfully solve the optimal local alignments problem. Although these methods solved

the mathematical problem, they turned out not to be very efficient for long sequences. Consequently, the biological problem at hand led to new research in which a combination of ideas and techniques from computer science and statistics were needed to compute the significance of the matches. This work resulted in the development of the BLAST software, published in 1990, which provided biologists with access to sophisticated database searches in order to compare their own sequences with known sequences. Many mathematical problems in this area, however, are not yet solved and new ones keep arising.

1.2.2 Today's interface

More recently, conservation biology, biodiversity, harvest planning, invasive species control, and wildlife management all heavily utilize general ecological and evolutionary genetics theory, combined with mathematical methods to address major public policy issues. Conversely, determining how natural systems are affected by interactions of space and time revolutionized the field of nonlinear partial differential equations.

Another present day example, for which appropriate methods do not yet exist, concerns the need for accurate models of molecular forces appropriate to biological systems. These models have to work well even when, like during protein folding, molecules form, break and remake bonds, a far more difficult and nonlinear situation than found in crystalline substances. New and efficient methods are needed to model the effect of solvents on important biological reactions. Purely stochastic methods are expected to be important, but, equally importantly, a theory will have to be built that supplies biologically meaningful probability distributions as input to these methods. In addition, the mathematical models must be amenable to efficient computational algorithms that can analyze realistic biological reactions.

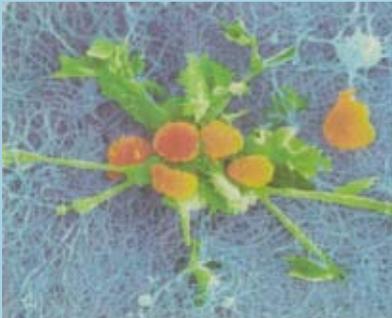
Challenging problems at the interface between mathematics and the life sciences also include the linking between scales. For example, how do evolutionary models that account for the dynamics of spatial structure relate to ecological models, which operate on shorter time periods? Or, how does genomic information assist in developing a theory for whole organism interactions with environment and the functioning of populations, communities, and ecosystems? Addressing these problems requires close collaborations between ecologists, evolutionary biologists, and mathematicians.

Although it is expected that these and other dynamic interactions between mathematics and the life sciences will further intensify, the precise way in which mathematics will facilitate new developments in the life sciences remains

Immunology

T-cells are produced in the bone marrow and are selected in the thymus. Their task is to defend our body against pathogens like bacteria, viruses and fungi. The human immune system carries 10^7 different types of T-cells. However, a total of 10^{15} different types of intruders need to be recognized, which raises the paradox: “How can so few soldiers fight successfully against so many enemies?”

The intruders manifest themselves as antigens: foreign molecules that elicit a specific response by the T-cells. These antigens are taken up by the antigen presenting cell (APC), which absorbs the antigens, breaks them down, and exhibits them on its surface as peptides, each consisting of some 10 aminoacids. The T-cell itself has only one type of T-cell receptor (TCR) on its surface, which is capable of recognizing a certain repertoire of peptides. The T-cell with its TCRs *samples* the APC with its peptides. This leads to a series of signals, which the T-cells add up. As soon as the total signal exceeds a certain threshold value, the T-cell becomes alarmed.



Extracellular matter (blue), with an APC-cell (green) surrounded by T-cells (orange), as viewed through an electron microscope.

The APCs carry a large number (up to 10^5) of different types of peptides on their surface, and therefore have a highly complex structure. Also the interaction between the T-cell and the APC is highly complex. Therefore the sampling of the APC by the T-cell can be modeled as a *random process*. Each APC has a large number of own – *self*– peptides and, possibly, a small number of foreign – *nonsel*f– peptides. T-cells only become activated when they recognize a nonsel

peptide on the surface of the APC. When this happens, the T-cell reproduces itself and triggers an immune reaction. The T-cell must not react to self peptides, since this would trigger a dangerous auto-immune reaction. Research has shown that, for a realistic range of parameters, the stochastic model is capable of solving the paradox of ‘few soldiers against many enemies’. It turns out that the probability to exceed the threshold value during the sampling process when no nonsel

peptides are present is much smaller than when there are nonsel peptides. The ratio of the probabilities determines the degree of resolution, not their absolute value. Both probabilities are very small, which is why the analysis requires sharp estimates, based on refined probabilistic limit theorems.

Central to the model is the fact that *deterministic recognition* of peptides is replaced by *stochastic recognition*, based on the complexity of the sampling process and on the large numbers of copies of T-cells and APCs involved in the process.

uncertain. Many areas of biological research are at points of instability. The ways in which these areas will develop, and hence also the way in which biomathematics will develop, is highly unpredictable. Therefore the next decade will shape the future of the interface between mathematics and the life sciences.

1.3 Synergies of benefit

1.3.1 Two approaches

There are two main approaches to biomathematics. In the first approach, mathematics is directly *motivated* by the life sciences: a particular biological problem is at the center of interest, and whatever mathematical tools can be used productively are applied to improve the understanding of the biological system. Frequently, the mathematical tools that are used are well understood, but in many cases existing tools need to be adapted for a novel application, or completely new tools and modeling methods need to be developed. In the second approach, mathematics is *inspired* by the life sciences, but not necessarily directed at solving a specific problem: the focus is on the development of mathematical tools, modeling methods, and theoretical concepts that may be essential in addressing a range of problems in the life sciences, but where the mathematical basis is sufficiently complicated and poorly understood so that a great deal of insight is achieved from the development of the theory within mathematics. Both approaches are equally important.

For example, in the field of epidemiology a researcher in the life sciences would have a particular disease of interest. As dictated by the characteristics of the disease, the available data and the purposes of the research (for example developing control strategies), the researcher would use mathematical tools like differential equations, Markov chains, neural network, evolution models, parameter estimation, model reduction, etc. This approach centers on the biological problem. Direct involvement of a mathematician in the analysis is needed when standard models and methods fail.

An approach centered on the mathematical problem might start from a lack of sufficient data. For instance, CT scans are often used to check for hidden abnormalities. When fewer than ten x-ray images are available, traditional reconstruction algorithms for tomography produce unsatisfactory results. However, this problem can be solved if the reconstruction process incorporates additional knowledge. In this application, not all grey scale values have to be computed to

produce a 3-D image. Black and white scales are sufficient to produce a useful image - the material is either present or absent. This type of reconstruction, using only a limited range of grey scales, is known as 'discrete tomography'. New algorithms for discrete tomography were recently developed. They solve the mathematical problem and produce much sharper 3-D reconstruction using fewer x-ray images. The potential of this approach was shown in a proof of principle study of osteoporosis in mice, where only a limited range of grey scale values are required because osteoporosis causes cavities in the bones. In other words, the bone material is either present or absent. This is exactly the situation that can adequately be solved with the new mathematical techniques.

1.3.2 Teaming-up

In both examples, it is essential that the mathematicians and the life scientists *team up* in multidisciplinary research teams to make further progress, while simultaneously creating challenging problems. There are many central questions in the life sciences where progress in answering questions is currently limited by the lack of fundamental work at the interface between mathematics and the life sciences, which in many cases is driven by specific biological problems. These questions include applied issues, such as preparing for and responding to threats of emerging diseases, or the design of efficient systems of drug delivery. Similarly, there are basic questions requiring new advances in biomathematics, such as understanding issues in evolution, growth and development, dynamics of cells, transport in tissues, structure of and dynamics in random media and biological networks. It is therefore highly important that more mathematicians and life scientists *recognize* the value of true collaboration. A prerequisite for such collaboration to be fruitful is that the involved researchers have sufficient knowledge about the other area, so that *adequate communication* is possible.

1.4 The international picture

The interactions between mathematics and other scientific disciplines are stronger than ever. In particular, as we have illustrated in the previous sections, the emergence of a strong and very promising relationship between mathematics and the life sciences, in which a more *predictive* and *quantitative* understanding of biological function is at the center, is underway. This development has resulted in a number of research initiatives, dedicated centers, and special institutes, notably in the UK and in the USA. These initiatives often also have an

educational component. In other foreign countries, such as Germany and France, biomathematics research initiatives exist on smaller scales, and plans for larger initiatives are being developed. Additionally, at several universities in Europe new educational programs, often named systems biology or integrated biology, have recently been started, in part addressing the gap between mathematics and biology. However, in most cases these programs do not teach mathematics in any depth. Within the scope of the present foresight study it is impossible to give a complete description of the biomathematics research abroad. Instead, we discuss a few important initiatives in the UK and in the USA in which mathematicians are playing a prominent role.

1.4.1 Biomathematics in the UK

In the UK, multidisciplinary approaches aimed at bringing together experimental and theoretical techniques, to tackle problems in the life sciences, have been boosted by a joint effort of the Biotechnology and Biological Sciences Research Council (BBSRC) and the Engineering and Physical Sciences Research Council (EPSRC). Since 2005, the initiative represents an investment of over £85M, and the goal is to maintain the UK's world-class bioscience research base. One of the central issues is to further establish the field of predictive biology, i.e., developing mathematical models in direct interaction with the design of experiments, so that experimental data can be used to optimize the next round of hypotheses to be tested. The joint effort of BBSRC and EPSRC recognizes the vital contribution that researchers from the physical sciences and engineering can make to this important developing area of interdisciplinary research. The initiative has, in particular, led to the establishment of six Centers for Integrative Systems Biology: CPIB (Centre for Plant Integrative Biology)¹, CSBE (Centre for Systems Biology at Edinburgh)², CISBIC (Centre for Integrative Systems Biology at Imperial College)³, MCISB (Manchester Centre for Integrative Systems Biology)⁴, OCISB (Oxford Centre for Integrative Systems Biology)⁵, CISBAN (Centre for Integrative Systems Biology of Ageing and Nutrition)⁶. The centers are using systems approaches to investigate bioscience questions that include circadian rhythms, complex plant root models, ageing and disease. Although mathematicians are involved and participate, the initiatives are broadly based and not directly

1 <http://www.cpiib.info/>

2 <http://csbe.bio.ed.ac.uk/>

3 <http://www3.imperial.ac.uk/cisbic>

4 <http://www.mcisb.org>

5 <http://www.bioch.ox.ac.uk/sysbio/>

6 <http://www.cisban.ac.uk/>

rooted in mathematics. A number of Departments of Mathematics and Statistics in the UK have reacted to these initiatives. In particular, the Departments of Mathematics and Statistics at Oxford and Warwick have impressive programs in biomathematics, both in education and research, linking up with these initiatives.

At the University of Oxford, the Centre for Mathematical Biology (CMB)⁷ is part of the Mathematical Institute and was established in 1983 as the first centre of its kind in the UK. Both the CMB and the Department of Statistics are closely linked to the new Oxford Centre for Integrative Systems Biology, and the research interests include: cancer modeling, spatial and spatial-temporal pattern formation, wound healing, tear film dynamics, dynamics in the lung, sperm dynamics, stochastic models of reaction-diffusion processes, chemotaxis, gene regulatory networks, multi-scale models in biology, and from individual to collective behavior in ecology.

At the Department of Mathematics at Warwick there is an interdisciplinary program for cellular regulation (IPCR). The program, co-headed by a mathematician, has as its main research theme the application of mathematical, statistical, computational and theoretical tools to the broad range of questions concerned with understanding the regulation and coordination of gene expression, the function and dynamics of the interaction networks made up of genes, their RNA and protein products and the way in which these structures mediate internal regulation of the cell and its interaction with the external environment. The primary funding of the program is a major Multidisciplinary Critical Mass Research Activity grant from the EPSRC and the BBSRC, which is entitled The Mathematical Architecture of Biological Regulation.⁸ In education there is the special doctoral training centre Molecular Organization & Assembly in Cells (MOAC).⁹ The aim is to equip students with the skills necessary to become effective life scientists of the future. The MOAC students have first degrees in Mathematics, Physics, Chemistry, Biology, Computing, Statistics, or Engineering. Over an 8-year period the program will produce a minimum of 50 PhD post-graduate students with a uniquely broad interdisciplinary training in biology, chemistry, mathematics and computing.

7 <http://www2.maths.ox.ac.uk/cmb/>

8 <http://www2.warwick.ac.uk/fac/sci/systemsbiology>

9 <http://www2.warwick.ac.uk/fac/sci/moac/>

1.4.2 Biomathematics in the USA

In the USA, there are a number of specific programs at Departments of Mathematics and at specific Institutes of Mathematics. Prominent examples include the Department of Mathematics and the Institute for Mathematics and its Applications (IMA)¹⁰ at the University of Minnesota, where there are special programs on the Mathematics of Molecular and Cellular Biology. The Department of Mathematics at the University of Utah has a special NSF-IGERT program for Cross-Disciplinary Research Training in Mathematical Biology¹¹ to train graduate students to use the tools of applied mathematics to study the challenging problems of modern biology. The broad research emphases of the program are bio-fluids, ecology, and evolutionary biology, neuroscience, and physiology. At the University of California, Berkeley, there is an active interdepartmental group in Biostatistics¹². This group offers a program with training in theory of statistics and biostatistics, computer implementation of analytic methods, with opportunities to use this knowledge to study research problems in the life sciences. The Mathematical Biosciences Institute at the Ohio State University¹³ has as its mission to foster innovation in the development and application of mathematical, statistical, and computational methods for the solution of significant problems in the biosciences; to engage mathematical and biological scientists in the solution of these problems; and to expand the community of scholars in mathematical biosciences through education, training, and support of students and researchers. To support this mission, the MBI organizes special emphasis year programs, current topics workshops, educational programs, and sponsored research projects.

