SimInSitu
In-silico Development- and Clinical-Trial-Platform for Testing in-situ Tissue Engineered Heart Valves

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1. Introduction

SimInSitu (EU Grant agreement ID: 101017523) is aiming to develop a sophisticated in-silico method to predict the short- and long-term behaviour of in-situ tissue engineered heart valves by combing advanced tissue remodelling algorithms with a personalized virtual heart modelling approach. The method will be specifically developed to predict the complex transformation process of biodegradable heart valves from the initially synthetic scaffold into a fully remodelled & functional valve. This transformation process, named ETR for Endogenous Tissue Restoration, is the core technology for a new generation of very promising biodegradable vascular devices. ETR makes the use of animal derived tissue, which is used in the majority of commercially available bioprosthetic heart valves, obsolete and avoids thereby durability related issues and potentially minimized the need for reoperations. Though, significant progress was made during the past years in developing ERT based devices, it remains very challenging, costly, time-consuming, and rich with obstacles. New knowledge can only be generated through a tedious trial & error process (requiring preclinical and clinical studies), since the restorative process cannot be replicated in an in-vitro environment. Advanced Computer Modelling & Simulation technologies have the potential to overcome this limitation by allowing to test new designs, modified scaffold compositions, or other applications in a virtual patient-specific environment – in-silico.

2. The next generation of heart valves

Currently-available transcatheter heart valve technologies and biological heart valves are based on animal-derived tissues to generate valve leaflets. Specifically, the pericardial tissue from large

animals is used by manufactures to generate valve leaflets that are then constrained to the metallic stent frame by sutures. There is a pressing need in reducing the cost associated to animal models, including those associated to the facility and feeding of animals. Moreover, ethical issues related to the animal sacrifice exist. To reduce costs of fabrication, many manufactures such as Boston Scientific are developing new technology based on polymeric valve leaflets; however, the investigation is far from clinical application. Polymeric valve suffers from fatigue damage of leaflets leading to tears at the free edge or commissures due to stress concentration and loading cycles and thus fails at low number of cycles. Polyurethane valves have shown remarkable durability but none of them have yet managed to overcome the three Achilles' heels of polyurethanes, namely degradation, calcification and thrombosis. The SimInSitu project will investigated the next generation heart valves fabricated with biodegradable synthetic materials to eliminate the need for animal models and thus reduce the cost related to device fabrication. Synthetic electrospun-based Xeltis devices have demonstrated to be safe in clinical applications, suggesting a new paradigm for heart valve technology not based on animal tissue materials. In the SimInSitu project, the efficacy of synthetic valve leaflets materials will be investigated by in-silico modelling to provide a reliable approach to design the next generation of heart valves and thus offer a numerical framework to test the efficacy of synthetic valve materials even to other heart valve manufactures and research group. The SimInSitu project will therefore relax restrictions imposed by cost and ethical considerations.

3. In-silico modelling

Medical devices need thousands of tests in the development stage. Just as in other engineering field and industries, the design and efficacy of biomedical devices can be greatly improved by using computer-aided-engineering (CAE), which has played a central role in the design, testing and validation of many mechanical and aerospace products and has helped companies produce more effective, reliable and safe solutions. Biomedical device development has been lagging in the adoption of CAE as compared to other engineering fields because of the lack of accurate models, standards and validation processes. In the SimInSitu project, a combination of different techniques for CM&S including FSI will be adopted to model the complex interaction of the device with the human body and thus provide realistic physiological and physical device implantation scenarios. The SimInSitu project will therefore optimize the design phase of the next generation heart valves, using the Xeltis device portfolio as an example. With the success of the project, an in-silico technology will be delivered to simultaneously assess the safety and efficacy of heart valve devices, traditionally dealing with challenges in the designing phase and clinical trial evaluations. This will allow to reduce the time-to-market and speed-up the clinical application of the next generation of heart valves. Researchers of the SimInSitu project will provide particular attention to impact of numerical setting and uncertainty for the device modelling and validation to provide reliable and standard numerical workflows that could be used by regulatory authorities for the approval of medical device based on CAE solutions. We are willing to have direct dialogue with, and advice from, regulatory agencies, and practicing cardiologists to forecast in-silico trials for faster heart valve device authorization and safely extend applications to less symptomatic patients that may benefit in the future of earlier

treatment of moderate valvular diseases

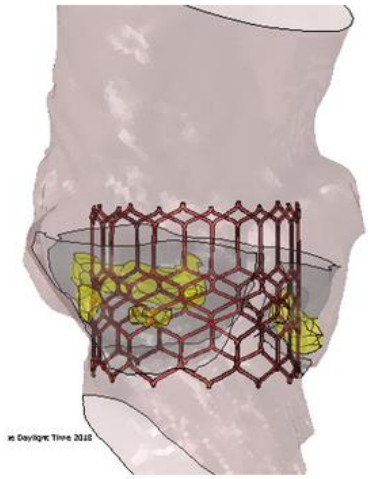

Figure 1 Development and V&V / Uncertainty Quantification hierarchy of the SimInSitu project

