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SimCardioTest - Simulation of Cardiac Devices & Drugs for in-silico Testing and Certification

Technical Report: Report on the standardised models for left atrial appendage occluder (LAAO) devices

Work Package 3 (WP 3)
Use case 2: Left Atrial Appendage Occluder

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EXECUTIVE SUMMARY

This report defines the workflow for modelling left atrial appendage occluder (LAAO) devices of Use Case 2, detailing the standards and input-output formats of the different components to be implemented in the cloud-based platform of SimCardioTest, where the in-silico trials for device efficacy and safety will be run.

1. Introduction

The main goal of WP3 is to generate in-silico personalised haemodynamic indices of left atrial geometries, complementing their morphological analysis, to identify the risk of thrombus formation in atrial fibrillation patients, improve patient selection for the implantation of left atrial appendage occluders (LAAO) and optimise their settings (e.g., size, positioning). A computational modelling pipeline is then required for generating patient-specific meshes and patient-specific boundary conditions in a large number of cases. Extensive sensitivity analyses and model calibration are also needed to determine optimal methodological choices in fluid simulations, as well as detailed verification and validation (V&V) studies to assess the credibility of the developed models. Out of the simulation results, in-silico haemodynamic indices need to be derived to assess the risk of thrombus formation, predict the benefit of LAAO implantation and optimise device settings to minimise the risk of device-related thrombus (DRT), in combination with appropriate drug therapy. The computational modelling pipeline will then be integrated onto the InSilicoTrials platform to be developed in SimCardioTest for device manufactures to run in-silico trials in different contexts of use such as for determining the risk of DRT of different device settings on different populations, as part of the device certifications.

The modelling pipeline in Use Case 2 (UC2) is composed of several components developed by different partners of the SimCardioTest consortium, including medical data processing, finite-element mesh building, in-silico simulations, and visualisation interfaces, involving data from multiple sources and different software tools. Therefore, it is critical to consistently define inputs and outputs of the different components in a standardised format for ensuring seamlessly user-experience of the final cloud-based platform.

More specifically, standardisation in the present document implies the use of common standards and language for data input/output and model formats. Here, we also include the definition and standardisation of technical requirements to ensure that, once developed, models will be properly integrated in the cloud-based platform, and will be made available to end-users. On the one hand, a standardised description of the models is provided to facilitate the interoperability of the different modelling software tools that will allow for more complex in-silico trials. On the other hand, standardisation of all different model inputs and outputs (including units, formats, model descriptions, etc.) will allow the creation of a user-friendly interface and ensure compatibility throughout the different stages of the pipeline.

The requirements for standardisation in SimCardioTest were initially introduced in Deliverable 1.1 (month 6), summarizing the answers to the survey performed to the partners on the Use Case 2 pipeline, and the technical requirements for the different software tools used in the present use case. Furthermore, a specific workshop on standardisation was organised by the members of the consortium in October 2021 (Nice, France), where general discussions and hands-on sessions in small working groups for each use case took place. During this workshop, but also in previous and posterior meetings, the members of the consortium agreed on how standardisation had to be tackled in the SimCardioTest project; these ideas are described in detail in the present deliverable, especially for Use Case 2 on LAAO devices. More specifically, technical standards were discussed during the workshop on the following aspects:

- In-silico models.
- Personalisation of models from clinical data.

- Simulation inputs and outputs.
- Different components of the simulation workflow.
- Required user-interfaces.
- Inter-operability of the different modelling tools within each use case and between all of them.
- Identification of sensitive/proprietary data that will require enhanced security protocols.
- Determination of required computational resources for each use case.