1.4.3 International biomathematics societies

Aside from these initiatives, there are also a couple of societies active in promoting the relationship between mathematics and the life sciences.

The *Society for Mathematical Biology* (SMB)¹⁴ is already active for more than twenty years. This society serves its members through the *Bulletin of Mathematical Biology* (the official SMB journal), an internet digest providing a moderated forum to the international mathematical biology community, a newsletter, and the organization of conferences and meetings.

10 <http://www.ima.umn.edu/>

11 <http://www.math.utah.edu/research/mathbio/igert/>

12 <http://www.stat.berkeley.edu/biostat/>

13 <http://mbi.osu.edu/>

14 <http://www.smb.org/>

The *Society for Industrial and Applied Mathematics* (SIAM)¹⁵ is active in all fields of applied mathematics and has members from all over the world. SIAM runs many journals and conference series, mostly at the interface of applied mathematics and important application fields, and a number of activity groups. The SIAM Activity Group on the Life Sciences was established to foster the application of mathematics to the life sciences and research in mathematics that leads to new methods and techniques useful in the life sciences. The activity group brings together researchers who seek to develop and apply mathematical and computational methods in all areas of the life sciences. It provides a forum that cuts across disciplines to catalyze mathematical research relevant to the life sciences and rapid diffusion of advances in mathematical and computational methods.

The *International Biometric Society* (IBS)¹⁶ is an international society that promotes the development and application of statistical and mathematical theory and methods in the biosciences, including agriculture, biomedical science and public health, ecology, environmental sciences, forestry, and allied disciplines. The IBS has as its members statisticians, mathematicians, biological scientists, and others devoted to interdisciplinary efforts in advancing the collection and interpretation of information in the biosciences. It publishes two journals, *Biometrics*, reporting communications consistent with the Society's mission, and, jointly with the American Statistical Association, the *Journal of Agricultural, Biological, and Environmental Statistics*.

1.4.4 Strategic studies abroad

In order to further develop the promising relationship between mathematics and the life sciences, a number of strategic studies have appeared in the United States as well as in Europe [1, 7-9, 11, 12, 14-15]. In three key studies the mathematical challenges that lie ahead of us in connection with the fundamental problems and questions that are arising at the interface of mathematics and the life sciences are clearly formulated. The conclusions and recommendations of these studies apply to a great extent also to the Dutch situation. We summarize them below.

In *Mathematics and the 21st Century Biology* [11], the main recommendation is to create and nurture a robust interface between mathematics and the life sciences. Progress in the life sciences will increasingly depend on deep and broad integration of mathematical analysis into studies at all levels. There are many instances where mathematical tools have already proven their utility in a broad range of biological applications. In some cases, limitations of the effectiveness of

15 <http://www.siam.org/>

16 <http://www.tibs.org/interior.aspx?id=508>

Genomics

Cancer is a genetic disease, often caused by abnormalities in the genetic material of cancer cells. Examples of such abnormalities are the copy number alterations (CNAs). CNAs are genomic segments with an abnormal copy number. The chromosomal DNA copy number is the number of copies of genomic DNA. Normal somatic cells have two copies of the autosomal chromosomes: the copy number is two. In cancer cells the copy number may vary considerably over the genome. CNAs are a key event in the development and progression of cancer. The position and direction of CNAs both vary from tumor to tumor and carry a certain tumor specificity.



Left: chromosomes of normal lymphocyte; two chromosomes contain the gene *hTERT* (red signal). Right: chromosomes of cancer cell; three chromosomes contain the gene *hTERT* (red signal).

Array comparative genomic hybridization (aCGH) is a high-throughput method to measure DNA copy number. In an aCGH experiment differently labeled test (read: cancer) and reference samples are hybridized together to the array. The reference sample is assumed to have copy number two. Image analysis then results in test and reference intensities. The \log_2 ratio of the test and reference intensities reflects the relative copy number in the test sample compared to that in the reference sample.

The aCGH data are pre-processed to arrive at an estimate of the copy number of a genomic segment. First, motivated by the underlying discrete DNA copy numbers of test and reference samples, *change-point analysis techniques* divide the genome into non-overlapping segments that are separated by breakpoints. These breakpoints indicate a change in DNA copy number and, consequently, the copy number does not change within a segment. Due to the relativity of the measurement, the exact copy number of a segment cannot be determined. However, via *mixture models* deviations from the normal copy number can be detected. The detection of these CNAs is not perfect, for example, due to experimental noise or unknown contaminations by normal cells. To address this imperfection, the CNAs are represented by a vector of probabilities, one for each type of CNA that is discerned. Such probabilities reflect both cell heterogeneity and precision of the aCGH data.

CNAs are, through the central dogma of biology, likely to result in increased (or decreased) mRNA transcription levels (as measured by gene expression microarrays) of the genes in the aberrated segment. The direct (i.e., disregarding feedback mechanisms) relationship between these two molecular levels can be described by a *non-parametric model*. The use of the CNA uncertainty, as reflected by the probability vector in this model, can be viewed as *error propagation*. The model enables the construction of non-parametric tests that detect genes whose expression differences appear to be driven by copy number changes. Such genes are candidate cancer genes. The breakpoint nature of the aCGH data implies that neighboring genes share the same copy number. One expects that their expression levels are affected in a similar fashion. The tests can be modified to borrow information across these genes, thus addressing the *spatial* nature of the data.

some of these tools become apparent because of the expanded range of application. There are opportunities for effective and important mathematical research that is less tightly tied to particular applications in the life sciences. However, it is recommended that research at the interface between mathematics and the life sciences always be biology driven. Promising research topics are characterized by high dimensionality, heterogeneity, robustness to perturbations, and the existence of strongly interacting, highly disparate spatial and temporal scales. The authors of the report opt for a patient, broadly based, vigorous effort to expand research at the interface between mathematics and the life sciences, rather than for a commitment to a small number of high-profile projects with monolithic goals. Mathematics can boast a number of successes, including population genetics, statistics of large data sets, imaging, and experimental design. The best developments may be expected there where theory and experiment meet (primacy of data). Integration of different perspectives and different expertises should be an overriding goal. Funding agencies must find a way to support biomathematics effectively. It takes much time and effort to integrate interests and develop a common language. A realistic standard must be set to referee research proposals that are truly interdisciplinary.

In *Towards 2020 Science* [16], the main recommendations concern the education of tomorrow's scientists, as well as science policy and funding. All biologists will need to be computationally and mathematically literate, and by 2020 it will be simply impossible to do science without such literacy. This has important implications for education policy right now. It is further expected that biology will create new paradigms for mathematics and computer science, and that biological systems can be handled as information systems. According to the authors of the report, end-to-end scientific data management is the key

challenge, i.e., from acquisition, via analysis and interpretation, to implementation and use. Research in the life sciences will slowly transform from technology-based to science-based. There is a pressing need for public awareness, and greater focus on long-term research, for institutions that focus on great challenges rather than on great disciplines, and for closer collaboration between academics and industry. Intellectual property should be valued as much as technological property.

In *Quantitative Biology for the 21st Century* [8], it is observed that current and future progress in biomathematics is hampered by a series of impediments, including: a lack of both quantitatively trained biologists and mathematicians with expertise in biology, difficulty in establishing and maintaining long-term collaborations among life scientists and mathematicians, institutional and cultural barriers that reduce the potential for funding in interface areas, and universities that encourage disciplinary work over interdisciplinary work. On the other hand, the report mentions a growing awareness of the need to allow for more fundamental research within biology. This quest is driven by the fact that research in the life sciences is becoming gradually more quantitative. The present explosion of available information allows for better measurements, requiring the development of a theoretical framework to interpret and guide this new information. Mathematical challenges around the theme of complexity go hand in hand with the enormous growth in computing power, requiring new bridges to facilitate this symbiosis.

The recommendations in the report concern special funding of interdisciplinary programs, special undergraduate training programs, grants for post-doc groups, building of a collaborative infrastructure via support of small research centers. It identifies four growth areas for biology within mathematics: stochastic analysis, spatial processes, networks, linking models to data.

1.5 The national picture

The Dutch biomathematics landscape is similar to the international one, albeit on a much smaller scale. There is a growing involvement of mathematics with other disciplines, and the need for new mathematical methods and techniques for solving vital social problems has considerably increased in recent years. Despite these developments, the volume of mathematical research has been *reduced* over the past decade, and as such the biomathematics potential has decreased accordingly.

1.5.1 Mathematics clusters

In the strategic study *Nieuwe dimensies, ruimer bereik* [13], a number of measures were proposed to strengthen and stress the distinctive features of Dutch research in mathematics. The most important of these measures was the creation of thematically oriented *research clusters in mathematics*. These clusters would provide centers for national and international cooperation both within mathematics and with other disciplines, and should initially exist for at least five years. So far, there are three clusters active in The Netherlands. Through these clusters, a number of tenure-track positions were created at the interface between mathematics and its application areas. The cluster Nonlinear Dynamics of Natural Systems (NDNS+)¹⁷ has several of its central mathematical themes associated to the interaction between mathematics, the life sciences and the earth sciences. The research interests of the mathematicians collaborating in the NDNS+ cluster include bifurcations and chaos, networks and delays, scientific computing, transient dynamics, multiple scales, patterns and waves, stochastic models, and statistics. At present, the NDNS+ cluster is involved in a number of research projects that involve the life sciences, in particular, problems in statistical genetics, epidemiology, analysis of high-dimensional data, modeling of networks, cell processes and population dynamics, and image analysis.

1.5.2 Foresight activities

In order to obtain more insight into the size, structure, and opinions of the Dutch biomathematics community, several activities were organized during the foresight study. Besides different inventories (see Sections 1.4, 2.1, 3.1 and 4.2.1), and interviews with secondary school students (Section 3.1.3), a start-up meeting and two brainstorm meetings were held, one for senior and one for junior researchers in biomathematics. The meetings were well attended, with approximately 70, 25 and 50 participants, respectively. The participants and speakers of the meetings did not only give valuable feedback to the Foresight Committee, but also enjoyed the opportunity to get to know each other and to become informed about each other's research. Ideas and opinions expressed during these meetings are integrated in the text and in the recommendations of the present report. Furthermore, both at the start-up meeting and via internet an inquiry via a questionnaire was performed. A summary of the results of the questionnaires can be found in Appendix 3.

¹⁷ <http://www.ndns.nl/>

1.5.3 Stimulation of Dutch biomathematics

The main conclusion from these activities is that, in the field of biomathematics, The Netherlands is a modest but high-quality player, with international focus and visibility. However, its present position is *vulnerable*. New interactions of mathematics with the life sciences are emerging, but on a small scale, and these are insufficient for keeping up with the rapid developments in the area. Therefore stimulation of Dutch biomathematics is necessary and timely. The observations that lead to this conclusion are described in the Chapters 2 and 3, where biomathematics research and education in The Netherlands are discussed in more detail.

1.6 Structure of the remainder of the report

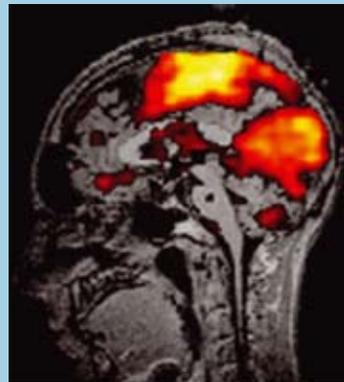
In Chapters 2 and 3 the current state, the challenges, and how to meet these challenges of biomathematics research and education in The Netherlands are described. Chapter 4 concerns the two main aspects of facilitating biomathematics research and education: organizational structure and funding. Short notes about industry are made at the end of each of these three chapters. In Chapter 5 opportunities and perspectives are sketched. In between the chapters, highlights of present-day biomathematics research are presented in which Dutch mathematicians are involved. The appendices contain the composition of the Foresight Committee, an overview of advisors and contributors, main results of the questionnaires, as well as a list of abbreviations.

Neuronal networks

Brain activity can be recorded using different techniques on different scales. *Microscopic* techniques (like gene expression microarrays and mass spectrometry), *mesoscopic* techniques (like patch clamp and multi-electrode recordings) and *macroscopic* techniques (like electroencephalography (EEG), magnetoencephalography (MEG) and functional magnetic resonance imaging (fMRI)) are all used to investigate functional *neuronal networks* on different space-time scales and for different aspects. Insight into properties and possible pathological changes of the healthy functional network is important to understand a variety of diseases (e.g. Alzheimer, Parkinson, epilepsy). Mathematical modeling and statistical analysis are indispensable in these investigations.

For example, with MEG and EEG electromagnetic brain activity is recorded outside the head. EEG measures electric potentials in sensors at the scalp and MEG records magnetic brain fields in sensors in a helmet around the head. Network analysis via MEG and EEG considers the *correlation* of brain activity between different brain areas. By modeling the different areas as *dynamical systems*, several mathematical measures have been constructed that can detect the coupling between different areas based on EEG and MEG data sets. Different measures catch different properties of the network. For instance, relating repeating patterns in different brain areas has shown that long range connections are typically lost in Alzheimer disease, while covariance analysis has shown that activity at different frequencies is generated in different spatial patterns.

In the fMRI scanner the brain is exposed to evoked magnetic fields. The so-called blood oxygen level dependent (BOLD) signal is recorded on thousands of volume elements (voxels). Active brain areas will generate a higher BOLD signal. Whereas in EEG and MEG a high temporal resolution can be achieved, in fMRI a high spatial resolution is accompanied by a low temporal resolution. Simultaneous analysis of EEG and fMRI data has turned out to be fruitful, since it combines high temporal resolution data with high spatial resolution data. However, the question of how to do this in an optimal way, is a difficult statistical issue. Relating the alpha rhythm in the EEG signal to the fMRI signal per voxel, in order to find those areas in the brain that correspond to the alpha rhythm yields large variations between subjects, which cannot be explained by natural variations in the underlying network. Recently, progress has been made by analyzing the signals on the level of *functional clusters* of voxels. This approach shows better reproducible results over subjects.



