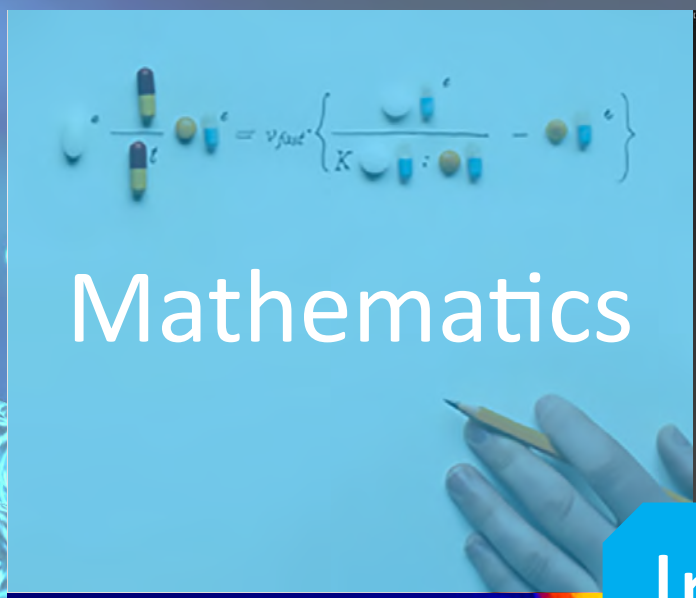
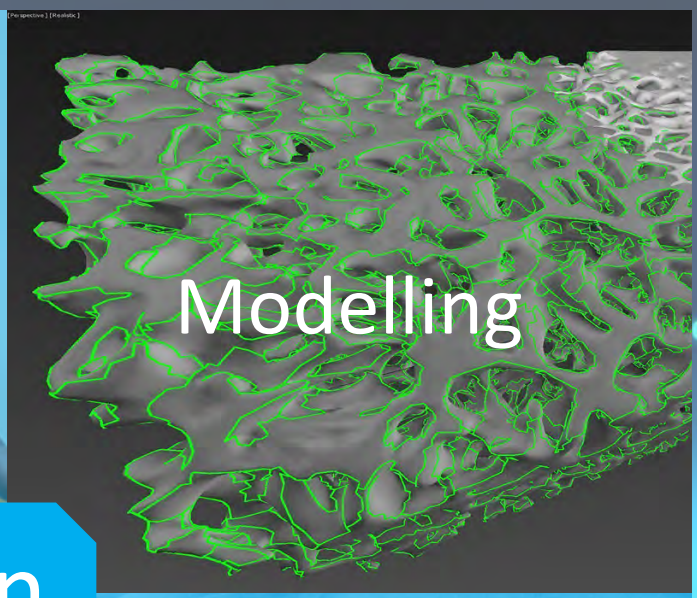
Book of Abstracts



Mathematics



Modelling

In

Imaging

Medicine

Student Chapter at TU Delft

SIAM Student Chapter Delft

Student Mathematical Modelling in Medicine day 2017

SIAM Student Chapter Delft

May 31, 2017

Sponsors:

doi:10.4121/uuid:da23e59e-0948-4ca6-bc27-c319d6af61e5

Program

The Student Mathematical Modelling in Medicine day takes place on May 31st, 2017 at Technische Universiteit Delft, Faculteit Elektrotechniek, Wiskunde en Informatica. We meet at **Van der Poelzaal; LB01.220**, Mekelweg 4, 2628 CD Delft, The Netherlands.

09:30 - 09:40		Welcoming
09:40 - 10:20	Alessandro Sbrizzi	Mathematical Modeling in Magnetic Resonance Imaging
10:20 - 10:45	Anna Kruseman	Model-based reconstruction methods
10:45 - 11:00		Coffee Break
11:00 - 11:25	Kirsten Koolstra	Modeling and Designing High Permittivity Pads for MRI (1)
11:25 - 11:50	Jeroen van Gemert	Modeling and Designing High Permittivity Pads for MRI (2)
		Chairman: Rob Remis
12:00 - 13:15		Lunch at Electron (HB01)
13:15 - 13:55	Liesbet Geris	Computational bone tissue engineering: in vitro, in vivo … in silico
13:55 - 14:20	Esmée Vendel	Towards a brain spatial drug distribution model
14:20 - 14:45	Jiao Chen	A model for cell migration in non-isotropic fibrin networks
14:45 - 15:00		Coffee Break
15:00 - 15:25	Lisanne Rens	Hybrid cellular Potts model explains cell response to substrate stiffness
15:25 - 15:50	Anja Rüten-Budde	The effect of surgical margins on disease progression in high-grade soft tissue sarcoma patients
16:50 - 16:15	Richard Beck	Direct T cell mediated killing of solid tumours is insufficient to explain tumour regression
		Chairman: Fred Vermolen
16:15 - 16:30		Closing remarks
16:30 - 18:00		Snacks & drinks at TU Delft

In the evening we will organize a BBQ. Everybody is welcome to join!

