KENT-ANDRE MARDAL

Let's get **physiological**

Kent-Andre Mardal investigates the velocity and flow of cerebrospinal spinal fluid and blood and highlights the developing individual healthcare approaches towards understanding human physiology

What led to the initiation of this project?

The project started after discussions about the cause of cerebral aneurysms with neurosurgeon Tor Ingebrigtsen, and the consequences of Chiari and syringomyelia with neuroradiologist Victor Haughton. From our computational perspective, the two different conditions appeared to have a common cause – unfavourable anatomy causing abnormal or focused flow which stress the surrounding tissue. This can advance into pathogenesis.

For those who are unfamiliar, what is computational life-science and how does it relate to the healthcare sector?

Computational life-science aims at providing and using computer simulations derived from engineering or physics in order to simulate human physiology. In particular we solve differential equations and have developed a novel software framework for such computations, named FEniCS.

Could you describe the FEniCS software package? What aspects of these packages are of value to your work?

FEniCS is our open source library for creating simulations based on partial differential equations describing, for instance, fluid flow, deformations of solids, electromagnetic waves, etc. FEniCS explores a novel approach where we combine scripting techniques, symbolic mathematics and state-of-the art linear algebra to make a platform that is extensible, but also simple to use and efficient. For us, it is vital to have a computational platform where we can easily implement new physics and test new hypotheses, in particular since computational life-science is emerging and new models and hypotheses are proposed all of the time.

Have you encountered any challenges in this study?

The main problem is the complexity – a simulation of a patient-specific case may take weeks on a cluster of parallel machines. Furthermore, there are many unknown factors that are difficult to quantify properly or are hard to identify on the medical images. It is not like a laboratory experiment where, in principle, you have full control over everything. Hence, performing accurate simulations and incorporating the uncertainties are at present very time consuming and this is currently the main limiting factor. Furthermore, the variability of the human anatomy calls for patient-specific simulations, meaning that these week-long computations probably must be performed for each individual patient in order to get a precise flow and stress analysis

What have been some of your key developments to date?

We have found that the complexity of the flow is higher than we previously thought. For instance, the blood flow in aneurysms might even be turbulent; that is, the flow does in some cases appear to have random fluctuations at several hundred Hertz. Previous research has largely neglected or under-resolved the flow in computational fluid dynamics (CFD) simulations. This discovery opens up new opportunities for diagnosing the severity of the conditions. For instance, the high frequency fluctuations create audible sounds. The high frequency of the disturbances is much higher than is detectable using MR or CT.

What do you hope will be the ultimate impact of this work?

The ultimate goal is to improve the lives of the people with the above-mentioned conditions. One practical application of our computational framework is that it allows for virtual surgery, giving the surgeons the possibility of exploring

different strategies virtually on a computer, prior to surgery. Furthermore, the medical images can be augmented with additional quantities such as pressure and stress, derived from physical principles, hence adding valuable information to the images provided by magnetic resonance (MR) or computer tomography (CT).

On what areas of research will you direct your efforts in the future and what are the next steps in your project?

An important issue now is to improve the efficiency of simulations to be able to perform more studies. Efficiency is of crucial importance for the practical application of the computational methods in clinics and currently accurate simulations take weeks on super computers. Often, the clinicians cannot wait weeks for a computation to finish. Furthermore, it is important to establish the robustness of the computed quantities with respect to uncertainties in the medical images, and the fact that images are obtained under resting conditions, while our daily life result in a wide range of different flow conditions, eg. flow and heart rate is very different during exercise and sleep.

Advancing simulations toward **patient-centred care**

A group of researchers at the **Centre for Biomedical Computing** in Norway have been developing patient-specific mathematical models which allow them to determine the effects on blood and cerebrospinal fluid flow from conditions such as syringomyelia, Chiari and stroke

PERFORMING INVESTIGATIONS INTO stroke (particularly those caused by aneurysms), syringomyelia and Arnold-Chiari malformations, with a focus on their relationship to each other, may seem perplexing. The three conditions do not appear to have much in common, except that they are all serious, affect the quality of a person's life and can be potentially life-threatening.

A stroke (cerebrovascular accident) occurs due to an abnormality or disturbance in the blood flow to the brain, which results in a rapid loss of function in the area of the brain that is affected. 50 per cent of stroke cases brought on by an aneurysm lead to sudden death, whilst a mere 20 per cent of these make a full recovery.

