Computer Engineering
ISSN: 10003428
Volume 13 | Issue 5 | Year 2024
https://journalofcomputerengineering.com/

A Computational Framework for Personalized Clinical Decision Support in Coronary Artery Disease Management

Andreas Georgiou, Sophia Markantonatou, Georgios Kalogeropoulos, Ioanna Karyda, Maria Vrachnis, Dimitris Tzovaras, Konstantinos Marias, Evangelos Sakkopoulos, Nikolaos S. Papageorgiou, Ioannis T. Pavlidis, Vassiliki G. Vlachogianni, Evangelia G. Zacharopoulou

Andreas Georgiou and Sophia Markantonatou, Computer Science Laboratory, Aristotle University of Thessaloniki, Greece;

***Abstract*— SMARTool aims to the development of a clinical decision support system (CDSS) for the management and stratification of patients with coronary artery disease (CAD). This will be achieved by performing computational modeling of the main processes of atherosclerotic plaque growth. More specifically, computed tomography coronary angiography (CTCA) is acquired and 3-dimensional (3D) reconstruction is performed for the arterial trees. Then, blood flow and plaque growth modeling is employed simulating the major processes of atherosclerosis, such as the lipids transportation, low density lipoprotein (LDL) oxidation, macrophages migration and plaque development. The plaque growth model integrates information from genetic and biological data of the patients. The SMARTool system enables also the calculation of the virtual functional assessment index (vFAI), an index equivalent to the invasively measured fractional flow reserve (FFR), to provide decision support for patients with stenosed arteries. Finally, it integrates modeling of stent deployment. In this work preliminary results are presented. More specifically, the reconstruction methodology has mean value of Dice Coefficient and Hausdorff Distance is 0.749 and 1.746, respectively, while low ESS and high LDL concentration can predict plaque progression.**

I. INTRODUCTION

Cardiovascular disease (CVD) and especially atherosclerosis is considered as one of the most common causes of death in western societies [1]. Treatment of atherosclerosis includes medical therapy, control of lifestyle and diet, and interventional practices, such as balloon and stent positioning and deployment. Atherosclerosis is affected by several factors, including biological and genetic interactions as well as rheological and mechanical factors [endothelial shear stress, (ESS)]. However, the optimal assessment of atherosclerosis is the prevention of plaque development by predicting high risk patients and regions which are prone to plaque growth. This may be achieved by using computational modeling of blood flow and plaque growth, integrating information from other fields, such as novel biomarkers of CVD risk, etc.

Computational modeling requires accurate 3D reconstruction of arterial segments and/or trees. Several imaging modalities are available for the visualization and assessment of the arterial stenosis. More specifically, intravascular ultrasound (IVUS), X-ray angiography, optical coherence tomography (OCT) and CTCA can be used for the reconstruction of coronary arteries. However, CTCA is the only one non-invasive modality which provides visualization of the arterial tree. Voros *et al*. [2] presented a study for the evaluation of 3D quantitative measurements of coronary plaque by CTCA against IVUS. Another similar approach was introduced by Graaf *et al*. [3]. A semi-automated methodology for 3D reconstruction of arteries and their plaque morphology using CTCA was presented by Athanasiou *et al*. [4], showing that CTCA can be used for the accurate assessment and reconstruction of coronary arteries.

The reconstructed arteries are utilized in computational modeling of blood flow or recently of plaque growth. Indeed, several studies demonstrate the low endothelial shear stress is responsible for plaque progression. This was proven in IVUS based reconstructions [5], but also in CTCA reconstructions [6, 7]. Additionally, coronary reconstruction has been used for the modeling of LDL transport. The modeling approaches can be classified depending on the interaction of endothelial membrane with LDL penetration in the arterial wall. In most cases, the endothelial membrane is assumed to be a semipermeable biological membrane and the LDL can accumulate in the arterial wall [8-10]. Finally, recently plaque growth modeling approaches consider the main mechanisms of atherosclerosis, including the LDL oxidation, the initiation of inflammation with the migration of monocytes and macrophages and the formation of foam cells and plaque [11, 12].