Foreword

The SIAM Student Chapter Delft is pleased to welcome you to the one-day workshop 2017. This one-day workshop is a yearly recurring event aimed at giving PhD candidates the opportunity to present their research and meet fellow PhD students working on similar topics.

In previous years this workshop day has been aimed at for example the mathematics behind Krylov methods (2015), and computational finance (2016).

This year, the one-day workshop will be on Mathematical Modelling in Medicine. The morning session is dedicated to imaging in medicine and the afternoon session is focused on modelling biological systems. In your hands, you have the book of abstracts containing the program of today, the abstracts of all the presentations, and room for notes at the end of the book.

One of the goals of this workshop day is to expand your horizon and show you how broad the subject of mathematics can be, even when applied to a singular subject such as medicine. Furthermore, we hope that you can be inspired by the work of your fellow researchers and maybe even find room for future collaborations in the field.

We hope you will enjoy this one-day workshop.

Kind regards,

Anne Markensteijn
President SIAM Student Chapter Delft

Mathematical Modeling in Magnetic Resonance Imaging

Alessandro Sbrizzi[*1]

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Magnetic Resonance Imaging (MRI) offers plenty of opportunities to apply mathematical techniques to realistic and socially relevant problems and is therefore increasingly attracting the attention of (applied) mathematicians. In this presentation, I will show how mathematical modeling is enabling the current development in the field of MRI and will sketch some possible future scenarios.

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Model-based reconstruction methods for MRI

Anna Kruseman[*1]

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When magnetic resonance imaging (MRI) was invented in the seventies, computer power was scarce. Nowadays computational costs are much lower. By employing model-based reconstruction techniques, we aim to shorten the scan duration, while maintaining image quality. Shorter scan times can greatly improve patient comfort as well as reduce hardware costs for the hospital.

In my research, I focus on reconstruction using a nonlinear Kalman-Filter method. The Kalman-Filter method explicitly models noise on the measurements, making it ideal for parameter estimation in highly perturbed situations. In fast scanning techniques undersampling of the data leads to large artifacts, which are treated as a pseudo-noise. The behaviour of the Kalman Filter in this case, however, seems different then when the noise is Gaussian.

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Modeling and Designing High Permittivity Pads for MRI

Jeroen van Gemert[*1] **and Kirsten Koolstra**[†2]

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A strong background field in MRI is beneficial in terms of the signal-to-noise ratio (SNR) of measured data. The increase in SNR allows for a higher spatial resolution in the scans. The frequency of the RF field that is required to obtain scans increases linearly with the background field strength. The wavelength in the body decreases for increasing frequency and therefore introduces inhomogeneities in the RF field. Consequently, the uniformity of the contrast in the images degrades. High permittivity materials can be used to correct for the non-uniformity in the RF field as they induce a secondary magnetic field when placed in an electric field. However, the dimensions, location, and constitution need to be determined carefully, currently involving many time-consuming simulations. This work aims for fast and accurate numerical simulations.

We show two methods to quickly solve for the electromagnetic fields due to an arbitrary dielectric pad. The Volume Integral Equation is illustrated first, which is fast as it exploits the FFT. The accuracy of this method is investigated by comparing simulations with an analytical solution of a double layered cylinder. Reduced order modeling is used as an alternative method to quickly solve the RF field. This latter method is subsequently used to minimize the following cost function

$$C(p) = \frac{\|B_1^+(p) - B_1^{(+;\text{desired})}\|_2^2}{\|B_1^{(+;\text{desired})}\|_2^2}, \tag{1}$$

where $B_1^{(+;\text{desired})}$ is the desired homogeneous RF field in a certain region of interest, and $B_1^+(p)$ is the modeled RF field as function of the dielectric pad. As illustration, we design a dielectric pad for cerebellum imaging at 7T in 30 seconds.

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Computational bone tissue engineering: in vitro, in vivo ... in silico

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One of the major challenges in tissue engineering and an essential step towards successful clinical applications is the translation of biological knowledge on complex cell and tissue behavior into predictive and robust engineering processes. Computational modelling can contribute to this, among others because it allows to study the biological complexity in a more quantitative way. Computational tools can help in quantifying and optimizing micro-environmental signals to which cells and tissues are exposed and in understanding and predicting the biological response under different conditions.