Syringomyelia, a cyst or syrinx (fluid filled spinal cavity) in the spinal cord, can progress over time, eventually damaging the spinal cord to such an extent that it is beyond repair. The cyst can expand and elongate, compressing the nervous tissue in the spine. Although this condition is less common, it can be lifelong and treatment is often only partially successful. Symptoms can range from headache to complete paralysis, and can affect children as well as adults. Chiari malformations (tonsillar herniation of the cerebellum) are the most common reason for the development of syringomyelia and depending on where the stress is concentrated on the central nervous system, one symptom could be a lack of balance control. They are less common, but can be incredibly destructive and damaging.

Each condition mentioned above interestingly shares a common link: blood supply and cerebrospinal fluid (CSF) velocity and flow are affected differently depending on whether a person has been affected by one of these conditions, or whether they are healthy. Kent-Andre Mardal, Assistant Professor at the SIMULA research centre, Norway, explains in greater detail: "The conditions/pathologies seem to have a common physical explanation – namely that unfavourable anatomy causes disturbances in the physiological flow, which again brings people with the conditions into a downward spiral with unfavourable remodelling of the anatomy because of the flow disturbances and hence, the conditions worsen".

WE'VE GOT THE FLOW

CSF is responsible for protecting the brain. It covers and submerses the brain and spinal cord. Essentially, the brain remains buoyant in the CSF which cushions it from inside the skull. CSF is a water-like substance and fairly little remains known about it, although it works continuously within our bodies, pumping fluid up and down the spine and brain. Disturbances or blockages to the flow can result in the development of cysts in the spine, which could eventually lead to the onset of headaches, blurred vision and neurodegeneration.

The biomedical flow of blood in the brain and CSF in the spine are two concerns for Mardal and his team of researchers. During their studies, they found that results differed among the two varying sets of patients. "By performing studies involving many patients, we aim to identify what are normal and abnormal variations in anatomy and consequently physiological flow," Mardal explains. "Variations in anatomy cause huge variations in velocity, pressure and stress in cases of non-ruptured and ruptured aneurysms." Their intentions are to improve knowledge and understanding of blood flow and ultimately stroke resulting from aneurysms, which they describe as 'balloon-shaped' ruptures on the surface of blood vessels. Ultimately, the team want to improve clinical practice, develop novel mathematical models and computer simulations to address human physiology and most importantly, improve the lives of patients.

BRIDGING THE GAP

The researchers hope that by using computer simulations, they can test their hypothesis effectively. They have predicted that

Figure 1. The left image shows a sagital MR image of a healthy individual, while the right image shows a person with the Chiari I malformation (Cerebellum occupying the subarachnoid space close to C1/Foramen Magnum) and syringomyelia (white cysts within the spinal cord).

INTELLIGENCE

PATIENT SPECIFIC MATHEMATIC MODELING

OBJECTIVES

To bridge the gap between engineering and clinical practice by performing patient-specific biomedical flow simulations and to develop new computational software and methods that are robust and efficient for clinical investigations.

KEY COLLABORATORS

Victor Haughton and **Charles Strother**, University hospital of Wisconsin

Søren Bakke and **Per Kristian Eide**, Oslo University Hospital

Ragnar Winther, University of Oslo

Tor Ingebrigtsen, University Hospital of Nothern Norway

Hans Petter Langtangen (leader of the Centre for Biomedical Computing), **Kristian Valen-Sendstad**, **Karen Støverud**, **Martin Alnæs**, **Øyvind Evju**, **Svein Linge**, Simula Research Laboratory

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KENT-ANDRE MARDAL recieved his PhD from the Department of Informatics at the University of Oslo in 2003. His interests concern the solution of PDEs. This includes both mathematical theory and practical implementation issues. For the past five years, his research has focused on biomedical flow problems concerning cerebral aneurysms and the Chiari I malformation. Mardal currently serves as Associate Professor at the University of Oslo and Senior Scientific Researcher at Simula Research Laboratory.