The main characteristic of atherosclerosis is that it is a multifactorial disease and for this reason a multi-disciplinary approach must be employed for the prediction of plaque progression. The majority of the previously presented studies focused mainly on ESS. This work presents the computational modeling approach, which is under development for the SMARTool system. In particular, the modeling approach adopts a multi-disciplinary strategy integrating patient-specific biomolecular and genetic data with imaging and computational modeling. Moreover, it integrates a Fractional flow reserve (FFR) calculation tool, as well as a stent deployment methodology. The above are integrated in a cloud platform, which provides to the medical doctors a decision support tool for the management of atherosclerotic patients.

II. MATERIAL AND METHODS

A. Concept and approach

SMARTool aims to carry out a multi-disciplinary approach, involving cardiologists, clinical imaging experts, biologists, chemists, policy makers, engineers, health economists, data mining experts and bioinformaticians. The project idea arises from the scientific outcomes of FP7 ICT

ARTreat project and aims at applying the raised foreground information to CAD management due to its widespread occurrence in Europe and high socio-economic impact. SMARTool aims at addressing these targets by developing a platform comprising patient-specific and site specific models which are combined at several clinically relevant levels in order to deploy a novel CDSS, which impacts on primary and secondary prevention of atherosclerosis, related to coronary plaque onset and progression (Figure 1). The heterogeneous data collected will include both imaging data (CTCA) and clinical, molecular and cellular data (clinical records, phenotype, genotype). Multiscale and multi-levels models will integrate these data to obtain a CAD stratification model for diagnosis, CAD progression prediction model for prognosis and a CAD treatment model for therapeutical/interventional treatment. The final CDSS can be applied in primary and secondary prevention of CAD related CHD.

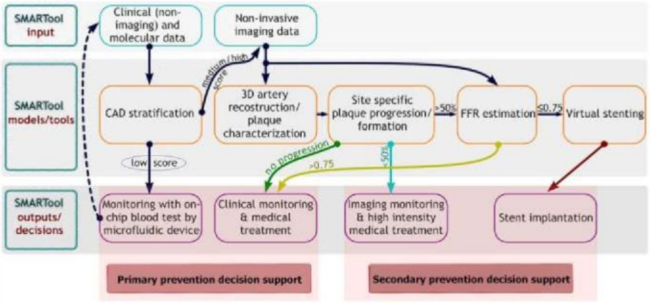

Figure 1. Overall concept and approach of clinical decision support in SMARTool.

B. Data acquisition

Patient-specific information will be selected from retrospective data recorded during the EVINCI study, and it will be used as baseline information, and it will be recollected, after 5±2 years, at patient recall during SMARTool follow-up re-evaluation. Quantitative data will be gathered in the following fields (i) CTCA imaging (ii) genomics (iii) gene expression, (iv) plasma biohumoral and lipid profile (v) inflammatory molecules and monocyte subpopulations; categorical data in clinical history and lifestyle including exposome. EVINCI database includes 515 patients and it is expected that prospective data from about 300 patients will be collected during SMARTool.

