InSilc: 3D Reconstruction and plaque characterization tool

Georgia S. Karanasiou, George A. Rigas, Savvas K. Kyriakidis, Nikolaos S. Tachos, Antonis I. Sakellarios, Dimitrios I. Fotiadis, Senior Member IEEE

***Abstract*— Coronary artery disease (CAD) is the leading cause of mortality in Europe and worldwide. Atherosclerosis is the most common pathologic process that is highly related with CAD, while the implantation of drug-eluting Bioresorbable Vascular Scaffolds (BVS) is the most widely performed procedure for treating patients with CAD. InSilc is an *in silico* clinical trial (ISCT) platform for the development and assessment of drug-eluting BVS. InSilc platform provides insight on the performance of drug-eluting BVS in their short term and medium/long term through the Mechanical Modelling Module, the Deployment Module, the Fluid Dynamics Module, the Myocardial Perfusion Module, the Drug-delivery Module and the Degradation Module. In order for the aforementioned modules to be developed, the utilization of the reconstructed patient specific arterial segment and the BVS design are required, which is achieved through the 3D reconstruction and plaque characterization tool.**

In this study, the overall architecture of the InSilc platform is presented with special emphasis on the 3D reconstruction and plaque characterization tool. The tool will be able to implement different medical image processing workflows. The workflows will require minimum user intervention in order to be used in large scale clinical trials.

I. Introduction

Coronary artery disease (CAD) remains the leading cause of mortality in worldwide, accounts for over 4 million deaths per year, which is close to 50% of all deaths in Europe [1]. CAD is a result of the growth of atherosclerotic plaques inside the coronary arteries, which prevent the blood flow to the heart muscle. Atherosclerosis is the most common pathologic process that can lead to myocardial infarction and stroke [2]. Percutaneous coronary intervention (PCI) is the most widely performed procedure for the symptomatic CAD treatment [3]. The introduction of coronary stents allowed PCI to diffuse worldwide and revolutionized the treatment of CAD. Impressive engineering innovation and clinical expertise enabled to routinely deliver stents in narrowed coronary arteries, such that these tubular structures are deployed into atherosclerotic plaques and recover the arterial flow of the dangerously restricted arteries.

In 2016, the global market of coronary stent devices reached €5 billion with a prediction of approximately €6 billion by the end of 2024 [4]. Based on the clinical outcomes, the stent implantation failure rate is more than 4% of the total stenting procedures [5]. Provided the billions of stent deployment procedures being carried out worldwide, even those low rates of complications, represent a large number of patients. Stent complications, such as stent thrombosis (ST) and in stent restenosis (ISR), prompted the advent of drug-eluting Bioresorbable Vascular Scaffolds (BVS), which is a major breakthrough for the treatment of coronary artery lesions [7]. The coronary artery interventional procedure has achieved brilliant advancements with drug-eluting BVS being very promising for successful implantation and reduction of induced adverse events, therefore special emphasis should be put on their design, development and evaluation.

However, today, the only conclusive and accepted way to ensure the safety and efficacy of a drug-eluting BVS is to test it initially in the laboratory (*in vitro)*, then on animals (*in vivo*) and finally on humans (clinical trial) [9]. Even if clinical trials have improved tremendously over the last years, this approach has left many key issues unmet. Specifically, the hugely complex nature of human diseases poses a significant difference between individuals, and an inevitable variability in the anatomy and pathology of the treated arteries. As a result, it is usual that a drug-eluting BVS performs exceptionally well in controlled laboratory setting and in animal testing, but presents several issues during or after clinical trials.

In general, healthcare is based upon a "one-size-fits-all' approach. However, every patient is different, presenting different type and progress of atherosclerosis, comorbidities and lifestyle. Current clinical trial designs essentially do not take into account this complexity, with the heterogeneity of the patients in a trial translating into a similar heterogeneity of responses to drug-eluting BVS implantation. Due to the differences in the patient's arterial cardiovascular physiology and other patient specific factors, some patients are expected to improve, but some might even get worse, due to a scaffold badly fitted to their biological make-up. Patients are provided with drug-eluting BVS that have been found statistically to be the best option for a similar group of patients.

