SIMCor

In-Silico testing and validation of Cardiovascular IMplantable devices

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Executive summary

The deliverable describes the preliminary definition of model templates that will be used during virtual cohort generation of both aortic valve disease and heart failure patients. The document gives an overview of the available models for simulating the physiology of these patient groups, both before and after *transcatheter aortic valve implantation* or insertion of a *pulmonary artery pressure sensor*, respectively. In addition, it describes the intended use of these models. Thereafter, it is presented how the optimal model complexity of our virtual cohort generator is selected, and how the models are validated on patient-level. Moreover, the document discusses surrogate models that are currently selected as potential candidates for fast model evaluations during uncertainty quantification, sensitivity analyses and virtual cohort generation. Finally, we describe how we envision integration of the model templates into the virtual research environment, and we speculate on future strategies for mapping engineering metrics into clinical outcomes.

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Acronyms

Acronym	Full name
TAVI	TransAortic Valve Implantation
PAPS	Pulmonary Artery Pressure Sensor
HF	Heart failure
CFD	Computational Fluid Dynamics
FSI	Fluid-Structure Interaction models
WSS	Wall shear stress
OSI	Oscillatory shear index
0D	Lumped parameter model
VKOGA	Vectorial Kernel Orthogonal Greedy Algorithm
PINNs	Physics-informed Neural Networks
VRE	Virtual Research Environment

Introduction

The generation of the virtual cohorts within SIMCor is done by means of mathematical models that mimic the cardiovascular physiology of both *aortic valve disease* (AVD) and *heart failure* (HF) patients. The rationale behind this approach is as follows.

Ideally, one would like to have a population distribution from which it would be possible to generate a sample that mimics a real patient. Such a sample should include a realistic geometry, mechanical properties and proper boundary conditions in terms of time- and spatially-dependent functional physiological metrics like pressure, stress, displacement and/or velocity fields. When such a sample would become available, the resulting geometry, parameters and boundary conditions can be used as a starting point for the virtual implantation of medical devices. In fact, multiple samples would provide medical device companies a large database of virtual patient data. A realistic sample of an AVD patient allows us to simulate *transcatheter aortic valve implantation* (TAVI), whereas a sample of a HF patient could be used to evaluate a *pulmonary artery pressure sensor* (PAPS).

However, defining an accurate population distribution that can sample realistic geometries and corresponding functional metrics is almost impossible based on data alone. You would need an almost infinite amount of data to find all dependencies and correlations between parameters, boundary conditions and geometries. Especially, because you also want to obtain samples in which the boundary conditions, geometry and parameters belong together and obey physiological and physical laws. For example, you do not want to find a sample in which the inflow is lower than the outflow conditions, hereby violating conservation of mass.

In the past decades, models have been developed that can mimic human cardiovascular physiology by integrating input data (geometry, boundary conditions and input parameters) into engineering concepts (e.g., pressure, flows, axial forces), thereby relating the data by means of established physiological and physical laws. These physiological models cannot only create virtual patients by varying their inputs, but can also be used to remove unrealistic combinations of inputs by assessing the physiological validity of the model outputs. For the latter, we will define a “filter” (see *Figure 1*).

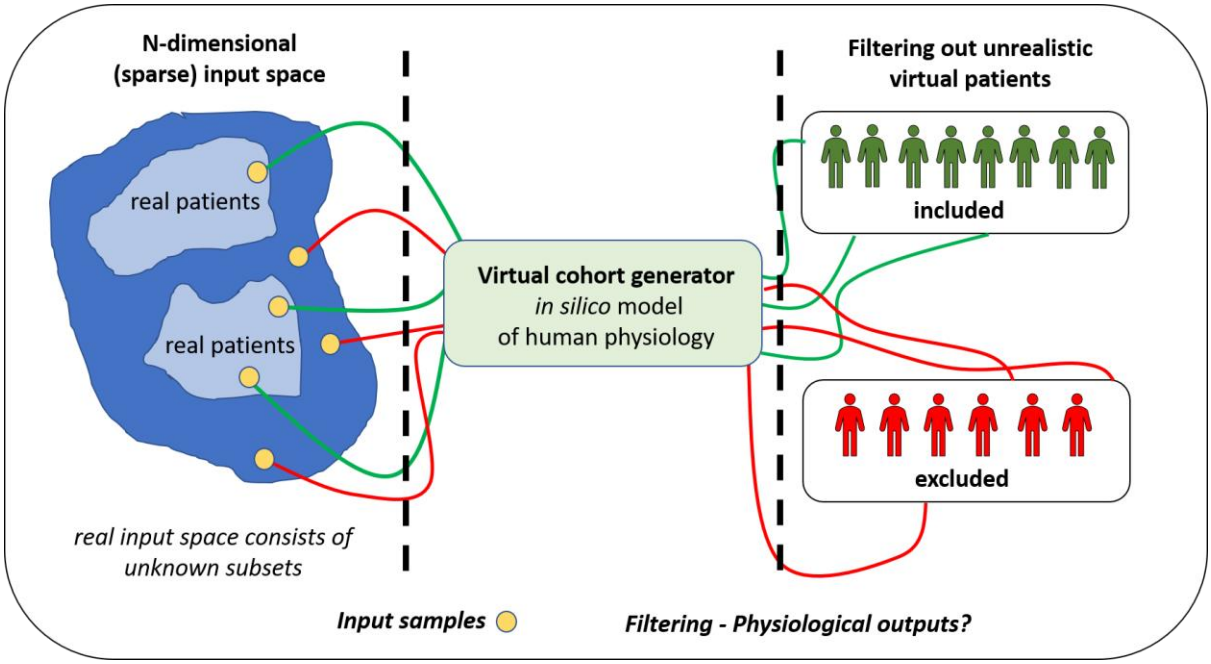

Figure 1: Schematic overview of the SIMCor methodology for virtual cohort generation.

To create a virtual cohort generator for AVD and HF patients, we first need to develop a model that can accurately predict the cardiovascular physiology of these patients both before and after TAVI and PAPS implantation, respectively. This model can then be used to create virtual cohorts by varying the model inputs, and subsequently by performing filtering on the outputs. However, even if we have demonstrated that our models are accurate for patients, it could still be possible that new patients cannot be represented by our models. It might be the case that we should adapt the governing equations, model assumptions and/or model complexity when more patients are evaluated during the Project (i.e., the model framework). To deal with possible model framework errors and to find the optimal balance between model complexity and model input uncertainty, we envision an iterative modelling strategy, to be described in the next section.

Strategy for model selection and patient-specific validation

The required level of model complexity is often based on expert opinions and includes the physical and physiological laws which are of importance. Such models are then able to investigate (patho)physiology or to simulate the effect of surgical or endovascular interventions. However, predicting the outcome of interventions at patient-specific level is challenging, as this requires proper personalization of model input, initial conditions, and boundary conditions. Assessing all this information patient-specifically is unfeasible, as not all model inputs can be measured or estimated by means of other measurements and inverse modelling techniques. Moreover, even if we could assess all inputs via clinical measurements, the burden on patients would become unacceptably large. Consequently, we always need to deal with sparse datasets that are often also hampered by significant measurement uncertainties. These uncertainties propagate to uncertainties in the model outputs, which affect the overall accuracy of our patient-specific simulations. It is therefore important to quantify the uncertainty due to model input uncertainty. Moreover, proper sensitivity analyses are required to determine which model inputs are most relevant, hereby guiding our measurement protocol.