Estimated locations of generators of α -activity based on an EEG-fMRI recording

2. Research in biomathematics

2.1 The current state

2.1.1 Size of biomathematics in The Netherlands

At present the total number of biomathematics researchers, including post-docs and PhD students, in Dutch academia is approximately 200, divided over some 20 groups (where isolated individual researchers are not counted). Many of these researchers have international collaborations, and the research is of excellent quality. The biomathematical research activity is not evenly spread over the universities and research institutes. Within mathematics the largest biomathematics group is at the VUA, followed by the UL, CWI, and, UM. Smaller biomathematics groups are active within the mathematics departments of the TUE, UU, RuG, and at EURANDOM. Most of the biomathematics research within mathematics takes place within the NDNS+ cluster. Within the life sciences biomathematics research is found in all universities, except the UT and UVT, with the RuG, TUE, UL, UU, VUA, and WU accommodating the largest numbers of biomathematics researchers, followed by the RU, TUD, and UVA. This is illustrated in Table 2.1, which gives a general impression of the spread of activity over the different universities and mathematical research institutes. We note that the table is meant to give a global view, rather than a precise enumeration. Single-person groups are not counted, and only *biomathematics* research as defined in Chapter 1 is included. This implies that biomathematics (biostatistics) research that is done within bioinformatics is included in the table, but bioinformatics research itself is not. The same holds for biomathematics research in bioengineering, biochemistry, and biophysics.

2.1.2 The involved mathematical and life science areas

The mathematical research areas that are involved in interdisciplinary research in the life sciences are mainly analysis, discrete mathematics, numerical mathematics, probability theory, statistics, and systems theory; with analysis and statistics being the most important. Below we give short descriptions of the biomathematical research activities and challenges in these areas. The main biological areas in which the Dutch mathematicians are involved are cell/organ modeling, ecology, epidemiology, image analysis, neuroscience, omics (genomics, proteomics and metabolomics), and systems biology. These areas have in part been discussed in Chapter 1 and will also return in the descriptions in Section 2.2.3. As illustration, in between the chapters of this report highlights of present-day biomathematics research are presented in which Dutch mathematicians are involved.

2.1.3 National biomathematics societies

In The Netherlands there is no general formal biomathematical organization or society. Three more specialized societies are active at the interface between mathematics and the life sciences. The Biometric section of the Society for Statistics and Operational Research (Vereniging voor Statistiek en Operationele Research), BMS, and the Dutch section of the International Biometric Society, IBS-ANed, cooperate in advancing statistics and its applications in the life sciences¹⁸. They organize meetings, in particular the bi-annual Biometric Conference, and take care of the registration of biostatisticians. The Dutch Society for Theoretical Biology (Nederlandse Vereniging voor Theoretische Biologie (NVTB))¹⁹ is a biological society for theoretical biology which also has many biomathematicians as its members. It organizes regular meetings and spreads a newsletter.

¹⁸ <http://www.bms-aned.nl/dnn/>

¹⁹ <http://www.bio.vu.nl/nvtb/>

Table 2.1 Overview of biomathematics research activity

University/ institute	Area											Group size	
	Analysis	Discrete math	Numer math	Prob theory	Statistics	Systems theory	Cell / Organ mod	Ecology	Epidemiology	Image Anal	Neuroscience		Omics
<i>within Mathematics</i>													
CWI	x		x			x	x					x	6-15
EUR													0
EURANDOM					x					x		x	2-5
RU													0
RUG						x						x	2-5
TUD													0
TUE	x	x					x				x	x	2-5
UL	x			x	x		x			x	x	x	6-15
UM					x	x	x	x					6-15
UT													0
UU	x							x	x				2-5
UVA													0
UVT													0
VUA	x			x	x	x	x	x	x	x	x	x	>15
WU													0
<i>within Life Sciences</i>													
EUR					x			x					2-5
RU					x			x					6-15
RUG	x				x		x			x			>15
TUD	x						x		x	x			6-15
TUE	x							x					>15
UL	x				x		x	x		x			>15
UM	x		x			x						x	6-15
UT													0
UU	x				x		x	x					>15
UVA	x				x		x	x		x	x	x	>15
UVT													0
VUA	x				x		x		x	x	x		>15
WU	x		x		x		x	x	x		x	x	>15

2.1.4 Mathematical disciplines and the life sciences

Analysis and life sciences

The modeling and mathematical analysis of biological systems is a challenge in analysis. A difficult problem in modeling the behavior of the cell is the fact that a cell contains billions of molecules. Recent investigations make clear that models based on an average mass description (i.e., systems of partial differential equations) do not always describe the dynamical behavior of such systems adequately. It turns out to be essential to take account of the discrete nature of the molecules. This results in hybrid models, coupled systems of cellular automata, coupled map lattices and lattice differential equations, and partial differential equations. The study of the qualitative behavior of such models leads to fundamental questions about large coupled dynamical systems, such as the stability of configurations, interaction between time scales, pattern formation and travelling waves. These can only be analyzed in close interaction with numerical analysis and require new methods and techniques from analysis and the theory of dynamical systems.

Discrete mathematics and life sciences

Discrete mathematics and optimization (in particular, combinatorial optimization) serve multiple purposes within modern biology. This is most visible in the context of designing fast and efficient algorithms for processing biological data, where it is often associated with classical bioinformatics applications, such as sequencing, haplotyping and motif-finding. Less well-known is the fact that discrete mathematics forms the foundation for several major branches of biomathematics, such as phylogenetics, (metabolic) network analysis, and genome rearrangement theory. Indeed, discrete mathematics contributes far more than speed to biology: the ability to calculate or estimate optima for discrete functions facilitates the inference of new biological insights, for example, regarding the optimality of the genetic code. It is expected that the coming years will see the importance of discrete mathematics and optimization grow considerably in such areas.

Numerical mathematics and life sciences

An alternative name for numerical mathematics is scientific computing, exemplifying its important role within advanced computer simulation based on mathematical models. For example, with numerical algorithms one can accurately simulate biological and biochemical systems exhibiting spatial and temporal transitions that can be modelled by differential equations or dynamical systems. One can think of biochemical reaction networks and diffusion processes in living cells,

chemotaxis processes in tumor growth, blood flow in the heart, etc. Numerical mathematics also provides tools for parameter estimation, sensitivity analysis, data fitting, etc., and for improving and validating laboratory experiments. Numerical mathematics has established a strong foothold in the engineering and the exact sciences. The coming decades will reveal an equal and challenging role within the biological sciences.

Probability and life sciences

Randomness and complexity abound in the life sciences. In genetics, Markov processes are used to model DNA-sequence evolution, e.g. the Galton-Watson branching tree or the Kingman coalescent. In epidemiology, interacting particle systems play a similar central role, like the contact process describing the spread of an infectious disease, while random graphs are used to model various types of interaction networks. In immunology, the study of T-cells interacting with antigen presenting cells via sampling of random signals offers a stochastic look at intruder-cell recognition. A particular challenge is to develop and study models in which different space-time scales compete with each other on an equal footing. Hierarchical models are used to combine the effects of these different scales, combined with techniques from renormalization. The notion of universality, in which whole classes of systems turn out to exhibit similar behavior on large space-time scales, is a driving force for much of the probabilistic theory.

Statistics and life sciences

The goal of statistics is to build statistical models for data. It also supplies and evaluates the techniques that can cope with the analysis of these data – often of high-throughput type – which the many new data platforms generate. Important is the role that statistics plays in the analysis of the different types of -omics data. In the area of statistical genetics, modern statistical approaches have given impetus to the search for genes underlying complex diseases. In the neurosciences and in molecular cell biology, statistical models play an increasingly important role, often in the form of networks of various types. Multivariate statistical methods are needed to infer interactions in such networks. Systems biology requires a new look at statistics for experimental design, and the development of efficient statistical methods for estimating parameters of multi-scale models. In general, there continues to be a growing need for descriptive as well as model-based statistical methods to deal with the high level of complexity of present-day life science data. One of the challenges is to design new ways to deal with high-dimensional noise of typically high-dimensional and dependent data.

Systems theory and life sciences

Control and system theory has recently been stimulated by novel problems arising from the advances of systems biology. Classically control theory was used to derive results for system identification and for control problems in physiology, in population dynamics, and in compartmental systems. The advances in genetics now focus research on the understanding and control of the dynamics of metabolic, signaling, and genetic networks. The mathematical models for such networks are often rational systems, meaning a set of ordinary differential equations with rational right-hand side. More generally, the first problem of biologists is to obtain estimates of parameter values of such systems, a problem of system identification. The second problem is system reduction due to the presence of multiple time scales. The third problem is realization of such systems including controllability, observability, and parameterization. Other areas that generate novel types of control problems are rational drug design, ecology, and optimization in biotechnology. These are mainly systems biology problems and require the development of new aspects of control and systems theory.

2.2 The challenge

Scientists are facing the challenge of turning the vast quantities of descriptive information arising from the revolution in molecular biology into useful knowledge that can aid the understanding of the overall function and behavior of biological systems. We are gradually entering a new era in the life sciences in which the mechanisms that underpin health and disease are progressively being uncovered. The complexity and the nonlinearity in these interrelationships, acting on multiple scales, pose a major challenge to our current level of mathematical understanding and require the development of new ideas, methods and techniques. Biology is more and more becoming a quantitative and data-intensive science, in which progress can only be made by combining different disciplines, with an important role for mathematics. The results of modeling complex systems are often counterintuitive. Beyond a certain degree of nonlinearity, qualitative thinking is not only inadequate, it can even be misleading. In The Netherlands new interactions of mathematics with the life sciences are emerging, but on a small scale, which is insufficient for keeping up with the rapid developments in the area.

2.2.1 Crosscutting themes

The urgency to increase the involvement of mathematics in the field of biology in order to develop quantitative and predictive mathematical models addressing biological systems is high. Given the wide range of new and often high throughput data acquisition technologies (e.g. the omics technologies), we begin to appreciate the extreme complexity of biological systems at all levels: molecules, cells, tissues, organs, organisms and ecosystems. Intuitive approaches do not suffice to efficiently tackle these systems. Here biomathematics faces a number of big challenges.

- Quantitative and predictive models that integrate all available information about a specific system, and allow one to identify the most telling experiments become indispensable. Eventually, a combination of such models should span the length and time scales of biological systems, ranging from the atomic scale (10^{-9} meters) to system earth (10^5 meters) and from the time scale of molecular changes (10^{-12} seconds) to changing eco systems (10^8 seconds).
- Another major challenge is to find ways to integrate highly heterogeneous data sets, such as genomic, proteomic and metabolomics data, describing the behaviour of thousands of components that continuously change in concentration and interact in dense networks. Moreover, such data sets must be combined with information for instance from imaging technologies, including microscopy and for instance whole body CT scans, integrating temporal and spatial aspects of biological systems.
- Numerous biomathematical technologies and methods have to be developed, such as for example novel pattern recognition tools for complex and temporally and spatially highly dynamic biological systems, and approaches to simplify extremely complex biological models to ones that still can make useful predictions.
- We have to learn how to use mathematical models to boost the efficiency and cost-effectivity of experimental research; a subfield named experimental design.
- These issues are further complicated by the fact that data sets in biology are noisy and inevitable contain many errors.

Biomathematics should not only create the basis for developing efficient integrated models that are predictive and can steer experimental research, it should also concentrate on systems analysis, identifying underlying system design

principles and how these developed during evolution. Successfully addressing these issues will result in major breakthroughs in biomedical and biotechnological research. Robustness, stochasticity and chaotic behaviour are just examples of issues that have to be dealt with.

What is touched upon above are daunting tasks. Dealing with this requires novel mathematical tools and theories that should be developed by mathematicians and biologists together. The need for this is felt internationally. The Netherlands has, based on its tradition of cooperation between different disciplines, an excellent position to take a leading role.

2.2.2 The driving force

The Foresight Committee shares the opinion, which is reasoned in [11], that biomathematics should be driven by questions from the life sciences and should be aimed at developing quantifiable mechanism-based theory in order to translate biological concepts and hypotheses into highly structured, testable mathematical structures: mathematical models. The development, analysis and simulation of such mathematical models allow life scientists to make qualitative predictions, test hypotheses, determine control and optimization strategies, and express theories, thereby enhancing the establishment of the field of predictive biology. Development of mathematical models by mathematicians in direct interaction with the design of experiments by life scientists makes that experimental data can be used to optimize the next round of hypothesis to be tested, and that the mathematical model can be used to design the next set of experiments. In multidisciplinary research teams, system integration must be the overriding goal, with end-to-end data management or translational research as the key challenge, i.e. from acquisition, via modeling, analysis and interpretation, to implementation and use. Naturally, this goes hand in hand with the growth of computing power.

Current biological areas of interest include problems in population biology, ecology and the environment, but also questions from neuroscience, physiology and cell biology. Because, as discussed earlier, it is unpredictable in which directions the different life science areas will develop, it is not clear which exactly the biological objectives of the coming decades should be. Research must be foremost driven by pragmatic issues and not be hindered by topical boundaries. Priority should be given to research that combines different themes and different levels of complexity, and that refines tools that have proven to be useful in the past. However, the goals should be realistic and not too far-fetched.