However, this approach does not always mean the majority of patients will recover after this implantation. It is expected that a fraction will respond positively, while others may actually present adverse outcomes effects or might even die. In addition, in case of stent failure during the clinical trials, the stent is abandoned, even if a small modification and improvement could resolve the issue. It is evident that there is ample room for improving the complete development chain of

* *Research supported by the InSilc project that has received funding from the European Union's Horizon 2020 research and innovation program under grant agreement No 777119.

G.S. Karanasiou, G.A. Rigas, S.K. Kyriakidis, N.S. Tachos, A.X. Sakellarios are with the Department of Biomedical Research, Institute of Molecular Biology and Biotechnology, FORTH, GR 45110, Ioannina, Greece, (email: g.karanasiou@gmail.com, george.a.rigas@gmail.com, savvasik21@gmail.com, ntachos@gmail.com, ansakel13@gmail.com).

D.I. Fotiadis is with the Department of Biomedical Research, Institute of Molecular Biology and Biotechnology, FORTH, Ioannina, Greece and the Dept. of Materials Science and Engineering, Unit of Medical Technology and Intelligent Information Systems, University of Ioannina, GR 45110, Ioannina, Greece (phone: +302651009006, fax: +302651007092, e-mail: fotiadis@cc.uoi.gr).

drug-eluting BVS and introduce alternatives to reduce the animal and human testing, while address the issue of imperfections of predictions of *in vitro* and *in vivo studies*.

During last decade, a huge investment in *in silico* modelling for the development of biomedical products has been achieved [10]. *In silico* technologies are of great value, and provide answers to several difficult questions. InSilc is an *in silico* clinical trial (ISCT) platform for the development and assessment of drug-eluting BVS [11]. In the field of Stent Biomedical Industry, *in silico* modelling is used in the early design phase, primarily using computer aided design and engineering software for the drug-eluting BVS design. InSilc platform will go beyond the available *in silico* tools and expand the computer modelling through the extension and integration of already available multiscale and multidisciplinary models.

A. InSilc Cloud platform

InSilc platform will provide insight on the performance of drug-eluting BVS in their short term, through the: (i) Mechanical modelling Module, (ii) Deployment Module, and in the medium/long term through the: (i) Fluid Dynamics Module, (ii) Myocardial perfusion Module, (iii) Drug-delivery Module, and (iv) Degradation Module. In order for the aforementioned modules to be developed, the utilization of the reconstructed patient specific arterial segment and the BVS design are required, which are the outputs of the 3D Reconstruction and plaque characterization tool. A description of the InSilc platform modules and their main functionalities is presented below.

Mechanical modelling Module.

The Mechanical Modelling Module will mimic the *in vitro mechanical t*esting that are performed according to technical standards, such as longitudinal compression, radial compression, bending/ flexion, and torsion [12].

3D Reconstruction and plaque characterization tool.

The 3D Reconstruction and plaque characterization tool will accurately reconstruct a part of the arterial tree including the lumen, the outer wall, as well as the calcified and non-calcified plaques [13]. Moreover, 3D Reconstruction and plaque characterization tool will be able to detect the stents and evaluate stent deployment in IVUS/OCT and Angio modalities.

Deployment Module.

The Deployment module will simulate the BVS deployment within a human stenosed coronary artery to evaluate the final BVS configuration, the vessel anatomical changes (residual lumen, vessel straightening), as well as the stresses and strains within the BVS and the arterial wall [14].

Fluid Dynamics Module.

The Fluid Dynamics Module will focus on two different levels: (i) the full characterization of the macroscopic flow phenomena in the area where the drug-eluting BVS is implanted, (ii) the flow patterns on a microscopic scale, where the blood components and the vessel wall are included on a cellular level and the impact of the several laminae on the process of ISR are also included [15], [16].

Myocardial perfusion Module. The Myocardial perfusion Module will model the myocardial perfusion through a 3D multi-compartment poroelasticity, which will capture the ischemia and the revascularization [17].

Drug-delivery Module.