When the level of model complexity increases, the model framework error is likely to become smaller, but the uncertainty caused by data uncertainty is expected to increase. Finding the optimal balance between model framework error and input uncertainty is therefore indispensable (Figure 2) when developing a patient-specific model.
To find this optimal balance we propose an iterative approach[1] in which a model is selected based on expert opinions and then extensively verified by means of (*in vitro* or *ex vivo*) laboratory experiments. We refer to such a model as a patient-generic model. Subsequently, the model is personalized by means of available clinical data, and the uncertainty in the model output due to data uncertainties is quantified by means of uncertainty analysis. In addition, a sensitivity analysis is performed to identify the most relevant inputs. When the output uncertainty and the difference between simulations and clinical measurements, either directly or indirectly, are acceptable for multiple patients, the model is sufficiently corroborated and can be used for virtual cohort generation. If the output uncertainty is too large, the results of the sensitivity analysis will inform us on either which input need to be determined more accurately for reducing the output uncertainty, or how we can reduce model complexity by identifying irrelevant components of our model[2,3]. We can also end up with situations in which the output uncertainty is low, but the difference between calculated and measured metrics is too large. In the latter case, we should most likely focus on increasing the complexity of the model, because we have neglected relevant physiological mechanisms in our model.

These steps are repeated until the model can accurately mimic the cardiovascular physiology of real patients. After validation of the model on patient-level, we can use the model for virtual cohort generation and validation (i.e., self-validation and independent cohort validation). Now we must determine whether our model is able to create virtual patients that give similar statistical input and output distributions as real patient cohorts. Our model will be further updated iteratively when the statistical distributions are not satisfactory. This can happen, for example, when new patients showing up during SIMCor are outside the input space used for virtual cohort generation and have not considered during model validation.

[1] Huberts et al., What is needed to make cardiovascular models suitable for clinical decision support? A viewpoint paper. Journal of Computational Science 24:68-84, 2018 - https://doi.org/10.1016/j.jocs.2017.07.006
[2] Saltelli et al., Global sensitivity analysis. The primer. John Wiley & Sons Ltd. England. 2009
[3] Eck et al., A guide to uncertainty and sensitivity analysis for cardiovascular applications. International Journal of Numerical Methods in Biomedical Engineering 32(8): e02755, 2016 - https://doi.org/10.1002/cnm.2755

Note that model updating is only allowed if we are still validating the cohort against the same cohort, or the model at patient-level. After this, we still need to validate our generated cohort by comparing it with another independent cohort of patients with comparable statistics and diseases.

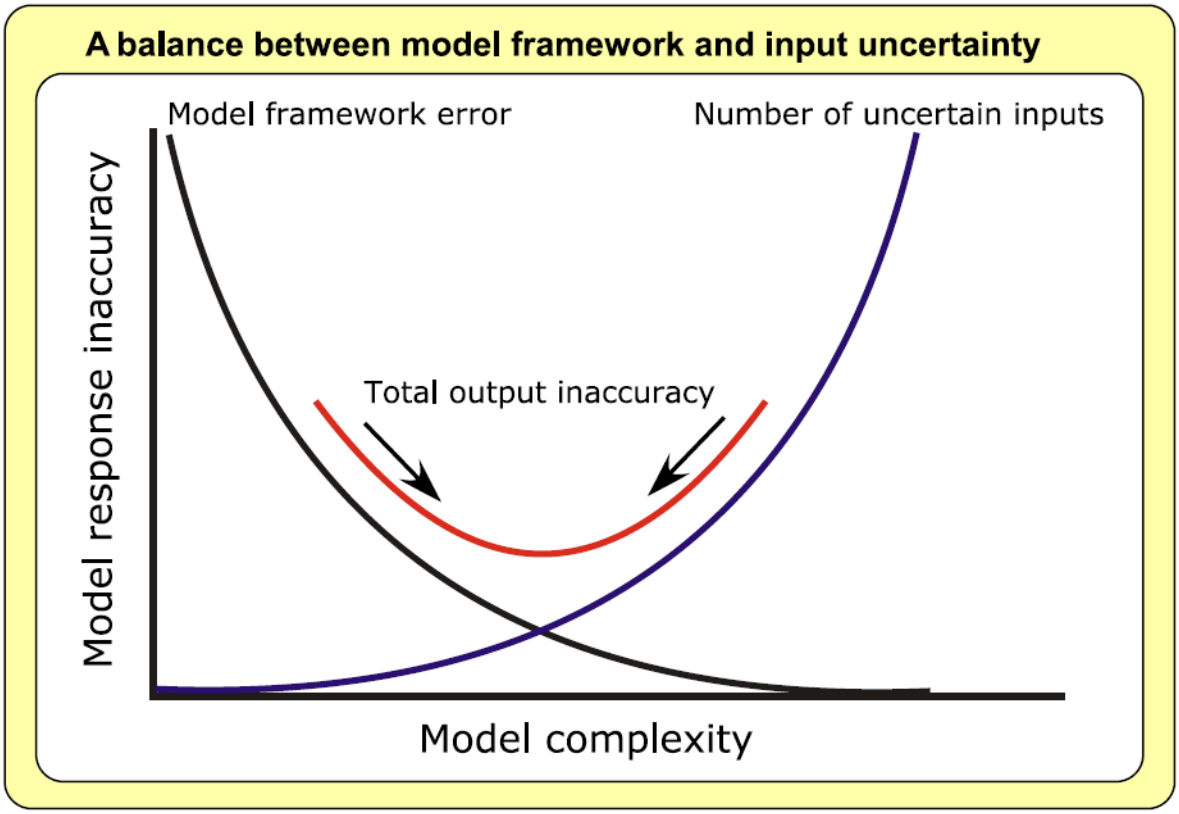

Figure 2: Optimal balance between model framework error and input data uncertainty.

It might be evident that uncertainty and sensitivity analyses are indispensable in each phase of model development and virtual cohort generation. There is, therefore, an unmet need to increase the evaluation speed of computationally demanding models (e.g., 3D FSI models). For this reason, we will consider multiple surrogate modelling techniques within SIMCor. In the next section, we describe models that are currently available or will be developed in the Project. Moreover, we will indicate the intended use of these models. Thereafter, a section is devoted to surrogate modelling techniques that we are planning to use.

Available physiological models

In this section we give an overview of the *in-vitro* and *in-silico* models that are available (or will become available) within the Consortium. Since most of our partners have a wide portfolio of models, we will only describe the models that are specifically designed for the simulation of the physiology of both AVD and HF patients, and models that are anticipated to be used, improved or adapted for virtual cohort generation, application or validation.

