# Gothenburg Mathematical Modelling Centre

## Annual Report 2008


Swedish Foundation for Strategic Research


UNIVERSITY OF GOTHENBURG

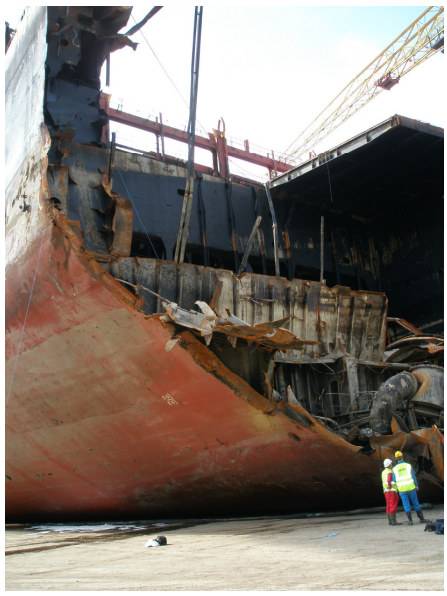

CHALMERS

# Midterm report for the Gothenburg Mathematical Modelling Centre (GMMC), September 2008

## 0. Executive summary

The mission of the Gothenburg Mathematical Modelling Centre is to sharpen the competitive edge of *industry* by providing new mathematical and statistical tools, to support *society* by access to safer and fairer ways of operating, and to provide all of *science* with the best tools for mathematical and statistical analysis and modeling.

December 2005 the Swedish Foundation for Strategic Research granted us 22 MSEK to build a strategic research centre, GMMC. Three months later, in March 2006, the GMMC teams on our focus areas "*Risk, Reliability, Quality*", *"Biomathematics",* and *"Optimization and Modeling*" were in full operation. The first postdoc arrived in August 2006, and at the same time the first GMMC Ph.D. students were recruited (from Moscow University and from Astra Zeneca). Here some highlights from GMMC's first two and a half years of operation:



*M/S Napoli broke in two and sank in December 2007, due to a fatigue failure. Copyright DNV*

- We have devised methods for detection of gene expression which beat established techniques.
- We have found criteria for checking if time delay models (e.g. for processes in cells) are determined by available data – this is a notoriously difficult problem.
- We are changing how Swedish manufacturing companies work to improve reliability.
- We have developed innovative methods for optimization of financial portfolios.
- We have started a new line of research: marine safety and ocean climate.

The *first step* of the development of GMMC is complete: We now have well tried out routines for working in our teams, have established mechanisms for bringing skills from all teams to bear on individual team projects, and cooperate with many companies and scientists from other areas. In Section 12 we apply for support for the s*econd step*: to cement and increase GMMC cooperation with other Swedish (and one Norwegian) research centers in our focus areas, through joint appointments of research associates (forskarassistenter) and postdocs, and of Ph.D. students for work in pairs, with one student coming from each center. Specifically, we ask for new funding for the following initiatives.

- GMMC alliances with other research centers for:
  - Systems biology modeling of lipid metabolism aimed at treatment of obesity.
  - Research on understanding mechanisms governing drug delivery and the taste of food, for use by the pharmaceutical and food industry.
  - Decreasing risks posed by the escape of drugs into the environment.
  - Improving methods for evaluation of gene expression and gene interaction.
  - Development of methods for managing contagious economic risks.
- GMMC collaborations on ship safety and on risks posed by climate change and new ship routes in harsh climates (e.g. The North West Passage).
- GMMC-ITWM collaboration on dynamic fiber networks, for "virtual paper making".

- GMMC collaboration with social science to explore possibilities to use mathematics to understand and resolve social dilemmas.

Finally we ask for support for the *Third Step:* to realize a major longstanding goal, an Applied Mathematics Research Institute similar to the very successful mathematics institutes such as the Newton Institute in Cambridge. The institute will be a place to which industry researchers, researchers from other parts of science, and mathematicians, from all around the world, will travel to participate in half-year long thematic programs. The center will make strategically important advances on many problems from industry and society.

This report describes GMMC's achievements and future through their impact on industry and science. However, we believe the advances we make in mathematics itself: high-dimensional statistics; differential equation modeling; extreme value methods; finite element technology; multi-objective optimization; and many more areas are equally important.

September 2008, after our first two and a half years, GMMC has extensive cooperation with 17 companies. Our collaborations range from developing and implementing a full strategy for the company's reliability improvement to simulation of arterial fibrillation aimed at drug design. GMMC has supported 8 postdocs; hiring of 4 research associates and 1 Professor; organization of 10 workshops and 8 courses for industry; and, the perhaps most important part, time for 22 senior researchers to work on GMMC projects. GMMC/SSF support has been acknowledged in 40 papers accepted for publication, in 32 papers which have been submitted but have not received a decision yet, and GMMC has supported development of 11 software packages. GMMC members have supervised about 50 masters theses, and 4 licentiate, and 9 Ph.D. theses. The full list of publications for GMMC members contains 218 items. GMMC members have been corecipients of grants awarded to 5 other research centers, and cooperation with these is an important part of the GMMC effort.

GMMC uses joint funding extensively. This leads to many synergies, and makes otherwise unreachable results possible. We plan to increase our joint funding of people and workshops further. In this report we attempt to give a full picture of all activities which GMMC have been involved in, whether fully or partially supported.

The impact of GMMC will be in three ways: First, through the concrete results described in this report. Second, through the people we train in collaboration between companies, scientists, and mathematicians, and by our contribution to increasing cooperation between Swedish Mathematics and Industry and Science. And third, we hope and plan for large and yet unforeseen gains. (An example: the 1979 results of Sture Holm – now retired, formerly GMMC researcher - on testing many hypothesis simultaneously, attracted little attention during its first decade. It has now been cited more than 3000 times.)

In the following sections we answer SSF's questions in the order they are posed.

## 1. Which are GMMC's relations to other research centra?

GMMC is hosted by the Department of Mathematical Sciences at Chalmers and University of Gothenburg. It combines four components: *The Gothenburg Stochastic Centre,* new *Applied Mathematics Research groups, Researchers from Quality Science,* and *FCC,* the *Fraunhofer-Chalmers Research Centre for Industrial Mathematics*. FCC is an applied mathematics industrial research institution which carries out research for industry, commerce, and society, and works with companies on a commercial basis. FCC started in 2001. Its turnover had increased to 3 Million Euro in 2007. Half of this came from industry. GMMC has close links to Fraunhofer ITWM in Kaiserslautern, FCC's mother institute. Through ITWM we have access to the enormous capabilities of the Fraunhofer-Gesellschaft.

Virtually all our use of mathematics involves working with experts from other areas. GMMC strives to create good environments for this. The best environment is often to join

forces with other research centers. Below we list the centers we have begun cooperation with. In addition the GMMC Risk and Reliability team plays an important role in UTMIS, the Swedish material fatigue network, as founding members, board members, and organizers of meetings and courses. GMMC has informal links to many more departments and centers from all around the world. The total number of GMMC coauthors from abroad is several hundred.

| Center | Formal links | Comment |
|---|---|---|
| *GSC, the Gothenburg Stochastic Centre (funder: the Swedish Research Council)* | Partner in GMMC, Jagers is grant recipient, Rootzén is chairman | |
| *Quality Science at Chalmers* | Partner in GMMC, Bergman is leader | |
| *FCC, the Fraunhofer-Chalmers Research Centre for Industrial mathematics* | Partner in GMMC, Nävert is director, Jagers is chairman | GMMC integrates FCC and Chalmers research |
| *ITWM in Kaiserslautern* | FCC's mother institute; ITWM's president is member of GMMC's Scientific Advisory Board | Close and broad collaboration GMMC/FCC-ITWM |
| *CMR, the Center for Cardiovascular and Metabolic Research( funder:SSF)* | Wennberg is a research leader, Lena Carlsson, coleader of CMR, is member of the GMMC board | Funding of postdoc, Ph.D. student, research in systems biology |
| *SuMo, the Supramolecular Biomaterials Structure Dynamics and Properties center (funder:Vinnova)* | Rudemo is research leader | Funding of research associate, joint research on drug delivery, taste of food |
| *Center for Theoretical Biology (funder: University of Gothenburg)* | Jagers is coleader | Partial funding of Jagers, research in population dynamics |
| *GSCB, Gothenburg Center for Systems Biology (funder: Chalmers, University of Gothenburg, EU)* | GMMC is a partner | Research in systems biology and genomics |
| *The Ecotoxology platform (funder: University of Gothenburg)* | Nerman is research leader | Research on environmental effects of toxic substances |
| *MP2, the Gothenburg Mathematics-Physics platform (funder: University of Gothenburg)* | Larsson is coleader in MP2 | Funding of Ph.D. student |
| *IFREMER, the French Marine Research Institute, and DNV, Den Norske Veritas* | Participation in the SEAMOCS EU project | Funding of two Ph.D. students, research on ship safety, ocean climate |
| *SP, The Technical Research Institute of Sweden* | Svensson works at SP | Research and courses in reliability |

## 2. Does GMMC live up to SSF's vision for a Strategic Research Center?

The first part of SSF's vision concerns the *strategic importance* of GMMC. A high-level perspective on mathematics is that, "the exploding importance of information to all sectors of society and the pervasive role of technology in maintaining security and prosperity have placed the mathematical sciences in a position of central importance" (slightly modified citation from a US National Science Foundation report). Reliability is crucial for manufacturing; financial risks have to be handled, as is underlined by the ongoing financial

crisis in the USA; optimization can save large sums and decrease accident risks, in industry and in health care; and a focused and strong biomathematics base is a competitive advantage for Swedish pharmaceutical industry – these are the areas GMMC contributes to.

Examples of testimony to the *scientific quality* of GMMC are the following: In addition to GMMC, Mathematical Sciences in Gothenburg hosts a VR strong research environment, the Stochastic Centre, and Chalmers was selected by the Fraunhofer-Gesellschaft as partner for FCC, its first joint research institution in Europe outside of Germany. In the 2008 Linneaus application evaluation we got the highest grade, and the summary said "The scientists all are outstanding, the proposal is world-class and timely, and the environment is excellent for pure and applied research in mathematics." Three GMMC researchers are members of the Royal Swedish Academy of Science, and one is member of the German academy of natural sciences, Leopoldina. Wermuth is President of IMS, one of the two major international organizations in mathematical statistics, and Jagers was Presidents of the other, the Bernoulli society, 2005-2007. Rootzén was appointed editor-in-chief for the major journal Bernoulli 2007.

How we achieve *integration* of the GMMC parts is a topic of Section 3 below. The GMMC member's offices are within 300 m of GMMC's physical heart "Mallvinden" which is used for all GMMC meetings and as working place for guests. We have very many daily informal encounters in coffee rooms, corridors and lunch restaurants – this is as important for our cohesion as the more structured approaches discussed in Section 3.

Indications of our *size* is the list of GMMC members (Encl. 1), the amount of funding we receive (Encl. 3), and the Centers we cooperate with (Section1). The *leadership* of GMMC and our *routines for making our results used* are set out in Sections 4 and 8 below. The final part of the SSF vision is that a strategic research center *solves large and complex problems on varying timescales, uses complementary scientific and technical skills, and covers the entire span from basic science to finished product*. For this, see Section 6.