The Drug-delivery Module concerns the 3D modelling of drug release [18] employing most novel types of anti-proliferation drugs, taking into account the flow-mediated convection of drug, transmural delivery of drug by plasma, effective diffusion inside the carrying polymer and porous tissue with anisotropic distribution of transport properties.

Degradation Module.

The Degradation Module will simulate the physico-chemical processes that are responsible for the material degradation, including a corrosion/degradation medium for considering the interaction of the degrading material with the surrounding environment.

InSilc platform will include "virtual" populations of patients with several kinds of stenosis. This will be achieved by implementing a plaque growth computational model [20], which describes the main mechanisms of atherosclerotic process through the inclusion of the intra-subject variability of the constitutive parameters and boundary conditions of the blood flow. The "virtual" population will be used to simulate the drug-eluting BVS performance and the relevant consequences in the arterial environment. Once this simulation is achieved, several "virtual" scenarios will be performed starting from the alteration of the scaffold design parameters to test anatomical compatibility, and continuing to more detailed functional assessments, typically associated with the analysis of the effects of the deployment, the hemodynamic alterations in the macroscopic and microscopic level, the drug release mechanisms and the process of degradation.

A. 3D Reconstruction and plaque characterization tool

The 3D Reconstruction and plaque characterization tool will reconstruct the arterial tree (arterial lumen, outer wall) and the atherosclerotic plaques (calcified, non-calcified plaques).

Specifically: (i) fusion of Intravascular Ultrasound/ Optical coherence tomography (IVUS/OCT) and angiography will be implemented incorporating the reconstruction of plaque lesions that are significant for accurate *in silico* deployment of the drug-eluting BVS. The 3D Reconstruction and plaque characterization tool will provide the ability to automatically detect stent struts from OCT or IVUS modalities. For the drug-eluting BVS deployment analysis with Computed Tomography (CT) images, the reconstruction methodology proposed by Athanasiou *et al.* [21] will be followed. The method will extract the interface of the scaffold that will be used to extract the corresponding measures. Moreover, using the stent profile, ISR will be also evaluated. The output of the 3D Reconstruction and plaque characterization tool will be used in the Deployment Module. Specifically: (i) all the information of the pre-treatment vessel and plaque will be used to create the 3D Finite Element (FE) model of the stenotic coronary artery, where the FE model of the drug-eluting BVS will be virtually deployed, (ii) the post-deployment vessel and drug-eluting BVS reconstructed geometries will be used for the validation of the Deployment Module.

An overview of the architecture of the 3D Reconstruction and plaque characterization tool is presented in Fig. 1.

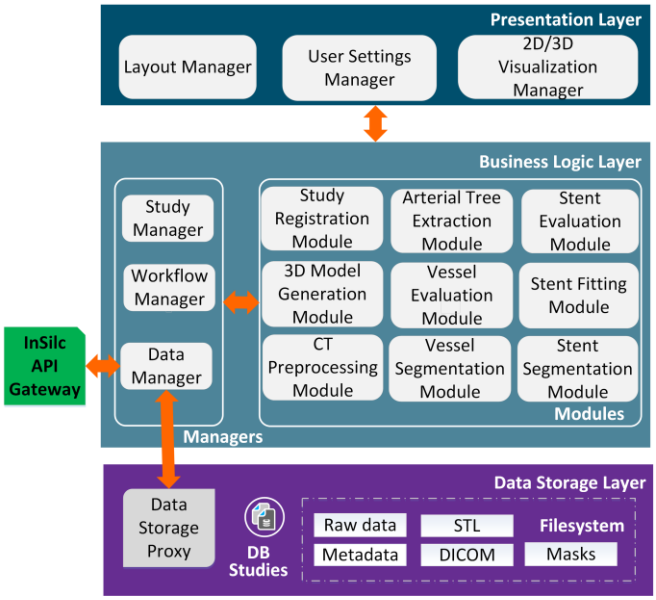

Figure 1. Detailed architecture of 3D reconstruction and plaque characterization tool.

The 3D Reconstruction and plaque characterization tool is based on a multilayered architecture consisting of the following layers:

(i) **Data storage layer**. This layer is responsible for storing the data in the filesystem and handling access to them. It includes the databases and the data storage proxy.