The description of the models will include the model type, the model inputs and outputs, its implementation, the stage of development, and its intended use. In addition, an estimation of the computational costs of the *in-silico* models are given. Some of the models still need to be developed during SIMCor, and will be indicated in the corresponding model descriptions.

Models for aortic valve disease patients

Models by BIO

No models of AVD patients available.

Models by CHA

3D Computational Fluid Dynamics Model

Model description: This model is used for calculation of peak-systolic haemodynamics across the aortic valve as well as within the ascending aorta. In general, the model uses a three-dimensional representation of the patient-specific anatomy of the left ventricular outflow tract, the aortic root, including either the aortic valve leaflets or a virtually implanted aortic valve prosthesis, as well as the aorta. The haemodynamics are then calculated using a commercially available finite volume solver. Only the peak-systolic haemodynamics are calculated, as this is the most vital time frame for evaluation of intra-aortic haemodynamics and as relevant diagnostic parameters, as for example the pressure gradient across a stenosed aortic valve, is maximal at this cardiac phase. Within the model, walls are modelled as rigid, therefore the Windkessel-effect of the aorta is neglected. This choice of a rather simple model focusing on peak-systolic haemodynamics was made to reduce manual interaction and computational costs to a minimum, as those are factors that prohibit clinical application more than the inaccuracies caused by these assumptions. This model was used and thus described in various studies[4,5,6,7].

Input:

- Patient-specific anatomy of the left ventricular outflow tract, aortic root, aortic valve leaflets and ascending aorta derived from either computed tomography or magnetic resonance imaging. The latter does not currently allow reconstruction of the aortic valve leaflets and is thus only sufficient for simulations of investigation of surgical aortic valve replacements.
- Either patient-specific peak-systolic volume flow rate, e.g., derived from change in left-ventricular volumes or measured using velocity encoded magnetic resonance imaging (VEC-

[4]Yevtushenko et al., Surgical aortic valve replacement: Are we able to improve hemodynamic outcome? Biophysical Journal 117(12):2324-2336, 2019 - https://doi.org/10.1016/j.bpj.2019.07.025
[5]Franke et al., Towards improving the accuracy of aortic transvalvular pressure gradients: rethinking Bernoulli. Medical and Biological Engineering and Computing 58: 1667-1679, 2020 - https://doi.org/10.1007/s11517-020-02186-w
[6]Hellmeier et al., Hemodynamic Evaluation of a Biological and Mechanical Aortic Valve Prosthesis Using Patient-Specific MRI-Based CFD. Artificial Organs 42(1): 49-57, 2018 - https://doi.org/10.1111/aor.12955
[7]Hellmeier et al., Hemodynamic Modeling of Biological Aortic Valve Replacement Using Preoperative Data Only. Frontiers in Cardiovascular Medicine 9(7): 593709, 2021 - https://doi.org/10.3389/fcvm.2020.593709

MRI), or patient-specific velocity profiles in the left ventricular outflow tract measured using VEC-MRI.

Output:

- Spatially resolved information on velocities and pressures within the aortic lumen as well as wall shear stresses at the aortic wall.
- From this information, further derived parameters are calculated that either describe intra-aortic haemodynamics of severity of aortic stenosis:
    - maximum velocity across the aortic valve;
    - peak-systolic pressure gradient across the aortic valve;
    - parameters describing eccentricity, helicity, and unevenness of the aortic haemodynamics in selected evaluation planes perpendicular to the aorta:
        - Secondary Flow Degree: ratio of in-plane and through-plane velocities;
        - Normalized Flow Displacement: Distance from the flow-weighted center of a plane compared to the geometric center.

Numerical implementation: A commercial solver (STAR-CCM+, v15.02) is used. Unlimited academic research licenses are available. Therefore, licensing is not prohibiting large numbers of simulations.

Stage of development: Already employed in multiple research projects. Enhancement of the model by Fluid-Structure-Interaction to allow simulation of whole cardiac cycles is planned in the future.

Computational costs:

- Direct numerical costs are low: simulations require a couple of hours (~6 h) per case on a local workstation. Running simulations on a cluster with 4 nodes and 96 cores per node allows computation in less than an hour.
- Manual costs for setting up the model are reduced to a minimum. If geometries and boundary conditions are generated using virtual cohort generation and/or statistical shape modelling, full automation of simulations becomes feasible. Thus, also large virtual cohorts can be simulated.

Intended use:

- TAVI-Thrombosis: the model might allow quantification of washout in the aortic sinus, shear rates and other parameters that are associated with thrombus formation.
- TAVI-Paravalvular Leakage: If geometries of implanted TAVI prostheses with remaining orifices between the native valve's leaflets and the TAVI stent are available, the model can be easily adapted to also calculate regurgitant flow across those orifices. Here, pressure boundary conditions at the ascending aorta and the left ventricular outflow tract will be imposed.

Reduced Order Model

Model description: This model is a simple reduced order model, which aims at quantification of the peak-systolic transvalvular pressure gradient using only information derived from CT-imaging. The pressure gradient is calculated as:

$$TPG = a \cdot Q^x \cdot AVA^y$$

Where TPG is the transvalvular pressure gradient, Q is the patient-specific peak-systolic flow rate across the aortic valve and AVA is the maximum aortic valve area, usually occurring during peak-systole, when the pressure gradient is also maximal. The model coefficients a, x, y, were calculated using a least square fit using simulation data derived from the 3D CFD model described above. The first description and set of model parameters is described in Franke et al.[5]

In a novel study[8], we aimed at validation of this model against catheter-derived pressure gradients. While we found no bias, meaning that the model neither systematically under- nor overpredicts the pressure gradient, it was also associated with severe uncertainty. However, this uncertainty was comparable to that of echocardiographic assessment of TPG, which is the current gold standard for assessment of aortic stenosis severity.

Input:

- Peak-systolic volume flow rate, usually derived from left ventricle segmentations (temporal derivative of the volume over time);
- Maximum cross-sectional area calculated from normal projection of aortic valve leaflets segmented using the segmentation tool provided by PHI (BrainViewer).

Output:

- Pressure gradient.

Numerical implementation: Currently in MATLAB, but the fit as well as the equation can be implemented using any tool or language, even Excel.

Computational costs: Effectively none.

Intended use: TAVI: estimation of the remaining pressure gradient, which is a relevant metric in evaluation of the success of aortic valve replacement.

[8]Franke et al., Computed Tomography-Based Assessment of Transvalvular Pressure Gradient in Aortic Stenosis, Frontiers in Cardiovascular Medicine 8:706628, 2021 - https://doi.org/10.3389/fcvm.2021.706628

Models by IIB

3D Computational Fluid Dynamics Model

Model description: This model is used to quantify the *paravalvular leakage* (PVL) of transcatheter aortic valve prostheses (TAVI). Paravalvular leakage is the reflux of blood between the prosthesis and the vessel wall during diastole. Anatomical geometries of the *left ventricular outflow tract* (LVOT) and native leaflets are required for the model, as well as the geometry of the implanted TAVI. The hemodynamic properties are calculated using a commercially available finite volume solver. Only the diastolic cardiac phase is investigated, since PVL only occurs during diastole due to the pressure difference between the aorta and the left ventricle. Within the model, the vessel walls and the TAVI are assumed to be rigid. The boundary conditions used are obtained from experimental studies of a circulation loop model of the left heart.
The model will be used to investigate the performance of a TAVI in terms of its leakage behaviour in non-circular or highly calcified annuli. In addition, future patient-prosthesis mismatches, which can cause a high leakage rate, can be avoided by virtual implantation.
This model was used and thus described previously[9].