C. 3D reconstruction of arterial trees

A new semi-automated methodology for the 3D reconstruction of coronary arterial trees and calcified plaques using CTCA images is presented and validated by the expert's manual annotations. The proposed methodology is summarized in seven stages. In the first stage, a vessel enhancement filter, the widely known Frangi Vesselness filter [13], is applied to identify the potential vessel regions. In the second stage, a minimum cost path-based [14] centerline extraction methodology is implemented, aiming mainly to create an initial vessel mask for the segmentation algorithm. In the third stage, a generalized bell shaped and two sigmoidal membership functions, adapted to mean lumen vessel intensity, are estimated for the discrimination of the lumen and of the outer wall and calcified plaques, respectively. In the fourth stage, a level set based segmentation approach is applied for the lumen segmentation, based on Chan *et al.* [15] methodology. The basic improvement of our segmentation algorithm is the incorporation of a prior shape comparison term [16] into the energy function of our Level Set based model. For the lumen, the prior shape is estimated based on the extracted centerline and is a tabular mask across centerline with a small radius. In the fifth stage, a similar segmentation algorithm is applied for the outer wall segmentation, taking into consideration as a prior shape term, the segmented lumen shape. In the sixth stage, a level set based approach is used for the calcified plaques segmentation and the calcium objects of significant size are detected. In the seventh stage, the segmented surfaces for each component are connected to construct the 3D models.

D. Plaque growth modeling approach

The existing multiscale and multilevel models for plaque progression prediction of the ARTreat study will be refined using additional genotyping and phenotyping features and tested by retrospective and prospective non-invasive CTCA imaging data plus non-imaging patient-specific information collected at follow-up from the EVINCI population.

Briefly, the existed plaque growth models include three levels of modeling: i) blood flow modeling, ii) mass transport modeling and accumulation in the arterial wall and iii) modeling of inflammation and plaque growth in the arterial wall. Blood flow modeling is achieved by employing the Navier-Stokes equations, assuming that flow is laminar and incompressible. Since CTCA cannot provide blood flow data to be applied as boundary conditions in SMARTool we will implement a novel approach which calculates the blood flow rate based on the total myocardial volume. The aim of the blood flow modeling level is the calculation of ESS, since low ESS is an independent predictor of plaque progression.

The second modeling level regards the simulation of mass transport in the reconstructed segments. More specifically, LDL, high density lipoprotein (HDL) and monocytes are transported by convection and diffusion in the arterial lumen and accumulate in the arterial wall. This simulation is achieved solving the convection-diffusion equations and assuming that the endothelial membrane is a semi-permeable biological membrane and this enables the use of the KedemKatchalsky equations [8]. The outcome is the estimation of accumulated LDL, HDL and monocytes in the arterial wall, whereas the calculated concentrations are used as input for the third modeling level. In particular, in the plaque growth model the major processes of plaque growth are described assuming that the accumulated LDL is oxidized, while the monocytes are modified into macrophages, which endocyte oxidized LDL to form the foam cells. A previous proof of concept study was published by the authors [11]. Then another equation describes the formation of plaque, accounting the total volume of macrophages and foam cells.

E. FFR estimation

FFR is considered as the invasive reference standard for the functional assessment of coronary stenoses and guidelines recommend its clinical application in patients undergoing

Invasive Coronary Angiography in the absence of previously non-invasively documented large inducible ischemia. The evaluation of virtual functional assessment index (vFAI) has been suggested as a valid surrogate to FFR, allowing to determine the hemodynamic status of a given coronary lesion with a few minutes long computation time. The algorithm uses 3D coronary anatomical data and steady-flow CFD simulations to compute the pressure gradient over the lesion for flows from 0 - 4 ml/s, normalized by the ratio over this range for a normal artery, offering a measure of CAD hemodynamic significance that is numerically equivalent to the average of the computed pressure ratio over this flow range.

F. Virtual stenting

Computational simulations of stent deployment procedure in idealized geometries can provide a first insight on the stent performance and the expected outcomes in the arterial morphology, however, the utilization of patient specific image based information enable clinical decision-making and provide useful planning for each individual patient. In addition, the comparison and evaluation of different procedural options taking into account not only the specific anatomical characteristics but also the mechanical properties of the arterial morphology, as well as the stent device, could reveal useful clinical information and assist in the improvement of the interventional planning and subsequently in the expected clinical outcome.