(ii) **Business Logic layer**. This layer includes all the algorithms and methods for performing the segmentation of the artery, the plaques and the BVS, the creation of the 3D geometries and the metadata extraction. The following modules are common for all imaging modalities: the vessel segmentation module, the vessel evaluation module, the 3D model generation module, and the Study registration module, whereas the Stent Segmentation module, the Stent fitting module, the Stent evaluation module, the Arterial tree extraction module and the CT preprocessing module are applicable when CT images are employed.

(iii) **Presentation Layer**, which includes the modules that are related to the user interface. Specifically, the following modules are included: Layout manager, User Settings Manager and 2D/3D Visualization.

Depending on the imaging modality (IVUS/OCT, CT) different information flows are followed. The information flow, which is focused on the process of stent segmentation and evaluation for IVUS/OCT cases is presented in Fig. 3. The process is the following:

Step 1. The user should select the medical data of a study (DICOM images IVUS/OCT and angiography), select the appropriate stent deformable model and annotate the centerline points of the lumen on the biplane angiography.

Step 2. Using the selected images, two separate segmentations will be performed in order to identify the vessel lumen and outer wall and the stent struts.

Step 3. The segmentation results will be combined with the centerline points that were annotated by the user during the first step, in order to transform the vessel lumen and wall and the struts into the original 3D space.

Step 4. A 3D stent model is constructed, using the transformed 3D point cloud of the struts and the stent deformable model that was selected in Step 1. The deformable model is transformed in such a way that fits into the arterial geometry.

Step 5. The 3D geometries of the vessel (lumen and outer wall), plaques and stent are extracted. **Step 6**. Several measures for the evaluation of the vessel (stenosis size, plaque burden, vessel length, area, perimeter) and the stent scaffold are extracted (fracture detection, number of unopposed struts, etc.) The information flow diagram, which is focused on the process of stent segmentation and stent segmentation and evaluation for CT cases, is the following:

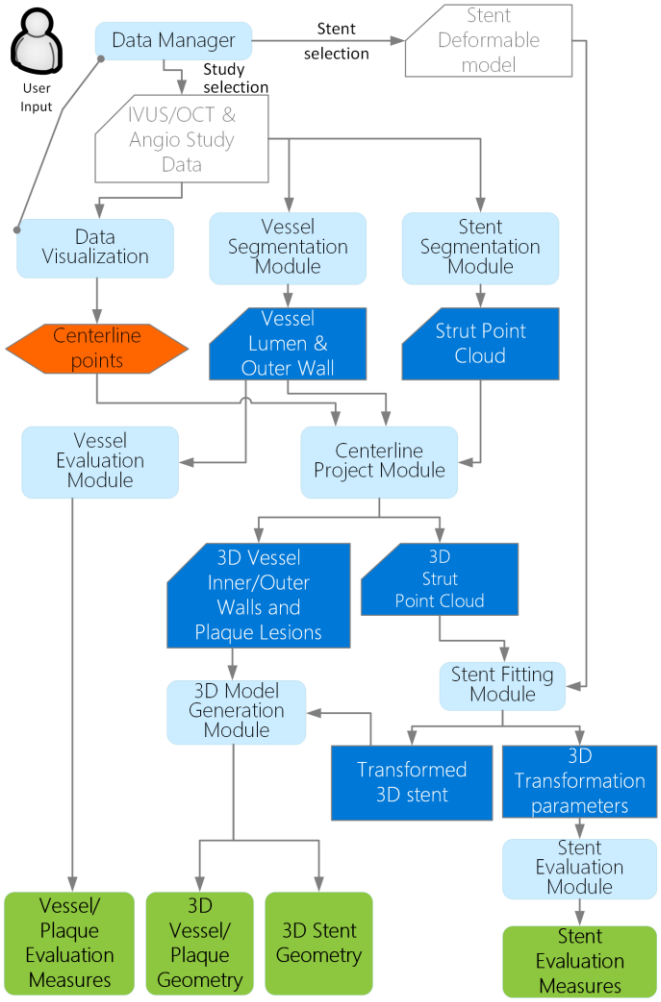

Figure 2. Information flow of 3D reconstruction and plaque characterization tool (IVUS/OCT case).