Input: Generic or patient-specific anatomical data are required for the model, as well as the geometry of the implanted TAVI. These data can be generated from a previous FE analysis of the TAVI implantation in the LVOT. The flow-inducing pressure difference between the aorta and left ventricle during diastole is required as a boundary condition. The pressure difference can be obtained from experimental studies with a cardiovascular model of the left heart or from clinical data.

Output:

- leakage rate during diastole;
- spatially resolved occurrence of a PVL jet;
- estimation of the severity of PVL.

Numerical implementation: A commercially available solver (Fluent ANSYS) is used. Limited academic licenses are available.

Stage of development: Fluid-structure interaction has already been used to calculate the haemodynamics of the entire cardiac cycle of generic TAVI models and anatomies. Due to the high computational complexity of an FSI simulation, only CFD simulations of patient-specific or generic anatomies with implanted TAVI will be calculated for the leakage investigations.

Computational costs: The computational cost of the simulations will take approximately one week for each geometry. In addition, there are manual costs to prepare and post-process each model.

Intended use: Reflux of blood during diastole through gaps between the TAVI and native leaflets or LVOT can be identified, and the severity of leakage quantified.

[9]Bianchi et al., Patient-specific simulation of transcatheter aortic valve replacement: impact of deployment options on paravalvular leakage. Biomechanics and modeling in mechanobiology 18(2):435-451, 2019 - https://doi.org/10.1007/s10237-018-1094-8

3D Structural Analysis Model

Model description: This model is used to study the durability of TAVI. For this purpose, the systolic and diastolic loads on the TAVI stent are studied in experimental or clinical data. The highest load is used to study the stent performance in a numerical model with occurring stresses and strains. If the occurring stresses and strains are below a required value, damage leading to malfunction of the TAVI can be excluded.

Input: Post-deflection of the TAVI stent is necessary for this model. This can be determined from experimental data. In addition, a suitable material model of the TAVI stent (for example nickel-titanium alloy) is required, as well as the geometry of the implanted TAVI.

Output: From the applied load (post-deflection) on the TAVI stent, occurring stresses and strains can be calculated. These metrics can be used to estimate whether a loss of function of the TAVI can be expected.

Numerical implementation: A commercially available solver (Structural ANSYS) is used. Limited academic licenses are available.

Stage of development: In many previous projects, structural mechanics FE analyses have already been performed for the expansion of TAVI. In addition, simulations of load cases such as crush resistance or radial force investigations have already been performed.

Computational costs: The computational cost of the simulations will take approximately one week for each geometry. In addition, there are manual costs to prepare and post-process each model.

Intended use: The durability of TAVI stents should be estimated based on loading situations that occur. If the stresses and strains are below a certain threshold, failure of the TAVI stent resulting in loss of function may be considered not expected.

3D Fluid-Structure-Interaction Model

Model description: To model the function of a TAVI, the complex interaction between fluid flow and motion of the valve leaflets must be considered. The occurring haemodynamics and valve deformation can be determined by coupling a fluid solver and a structural solver. In this way, a complete cardiac cycle of an implanted TAVI can be simulated. Virtual studies of thrombosis risk can be performed in this manner. Thrombosis risk is often quantified by time-dependent metrics. Examination of *time-averaged wall shear stress* (TAWSS) or *oscillatory shear index* (OSI) has been used to assess thrombosis risk in previous studies. In order to reach conclusions about the risk of thrombosis not only at the vessel walls, the FSI approach allows the use of a scalar transport of a species to estimate the washout in the neo-sinus and native sinus. A low washout is thereby associated with an increased risk of thrombosis. FSI simulations of prosthetic heart valves have been the subject of many studies.[10,11,12,13,14,15,16]

Input: The FSI model requires generic or patient-specific geometry of the LVOT, aortic root and native leaflets, and implanted TAVI. A flow boundary condition at the inlet is also required as input, which may be based on clinical parameters such as mean aortic pressure, heart rate, cardiac output, etc.

Output: The model can be used to calculate the movement of the prosthetic leaflets as well as the time-resolved three-dimensional velocity fields within the aortic root around the TAVI. The model can be used to calculate the movement of the prosthetic leaflets as well as the time-resolved three-dimensional velocity fields within the aortic root around the TAVI. Metrics, such as OSI or TAWSS, can be derived from the velocity fields and used to estimate the risk of thrombosis. The main focus is on washout assessment using a scalar transport equation. This can be used to calculate the residence time of blood in native sinus and neo-sinus.

Numerical implementation: Commercially available solvers are used for FSI simulation. The partitioned approach allows the use of the specific FE and CFD solvers, which are connected by a coupling algorithm. Each solver requires a single license, so the number of licenses for FSI calculation is limited.

Stage of development: FSI simulations generic aortic root model with simplified TAVI models have been performed and are under continuous development. The FSI simulations are currently still in academic use and require a time-consuming development of a working parameter set with which the necessary convergence of the calculation can be evaluated.

Computational costs: The manual preparation of an FSI simulation requires about one day. Pure simulation time is about 1-2 weeks with the partitioned approach and the ALE method as the mesh adaptation algorithm. Post-processing should also be scheduled for one week. The FSI simulations are the most complex and time-consuming calculations to be performed in this project and for this reason are very limited regarding the number of feasible simulations.

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[10]Bavo et al.,Fluid-Structure Interaction Simulation of Prosthetic Aortic Valves: Comparison between Immersed Boundary and Arbitrary Lagrangian-Eulerian Techniques for the Mesh Representation. PLoS ONE 11(4):e0154517, 2016 - https://doi.org/10.1371/journal.pone.0154517

[11]Luraghi et al., Evaluation of an aortic valve prosthesis: Fluid-structure interaction or structural simulation? Journal of Biomechanics 14(58): 45-51, 2017 - http://dx.doi.org/10.1016/j.jbiomech.2017.04.004

[12]Pan et al.,Fluid-structure interaction simulation of aortic valve closure with various sinotubular junction and sinus diameters. Annals of Biomedical Engineering 43(6): 1363-1369, 2015 - 10.1007/s10439-014-1120-7

[13]Ghosh et al., Numerical evaluation of transcatheter aortic valve performance during heart beating and its post-deployment fluid-structure interaction analysis. Biomechanics and Modeling in Mechanobiology 19(5): 1725-1740, 2020 - https://doi.org/10.1007/s10237-020-01304-9

[14]Vahidkhah et al., Valve thrombosis following transcatheter aortic valve replacement: significance of blood stasis on the leaflets. European Journal of Cardiothoracic Surgery 51(5): 927-935, 2017 - https://doi.org/10.1093/ejcts/ezw407

[15]Hansen et al., Mechanical Platelet Activation Potential in Abdominal Aortic Aneurysms. Journal of Biomechanical Engineering 137(4): 041005, 2015 - https://doi.org/10.1115/1.4029580

[16]Menichini et al.,Mathematical modeling of thrombus formation in idealized models of aortic dissection: initial findings and potential applications Journal of Mathematical Biology 73(5): 1205-1226, 2016 - 10.1007/s00285-016-0986-4

Intended use: FSI simulations will be used to evaluate the risk of thrombosis from TAVI, which requires high temporal and spatial resolution. With the evaluation of washout behaviour throughout the cardiac cycle, an assessment of thrombosis risk can be made.