Indeed, there is a crucial need to standardise and homogenise the existing cardiac modelling and simulation tools before entering the regulatory pathway. The standardisation of all aspects of the in-silico trial platform (input/output and models) will facilitate the evaluation of the accuracy and predictive value of the simulation results, thus easing external assessment of the platform by authorities and regulatory bodies. In the last 20 years the scientific community has undertaken big efforts to build centralised databases to store mathematical models of biological systems in standard formats, making them easily accessible and reusable, such as CellML Model Repository (http://www.cellml.org/models) (Lloyd et al., 2008). CellML is used in cellular and physiological modelling and allows modular construction of models, being considered as a community standard. Whole-cell models need to be integrated in multi-scale frameworks to encompass tissue, organ, or organism levels, and to this aim principles for complex model construction with the Physiome standard modelling protocol have been designed (Cooling et al., 2016).

The fluid simulations relevant for Use Case 2 are based on Computational Fluid Dynamics (CFD) numerical techniques that solve Navier Stokes equations. The input of the simulations are usually geometries of the object under study that can be built either from data or from Computer-Aided Design (CAD) tools, together with a set of boundary conditions. These geometries are discrete representations of the object in the form of computational meshes, where finite-element or – volume methods are employed to obtain simulation results. The output of fluid models in Use Case 2 are 3D vector fields representing blood flow velocities or pressures. Moreover, post-processing steps are usually implemented to derive in-silico indices such as wall shear stress or vorticity to better characterise the simulated flows. The outputs are usually visualised with software tools such as the popular Open Source Paraview (https://www.paraview.org/).

Despite widespread use of CFD techniques and fluid modelling in multiple industrial (e.g., airplane design, nuclear plant simulations, etc.) and academic applications, with several commercial software solutions (e.g., Ansys, COMSOL, Abaqus), Open-Source initiatives (e.g., OpenFOAM, FEniCS) and benchmark studies (e.g., FDA Nozzle benchmark), consensus standards for fluid simulations have not been created, unlike for electrophysiological modelling (i.e., cellML). However, the large community on fluid simulations has long-standing experience of using multiple software tools, and thus it is possible to define input/output formats that can be understood by most of them and ensure compatibilities. This is the standardisation strategy we have followed in Use Case 2 of SimCardioTest, establishing a fluid modelling pipeline allowing to start from patient-specific medical images and producing in-silico indices of blood flow patterns to evaluate the performance of LAAO devices. The pipeline includes several components that are fully integrated, seamless communication among them. Its design is defined in a modular way, and thanks to the chosen standards, a given module can be updated at any point in the future by a refined version, without disrupting the whole workflow. Such a modular structure will ease the integration of the fluid models onto the project common platform.

2. Modelling pipeline for left atrial appendage occluder devices

The modelling pipeline for the in-silico evaluation of left atrial appendage occluder devices is illustrated in Figure 1. The first step starts from medical images of the patients to reconstruct the geometry of the left atria. In SimCardioTest, a large database of computed tomography (CT) images is available from patients, before and after implantation of a LAAO device. These images are processed in-site (i.e., no sensitive data is getting out of the hospital) with deep-learning (DL)-based segmentation algorithms developed by partners of SimCardioTest (Inria Sophia-Antipolis), resulting in a binary mask of the LA that is sent to modelling researchers. In addition, echocardiographic images of the same patients are also analysed to extract boundary conditions (BC) to personalise and improve the realism of the fluid simulations. As part of the project, due to the lack of consensus in the literature on the optimal set of BC for LA-based fluid modelling, sensitivity analyses are being carried out to determine the most appropriate ones. For example, if available, mitral valve velocity profiles from Doppler studies are imposed as BC to the models. Furthermore, if dynamic CT images or from echocardiographic speckle tracking are at hand, they are used to extract LA wall deformation that is also imposed it on the fluid simulations.