Step 1. The user should select the medical data of a study (CT images).

Step 2. The CT images go through a preprocessing stage which contains a filter that removes irrelevant details and identifies vessel candidate regions.

Step 3. The user should annotate the starting and ending points of the vessel segment.

Step 4. This step performs either a segmentation of the vessel or extraction of the complete arterial tree. The 3D models of the vessel lumen, wall and plaques are generated.

Step 5. The 3D geometries of the vessel (lumen and outer wall), plaques and stent are extracted into a suitable format.

Step 6. Several measures for the evaluation of the vessel are extracted (stenosis size, plaque burden, vessel length, area, perimeter, etc.).

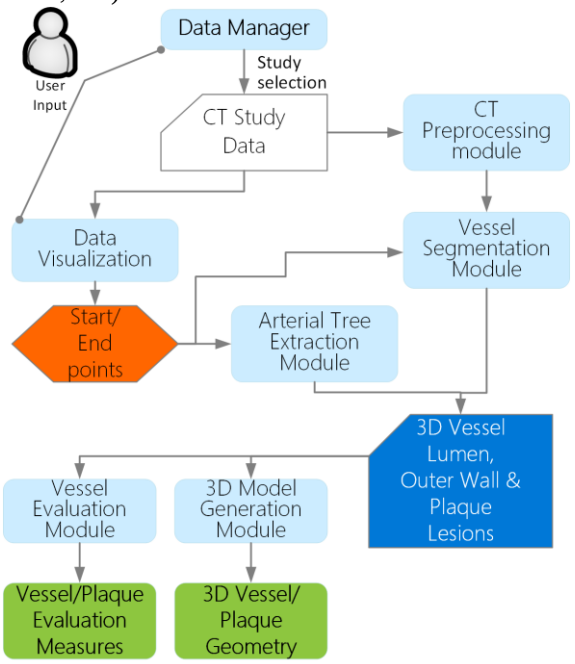

Figure 3. Information flow of 3D reconstruction and plaque characterization tool for the CT case.

The 3D reconstruction and plaque characterization tool is based on VTK [22] , ITK [23], and VMTK [24] platforms and developed in C# and C/C++.

II. Conclusion

The present manuscript presented a novel *in silico* platform for clinical trials involving stent deployment. Focus was given to the multi-modality 3D reconstruction and plaque characterization tool which will be used both from the scientists in order to evaluate the accuracy and efficacy of the platform and the end-user physicians for case specific stent deployment simulations.

The tool will integrate functionalities such as the automatic reconstruction of 3D arterial wall and plaque components and the stent scaffolds. All the above will be implemented in a user-friendly graphical environment. Extensive validation of the software will be followed based on retrospective and prospective data collected during the project.

References

[1] F. Sanchis-Gomar, C. Perez-Quilis, R. Leischik, and A. Lucia, "Epidemiology of coronary heart disease and acute coronary syndrome," *Ann Transl Med*, vol. 4, no. 13, Jul. 2016.

[2] A. K. Shrivastava, H. V. Singh, A. Raizada, and S. K. Singh, "C-reactive protein, inflammation and coronary heart disease," *The Egyptian Heart Journal*, vol. 67, no. 2, pp. 89–97, Jun. 2015.

[3] T. Lancet, "40 years of percutaneous coronary intervention: where next?," *The Lancet*, vol. 390, no. 10096, p. 715, Aug. 2017.

[4] "Coronary stent market Size To Reach $15.2 Billion By 2024." [Online]. Available: https://www.grandviewresearch.com/press-release/global-coronary-stent-industry.

[5] B. Varda *et al.*, "National rates and risk factors for stent failure after successful insertion in patients with obstructed, infected upper tract stones," *Can Urol Assoc J*, vol. 9, no. 3–4, pp. E164–E171, 2015.