TAVI – Steady Flow Measurement (Status)

Model Description: This model is used to quantify *paravalvular leakage* (PVL) of transcatheter aortic valve prostheses (TAVI). Paravalvular leakage is the backflow of blood between the prosthesis and the vessel wall during diastole. Simplified anatomical geometries, as well as generic geometries (non-circular or severely calcified annuli), can be used as fixation of the TAVI in the model. The fixation is made by 3D printing (stereolithography) either by direct printing elastic material, or a combination of 3D printing and silicone casting. Crucial for the complexity of the geometry is the possibility of being printed. The model setup includes static pressure application due to a temperature-controlled fluid. Pressure can be measured proximal to the valve. The flow is measured distal to the valve. In this way, the diastolic cardiac phase can be studied, since PVL occurs only during diastole due to the pressure difference between the aorta and the left ventricle. This in vitro model can be used to validate in silico models for the determination of PVL. This model[17] is a custom-built by IIB and has been used and described in several studies.

Input: Generic or patient-specific anatomical data are required for the model, as well as a commercial TAVI or TAVI prototype. The flow-induced pressure difference between the aorta and left ventricle during diastole is required as a boundary condition.

Output:

- Leakage rate during diastole.
- Estimation of the severity of PVL.
- Post-deflection of the TAVI stent

State of development: This in vitro model is a custom-built by IIB and has been used to study leakage of TAVI in generic aortic annuli. The use of patient-specific anatomical geometries remains to be investigated in terms of the high-quality 3D printing required for this purpose.

Computational Cost: The time required per measurement of TAVI in one annulus geometry is one day, but multiple pressure differences can be measured. Pre- and post-processing time is estimated to a total of 4 days, including printing.

Intended Use: Blood leakage during diastole can be measured and the severity of leakage quantified. These data can also be used to validate numerical models. This model can be used to generate input data for in-silico study of the durability of TAVI

Pulsatile Flow Loop System

Model Description: Two commercial pulsatile flow loop systems (BDC Laboratories, Vivitro Labs.) are available to simulate the left ventricle according to ISO 5840:3. Both setups are able to: control the temperature; measure the ventricular, aortic and atrial pressure; measure flow volume. In addition, high-speed videos of opening and closing behaviour synchronized to the cardiac cycle can be obtained. A wide range of physiological and pathological flow and pressure conditions can be set. For example, heart rate, pump volume, flow waveform and systolic and diastolic pressure conditions, can be specified. Simplified anatomical geometries, as well as generic geometries (non-circular or severe calcified annuli), can be used as fixation of the TAVI in the model. The fixation is made by 3D printing (stereolithography) either by direct printing elastic material, or a combination of 3D printing and

[17]Kaule, Minimalinvasiv implantierbare Herzklappenprothesen : Beiträge zur Beurteilung der Qualitätsparameter und zur hydrodynamischen Charakterisierung von Klappendesigns. Menzel-Verlag Germany, 2019 - https://doi.org/10.18453/rosdok_id00002856

silicone casting. Crucial for the complexity of the geometry is the possibility of being printed. These or related models are used in various studies.[17,18,19,20,21]

Input: Generic or patient-specific anatomical data are needed for the model, as well as a commercial TAVI or TAVI prototype. In addition, inputs such as heart rate, pump volume, flow waveform, and systolic and diastolic pressure ratios are required.

Output:

- Time-resolved pressure (aortic, ventricular, atrial) and flow.
- Effective orifice area, positive pressure difference, occlusion volume, leakage volume.
- High-Speed videos (geometric orifice area, post-deflection).

State of development: Hydrodynamic measurements according to ISO5840:3 is performed on commercial TAVI and prototypes in many previous projects.

Computational effort: Preparation of measurement involves 3D printing of the aortic geometry/annulus models, which takes a total of 3 days. With the combination of TAVI and aortic model, a wide range of boundary conditions can be set and measured. Measurement of one setting, including post-processing, requires approximately 30 min.

Intended use: Hydrodynamic measurements with flow-loop systems can be used for FSI-Simulation validation, as input for virtual cohort generation, and input generation for durability simulation (post-deflection) in device effect simulations.

Pulsatile Flow Loop System with Particle Image Velocimetry

Model Description: Particle Image Velocimetry is a non-contact optical measurement method of velocity fields. The model consists of a pulsatile flow loop system (ViVitro Labs.), described earlier, and a Particle-Image-Velocimetry setup (Dantec Dynamics). The PIV setup consists of an Nd:Yag laser and high-speed cameras. Everything is synchronized with the flow loop system. This setup allows triggered measurements of any time point in systole or diastole, as well as phase-triggered measurement of the entire cardiac cycle. The measured flow velocities provide information on local velocity distributions and vortex formation. Further derivations from the measured velocities can for example be shear stress and stagnation zones, which provide information about the risk of thrombosis. To further estimate the thrombosis risk, virtual fluid particle trajectories can be calculated based on the measured velocity fields to estimate the washout in the neo-sinus and native sinus. In this context, a low washout is associated with an increased risk of thrombosis. PIV measurements on prosthetic heart valves have been the subject of ISO standards[22] and some studies.[23,24,25,26]

[18]ISO standards: ISO/DIN 5840-3:2021
[19]Azadani et al., Effect of transcatheter aortic valve size and position on valve-in-valve hemodynamics: An in vitro study. Journal of Thoracic and Cardiovascular Surgery 153(6): 1303-1315, 2017 - https://doi.org/10.1016/j.jtcvs.2016.12.057
[20]Rahamani et al., In Vitro Hydrodynamic Assessment of a New Transcatheter Heart Valve Concept (the TRISKELE). Journal of Cardiovascular Translational Research 10: 104-115 , 2017 - https://doi.org/10.1007/s12265-016-9722-0
[21]Midha et al. ,Valve Type, Size, and Deployment Location Affect Hemodynamics in an In Vitro Valve-in-Valve Model. Journal of the American College of Cardiology: Cardiovascular Interventions 9 (15): 1618–1628, 2016 - https://doi.org/10.1016/j.jcin.2016.05.030
[22]ISO standards: ISO/DIS 5840:2021
[23]Barakat et al., Fluid Dynamic Characterization of Transcatheter Aortic Valves Using Particle Image Velocimetry. Artificial Organs 42(11): E357-E368, 2019 - https://doi.org/10.1111/aor.13290
[24]Hatoum et al., Aortic sinus flow stasis likely in valve-in-valve transcatheter aortic valve implantation. Journal of Thoracic and Cardiovascular Surgery 154(1): 32-43.e1, 2017 - https://doi.org/10.1016/j.jtcvs.2017.03.053
[25]Ducci et al., Transcatheter aortic valves produce unphysiological flows which may contribute to thromboembolic events: An in-vitro study. Journal of Biomechanics 49(16): 4080-4089, 2016 - https://doi.org/10.1016/j.jbiomech.2016.10.050
[26]Midha et al., The Effect of Valve-in-Valve Implantation Height on Sinus Flow. Annals of Biomedical Engineering 45(2): 405-412, 2017 - DOI: 10.1007/s10439-016-1642-2

Input: The PIV model requires generic or patient-specific geometry of the LVOT, aortic root and native valve leaflets, and implanted TAVI. In addition, inputs such as heart rate, pump volume, flow waveform, and systolic and diastolic pressures are required.

