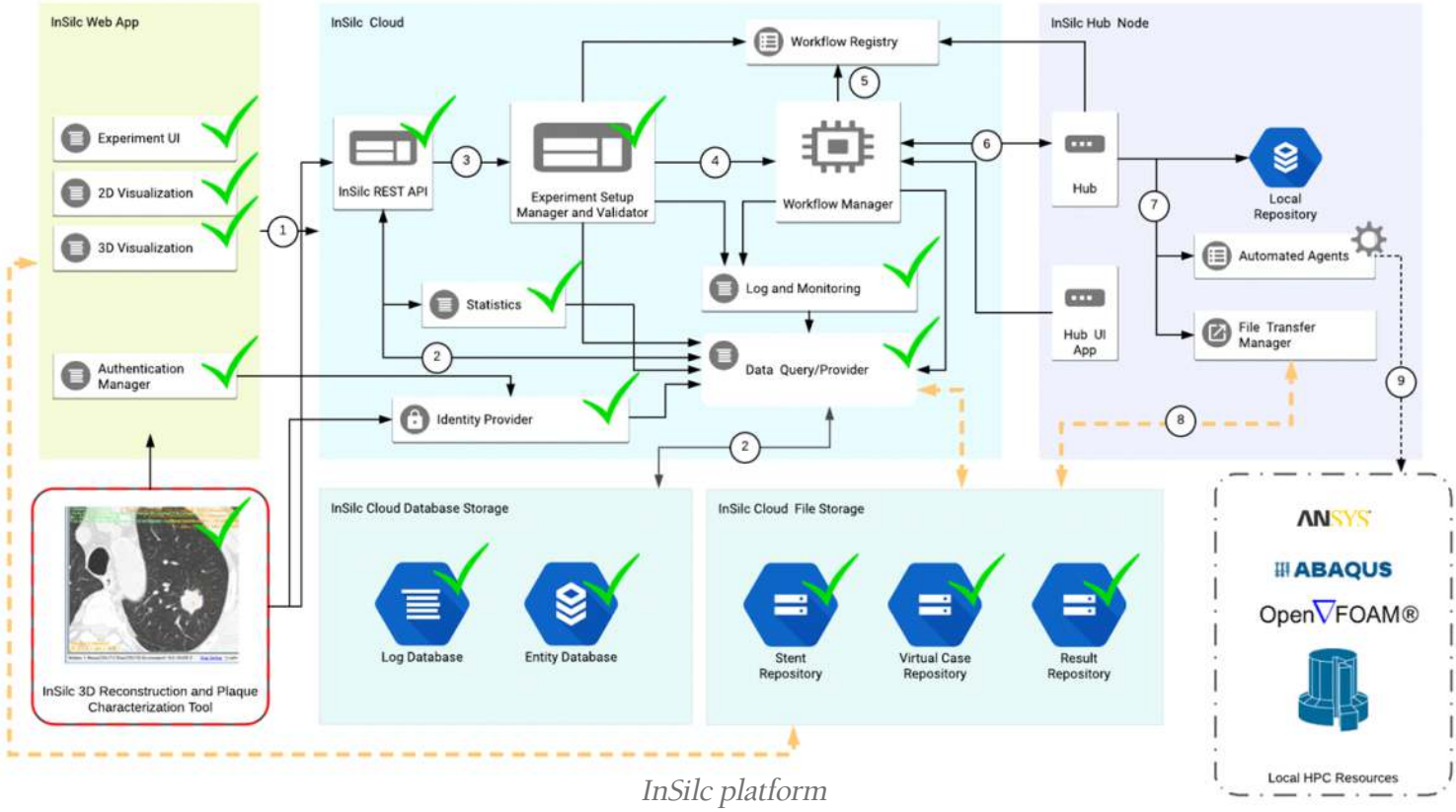
NEWSLETTER 3

***In silico* trials for drug-eluting BVS design, development and evaluation**

Introduction

InSilc is a Cloud based platform integrating beyond the state of the art *in silico* multiscale and multidisciplinary models towards the delivery of optimized and advanced prediction of short and medium/long term Bioresorbable Vascular Scaffolds (BVS) performance.

