ERC Advanced Grant
Research Proposal

Mathematical Modelling and Simulation of the Cardiovascular System

MATHCARD

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Proposal duration: 60 months

Proposal Summary:

This research project aims at the development, analysis and computer implementation of mathematical models of the cardiovascular system. Our goal is to describe and simulate the anatomic structure and the physiological response of the human cardiovascular system in healthy or diseased states.

This demands to address many fundamental issues. Blood flow interacts both mechanically and chemically with the vessel walls and tissue, giving rise to complex fluid-structure interaction problems. The mathematical analysis of these problems is complicated and the related numerical analysis difficult.

We propose to extend the recently achieved results on blood flow simulations by directing our analysis in several new directions. Our goal is to encompass aspects of metabolic regulation, micro-circulation, the electrical and mechanical activity of the heart, and their interactions. Modelling and optimisation of drugs delivery in clinical diseases will be addressed as well. This requires the understanding of transport, diffusion and reaction processes within the blood and organs of the body.

The emphasis of this project will be put on mathematical modelling, numerical analysis, algorithm implementation, computational efficiency, validation and verification. Our purpose is to set up a mathematical simulation platform eventually leading to the improvement of vascular diseases diagnosis, setting up of surgical planning, and cure of inflammatory processes in the circulatory system.

This platform might also help physicians to construct and evaluate combined anatomic/physiological models to predict the outcome of alternative treatment plans for individual patients.
Extended Synopsis of the Project Proposal

The past ten years have witnessed an important research activity in the development of mathematical models of the functioning of the human cardiovascular system and of numerical tools for its simulation. This exciting and challenging endeavor still requires to address many fundamental issues. Indeed, we are facing an integrated system with a high level of complexity and variability. The quest for this type of modeling arise from several applications, a few of which will be addressed directly by the present proposal.

Firstly, we mention the need to better understand the onset and development of important pathologies, like arteriosclerosis or vascular aneurysms. Effective numerical simulations, possibly coupled with tools of statistical analysis, may for instance help to explain why certain blood flow patterns or vascular morphologies induce the onset of the inflammatory mechanism which initiates fat deposit in the wall of some arteries.

Secondly, the advances in medical imaging and geometry reconstruction techniques makes it possible to obtain an accurate description of a vascular compartment of a specific individual. This enables the use of simulations for surgical planning and the optimisation of prostheses or other devices, provided that the computational cost of a simulation is acceptable.

Thirdly, the effect of localised drug delivery from implantable devices, for instance the anti-inflammatory agent emitted by a drug-eluting stent used to open up a stenosed coronary, may be better studied having at disposal mathematical and numerical models of the transport/diffusion process and the interactions between the drug and the tissue.

There is a recurring need by medical doctors of syntetic indicators of the risk factors for a particular therapeutic choice. For instance, how can the possible negative post operational side-effects of a surgical operation to exclude a cerebral aneurysm be weighted against the risk of rupture? To give a reliable answer to this question we need to find a correlation between the information which may be gained non-invasively, like the morphology of the vessel and of the aneurysm as well as general patient data, with the likelihood of rupture. Enriching the data set by the result of numerical simulations of blood flow may help to better characterise the patient and increase the confidence of the estimate.

This project will rely on the long-standing expertise of my research group both at EPFL, Lausanne and MOX, Politecnico di Milano on the development of such models. In particular, we will strongly benefit of the experience gained during the former HaeMOdel European project, whose activities and achievements are documented on the web site http://mox.polimi.it/haemodel.

From this groundwork we will move on to several directions. Some aim at reinforcing and completing already opened fields of research, others are completely new and will allow a decisive move towards the applications previously mentioned.

This is fundamentally an applied mathematics project. Nevertheless, we want to address the applied and multidisciplinary nature of the field, thus we will largely benefit from the active collaboration of the “end users” of these methodologies. Indeed, we plan to tackle specific problems of clinical relevance, which will inspire our methodological developments, and we will exploit our long standing collaboration with bio-engineers, medical doctors and biomedical industries.

