WORKSHOP ON COMPUTATIONAL MODELS IN BIOMEDICINE

DATE AND TIME: FEBRUARY 11 2015, 09:00 – 16:30

09:10-09:20	***Welcome and Introduction*** Prof. Dr. Are Magnus Bruaset, Section Director, Computing and Software, Simula
09:20-10:10	***Modeling noise & heterogeneity in biological systems*** Prof. Dr. Fabian Theis, Director of Institute of Computational Biology (ICB), Helmholtz Zentrum München, Professor at Technical University München
10:10-10:45	***Inference of signaling networks using a linear programming approach*** Dr. Bettina Knapp, Team Leader Computational Phenomics, Institute of Computational Biology, Helmholtz Zentrum München
10:45-11:00	**Coffee Break**
11:00-11:40	***Cardiac Modeling and the Centre for Cardiological Innovation*** Dr. Samuel Wall, Head of Cardiac Modeling Department, Simula
11:40-12:20	***New simulation technology driven by medical challenges: the Biomedical Computing Department @ Simula*** Dr. Marie E. Rognes, Head of Biomedical Department, Simula
12:20-13:15	**Lunch at IT Fornebu**
13:15-13:45	***Modeling the human atria: the action potential, calcium handling and electrophysiology from cell to organ*** Dr. Mary Maleckar, Director of Simula School of Research and Education
13:45-14:15	***Metamodeling of bi-ventricular structural abnormalities in the ARVC heart*** Dr. Kristin S. McLeod, Postdoctoral Fellow, Simula
14:15-14:45	***Insight into model mechanisms and more efficient model development and validation by multivariate metamodeling*** Dr. Kristin Tøndel, Research Scientist, Simula
14:45-15:00	**Coffee Break**
15:00-15:30	***'Patient-specific' blood flow simulations: They are all wrong, but are some of them useful?*** Dr. Kristian Valen-Sendstad, Postdoctoral Fellow, Simula
15:30-16:00	***FEniCS: algorithmic approaches to scientific computing at Simula*** Dr. Simon W. Funke, Postdoctoral Fellow, Simula
16:00-16:30	***Discussion & Closing Remarks***

SELECTED ABSTRACTS

Modeling noise & heterogeneity in biological systems (Fabian Theis, ICB)

Abstract:

Systems biology aims at the model-based interpretation of biological data. The statistical and/or dynamical models are abstractions of biological processes, validated with the measured data, and used to guide further experimentation. Current methodological challenges arise from low sample numbers, noisy measurements and biological variability.

In this talk, I will show how we can account for these challenges in the inference process on different scales using probabilistic and Bayesian modeling. First, I will focus on parameter estimation in chemical reaction kinetics, which we describe as a combination of ODEs and mixture modeling. I will then switch gears and review our large-scale approaches on genomic data sets and how we quantify heterogeneities on that level. Finally, I will give a brief overview over the Institute of Computational Biology and experimental partners at the Helmholtz Zentrum München.

Inference of signaling networks using a linear programming approach (Bettina Knapp, ICB)

Abstract:

Within the last years, improved high-throughput experimental technologies go along with the development of many network inference algorithms. The aim is the inference of the underlying signaling network to understand the biology on a systems wide level. Although many algorithms and models exist, many problems are yet to be solved, such as high computational complexity, robustness of the results, and flexibility of the methods to cover different types of data and different biological assumptions. Therefore, I present a fast and flexible algorithm based on a linear program to infer signaling networks from a combination of perturbation or non-perturbation and steady-state or time-series data.

Cardiac Modeling and the Centre for Cardiological Innovation (Samuel Wall, Simula)

Abstract:

In recent years, the field of computational cardiac modeling and simulation has matured in both scope and methodology such that it can contribute significantly to the present understanding of heart physiology and disease. The CaMo (Computational Cardiac Modeling) department at Simula is an integrated team of researchers working collaboratively with both experimentalists and clinicians to address current challenges in cardiology through basic research and industrially driven innovation projects.

A particular strength of the CaMo group is a diverse set of backgrounds and skill-sets, enabling research into numerical and computational methods to develop state-of-the-art heart simulation tools as well as the targeted application of these tools to gain mechanistic insight into diverse biophysical cardiac phenomena. Research in biophysical models of the heart spans a wide range of spatial and temporal scales, from investigation of detailed

subcellular calcium ion channel phenomena to organ-level analysis of the heart driven by clinical data. The CaMo group also works in the development of metamodeling.

A large effort is currently being made into data driven patient specific models through Simula's partnership in the Center for Cardiological Innovation SFI. This Center is a collaboration between research partners in cardiac simulation, industrial experts in cardiac imaging and treatment, and cardiologists at Oslo University Hospital. The aim of the Center for Cardiological Innovation (CCI) is to develop the next generation of ultrasound systems for cardiology and new tools for treating cardiac disease.

In this talk we provide a detailed overview of the activities of the CaMo Department and Simula's role in the CCI.