Genetical association and linkage

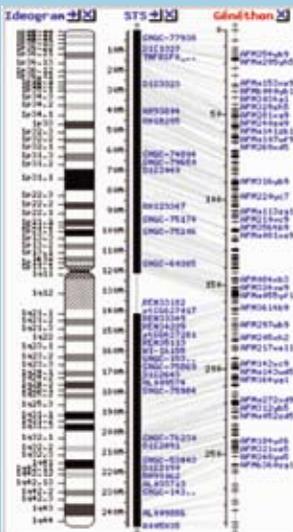
Genetics has always had strong links to statistics, as is illustrated in the person of Sir Ronald Fisher, who was both a founding father of statistics and a premier geneticist.

Statistical genetics tries to find genes that make an individual susceptible to a disease or that are responsible for a personality trait. A main challenge is: how to deal with high dimensionality caused by the number of possibly relevant variables. Linkage studies relate the (observed or inferred) inheritance patterns of genes in families to the observed traits of the individuals. In association studies samples of diseased and healthy individuals are compared in a 'case-control' design. The large dimensionality results from the number of genes under consideration. While many genes that cause a disease by an aberration on just this single gene have been successfully identified in the last decade, it is notably difficult to find groups of genes that are jointly responsible for traits, with each gene having only a small effect.

Due to random variations, a simple test of every gene in a large set is sure to result in finding genes that are different in the sampled diseased and healthy individuals. Statistical methods are essential to separate systematic differences from those caused by random fluctuations. Appropriate mathematical models for inheritance and penetration allow here to call on excursion theory for stochastic processes.

The discovery of interacting groups of causal genes can be formulated as a problem of model selection. Strategies based on penalization or Bayesian prior distributions are a hot topic of current research in general statistics. One hopeful finding is that sparse models can be selected with only a minor penalty for taking a very large number of models into consideration.

Genetic influences often also develop over time, and interact with lifestyle and environment. *Genetic epidemiology* incorporates genetic markers as covariates into models from survival analysis, and again runs into the challenge of dimensionality. For linkage analysis new models of (family) dependence are proposed. A next step will be to incorporate variables at the cellular level (RNA, proteins, metabolites) into the models.



linkage analysis new models of (family) dependence are proposed. A next step will be to incorporate variables at the cellular level (RNA, proteins, metabolites) into the models.

Ideogram of chromosome 1 (left), a physical map (middle) and a genetic map (right), with connections between the physical and the genetic map shown by lines crossing the displays. The ideogram shows on the left the classical method of addressing genomic positions in terms of the p- and q-arms and numbered colored band. The STS- and Généthon-maps are given, together with rulers showing position in terms of base pairs (0-240,000,000 bp) and centi-Morgan (0-290 cM), respectively. Corresponding positions on the rulers are connected by a line.

(Source NCBI map viewer, Homo Sapiens, Build 36.3, <http://www.ncbi.nlm.nih.gov/mapview/>).

2.2.3 Present-day biomathematics problems in the life sciences

As is discussed in [11], the time does not seem to be ripe for concentrating on one or two grand challenges. It is argued that concentration of all biomathematics research efforts with the collective goal of, for instance, a comprehensive, predictive model of a particular free living cell, organ, or ecosystem, is in view of the current state of the relevant biological areas far from realistic. The unpredictability of future biological developments prompts for a long-term, broad, and diversified nurturance of the interface between mathematics and biology instead. For the same reasons the Foresight Committee recommends Dutch biomathematics research not to be directed to one or two major research themes. At present many exciting developments occur in Dutch life science research that bring along a great diversity of challenging mathematical problems. Opportunities need to be created for the biomathematics community to develop its scope accordingly broad, both from the point of view of mathematics and from that of the life sciences. On the other hand, the Dutch community should not try to catch up with everything that is happening abroad. The Foresight Committee suggests a broad and long-term stimulation, and to only stimulate mass in a few strong niches after focus has been established. Below we describe some of the most important present day issues. This description is not exhaustive, but it illustrates the broad range of present day biomathematics challenges. It also shows that it indeed cannot yet be pinpointed which exactly the few strong future niches will be, and that promising research topics are characterized by high dimensionality, heterogeneity, robustness to perturbations, and the existence of strongly interacting, highly disparate spatial and temporal scales.

Systems biology

Systems biology is the logical sequel to the information explosion arising from genomics type of analyses of biological systems. Systems biology exploits the iterative cycle of, on the one hand, experimentation that is driven by quantitative and predictive models and, on the other hand, data integration and system analysis based on data-driven modelling. The information explosion in biology has not resulted in a true understanding of biological systems. This is seen, among others, from the paucity in the rational development of new drugs and therapies for multi-factorial diseases. The major hurdle is the extreme complexity of biological systems. Systems biology addresses this issue by integrating diverse types of biological information in predictive and quantitative computer-based models that integrate information, that can be interrogated about system behaviour, and that allow the uncovering of underlying system principles. Biologists are

often poorly equipped to cope with the complexity hurdle. In the systems biology field they team up with physicists and engineers, who are used to translating experimental data into computer models. At the same time mathematicians play a crucial role in developing a solid basis for translating complex and multi-scale biological systems into useful mathematical models, and in solving the statistical issues regarding the analysis of correspondingly complex data sets. Importantly, these disciplines discover that biological systems hold many scientifically exciting new challenges in their own fields. Systems biology is rapidly developing in The Netherlands and at the international level.

Neuroscience

Brain functioning is based on the dynamic patterns of activity within networks of nerve cells via the exchange of electrical and chemical signals through a multitude of synaptic connections. Exploring the dynamic repertoire of activity in relation to structural and functional network connectivity is therefore crucial for understanding how the brain works. During the last decades research on brain dynamics has yielded new insights into the biophysics of ion channels, of neuronal membranes, of synaptic processes, and of genetic factors that play a role in the development of the nervous system. There is, however, still a large gap between the knowledge about the working of one or a small number of neurons, and the knowledge about the joint behavior of many nerve cells in higher brain functions and cognitive processes. With modern techniques like positron emission tomography (PET), functional magnetic resonance imaging (fMRI), magnetoencephalography (MEG), high-speed photodiode array monitoring (HS-PAM), and multi-electrode array (MEA), many large and complex data sets are being collected that may shed light on this problem. Due to the complexity and the size of these data sets, their analysis needs a joint effort of mathematicians, computer scientists, physicists and neuroscientists. The development of mathematical models, based on non-linear dynamics, probabilistic models or a combination of both, is an indispensable ingredient of this collaboration. Also, new theories based on statistical methods and signal processing are needed. For instance, new techniques based on Bayesian statistics are already being used successfully in research concerning perception. One of the major challenges is to model and infer the complex interaction structure between different network components of the same type and of different types, on different spatial and temporal scales. For example, interaction between spiking neurons, local field potentials or MEG signals of different brain areas generally are investigated pair-wise or by means of classical techniques like cluster analysis. Although this yields important information,

there is an urgent need for new multivariate statistical techniques, descriptive as well as model based, and both for the time domain and for the frequency domain, from which more complex network connectivity patterns can be inferred.

Medical sciences

Within the field of medical applications there is an ever increasing need for the mathematical and computational sciences. For mathematics this concerns various areas of research, but increasingly also applications in the clinical setting. At present, the two largest applications of biomathematics are found in genomic research and in the field of imaging. Genomic research is one of the fastest developing areas in medical research. This includes genetic research, in which large series of patients are characterized with arrays including hundred and thousands of single nucleotide polymorphisms (SNPs). Although the statistical analysis is rather straightforward, there are a number of important questions unresolved (e.g. data imputations, testing for interaction, pathway analysis) for which there clearly is a need for mathematicians. The same argument can be made for transcriptomics, in which the expression of genes is studied. Here, in particular, the analysis of pathways and their predictive value need to be evaluated in the research setting, but even more so within clinical applications. Perhaps the most important future challenge for mathematicians will be in the field of proteomics and metabolomics, where the goal is to study the structure, clustering and pathways of proteins and their metabolites. Within this line of research, there will be a high demand for mathematicians within biotechnological industries, universities and hospitals (translating research into medical decision making). The second large area of applications in medicine for mathematics is that of the analysis and evaluation of medical imaging data. Within radiology, there is a huge demand for data interpretation and pattern recognitions, which is still in a very early stage of development. For this, methods from analysis, statistics and numerical techniques are needed. The ultimate challenge lies in the field of diagnostics, in particular, early diagnosis, in which there still is only a very limited use of computer assisted interpretations of structures, hampering the high-throughput and low-cost analysis of images. This concerns a very wide range of applications, varying from vascular systems, the brain and other neurological structures, to other organs and systems. Further applications will be found in the area of screening for prevention and therapy, including surgical procedures. These will have important implications both in the clinical setting (hospitals) and in industry.

Pharmaco-genomics

Within the field of pharmaco-epidemiology it has become evident that identifying and characterizing patient phenotypes with respect to response to pharmacotherapy is critical for optimizing treatment. Variability in individual treatment response may be due to many factors, such as the type and severity of disease, intercurrent illness, co-medication, treatment compliance, age, environmental exposures and genetic factors. Pharmaco-epidemiological tools are routinely used to study the involvement, association and importance of these factors, and in the last decade the focus included pharmaco-genomics. Many proteins, and therefore many genes, and even more SNPs, may influence the effects of drugs. Results from univariate approaches are often contradictory, and it would be more appropriate to search for sets of marker loci in different genes and analyze these markers jointly, or scan the whole genome, rather than testing each marker in isolation. However, multi-locus approaches introduce methodological and statistical challenges, and creative and new methods are needed for analyzing and interpreting data. We need methods to analyze gene-drug interactions in large biological datasets (e.g. SNPs, microarrays, mass spectrometry) in order to gain insight into the molecular basis underlying treatment response and to identify new biomarkers. A likely approach to tackle this problem would be adaptation of existing mathematical algorithms or machine-learning methods, or development of new mathematical modeling tools for pharmaco-genomic studies.

Agriculture

In the agricultural sciences mathematical models have been extensively used since the 1960s. Theoretical production ecologists have developed exploratory, predictive and explanatory models. In particular, explanatory models were, and still are, heavily used to connect theory and experiment, to exploit different aggregation levels, and to obtain insight into the functioning of both agricultural and natural ecosystems. Theoretical production ecology is the core of production ecology – the modern agricultural science – and is a typical result of the reciprocal fertilization of physics, chemistry and biology on the one side, and mathematics on the other side. A new generation of problems in this area is expected to arise from a systems biology approach. At the same time statistical techniques are indispensable for making correct inferences and reliable predictions from the experimental data. Statistics also plays an important role in genetics, which has been indispensable for applications in agriculture from the very beginning of its existence. Modern statistical techniques, combined with the advances in genetics and molecular biology, have put statistical genetics for the agricultural sciences on a completely new level.

2.2.4 Horizon

Biomathematics research requires a long-time horizon. Indeed, a consistent and adequate mathematical formulation of a problem in the life sciences is as important as its solution. Many times, complex problems, such as emergent infectious diseases in animal populations or the dynamics of gene regulatory networks, can be better attacked if correctly formulated in a multidisciplinary approach with an interdisciplinary methodology. Frequently, the initial formulation of a biological problem is mathematically ill-posed (or in other words, incompletely posed), and the process of translating the biological problem into the formal language of mathematics introduces a rigor that often uncovers new questions which might otherwise not have been asked. This translation process requires a common language for mathematicians and life scientists, so that the essential richness of a problem in the life sciences can be formulated in solid mathematical terms. Only if life scientists and mathematicians are able to communicate can they think carefully about all the parts of the biological system that have to be taken into account, and decide systematically which variables, effects and interactions are to be taken into account during the modeling process. Only then will truly new synergies of benefit come about. This means a serious long-time commitment from both the mathematicians and the life scientists in the research team.

2.2.5 Integration: the direct link

The major challenge in developing biomathematics is to merge the field of mathematics with that of biology in general and with biomedicine, biotechnology and ecology in particular. Here mathematics should create the solid fundament to integrate data sets obtained from the extremely complex biological systems that we deal with. In The Netherlands, as well as abroad, there is only limited experience in tight cooperation between these fields. Interestingly, at present scientists with an engineering or physics background are the most common liaison between biologists and system models. They are trained from the very beginning to combine mathematical modelling with the experimental analysis of complex systems. In general, neither biologists, nor mathematicians have this background, leaving a considerable gap between the two fields.

2.3 Meeting the challenge

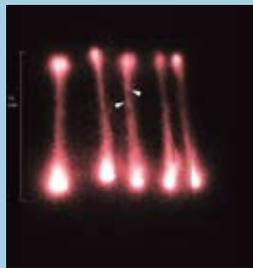
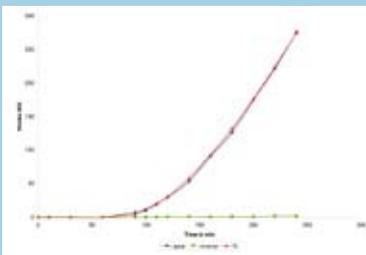
Integration of mathematics and biology should occur along two parallel routes. The first step is to start *collaborative research programs* between mathematicians and experimental life scientists, focusing on concrete biological issues. An example that such approach can be quite successful is the NWO research program

Modeling the dynamics of polar auxin transport

Auxin is a plant hormone endowed with a unique polar transport system. Interest in auxin transport dates back to 1881, when Charles Darwin published a paper about a transmissible signal that was involved in the phototropism of canary grass coleoptiles. This signal molecule was later identified as auxin. In the 1960's and 70's classical donor-receiver experiments with agar blocks led to the conclusion that auxin is transported through plant tissue in a unidirectional polar fashion. Recent studies have emphasized a key role for auxin transport during embryogenesis, root and shoot formation, vascular differentiation and pattern formation in plants.