## 3. Does GMMC live up to its own vision?

The GMMC vision is *"to be a role model for cooperation industry-society-science"*. We live up to our vision by developing new ways of organizing research and collaboration. A main part of this is our by now seamless integration between university research and research at FCC. We hope this inspires other Swedish departments and other industrial research institutes to try similar forms of cooperation.

*GMMC at work*

A second part is close interaction between our research teams. This is obtained through new and deeper personal links, joint papers, many seminars, regular centerwide meetings with scientific presentations and discussion of research and strategy, and our series of international workshops (by now we have organized 10) with crossteam participation.

Traditionally, research in the mathematical sciences was largely done by individuals working alone. More recently joint research has become more usual, but stable and cohesive research groups are still uncommon. A third part of our effort is to build much broader and larger research teams than has been possible before – this is important because our strategic and crossdiciplinary research requires access to many different mathematical skills. In Risk,

Reliability, Quality we use frequent lunch-to-lunch retreats to keep team members from mathematics, quality science, and FCC integrated and focused on GMMC work. Our biomathematics team organizes joint scientific seminars, and collaborates on writing papers in varying constellations which together connect the entire team. The Optimization and Modeling team functions as a traditional research group – this is of course standard in natural science, but even now rare in Swedish mathematics.

A further consequence of our vision is that our dissemination of results to industry and to other science now is more structured than it was before. In particular we plan for a good mix between "person-to-person sell"; courses; presentations at workshops and conferences; research papers; books; and software development. Conversely, we also improve our methods to import knowledge from industry through FCC, and via industry collaborations, and from academia through guest researchers, postdocs, visits to other departments, and workshops.

## 4. How is GMMC organized and led?

| | |
|---|---|
| *GMMC board* | promotes external contacts, gives advice, makes final strategic decisions |
| *Centre leader* | makes day-to-day decisions, prepares for strategic decisions |
| *Leader +deputy leader* | day-to-day running, cooperation with heads of FCC, Mathematics, Mathematical Statistics and Quality Sciences |
| *Council: all GMMC members (Encl. 1)* | main forum for discussions, consensus decisions |
| *Scientific Advisory Board* | gives technical advice on research and advice on overall strategy |

The GMMC board consists of Jan S. Nilsson (Chairman, former President University of Gothenburg, former Executive Member Wallenbergstiftelsen), Nibia Aires (Principal Statistician, AstraZeneca), Lena Carlsson (Professor Clinical Metabolic Research, Codirector of CMR), Thomas Morsing (Head of division for quantitative asset management, 2:a APfonden), Anders Ydergård (Vice President for product development, Volvo 3P).

Scientific Advisory Board members are sir David Cox (Professor, Oxford University), Gunnar Andersson (President KP Pension & Försäkring), Magnus Johansson (President SKF China – leaving the SAB 2008), Hilary Ockendon (Professor, Oxford), Dieter Prätzel-Wolters (Director of ITWM, Professor University of Kaiserslautern), and Simon Tavaré (Professor USC and Cambridge Research Institute).

The GMMC Board has met once in 2006, twice in 2007, and three times in 2008. The Scientific Advisory Board had a first meeting May 2006 to help shaping the initial GMMC strategy. The second meeting was held three days in January 2008. All GMMC projects were then presented in detail. The Scientific Advisory Board contributed new insights, perspectives, information and ideas to individual projects – some quite vital. The advice the board gave on overall strategy has been influential in forming our plans for the future.

The GMMC leadership concentrates on selecting and supporting the best industrial and scientific projects (see Sections 6, 12); achieving cohesion and creating a supportive, open, and productive environment for our centre (Sections 3, 9, 11); planning and encouraging external cooperation (Sections 1, 10); and making GMMC results used by industry and society (Sections 7, 8). We have been able to keep consensus about using funding where it is most needed and where it has the biggest effects. During GMMC's two and a half years of operation we have made substantial changes in the proportions of funding given to our three teams, and we expect to make such changes also in the future.

## 5. What is the added value from GMMC?

More and more science and engineering, in particular in our focus areas, from molecular biology to financial economics, and from mechanical reliability to radiation therapy, depend on advanced mathematical modeling. High speed computing and advanced visualization tools multiply the opportunities inherent in modern mathematics. This development makes new demands: The growing size, complexity and sophistication of projects, systems and companies, and the ever faster pace of industrial development require high-speed access to a very wide range of mathematical knowledge and skills.

This is the major "added value" from GMMC: that we now can meet such demands in a way which earlier was out of reach. GMMC has made it possible for us to assemble and achieve cohesion of a broad range of mathematical modeling skills, and to bring these skills to bear on many problems. Further added values, which could not be obtained from smaller individual grants, include:

+ Through GMMC we have, and use, the ability to shift resources quickly, to meet new challenges and to increase support to successful efforts, and we can use FCC capabilities to make our results used by industry.

+ GMMC provides a structure where skills and results obtained in one area rapidly are brought to bear on problems in other areas.

+ GMMC contributes to a change of the mindsets of Swedish Industry and Science, towards integration of mathematics into all of research and development. A concrete indication is the increasing amount of money invested into mathematics by industry. More intangibly, we feel that Swedish Mathematics more and more begins see cooperation with Industry and Science as a natural and positive part of its tasks.

+ The existence of GMMC "puts us at the center of the world": our workshops collect the world's best researchers; we now can recruit much more efficiently, from all over the world; we are partners of equal standing in cooperation with other large centers.

## 6. Which are GMMC's main research results and how do they compare with its goals?

The goal of GMMC is strategic: research done together with industries aiming at immediate use, and research where the aim is practical use in a 5-10 year perspective. For our Biomatematics team, the goal is improved health care and use by pharmaceutical companies. Use often comes through partners in medicine and biology. Typically our Risk, Reliability, Quality, and Optimization and Modeling teams collaborate directly with companies. In this section we describe some of the results of GMMC work. To avoid repetition we do not list the companies involved in each subproject, but instead collect the collaborating companies at the end of the description of each team's results. More information on our two first years is given in GMMC's yearly reports (http://www.chalmers.se/math/EN/research/gmmc).

.

***Biomathematics:*** The GMMC biomathematics team provides a broad mathematical base for Swedish biology and medicine, from gene study to analysis of patient data. Results include:

- We have developed differential equation models and computational tools for lipid metabolism, and for signaling in cells and in the heart. The end goal is increased understanding of the effects of drugs.
- We have devised methods for evaluation of gene expression and gene interaction, and for quality improvement of experiments, and have applied these to a wide variety of problems, including environmental risk assessment.
- We have used and developed spatial and image analysis methods for modeling of drug delivery and food uptake, and for early detection of neuropathy.

- We have given methods for evaluating the effects of interventions, such as preventive medication, and guidelines for imputing missing values in intervention studies.

One GMMC focus is S*ystems Biology and Bioinformatics.* On the cell level, we work on modeling and understanding metabolic and signaling pathways in cells, using yeast (S. Cerevisia, and in particular the pathway RAS/cAMP/PKA) as biological model. On the organism level, we have started developing models for lipid metabolism and how to fit these to measurements, in particular using multi-compartment methods.

We have made substantial progress on building a detailed differential equation model of the electrophysiology of canine heart tissue (including full scale surface geometry of the left and right atrium). The ultimate aim is development new treatments for prevention of heart fibrillation. A main part of our effort is to produce software for system identification, model reduction, and quantitative bioimaging [60]. The differential equations in the models contain delay terms. We have derived criteria for deciding if the coefficients in these models can be identified from data [3, 4, 28, 29].

A new development is predictive dynamic models of human response to drugs. Often the models build on time series of blood plasma concentrations. We work on a number of problems in this area: How can one resolve uncertainty caused by measurement variation? How can model errors be taken into into account? How can measurements be used dynamically to adapt treatments to individual variation? These are crucial factors in the new paradigm personalized medicine which pharmaceutical companies are beginning to explore.

One of our methods for detection of Gene Expression has been compared to 11 published methods on five spike-in data sets, and came out on top for four of the five data sets [5, 6]. A related effort is directed at quality improvement and analysis of molecular level effects of salt and arsenic stress on yeast. A paper [13] on evolutionary conservation of human drug targets in organisms, aimed at environmental risk assessment indicates that it is important to use higher organisms for evaluation or risks posed by escape of drugs into aquifers. Other research collaborations include studies of cancer tumors [23].

*PCR* (the Polymerase chain reaction) is a major DNA amplification technology for molecular biology. Quantitative analysis of PCR aims at determining the initial amount of DNA from PCR amplification curves. This is of interest in gene expression analysis, virology, and food quality control. We have developed probabilistic models for PCR, maximum likelihood methods (which rely on the EM-algorithm) to estimate the initial amount of DNA, and methods to decide on when to extract samples. The methods have been evaluated in a simulation study which mimicked the population dynamics of a mixture of wild type C. Elegans and a mutation of it. In the area of general theoretical biology we have investigated the time and path to extinction in stably subcritical circumstances [17].

A second focus is *spatial and image analysis.* We have developed methods for identifying and simulating three dimensional gel microstructures from transmission electron micrographs, and a simulation model for diffusion of particles in complex 3-D gel networks [24]. The simulation model [40, 41] uses an adaptive time-stepping solver for stochastic differential equations, with the surrounding geometry as an obstructing medium. A further development concerns tracking of 3-D particle movements from sequences of 2-D images. The accuracy of our position estimates go well beyond sub-pixel accuracy [19]. We have developed new likelihood based methods to estimate diffusion coefficients from FRAP (Fluorescence Recovery after Photo Bleaching) images [18]. The aim of this research is understanding and tuning of drug delivery and food uptake.

The first steps toward non-intrusive methods for early detection of neuropathy has been taken in the papers [25, 43, 44]. The methods quantify changes in the epidermal nerve fibers caused by the progression of disease. We have applied closely related mathematical tools

[26] to two quite different problems. One is to use 3-D topographic images of air pores in the polar ice to track compactification and drift of the ice [42]. This is important for measurement of the climate history of the earth. We have built accurate models of sintering in copper [32].

Attempts to understand effects of interventions are motivating research in many fields of science, specifically so in preventive health and drug testing. Graphical Markov models developed during the last 30 years provide a general framework. We have given techniques based on matrix representations of graphs that make consequences of interventions transparent [22, 27, 45, 46]. We also evaluated advantages and shortcomings of different methods for imputing missing data to give guidelines for imputation which depend on the specific features of the data [47].

The work described in this subsection is in collaboration with the biological centers listed in Section 1, with the department of Cell- and Molecular Biology, University of Gothenburg, with the department of Chemical and Biological Engineering, Chalmers, with Edda Klipp's group in Berlin, with Emory University, with University of Minnesota, with the Swedish Institute for Food and Biotechnology, with Astra-Zeneca, and with Unilever.

The other GMMC teams also contribute to biomathematics research. Example include the Optimization and Modeling team's results on cancer radiation therapy and use of extreme value statistical techniques in gene expression analysis

***Risk, Reliability, Quality:*** The research of the GMMC Risk, Reliability, Quality team is in close collaborations with many companies and public institutions. Our results include:.