What follows is a brief description of the main tasks of this research project.

Task A. Mathematical Models for the Integrated Cardiovascular System. The desire to model the cardiovascular system is longstanding. However, only in the past few decades the application of mathematical models have become widespread within the bioengineering and medical research community, due mainly to the advancements in the power of modern computers, the progress in imaging and geometry extraction techniques as well as the development of better numerical algorithms.

We will identify a hierarchy of models, each suited for a different type of investigation or to different parts of the system and devise strategies to couple them, using a multiscale framework.

This strategy is based on the use of mathematical and numerical models of the short-term cardiovascular regulation (seconds to minutes) and accounts on one hand on factors determining variations in
nominal arterial pressure, such as variations in cardiac flow rate, peripheral resistance, blood volume, and, on the other hand, on the reaction of selected central mechanisms of arterial pressure regulation, such as baroreceptors, chemoreceptors, and thermal regulation.

From the mathematical point of view, we need to treat differential problems of different kind: Navier-Stokes equations (possibly coupled with structural models) for the flow in main blood vessels, non-linear one-dimensional hyperbolic equations for pulse wave propagation along the arterial tree, and, finally, systems of differential-algebraic equations for the systemic behaviour and auto-regulation mechanisms.

Also different time-scales are here at play. While the identification of local flow patterns requires to simulate phenomena on the time scale of the heart beat, we will need also to account for the mid/long-term cardiovascular adaptation or pathology developments, on the scale of days and more, to investigate the effect of surgical procedures, malformations etc. Special numerical techniques will be implemented for this purpose.

Parameter identification is another essential ingredient of this task. Methods to derive parameters for our models starting from measurements or numerical simulations will be developed together with a sensitivity analysis to parameter changes. Besides, methods to account for uncertainty in data and geometry will be set up. An important task is to target the sensitivity analysis to a specific output of biomedical interest. For instance, in investigations aiming at studying the onset of arteriosclerosis, the desired output could be a measure of wall shear stress distribution (the oscillatory wall shear stress index) which is correlated to the onset of inflammatory processes in the vessel wall.

**Task B. Mathematical Models of the Interaction between Circulation, Tissues Perfusion, Biochemical and Thermal Regulation.** Strongly related with task A is the development of mathematical models of the peripheral circulation accounting for the exchange of biochemicals or drugs with the tissues. The role of fluid dynamics and mass transport processes in the physiological and patho-physiological functions of the vascular system are of great interest, as the local mass transfer between the blood and the arterial wall affects the transport of nutrients to the cells, the removal of metabolic wastes from the wall, and the accumulation of potentially atherogenic molecules [18]. Furthermore, mass transfer phenomena are fundamental to determine the distribution and the efficacy of drug delivered to heal the arteries affected by pathologies. We will analyse those cases in which the mechanical behaviour of the vessels depends on the local metabolism. In fact, while the most important features of mass transport take part at the microscale, the final goal is the description of the blood flow and chemical concentrations at the macroscopic level. The coupling between perfusion/biochemical reactions/thermal regulation in the tissue and the blood flow and mass transport requires a proper mathematical analysis and a convenient numerical treatment, with possibly ad-hoc strategies for handling the embedding of a vessel network in the surrounding tissue. This is a rather novelendeavour; a preliminary study can be found in [8] where the vessel network feeding a tissue is represented by a one-dimensional subset of a three-dimensional domain, where blood flow takes place through the capillary matrix, thus requiring a specific framework for the proper mathematical setting and analysis.

The coupling with the already available models for circulation in large vessels will be studied as well. This could provide important information about the mechanical and biochemical interplay between central circulation and the peripheral compartments.