The objective of present research in this area is two-fold: (i) to gain insight in the mechanism and location of polar transport in arabidopsis stems and (ii) to develop a *continuum model* for polar auxin transport which can predict quantitatively characteristic transport properties such as speed, flux, and distribution of auxin over the length of the stem, as these properties evolve over time. To this end donor-receiver experiments were conducted in which 16 mm segments of Arabidopsis stems were exposed at one end to radioactively ^3H -IAA labeled auxin contained in a donor compartment, the polar direction pointing away from the donor compartment. At the other end of the segment, auxin was released in a receiver compartment, where auxin accumulation was measured. In the figure below a typical receiver accumulation curve has been shown (blue). The figure also shows the distribution of auxin over the length of the stem and especially near the donor and receiver after a 330 minute period of exposure to auxin.

A first generation of mathematical models for this transport process was proposed in the 1960's and 70's. Building on these models and on more recent insights in the plant physiology of arabidopsis, a continuum model has been devised for transport in the stem, uptake at the donor and release at the receiver. This model involves *convection-diffusion equations* for the stem and, separately, for the donor and receiver ends of the stem. The model has shown to possess predictive power, in that it can predict quantitatively accumulation curves such as shown in the figure (see red curve) and the distribution of auxin over the length of the stem.



Receiver content (left) and auxin distribution (right). The accumulation of auxin is given in femto moles versus time in minutes; the blue curve is experimental and the red curve is a simulation. The green curve gives the accumulation when the polar direction has been reversed, the polar direction now pointing towards the donor compartment. The distribution of ^{14}C -labeled auxin is given after 330 min of exposure to auxin in the donor compartment. Note the high concentration of auxin near the donor end (bottom) and slight accumulation near the receiver end (top).

‘*Fysische Biologie*’ (*Physical Biology*), in which only projects that were highly challenging in both physics and biology were funded. The second step is to start *new educational programs* at Dutch universities that intensively combine mathematics and biology. This will be discussed in Chapter 3.

The present relationship between mathematics and biology is comparable to that between physics and biology a decade ago. Both fields could gain scientifically by creating activities at the interface. A limited, but well-focused, investment in the field of biophysics by NWO (*Programma Fysische Biologie 1 en 2*) did have the desired effect, resulting in a situation in which biophysical research is now a recognized and flourishing area of Dutch academic research. The investments literally enforced collaborative projects that were scientifically highly challenging for physicists and for biologists. In parallel the program allowed a small number of chairs in this field to be established, and to create a few junior groups. These efforts contributed to the development of the desired common scientific language and cooperation between physicist and biologists, and biophysics in The Netherlands has become a flourishing research field. A similar approach might very well work in boosting biomathematics, and is advised strongly.

For the continuation of the field and of the careers of young biomathematicians it is of utmost importance that a sufficient number of *tenure tracks* will be created for young talent at the interface. Offering career perspectives to young people is a prerequisite for the development and establishment of successful biomathematics groups. It must be avoided that the best talent seeks a career abroad. The universities should complement the investments of a research program by guaranteeing permanent positions for successful young biomathematics researchers.

In conclusion, an investment in collaborative research and starting focused educational programs across disciplines is a direct road towards creating a solid basis for the development of biomathematics in The Netherlands. Biomedical and biotechnological research will strongly profit from this.

2.4 Industry

2.4.1 The pharmaceutical industry

The pharmaceutical sector will also greatly benefit from enhanced research efforts in biomathematics. Over the last decade, the average cost of developing new drugs has increased dramatically (from 1.1 billion dollars in [1995-2000] to

1.8 billion dollars in [2000-2003]). This has been accompanied by an increase in the average total development time for drugs (from just over 8 years in the 1960s to just over 14 years in the 1990s). In addition, current estimates indicate that only 8% of the newly developed molecules produce a marketable output. In The Netherlands the life science sector pursues a three pillar build – bundle – benefit strategy of exploratory research, long-term strategic translational research, and applied/industrial research. See the roadmap for the Innovative Medicines Initiative (IMI)²⁰. Especially in the context of exploratory research there are many good opportunities for researchers in biomathematics, for instance in the recently established Top Institute Pharma²¹, in which industry strongly participates, or in the Center for Translational Molecular Medicine (CTMM)²². The latter is a public-private consortium that comprises a multidisciplinary group of parties – universities, academic medical centers, medical technology enterprises and chemical and pharmaceutical companies – and which aims to develop medical technologies that enable the design of new and personalized treatments and the rapid translation of these treatments to the patient.

In the pharmaceutical industry there is hardly any field in the workflow of the pharmaceutical industry where no advanced statistical or other mathematical expertise is needed. This ranges from target discovery and in vitro or in vivo experiments for testing the efficacy and toxicity of compounds, to the first experiments in men and the large clinical trials for proving efficacy and safety of drugs. As the development of drugs is more and more driven by technical improvements in molecular biology, genomics and genetics there are huge challenges in the development and introduction of innovative statistical tools as well. Technical advancements that allow for the simultaneous testing of 100,000s of genes of one individual necessitate the development of statistical and mathematical tools to select the right genes for prediction of efficacy and safety for (groups of) patients. Moreover, innovative mathematical models of biological networks are needed that can be iteratively refined in line with the increasing knowledge about the network. These models can assist in the challenge of identifying multiple targets, in the context of biological networks underlying the development of complex diseases, which will eventually result in the delivery of new medicine.

20 <http://www.imi-europe.org>

21 <http://www.tipharma.com/pro1/general/home.asp>

22 <http://www.ctmm.nl/>

2.4.2 Industrial application of micro-organisms

In the area of industrial application of micro-organisms, systems biology is currently leading to rapid new developments. The formulation of models that help to elucidate the underlying principles is causing a breakthrough. The rapidly increasing capacity to follow changes in genomes, proteomes and metabolomes urges for evaluating and analyzing the large data flows with the help of biostatistics and bioinformatics. Especially searching for the relevant information in these data sets remains a challenge. This supports new approaches for developing new industrial conversion processes through evolutionary engineering in synthetic biology.

In metabolic engineering one seeks to change the metabolism and physiology of an organism to suit the needs or desires of the farmer, the breeder, the genetic engineer, and the scientist. Targeted selections for more flavorful wines or for higher milk production are examples of metabolic engineering products that have been largely successful. In all of these instances, the metabolism of the organism was altered in such a way as to allow that organism to display the desired traits. However, such breeding-program driven projects are expensive, very slow to produce results and often end in failure. The exact changes in the organism that result in the altered phenotype are often unknown, making reproduction of the same changes in these or similar organisms almost impossible. This leads to numerous challenges that are increasingly often of mathematical origin, for example, regarding system integration (system [re]design, prediction, and control) in order to discover the system design principles so that optimization methods can be applied.

2.4.3 What is needed

Biomathematicians working in industry should have a broad interest and expertise. For instance, biostatisticians need to master both the traditional areas of statistics, such as experimental design, multivariate analysis, (non-)linear and generalized linear models, as well as new statistical methodology, such as modern Bayesian statistics. Besides, due to the advances in computing capacity, industrial biomathematicians need to be able to put statistics and numerical mathematics into working software and to judge the usefulness of software developed by others. They have frequent contacts with specialists from a broad range of scientific or medical backgrounds: molecular biologists, chemical engineers, bioinformaticians and medical doctors. To be successful in transforming their mathematical knowledge into practical solutions, they must understand the language and the needs of these specialists.

2.4.4 Industry can stimulate biomathematics research

Industry can stimulate biomathematics research between universities, spin-off companies and industry via a voucher system. It is recommended to organize a yearly ‘Study Group Mathematics and Biology’, along the same lines as the successful ‘Study Group Mathematics and Industry’.

HIGHLIGHT 6 BY M.C.M. VAN LOOSDRECHT AND C. PICIOREANU
(BIOTECHNOLOGY, TUD)

Biofilms

More than 90% of all microorganisms are associated with interfaces. These microbial communities growing in layers attached to a surface are termed *biofilm systems*. Biofilms are of utmost significance in the medical field, where they cause serious infections persistent to antibiotic treatment. Biofilms are also present in nearly all technical systems where they cause biofouling, biodeterioration and biocorrosion. In order to control biofilm formation, or to design strategies for removal of pathogenic biofilms, it is important to understand the structure and function of biofilm communities as well as the mechanisms that regulate biofilm processes. However, biofilm researchers invariably face the challenge of understanding complex relationships between physical, chemical and biological processes occurring at very different spatial and temporal scales.

The best tool available for integrating the overwhelming amount of dispersed experimental observations in a rational environment is mathematical modeling. In biofilm models physicochemical processes represent the solute and cell transport, several metabolic reactions, hydrodynamics, and simple biomass growth and detachment. Several biological processes of crucial importance for biofilm development also need to be incorporated: cell-cell communication, gene transfer, pili and flagellum formation. All of these affect biofilm life by regulating the biofilm polymeric matrix formation and lysis, by inducing microbial detachment, by controlling microbial motility (Figure 1), or by inducing various microbial morphologies.

From mathematical and numerical points of view this approach faces multiple challenges. First, complexity arises from the fact that natural biofilms are made of multiple microbiological species, and consume/produce a large variety of chemical species. This leads to large systems of *coupled non-linear algebraic/partial-differential equations*. Also, the discrete and in some aspects stochastic individual-based models needed to describe the behavior of large numbers of microbial cells need to be integrated with continuum-based deterministic models for the biofilm matrix. Moreover, the multiple spatial and temporal scales must be linked, and the presence of multiple phases involves interactions between gas, liquid, biofilm and the solid substratum (Figure 2). It follows that the spatially multidimensional (3-D) and time-dependent models of biofilm development will be inherently computationally intensive. Finally, the parameter

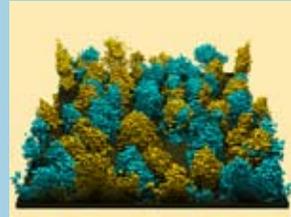


Figure 1. Simulation of biofilm development with an individual-based biofilm model with motile (yellow) and non-motile (blue) bacteria.

estimation of such complex models will not be a trivial task. Multidisciplinary knowledge is essential for this, because the problem involves a combination of methods used in (bio)chemical engineering, microbiology, ecology, mechanical engineering, computational physics and applied mathematics.

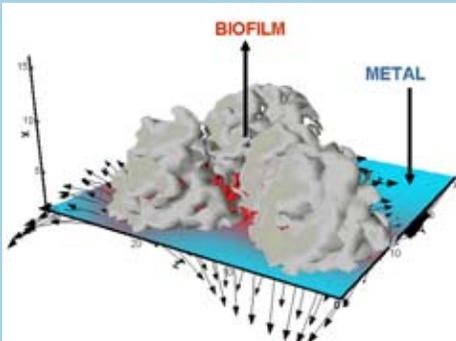


Figure 2. A biocorrosion model shows the formation of anodic (red – ionic current arrows pointing to the biofilm) and cathodic areas (blue – currents pointing to the metal).

3. Education in biomathematics

3.1 The current state

An inventory was made of the mathematics courses in life science programs and of the life science courses in mathematics programs that are available on internet. As the composition of a program may change from year to year, and not all programs present digital course listings, the results of the inventory need to be interpreted as a global picture rather than as a complete or detailed representation. Nevertheless, these results give a good impression of the current situation.

3.1.1 Mathematics for students in the life sciences

Tables 3.1 and 3.2 give an overview of the mathematics courses within life science programs for bachelor and master students, respectively. For compactness different life science programs of one university are clustered within one row. An 'x' in a cell means that at least one of the programs in the corresponding row contains the course in the corresponding column. The term 'Mathematics (general)' in the tables stands for introductory mathematics courses. These usually contain some introductory calculus and linear algebra, and sometimes also statistics. Statistics blocks taught within medical programs or taught under the name bioinformatics are not included.

During the past years the number of mathematics courses in the life science curricula has decreased. Tables 3.1 and 3.2 are somewhat misleading in that respect, since in many cases the x's originate from of a course in only one or two

Table 3.1 Mathematics courses in life science bachelor programs on internet

Note: for the UM program Moleculaire levenswetenschappen no course listing was available.

University	Programs	Area								
		Analysis	Decision theory	Linear Algebra	Mathematics (general)	Modelling	Numerical mathematics	Probability theory	Statistics	Systems theory
EUR	Medicine								x	
RU	Biology; Biomedical Sciences; Medicine; Molecular Life Sciences; Dentistry				x				x	
RUG	Human Movement Sciences; Biology; Pharmacy; Genomics, Proteomics and Bioinformatics; Medicine; Life Science & Technology; Dentistry			x	x		x		x	
TUD	Life Science & Technology (icw UL)				x	x			x	
TUE	Biomedical Engineering	x		x	x		x		x	
UL	Biopharmaceutical Sciences; Biology; Biomedical Sciences; Life Science & Technology (icw TUD); Medicine				x	x			x	
UM	Molecular Life Sciences; Medicine								x	
UT	Biomedical Engineering; Technical Medicine			x	x	x	x		x	
UU	Biology; Veterinary Medicine; Pharmacy; Medicine								x	x
UVA	Biology; Biomedical Sciences; Medicine					x			x	
UVT	--									
VUA	Biology; Biomedical Sciences; Pharmaceutical Sciences; Medicine; Medical Natural Sciences	x		x	x	x		x	x	
WU	Agricultural and Bioresource Engineering; Biology; Biotechnology; Animal Sciences; Molecular Life Sciences; Plant Sciences	x	x		x	x			x	x

Table 3.2 Mathematics courses in life science master programs on internet

Note: for the ruG programs Biology, Ecology, Marine Biology, Medical Biology, Molecular Biology and Biotechnology, and Biomedical Engineering, and for all UM programs except Molecular Life Sciences, there was no course listing available.