As InSilc project is currently at its 3rd year of implementation, all technical modules are now implemented and are in the validation phase towards their integration in the Cloud platform. In this newsletter the reader can find information on the individual modules.



InSilc platform

This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 777119

3D Reconstruction and plaque characterization Tool & Virtual Population

The 3D Reconstruction and plaque characterization tool is an integrated software tool that can be used to accurately reconstruct a part of the arterial tree including the lumen, the outer wall, as well as the plaques.

The "virtual" population database allows the evaluation of BVS efficacy and safety and the prediction of the interaction with the surrounding environment and the scaffold performance through the different virtual scenarios.

The project is funded by the European Union

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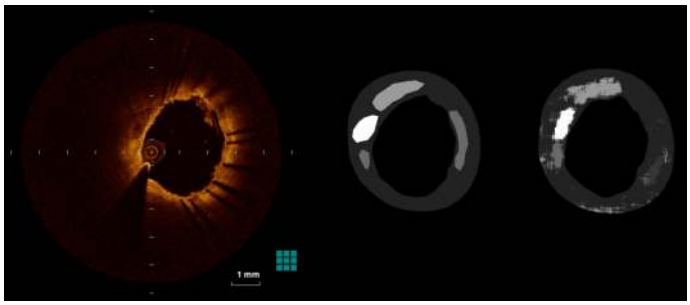
In silico trials for drug-eluting BVS design, development and evaluation

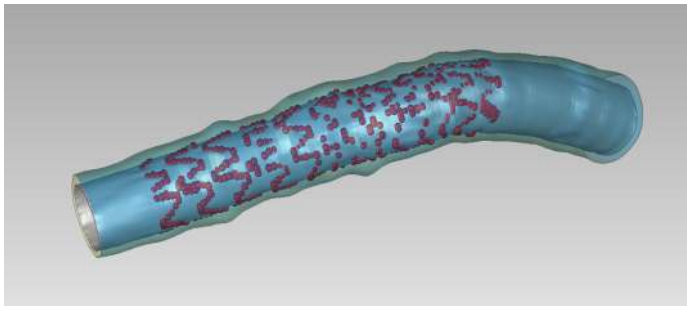


Case example of plaque characterization of human OCT frame. Left: original OCT frame, middle: manual annotation, right: output of the model.

The InSilc 3D reconstruction and plaque characterization tool is the only available comprehensive application software which enables the reconstruction of the coronary arteries using several imaging modalities (CTCA) or using the fusion of them (IVUS or OCT and X-ray angiography). Using fusion of Optical Coherence Tomography (OCT)/ Intra-Vascular Ultrasound (IVUS) and angiography, four plaque types can be identified: calcified, lipid, fibrous, fibrofatty.

The methodology combines and integrates several novel algorithms and provides advanced functionalities, such as the automate calculation of significant metrics for the disease assessment or the manual correction of the identified borders in several views. The developed algorithms have been validated by using human and animal experimental data annotated by experts and have been fully integrated into a user friendly tool.

For the development of "virtual" patients database, a two-step approach is followed; (i) development of a novel plaque growth model, which simulates the progression of atherosclerotic disease providing new "virtual" arterial geometries, using as input realistic patients' data. The information concerns pathologic clinical conditions, such as hypertension, diabetes, tachycardia including also other patient characteristics (age, gender), (ii) creation of "virtual" patient's clinical data, generated based on real data from a real patient population.

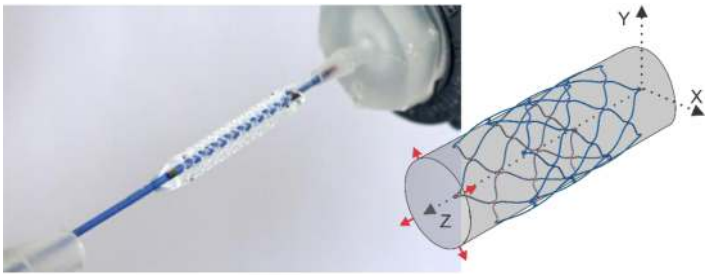


3D stent representation

Mechanical Modeling Module

The Mechanical Modeling Module provides a new approach to end users by providing them all stent standard tests *in silico*.