Output: Velocity fields within the aortic root around the TAVI. Metrics such as shear stress or Reynolds-shear-stress can be derived from the velocity fields and used to estimate thrombosis risk. A washout assessment using a Lagrangian particle path calculation of fluid particles can be used to calculate fluid residence time in native sinus and neo-sinus.

Numerical implementation: Adaptive cross-correlation algorithms to compute velocity fields from particle images are performed within Dantec Dynamics software Dynamic Studio. Lagrangian particle trajectories are computed using Runge-Kutta solver in Matlab (University Access).

Development status: PIV measurements on a generic aortic root model with simplified TAVI models have been performed in 2D – measuring 2 velocity components and are under continuous development.

Computational Effort: Preparation time is approximately 1.5 weeks. Measurement time is approximately 2 weeks. Post-processing should also be scheduled for 1.5 weeks.

Intended use: PIV measurements are the most complex and time-consuming in vitro measurements performed in this project, and for this reason, their use is very limited. Mainly we plan to use PIV for validation of FSI and CFD simulation.

Models by PHI

Mechanical TAVI model

Model description: The model, based on a FE solver, describes the virtual implantation of a TAVI device in the aortic root.

Input: Geometry of the anatomical structures (aortic root, native leaflets etc.), geometry of the device and associated material properties for both tissue and device are needed as input.

Output: position of the device in place, stresses on the annulus and on the device.

Numerical implementation: FEM.

With or without licenses? With (currently in Abaqus to be transferred to Ansys during the Project).

Stage of development: Initial model set-up, but refinement of material properties is needed. This will be done by comparing the obtained deployment with post interventional images derived from patients.

Computational costs: Medium (hrs).

Intended use: Assess mechanical fitting of the device, aid device selection and positioning, identification of device weak points.

CFD TAVI model

Model description: The model, based on a FV solver, describes the flow occurring before and after the virtual implantation of a TAVI device in the aortic root.

Input: Geometry of the anatomical structures (aortic root, native leaflets etc.), geometry of the implanted device (used only for the post-op assessment), pressure boundary conditions, motion of the ventricle.

Output: flow velocity, pressure gradient in the pre-op condition, paravalvular leakage etc.

Numerical implementation: Finite Volume.

With or without licenses? With (currently implemented in StarCCM+, to be seen whether it is needed in the project).

Stage of development: Initial basic model set-up, no FSI.

Computational costs: High.

Intended use: Identify risks of paravalvular leakage after implant.

Models by TUE

In vitro Mock loop circulation model

Model description: An integrated mock circulation system is available that functions in a physiological manner for testing and evaluating cardiovascular devices under well-controlled conditions[27]. The model consists of a systemic, pulmonary, and coronary circulation, and an elaborate heart contraction model (e.g., single fiber models for the four cavities). Moreover, after 2014, the model has been extended with physiological pressure regulation modules such as the baroreflex[28,29], a gas exchange model[30] and blood volume regulation[31].
The Mock circulation has been used to study the (patho)physiology of a wide range of cardiovascular applications, e.g. [32], and to verify physiological models[33]. In addition, it has been used to evaluate medical devices such as wires to assess coronary artery flow[34], LVADs[35,36], and intra-aortic balloon pumps[32]. More recently, the Mock circulation loop is used to study the haemodynamics and cardiac load due to VA-ECMO, and to examine both calcified and non-calcified aortic valve haemodynamics. For the latter, even a complete TAVI procedure was performed by a team of interventional cardiologists and engineers, which allows investigating the pre-, peri- and postoperative physiology. A video of this procedure and the resulting hemodynamic pressures and flows can be found as supplementary material of Zelis et al[37].

Input:

- A 3D-printed aortic valve model based on CT imaging.
- Settings of model parameters of the heart and vascular system as the Mock loop is completely driven and controlled by a real-time multiple in multiple out (MIMO) model reference feedback control system.

Output:

- Pressure and flow waveforms, cavity pressures and volumes in different compartments of the human cardiovascular circulation.

[27]Schampaert et al., A mock circulation model for cardiovascular device evaluation. Physiological Measurements 35(4):687-702, 2014 - 10.1088/0967-3334/35/4/687
[28]Ursino and Magosso, Acute cardiovascular response to isocapnic hypoxia. II. Model validation. American Journal of Physiology, Heart and Circulatory Physiology 279 (1), 2000 - https://doi.org/10.1152/ajpheart.2000.279.1.H166
[29]Magosso and Ursino, Effects of cardiovascular parameter changes on heart rate variability: Analysis by a mathematical model of short-term cardiovascular regulation, In The 26th Annual International Conference of the IEEE Engineering in Medicine and Biology Society, 2004 - https://doi.org/10.1109/IEMBS.2004.1404092
[30]Riley et al., Ideal Alveolar Air and the Analysis of Ventilation-Perfusion Relationships in the Lungs. Journal of Applied Physiology 1(12):825{847, 1949 - https://doi.org/10.1152/jappl.1949.1.12.825
[31]Rosalina et al., A mathematical model to investigate the effects of intravenous fluid administration and fluid loss. Journal of Biomechanics 88: 4-11, 2029 - https://doi.org/10.1016/j.jbiomech.2019.03.0022019
[32]Schampaert et al., In vitro comparison of support capabilities of intra-aortic balloon pump and Impella 2.5 left percutaneous. Artificial Organs 35(9):893-901, 2011 - https://doi.org/10.1111/j.1525-1594.2011.01286.x
[33]Experimental validation of a time-domain-based wave propagation model of blood flow in viscoelastic vessels. Journal of Biomechanics 41(2), 2008 - https://doi.org/10.1016/j.jbiomech.2007.09.014
[34]Van 't Veer et al., Continuous infusion thermodilution for assessment of coronary flow: theoretical background and in vitro validation. Medical Engineering and Physics 31(6):688-694, 2009, doi: 10.1016/j.medengphy.2009.01.006
[35]Pennings et al., Estimation of left ventricular pressure with the pump as "sensor" in patients with a continuous flow LVAD. International Journal of Artificial Organs 38(8):433-43, 2015 - https://doi.org/10.5301/ijao.5000424
[36]Bozkurt et al., Arterial pulsatility under phasic left ventricular assist device support. Biomedical Materials and Engineering 27(5):451-460, 2016 - 10.3233/BME-161599.
[37]Zelis et al.,3D-printed stenotic aortic valve model to simulate physiology before, during, and after transcatheter aortic valve implantation. International Journal of Cardiology 313: 32-34, 2020 - https://doi.org/10.1016/j.ijcard.2020.04.087

- From this information, further derived parameters are calculated that can for example describe the severity of aortic valve stenoses, such as pressure gradient, Stress Aortic Valve Index[38] or the power transfer coefficient[39].