University	Programs	Area								
		Analysis	Decision theory	Linear Algebra	Mathematics (general)	Modelling	Numerical mathematics	Probability theory	Statistics	Systems theory
EUR	Clinical Epidemiology; Clinical Research; Epidemiology; Genetic Epidemiology; Molecular Medicine; Neuroscience			x					x	
RU	Biology; Biomedical Sciences; Cognitive Neuroscience; Medical Biology; Molecular Life Sciences; Molecular Mechanisms of Disease				x				x	
ruG	Behavioural and Cognitive Neurosciences; Human Movement Sciences; Biology; Biomedical Engineering; Clinical and Psychosocial Epidemiology; Ecology; Pharmacy; Marine Biology; Medical and pharmaceutical drug innovation; Medical Biology; Medical Pharmaceutical Sciences								x	
TUD	Biochemical Engineering; Biomedical Engineering; Life Science and Technology (icw UL)	x				x	x		x	x
TUE	Biomedical Engineering	x				x	x			
UL	Biology; Biomedical Sciences; Biopharmaceutical Sciences; Life Science & Technology (icw TUD)					x			x	
UM	Cardiovascular Biology and Medicine; Molecular Life Sciences; Cognitive Neuroscience, Neuropathology and Psychopathology; Physical Activity and Health								x	
UT	Medical Engineering; Technical Medicine	x				x	x			x
UU	Biology and Biocomplexity; Biology of Disease; Biomedical Image Sciences; Biomolecular Sciences; Cancer Genomics and Developmental Biology; Drug Innovation; Epidemiology; Pharmacy; Immunity and Infection; Neuroscience and Cognition				x	x	x		x	
UVA	Biological Sciences; Biomedical Sciences; Cognitive Science; Life Sciences								x	
UVT	--									
VUA	Biology; Biomedical Sciences; Ecology; Human Movement Sciences; Medical Natural Sciences; Neurosciences; Pharmaceutical Sciences								x	
WU	Animal Sciences; Aquaculture and Fisheries; Biology; Biotechnology; Management of Marine Ecosystems; Molecular Life Sciences; Organic Agriculture; Plant Biotechnology; Plant Sciences	x			x	x			x	x

of the programs in that row. In fact, in many of the life science programs students follow a few basic mathematics courses during their bachelor program, but very few or none thereafter. Quantitative master courses are either not offered or, when they are offered – like for instance at the wU – the number of students taking the courses is too small, given the large number of jobs that is offered in modeling. As a result, there is serious concern in the field about the inflow of students into research projects within the life sciences that aim for modeling and development of theory. With the current educational programs, master students in life sciences often cannot flow into their own department's PhD programs. Although PhD students can be recruited from abroad, this is generally considered as an undesirable situation.

3.1.2 Life sciences for mathematics students

Presently, very few life science courses can be found within mathematics programs: see Tables 3.3 and 3.4. At the time of writing this report, only the VUA offers a program 'Mathematics with life sciences'. The UM has a close link to the biostatistics program in Hasselt.

3.1.3 Pre-university

In the coming years it will be highly important for the future of biomathematics to attract a sufficient number of students. Both mathematics and biology suffer from low numbers of first-year students. To investigate the motives for choosing a particular academic study and to obtain insight in the ideas that future students entertain about biomathematics, interviews were held with secondary school students. We report here the main conclusions of the interviews. A detailed report is included in Appendix 4.



Figure 3.1 Interview session with secondary school students

Table 3.3 Life science courses in mathematics bachelor programs on internet

University	Program	Area								
		Cell Modelling	Ecology	Epidemiology	General	Image Analysis	Microbiology	Neuroscience	Omics	Organ Modelling
EUR	--									
RU	Mathematics									
RUIG	Mathematics, Applied Mathematics									
TUD	Technical Mathematics									
TUE	Technical Mathematics									
UL	Mathematics	x								
UM	--									
UT	Applied Mathematics									
UU	Mathematics									
UVA	Mathematics	x								
UVT	--									
VUA	Mathematics	x	x		x		x	x	x	
WU	--									

Table 3.4 Life science courses in mathematics master programs on internet

University	Program	Area								
		Cell Modelling	Ecology	Epidemiology	General	Image Analysis	Microbiology	Neuroscience	Omics	Organ Modelling
EUR	--									
RU	Mathematics									
RUIG	Applied Mathematics, Mathematics									
TUD	Applied Mathematics				x					
TUE	Industrial and Applied Mathematics									
UL	Mathematics				x					
UM	--									
UT	Applied Mathematics									
UU	Mathematics			x						
UVA	Mathematics; Stochastics and Financial Mathematics									
UVT	--									
VUA	Mathematics	x						x	x	
WU	--									

For the interviewed high school students, mathematics and the life sciences are subjects that are very far away from each other. The students still entertain the classical images of mathematics and biology (and of mathematicians and biologists). This prevents them from imagining that these areas can be fruitfully combined into a single study. After some explanation, the general opinion about a biomathematics study is, however, mainly very positive.

3.2 The challenge

Since there is a growing demand for mathematicians who are able to collaborate with life scientists and vice versa, both in mathematics and in life science curricula more attention should be paid to inclusion of topics at the interface. What is currently being offered nationwide in terms of biomathematics teaching is far too scarce. As mentioned in Section 2.3, parallel to collaborative research programs, new educational programs should be started that intensively combine mathematics and biology.

3.2.1 Major/minor programs

These new programs could be specific curricula in biomathematics at the BSc and MSc level. Alternatively, biology could be integrated much more explicitly in mathematical curricula – and the other way round – for instance by making separate educational tracks in biomathematics. However, the general opinion is (see Appendix 3) that major/minor programs are to be preferred above separate bioinformatics curricula. Within such major/minor set-up mathematics and life science courses should not lead a separate life. Ample attention should be given to the integration of the two subjects. New integrative courses, forming leading threads through the programs, need to be developed. This will result in integrated curricula in which during the bachelor phase interest is generated and basic training is provided in the area of the minor, while during the master phase the focus is increased and more advanced mathematical and biological concepts are addressed. In addition, opportunities for mutual internships should be created, and catching-up courses at the PhD level should be organized for graduate students with insufficient background.

3.2.2 Mathematics for students in the life sciences

As noted above, there is a serious concern in the field about the small number of mathematics courses in life science curricula. Presently, there is too little

mathematics in the relevant life science curricula, and it is mostly included in the BSc programs only. There often exists a lack of continuity between the mathematics taught in the life science programs during the first year of the BSc programs and the use of mathematical and statistical methods in the MSc programs and in PhD research. It is important to note that practice has shown that for life science students a thorough education in mathematics combined with biology should optimally start at the BSc level. MSc or post-doctoral education in mathematics after a BSc in the life sciences, although useful, generally has only a limited effect, or takes much longer to be productive.

The long-term solution is to explicitly incorporate mathematics in biology-related curricula at the BSc- and MSc-level. It is a matter of debate how much a biologist should know about mathematics. Minimally, a biology student should be aware that mathematics is essential for dealing with any complex biological system. He/she should at least be able to handle basic calculus and statistics. In specific biological MSc tracks, this knowledge can be extended and deepened.

3.2.3 Life sciences for mathematics students

The other side of the coin is that mathematics students should come in contact with applications of mathematics to systems from the natural sciences, among others biological systems. The goal is that a mutual level of understanding be reached that allows a dialogue between the two disciplines. For mathematics students the effect of starting with biology in a somewhat later stage, seems less strong. Often mathematics students become genuinely interested in application of the mathematical theory to other areas only the later stages of their bachelor phase. Therefore besides major/minor bachelor programs and their follow-up master programs, for those mathematics students who get interested in life science applications in this later stage, opportunities should be created to start their biological education in the MSc phase.

3.2.4 Recruitment

Finally, to recruit a sufficient number of students in the biomathematics bachelor programs, it is important to change the prevailing image of biomathematics that secondary school students have (see Section 3.1.3).

3.3 Meeting the challenge

Implementation of biology courses in mathematics curricula, and vice versa, should ideally take place in the form of integrated *major/minor programs*. In this way, students obtain a thorough education in their own discipline and at the same time learn exactly those skills and concepts in the other discipline which they need. Via interdisciplinary projects in these programs they should be able to practice their skills at the interface. In the bsc-phase, interest for the other discipline needs to be generated, and basic training needs to be provided. The msc-phase will be more focused, addressing both mathematical and biological concepts. For phd students with insufficient backgrounds catching-up courses need to be organized. From this perspective, it is not advised that separate biomathematics bsc or msc curricula are offered. Another reason is that, at present, such separate biomathematics training will attract too small a number of students to be viable.

The Foresight Committee advises that *in the life science programs mathematics be taught on both the BSc and the MSc level*, and right from the start. This concerns mathematical subjects as well as integrated subjects. In the bachelor phase, mathematics is mainly needed for training in abstract thinking and for creating interest. Hence, in the bachelor phase it is sufficient to primarily teach basic mathematical theory (including statistics). In the master phase the focus should be on interaction between mathematics and applications. Future life science students should have the opportunity to follow a complete quantitative track. To achieve this, appropriate action should be taken, for a large part in the form of *service teaching by mathematicians*. The msc service teaching in mathematics should preferably be developed nationwide. MasterMath, the national program of mathematics courses at the msc level serves as an example. *Catching-up courses* for phd students with insufficient background should be offered as well.

In view of the current low numbers of first year mathematics students, it is not evident that every university should offer bsc and msc programs with a *major in mathematics and a minor in biology*. Within the Dutch landscape it would be enough to have a *few universities* take the lead. Integrated courses for msc programs, should, like MasterMath, be developed, offered and coordinated on a *national level*. Here too the national msc program of mathematics courses, MasterMath, serves as an example. The mathematics clusters, in particular NDNS+, are to take a pro-active role in developing the national teaching agenda.

Part of the above mentioned **coordinated activity with respect to the organization of education** should be the stimulation of *joint preparation* of biomathematics teaching material. For this, time of staff must be bought out. Modules should

be prepared jointly, and where possible borrowed from institutions abroad. An additional advantage of nationally coordinated preparation of teaching material is that the result is almost instantly state of the art, and will automatically follow current research themes.

To make biomathematics more attractive and visible, and to enable students to deepen and specialize their knowledge, *Honours Programs* in biomathematics for a highly selected group of students could be organized. To this end, formal barriers between teaching of different disciplines should be removed and, where possible, extra study financing should be provided for longer trajectories. Input could be given by top researchers from abroad who visit The Netherlands for short periods. These programs should be made attractive by linking them to societal issues.

In order to recruit a sufficient number of biomathematics students, and to change their prevailing image of biomathematics (see Section 3.1.3), suitable *propaganda material* should be developed. It is obvious that, in order to attract students to a biomathematics curriculum, a lot of publicity needs to be made, and a lot of information needs to be provided. For the secondary school students this information should be very concrete: what are the courses, how long will the study take, what exactly can be done with it afterwards, etc. Of course, it would be even better when already at the secondary school students get acquainted with the interface between mathematics and biology. The Foresight Committee therefore strongly supports the development of *biomathematics modules for highschool students*. Moreover, establishing better links between the universities and the HBO could open up new ways of educating young people in the field.

3.4 Industry

In biomathematics education and training industry can play an important role by offering the above mentioned *internships* for students. This will provide important additional training for biomathematics students trying to bridge the two different cultures and languages. Industry can also contribute to the Honours programs by presenting lectures and organizing workshops, and by providing grants for participants.

4. Facilitating biomathematics

4.1 The current state

It is evident that biomathematics research and education cannot bloom without a good organizational structure and sufficient funding.

4.1.1 Organization structure

Biomathematics research in The Netherlands generally takes place locally. There are several good examples where intensive collaboration between mathematicians and life scientists is already happening: the Kluiver Center (Delft, Leiden, Groningen, Wageningen)²³, the Netherlands Institute for Systems Biology (NISB)²⁴ (Amsterdam), Center for Neurogenomics and Cognitive Research (CNCR)²⁵ (Amsterdam), and the Center for Medical Systems Biology (CMSB)²⁶ (Leiden, Amsterdam, Rotterdam).

A national biomathematics structure is presently lacking. A beginning of forming a national biomathematics platform has been made by means of the establishment of a national biomathematics mailing list.

23 <http://www.kluivercentre.nl/>

24 <http://www.sysbio.nl/>

25 <http://www.cncr.vu.nl/>

26 <http://www.cmsb.nl/home/index.php>

4.1.2 Funding

At the national level programs that are exclusively open for research proposals in biomathematics do not exist. Various funding opportunities for biomathematics do exist, but all are in programs with a wider scope, open to a wide range of proposals in the (life) sciences and/or concerning only part of biomathematics.

NWO

For example, the Dutch science foundation *NWO* finances applied mathematics research with a biomathematics focus, through generic programs such as the ‘*Vrije Competitie*’ (Free Competition), the *VENI-VIDI-VICI* program, where the proportion of honored biomathematics proposals is, like that of mathematics, very low (see Table 4.1.), and through the broad dedicated program *Computational Life Sciences* (*CLS*).

