Universitatea *Transilvania* din Braşov

HABILITATION THESIS

SUMMARY

Computational Methods for Personalized Cardiovascular Medicine

Domain: Systems Engineering

Author: Lecturer dr. ing. Lucian Mihai ITU

University: Transilvania University of Braşov

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The goal of personalized medicine is to personalize the treatment strategy to individual features, conditions, needs and particularities of a patient during all stages of care, ranging from prevention, diagnosis, treatment and follow-up. Cardiovascular disease is the leading cause of death, globally and, this work focuses on personalized cardiovascular medicine, and specifically on computational methods spanning the following research areas: patient-specific multiscale modeling of arterial hemodynamics, and machine learning and parallel processing in multiscale hemodynamic modeling. All three areas are crucial to achieve the final goal of applying the models in routine clinical settings for the non-invasive, patient-specific assessment of cardiovascular pathologies.

First a hierarchical parameter estimation framework for performing patient-specific hemodynamic computations in arterial models is introduced, which use structured tree boundary conditions. A calibration problem is formulated at each stage of the hierarchical framework, which seeks the fixed point solution of a nonlinear system of equations. Common hemodynamic properties, like resistance and compliance, are estimated at the first stage in order to match the objectives given by clinical measurements of pressure and/or flow rate. The second stage estimates the parameters of the structured trees so as to match the values of the hemodynamic properties determined at the first stage. A key feature of the proposed method is that, to ensure a large range of variation, two different structured tree parameters are personalized for each hemodynamic property.

Next, a parameter estimation framework for automatically and robustly personalizing aortic hemodynamic computations from 4D Magnetic Resonance Imaging data is introduced. The framework is based on a reduced-order multiscale fluid-structure interaction blood flow model, and on two calibration procedures. First, windkessel parameters of the outlet boundary conditions are personalized by solving a system of nonlinear equations. Second, the regional mechanical wall properties of the aorta are personalized by employing a non-linear least squares minimization method. The two calibration procedures are run sequentially and iteratively until both procedures have converged. The parameter estimation framework was successfully evaluated on 15 datasets from patients with aortic valve disease. Overall, the computational model was in close agreement with the clinical measurements used as objectives. Given its level of automation, robustness, and the short execution time, the framework is potentially well suited for a clinical setting.

Furthermore, a methodology for separating the total stiffness of arteries, determined in vivo, into stiffness of the arterial wall and stiffness of the surrounding tissue is introduced. An effective perivascular pressure is considered which introduces a radial constraint. Next, based on vivo data, acquired at diastolic pressure, the cross-sectional area at zero pressure is estimated. Finally, the stiffness of the arterial wall and of the surrounding tissue are determined based on a model with two parallel springs. By employing a reduced-order multiscale model, the methodology is used for studying the global effects of surrounding tissue support on arterial hemodynamics. The main effects are: higher wave speed, earlier arriving backward travelling pressure and flow rate waves, lower total compliance, higher pressure pulse, and reduced arterial cross-sectional areas.

Next, a model-based approach for the non-invasive estimation of patient specific, left ventricular PV loops is introduced. A lumped parameter circulation model is used, composed of the pulmonary venous circulation, left atrium, left ventricle and the systemic circulation. A fully automated parameter estimation framework is presented for model personalization, composed of two sequential steps: first, a series of parameters are computed directly, and, next, an optimization-based calibration method is employed to iteratively estimate the values of the remaining parameters.

One of the most interesting methodologies presented herein is based on a machine learning model for predicting Fractional Flow Reserve (FFR) as an alternative to physics-based approaches is presented. The model is trained on a large database of synthetically generated

coronary anatomies, where the target values are computed using the physics-based model. The trained model predicts FFR at each point along the centerline of the coronary tree, and its performance was assessed by comparing the predictions against physics-based computations, and against invasively measured FFR for 87 patients and 125 lesions in total. Correlation between machine learning and physics-based predictions was excellent and no systematic bias was found in Bland-Altman analysis. Compared to the physics based computation, average execution time was reduced by more than 80 times, leading to near real-time assessment of FFR.

The geometric multigrid method (GMG) is one of the most efficient algorithms for solving large systems of sparse linear equations and is well suited for parallelization. An in-depth analysis of a Graphics Processing Unit based GMG implementation was performed and the results are compared against an optimized preconditioned conjugate gradient method. The tests indicate that the smoothing step is the most time consuming operation, and the best performing GMG variant is the V-cycle scheme with 312 smoothing step configuration. The discretization stencil has a major effect on the runtime and its choice requires a trade-off between execution time performance and numerical accuracy.