**Task C. Modelling Drug Delivery in Prosthetic Implants.** Prosthetic implants such as drug eluting stents are medical devices used to restore blood flow perfusion into stenotic arteries. Their design is a very complex task because their performance in widening the arterial lumen and preventing further restenosis is influenced by many factors such as: the geometrical design of the stent, the mechanical properties and the bio-compatibility of the metal struts and of the stent outer surface, the chemical properties of the drug that is released.

In this research, we address several challenges. Micro-structured materials can store and deliver drugs after implantation, as in drug-eluting cardiovascular stents. Drug delivery from either polymeric or ceramic matrices involves complex phenomena at the nanoscopic and microscopic scales as brownian
ratchet effects, hydrophobic/hydrophilic transitions, phase transitions (solid/liquid) and material erosion. The combination of the chemical reactions and heterogeneous physical properties at nano and micro scales may generate very steep and non-stationary internal layers. We want to devise mathematical models and numerical techniques for intelligent delivery, able to treat different release devices, drugs and drug carriers and targeted biological tissues. Since they have to capture properly the space and time scales that are relevant for the local drug release from nano/micro structured materials, we will investigate and develop different kind of multiscale methods: geometrical multiscale methods using models of different space dimension, variational multiscale methods devised to approximate solutions featuring separable scales, projective integration methods to treat different time scales.

On the practical side, we address the general problem of feeding the aforementioned models with suitable coefficients characterizing the biological tissues where mass transfer takes place. Because of the natural variability of biological tissues, this objective requires to determine the transport properties of porous media whose structure cannot be described as a periodic distribution of obstacles. To this purpose, we aim to develop suitable numerical methods to quantify the average transport properties of a given sample of tissue.

Moreover, we want to address the problem of simulating the behaviour of the new generation of biodegradable stents which requires special modelling of the elution/degradation process, effectively described by a strongly nonlinear system of parabolic/hyperbolic differential equations. Our objective is to combine the reduced model for mass transfer with suitable numerical discretization methods to obtain simulations involving realistic expanded stent geometries and long time scales.

**Task D. Modelling Electrical Activity, Fluid Dynamics and Wall Mechanics of the Heart.** The mathematical modelling of the heart is an important part for the set-up of an integrated simulation of the cardiovascular system. A preliminary activity of the research group has started in collaboration with other institutions, like the Universities of Milan and Pavia.

We will rely on the cited collaborations for what concerns the modelling and efficient numerical solution of the electrical part and we will concentrate instead on the electromechanical coupling. We will develop a model that, despite some necessary simplifications in the underlying physics, is capable to address the complete mechanical/electrodynamical system. The goal is to simulate physiopathological situations of medical interest at acceptable computational costs. A first step in this direction could be to model the activation and contraction of the myocardium muscle fibers for a given electric wavefront, computed using the bi-domain model.

A strongly integrated cardio-circulatory simulation is needed, for instance, in the study of coronary circulation and perfusion of the myocardium tissue itself. Here also perfusion models as considered in Task B have to be included.

**Task E. Efficient Methods for Control and Optimisation.** Besides their employment in medical research, numerical models of vascular flows can also provide a virtual experimental platform to be used as training system for new vascular surgeons or anaesthesiologists. In perspective, they can give specific design indications for the realisation of surgical operations [32, 24] or for the design of better prosthetic devices. For instance, numerical studies have shown how shape optimisation techniques may be used for minimising the downstream vorticity in coronary by-pass grafts [1, 30]. Investigations of this type can help surgeons in understanding how different surgical solutions may affect blood circulation and guide the choice of the most appropriate procedure for a specific patient or type of patients.