In the proposed approach the stent geometry, in its unexpanded configuration, is positioned in the center of the stenosed arterial segment. Mesh generation is achieved using higher order 10 node elements. We assume that the arterial wall is a homogeneous material described using a MooneyRivlin hyperelastic material model. The stent is assumed to have bilinear elasto-plastic material properties. Regarding the boundary conditions we assume that the ends of the arterial segments are not allowed to move and rotate and they can move only in the axial and radial directions of the stent. The deployment of the stent is pressure-driven.

III. RESULTS

CTCA from 12 patients has been acquired and 3D reconstruction was performed. Validation of the proposed methodology is made using the manual annotations of the CTCA images by an expert radiologist. Preliminary results from these patients show that our algorithm performs well and the reconstructions are in good agreement with expert's annotation. In particular, the evaluation procedure indicates that the semi-automated and the manual segmentation methodology provide a similar geometry and plaque distribution of coronary arteries. The comparison metrics are derived by the reconstruction of 12 arteries and demonstrate a good agreement, since the mean value of Dice Coefficient and Hausdorff Distance is 0.749 and 1.746, respectively.

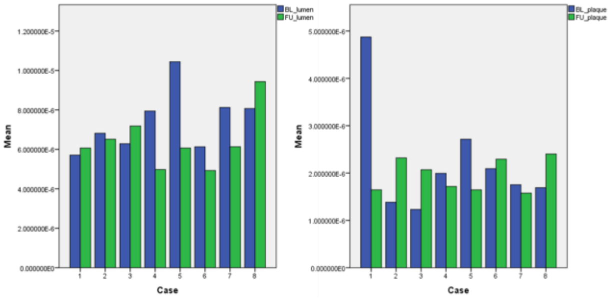

Figure 2. The mean areas of the lumen (left) and the plaque (right) for the baseline (blue bars) and the follow-up (green bars) examinations.

In the reconstructed segments we have performed blood flow and LDL transport modeling (Fig. 3) and we compare the computational results of ESS and LDL concentration with plaque progression utilizing the follow-up CTCA examinations. The aim of this work is to demonstrate whether ESS and LDL concentration are associated with disease progression and can be used as predictors of plaque growth. As it is shown in Table 1 and in Fig. 4, low ESS and high LDL concentration are associated with lumen area change and plaque change from baseline to follow-up time point.

Finally, in a dataset of 36 3D models of coronary arteries with intermediate stenoses (stenosis degree ranging between 30%-70%) deriving from CTCA, the vFAI was calculated and compared to the invasively measured FFR, presenting a strong correlation (R=0.88) and a good agreement (mean difference=0.039, SD=0.04) by the Bland-Altman method of analysis.

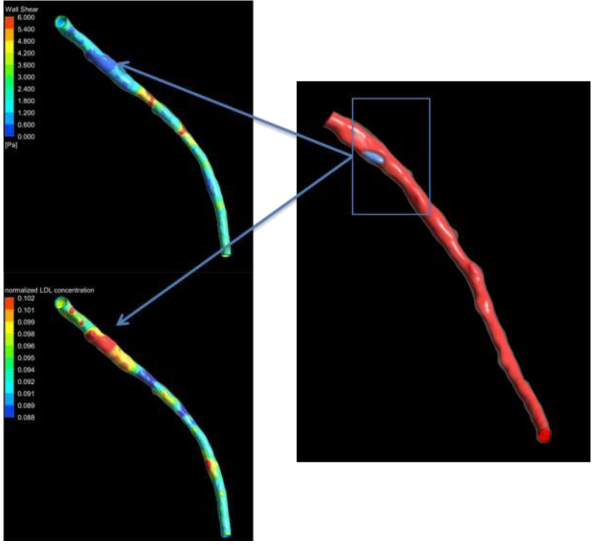

Figure 3. A case example of ESS and LDL concentration in a reconstructed coronary artery and the prediction of a region of plaque growth at the follow-up (right panel) based on the existence of low ESS and high LDL concentration (arrows).