- We have introduced a system which helps manufacturing companies improve the reliability of their products. The system treats uncertainties about loads, material variation, and parameter values, and model uncertainty within the same framework. It uses Robust Design methodology to design for increased reliability.
- We have developed better mathematical methods for ship routing, for estimation of the reliability of marine structures, and for estimation of extremes in the ocean climate.
- We have produced methods to optimize financial portfolios, to prize credit derivatives, and to evaluate catastrophic risks.

Reliability is necessary for product quality – if products break down, then high quality in all other respect does not help. Costs due to unreliability of equipment and processes, and warranty costs, can rise to one third of the total turn-over in some companies. Failures can also cause risk of life and limb. An essential source of unreliability in mechanical and electromechanical systems is fatigue; another one is corrosion. Present practice in reliability engineering in Sweden is unsystematic and there is a very large scope for improvement.

We are developing a unified approach to industrial reliability improvement. It includes all aspects from the end goal of customer satisfaction down to detailed technical modeling, and exploits and quantifies engineering experience, service measurements, experimental results, and frontline scientific research. A main effort is to present our general approach, and many new results, in a book "Robust design methodology for reliability – exploring the effects of variation and uncertainty". As contracted we will deliver the manuscript to Wiley February 2009.

In addition to the book, we have developed a guide to life prediction for Volvo Aero. It has been tried on test cases and is now in use. In a commercial project supported by DAF, Daimler, IVECO, MAN, Scania and Volvo, we produce a guide to load analysis , where old and new methods to collect, model and estimate load signals are collected, compared and discussed. Fatigue failure is one focal point for this research. We also develop models for evaluation of results from corrosion tests [12]. We are heavily involved in Volvo 3Ps efforts

to create a robust engineering system for increased Reliability and Customer Satisfaction. At SKF we have supported a similar initiative, there called Design for Six Sigma.

General concerns about higher than designed for risks with maritime operations call for better methods to describe time-space variability of the environment and better models of responses of structures to loads. Higher risk is sometimes caused by errors in the design or unknown/neglected variability, or human error, but sometimes also by the design practice itself. This is because present design rules only put requirements on bending moments or section modulus but do not prescribe a safety level, and do not include load considerations. They instead rely on experience from previous very conservatively designed ships.

If e.g. high tensile steel is introduced and size is increased, whipping gets worse, and the old design rules are not reliable anymore. One example of this is the MSC Napoli container vessel which broke in half January 2007. Maritime operations are undergoing rapid change: globalization leads to an increase of transports and new shipping routes, possible climate changes may lead to more severe storms, and the melt of ice that opens the possibility to use the North West passage for transporting goods between EU and Asia. This often leads to ships and structures now being exposed to more severe loads than before. The risk of failure can be high even for well designed structures if they are exposed to more severe loads than designed for.

We are develope methods for ship routing which minimizes the risk of fatigue failure, and fuel consumption. For this we model the variability of the loads that cause damage during a trip [1, 2, 8, 10]; investigate damage mechanisms at different locations of the structure [9]; and develop methods to predict the damage from indirect measurements. A further problem is to model the uncertainties in sea weather predictions used for planning ship routes [7].

The world's financial institutions are in convulsions at the time of writing. On a micro scale, two of our research directions in financial risk management are in directly relevant areas: Credit derivatives are used to manage default risks, and the market for these instruments has grown rapidly. We have introduced a class of Markov Models, and methods to make these computationally tractable, which makes it possible to price new and more complicated credit derivatives, such as CDO-s. [15, 16, 36]. Standard Markowitz-like methods for optimizing portfolios of financial instruments are unrealistically sensitive to assumptions of normal distribution, and to estimates of expected returns. We have developed new models which circumvent these problems, a software package which implements parts of this, and a package for full Assset Liability Modeling [20, 21, 57, 58]. Natural catastrophes, such as very damaging windstorms, continue to pose threats. Methods to estimate risks of simultaneous occurrence of several types of damage have been developed, and applied to wind storm insurance [34].

Our research on Risk, Reliability, Quality is in collaboration with many companies, including DAF, Daimler, the Swedish Insurance Federation, IVECO, MAN, the Länsförsäkringar group, Scania, the Second Swedish National Pension Fund, SKF, Volvo Car, Volvo Aero, and Weavering Capital.

Members of this team are also part of Optimization and Modeling projects [33], and are involved in gene expression analysis [48].

***Optimization and modeling:*** Modern engineering optimization combines simulation with traditional engineering techniques, and often tries to attain several goals simultaneously. This requires multi-objective optimization tools which can accommodate both simulation and differential equation models. We create such a platform of such tools by working on concrete projects. The hub of our effort is optimization, but we use the entire GMMC capability, from statistical analysis to finite element computation. Projects include:

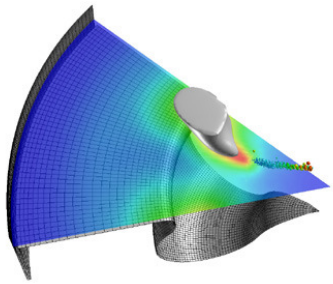
- We have developed methods for improving dose plans for radiation treatment of cancer.

- We have built and tested a system for multi-objective combustion engine optimization.
- We have produced new decision support tools for antenna optimization.
- We are developing efficient finite element methods for optimal control of ordinary differential equations, in particular aimed at steering of heavy trucks.

The goal of dose planning is to deliver enough radiation to the cancer tumor to make the probability of curing high, and to minimize damage to organs-at-risk and surrounding normal tissue. Oncologists use computer-generated 3-D transport (or, dose) calculations that approximate the effect of radiation beams penetrating human tissue. It is not clear how accurate the calculations are – but accuracy is of vital importance. In particular large-angle scattering is often neglected, but can be significant. We have developed more accurate calculation methods for simplified, 2-D, problems and started work on full 3-D models.

An optimal objective function for use in Intensity Modulated Radiation Therapy (IMRT) would give voxel-based target ordinations based on properties such as the tumor's doubling time, cellular radio-sensitivity, density of clonogenic cells, and degree of hypoxia. This function then, through optimization routines, provides the controls for the treatment machine to produce the best possible radiation at each voxel. We have developed a general form for such an objective function, based on known cellular biology. There are many uncertainties about the parameters of this function, including those that stem from variations in dose responses across individuals. Some will be resolved when we get the results of the recently completed national ARTSCAN study on side effects from IMRT. However, some will remain, such as those due to patient and organ movement and variations in the performance of treatment machines. We have developed a stochastic optimization model to take these remaining uncertainties into account. The formulation is convex and has been shown to yield treatment plans that are robust to parameter variation [35]. The new optimization model may ultimately reduce, or even remove, the need for the ad hoc margins used in current dose plans.

Today it is possible to simulate the physical and chemical processes inside combustion engines using appropriate software and high-performance computers. These simulations can predict fuel consumption and emission of soot and nitrogen oxides of the engine. The goal is to design engines which are fuel efficient but at the same time meet the conflicting goal of low emission of soot and nitrogen oxides, over a range of load and speed conditions. One engine simulation can consume several days of computer time. Very efficient specialized optimization algorithms are therefore required. We have developed and implemented a multi-objective optimization algorithm based on approximation with radial basis functions which achieves this [37, 38]. The algorithm has been used to optimize a Volvo D5 diesel engine.



*An engine simulation. Colors show temperature. Grey is isosurface for soot, contour plot shows fuel concentration.*

The optimization algorithms developed in the combustion engine project have been further refined and adapted to optimization of antenna systems. A decision support system that integrates multiple-criteria optimization and simulation has been developed [53]. The simulations are performed with a commercial electromagnetic solver partly developed by FCC researchers. The decision support system is successfully used in a project with the Antenna Research Centre at Ericsson [30]. Development of the system started in a project to improve an antenna system for localization in space-time radiotherapy of prostate cancer. It turned out that the combination of the operating frequency of the system and the physical

dimensions made efficient simulations and therefore optimization infeasible. In fact, Micropos has after the project changed operating frequency of the system.

We have developed numerical methods for solving the differential and algebraic equations that arise in connection with optimal control of the dynamics of heavy vehicles. The stiff boundary value problems that occur are usually solved by shooting methods or collocation methods. Our approach is to use finite element methods which allow error control and adaptive computational meshes. The algorithms have been implemented in software and found to work well in collision avoidance maneuvers for trucks [31, 39, 49, 55].

The work of the Optimization and Modeling team is in collaboration with ABB, Ericsson, Medical Radiation Physics at Karolinska Institutet, Micropos, Therapeutic Radiation Physics at University of Gothenburg, Vehicle Safety at Chalmers, Volvo Powertrain, Volvo 3P and Volvo Car Company.

Optimization and finite element computation, the expertise of this team, is also used in GMMC work on risk and reliability.

***Comparison of results with goals:*** In the final agreement with SSF we set out five general three year milestones: a) vertical integration, of research at Chalmers, FCC and industry, b) horizontal integration between our teams, and inside the teams, c) integration of guest researchers, workshops and conferences into our work, and d) to encourage informal encounters. The fifth, and most general, and very important goal was "To build a supercritical, open, creative and international environment where people can develop to the full of their potential and where they have fast and easy access to a wide range of knowledge"

We have now achieved these five goals, as discussed in Sections 1-3, 5, 9, and 11. We also agreed on 13 concrete three year milestones. Of these we have substantially exceeded 4, have met 7, are well under way with 2, and in one project the goal has turned out to be unreachable, because of constraints in the physical system we worked with, see Encl. 7.

## 7. How does GMMC contribute to Sweden's competiveness and economic growth?

Mathematics and stochastics are emerging as key technologies (cf. beginning of Section 2). In a long perspective it is the people we train, the collaborations and new ways of working we initiate, and the mindsets we create which count. Six GMMC Ph.D-s and postdocs have been hired by Swedish industry, and four by industry abroad – all are important for Sweden's competitiveness, we believe. Many of our new collaborations are described in Section 6.

On a short time horizon, the concrete results of GMMC research is our most important contribution, see Section 6. Our workshops attract the best people to Sweden and give immediate access to the newest result for our researchers – good people and knowledge is indispensable for Sweden.

## 8. How are GMMC's results put to use?

We "sell" GMMC and GMMC results through people, projects, courses, workshops, conferences and through industrial and scientific publications. A unique asset is that we can use FCC's professional commercial organization for this. A cornerstone in our strategy is to make our industrial partners work actively in joint projects. We believe the most effective way to attract new projects is a good reputation plus a well-designed web pages. We are striving to reach this state. There are some signs of success.

We draw considerably on our network through the former Swedish Association for Industrial Mathematics (STM); in some cases we also call a new company and suggest a meeting to present ourselves. Our partner Fraunhofer-ITWM regularly goes to fairs. We have not yet done this, but are in the process of producing a GMMC flyer, for use at fairs and other

suitable occasions.

A new initiative is the creation of an Industrial Partner Group (IPG) in 2007. The group meets four times a year to define a research scenario, an industrial scenario, a synthesis, and a research program. Discussions with four companies in IPG on papermaking and paperboard package quality were the starting point for a new project *Dynamic fiber networks - a step towards "virtual paper making"*. We ask for partial SSF funding of this project in Section 12.