Moreover, optimisation methods can be applied to the design of drug-eluting devices to ensure the delivery of the correct dose of drugs during the time of the therapy, avoiding levels of concentration which may harm the tissues. A further challenge is to couple this analysis with techniques that account for the possible uncertainties, for instance in the knowledge of the transport characteristics of the vessel tissue, with the objective of providing certifiable results of the effectiveness of a certain type of coating.
**Task F. Risk Evaluation.** Another important aspect in current medical practice is the constant need to weigh the possible advantages of a therapy with its inevitable side effects and possible risks. This is a rather new field for mathematical modelling and often requires the integration with tools from other disciplines like statistics. For instance, cerebral aneurysms are characterised by a bulge of the vessel wall that can undergo rupture, with almost always fatal consequences. Yet, the possible therapies, both endovascular or surgical treatment, present a non negligible probability of negative consequences. It is strongly believed that, besides possible genetic and other facts like smoking etc., the fluid dynamics induced by the particular morphology of the cerebral vessel is a crucial agent of the onset and development of the disease.

Therefore, having at disposal an ensemble of clinical cases, statistical tools like functional data analysis and geometry registration techniques may be successfully applied to a data set enriched by the data emerging from numerical simulations. This example stems from a current research project by the group where the data set is provided by the Niguarda Hospital of Milan. We plan to extend the analysis to other pathologies, such as atherosclerotic development.

**Task G. Software Development.** For our simulations we are going to use LifeV, a parallel finite element library which has been jointly developed by the CMCS group at the EPFL, the MOX Laboratory at the Politecnico di Milano, and INRIA (REO project) since 1999/2000 (see http://www.lifev.org).

LifeV is an ideal platform to implement and compare novel numerical algorithms, to propose new mathematical models, to address new (and diversified) applications, not only in the field of haemodynamics. Virtually, all kind of areas that have been illustrated in the previous tasks can be addressed by mean of LifeV: moving domains using the ALE formulation (as required, for example, for fluid-structure interaction simulations); multiphysics problems (e.g., fluid-structure, coupling of blood flows and biochemical reaction-diffusion problems, like those addressed in Tasks B and C); geometrical multiscale problems (coupling of 3D-1D-0D models required for an overall simulation of the circulatory system). Moreover, LifeV provides the users with several types of finite element spaces, algebraic solvers, as well as preconditioners and ad-hoc acceleration techniques for haemodynamics simulations.

The library, implemented in C++ and currently consisting of about 80’000 lines, is distributed under the LGPL license, i.e., the code is free for the public and the sources are available. Periodic updates guarantee the availability of the latest advances to the members of the research community. Moreover, the modularity and flexibility of the library allows the users to add contributions from their own field of expertise and to couple it with other existing software.

**Task H. Further Relevant Clinical Applications.** Following our traditional approach, we plan to apply the methodologies previously listed to some real case problems (besides those already mentioned above), possibly in collaboration with external institutions and industries. In particular, we mention: (a) Numerical simulation of the action of atrio-ventricular and semilunar heart valves in physiological and pathological conditions (in collaboration with Prof. L. von Segesser du Centre Hospitalier Universitaire Vaudois (CHUV), Lausanne); (b) Simulation of the effect of surgical procedures for congenital heart diseases affecting the systemic and pulmonary circulation (in collaboration with Dr. A. Corno, Alder Hey Royal Children Hospital, Liverpool); (c) Simulation of local and central autoregulation affecting blood vessels mechanical properties and cardiac output, especially in pathological cases or under effort conditions (taking advantage of the expertise developed in the framework of the Sport and Rehabilitation Engineering (SRE) project http://sre.epfl.ch); (d) Analysis of performances of implantable medical devices, in particular drug eluting stents (in collaboration with the Laboratory of Biological Structure Mechanics (LaBS), Politecnico di Milano and the Great Ormond Street Hospital for Children, London (GOSH)); (e) Application of numerical simulations and data-mining to estimate the risks of rupture of brain aneurysms (in collaboration with Siemens and the Niguarda Hospital in Milano, Italy).

The following Figure encompasses the different tasks and the way they are functionally interrelated.
Figure 1: Illustration of the MATHCARD project structure.
References