TABLE 1. CORRELATION OF BASELINE ESS AND LDL CONCENTRATION WITH THE CHANGES OF LUMEN, PLAQUE AND PLAQUE BURDEN.

		Delta lumen	Delta plaque	Delta plaque Burden
Baseline ESS	Pearson Correlation	0.366**	-0.030	-0.243**
	Sig. (2-tailed)	<0.0001	0.319	<0.0001
Baseline LDL concentration	Pearson Correlation	-0.490**	0.020	0.216**
	Sig. (2-tailed)	<0.000	0.501	<0.0001

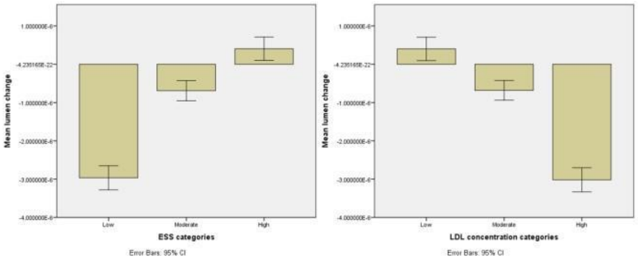

Figure 4. Correlation between the lumen change with the ESS (left) and LDL concentration (right) categories. ESS and LDL concentration values are categorized into low, moderate and high using the distribution of all values.

IV. DISCUSSION AND CONCLUSIONS

SMARTool aims to collect imaging/non-imaging information from subjects with suspected CAD at different time points (baseline and follow-up), into a patient-specific standardized repository. Historical data are available retrospectively through the EVINCI cohort, while current data from the same subjects will be collected prospectively at follow-up. The objective of collecting these data is the development of a platform that integrates all local and systemic risk factors into a unique tool for clinical decision support in stratification, diagnosis, prediction and treatment, through a personalized approach.

This tool will be based on 3D reconstruction of arterial trees and segments and in advanced modeling of blood flow for vFAI estimation and plaque growth. Moreover, stent deployment will also be performed. The preliminary results show that computational modeling can be used for the purpose of prediction of regions which are prone for disease progression. Indeed, in this work we present that a noninvasive imaging modality (CTCA) can be used for accurate reconstruction and consequently for computational modeling to support decision making for the stratification of the atherosclerotic patients.

REFERENCES

[1] W. H. O. (WHO). *The atlas of heart disease and stroke*. Available: http://www.who.int/cardiovascular_diseases/en/cvd_atlas_16_death_from_stroke.pdf

[2] S. Voros, S. Rinehart, Z. Qian, G. Vazquez, H. Anderson, L. Murrieta, *et al.*, "Prospective validation of standardized, 3dimensional, quantitative coronary computed tomographic plaque measurements using radiofrequency backscatter intravascular ultrasound as reference standard in intermediate coronary arterial lesions: results from the ATLANTA (assessment of tissue characteristics, lesion morphology, and hemodynamics by angiography with fractional flow reserve, intravascular ultrasound and virtual histology, and noninvasive computed tomography in atherosclerotic plaques) I study," *JACC: Cardiovascular Interventions,* vol. 4, pp. 198-208, 2011.

[3] M. A. de Graaf, A. Broersen, P. H. Kitslaar, C. J. Roos, J. Dijkstra, B. P. Lelieveldt*, et al.*, "Automatic quantification and characterization of coronary atherosclerosis with computed tomography coronary angiography: cross-correlation with intravascular ultrasound virtual histology," *The international journal of cardiovascular imaging,* vol. 29, pp. 1177-1190, 2013.