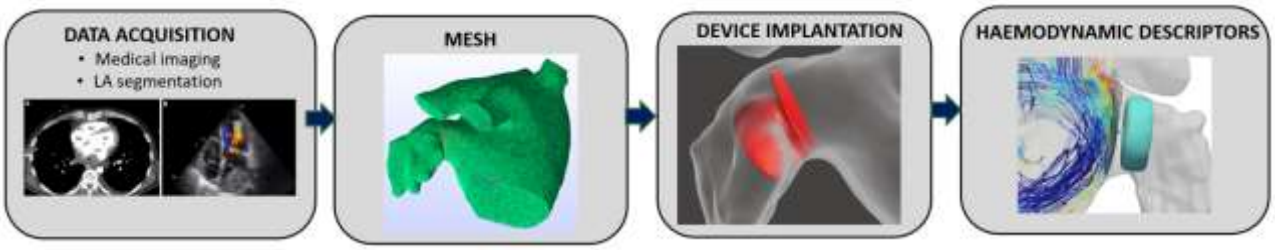

Figure 1: Modelling pipeline to perform fluid simulations on left atrial appendage occluder (LAAO) devices, deriving haemodynamic descriptors to guide in-silico clinical trials.

Once the binary mask is obtained from the segmentation algorithms, a 3D computational mesh is built. First, the classical marching cubes algorithm is used to build a surface mesh, followed by a smoothing process to correct irregularities generated by the segmentation process. A Taubin filter smoothing is then applied (λ = 0.5 and μ = -0.53), followed by manual removal of self-intersecting faces and non-manifold edges wherever necessary. The software tools to reconstruct the models are Meshlab 2016.12 (http://www.meshlab.net), and Meshmixer 3.5 (http://www.meshmixer.com). The pulmonary veins can directly be reconstructed from the CT-based segmentation. To consistently define the inlets of the computational models for all 3D models, we follow a common criterion to determine the PV length, defining a cut just before the first branch coming out from the LA.

To solve the fluid domain inside the LA, a volumetric mesh is required. The Delaunay algorithm available in the Open-Source software Gmsh 4.0.4 (http://gmsh.info) is used for this purpose. Mesh convergence studies to determine the optimal number of mesh elements are also being performed in the framework of Use Case 2. The next step in the modelling pipeline involves the creation of CAD models of different LAAO devices, representing the ones most used and available nowadays in the market. Then, they are virtually implanted with different sizes and positions with the left atrial appendage for a given patient to have fluid simulations with different device settings and find the optimal one.

Fluid simulations are run in the LA computational meshes with the implanted LAAO devices, solving the Navier-Stokes equations with finite volume numerical techniques. In SimCardioTest, we are using two different and complementary solvers: 1) the Ansys Fluent (https://www.ansys.com/products/fluids/ansys-fluent) commercial software tool; the Oasis Open-Source tool (https://github.com/mikaem/Oasis), developed by members of the project (Simula SRL). The use of the commercial software allows the acceleration of V&V40 requirements and regulatory approval since several verification studies have already been performed by the company (https://dokumen.tips/reader/f/ansys-fluid-dynamics-verification-manual). On the other hand, there is a limited control on what it can be done and included into the software. Conversely, the Open-Source tool, which is less tested and verified, permits full control of the fluid modelling pipeline, allowing the incorporation of complex functionalities. More importantly, the use of common input/output formats and standards facilitates the combination of each solver's advantages, minimising their weak points.

The final phase of the modelling pipeline involves the post-processing of simulation results and their visualisation. Several in-silico indices are estimated to fully describe the simulated blood flow patterns, with special emphasis on detecting regions with high risk of thrombus formation after LAAO implantation (i.e., device-related thrombus). The obtained in-silico indices are usually visualised in the form of 3D colourmaps superimposed on the LA computational mesh, flow streamlines/pathlines, and 1D temporal curves of certain quantities at key geometrical points (e.g., blood flow velocities, pressures at the interface of the LA and LAA, so called the ostium).