A Center for Healthcare Improvement http://www.chi-net.se/ is being built up. Its aim is to transfer academic and industrial knowledge on Safety and Quality Improvement to hospitals. This is partly a GMMC spinoff.

For concrete examples of how GMMC results are used, see Section 6 and Encl. 7.

### 9. How does GMMC contribute to Ph.D. education and recruitment of researchers?

Twenty or thirty years ago undergraduate and graduate students in mathematics (except maybe statistics students) were rarely exposed to problems from the real world or to joint work with people not from mathematics - or to working with others at all. This situation is changing, slowly at first and more rapidly recently. Centers like GMMC play an important role in this.

Efficient recruitment starts early. An exciting development is a five-year masters program in Technical Mathematics which started at Chalmers in 2008. The program attracted many and good applicants, and accepted thirty-five students the first year. GMMC was an inspiration for creating this program and contributes significantly to its industrial profile.

We want to give Chalmers' students at all stages - and their teachers – exposure to work onproblems from industry and society. The interplay between learning and application gives added understanding and skills, and adds value on the labour-market. We need a continuous flow of young people through the Centre, and the ideas they bring.

GMMC activities directed at undergraduates also include the existing Chalmers international master programme "Engineering Mathematics" and University of Gothenburg students. We have supervised around 50 masters theses (12 at FCC), and continuously advertise and start new masters theses projects. We will invite the new students to lunch seminars on "Mathematics as Technology" and "Earn Money on Mathematics" and FCC will offer up to a dozen jobs (10% of full time) to talented undergraduate mathematics and statistics students. GMMC is a good source of bachelor thesis projects. Some of the projects are done at FCC (four proposed for 2008-09) and give the added value that the student gets exposed to the entire range of industrial work done there.

During the last few years Mathematics in Gothenburg has attracted very good Ph.D. students. We believe GMMC is one of the causes for this. In addition to skills needed for research on problems from industry and other science, GMMC work typically give graduates experience of and skill in working in interdisciplinary teams. GMMC is also active in teaching of how to write research applications and contracts.

It has been easy for GMMC Ph.D-s to find work in industry. Their interdiciplinary and teamwork experience - and contacts – gotten from GMMC work has contributed to this.

### 10. How does GMMC's help its members to enter into EU and other international programs and international collaboration, and how valuable is the help?

GMMC researchers participate in the BIOSIM, CANCERSYS, EU-EST, SEAMOCS, and UNICELLSYS EU-projects. They also are part of the "Future SME" and SysBio EU projects and in the ESF projects "European Research Network for Yeast Phenomics" and Europhen which all four are in the final phases of contract negotiations. GMMC has arranged a seminar

on how to apply for EU projects, and will fund work on new applications – provided costs are not covered in some other way.

The GMMC workshops (10 up to now, see Encl. 7) are our main way of starting and encouraging international (and Swedish) collaborations. They have been quite effective. GMMC gives added visibility which makes us more attractive as partners, and economic flexibility which helps in making rapid startup of collaborations.

### 11. How does GMMC promote gender equality?

The proportion of women in mathematics departments in Sweden and in Northern Europe is typically low, perhaps 10-20% . The result is that many opportunities for mathematics and chances for industry and society are lost. GMMC contributes to changing this in two ways.

One is by creating an exciting and open environment which emphasizes collaboration, teamwork, transdisciplinary research, extensive international collaboration, and usefulness to society and industry. We believe this makes our center attractive for women, and for men.

The second is our hiring strategy. The majority - and the most important ones - of our GMMC-funded appointments have been recent Ph.D.'s: all 4 research associate appointments made by GMMC are women, and 5 of our 9 postdocs are women.

### 12. **The future!**

GMMC plans for the next two and a half years, assuming *current funding* levels, include the following projects – old and new:

- We will conduct broad research in biomathematics, aimed at the pharmaceutical, food, and manufacturing industry. Topics, include modeling of lipid metabolism; methods for analysis of gene expression interaction; spatial modeling of gels, epidermal nerve fiber layers, and carbon nanotubes; and environmental effects of pharmaceuticals.
- We will widen the scope of our approach to manufacturing reliability improvement, and extend it to apply to the quite different problems which occur in microelectronics and software reliability. We will work on ship safety, ship routing, ocean climate and management of financial risk.
- We will produce methods for optimization of radiation treatment of cancer, maintenance optimization will become a new focus, and we will start a new project on EEG source localization for surgical treatment of epilepsy.

We apply for *additional funding* for the second step of the development of GMMC: to get maximum mileage out of the new GMMC structures by teaming up with other research centers. We have found joint appointments with other centers productive, and much of the new resources would be used for positions where both centers provide parts of the funding. Specifically we apply for support for the following (for explanation of abbreviations of center names, see Section 1; CIAM is the SSF-supported Center for Industrial and Applied Mathematics; SFI2 is the large new Oslo center Statistics for Innovation in Industry):

- With CMR, to develop differential equation and stochastic models for high-level understanding of lipid metabolism, aimed at improved treatment of obesity.
- With SuMO, on modeling of the local diffusion coefficient, for understanding of delivery of active substances from tablets and taste substances from food.
- With GSBC, on using yeast as a model for understanding fundamental life mechanisms, and on prediction of effects of multiple cancer drugs.
- With DNV and IFREMER, for managing risks of structural failures in marine operations.
- With CIAM and SFI2, to develop methods to manage contagion of economic risks.
- With researchers from Social Science on using mathematics for understanding and resolving social dilemmas.

Finally, we also ask for new support for the third step of the development of GMMC: to realize a major goal – a Research Institute for Applied Mathematics similar to the enormously successful such institutes which exist in pure mathematics.

***Plans for use of already available funding***

**Biomathematics:** We will pursue ongoing projects (Section 6) in mathematical modeling of metabolic and signaling pathway; on gene expression analysis; and on image analysis and simulation methods for drug delivery and food uptake. Projects will evolve and change as new results are obtained.

We will work on strategies for mammal-to-fish extrapolations of characteristic gene expression changes, as a way to judge environmental effects of pharmaceuticals [13, 14]. New directions will be use of microarrays for identification of antibiotic resistance genes in bacteria and design of SNP-chips for environmental monitoring of fish along in the Baltic.

Stronger and/or electrical conductive fibers are needed for reinforcement fibers, smart clothing and electromagnetic shields. Because of their good mechanical and electrical properties carbon nanotubes are interesting as fillers in the production of such fibers. Alignment is important for good mechanical properties. Preliminary experience is that the anisotropy of nanotubes cannot be captured by the classical "rose of directions". We will develop techniques for modeling and classifying anisotropies, and apply these to TEM images of nanotubes. In [69] the autors have experienced that electrical conductivity is lost with increasing "draw down ratio" in production and believe that this is due to increasing orientation and decreasing curvature of nanotubes. One of our aims is to investigate and quantify this belief.

Our study of sintered copper (Section 6) will be a starting point for a larger project on microstructure of sintered materials. Sintering is important for industrial production of metals and also for non-metallic materials such as concrete. Earlier studies, e.g. [65] use the Force Biased (FB) algorithm to generate random close packings of balls as models of microstructures. However, the microstructures obtained from the FB algorithm are too regular. We will investigate an alternative to FB, viz. immigration growth interaction processes with moving balls, which we believe will generate more realistic patterns.

In our work on methods to understand the effects of interventions (see Section 6), we plan to study methods of imputing missing data for models which combine parameter smoothing with independence structures; to characterize Markov equivalent models, needed for algorithms to learn structure and for alternative interpretations; to apply the graphical results concerning distortions to meta-analyses, that is to comparing evidence from distinct studies, all bearing on a broadly similar specific issue; and to expand the computer package ggm within the open statistical software system R.

**Reliability, Risk, Quality:** Simplifications were necessary in the team's development of a unified approach to mechanical reliability (as set out in our book manuscript, see Section 6). We will study the impact of the simplifications, and how they can be accommodated into our method. In which situations is linearization too simplistic? When can non-linearities be exploited to make designs more robust? How can suitably designed experiment be used for this? What are the consequences of treating modes errors as random variables? How can time dynamics be incorporated into our system? How can the basic concepts of exchangeability, statistical control, stationarity, and ergodicity be operationalized in an engineering context?

The next step will to be to produce courses and a text book for industry. Further challenges will be microelectronics reliability and software reliability. We will explore possibilities to create robustness with respect to both variation and uncertainty.

We will work on better ship routing, increasing ship reliability and modeling ocean climate. In financial risk management aggregation of dependent catastrophic risk will be one center of interest. A new research direction is mathematical understanding of "pairs trading" where hedge funds "bet" on the difference between two assets, and not on the assets themselves.

**Optimization and Modeling**: The team's research on radiation therapy for curing cancer; antenna optimization, and numerical optimal control will continue. We will hire a postdoc for work on charged particle beams in radiation oncology, with 50% financing from GMMC and 50% financing from the Research Center for Radiation Therapy, the Department of Medical Radiation Physics at Karolinska Institutet. We will involve other companies in further development of the decision support system developed in our antenna project with Ericsson .

Maintenance is necessary for the operation of virtually every enterprise. According to recent findings both in Sweden and in the US it is very seldom planned well. Mobley, 2004, www.uhfg.se, reports figures like excess costs of 100 billion dollars/year for the USA.

We have an ambitious long-term goal – to build a large interdisciplinary research group in maintenance optimization which spans the entire range from collaboration with many Swedish and foreign companies to basic research. GMMC is the right environment for building this. A beginning is two NFFP/Vinnova projects with Volvo Aero Corporation (VAC) which resulted in new schedules for VAC's aircraft engine maintenance [50] and a Swedish Energy Agency project on maintenance in electricity supply. We have joint Ph.D. students with the RCAM (Reliability Centered Asset Management) group at KTH.

Epilepsy is one of the most common neurological diseases and about 1% of the population suffers from it. Surgical therapy has become an important therapeutic alternative. Correct and anatomically precise localization of the epileptic focus is mandatory to decide if resection of brain tissue is possible. EEG is the most important non-invasive diagnosis tool used at epilepsy surgery centers. To find the brain sources is an "inverse" – and hence difficult – problem. The major problem is poor spatial accuracy, which is attributed to low resolution of earlier EEG systems and to the use of simplified spherical head models for solving the inverse problem. Presently available computational techniques are not yet part of the standard pre-surgical diagnostic setup.

In a new project we will develop software tools take full advantage of new high resolution multichannel EEG systems. The Department of Signals and Systems (S2) at Chalmers and the Department of Neurophysiology, the Sahlgrenska University Hospital will develop realistic head models, and GMMC will produce FEM solvers of the inverse problem. The concept of reciprocity, we believe, will result in large savings in computation time.

***Application for new funding*** We apply for funds to advertise "paired Ph.D. student projects", and postdoc and research associate positions (see "budgets" below) which will be jointly funded by GMMC and our partner centers.

*The CMR – GMMC collaboration: Understanding the human lipid metabolism.* The main goal of CMR is to clarify underlying mechanisms of the metabolic syndrome and to identify targets for pharmacological and surgical interventions in order to prevent and treat complications. Research ranges from experiments with mouse models, epidemiological studies and clinical trials. One CMR and the GMMC collaboration will be on the analysis of gene expression data from e.g. the Swedish Obese Subjects Study.