The Mechanical Modelling Module consists of a number of FE simulations mimicking the *in vitro* mechanical testing according to ISO 25539. Among the *in silico* tests are the dimensional verification, foreshortening, dogboning, radial force, local compression, crush resistance with parallel plates, three point pending and fatigue.



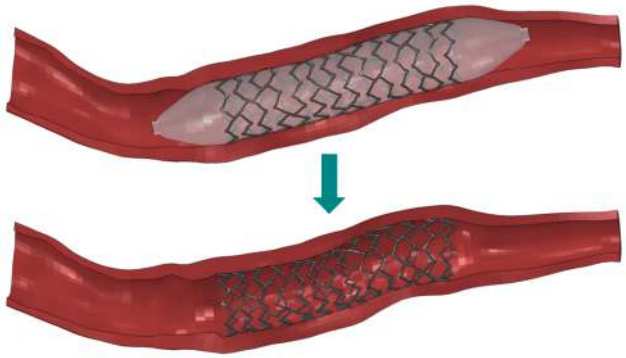
In silico inflation step

Deployment Module

The purpose of the model is to make an *in silico* prediction of the effects of the stenting procedure just after the stent deployment.

The Deployment Module, numerically replicates the main three phases of the stent deployment procedure by using numerical analyses based on the Finite Element Method (FEM) and simulations.

These numerical simulations have been built as a sequence of three steps, each one associated with the phases of the real deployment process. The adopted numerical strategy has been tested and validated by comparing the numerical results to the experimental evidence of *in vitro* studies (the deployment procedure was performed within 3D printed mock vessels) and *in vivo* animal cases.



In silico deployment step

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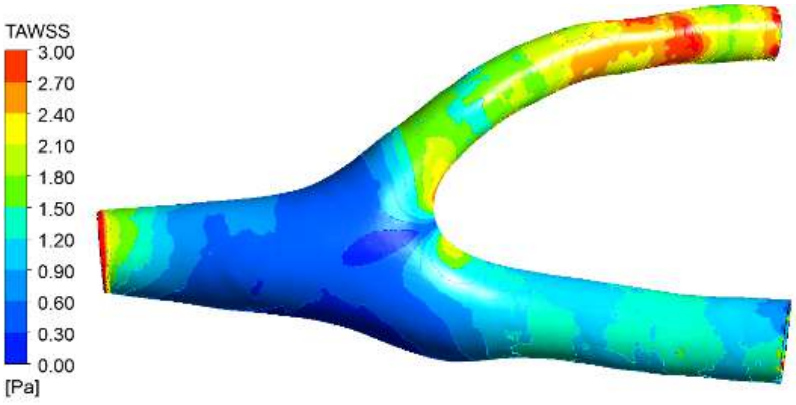
Fluid Dynamics Module

The Fluid Dynamics module focuses on developing tools for the InSilc pipeline to determine patient-specific velocity and wall shear stress patterns in human coronary arteries with a scaffold.

In this module, generation of appropriate protocols for the meshing procedure and definition of the patient specific boundary conditions has been approached from a macroscopic and microscopic point of view. For the latter we investigated the potential added value of integrating microscopic modeling into the InSilc project. Previously developed models are the so-called agent-based models. These models describe the vessel wall on a cellular level and can be used to predict in-stent restenosis. This is a complex process, leading to formation of new tissue inside the scaffold. It can lead to re-occlusion of the scaffolded segment.