A wide variety of model systems has been presented in the context of tissue engineering ranging from mechanistic models (hypothesis-based) over gene network models to empirical models (data-driven), targeting processes at the intracellular over the cellular up to the tissue level. Each model system has its own benefits and limitations which delineate the context in which it can be used. Whereas mechanistic models are used as in silico tools to design new therapeutic strategies and experiments, empirical models are used to identify, in large data sets, those in vitro parameters (biological, biomaterial, environmental) that are critical for the in vivo outcome.

In this talk I will give an overview of various application of in silico regenerative medicine that were developed to answer questions from the experimental researchers and clinicians in our Tissue Engineering platform. Models of intracellular signaling, biomaterial design, bioprocess design and in vivo regeneration under challenging conditions will be discussed. I will end with a discussion of a number of challenges we are facing in the in silico medicine community as a whole as it pertains to establishing credibility of our models and technologies.

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Towards a brain spatial drug distribution model

Esmée Vendel[*1], **Vivi Rottschäfer**[1] **and Elizabeth de Lange**[2]

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A better understanding is needed of the complex processes that govern the concentration- time profile of a drug in the brain. So far, the studies on drug distribution into the brain have mostly focused on the transport of drugs through the blood-brain barrier (BBB), but not on drug transport and binding within the brain. To get a better insight into the distribution of drugs in the brain, we define a new spatial model for a 2D brain square tissue unit, consisting of brain extracellular fluid (ECF) with drug binding sites, and being surrounded by capillaries. We describe the change in the concentration of free and bound drug in the brain ECF. For this we take diffusion, ECF bulk flow and binding to specific as well as non-specific binding sites into account. Additionally, we consider how a drug enters and leaves the brain ECF by passing the BBB, which is located between the brain ECF and the capillaries.

We study the influence of parameter values for BBB permeability, ECF bulk flow, drug diffusion and drug binding kinetics, on the concentration-time profiles of free and bound drug. Moreover, we analyse the spatial brain distribution of the drug. This new model serves as a tool to understand the influence of the complex processes that govern the PK of a drug in the brain.

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A model for cell migration in non-isotropic fibrin networks with an application to pancreatic tumor islets

Jiao Chen[*1], **Daphne Weihs**[2] **and F.J.Vermolen**[1]

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Cell migration is crucially important for tumor growth, immune response as well as other biomedical processes. This work presents a cell-based model to describe T-lymphocytes migration in non- isotropic fibrin networks around the vicinity of the T-islet in pancreatic cancer. This migration is determined by the mechanical strain energy density as well as cytokines-driven chemotaxis. Cell displacement is modelled by solving a large system of ordinary stochastic differential equations where the stochastic parts result from random walk. The stochastic differential equations are solved by the use of the classical Euler-Maruyama method. In this work, the influence of anisotropic stromal extracellular matrix in pancreatic tumor islets on T-lymphocytes migration in different immune systems are investigated.

This model presents the first description of cancer development in the pancreatic cancer under the influence of orientation of the surrounding collagen. As we expected, stromal extracellular matrix impedes the immune response of T-cells through changing direction of their migration. Its obstruction effect increases with the increase of k value which is used to denote a measure for the amount that anisotropy contributed to T-lymphocytes migration. Moreover, the model predicts the unlimited proliferation of carcinoma cells if the immune system is weak, and a state of equilibrium where cancer cells are eliminated if the immune system is sufficiently strong.

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Hybrid cellular Potts model including focal adhesions as catch bond clusters explains cell response to substrate stiffness

Lisanne Rens[*1,2]

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[2]Mathematical Institute, Leiden University, Leiden, the Netherlands