Modeling the human atria: the action potential, calcium handling and electrophysiology from cell to organ (Mary Maleckar, Simula)

Abstract:

The two superior chambers of the mammalian heart, known as the atria, are widely susceptible to pathological changes leading to rhythm disturbances (arrhythmia). Atrial fibrillation (AF), the most common cardiac arrhythmia, sharply increases the risk of cerebrovascular stroke and is associated with a number of other severe cardiac pathologies, particularly heart failure. Because age is the most powerful predictor of AF risk, the impact of AF is projected to increase dramatically in coming decades as Westernized populations continue to grow older. With this rapidly expanding disease burden, it is sobering to think that radiofrequency ablation remains the most effective treatment for preventing recurrence of AF in the clinic - as it has been for approximately 15 years. This lack of new therapies is due, at least in part, to our relatively poor understanding of how the cellular determinants of AF manifest as self-sustaining arrhythmia. More than half of all ablation patients and approximately 3 in 4 patients undergoing first-line pharmacotherapy experience recurrence of AF within 2 years. Thus, new strategies for treatment of AF are urgently needed, and such developments hinge upon improved understanding of how abnormalities in cellular structure and function initiate and maintain AF. This talk will summarize contributions made in CaMo, outline new work, and highlight future ambitions.

Metamodeling of bi-ventricular structural abnormalities in the ARVC heart (Kristin McLeod, Simula)

Abstract:

Arrhythmogenic right ventricular cardiomyopathy (ARVC) is an inherited cardiomyopathy characterized by fatty and fibrotic replacement of cardiac tissue, which ultimately affects the structure, function and electrical propagation of the ventricles. Diagnosis of ARVC is challenging and is currently guided by the 2010 Task force criteria (2010TFC), which includes criteria identified from imaging, ECG and family history. Multivariate metamodeling techniques provide a suitable framework for analyzing the relationship between cardiac models and clinical indices. Suitable techniques will be discussed with an application to structural analysis and correlation with the 2010TFC indices for the ARVC heart.

Insight into model mechanisms and more efficient model development and validation by multivariate metamodeling (Kristin Tøndel, Simula)

Abstract:

Modeling in biology and physiology is increasingly realizing its potential to provide a deeper understanding of biological function, guide the development of new intervention strategies and inform treatment optimization in personalized medicine. However, the development and validation of large, multi-scale models remain hampered by several significant challenges that limit the clinical applicability of models and their adaptation to fit new contexts.

The complexity of the models needed in order to account for our rapidly increasing knowledge of physiological mechanisms (1), poses considerable challenges for uniquely linking model parameters to experimental and clinical data. Additionally, including a high level of biophysical detail in large multi-physics models leads to computationally demanding simulations, the results of which are hard to validate sufficiently since they can not be run under sufficiently diverse conditions within a reasonable computational time. To ensure robust parameter fitting to measured experimental or clinical data requires models which can be solved rapidly to allow a comprehensive exploration of the parameter space.

In many cases the model structure is such that the inverse problem of parameter fitting is ill-posed due to multiple parameter values producing the same model output (model sloppiness) (2), leading to low identifiability of many parameters from available data. This situation is exacerbated by the lack of consensus on the optimal method for fitting model parameters to data, taking into account the, often, poor signal to noise ratio in the measurements, as well as ill-defined cost functions. Including an excessive complexity increases the risk of parameters being fitted to noise, limiting the applicability of the models to new cases.

The high complexity of the models also makes it challenging to foresee the relationships between the variables in the system, and select the most informative metrics to measure in order to fit individual or groups of parameters. However, including too little detail limits the flexibility of models to provide the necessary level of insight into the biological phenomena they are intended to represent. Additionally, in the multi-scale context, being able to effectively pass on the relevant metrics from one scale to the next, including the appropriate level of detail, is crucial for clinical applicability of models.

Metamodeling, i.e. statistical modeling of the relationships between model inputs and outputs, has the potential to allow us to overcome a number of these challenges by reducing computational demand, efficiently extracting the most relevant features describing the system functionality, facilitating model reduction and transparent integration of modeling results with experimental data. Especially in the development and validation of large, multi-scale models, the ability to robustly select the most important metrics affecting higher-level functionality becomes increasingly important. Multivariate metamodeling may therefore be of significant value for future model development, including the search for patient-specific or patient group-specific parameter values, something that is likely to highly increase the clinical applicability of computational models.

References:

1. Nickerson DP, Hunter PJ. The Noble cardiac ventricular electrophysiology models in CellML. Prog Biophys Mol Biol. april 2006;90(1-3):346–59.

2. Gutenkunst RN, Waterfall JJ, Casey FP, Brown KS, Myers CR, Sethna JP. Universally Sloppy Parameter Sensitivities in Systems Biology Models. PLoS Comput Biol. 5. oktober 2007;3(10):e189.

'Patient-specific' blood flow simulations: They are all wrong, but are some of them useful? (Kristian Valen-Sendstad, Simula)

Abstract:

It has been estimated that around 2-5% of the adult population harbor cerebral aneurysms. A cerebral aneurysm is essentially a defect blood vessel, often shaped like a balloon, which is weaker, more fragile, and more brittle than a normal compliant artery. There is a little chance of rupture which is estimated to 1% annually. However, a rupture results in a cerebral stroke, often with deadly outcome. Most aneurysms are asymptomatic and often found during routine scans. The physicians' dilemma is how to offer optimal treatment, i.e., which one's to perform surgery on and which one's to follow in time.

Computational fluid dynamics (CFD) is increasingly relied upon for elucidating blood flow dynamics in cerebral aneurysms, and their possible role in determining rupture risk. Compared to a decade ago, when 'patient-specific' aneurysm CFD studies were confined to a few specialized labs, often using their own in-house solvers, today the use of CFD in aneurysm research is widespread, facilitated by more-user-friendly commercial solvers as well as the now-routine availability of 3D angiography. With this popularity, however, has come increased scrutiny by clinicians. While the many underlying physical assumptions and approximations behind CFD models have been roundly questioned, much less attention has been paid to reliability of the CFD solutions themselves. We here provide a critical review of the aneurysm CFD literature and put the effects of various modeling choices in perspective.