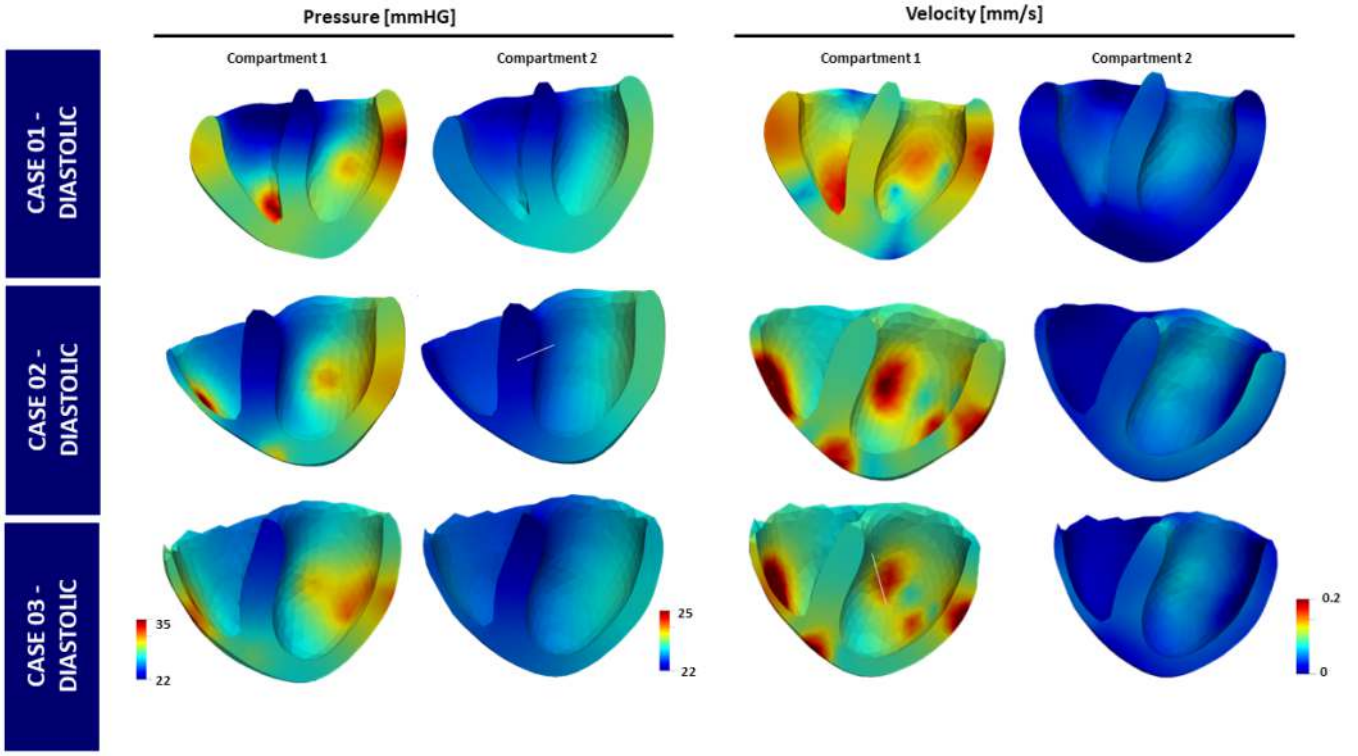


The Time-average Wall Shear Stress distribution in the coronary bifurcation for the mean flow rate.

Myocardial Perfusion Module

The utilization of the Myocardial Perfusion Module allows for a more realistic simulation of post-operative coronary flow.

The utilization of the Myocardial Perfusion Module allows for a more realistic simulation of post-operative coronary flow in patients with local myocardial perfusion defect by describing the local response of the cardiac muscle and the coronary autoregulation system. The goal of treating coronary disease by stenting is to improve the myocardial function. The predicted perfusions of the Myocardial Perfusion Module have been validated against CT measured perfusion maps and the results have shown that the myocardial perfusion predicted by the module can be used to predict major adverse cardiac events.



Pressure and velocity fields predicted by the myocardial perfusion model for three in the arteriolar and capillary compartments.