Another will be on vivo studies of "dyslipidaemia", i.e. abnormalities in the lipid metabolism, such as reasons for andimplications of high levels of "bad cholesterol". The relevant quantities are measured indirectly using experiments with stable isotopes. Mathematical modeling is essential for interpretation of the data [64]. Present models rely on modeling patients individually, but for a better understanding population data should be include into the models. We intend to develop a class of nonlinear mixed effects differential equation models adapted to the experimental situation. As we gain more detailed knowledge it be will possible to make more realistic mathematical models, both for the physiological system and for the experiment as a whole. We will implement these models in a toolbox for population kinetics which has a good trade-off between simplicity, user friendliness and calculation power, and which has considerable extra functionality over existing software.

The strength of the collaboration will be the ability to ask the clinically relevant questions and to pose the correct hypothesizes; to address the problems with novel experiments and state of the art technology; and to develop mathematical models and statistical methods which use of experimental results efficiently.

Astra-Zeneca is industrial partner in this research.

*The SuMo-GMMC collaboration: Statistical methods for microrheology: release of active substances in pharmaceuticals and taste in food.* We will model and simulate the basic mechanisms of diffusion in heterogeneous media such as delivery of active medical substances from tablet and delivery of taste substances from food. The diffusion coefficient of a probe particle moving in a surrounding medium is D=kT/f, where the frictional coefficient f is constant for a probe moving in a homogeneous medium but varies in heterogeneous media. Microrheology is concerned with the measurement of the local diffusion coefficient as a function of spatial position. A number of different measurement techniques are available [66] such as magnetic tweezers, atomic force microscopy, one- and two-particle tracking, diffusing wave spectroscopy and fluorescence recovery after photo-bleaching (FRAP). Statistical methods for FRAP techniques are currently being extended to cover heterogeneous media in a joint project supported by GMMC and SuMo. We will also develop statistical methods for other techniques of microrheology measurements such as one- and two-particle tracking. The object is to relate the microrheology to spatial statistical variations measured by microscopy techniques, for use in the pharmaceutical and food industry. SIK – the Swedish Institute for Food and Biotechnology and Unilever will participate in this research.

*The GSBC – GMMC collaboration: Yeast as a model for understanding fundamental life mechanisms, prediction of multiple cancer drug effects.* Using support from large grants from SSF, KAW, Chalmers Foundation, and the National Research School in Genomics and Bioinformatics, we have built a collaborative research culture which joins mathematics, computer science and statistics as tools for bioinformatics, genomics and systems biology. This process has been driven by senior researchers who have broadened their research directions and by Masters and Ph.D. programs. This development received new strength from the creation of GMMC.

GSBC includes CMR, Stefan Homann's University of Gothenburg research platform, and the new Chalmers systems biology effort spearheaded by a new recruitment from DTU, Jens Nielsen. GMMC aims to put major efforts into this center. A whole range of talented young scientists trained by us work in temporary research positions in Gothenburg, Sweden and abroad. Around 10 of these are hot candidates for positions at GSBC partners, and our environment is attractive also for researchers from abroad. To catch these opportunities for

advancing biological and industrial knowledge, we apply for our part of joint funding of postdoc and research associate positions

A common thread for much of this research is yeast. Yeast as a model organism has substantial technical advantages, and makes large scale genetic manipulation feasible. Yeast research is expected to give generic knowledge of fundamental life mechanisms which then can be translated to higher organisms, and in the end to humans, to give understanding of human responses to food and drugs. Yeast is also industrially important. Much is already known on the effects of individual genes on a genome wide scale. The next step – to understand the complex interactions in networks of genes is even more challenging, and probably also more important [67, 68]. We will work on quality control, experimental planning, and statistical interpretation of yeast experiments. New challenges come from very high throughput "combinatorial experiments". Part of our effort will be to collaboration on the very high indeed throughput experiments done by Charlie Boone's Toronto group.

A second research focus will be prediction of multiple cancer drug effects by reconstruction of biological pathways. The predictions will combine carefully chosen molecular phenotypic readouts with an explicit causal model of suitable complexity [23].

*The DNV, IFREMER, Department of Shipping and Marine Technology Chalmers – GMMC collaboration: managing risks of structural failures in marine operations.* Marine safety is an important concern for society. Problems are complex and require both advanced mathematical models and practical knowledge, and can only be solved through people with different backgrounds working together. The entire range from developing basic science to work on specific problems is needed. Besides the immediate benefits it is important to educate researchers for industry and university careers in this area. We will attack the following problems.

Safety at design stage: The challenge is "good" design criteria. The designed and built dimensions are in present standards reduced in safety estimation, to account for material deterioration, e.g. corrosion. The true deterioration can be much smaller than specified. We will estimate the conservatism of present rules, with the aim to be able to build lighter and therefore environmentally friendlier ships. Today one describes the extreme load by the value which has 30% probability of being exceeded during 20 years. Is this a good choice? Should the definition of the extreme level include the effects of still water and dynamic loading?

Safety of existing structures/vessels: We need to monitor the damage in "old" oil rigs and "old" ships that operate on new routes. E.g., it has become popular to convert single skin tankers to double skin tankers. Then, what is the remaining fatigue life given the changes in trade and structural configuration? Should the inspection intervals adapt to the observed fatigue damage, measured in numbers and sizes of detected cracks?

Safety of large vessels: We will to produce methods for estimating the long term distribution of the sea states that a vessel will encounter during its lifetime, including uncertainty due to possible ocean climate change. These will be combined with hydrodynamical and mechanical models of the stress distributions which is caused by these wave and wind loads, to estimate risks of structural failure. Ice loads in Arctic environments pose additional challenges.

Material resistance to fatigue in variable stress fields: We will work on statistical models for the damage accumulation process and on propagation models for multi-axial fatigue. A special interest is how ship life length depends on the time of the first major storm. It is tempting to prefer to encounter such a big storm in the first year of operation thinking that the repair costs will be met by the insurance, but this may in fact be quite a bad strategy.

Dealing with large amounts of data: Concerns over risks of breaking are often met by large measuring campaigns. For example, vehicles are equipped with electronics that measure

loads and which produce massive amounts of data. We will develop statistical methods for capturing what is essential for fatigue damage accumulation process from such data sets.

*The ITWM – GMMC collaboration: Dynamic fiber networks - a step towards "virtual paper making".* The core of papermaking is to form the paper web from cellulose fibers. Subsequent production and finishing steps, and the quality of the finished paper or board, crucially depends on the fiber structure. Simulations can provide deep insight into this. Most of today's models treat the pulp and the fiber web as a continuum and do not take microstructure into account. We plan to develop a dynamic fiber web model which keeps track of the microstructure during the entire production process, including deformation during pressing and drying.

The first part of the model will be stochastic simulation of the fiber network at a fixed point in time. This network will be characterized by local properties, obtained from microscopy, such as the distribution of angles between intersecting fibers and lengths of fibers. A MCMC algorithm will generate a 3-D fiber network with these properties. In a second step the segments and nodes obtained from the MCMC algorithm are discretized and used as input to a FEM solver which tracks the dynamic evolution of the fiber web. The fiber or segment is approximated as a beam and deformation is described by the Euler-Bernoulli beam equation. The segments are also allowed to break. The FEM models of the models in the fiber network will coupled in a variational formulation. We will develop stable and efficient solution algorithms for the resulting linearized system of equations.

*Tomographic image of a paper fiber web*

The results from this research will also be applied to mass transport in porous materials. Industrial applications include diapers and hygiene tissues, where fluids are transported through a fiber network to which superabsorbent polymers are added. The rapid kinetics of fluid uptake at the superabsorbent and the subsequent swelling and formation of a hydrogel is vital for the function of the hygiene products.

Albany International, EKA Chemicals, Stora Enso and Tetra Pak will be industrial partners in this project.

*A new CIAM – SFI2 – GMMC collaboration: Managing contagion of economic risk.* Recent advances in basic theory and industry practice have revolutionized how economic risks are measured, evaluated, hedged and managed. Recent financial regulation mechanisms, such as Basel II and Solvency II, are largely mathematically based. Mathematics continues to be central to the insurance industry, but its scope there has grown from measurement of insurance risk to include the income and credit sides of companies.

A big challenge right now is risk contagion; that economic problems can spread like a wildfire from one company to the next, and from one part of the economy to another. These scenarios are rare but damaging to the economic stability. To limit the damage regulatory authorities require companies to hold capital to cover potential losses. There is a heated debate on appropriate rules and methods to determine the size of the regulatory capital. Accurate modeling and fast computational techniques are central for resolving these issues. We want to build a new academy-industry cooperation aimed at the following:

- Regulators may require a company to hold a total buffer capital which is the sum of its units' buffer capitals minus diversification effects. We will develop accurate methods for estimating diversification effects. This is the other side of risk contagion.

- We will develop methods to estimate catastrophic risks of simultaneous occurrence of rare events, such as a winter windstorm causing electricity failure and large-scale freezing of water pipes and preventing repair, leading to very costly water damage to buildings.
- Computation of risk measures and option prices is challenging, and seemingly simple evaluations may incur a large computational cost. We will use dynamic importance sampling for fast evaluations in situations where risks posed by rare events dominate.
- An overall goal will be full Asset-liability Modeling (ALM). This is the art and science of taking acceptable risks to achieve total asset returns which meet cash-flow liabilities.

Researchers from KTH (Djehiche, Hult, Lindskog) will be attached to FCC as scientific advisors. The Second National Swedish Insurance Fund – AP2, the Swedish Insurance Federation and Weavering Capital will be initial industrial partners.

*The new Social Sciences – GMMC collaboration: using mathematics for understanding and resolving social dilemmas.* We plan to follow up the GMMC workshop "Samhälle och sociala dilemman: spelteoretisk och annan matematisk modellering" which was organized by Häggström with a study of problems concerning spread of corruption, "tragedy of the commons"-like situations and inter-generational allocation of resources. The latter typically translates into a discount rate representing how important our own welfare is considered to be compared to our grandchildren's. Problems such as these are crucial to a number of pressing issues including how to deal with global warming, and there is scope for mathematical and game-theoretic contributions to the task of solving them.

***The Applied Mathematics Research Institute:*** The importance for mathematics of meetingplaces like the German Mathematisches Forschungsinstitut Oberwohlfach – the CERN of mathematics – of institute Mittag-Leffler in Stockholm, or of the Newton Institute in Cambridge cannot be overestimated. We want to create a similar institute for applied mathematics. It will be a place to which industry researchers, researchers from other parts of science, and mathematicians, from all around the worls, travel to participate in half year long thematic programs. Proposals for such programs would be solicited from all of Sweden. An further activity will be a "Research in Pairs"-program. In this program a mathematician or statistican will team up with a researcher from industry or science to work on some important problem. The institute will also host "Special Interest Group" meetings: weeklong programs where industries present pressing problems to a group of mathematicians, to form a nucleus for later long-tem research collaborations. A steering committee from Industry, Science and Mathematics will evaluate proposals for center activities and make decisions on strategy.

The center will start with its first two programs in 2010. Possible themes are "Virtual Paper Making", "Asset-Liability Modelling", "Differential Equation Modelling of Biological Systems", "Moving Drug Development from Experiments on Animals and Humans to the Computer", and "Marine Safety" – further proposals will be solicited.

