InSilc: a cloud platform for *in silico* clinical trials for bioresorbable vascular scaffolds *

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***Abstract*—Coronary artery disease (CAD), the most common cardiovascular disease, is the leading cause of mortality in Europe and worldwide. Recent years have introduced drug-eluting Bioresorbable Vascular Scaffolds (BVS) for the treatment of atherosclerosis. InSilc is an *in silico* clinical trial (ISCT) platform that targets the development and assessment of drug-eluting BVS. Specifically, the platform predicts through the application of multi-disciplinary and multiscale models the performance of drug-eluting BVS in the short and medium/long term. In this study, we present the InSilc overall and detailed architecture, the users, the involved *in silico* modules and their communication, as well as the key blocks required for the implementation of the platform from the technological perspective.**

I. Introduction

Coronary artery disease (CAD) is caused by the accumulation of atherosclerotic plaques inside the coronary arteries. This disease is the leading cause of mortality in Europe and worldwide, causing more than 4 million deaths per year [1]. To treat the arterial disease, percutaneous coronary intervention (PCI) is the most widely performed interventional procedure. The innovation in stents, from the engineering perspective, enabled the delivery and expansion of such tubular scaffolds in narrowed coronary arteries achieving the recovery and restoration of blood flow.

The global market of coronary stents is vast and dynamic and is rapidly growing, as a result of the: (i) increase in the CAD prevalence, (ii) innovations in stent technology related to the platform, the material, the coating and the drug, and (iii) need for effective therapies with reduced risk of complications, such as in stent restenosis (ISR) and thrombosis. In 2011, the sales of stents reached approximately €7.1 billion, while it is estimated that this number will reach €15.2 billion till 2024 [2].

Initially, bare metal stents (BMSs), made from metallic materials, were developed to overcome the ISR triggered by recoil. A reduction in ISR was achieved through appropriate modifications and improvements of the stent platform, such as utilization of new metals and design of thinner stent struts [3]. Later, the introduction of new drug delivery systems and the evolution in polymer coatings allowed the Drug-eluting stents (DESs) to achieve better clinical outcomes, in terms of reduced numbers of cardiac death, myocardial infarction and vessel revascularization [4].

However, increased rates of stent thrombosis were also reported in first- and second-generation DESs [5]. This could be explained by the fact that the permanent delivery of a metallic platform may prevent the natural healing of the arterial wall and contributes to a prolonged inflammatory response and in turn poor clinical outcomes. PCI with a bioresorbable vascular scaffold (BVS) has emerged as an alternative, since the materials used degrade over time and the presence of the scaffold in the coronary artery is transient. The concept behind bioresorbable materials is that such materials can initially provide the necessary radial force and mechanical support until the scaffold degrades, allow the secretion of the anti-proliferative drug, achieving the prevention of neoatherosclerosis development, stent fracture and stent thrombosis [6].

Nowadays, to ensure the safety and efficacy of a BVS, the scaffold should be initially tested in laboratory settings, (*in vitro*) (EN 14299), then on animals (*in vivo*) (EN 14299, EN ISO 14630, EN 12006-3) and finally on patients, though clinical studies [7].

With stricter requirements from the regulatory perspective, stent manufacturers should provide evidence on the low risk for stent failure. Therefore, stent mechanical testing is performed *in vitro* to support the stent designers and developers to gather and evaluate performance data prior to device approval and clinical application. The *in vitro* testing concerns, among other, the mechanical evaluation of the metals and polymers, the compression and flexural testing of the complete scaffold, as well as the dynamic simulation of pressure pulsation.

Through the history of vascular stents, a variety of animal studies have been performed using mouse, rabbits, and pigs [8] with the aim of: (i) providing a better understanding of the vessel healing and the ISR pathophysiology, (ii) evaluating the feasibility of new stents, (iii) testing the efficacy and safety of a stent in terms of improved clinical outcomes. Following the *in vitro* and animal studies, different phases of clinical studies are performed, usually carried out in three phases prior to the product launch in the market [9]: (i) *Phase I.* xxxxxxxxxxxx. (ii) *Phase II and Phase III.* The stent is tested on a larger number of patients to test its effectiveness (Phase II) and in multiple hospitals and countries, with a much larger number of

* This work is 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. This work reflects only the author's view. The Commission is not responsible for any use that may be made of the information it contains.

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patients to test its efficacy (Phase III). To further assess and compare the efficacy and effectiveness of a stent, compared to the existing in the market stents, in a wider population with diversities in CAD severity, medications, comorbidities, post-marketing studies are conducted.