[4] L. Athanasiou, G. Rigas, A. I. Sakellarios, T. P. Exarchos, P. K. Siogkas, C. V. Bourantas*, et al.*, "Three-dimensional reconstruction of coronary arteries and plaque morphology using CT angiography – comparison and registration with IVUS," *BMC Medical Imaging,* vol. 16, p. 9, 01/19

[5] P. H. Stone, S. Saito, S. Takahashi, Y. Makita, S. Nakamura, T. Kawasaki*, et al.*, "Prediction of Progression of Coronary Artery Disease and Clinical Outcomes Using Vascular Profiling of Endothelial Shear Stress and Arterial Plaque Characteristics The PREDICTION Study," *Circulation,* vol. 126, pp. 172-181, Jul 10 2012.

[6] A. Sakellarios, C. V. Bourantas, S. L. Papadopoulou, Z. Tsirka, T. de Vries, P. H. Kitslaar*, et al.*, "Prediction of atherosclerotic disease progression using LDL transport modelling: a serial computed tomographic coronary angiographic study," *Eur Heart J Cardiovasc Imaging,* Mar 16 2016.

[7] C. V. Bourantas, S. L. Papadopoulou, P. W. Serruys, A. Sakellarios, P. H. Kitslaar, P. Bizopoulos*, et al.*, "Noninvasive Prediction of Atherosclerotic Progression: The PROSPECT-MSCT Study," *JACC Cardiovasc Imaging,* vol. 9, pp. 1009-11, Aug 2016.

[8] A. I. Sakellarios, M. I. Papafaklis, P. Siogkas, L. S. Athanasiou, T. P. Exarchos, K. Stefanou*, et al.*, "Patient-specific computational modeling of subendothelial LDL accumulation in a stenosed right coronary artery: effect of hemodynamic and biological factors," *American Journal of Physiology-Heart and Circulatory Physiology,* vol. 304, pp. H1455-H1470, Jun 2013.

[9] N. Sun, R. Torii, N. B. Wood, A. D. Hughes, S. A. Thom, and X. Y. Xu, "Computational modeling of LDL and albumin transport in an in vivo CT image-based human right coronary artery," *J Biomech Eng,* vol. 131, p. 021003, Feb 2009.

[10] U. Olgac, J. Knight, D. Poulikakos, S. C. Saur, H. Alkadhi, L. M. Desbiolles*, et al.*, "Computed high concentrations of low-density lipoprotein correlate with plaque locations in human coronary arteries," *Journal of Biomechanics,* vol. 44, pp. 2466-2471, Sep 2 2011.

[11] A. Sakellarios, L. Raeber, C. Bourantas, T. Exarchos, L. Athanasiou, G. Pelosi*, et al.*, "Prediction of Atherosclerotic Plaque Development in an in Vivo Coronary Arterial Segment Based on a Multi-level Modeling Approach," *IEEE Trans Biomed Eng,* Oct 19 2016.

[12] O. Parodi, T. P. Exarchos, P. Marraccini, F. Vozzi, Z. Milosevic, D. Nikolic*, et al.*, "Patient-Specific Prediction of Coronary Plaque Growth From CTA Angiography: A Multiscale Model for Plaque Formation and Progression," *Ieee Transactions on Information Technology in Biomedicine,* vol. 16, pp. 952-965, Sep 2012.

[13] A. F. Frangi, W. J. Niessen, K. L. Vincken, and M. A. Viergever, "Multiscale vessel enhancement filtering," in *Medical Image Computing and Computer-Assisted Intervention — MICCAI'98: First International Conference Cambridge, MA, USA, October 11–13, 1998 Proceedings*, W. M. Wells, A. Colchester, and S. Delp, Eds., ed Berlin, Heidelberg: Springer Berlin Heidelberg, 1998, pp. 130-137.

[14] C. Metz, M. Schaap, A. Weustink, N. Mollet, T. van Walsum, and W. Niessen, "Coronary centerline extraction from CT coronary angiography images using a minimum cost path approach," *Medical physics,* vol. 36, pp. 5568-5579, 2009.

[15] T. F. Chan and L. A. Vese, "Active contours without edges," *IEEE Transactions on image processing,* vol. 10, pp. 266-277, 2001.