Pattern formation and individual cell behavior in tissues with high concentrations of extracellular matrix (ECM) depends on mechanical ECM parameters, including stiffness. Cellular response to ECM stiffness include changes in cell shape: On soft matrices, cells are generally small and rounded, while on stiffer matrices cells assume spindle-like shapes, and on glass-like substrates cells generally spread out like pancakes. This behavior has been observed for many cell types, including fibroblasts and endothelial cells. Here we introduce a mathematical model to explain how matrix stiffness regulates cell shape. Translation of matrix stiffness to intercelullar signals is mediated trough transmembrane integrin molecules. Such integrins behave as catch bonds whose strength increases under tension. Focal adhesions, large assemblies of integrins that strongly bind the cell to the matrix, indeed grow larger on stiffer matrices. We extended a current hybrid cell-based continuum model (van Oers, Rens et al. PLoS Comp Biol 2014, Rens and Merks BJ 2017) to describe such molecular mechanics. This multiscale, hybrid model couples detailed descriptions of focal adhesions, based on a published ordinary-differential equation model (Novikova and Storm, Biophysical Journal 2013). The model includes 1) A finite-element model describes the ECM; 2) a cellular Potts model, to describe cell shape changes; 3) one set of ordinary-differential equations describing the growth and decay of individual focal adhesion. The simulation proceeds as follows. First, cells move and pull on the ECM. This leads to a slow build-up of tension on the FA, which changes the FA's size. The focal adhesions finally inhibit the cell's pseudopod retractions from the ECM.These minimal model assumptions reproduce the observed cell shape behavior on matrices of varying stiffness. On soft matrices, tension builds

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up slowly, such that the focal adhesions cannot grow and the cell cannot spread. On stiffer matrices, a symmetry breaking occurs in which random protrusions can generate enough matrix tension so that focal adhesions will grow. This further promotes tension generation and cell spreading in this direction, thus driving cell elongation. On rigid surfaces, focal adhesions will grow everywhere around the cell membrane, so that cells start to spread. Our model results increase our understanding of the molecular mechanism behind cell shape changes in response to matrix stiffness. Our model can be further extended to study the effect of cyclic matrix stretching on cell orientation or to study tissue patterning in response to matrix stiffness or different type of integrins.

The effect of surgical margins on disease progression in high-grade soft tissue sarcoma patients: through the eyes of a multi-state model

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While the treatment of high-grade soft-tissue sarcomas (STS) of the extremities has improved over the years, local recurrence (LR) and poor survival remain of great concern. Although several prognostic factors are recognized, the effect of surgical margins is still unclear. This study aims to investigate the effect of margins and LR, in the presence of individual baseline characteristics, on survival in a large population of high-grade STS of the extremities by using a multi-state analysis.

A retrospective multicenter analysis of prospectively collected data for 687 patients with high-grade STS of the extremities was performed. The effect of prognostic factors on overall survival was estimated with a Cox regression model with LR as a time-dependent covariate. Disease progression after surgery was investigated with a multi-state model. Patient-specific probabilities for different states of disease progression presented in stacked charts provide insight into the effect of treatment, given a set of baseline characteristics, margins and the occurrence of events after surgery.

Results based on the multi-state model showed that tumor size is associated with the occurrence of both LR and distant metastases. Resection margins only had a significant impact on LR. The multi-state model is used to obtain predictions at a certain time after surgery for a patient with a given set of risk factors at baseline and a given set of post-surgery events.

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Direct T cell mediated killing of solid tumours is insufficient to explain tumour regression

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Adoptive transfer of tumour infiltrating Lymphocytes (TILs) is an effective treatment for melanoma, and shows promise as a treatment for other forms of cancer. However, the number of TILs is often small relative to the number of tumour cells, and a relatively low in-vivo killing rate of 3 tumour cells per CTL per day has been reported. It is unclear to what extent regression is mediated directly via the lytic activity of T cells, versus indirect effects exerted by them on the tumour micro-environment. We have developed a simple Ordinary Differential Equation (ODE) model of tumour regression, parameterised with data taken from a murine model of a solid tumour. Our ODE model suggests that the reported slow in-vivo killing rate is insufficient by at least one order of magnitude to explain the observed tumour regression, suggesting that TILs have additional effects apart from killing activity through long-term interactions with tumour cells. To more accurately quantify the contribution of direct T cell lysis to tumour regression, we have developed a spatial agent-based model (ABM), to allow consideration of factors such as T cell migration and their scanning for targets. Results from the ABM support the ODE model prediction that additional factors apart from direct cytotoxic activity are needed to explain population-level tumour regression.

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http://sscdelft.github.io/

Notes

Notes

SIAM Student Chapter Delft
Workshop Day 2017

Mathematics in Medicine
From Imaging to Modelling

This workshop was held on the 31st of May 2017 in the "Van der Poelzaal" at the faculty of EEMCS, Delft University of Technology.

This book of abstracts contains contributions of:

Allessandro Sbrizzi, Anja Rüten-Budde, Anna Kruseman, Esmee Vendel, Jeroen van Gemert, Jiao Chen, Kirsten Koolstra, Liesbet Geris, Lisanne Rens, and Richard Beck