[6] R. A. Byrne, M. Joner, and A. Kastrati, "Stent thrombosis and restenosis: what have we learned and where are we going? The Andreas Grüntzig Lecture ESC 2014," *Eur Heart J*, vol. 36, no. 47, pp. 3320–3331, Dec. 2015.

[7] E. Charpentier, A. Barna, L. Guillevin, and J.-M. Juliard, "Fully bioresorbable drug-eluting coronary scaffolds: A review," *Archives of Cardiovascular Diseases*, vol. 108, no. 6, pp. 385–397, Jun. 2015.

[8] R. A. Byrne *et al.*, "Report of an ESC-EAPCI Task Force on the evaluation and use of bioresorbable scaffolds for percutaneous coronary intervention: executive summary," *Eur. Heart J.*, Aug. 2017.

[9] R. D. Alexy and D. S. Levi, "Materials and Manufacturing Technologies Available for Production of a Pediatric Bioabsorbable Stent," *BioMed Research International*, vol. 2013, p. e137985, Sep. 2013.

[10] R. B. Colquitt, D. A. Colquhoun, and R. H. Thiele, "In silico modelling of physiologic systems," *Best Pract Res Clin Anaesthesiol*, vol. 25, no. 4, pp. 499–510, Dec. 2011.

[11] "InSilc: In silico trials for drug-eluting BVS development and evaluation." [Online]. Available: https://insilc.eu/. [Accessed: 17-Jan-2018].

[12] N. Filipovic, N. Dalibor, I. Saveljic, T. Exarchos, and O. Parodi, "Experimental testing and numerical modelling of stents in the coronary arteries," *Contemporary Materials*, 2016.

[13] A. Sakellarios, G. Rigas, T. Exarchos, and D. Fotiadis, "A methodology and a software tool for 3D reconstruction of coronary and carotid arteries and atherosclerotic plaques," *Conference on Imaging Systems and Techniques (IST)*, 2016.

[14] D. Martin and F. J. Boyle, "Computational structural modelling of coronary stent deployment: a review," *Comput Methods Biomech Biomed Engin*, vol. 14, no. 4, pp. 331–348, Apr. 2011.

[15] H. Tahir, I. Niculescu, C. Bona-Casas, R. M. H. Merks, and A. G. Hoekstra, "An in silico study on the role of smooth muscle cell migration in neointimal formation after coronary stenting," *J R Soc Interface*, vol. 12, no. 108, p. 20150358, Jul. 2015.

[16] C. Chiastra *et al.*, "Computational fluid dynamic simulations of image-based stented coronary bifurcation models," *J R Soc Interface*, vol. 10, no. 84, p. 20130193, Jul. 2013.

[17] K. May-Newman and A. D. McCulloch, "Homogenization modeling for the mechanics of perfused myocardium," *Progress in Biophysics and Molecular Biology*, vol. 69, no. 2–3, pp. 463–481, Mar. 1998.

[18] L. Lei, S.-R. Guo, W.-L. Chen, H.-J. Rong, and F. Lu, "Stents as a platform for drug delivery," *Expert Opin Drug Deliv*, vol. 8, no. 6, pp. 813–831, Jun. 2011.

[19] J. S. Soares, J. E. Moore, and K. R. Rajagopal, "Constitutive framework for biodegradable polymers with applications to biodegradable stents," *ASAIO J.*, vol. 54, no. 3, pp. 295–301, Jun. 2008.

[20] A. I. Sakellarios *et al.*, "Prediction of Atherosclerotic Plaque Development in an In Vivo Coronary Arterial Segment Based on a Multilevel Modeling Approach," *IEEE Trans Biomed Eng*, vol. 64, no. 8, pp. 1721–1730, Aug. 2017.

[21] L. Athanasiou *et al.*, "Three-dimensional reconstruction of coronary arteries and plaque morphology using CT angiography – comparison and registration with IVUS," *BMC Med Imaging*, vol. 16, Jan. 2016.

[22] "VTK - The Visualization Toolkit." https://www.vtk.org/.

[23] "ITK - Segmentation & Registration Toolkit." https://itk.org/. [Accessed: 28-Jan-2018].

[24] "vmtk - the Vascular Modelling Toolkit." http://www.vmtk.org/.