***Budgets*** In the budget for the *already available* funding for 2009 and 2010, the first post is for partial funding of three research associates (forskarassistenter). By using stipends to the extent possible, the budget will also cover costs for 4-6 postdocs. The main part of the funding for the graduate student comes from partners in the SEAMOCS cooperation. GMMC work involves many more graduate students, but these are financed from other sources. The post "Senior scientists" is for the perhaps most scarce recourse of all, time for applied projects for Chalmers researchers and for strategic research for FCC engineers.

In the 2008 GMMC budget, 25 % goes to the Biomathematics team 45 % to the Risk, Reliability, Quality team, and 15% to the Optimization and modeling team. The main part of

the remaining 25% is for workshops, guests, and travel. These proportions were substantially different in 2006 and 2007, and will change in 2009 also, in response to available opportunities, needs, and successes.

For *step two* in our application for new funding we ask for 3-4 research associates and 4-5 graduate students with joint appointments in our partner centers, and for 6-8 postdocs, most of them shared with other centers. The budget also includes smaller amounts for workshops, research time for senior scientists, travel, and leadership.

The full costs for *step three*, the Applied Mathematics Research Institute will be about 16 MSEK per year. Half of this will come from other funding agencies and from industry. Chalmers will help with initial housing of the center. The budget covers visits by 40-50 researchers, equipment and secretarial costs.

***Budget, available funding (KSEK)***

| *Specification* | 2009 | 2010 |
|---|---|---|
| Research associates | 800 | 900 |
| Postdocs | 775 | 725 |
| Workshops guests | 250 | 250 |
| Graduate student | 100 | 100 |
| Senior scientists | 1,850 | 1,850 |
| Leadership, travel | 525 | 525 |
| *Sum of direct costs* | 4,300 | 4,300 |
| *Inclusive overhead* | 5,800 | 5,800 |

***Budget, application for new funding (KSEK)***

| *Specification* | 2009 | 2010 | 2011 | 2012 | 2013 |
|---|---|---|---|---|---|
| Research associates | 1,900 | 1,950 | 2,000 | 2,050 | 0 |
| postdocs | 2,000 | 2,000 | 200 | | |
| Workshops, guests | 200 | 200 | | | |
| Graduate students | 1,900 | 1,700 | 1,000 | 800 | 300 |
| Senior scientists | 300 | 300 | | | |
| Leadership, travel | 0 | 0 | 150 | 150 | |
| *Sum of direct costs* | 6,300 | 6,150 | 3,350 | 3,000 | 300 |
| *Inclusive overhead* | 8,200 | 8,050 | 4,450 | 4,000 | 400 |
| Research institute | 0 | 8,000 | 8,000 | 8,000 | 8,000 |
| *total* | 8,200 | 16,050 | 12,4500 | 12,000 | 8,400 |

***External references.*** *References* [1] *to* [63] *are listed in Enclosure 2.*


[64] M. Adiels, S.O. Olofsson, M.R. Taskinen, and J. Borén, *Overproduction of very low-density lipoproteins is the hallmark of the dyslipidemia in the metabolic syndrome.* Arterioscler. Thromb. Vasc. Biol.**28** (2008), 1225-1236.

[65] F. Ballani, D. Daley, and D. Stoyan, *Modelling the microstructure of concrete with spherical grains.* Comp. Materials Sci. **35** (2006), 399-407.

[66] M.L. Gardel, M..T Valentine and D.A. Weitz Microrheology. In Microscale Diagnostic Techniques K Breuer (Ed.) (2005) Springer Verlag. http://www.seas.harvard.edu/projects/weitzlab/

[67] S. Homann, *The Yeast Systems Biology Network: mating communities.* Curr. Opin. Biotechnol. **16** (2005), 356-60.

[68] D. Petranovic and J. Nielsen, *Can yeast systems biology contribute to the understanding of human disease?* Trends Biotechnol. **16** (2008) Sep 16. [Epublished ahead of print]

[69] P. Pötschke, H. Brunig, A. Janke, D. Fischer, and D. Jehnichen, D. Orientation of multiwalled carbon nanotubes in composites with polycarbonate by melt spinning. Polymers **46** (2005), 10355-10363.

**Enclosure 1. GMMC members**

***Coapplicants who still are active in GMMC***

Marina Axelson-Fisk, Senior Researcher, the Swedish Research Council
Michael Patriksson, Professor, Mathematics
Bo Bergman, Professor, Quality Science
Olle Häggström, Professor, Mathematical Statistics
Peter Jagers, Professor, Mathematical Statistics
Stig Larsson, Professor, Mathematics
Uno Nävert, Director FCC
Holger Rootzén, Professor, Mathematical Statistics
Aila Särkkä, Docent, Mathematical Statistics
Bernt Wennberg, Professor, Mathematics
Nanny Wermuth, Professor, Mathematical Statistics

***GMMC associated researchers***

Of the associated researchers, de Maré and Rudemo are scientific advisors at FCC, de Maré is leader of the GMMC reliability effort, Nerman and Rudemo are together with Wennberg coleaders of the biomathematics team. Rychlik leads of our work in marine safety and climate, and was recruited to Gothenburg with partial support from GMMC. All three have had support from GMMC, directly, for postdocs, graduate students, workshops. Asadzadeh's work on x-ray treatment has been partially funded by GMMC, and is an important component of our radiation therapy research.

Integration of Chalmers and FCC work is a main aim of GMMC. Uno Nävert, director of FCC is a coapplicant. The FCC researchers below are those who have worked on GMMC projects and have received funding from GMMC.

Joachim Almquist, FCC
Björn Andersson, FCC
Mohammad Asadzadeh, Docent, Mathematics
Jacques de Maré, Professor, Mathematical Statistics
Fredrik Edelvik, Docent, FCC
Jonas Hagmar, FCC
Stefan Jacobsson, FCC
Mats Jirstrand, Docent, FCC
Per Johannesson, Ph.D., FCC
Joachim Johansson, Ph.D., FCC, now at Swiss Re, Zurich
Mats Kvarnström, Ph.D., FCC
Sara Lorén, Ph.D., FCC
Olle Nerman, Professor, Mathematical Statistics
Mats Rudemo, Professor, Mathematical Statistics

Igor Rychlik, Professor, Mathematical Statistics
Henning Schmidt, now at University of Rostock
Ann-Brith Strömberg, Docent, FCC, now at Mathematical Sciences, Chalmers
Mikael Sunnåker, FCC
Thomas Svensson, Ph.D., FCC, now Swedish Testing and Research Institute, still GMMC member

### *Research associates (forskarassistenter) and postdocs*

Frida Abel, postdoc
Milena Anguelova, Ph.D. 2007, postdoc, tenure track to research associate
Martin Arvidsson, research associate now at Effort AB
Anastassia Baxevani, research associate
Larisa Beilina, research associate
Gunnar Cedersund, postdoc
Peter Gennemark, postdoc
Jochen Hardt, postdoc, now at University of Mainz
Jenny Jonasson, research associate
Nadia Lalam, postdoc, now at AXA Insurance, Paris
Claudia Lautensack, postdoc, now at ITWM, Kaiserslautern
Sofia Åberg, postdoc, now at Awapatent

### *Ph.D. students*

Erik Brodin, Ph.D. 2007, now at Merill Lynch, London
Christoffer Cromvik, Licentiate 2006, Ph.D. student
Thomas Galtier
Gwenaëlle Genet, Ph.D. 2006, now at the Volvo-owned Renault Trucks, Lyon
Azadeh Fazl, Volvo 3P industrial Ph.D. student
Oscar Hammar
Torben Hasenkamp
Alexander Herbertsson, Ph.D. 2007, now at the University of Gothenburg Business School
Alexandra Jauhiainen, licentiate 2007, Ph.D. student
Magnus Karlsson, Ph.D. 2007, now at Volvo trucks
Karin Kraft, licentiate 2008, Ph.D. student
Jan Lennartsson
Carl Lindberg, Ph.D. 2005, now at Weavering Capital, Gothenburg, still active in GMMC
Peter Lindroth
Åke Lönnkvist, Volvo Car industrial Ph.D. student
Wengang Mao
Viktor Olsbo
Anna Rudvik
Fredrik Saeredpahra, Licentiate 2007
Janeli Sarv
Anders Sjögren, Ph.D. 2007, now at TIBCO
Erik Svensson, Ph.D. 2006
Johan Svensson, Ph.D. 2007, now at Department of Statistics, University of Umeå
Karin Thörnblad
Adam Wojciechowski

Dimitrii Zholud
Magnus Åstrand, Ph.D. 2007, now at Astra Zeneca

These are the graduate students of the GMMC researchers who have worked on GMMC projects. Only Åstrand, Hasenkamp, and Mao have received salary support.

**Enclosure 2. Publications 2006 – Sept 2008**

A complete list of GMMC publications is given at http://www.chalmers.se/math/EN/research/gmmc/publications. It contains 218 items, including both publications which acknowledge SSF/GMMC support and publications which do not. In the startup period, discipline wasn't perfect, and some authors forgot to acknowledge when they in fact should have done so. The list of invited talks by GMMC members http://www.chalmers.se/math/EN/research/gmmc/talks lists more than 40 talks. In addition to 50 papers we also list the progam packages which go with some of the papers.

***Refereed and published or accepted articles (27 of 40)***


[1] S. Åberg, K. Podgórski, and I. Rychlik, *Fatigue damage assessment for a spectral model of non-Gaussian random loads*, Probab. Eng. Mech. (2008), to appear.

[2] S. Åberg and I. Rychlik, *Doppler-shift approximations of encountered wave statistics*, Ocean Eng. **34** (2007), 2300–2310.

[3] M. Anguelova, G. Cedersund, M. Johansson, C.-J. Franzén, and B. Wennberg, C*onservation laws and unidentifiability of rate expressions in biochemical models*, IET Systems Biology **1** (2007), no. 4, 230–237.

[4] M. Anguelova and B. Wennberg, *State elimination and identifiability of the delay parameter for nonlinear time-delay systems*, Automatica **44** (2008), no. 5, 1373–1378.

[5] M. Åstrand, P. Mostad, and M. Rudemo, *Improved covariance matrix estimators*

*for weighted analysis of microarray data*, J. Computational Biology **14** (2007), no. 10, 1353–1367.

[6] _____, *Empirical Bayes models for multiple probe type microarrays at the probe level*, BMC Bioinformatics **9** (2008), article 156.

[7] A. Baxevani, S. Caires, and I. Rychlik, *Spatio-temporal statistical modeling of significant wave heigth*, Environmetrics (2008), to appear.

[8] A. Baxevani and I. Rychlik, *Fatigue life prediction for a vessel sailing the North Atlantic route*, Probab. Eng. Mech. **22** (2007), 159–169.

[9] A. Bengtsson, K. Bogsjö, and I. Rychlik, *Uncertainty of estimated rainflow damage for random loads*, Marine Structures (2008), 1–19, to appear.

[10] A. Bengtsson and I. Rychlik, *Uncertainty in fatigue life prediction of structures subject to Gaussian loads*, Probab. Eng. Mech. (2008), to appear.

[11] B. Bergman, *Conceptualistic pragmatism: A framework for Bayesian analysis?*, IIE Transactions **41** (2009), no. 1, to appear.