Table 4.1 Honoured Talent grants 2002-2007

type	total	math	percent	biomath	percent	period
Veni	822	28	3,4%	6	0,7%	2002-2007
Vidi	540	14	2,6%	2	0,4%	2002-2007
Vici	168	7	4,2%	4	2,4%	2002-2007

The *CLS* program is particularly aimed at collaboration between exact scientists and life scientists. In 2003, and between (bio)informaticians, (bio)mathematicians and life scientists in 2007/2008. In the round of 2003, for which mathematicians, physicist and computer scientists could apply, there was 5,5M€ available for proposals concerning modeling and simulation of biological processes in which interactions between large numbers of units take place on different time- and space scales. Of the 44 proposals that were assessed and 16 were honored; 5 of the 16 proposals had a mathematician as main applicant, in 2 others a mathematician participated in the research team. For the 2007/2008 rounds the focus has changed to dynamic modeling of biological networks on different scales. In 2007 the call was open to teams of which the members belong to 2 out of the 3 disciplines (bio)informatics, (bio)mathematics and life sciences. In this round there was 2,3M€ available. There were 41 proposals assessed, 5 honored. Of none of these 5 was the main applicant a mathematician; in 2 of them a mathematician participated in the research team. For 2008 2,5M€s available for the same theme, but this time the research teams will have to contain (bio)informaticians, (bio)mathematicians and life scientists. The *CLS* program certainly contributes to the starting up of a biomathematics community – a reasonable proportion

of the funded positions are for biomathematics post-docs or PhD students – but the investments in biomathematics via this program are still relatively small compared to what is needed. Moreover, the program covers only part of the broad range of biomathematics research.

NWO also supports research in biomathematics through the *mathematics cluster NDNS+*. Via the NDNS+ cluster a couple of permanent positions for mathematics research aimed at applications in the life sciences could be realized. Additionally, the organization of a couple of biomathematics workshops and the invitation of foreign scientists was sponsored. This was another welcome initiative that helped the biomathematics research community grow to its present size.

Other support on the national level

The Dutch government supports research in the life sciences through *Bio-Partner*, the *Netherlands Genomics Initiative (NGI)*²⁷, the *Bsik* programs *Biorange* (2004-2009)²⁸ and *BRICKS* (2004-2009)²⁹ run by NBIC and CWI, respectively, but only a small fraction of the funding is used to carry out biomathematics research. Furthermore, the biomathematics research projects within these frameworks are to a large extent uncorrelated, cover only part of the scope of biomathematics research, and the establishment of multidisciplinary research teams involving mathematicians has little priority.

Support on the international level

The situation at the international level seems to be similar to the one in The Netherlands. Within Europe and worldwide, funding programs exist wherein some level of biomathematics is found, but as a rule in a hidden form. Positive exceptions exist, e.g., in the UK, where the EPSRC runs multidisciplinary critical mass centers of which a number are devoted to biomathematics programs³⁰, and in the USA, where the NSF runs a program called *Mathematical Biology* in which applied mathematics plays a central role³¹ (see also Section 1.4). Specific focused biomathematics funding across borders seems as yet quite rare. At the European level such programs do not seem to exist. The NIH in the USA does allow proposals for interdisciplinary research consortia in which foreign researchers can partici-

27 <http://www.genomics.nl>

28 <http://www.nbic.nl/research/biorange/>

29 <http://www.bsik-bricks.nl/>

30 <http://www.epsrc.ac.uk/ResearchFunding/Programmes/Maths/MultidisciplinaryCriticalMassCentres.htm>

31 http://www.nsf.gov/funding/pgm_summ.jsp?pims_id=5690

pate³², but chances for research with a strong mathematical flavor are low, as evidenced by an inquiry of the SMB³³.

The above described funding all concerns the financing of research. Existing biomathematics education and training is generally financed by the universities that offer it. For the funding of new and nationally coordinated initiatives, but one could learn perhaps from the biomathematics training programs that are being developed in the UK and the USA (see Section 1.4) too. The Division of Mathematical Sciences of the US National Science Foundation and the National Institute of General Medical Sciences at the National Institutes of Health, for example, do not only support research in mathematics and statistics related to biology research. Both agencies also recognize the need and urgency for training at the boundary between the mathematical sciences and the life sciences. The NSF has started, for instance, a program on *Interdisciplinary Training for Undergraduates in Biological and Mathematical Sciences*.

4.2 The challenge

To cope with the increasing demand, to enhance the visibility of Dutch research in biomathematics and to stay aligned with the international developments, it is important to stimulate the building of an international network of researchers in biomathematics.

The most effective way to encourage interaction between life scientists and mathematicians is through direct co-involvement with a particular problem. This applies at all levels from undergraduate through senior scientist. We must look at the complete research process and not just at separate pieces. For this we need long-term result horizons. Resources should be used to build on existing strengths. We are still in a phase in which we need strong models of success, and so we need to support the creation of these models. Furthermore, linking interdisciplinary groups will build a network of people working at the interface.

4.2.1 Small groups, different themes, national coordination

The choice for broadness and ‘mass after focus’ implies that in the coming years biomathematics research will primarily be performed in small groups and on different themes. The infrastructure should provide optimal opportunities for such a setting. Only then unique and successful biomathematics groups can be

32 <http://grants.nih.gov/grants/guide/rfa-files/RFA-RM-06-008.html>

33 <http://www.smb.org/newsletter/11.2/NIH.shtml>

established. As indicated before, direct collaboration between mathematicians and life scientists is very important to stimulate this. At the same time coordinated activity with respect to the organization of research and education, and public relations on a national level is needed.

4.2.2 Priority Program

Although there are several opportunities to obtain funding for research at the interface of life sciences and mathematics, in order to make a significant and structural difference, novel support aimed at strengthening the position of *biomathematics* in The Netherlands is needed. This support should stimulate the biomathematics research over a broad spectrum. In view of the inherent long-term nature of the interdisciplinary research, and to sustain the changes initial support can spark, it should also be long-term. To accommodate all aspects of the establishment of the field, several modes of support need to be considered, but the first priority should be a Priority Program for biomathematics along the lines of the NWO ‘*Fysische Biologie*’ (Physical Biology) program³⁴.

This program should establish a *structural anchoring* of biomathematics research and a *long lasting collaboration* between mathematicians and life scientists.

An additional reason to opt for dedicated biomathematics funding on top of programs such as the ‘*Vrije Competitie*’ (Free Competition) and the *VENI-VIDI-VICI* program, is that the rapid growth and success of biomathematics should not happen at the cost of the development of mathematics as a mono-discipline, nor lead to direct competition for funding with other mathematicians. A solid amount of basic mathematics research is indispensable for the applied mathematics research to build on. In conclusion, a well thought, broad and concerted program on biomathematics, stimulating national and international cooperation, would be an asset for the nascent Dutch research community across mathematics and the life sciences, as well as for the mathematics community as a whole.

4.2.3 Selection procedures

Lastly, there is serious concern about the selection procedure for biomathematics research projects. Funding of biomathematics research must come from different sources and must cross disciplinary boundaries. Like other multidisciplinary research, biomathematics, more than research in the mono-disciplines, runs the risk of not being well-reviewed. Often this happens because the reviewers are

34 http://www.nwo.nl/nwohome.nsf/pages/NWOP_6HLHH8

too strongly mono-discipline oriented, but also because proposals are judged by reviewers with the wrong background. Accordingly, it is necessary to develop a project selection procedure that is *adapted* to deal with this type of interdisciplinary research in question, allowing the combined aspects of the involved disciplines to be properly valued.

4.3 Meeting the challenge

4.3.1 Organizational structure

Experience shows that direct collaboration between mathematicians and life scientists is achieved most easily in one building. Several examples where this is already happening were mentioned above. Therefore, the general conclusion is that *several good meeting places are needed*, but that it is not desirable to strive for one (or a few) national biomathematics institute(s). The main risk of (a) separate biomathematics institute(s) is that the participating scientists become isolated from their colleagues in their own (mono)-discipline. On the other hand, biomathematics research needs to be visible and valued, and should not disappear in strongly discipline-oriented research.

It is also essential to bring mathematicians in touch with practice. Ideally this should begin at the start of a biomathematician's career, by *coupling the theoretical work of the young mathematician to the practical research of a young life scientist*; preferably in the PhD phase. This teaming-up of two PhD students, one in mathematics and one in the life sciences, working together on the same problem, will be very productive and mutually stimulating, and can happen within the above mentioned buildings.

While the biomathematics research itself takes place locally, there is a strong need for a *national biomathematics platform* to stimulate mutual contacts, visibility, and outreach. A beginning has been made during the process of the present foresight study. However, a follow up is necessary, in the form of coordinated activity with respect to the organization of research and education, and public relations on a national level. These activities should be tuned with the existing societies SMBS, IBS-ANed, and the NVTB.

4.3.2 Funding

The best way to support research in biomathematics in The Netherlands is by starting up a *Priority Program* in biomathematics, allowing for a number of

smaller projects with appropriate flexibility and proper incubation period. This program should run for a period of at least 8-12 years and should set a national research agenda. It should also facilitate the establishment of a solid Dutch biomathematics community with a common agenda and portal function, i.e., a national biomathematics platform necessary for mutual contacts, visibility and outreach. The program should have two tracks, one to *stimulate new research kernels*, and one to fund *innovative research programs*. The successful NWO program '*Fysische Biologie*' (Physical Biology), which started 8 years ago between physics and biology and had a budget of 8.2M€, may serve as a guiding example. Also the success of the past NWO-programs '*Landelijk Samenwerkingsverband Mathematische Fysica*' (National Research Cooperation Mathematical Physics) and '*Non-Linear Systems*' motivates this choice. Indeed, as a result of these programs a new generation of mathematicians in the corresponding areas of mathematics has been formed, and is now starting to address itself to a wide variety of new and even more complex research questions, many of them coming from the life sciences. However, the intended Priority Program in biomathematics should be of a different type, larger and of a broader scope. The universities are expected to take *flanking initiatives* to consolidate the biomathematics platform.

Funding should be offered for *white projects*, i.e., projects not within a predefined program structure, but rather based on ideas by talented people with a track record, who are offered support on the basis of bottom-up suggestions. Projects with a calculated risk and with a long-term horizon are welcome, and should be judged by international peers. Funding should come from within larger funding schemes such as the FES rounds and NGI.

For multidisciplinary projects, such as biomathematics, better *project selection procedures* need to be developed that allow the combined aspects of the involved disciplines to be properly valued. In the opinion of the Foresight Committee this is not guaranteed by the introduction of a single window for the disciplines involved. It is only guaranteed when the reviewers and the members of the jury committee are selected according to appropriate rules, and by people who are able to distinguish the different research areas. This is an important issue.

4.4 Industry

A number of ways in which industry can facilitate biomathematics research and training have already been mentioned. In particular, by attracting funding via a *voucher system*, offering *internships* for students, providing *grants for participants*

of the Honours programs, and organizing a yearly ‘*Study Group Mathematics and Biology*’ industry could make valuable contributions to Dutch biomathematics.

An important initiative is the recently launched Business to Science Portal³⁵, which aims at providing a central contact point for knowledge-related questions from enterprises. The portal is run by Leiden University, the Leiden Medical Center, Delft University of Technology and the Erasmus Medical Center, which have joined forces in an initiative called Medical Delta³⁶, in cooperation with TNO. The portal is created to streamline interaction between innovative small and medium enterprises (SME) in the health and life sciences on the one hand and academic institutions on the other. This is a new approach for The Netherlands. Oxford and Edinburgh are examples of places where this formula has proved to be successful. It is envisaged that biomathematicians can play an important role in the Business to Science Portal.

35 <http://www.businessstoscienceportal.nl/>

36 <http://www.medicaldelta.nl/>

5. Opportunities

From the foregoing chapters it will be clear that biomathematics, with its specific challenges and opportunities, is much more than a straightforward combination of two existing disciplines. The Netherlands is in an excellent position to initiate a well-chosen stimulation of Dutch biomathematics research and education. This is both important and timely, and will capitalize on the scientific excellence present in The Netherlands. A joint effort of the scientific community, industry and the government is needed, in line with a number of recent initiatives, developments and perspectives.

Biomathematics research has a wide variety of benefits, but these are often delivered through complex pathways and interactions. The necessary spectrum of biomathematics research in a healthy research base should comprise at least two modes: *basic* and *translational & applied* (see also section 1.3.1.). Basic research in biomathematics investigates the essentials of phenomena, has a powerful potential to redefine our knowledge, creates new explanations, and raises new questions. It can have an immense impact on technology and society in redefining priorities for translational & applied research, which uses existing knowledge – some very long-standing – and explores ways in which this knowledge may be used to solve problems in the life sciences.

Currently, in The Netherlands there is a strong emphasis on ‘hands-on’ stimulation of translational & applied research in biomathematics and the life sciences. This is illustrated by a number of recent initiatives.

- The Netherlands Institute for Systems Biology (NISB)²⁴ in Amsterdam. The NISB was founded by AMOLF (physics), CWI (mathematics and computer science), and life science groups from UVA and VUA. The aim is to foster

multidisciplinary research for understanding the functioning of living cells in humans, animals and plants, with the long-term challenge of a better understanding of life. Systems biology, integrating biology with beta-sciences, is considered instrumental for such fundamental understanding. The NISB can facilitate and organize international cooperation with similar institutes abroad.

- The NGI, has recently initiated the Netherlands Consortium for Systems Biology (NCSB)³⁷, a 15 million Euro national research program to implement systems biology in ongoing research lines of seven high-ranking Dutch research groups in the fields of biomedical and biotechnological research.
- The Center for Medical Systems Biology (CMSB)²⁶, a joint NGI-center initiated by EUR, UL and VUA.
- The Top Institute TI Pharma²¹ (130 million Euro from the FES round 2005).
- The Center for Translational Molecular Medicine (CTMM)²² (150 million Euro from the FES round 2006).