Numerical implementation: The Mock circulatory system is essentially a multiple in multiple out (MIMO) model reference feedback control system using custom code, implemented in MATLAB Simulink real-time workshop, in C code. All model parameters can be adjusted on-the-fly, to provide flexibility in doing experiments. The physiological models typically provide setpoints for the controllers, which output is used to drive the motion of the hardware (piston pumps and resistance controllers). Physiological signals such as pressures, flow rates, saturation levels etc. are measured and/or calculated in real time, to provide immediate physiological feedback to the user.
Physiological processes with long characteristic times (typically kidney function and interstitial fluid exchange) can be accelerated a few orders of magnitude, to limit the time required for reaching a new steady state after the simulation of an intervention.

Stage of development: Already employed in multiple research projects. The physiological output of the Mock circulation has been benchmarked against existing literature, expert opinions, physiological models, and patient data.

Computational costs:

- The model provides real-time physiological output.
- Setting up, creating the valves, and designing specific Mock loop experiments will take most of the time. The required time for this is largely dependent on the application but can be done within 1 day for the TAVI experiments.

Intended use:

- The Mock circulation model will be used within the SIMCor project to verify (surrogate) models as one step of the validation of the virtual cohort generator at patient-level.

Reduced Order Lumped Parameter Model (0D)

Model description: This model is specifically developed for the prediction of the changes in hemodynamic parameters (blood pressures, flows and volumes) after aortic valve replacement in patients with stenotic aortic valves. The model consists of a mitral (diode) and aortic valve (dynamic valve model of Mynard et al.[40]), a single fibre model of the heart[41,42] with a fixed pulmonary venous pressure as preload. The systemic circulation is modelled by multiple Windkessel models. The number of Windkessels can be set by the user.

The single fiber model was first introduced by Arts et al.[41] and later extended to a thick-walled sphere formulation by Bovendeerd et al.[42] When assuming homogeneity in fibre stress they were able to derive a relationship that describes how left ventricular pressure and volume are related to local tissue

[38]Johnson et al., Pressure gradient vs. flow relationships to characterize the physiology of a severely stenotic aortic valve before and after transcatheter valve implantation. European Heart Journal 39(28): 2646-2655, 2018 - https://doi.org/10.1093/eurheartj/ehy126
[39]Meiburg et al., Model-based aortic power transfer: A potential measure for quantifying aortic stenosis severity based on measured data. Medical Engineering and Physics 90: 66-81, 2021 - https://doi.org/10.1016/j.medengphy.2021.02.009
[40]Mynard et al., A simple, versatile valve model for use in lumped parameter and one-dimensional cardiovascular models. International Journal of Numerical Methods in Biomedical Engineering 28(6): 626-641, 2011 - https://doi.org/10.1002/cnm.1466
[41]Arts et al., Modeling the relation between cardiac pump function and myofiber mechanics. Journal of Biomechanics 36(5): 731-736, 2003
[42]Bovendeerd et al., Dependence of Intramyocardial Pressure and Coronary Flow on Ventricular Loading and Contractility: A Model Study. Annals of Biomedical Engineering 34(12): 1833-1845, 2007 - http://dx.doi.org/10.1007/s10439-006-9189-2

properties, i.e., fibre stress and strain, and radial wall stress and strain. Another benefit of this model is that it allows for cardiac adaptation (e.g., hypertrophy) caused by mechanical triggers[43,44].

The parameters of the model can accurately be assessed for individual patients, either directly, based on literature (less influential parameters), or by means of parameter optimization using other clinical measurements. Regarding the latter, Meiburg et al. successfully applied unscented Kalman filtering to noisy synthetic data, i.e., left ventricular pressure, mitral valve flow, aortic valve flow and aortic pressure, to estimate cardiac, valvular and Windkessel parameters. Note that the used data can easily be determined in clinical settings. The UKF method is not only fast but also provides probability distributions of the parameter estimates, which allows for quantification of the uncertainty in model predictions due to input uncertainty.

Input:

- Parameters to be measured directly such as the cardiac cycle time, ventricular wall volume and the ratio between contraction time and cardiac cycle
- Parameters to be estimated based on other clinical measurements to estimate cardiac, valvular and Windkessel parameters
- Literature values for the parameters that are relevant for the model structure but have minor impact on the model outputs of interest.

Output:

- Hemodynamic metrics such as blood pressure, volumes and flows both before and after aortic valve replacement.
- The uncertainty in the outputs of interest due to uncertainties in the input.

Numerical implementation: Currently in MATLAB, but the model can be implemented using any tool or language.

Computational costs:

- Effectively none, the model runs in real-time, although the parameter estimation step takes approximately 90s. Thereafter, the model can be used to predict hemodynamic changes after aortic valve replacement.

Stage of development: The model is qualitatively corroborated with clinical observations done by Johnson et al. The model was further improved so that it can simulate the different pressure-flow relationships observed in aortic valve stenosis patients, i.e., linear, sub-linear and quadratic. Moreover, it was shown that the model could be calibrated, by using UKF, to individual patient measurements of left ventricular pressure, aortic pressure and aortic valve flow, at different levels (concentrations) of dobutamine administering[45].

Intended use:

- This model can serve as a low computational demanding model for virtual cohort generation, especially to find proper boundary conditions in terms of cavity pressures, cavity flows,

[43]Arts et al., Control of whole heart geometry by intramyocardial mechano-feedback: a model study. Plos Computational Biology 8(2): e1002369, 2012 - https://doi.org/10.1371/journal.pcbi.1002369

[44]Rondanina et al., Stimulus–efect relations for left ventricular growth obtained with a simple multi-scale model: the influence of hemodynamic feedback. Biomechanics and Modeling in Mechanobiology 19: 2111-2126, 2020 - https://doi.org/10.1007/s10237-020-01327-2

[45]Meiburg et al., Model-based aortic power transfer: A potential measure for quantifying aortic stenosis severity based on measured data. Medical Engineering and Physics 90: 66-81, 2021 - https://doi.org/10.1016/j.medengphy.2021.02.009

transvalvular flows, arterial pressure and flows, or in terms of Windkessel parameters to mimic the distal vasculature.

1D Pulse Wave Propagation Model

Model description: A pulse wave propagation model, based on the 1D momentum and mass balance equations derived by Hughes and Lubliner[46] is available. These models can simulate pressure and flow wave propagation along the complete arterial and venous tree. A review regarding 1D pulse wave propagation models is given by Stergiopulos and van de Vosse[47].