[12] A.-L. Fougeres, J. Nolan, and H. Rootzén, *Mixture models for extremes*, Scand J. Statist (2008), to appear.

[13] L. Gunnarsson, A. Jauhiainen, E. Kristiansson, O. Nerman, and D. G. J. Larsson, *Evolutionary conservation of human drug targets in organisms used for environmental risk assessments*, Environmental Science and Technology **42** (2008), 5807–5813.

[14] L. Gunnarsson, E. Kristiansson, L. Förlin, O. Nerman, and D. G. J. Larsson, *Sensitive and robust gene expression changes in fish exposed to estrogen – a microarray approach*, BMC Genomics **8** (2007), no. 149.

[15] A. Herbertsson, *Pricing synthetic CDO tranches in a model with default contagion using the matrix-analytic approach*, The Journal of Credit Risk (2008), to appear.

[16] A. Herbertsson and H. Rootzén, *Pricing k-th-to-default swaps under default contagion: the matrix-analythic method*, J. Computational Finance **12** (2008), no. 1, 1–30, to appear.

[17] P. Jagers, F. C. Klebaner, and S. Sagitov, *On the path to extinction*, Proc. Nat. Acad. Sci. **104** (2007), 6107–6111.

[18] J. Jonasson, N. Lorén, P. Olofsson, M. Nydén, and M. Rudemo, *A pixelbased likelihood framework for analysis of fluorescence recovery after photobleaching data*, J. Microsc. (2008), in press.

[19] M. Kvarnström and C. Glasbey, *Estimation of centers and radial intensity profiles of spherical nano-particles in digital microscopy*, Biom. J. **49** (2007), 300–311.

[20] C. Lindberg, *The estimation of a stochastic volatility model based on the number of trades*, Appl. Stoch. Models Bus. Ind., to appear.

[21] _____, *Estimating expected stock returns and Markowitz' problem in continuous time*, Bernoulli (2008), to appear.

[22] G. M. Marchetti and N. Wermuth, *Matrix representations and independencies in directed acyclic graphs*, Annals of Statistics **46** (2008), to appear.

[23] S. Nelander, W.Wang, B. Nilsson, Q.-B. She, C. Pratilas, N. Rosen, P. Gennemark, and C. Sander, *Models from experiments: combinatorial drug perturbations of cancer cells*, Molecular Systems Biology **4** (2008), article 216.

[24] R. Nisslert, M. Kvarnström, N. Lorén, M. Nydén, and M. Rudemo, *Identification of the three-dimensional gel microstructure from transmission electron micrographs*, J. Microsc. **225** (2007), 10–21.

[25] V. Olsbo, *On the correlation between the volumes of the typical Poisson-Voronoi cell and the typical Stienen sphere*, Adv. in Appl. Probab. **39** (2007), no. 4, 883–892.

[26] A. Särkkä and E. Renshaw, *The analysis of marked point patterns evolving through space and time*, Comput. Statist. Data Anal. **51** (2006), 1698–1718.

[27] N. Wermuth, M. Wiedenbeck, and D. R. Cox, *Partial inversion for linear systems and partial closure of independence graphs*, BIT, Numerical Mathematics **46** (2006), 883–901.

***Refereed conference contributions (5 of 7)***

[28] M. Anguelova and B. Wennberg, *Identifiability of the time-lag parameter in delay systems with applications to systems biology*, Proceedings of FOSBE 2007 (Foundation of Systems Biology in Engineering) (Stuttgart, Germany), 9–13 September 2007.

[29] _____, *State elimination and identifiability of delay parameters for nonlinear systems with multiple time-delays*, Proceedings of IFACWorkshop on Time Delay Systems – TDS'07 (Nantes, France), 17–19 September 2007.

[30] S. Jakobsson, F. Edelvik, and B. Andersson, *Multiobjective optimization in computational electromagnetics*, EMB07 (Gothenburg, Sweden), October 2007, pp. 99–104.

[31] K. Kraft, S. Larsson, and M. Lidberg, *Using an adaptive FEM to determine the optimal control of a vehicle during a collision avoidance manoeuvre*, Proceedings of the 48th Scandinavian Conference on Simulation and Modeling (SIMS 2007) (D. F. P. Bunus and C.

Führer, eds.), Linköping University Electronic Press, 2007, available online at http://www.ep.liu.se/ecp/027/ (accessed September 26, 2008).

[32] C. Lautensack, K. Schladitz, and A. Särkkä, *Modeling the microstructure of sintered copper*, Proceedings of the Stereology, Spatial Statistics and Stochastic Geometry 6th International Conference (Prague, Czech Republic), 26–29 June 2006.

***Submitted manuscripts (14 of 32)***

[33] T. Almgren, N. Andréasson, D. Anevski, M. Patriksson, A.-B. Strömberg, and J. Svensson, *Optimization of opportunistic replacement activities: A case study in the aircraft industry*, Department of Mathematical Sciences, Chalmers University of Technology and University of Gothenburg, SE-412 96 Gothenburg, Sweden, submitted to European J. Oper. Res., 2007.

[34] E. Brodin and H. Rootzén, *Univariate and bivariate GPD methods for predicting extreme wind storm losses*, submitted, 2008.

[35] C. Cromvik and M. Patriksson, *On the robustness of global optimal solutions and stationary solutions to stochastic mathematical programs with equilibrium constraints*, submitted, 2008.

[36] A. Herbertsson, *Modelling default contagion using multivariate phase-type distribution*, submitted.

[37] S. Jakobsson, M. Saif-Ul-Hasnain, R. Rundqvist, F. Edelvik, B. Andersson, M. Patriksson, M. Ljungqvist, D. Lortet, and K.Wallesten, *Combustion engine optimization: A multiobjective approach*, Department of Mathematical Sciences, Chalmers University of Technology and University of Gothenburg, SE-412 96 Gothenburg, Sweden, submitted to Optim. Eng., 2008.

[38] S. Jakobsson, J. Rudholm, M. Patriksson, and A. Wojciechowski, *A method for simulation based optimization using radial basis functions*, submitted to Optim. Eng., 2008.

[39] K. Kraft and S. Larsson, *The dual weighted residuals approach to optimal control of ordinary differential equations*, Department of Mathematical Sciences, Chalmers University of Technology and University of Gothenburg, preprint 2008:2, submitted to SIAM J. Numer. Anal., 2008.

[40] M. Kvarnström, A. Westergård, N. Lorén, and M. Nydén, *An adaptive time stepping algorithm for Brownian dynamics simulations*, submitted, 2008.

[41] _____, *Brownian dynamics simulations in hydrogels using an adaptive time stepping algorithm*, submitted, 2008.

[42] C. Lautensack, A. Särkkä, J. Freitag, and K. Schladitz, *Anisotropy analysis of pressed point processes*, submitted.

[43] V. Olsbo and L.Waller, *Development and evaluation of spatial point process models of epidermal nerve fibres*, submitted, 2008.

[44] L. A. Waller, A. Särkkä, V. Olsbo, I. G. Panoutsopoulou, W. R. Kennedy, and G. Wendelschafer-Crabb, *Second-order spatial analysis of epidermal nerve fibers*, submitted, 2008.

[45] N. Wermuth, *Probability distributions with summary graph structure*, submitted to the Annals of Statistics, 2008.

[46] M. Wiedenbeck and N. Wermuth, *Changing sets of parameters by partial mappings*, Statistica Sinica (2008), accepted up to minor revison.

***Working papers***

[47] J. Hardt and N. Wermuth, *Multiple imputation of missing data: Results from a simulation study on a binary response*, in preparation, 2008.

[48] D. Zholud, O. Nerman, H. Rootzén, and A. Blomberg, *Positional effects in biological experiments*.

***Theses***

[49] K. Kraft, *Adaptive finite element methods for optimal control problems*, thesis for the degree of licentiate of engineering, Department of Mathematical Sciences, Chalmers University of Technology and University of Gothenburg, preprint 2008:1, 2008.

[50] J. Svensson, *Assessment of residual life for opportunistic maintenance*, Ph.D. thesis, Department of Mathematical Sciences, Chalmers University of Technology and University of Gothenburg, 2007.

***Computer software***

[51] M. Anguelova, G. Cedersund, C.-J. Franzén, M. Johansson, and B. Wennberg, *Mathematica code for identifiability analysis in [3]*, 2007, available online at http://www.math.chalmers.se/~wennberg/Code/ symBer_v2.zip .

[52] CellStat, Software demonstrator in Matlab with a graphical user interface for automated recognition and subsequent quantification of protein expressions in yeast cells. M. Kvarnström, FCC, is a main contributor.

[53] F. Edelvik, COSMO – A decision support system that integrates multiple criteria optimization and simulation.

[54] J. Jonasson, N. Lorén, P. Olofsson, M. Nydén, and M. Rudemo, *MATLAB software for estimating the diffusion coefficient in [18]*, 2008.

[55] K. Kraft, *Lin-HADOC*, an h-adaptive finite element solver for quadraticlinear optimal control problems.

[56] G. M. Marchetti and M. Drton, *ggm – Graphical Gaussian Models*, 2006, R-package implementing some first algorithms connected to the summary graph, compare G. M. Marchetti, *Independencies induced from a graphical Markov model after marginalization and conditioning: the R package ggm*, Journal of Statistical Software **15** (2006), no. 6. Available online at http://cran.r-project.org/web/packages/ggm/ .

[57] *RoPox*, 2007, Excel plug-in for computing optimal portfolio weights and judging portfolio stability, http://www.fcc.chalmers.se/risk/products.

[58] *SimIns*, 2007, modeling tool for Asset Liability Management, http://www.fcc.chalmers.se/risk/products.

[59] M. Sunnåker and M. Jirstrand, *NLMEtools – a Matlab toolbox for nonlinear mixed effects modeling using stochastic differential equations*, 2008.

[60] *Systems biology toolbox for Matlab*, available online at http://www.sbtoolbox.org/ .

[61] WAFO – a Matlab toolbox for the analysis of random waves and loads, 2008, available online at http://www.maths.lth.se/matstat/wafo/ . GMMC supports preparation of the new version of the WAFO-manual by financing work of Pär Johannesson, FCC, I. Rychlik is a main contributor.

[62] M. Åstrand, *wame.em*, 2007, the R-package for the methods developed in [5], available online at http://www.math.chalmers.se/~astrandm/wame_em/ .

[63] _____, *plw*, 2008, an R implementation of Probe level Locally moderated Weighted median-t (PLW) and Locally Moderated Weightedt (LMW), from [5], available online at http://www.math.chalmers.se/~astrandm/plw/ and at http://bioconductor.org/packages/release/bioc/html/plw.html .

**Enclosure 3. Grants 2006-2008**

This enclosure lists grants larger than 250.000 Swedish crowns given to GMMC members. In the summary table below we only include the part of the grant which corresponds to the years 2006-2008. See the following pages for the full list.