However, the complex nature of CAD disease results in a significant difference among patients and a subsequent variability in the anatomy and pathology of the diseased arteries. As a result, a BVS may behave extremely well during controlled laboratory and animal testing, but not have the same satisfactory performance during or after clinical trials. In such case, even if insights on the safety or effectiveness of BVS are provided, there is no indication on the reason behind this failure and on the potential improvements or modifications that could be applied.

InSilc is a cloud-based *in silico* clinical trial platform for designing, developing and assessing drug-eluting bioresorbable vascular scaffolds (BVS) [10]. The platform is built taking into consideration the biology mechanisms and applies biomedical knowledge and advanced *in silico* approaches, towards simulating the BVS implantation performance and the associated interaction with the individual cardiovascular physiology. Specifically, the multidisciplinary and multiscale *in silico* models simulate the BVS mechanical, deployment and degradation behaviour, the fluid dynamics (micro- and macroscale) and the myocardial perfusion and predict the short- and medium/long term BVS-arterial wall interaction.

The objective of the study is to present the InSilc overall and detailed architecture, the users, the involved *in silico* modules and their communication, as well as the key blocks required for the implementation of the platform from the technological perspective.

I. Materials And Methods

A. InSilc Users

The users of InSilc platform can be grouped in the following categories: (i) ***Stent Industry experts.*** The InSilc platform has as a primary target the Stent Industry (User role hierarchy: High). The design and development of a medical device of Class III and stent, in particular, is a highly complex, standardized process subject to numerous directives and regulations. Therefore, the cost and risks of stent design and development are of particular interest and the investments performed in design verification and validation are enormous. Through InSilc platform, the stent industry experts are able to test their devices using state-of-the-art *in silico* models and resources made available by high profile research organizations. Moreover, InSilc includes a Virtual Case repository (virtual patients) annotated with specific anatomical criteria. The users are able to define a population according to their intended use and apply the simulation modules to virtual cases of high interest. (ii) ***Contract Research Organizations (CROs).*** CROs *(*User role hierarchy: High) primary interest is the efficient clinical study design for ensuring that the study endpoints are statistically sound with the minimum number of patients. The InSilc platform assists the CROs to efficiently define specific inclusion/exclusion criteria based on the Virtual Case repository and apply appropriate statistical and data analytics methods to minimize the number of required patients for specific endpoints. (iii) ***Interventional Cardiologists.*** The Interventional Cardiologists (User role hierarchy: Medium) use the InSilc platform for evaluating the performance of a specific stent and decide on the scaffold that can minimize the post implantation complications. (iv) ***Researchers.*** The Researchers (User role hierarchy: xxxxxxxxx) have access to the Virtual Case repository and to a pool of Stent computer-aided design Models. These users may download high fidelity CAD models for research only purposes and through the platform available data, register a model/computational resource as a "under validation" model and use the InSilc with supported solvers to run the simulation on a number of pre-validated meshes (geometries and stents).

C. Conceptual Architecture

The conceptual architecture of InSilc is presented in Fig. 1. The main features of the InSilc conceptual architecture are: (i) The tools and apps provided to InSilc users. InSilc Web APP is the interface between the end-users and the InSilc cloud infrastructure and services. (ii) The cloud hosted workflow engine for the realization of InSilc *in silico* clinical trials. (iii) The modules of InSilc platform.

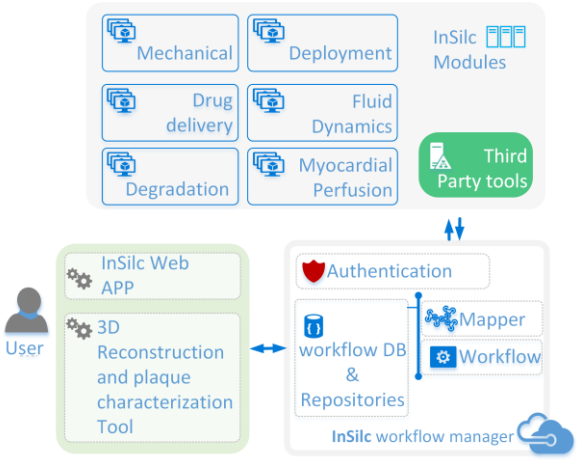

Figure 1. InSilc conceptual architecture.

D. InSilc modules

The modules of the InSilc platform are the following:

Mechanical Modeling Module. The aim of Mechanical modeling Module is the creation of a number of Finite Element (FE) simulations mimicking the *in vitro* mechanical testing. The following mechanical tests are simulated *in silico*: foreshortening, dogboning, radial force, local compression, crush resistance with parallel plates, three point pending and fatigue [11]. Risk of fatigue failure is also calculated using fatigue criteria for the metal stents with polymer.