3. Integration of left atrial occluder device modelling onto platform

The integration of the modelling pipeline described in Section II onto the SimCardioTest platform will be achieved based on two different scenarios that consider complementary contexts of use and user experiences. A scheme of Scenario 1 is shown in Figure 2. It is based on the idea of having a virtual database of pre-computed fluid simulations (with the Oasis solver) on a large cohort of patient-specific LA geometries with different device settings. The user uploads a new dataset into the platform to find out the closest cases in the virtual database to find out the optimal LAAO configuration in pre-computed cases and the potential reasons for post-implantation complications, as part of the pre-procedural planning, to assess DRT or to tailor drug therapy follow-up. Within SimCardioTest, the user may upload the anonymised CT images (in DICOM format), which will be processed on-site with the developed DL-based algorithms, or directly the segmented binary masks. Additionally, device settings and patient characteristics can be chosen to filter out cases in the database search. Subsequently, the UC2 platform will find the most similar LA cases in the virtual database and send them, together with the simulation results for visualisation. A global report will be shown, including DRT vs non-DRT distribution, and geometrical characteristics, among other parameters. Additionally, simulation results for most interesting samples will be individually visualised in 3D, including different LAAO configurations and the follow-up of the real implantation. The main advantage of Scenario 1 is that computationally costly fluid simulations (up to 24 h per patient, depending on simulation settings) are not required since they have been pre-computed on many cases.

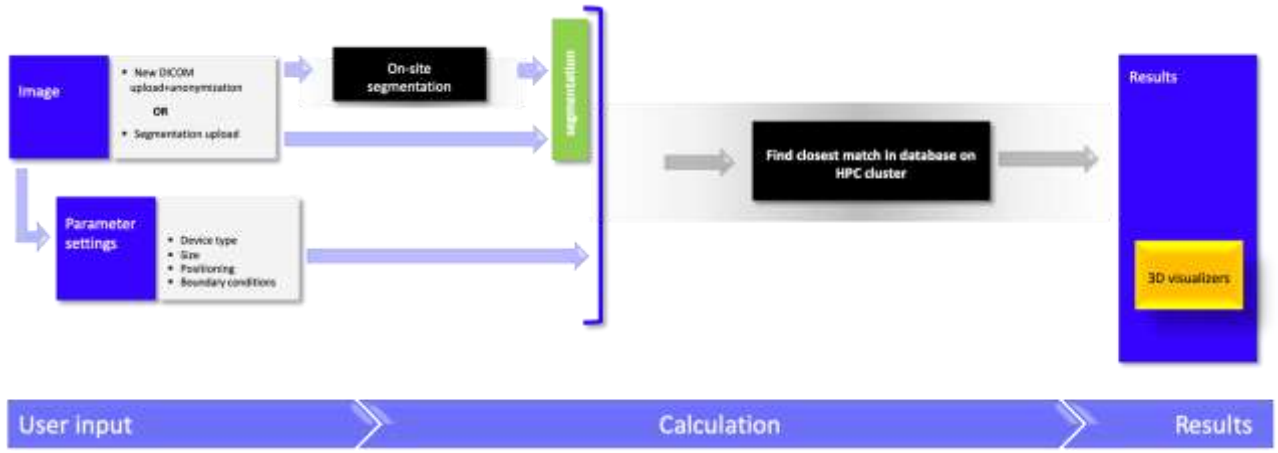

Figure 2: Scenario 1 for the Use Case 2 on left atrial appendage occluder devices in the SimCardioTest platform.

Figure 3 illustrates the complementary Scenario 2, where fluid simulations are run on LA geometries already available in the database. The user initially selects a subset of the existing LA geometries and patients based on the question of interest to be answers. For instance, to assess the performance of a given type of LAAO device settings (e.g., non-disk based, deep LAA implantation) on a particular type of LAA morphologies (e.g., chicken wing type, small ostium). The user will also have the possibility of uploading a new device CAD model to be tested. Next, some pre-defined positions of the device to be implanted in the selected cases would be suggested, but interactive positioning may also be possible. The next step will consist in running the fluid simulations on a High-Performance Computing (HPC) cluster (with Ansys fluent), which could take up to 24 h per patient, depending on the simulation settings. When finished, the SimCardioTest platform would alert the user for visualising simulation results in the platform, in a similar way as described for Scenario 1. The large database of LA geometries and patients available in SimCardioTest (from CHU Bordeaux) makes Scenario 2 very attractive to device manufacturers, often having issues to gather significant amounts of data for the in-silico testing of new device designs.