***Sum of grants to GMMC members 2006-2008 (Million Swedish crowns)***

| *Type of grant* | *Given by* | *Amount* |
|---|---|---|
| Industry projects | Swedish and foreign companies | 30.0 |
| Individual grants | Swedish Research Council | 13.0 |
| Individual grants | Other financers | 11.1 |
| Quality Improvement in Healthcare | Vinnvård | 4.5 |
| The Gothenburg Stochastic Centre | Swedish Research Council: Strong Research Environment & frame grant | 19.1 |
| GMMC | Swedish Foundation for Strategic Research, Chalmers, University of Gothenburg | 13.2 |
| VINN Excellence Center SuMo | Vinnova | 0.2 |
| EU grants | EU | 4.2 (+ 0.65 in negotiation) |
| Other | See list | 21.7 |
| *Sum* | | 117.2 |

**Enclosure 4. Plans for 2010 –**

Two of the four GMMC partners belong to the department of Mathematical Sciences at Chalmers and University of Gothenburg. The department has during the last decade transformed from a traditional theoretical mathematics/statistics department to an internationally recognized hub not just in mathematics and mathematical statistics, but in several applied quantitative research fields in technology and life sciences. This development will be further boosted by the start this year of a new undergraduate Technical Mathematics program at Chalmers. Strategic recruitment of senior applied mathematicians and statisticians, retraining of young theoretically trained researchers towards applied areas, and close collaborations on all academic levels with FCC, industrial partners, and key centers in the Gothenburg academic environment will be tools for continuing the metamorphosis.

Support of this development is a central part of the strategic plan for Mathematical Sciences. The plan also stresses the importance for the department of the larger and more longterm research made possible by its research centers. Collaboration with industry is also at the center of the interests of GMMC's third component, Quality Science at Chalmers. The purpose of the fourth component, FCC, is collaboration between industry and mathematics and science. GMMC's mother organizations will work hard to make it possible to use the GMMC way of working. They will support new applications for funding and will put substantial resource of their own into our work.

Our vision for the future is to be part of bringing all the resources inherent in mathematics to bear on Swedish (and foreign) industry and science. Precisely how we will do this 2010 and later will depend on future funding opportunities – it may be through many applications for individual grants, or by applying for center grants if available then - and what the exciting and important industrial and scientific problems are at that time. A vision is to grow from GMMC, the Gothenburg Mathematical Modeling Centre, to GMM*C* the Gothenburg Mathematical Modeling *Cluster* which will give support to all Gothenburg cooperation mathematics – industry – society

The foundation built through GMMC's contacts, partnership with industry, and research, - and the importance of mathematics for modern industry make us confident that the GMMC way of working will live on long after 2010. This may be as GMM*C* or perhaps under a quite different guise determined by funding opportunities and decisions, and on how interests and research directions change as we recruit new researchers.

## Enclosure 5. Communication strategy

***This is an official document, hence written in Swedish***

Fastställt vid styrelsemöte 061129

**Publikationer:**
1. Resultat av GMMC:s forskning ska publiseras internationellt, i referentgranskade vetenskapliga tidskrifter, i böcker och som konferensbidrag. Att finansiellt stöd som getts av SSF-GMMC ska noteras i publikationerna när så är görligt.
2. GMMC:s, SSF:s, Chalmers och GU:s logotyper ska normalt finnas med vid vetenskapliga och andra presentationer.

**Konferenser och seminarier:**
3. GMMC ska delta aktivt i anordnandet av i genomsnitt 1–2 workshops per år (ansvarig: Holger Rootzén).
4. GMMC ska delta aktivt i organiserandet av internationella konferenser inom Centrets arbetsområde.
5. Forskare inom GMMC ska genom populärvetenskapliga aktiviteter medverka i spridandet av information om Centrets verksamhet, t.ex. genom Vetenskapsfestivalen och Universeums verksamhet.

**Utbildning:**
6. GMMC ska hålla kurser för industrin.
7. Resultat av GMMC:s forskningsverksamhet ska inkorporeras i grundutbildning och forskarutbildning vid Chalmers och GU i möjligaste mån, speciellt genom forskarnas egna utbildningsengagemang.

8. En gemensam struktur ska upprätthållas för genomförandet av examensarbeten inom Centrets verksamhet.

**Industri och samhälle:**
9. FCC:s industriella nätverk, kontakter och försäljningsansträngningar ska användas för att sprida kännedom om GMMC till industri och samhälle, bland annat genom aktivt deltagande vid industrimässor (ansvarig: Uno Nävert).

## Enclosure 6. Relations to Chalmers and University of Gothenburg

GMMC's relations with Chalmers and University of Gothenburg have been consistently good and smooth. We have felt a strong support from both universities. All promises of administrative, material and economic support have been fulfilled, and we in fact have received more financial support than promised.

**Enclosure 7. Comparison of results with goals**

Our application was for 12 MSEK/year. SSF granted us 4.4 MSEK/year, and we obtained additional funding of around 1.4 MSEK/year from Chalmers and University of Gothenburg, thus the present total funding which goes directly to GMMC for 2006-2010 is about 5.8 MSEK/year. Subsequently SSF and GMMC agreed on an adjusted set of goals (used below to measure progress against), and that the lower funding should be absorbed in two ways:

- The application plans for five teams were adjusted so that GMMC now only consists of three teams.
- Extensive use of cofinancing of activities with the Gothenburg Stochastic Centre and FCC.

The latter has lead to important synergies and allowed us to realize much more of the original GMMC plans than would otherwise have been possible. We also agreed on the following concrete three-year milestones.

- *One major company implements our reliability approach:* Volvo Aero has done this.

- *Give course(s) for Swedish industry to spread our ideas on reliability:* We have given 8 courses for industry.

- *Make substantial advances in the development of theory and methodology for designing and analyzing experiments where extreme values are the responses:* We have introduced a new class of models for such experiments [12]. Much more remains to be done.

- *Increase our cooperation with the Swedish insurance and banking industry:* We have produced two software packages, SimIns and RoPox for asset-liability management and portfolio optimization, respectively, and have worked with Länsförsäkringar, The Second National Swedish Insurance Fund – AP2, the Swedish Insurance Federation, and Weavering Capital. Our Ph.D.'s in the area now work at Swiss Re, Zurich; Weavering Capital, Gothenburg; Bank of America, London; and the Business School, University of Gothenburg.

- *Establish a successful seminar series on "Mathematical and statistical methods in biotechnology and medicine", with participants from both academia and industry:* We have had many such seminars.

- *Develop a good spatial model for signaling pathway:* Colleagues at Mathematical Sciences, Chalmers, (Heintz, Gebäck) who are not supported by GMMC have developed mathematical models for diffusion of proteins inside cells aimed at describing signaling pathways. The results concern numerical methods for systems of reaction diffusion equations, and models for subdiffusion, and indicate qualitatively different diffusion behavior of proteins than formerly expected. The model has been corroborated by Fluorescence Correlation Spectroscopy experiments.

- *Develop 3D gel structure models and software for industrial use in delivery of drugs from tablets in pharmacy and of taste substances in food industry:* In [24] a method has been developed for identifying and simulating gel structures from transmission electron

micrographs. For analysis of how probe molecules diffuse in gel networks a method for efficiently utilizing pixel-value information in fluorescence recovery after photobleaching experiments has been established, [18]. Software for the method is available in [60]. After a visit to Unilever in Vlardingen, Holland, the scientists there became so impressed by this method that they developed a MATLAB toolbox for our method, which considerably simplifies the use of it.

- *Develop tools for quality control and improved experimental designs for microarray Experiments:* A new method, WAME, for analysis, quality control and experimental design of microarray experiments has been developed and streamlined in a series of papers including [5], with an accompanying programme, [62]. In [6] with accompanying program [63] it is further refined, generalised and compared to 11 other methods for analysing Affymetrix-type microarrays. The comparison is performed by use spike-in experiments with known answers typically corresponding to dilution series with known amounts. The main method of [6], PLW, clearly outperfoms the other methods in four out of five available spike-in experiments. We expect PLW to become the preferred analysis method for Affymetrix-type microarrays, which is currently the industry-standard for microarray experiments.

- *Create a new biological objective function for use in Intensity Modulated Radio Therapy and obtain intitial results on new model using multiobjective optimization:* We have devised new biological objective functions that take into account both the probability of curing and the risks of future complications. Initial guesses on the values of the biological parameters, in particular dependence on the fractionation of the dose delivery, has been made. Further, other uncertain parameters are taken into account in a robust optimization model, whose properties have been investigated. Computer software for the optimization of two objectives has written [35]. More precise parameter estimates will be possible when data from ARTSCAN becomes available.

- *Start a research collaboration on antenna optimization modelling for prostate localization*: We did start this collaboration – as it turned out the low frequencies used in the positioning system made it impossible to obtain accurate localization with existing simulation software. Results from the project have been used in a GMMC project with Ericsson on optimization of Multiple-Input-Multiple-Output antennas for mobile phones.

- *Develop a new dedicated software for simulation based engine optimization, to the stage where Volvo takes over the main financial responsibility:* We have developed a decision support system based on multi-criteria optimization of "expensive" goal functions, such as those in engine optimization, where one simulation can take a day or more. The tool helps the design engineer to navigate efficiently between different Pareto-optimal solutions. Despite good results obtained on engine test cases, Volvo chose to continue with their in-house tools. However, instead the methods have been implemented in a computerized decision support system for antenna optimization, in a new project with Ericsson. Additionally, discussions with Saab Microwave on further development of the system are ongoing.

- *Initialise research collaborations within maintenance optimization with at least one Swedish nuclear power plant and the RCAM Group at KTH:* We have devised a general maintenance scheduling optimization model for the optimization of a working system, possibly with redundant subsystems, and taking into account uncertain component lives in a stochastic optimization model. The stochastic model has been implemented in the optimization modelling framework AMPL. Two Ph.D. students working at KTH, focusing on

nuclear and wind power production, respectively, are presently learning the model and will apply it to data from the Forsmark and Lillgrund power plants, respectively.

- *Publish at least ten papers per year in international journals:* We have published 40 papers with SSF/GMMC acknowledgement and submitted 32 which have not yet received a decision.

- *Organize at least four international workshops.* We have organized the following workshops:

1. Mathematical Aspects of Systems Biology, March 21-24, 2007
2. Stochastic approaches to Evolution, May 26-30, 2007
3. Spatio-Temporal Stochastic Models in Geophysical Sciences, September 26-28, 2007
4. Robust Multi-objective Design Optimization With Simulation, December 3-4, 2007
5. Spatio-temporal Stochastic Models with Environmental and Marine Applications, May 2008
6. Samhälle och sociala dilemman: spelteoretisk och annan matematisk modellering, May 22-23, 2008
7. The Sixth European Finite Element Fair, May 30-31, 2008
8. Statistical methods for longitudinal studies, July 29-August 2 2008
9. Pre conference tutorials for ICSB2008, August 27-28, 2008
10. Invited Symposium on radiobiologically based optimization for IMRT, September 13, 2008

Workshops 1, 2, 3, and 8 have been jointly funded with the Gothenburg Stochastic Centre, and 2 in addition received funding from the University of Gothenburg platform in Theoretical Biology. The workshops are of central importance for GMMC, as discussed in Section 2.

**GMMC**
Gothenburg Mathematical Modelling Centre
Department of Mathematical Sciences
Chalmers University of Technology and University of Gothenburg
SE-412 96 Göteborg
Sweden

www.chalmers.se/math/EN/research/gmmc