3D Reconstruction and plaque characterization tool. The 3D reconstruction and plaque characterization tool is a standalone application which is not embedded in the final InSilc platform but rather exchanging data with InSilc Cloud via REST services. The 3D reconstruction and plaque characterization tool is used for imaging data analysis (CT, OCT, IVUS) for virtual case repository creation and other module validation (during the platform development and

validation). In detail, this tool performs the 3D reconstruction of the arterial tree including the lumen, the outer wall, as well as the calcified and non-calcified plaques [12].

Deployment Module. The purpose of this module is the simulation of the drug-eluting BVS implantation within stenotic coronary artery models reconstructed from patient-specific images. This simulation provides detailed information of the short-term outcome post BVS implantation. In particular, it allows evaluating: (i) the BVS configuration and vessel anatomical changes after BVS deployment, and (ii) the stresses and strains within the BVS and arterial wall due to the balloon-stent-wall interaction [13].

Fluid Dynamics Module. The purpose of this module is to simulate the blood flow in coronary segments containing a BVS. The part of the module that is integrated in the InSilc platform focuses on the macroscopic environment. The microscopic blood flow simulations (3D in-stent restenosis model –ISR3D) is carried out in parallel to validate the assumptions made using the macroscopic approach [14], [15]. The ISR3D is a multiscale model of tissue growth and proliferation in stented coronary vessels under flow conditions. It is composed of several single-scale sub-models, each with its own spatial and temporal scale, that are used to model blood flow inside the vessel, stent deployment and tissue growth and proliferation. These sub-models communicate relevant values to each other during the simulation.

Myocardial perfusion Module. The purpose of the Myocardial perfusion Module is to simulate the post-treatment recovery and estimate post-intervention performance of the BVS in improving myocardial perfusion [16]. The Myocardial perfusion Module is coupled to the Fluid dynamics module to provide more accurate distal resistance boundary conditions in scenarios where the flow distribution changes after treatment with a BVS.

Drug-delivery Module. The Drug-delivery Module simulates the 3D modelling of drug release [17] using novel types of anti-proliferation drugs, accounting on the flow-mediated convection of drug and the transmural delivery of drug inside the carrying polymer and porous tissue.

Degradation Module. The Degradation Module predicts the medium- to long-term mechanical performance of implanted BVS. In detail, it includes: (i) the spatiotemporal progression of mechanical degradation within the scaffold, (ii) the associated stress and strains states within BVS and (iii) the stress, strain and deformation within the vessel as degradation progresses are provided.

E. Detailed Architecture

The detailed architecture of InSilc is presented in Fig. 2 as a layer diagram. The first layer is a service invocation workflow, where the Experiment Setup performed in the InSilc Web App is forwarded to the Workflow Manager via rest services. Experiment setup is validated and if it is valid the workflow manager is using the workflow registry to convert the experiment setup (JavaScript Object Notation - JSON object) to a workflow definition, decompose to workflow tasks and also create the number of user provided input files for starting the workflow. The second layer is a pool-based workflow engine, where the tasks decomposed are assigned (or requested) by workflow agents. Workflow agents retrieve tasks and related task input from the InSilc cloud and execute the task on their own workspace (residing on cloud or on distributed InSilc nodes). The communication between the InSilc Cloud Workflow Manager and the Workflow agents is proxied by InSilc Hubs. The third layer resides inside workflow agents. Many agents may execute tasks using an internal workflow engine (agent specific nested workflows).

In detail, the key blocks of this architecture are: (i) InSilc Web App. The InSilc web could be considered as the Science Gateway of the InSilc platform and consists of a number of client modules (Html/Javascript/Typescript) that implement the front end of the Science Gateway connected with the InSilc Cloud through InSilc REST API. (ii) InSilc Cloud. InSilc Cloud is used as a back-end for the InSilc Web and workflow orchestration. The InSilc Private cloud consists of the REST API, the Experiment Setup Manager, the Data Query/ provider, the Workflow Manager and the Workflow Registry. (iii) InSilc Hub Node. InSilc workflow execution is performed distributed on several premises or cloud InSilc Hub Nodes based on the pool architecture pattern. InSilc Hub nodes hosts a number of workflow agents. Each InSilc Hub nodes hosts a number of agents that are executing workflow tasks. (iv) InSilc Cloud File and Database storage. The InSilc Cloud Database Storage employs Structured Query Language (SQL) and NoSQL databases for the storage of InSilc database entities as well as event and audit logs for monitoring and traceability purposes. InSilc Cloud File Storage includes the Stent Repository, the Virtual Case Repository and the Result Repository.