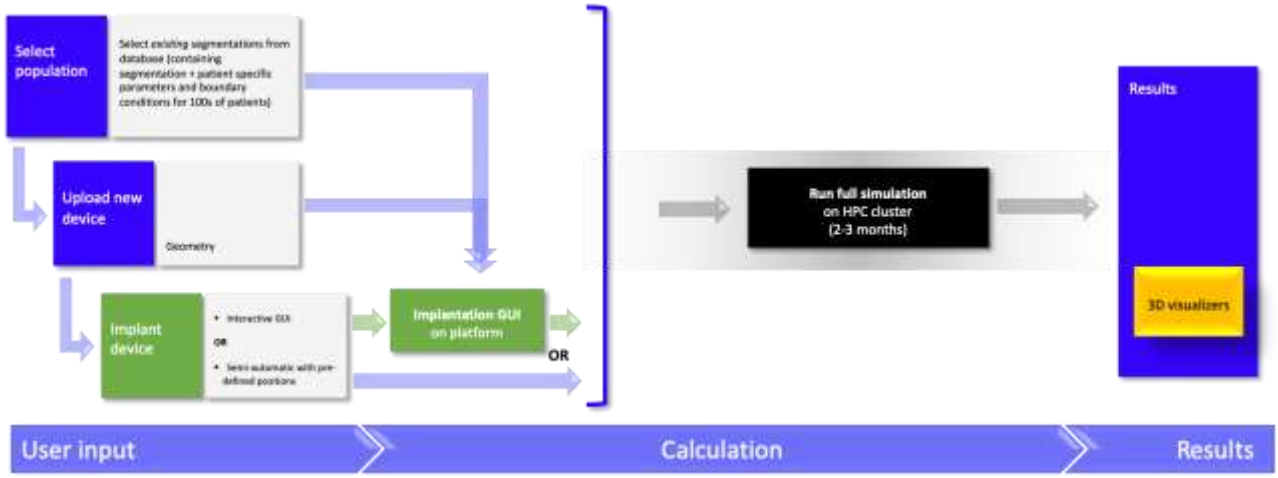

Figure 3: Scenario 2 for the Use Case 2 on left atrial appendage occluder devices in the SimCardioTest platform.

4. Definition of standards and input/output formats

The standards and input/output formats that have been designed for the modelling pipeline in Use Case 2 are detailed in this section. They allow the connection between the different components of the pipeline and include the exchange of imaging data, demographic information, and simulations results. Below there is a complete description of the input and output data as well as the configuration set up for the simulations. The supported datatypes are the following:

- Int = signed 32-bit integer
- Float = signed double-precision floating-point value
- String = UTF-8 character sequence
- Boolean = True or False
- Datetime = string representation of date and time in UTC time
- ID = unique identifier alphanumeric
- File = file specified by format (extension)

Input data:

Qualitative explanation of data: as explained in Section II and Section III, the required input data for the two scenarios of Use Case 2 in the SimCardioTest platform includes computed tomography images (or alternatively the corresponding LA segmentation mask) for Scenario 1, and potentially a CAD model for a new device to be tested (Scenario 2), which are then used to build the LA computational meshes required to run the fluid simulations. Then, a set of boundary conditions are defined to guide the CFD solver. Scenario 1, which is based on the availability of a virtual population of pre-computed simulations, also requires information to find the closest cases to the input data, both in relation to LA/LAA morphology and patient characteristics. The chosen formats of the different files are the ones widely used by the imaging and modelling community, compatible with most commercial and Open-Source software tools.