4. Tissue & Growth remodelling

Predicting the short terms response of the implanted electrospun heart valve is a central part of the SimInSitu project. The response of human body to the Xeltis endogenous restoring heart valve is governed by multiple mechano-biological factors that may lead to patient complications and ultimately the failure of the implanted device. The SimInSitu project will not only introduce novel bioengineering approaches for the design of heart valves but also addresses important basic science questions: How electrospun valve leaflets translate into a specific mechanical response and organ level function when the device is implanted? Does a bioispired material control of structure-function lead to a more desirable remodelling outcome in-vivo? The multidisciplinary team of SimInSitu consortium composed of clinicians and engineers will address the limited understanding of a number of important mechanisms associated to the device remodelling and outcome such as the biomaterial degradation and the inflammatory response after implantation, the de-novo tissue deposition on the electrospun leaflet scaffold, the cell recruitment and, most importantly, the stability of the newly formed tissue and its impact on the inter-species/patient variability. To address such important mechanisms, the SimInSitu project will combine experimental material testing with the state-of-the-art of computational growth & remodelling predicting tools. Demonstrating, in situ tissue regeneration on a clinically relevant model is a critical challenge for the field of heart valve tissue engineering.

5. Computer Modelling Credibility through VVUQ

Verification, Validation, and Uncertainty Quantification of computer models together with a hierarchical modelling approach will be the backbone of establishing credibility of in-silico

methods within SimInSitu. Together with external experts, the SimInSitu team will make use of well established ASME standard and will work within current initiatives to develop guidance and regulatory framework on CM&S for the medical device industry.

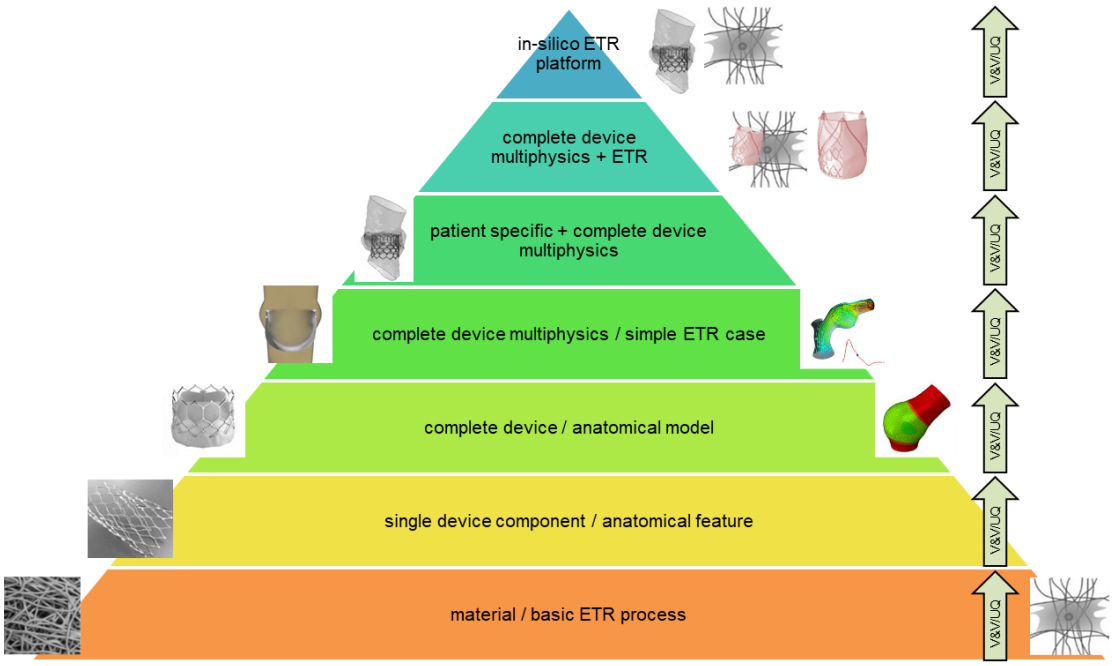

Figure 2 Development and V&V / Uncertainty Quantification hierarchy of the SimInSitu project