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Center for Biomedical Computing

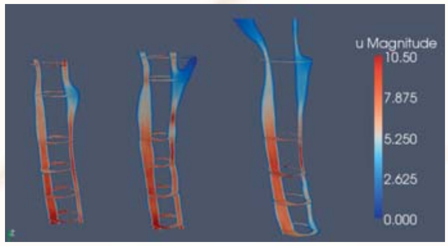

FIGURE 2. PEAK SYSTOLIC VELOCITY MAGNITUDE IN THREE CHIARI PATIENTS

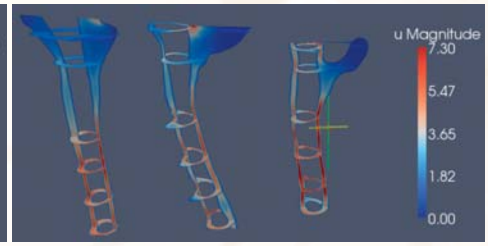

FIGURE 3. PEAK SYSTOLIC VELOCITY MAGNITUDE IN ONE VOLUNTEER (LEFT) AND TWO POSTOPERATIVE PATIENTS WITH SIGNS OF TONSILS AT FORAMEN MAGNUM

abnormalities in a person's anatomy cause abnormal fluid flow, which in turn leads to pathogenesis. Using mathematical modelling to accurately identify abnormal flow can be time-consuming and also complex, however the rewards could be very satisfying: "It will increase our understanding of the human physiology and determine which variations are normal and which cause the downward spiral," Mardal examines. "With today's powerful computers it is possible to simulate the interaction between the fluids and tissue (which are very similar in density) in an individual patient-specific manner, determining whether the stress is within normal range or not, and what could be done to obtain normal stress."

The investigation also focuses on the relationship between Chiari malformation and syringomelia, in which a model was developed to improve knowledge about the distance and placement between the tonsils and the syringomyelia that develops as a result of cysts on the spinal cord. The porosity (measurement of the void) between the spinal cord and the central canal allows for greater stress, and this could help to further understand the movement downwards in the spinal cord, where the syrinx is formed. Simulation tools, software and novel patient-specific models are in development to enhance the success of their reserach, which will be applied to large numbers of patients.

MATHEMATICAL AND COMPUTATIONAL DEVELOPMENTS

Mardal and the research team at the Centre for Biomedical Computing have been busy investigating new methods and strategies for developing person-centred models toward clinical and medical diagnosis. A wide range of models and numerical algorithms have been proposed, all of which vary in terms of complexity (eg. differential equations and nonlinear algebraic equations).

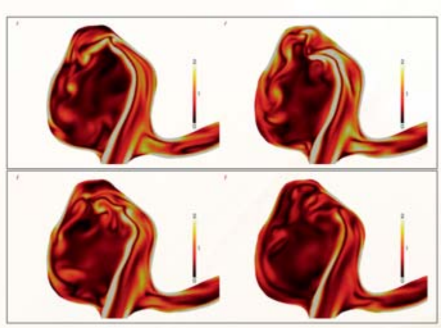

FIGURE 3. TURBULENT FLUCTUATIONS IN AN ANEURYSM

They have discovered that the blood flow in aneurysms might even be turbulent; that is, the flow does (in some cases) appear to have random fluctuations at several hundred Hertz. Previous research has largely neglected or under-resolved the flow in their computational fluid dynamics (CFD) simulations. Their findings have created new opportunities towards the diagnosis of the severity of the these conditions.

At the centre of the computational methodologies that have been developed by Norway's Centre for Biomedical Computing, is FEniCS, an extensive piece of software that has a number of different functions towards efficient and effective solutions for differential and partial differential equations. While FEniCS is relatively simple to use, it is an extremely complex open source library, and creating the software for it requires adequate time and manpower. It is an innovative open source library aiming to automate the solution of differential equations. Creating this package is a substantial effort. So far, the project members have launched the first version last fall and a book was published this spring.

The launch of FEnicCS has begun, offering tutorials, books and conferences among other activities, designed to attract attention and to help generate knowledge about it. The team are using software packages like this as a platform to study innovative solutions that are geared towards developing technology for clinical practise.

AN EYE TO THE FUTURE

The project runs successfully under a multidisciplinary approach and aims to collaborate on a number of different levels. While communication can be a challenge between the different groups, the work produced far exceeds their expectations: "It is stimulating to work with clinicians and biomechanical modellers, myself being an applied mathematician, and I learn a lot about human physiology," Mardal concludes. The project has already been published in a number of medical journals, and is excited about future developments in computational science and human physiology. Enhancing the robustness and efficiency of their simulations is the next step.