Standardised input data:

- Computed tomography images [file, format = .dcm, .mha, .nifti]
- Segmentation mask from standard clinical images [file, format = .mha, .nifti]
- LA computational meshes [file, format = .vtk, .stl, .ply]
- Boundary conditions of the simulations [file, format =.csv, .dat, .json]
- Max E-wave & A-wave velocity [float, units = m/s]
- Displacement field of LA wall from medical images [file, format =.csv, .dat, .json]
- Computer Aided Design models of LAAO devices [file, format = .igs, .vtk]
- LA/LAA geometrical indices for finding closest cases in virtual database [file, format = .csv, .txt]
    - LA volume category [string, list = Large/Normal/Small]
    - LA volume value [float, units = ml]
    - LA ostium category [string, list = Large/Normal/Small]
    - LA ostium diameters [maximum/minimum diameter, float, units = mm]
    - LA ostium area [float, units = mm^2]
    - Type of LAA geometry [string, list = chicken wing/cactus/cauliflower/windsock]
    - Number of pulmonary veins [int, units = 3-7]
- Patient characteristics for finding closest cases in virtual database [file, format = .csv, .txt]

- Sex [string, list = Female/Male]
- Age [int, units = years]
- Weight [float, units = kilograms]
- Height [float, units = meters]
- Pharmacological treatment [string, list = Vitamin K antagonists (VKA)-Warfarin/non-VKA oral anticoagulants (NOACs)/Single or Dual antiplatelet therapy]
- CHA_2DS_2-VASc [int, range = 0-9]
- History of stroke [string, list = Yes/No]
- Type of atrial fibrillation [string, list = Paroxysmic/Permanent]

Model/Simulation:

Simulation protocol: fluid models are set up considering several assumptions and setting up certain parameters based on the sensitivity analyses to ensure robust and accurate simulation results. For each LA simulation, a .txt file will be stored with the following information about the model set up:

- Solver tool [string, list = McDonalds/MasterChef]
- Type of solver and numerical discretisations [string, list = 1^{st}/2^{nd}/higher order, implicit/explicit]
- Nature of the problem [string, list = Newtonian/Non-Newtonian, Compressible/Incompressible]
- Solution method [string, list = Finite-Element Method/Finite-Volume Method]
- Computational resources [string, list = personal computer/name of HPC cluster; int, number of cores/nodes = 1-100000]
- Number of mesh elements [int, range = 1K-100M; software tool used, string, list = Gmsh/CGAL/others]
- Mesh processing [string, type of smoothing, list = Taubin/Laplacian; string, software used, list = Meshlab/Meshmixer; string, manual removal of incorrect faces, list = Yes/No; string, addition of pulmonary vein tubes, list = Yes/No]
- Time-step [float, range = 0-0.1]
- Convergence criteria [float, range = 0-0.1]
- Number of cardiac cycles [int, units = 1-50]
- Viscosity [float, units = Pascal-second]
- Type of left atrial wall behaviour [string, list = Rigid/Dynamic mesh of the mitral valve/Full LA deformation]
- Type of boundary conditions at inlets/outlets [string, list = Velocities/Pressures, Generic/image-based]

Software: Open-Source Oasis solver, commercial Ansys fluent solver.
Platform: the UPF high-performance computing and storage services; the Cloud-based InSilicoTrials platform.

Output data:

Qualitative explanation of the data: as detailed in Section II and Section III, the output data of the modelling pipeline and the SimCardioTest platform, independently of the two designed scenarios, will consist in a set of files resulting from the fluid simulations to be visualised by the platform user. It will include 3D computational meshes of the LA with colourmaps representing several in-silico indices and blood flow patterns in the form of streamlines/pathlines, 1D temporal curves of relevant

quantities at key morphological landmarks in the LA, spreadsheets with the most relevant statistics on morphological and in-silico haemodynamics indices, and a final decision support score assessing the risk of adverse events for each analysed case.