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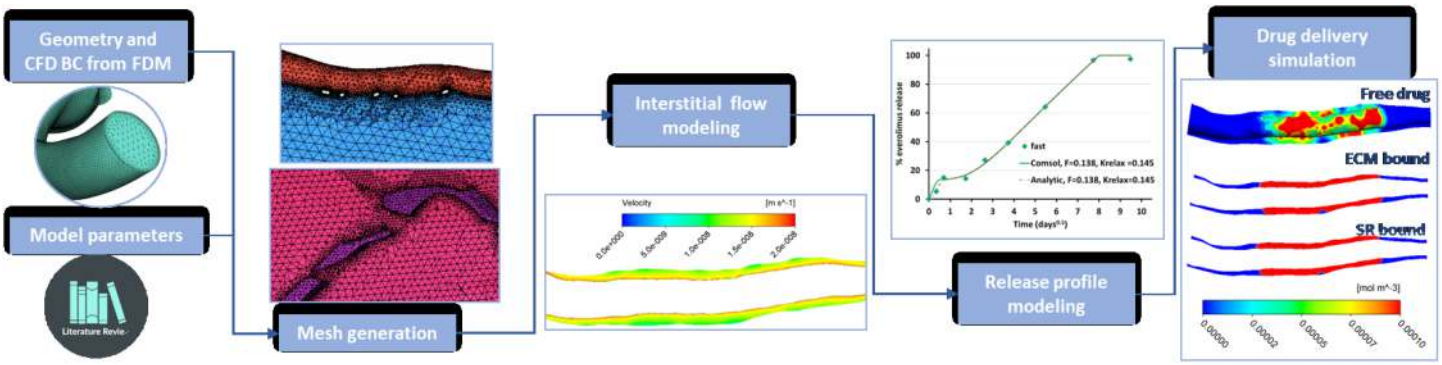
Drug-Delivery Module

Drug-Delivery is key for the performance of stent design, rendering the Drug-Delivery Module one of pivotal pillars of any *in silico* clinical trial to design and develop combination endovascular implants.



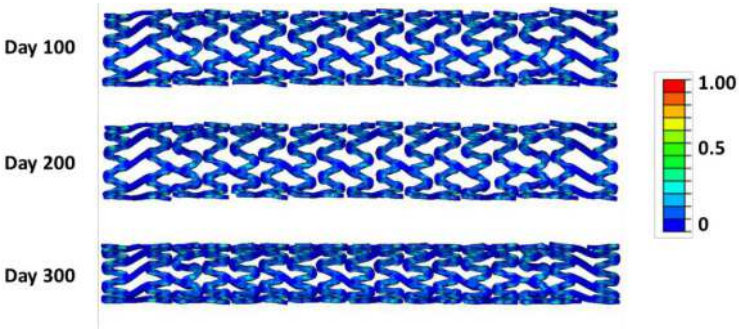
Drug-delivery module work flow

We developed and validated a Drug-Delivery Module to generate simulation-based estimates of drug uptake by the tissue over a long period of time to optimize the pharmacokinetics and design of endovascular implants, as well as correlating the biological responses and pharmacodynamics to localized drug distribution. Patient-specific geometries have been received from the Deployment Module and hemodynamic inputs have been provided by the Fluid Dynamics Module.

The Drug-Delivery module has been quantitatively verified and validated by comparing model-predicted drug occupancy and tissue drug uptake, against published results and experimental measures provided by device manufacturers. Validation results showed excellent agreement with *in vivo* tissue uptake in porcine arteries over a month of drug delivery, a standard duration for many preclinical studies.

Degradation Module

The InSilc Degradation module has been developed to predict the degradation and long-term mechanical performance of the several bioresorbable material / device systems, through an advanced modelling framework.



Contour plot shown maximum principal strain in the BSL prototype BVS deployed within a mock vessel

The Degradation Module predicts the long-term mechanical performance of the device, with the timeframe dependent on available material data (typically 1-2 years).

A key consideration during the development of this module has been to ensure compatibility with modelling approaches employed by the InSilc Deployment module, resulting in a consistent framework for both short-term and long-term mechanical behaviour.

This module's validation process uses *in vitro* experiments, whereby prototype BVS devices have been already been deployed into silicone-based mock vessels. The InSilc Degradation module predicts the implanted configuration of the device implanted in an artery and undergoing degradation.