The main interactions in the architecture are the following (presented in numbered circles in Fig. 2): (1) InSilc Web App is exchanging data with the InSilc Cloud via the InSilc REST API. (2) The REST API uses the Data Query/Provider to select the Virtual Population/Stent(s)/Virtual Test(s) and parameters of the experiment. (3) The InSilc REST API uses the Experiment Setup Manager for the validation of the experiment/simulation configuration provided by users. (4) The Experiment setup provided by the user is translated to a Workflow definition and corresponding tasks that the Workflow Manager handles. (5) The Workflow Manager uses the Workflow Registry in order to assign tasks to specific agents. (6) The InSilc Hubs are used to get the tasks assigned to agents residing in the same InSilc Node and also notify workflow manager for task execution. (7) The InSilc Hub gets a task assigned to a specific agent from the Workflow Manager and invokes the corresponding agent with the specific task definition (JSON task description). When a task either completes or fails the Hub notifies the task manager. (8) The Workflow agents get all required input files (artery/stent CADs, results etc.) for the task. (9) The Workflow agents may invoke (if required by the task) solvers using Local HPC resources through an automation script supported by each solver.

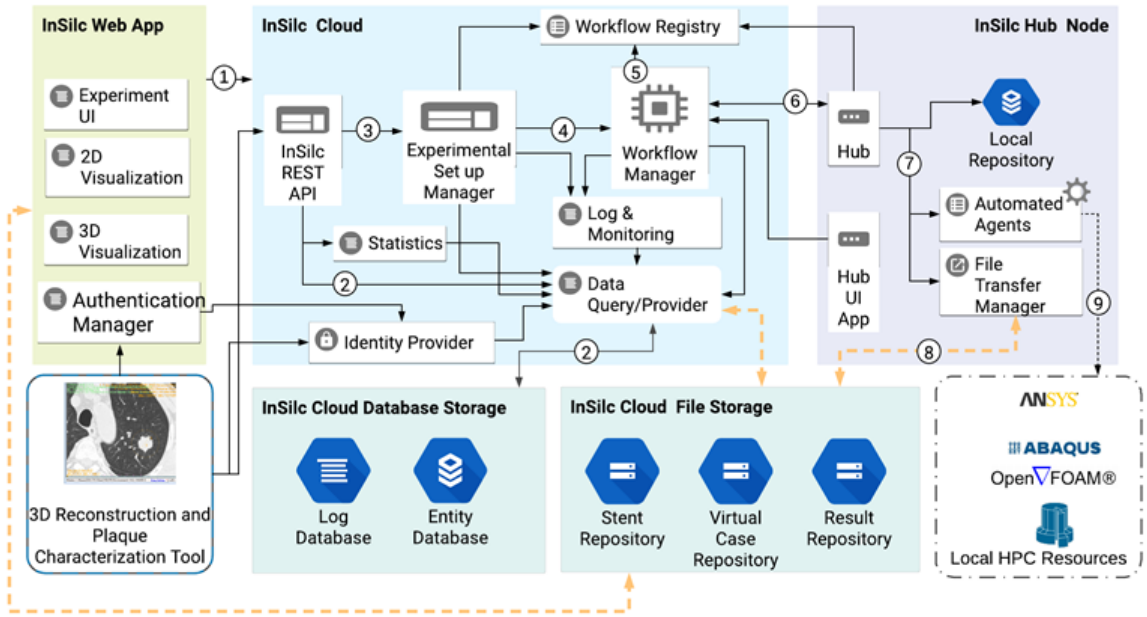

Figure 2. InSilc detailed architecture.

F. *Scenarios*

InSilc plays an important role in refining and reducing the cost of the preclinical assessment of BVS and complements the real clinical trials by offering the ability to examine the following "use-case scenarios": (i) *Scenario I:* xxxxxxxxxxxxxxxx (ii) *Scenario II:* xxxxxxxxxxxxx, (iii) *Scenario III:* xxxxxxxxxxxxxxxxx, (iv) *Scenario IV:* xxxxxxxxxxxxxxxxxxxxxxxxx.

II. Conclusion

In the current manuscript, the architectural design of InSilc platform was presented. To achieve this, the key phases of the software development life-cycle according to ISO 12207 [18] were followed, including user need analysis and user-requirements, specification of functional and non-functional system requirements. InSilc is a collaborative *in silico* Cloud platform that through the utilisation of multi-disciplinary data and multi-scale computational models achieves the translation of data into predictors of short and medium/long term BVS implantation outcomes and provides the opportunity for: (i) improving the complete development chain of BVS, (ii) predicting BVS performance in the human arterial anatomy, (iii) reducing the animal testing, (iv) reducing, refining, and partially replacing real clinical trials.

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