Standardised output data

- Simulation results and in-silico indices in the form of 3D maps on computational meshes and flow streamlines/pathlines [file, format = .h5, .encas, cgns, .vtk, .vtu] (compatible with Paraview 3D viewer): wall shear stress, oscillatory shear index, endothelial cell activation potential, residence times, shear rate
- 1D temporal curves of velocities and pressures at several LA points [file, format= .csv, .pdf]
- Spreadsheet with statistics on the in-silico indices in different LA regions [file, format= .csv, .pdf]
- Morphological parameters [file, format= .csv, .pdf]: LA/LAA volumes, ostium diameters, LAA centreline length and tortuosity, LAA bending angles, landing zone diameters, LAA depth
- Decision support score for the risk of adverse outcomes integrating the most relevant morphological and in-silico indices [file, format = .csv, .pdf]

5. Discussion and Conclusion

Patient-specific fluid modelling of left atrial appendage occluder devices involves a complex computational pipeline that requires the integration of heterogeneous, multi-dimensional and multi-modal data from multiple sources, the generation of 3D computational meshes of complex geometries, the development of sophisticated multi-physics simulations and the use of advanced visual analytics tools. It necessarily asks for a multi-disciplinary and team-work effort, with experts on the different involved domains. Moreover, the complexity of such a complex modelling pipeline hampers the possibility of having all required components in a single software environment, requiring the use of numerous algorithmic steps and software tools. In consequence, it is compulsory to define a set of standards and input/output formats to link the different steps of the pipeline.

In SimCardioTest, all members of the consortium have been jointly working on this topic from the beginning of the project so that interaction between the different modules in the modelling pipelines of the three use cases is established at early stages. The organised workshop focused on standardisation was key for collectively defining the standards and formations to be used until the end of SimCardioTest. It will have an immediate and positive impact on the organisation of the large number of simulations to be performed in Use Case 2, including complete sensitivity analyses and the creation of a large virtual population of simulations.

Unlike other modelling applications, the fluid modelling community has not reached a consensus on the standards to be used, without universal repositories of curated and reproducible fluid models such as cellML. However, the long-standing research on this field and several Open-Source initiatives exist (e.g., OpenFOAM, FEniCS, etc.) has led to the existence of various software tools that are compatible with several input/output formats of simulation results, without being difficult to adapt them from one to another. We reckon that the work performed in WP3 of SimCardioTest for the fluid modelling of LA-based applications, including the creation of the modelling pipeline using clear standards and input/output formats, would help other investigators for sharing their work and foster

research on this field. Additionally, it could also contribute to define benchmarks where different fluid solvers could be tested on the same data. There is definitively a need in LA-based fluid modelling for more collective efforts as a community on reproducible research and knowledgebase sharing.

The use of the Open-Source Oasis software in Use Case 2 allows infinite customizability to the problem at hand, being able to test different numerical approaches and boundary conditions, which is ideal for the sensitivity analyses required to build trust and credibility in fluid simulations, as part of the V&V40 guidelines. However, it is also very positive to have access to the commercial Ansys fluent tool to accelerate the integration with the InSilicoTrials platform and the validation part of the regulatory process due to its robustness. Still, both solver solutions share the main bottleneck for the modelling pipeline automatization, which is the computational mesh building. Despite the use of DL-based segmentation algorithms to extract the LA geometry, the construction of surface and volumetric meshes of complex structures such as the LA often involves manual correction of incorrect mesh elements, which is also difficult to standardise. Furthermore, substantial work is still required among different members of the consortium to design and implement the final interface of the platform for the visualisation of fluid simulation results. Special attention will be given to the limitations of web-based interface solutions and the large amount of data generated for each case and for the overall in-silico trials.

Finally, despite focusing our research on fluid simulations of LAAO devices, the developed modelling pipeline, as well as the decided standards and input/output formats, are also valid for other applications such as transaortic valve implantations or stents in cerebral aneurysms.

6. References

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