These and other initiatives have led to the proposal of a long-term EZ innovation program *Life Science and Health: Capitalizing on Knowledge*³⁸. Aligned with this proposed innovation program, there are currently new developments around the NWO themes *Systems Biology* and *Brain and Cognition*. In particular, the *Taskforce Life Sciences* (ALW, CW, NGI and ZonMw) together with EW, FOM and STW, has initiated a theme preparation committee to develop a strategic action plan *Systems Biology* [14].

All the above listed initiatives belong to the major application areas of biomathematics and lead to ample opportunities for mathematicians to get involved in this active research area. There are also excellent opportunities for mathematicians to hitch-hike on recent initiatives in bioinformatics, biophysics, biochemistry and bioengineering. These areas offer valuable bridges between mathematics and the life sciences. For instance, currently about 30 percent of Dutch physics is concerned with ‘living matter’. During the past 10 years a number of core questions in biophysics have filtered out, which pose new challenges to mathematics too. Another indication of the timelines of a well-chosen stimulation of Dutch biomathematics research and education is the large number of proposals that was submitted to the NWO *Computational Life Sciences* program, of which only a small number could be granted.

37 <http://www.genomics.nl/GenomicsCentres/Enabling%20technologies/NCSB.aspx>

38 <http://www.lifesciencesgezondheid.nl>

Although these initiatives did spark the interest in biomathematics research in general, and, consequently, strongly increased the demand for biomathematicians, they all have their main focus in translational & applied research areas. Indeed, the current approach in The Netherlands, at least within the larger funding schemes such as NGI and the FES rounds, is to place a strong emphasis on ‘hands-on’ translational & applied research, co-funded by industry. However, to attract talented mathematicians to this emerging field, and let them make long term research commitments in the direction of biomathematics, more is needed. In a recent AWT study [18] it was noticed that other approaches might be more effective. For example, Switzerland chooses for a ‘hands-off’ stimulation of basic research within the larger funding schemes. The idea is that basic research in the life sciences, when of outstanding quality, is capable of sparking directly translational & applied research.

The Foresight Committee believes that stimulating *basic* biomathematics research in the life sciences on a structural basis *also* within the larger funding schemes is crucial for a healthy development of biomathematics in The Netherlands. The above mentioned initiatives make this timely and urgent. The recommendations to establish a *Priority Program Biomathematics* and to offer funding for *white projects* are directly aimed at this.

In the meantime there are already a number of recent developments that show a gradual shift from translational & applied to basic research in the funding schemes. One example is the establishment of the mathematics clusters by NWO. Mathematicians from the NDNS+ cluster, as well as from the newly planned stochastic cluster and EURANDOM, will play a determining role in the further development of basic research in biomathematics in The Netherlands. Another example is the recently launched NWO program on *Complexity*. Biomathematics research fits very well within this theme. The generic character of mathematical results obtained for application to complex systems in the life sciences will naturally lead to the solution of similar problems for complex systems in other areas.

In order to further establish an active research community in biomathematics, the Lorentz Center³⁹ (Leiden) can play an important role. The Lorentz Center coordinates and hosts international scientific workshops where personal interaction, new collaborations and interactions between different fields are central. Since its start, in 1997, the center has organized many successful workshops in astronomy, computer science, mathematics and physics. It has recently extended the scope of the workshops to include workshops in the life sciences, including biomathematics. Already, the NDNS+ mathematics cluster is organizing some of

39 <http://www.lc.leidenuniv.nl/>

the workshops devoted to biomathematics at the Lorentz Center, and the same is done at EURANDOM. The CWI has recently made *Mathematics and the Life Sciences* one of its major research themes. These and similar new initiatives are expected to flourish in the coming decade. Of course, perspectives for national and international cooperation in biomathematics can only be healthy with a proper infrastructure and a sufficient level of funding.

In the 2008 strategic documents '*Concentratie & Dynamiek. Een strategie voor de Wiskunde*' [4] and '*Masterplan Toekomst Wiskunde*' [10] the Dutch mathematics community has laid down its plans for the next decade. Central in the document are the need for interdisciplinarity, the need to recruit and train junior researchers, and the need to provide senior researchers with enough time to develop new interfaces. The document positions biomathematics as a key area for the future to which all these needs apply, and targets the Dutch researchers in mathematics and the life sciences as key partners. The above proposed strategy fits well with these observations.

The excellent position of Dutch research groups has to be safe-guarded in the future. Therefore it is particularly urgent to reshape existing education and to offer new and dedicated educational tracks to students with the ambition to become biomathematicians. Challenging educational programs to train a new generation of researchers at the crossroads of mathematics and the life sciences need to be developed. Participation of life scientists in dedicated biomathematics tracks within the mathematics bachelor and master programs will generate extra opportunities for both scholars and students. It is timely and urgent to create a scientific environment in which graduate and undergraduate mathematics students can work in a lab environment as part of their professional training.

The job prospects for trained biomathematicians are excellent. In recent years, many research groups have appointed staff specifically focusing on biomathematics. Hence it may be expected that graduates will have very good job perspectives within this emerging field. Already now the chances for finding a position within biomathematics as a PhD student or a post-doc can be called good. The Society for Mathematical Biology, for example, publishes job listings on studentships, post-doctoral positions and faculty positions.⁴⁰ Needless to say, the number of tenured faculty positions within biomathematics at the Dutch universities and at academic research institutes like CWI will remain limited. However, individuals with a solid background in mathematics and an open eye for life sciences are in high demand at academic groups, research institutes, and technological companies like DSM, Philips Medical Systems, Shell, and Unilever.

⁴⁰ <http://www.smb.org/jobs/index.shtml#student>

The job prospects for young biomathematicians within the life sciences and biotechnology are expected soon to be as good as they are nowadays within the flourishing financial and ICT sectors.

Therefore the Foresight Committee firmly believes that now is the time to seize the opportunity to give proper impetus to the development of biomathematics and to solidify the biomathematics community.

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Appendices

Appendix 1. The Foresight Committee

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41 <http://www.biofilms.bt.tudelft.nl/>

42 <http://www.viautrecht.nl>

Appendix 3. Main results questionnaires

This appendix summarizes the main results of the questionnaires that were held at the start-up meeting and via internet.

General

In total 118 people completed a questionnaire, 34 during the start-up meeting and 84 via internet. Of the respondents from the start-up meeting, 19 were mathematicians, 10 life scientists, while 5 were from other disciplines (bioinformatics, physics and engineering); for the internet group these numbers were 41, 35 and 8. Below, each triple of numbers denotes the results of the questionnaire from the start-up meeting, from the internet questionnaire and from the combined group of respondents, respectively.

Research

For (91, 83, 86)% of the respondents biomathematics is important in their own research.

Table A3.1 shows how these percentages are divided among the disciplines.

Table A3.1 Is biomathematics important in your research?

	math	life sci	other	total
yes	48	42	12	102
no	12	3	1	16

For the respondents for whom biomathematics plays a role in their research or will play a role in the coming years, the following areas of mathematics are most important (i.e. above 25% in the combined group) for biomathematics research: analysis (58, 63, 62)%, statistics (81, 49, 58)%, numerical mathematics (58, 44, 48)%, probability theory (48, 29, 35)%, and system and control theory (35, 33, 34)%. For these respondents the life science that is important for their biomathematics research is biology (97, 67, 75) %, medical research (19, 38, 33)%, pharmacology (10,13,12)%, and agricultural science (0,11,8)%.

Of all the respondents (91, 89, 90)% judges that biomathematics will play an important role in mathematics or life sciences research. Especially the need for mathematical modeling to help understand biological systems and the need for statistical analysis to interpret data, are mentioned. The fact that biological research has become much more quantitative and that life science journals ask for a statistical foundation of experimental results are considered important reasons.

Education

According to (79, 82, 81)% of the respondents biomathematics will play an important role in life science and/or mathematics education. Ideas about the future implementation of this role differ: (88, 76, 80)% thinks that the current curricula do not provide the means to fulfill the needs of biomathematicians. The majority of them advocates the introduction of a major/minor set-up. The bsc mathematics/minor biology combination scored 35%, the msc mathematics/minor biology 47%, whereas separate biomathematics programs scored much lower: the bsc biomathematics program 26%, the msc biomathematics program 28%. The reverse combinations were investigated only in the electronic interview: the bsc biology/minor mathematics scored 34%, the msc biology/minor mathematics 45%.

Appendix 4. Report of interviews with secondary school students

Introduction and background

To investigate the motives for choosing a particular university study and to obtain insight in the ideas that future students entertain about biomathematics, interviews were held with secondary school students. The students were selected from a group that can be expected to include future biomathematics students. In order to optimize the chance of obtaining the relevant information, a small-scale, in-depth, qualitative investigation was chosen. Two groups of five students each were interviewed. The students were 5th and 6th grade vwo students, between 15 and 19 years old, of different schools from different regional areas. They all had a 'Natuur en Techniek' or 'Natuur en Gezondheid' profile. The goal was to find out what their expectations and motivations are for choosing an academic study in general, what their expectations and perceptions are with respect to a biomathematics curriculum and a career in biomathematics, and how the students obtain, c.q. prefer to obtain, their information about university studies.

The interview sessions were executed by a professional company. Each session took 1.5 hours. During the conversations, visualization, projection and sorting techniques were used. From these meetings the following picture emerged.

General

The main motivation for choosing a study is what can be done with it afterwards. This means that the possible career paths and professions should be clear and concrete for future students. Scientist and teacher are not considered to be attractive professions. Studies that are thought to lead only to these two professions (or studies after which a job is not guaranteed) are therefore not interesting. Earning a lot of money or obtaining a high status is considered to be a bad guideline as well. Quite a few boys, though, opt for the prospect of a high salary afterwards. Another leading motive for a particular choice of study is that one should like it and should be good at it. Furthermore, it is considered to be important to study in a city where one feels at home.

Information is obtained primarily through Internet and through the secondary school's study advisor. The latter provides brochures and guides, of which the 'TKM&T Magazine' and the 'TKM&T gids' are the most popular. The information provided should be concrete and clear. It is important that curricula from different studies or different universities can be compared easily. Brochures with

a lot of text and fancy web pages are not appreciated. Open days are judged to be often too general, too superficial, or too ‘artificially nice’; they are often considered as nice outings (a day off from school!) rather than as informative events.

Biomathematics

Because mathematics and biology have a very different image in the minds of the students, the combination of both studies in some or other form is not self-evident. Mathematics is thought of as a difficult study that takes a lot of effort and time, and hence has a large impact on the student’s life. It is viewed as a study for individualistic and curious people, who like to solve puzzles and do not have a sparkling social life. Mathematicians are thought to be orderly, polite and precise. The interviewed students have no idea what kind of professional career one can have after a mathematics study, except for becoming a teacher. Therefore the picture of a difficult and somewhat boring profession is prevalent. Biology, on the other hand, is thought to be much more general and accessible as an academic study. It continues to evoke the classical image that it predominantly deals with plants and animals and, hence, is suited for people who care for nature and environment. Professional biologists still are typically ‘men with beards’. The future perspective of biologists is good according to these students: “There is a lot to do these days about environmental issues”.

In general the interviewed students see the potential of a combination of different areas, although their notion of the role of mathematics in the life sciences is very vague. A combined curriculum of mathematics and biology is, according to these students, mainly advantageous for mathematics: it makes the study more accessible and gives it social relevance. The added value for biology is less clear to them. The problem is that, due to the divergent perceptions the students have of mathematics and biology, it is difficult for them to imagine what a biomathematics study would stand for, what type of student would choose such combination study, and what profession would follow it. Presently, they do not see very many students going for this combination. Overall, the students who were interviewed see the best chances for a combined mathematics-biology curriculum in the form of a major in mathematics with a minor in biology

Appendix 5. Abbreviations

ALW	nwo-division Earth and Life Sciences
AWT	Advisory Council of Science and Technology Policy
CW	nwo-division Chemical Sciences
CWI	Centrum Wiskunde & Informatica – Center for Mathematics and Computer Science
EUR	Erasmus University Rotterdam
EURANDOM	European Research Institute for Stochastic Sciences
EW	nwo-division Physical Sciences
EZ	Ministry of Economic Affairs
FES	Fund for Economic Structure Enhancement
FOM	Foundation for Fundamental Research on Matter
HBO	Hoger Beroeps Onderwijs – Profession Oriented Higher Education (Universities of Applied Sciences)
KNAW	Royal Netherlands Academy of Arts and Sciences
MKB	Midden- en Klein Bedrijf – Small and Medium Sized Enterprises
NGI	Netherlands Genomics Initiative
NSF	National Science Foundation
NWO	Netherlands Organisation for Scientific Research
OCW	Ministry of Education, Culture and Science
RIVM	National Institute for Public Health and Environment
RU	Radboud University Nijmegen
RUG	University of Groningen
STW	Technology Foundation
TNO	Netherlands Organisation for Applied Scientific Research
TUD	Delft University of Technology
TUE	Eindhoven University of Technology
UL	Leiden University
UM	Maastricht University
UMC	University Medical Center
UT	University of Twente
UU	Utrecht University
UVA	University of Amsterdam
UVT	Tilburg University
VSNU	Association of Universities in The Netherlands
VUA	vu University Amsterdam
WOTRO	nwo-Foundation for the Advancement of Tropical Research
WU	Wageningen University
ZonMw	The Netherlands Organisation for Health Research and Development