Input:

- Vascular geometry and topology
- Mechanical vessel properties
- Parameters that represent the capillary bed (e.g., Windkessel parameters)
- Arterial inlet pressure or flow waveform. These waveforms can also be extracted from a 0D cardiac model such as the single fibre or elastance model.

Output:

- Pressure and flow waveforms at different locations throughout the cardiovascular system.
- Rough estimations of wall shear stress waveforms over time.

Numerical implementation: We have the 1D code available in Fortran, Python and MATLAB. MATLAB has been used the most but recently we moved to Python. The Python implementation is programmed in a modular way and will serve as the backbone for future developments.

Computational costs: The computational cost is low and mainly determined by the element size and thus the level of detail of the geometry used for simulation. The full ADAN model with 62 arteries, which is used as benchmark for several 1D schemes (ref), took approximately 130 s (15 cycles) for the MATLAB implementation on an ordinary laptop PC with an Intel Core i7 processor. The element length used was 5 mm and the time step 10 ms.

Stage of development: The numerical implementation has been benchmarked against other numerical schemes by Boileau et al.[48]. In this benchmark study, all governing equations were exactly similar. However, we most often use an implementation in which the wall shear stress and advection term of the 1D momentum equation are estimated by means of an approximate velocity profile, which better mimics the real physics[49]. This implementation has been verified against *in vitro* experiments with both elastic and visco-elastic silicone tubes[50]. Moreover, we have used this model for multiple cardiovascular applications such as coronary artery haemodynamics[51]. Moreover, these models are combined with veins, 0D models of the heart and 0D models of the pulmonary circulation to obtain

[46]Hughes and Lubliner, On the one-dimensional theory of blood flow in the large vessels. Mathematical Biosciences 18:161–70, 1973
[47]Stergiopulos and van de Vosse,Pulse Wave Propagation in the Arterial Tree. Annual Review of Fluid Mechanics 43(1): 467-499, 2011 - http://dx.doi.org/10.1146/annurev-fluid-122109-160730
[48]Boileau et al., A benchmark study of numerical schemes for one-dimensional arterial blood flow modelling. International Journal of Numerical Methods in Biomedical Engineering 31(10), 2015 - http://doi.org/10.1002/cnm.2732
[49]Bessems et al., A wave propagation model of blood flow in large vessels using an approximate velocity profile function. Journal of Fluid Mechanics (580): 145-168, 2007 - https://doi.org/10.1017/S0022112007005344
[50]Bessems et al., Experimental validation of a time-domain-based wave propagation model of blood flow in viscoelastic vessels. Journal of Biomechanics 41(2), 2008 - https://doi.org/10.1016/j.jbiomech.2007.09.014
[51]Van der Horst et al., Towards Patient-Specific Modeling of Coronary Hemodynamics in Healthy and Diseased StateComputational and Mathematical Methods in Medicine, 2013 - http://dx.doi.org/10.1155/2013/393792

closed-loop circulations[52]. Several of these applications also used this model to perform virtual surgery[53] or to determine boundary conditions for 3D models[54].

Intended use:

- For the generation of more realistic (outflow) boundary conditions for 3D simulations.
- Possibly it can be used as surrogate model for computationally demanding 3D FSI models.

3D CFD model aortic valve stenoses

Model description: This model aims to calculate the peak-systolic pressure drop across an open but stenosed aortic valve. The pressure drop due to the presence of the valve is defined as the pressure difference between the left ventricular outflow tract (LVOT) and the aortic pressure after pressure recovery.

Segmented anatomical structures of the LVOT and the aortic valve are extracted from CT images at mid-systole and are used to create a volumetric mesh. Volumetric meshing will be performed with ANSYS Fluent Meshing R2021R1 (ANSYS Inc, Canonsburg, Pennsylvania, United States). Manually a plane is defined two to five millimetres proximal to the valve annulus and orthogonal to the valve axis. The outflow tract is extended by 3.5 times the diameter of the ascending aorta, whereas the inflow boundary is extended by 1.5 times LVOT diameters[55]. At the inflow boundary of the model a plug velocity profile is prescribed that mimics peak systolic flow. At the vessel wall a no-slip boundary condition is applied, and at the outflow boundary a zero-pressure boundary is used.

Though the model makes use of a constant input flow, the model has also been evaluated for transient inflow waveforms, either prescribed directly (i.e., the truncated transient model) or calculated by including the image-derived left ventricular (full model) contraction. Ventricular contraction was derived from ECG-gated CT acquisitions. However, for the calculations of the pressure losses, the simplified models were proven to be sufficiently accurate for pressure losses larger than 10 mmHg (i.e., the non-healthy cases). When interested in more detailed flow disturbances the truncated transient model or model with ventricular contraction is recommended[55].

Input:

- Geometries of the aortic valve, LVOT, proximal ascending aorta and a small part of the LV (connected to the LVOT, see our model description).
- A peak-systolic flow rate.

Output:

- Pressures losses along the centreline from which derived metrics such as the Bernoulli pressure loss, the effective pressure loss and the valve pressure loss.
- Velocity fields. But note that the velocity fields of the steady simulation represent a time averaged flow field which may not be entirely representative of the pulsatile nature of aortic-valve flow.

[52]Keijsers, Numerical analysis of the hemodynamic response to orthostatic stress. PhD thesis, Chapter 5, Eindhoven University of Technology, 2016 - https://pure.tue.nl/admin/files/52365208/20170116_Keijsers.pdf
[53]Huberts et al., A pulse wave propagation model to support decision-making in vascular access planning in the clinic. Medical Engineering and Physics 34(2): 233-248, 2012 - https://doi.org/10.1016/j.medengphy.2011.07.015
[54]Blatter, The construction of a framework that enables patient-specific hemodynamic modelling of aortic dissections. MSc. thesis, Eindhoven University of Technology, 2018 - https://pure.tue.nl/admin/files/140385287/20190829_0773304_ReportMFJBlatter.pdf
[55] Hoeijmakers et al., Estimation of valvular resistance of segmented aortic valves using computational fluid dynamics. Journal of Biomechanics 94: 49-58, 2019 - https://doi.org/10.1016/j.jbiomech.2019.07.010

Numerical implementation: The governing equations are solved with ANSYS fluent R2021R1 (ANSYS Inc, Canonsburg, Pennsylvania, United States) which uses a finite volume method and assumes incompressible Newtonian fluid properties for the blood. Moreover, a Shear Stress Transport *k-ω* model is used to capture viscous losses due to turbulence. For the pulsatile flow conditions Large Eddy Simulations are done to consider the turbulent effects.
A limited number of research licenses are currently available which can prohibit running large numbers of simulations. However, we expect that we can resolve this issue with ANSYS, with whom we closely collaborate in multiple research projects. Therefore, licensing is not expected to hamper execution of large numbers of simulations.

Computational costs: The simulations of the steady simulations take approximately 15 minutes on one single computing node with 4 CPUs. Hence, individual simulations may be performed on an ordinary laptop / PC. The truncated transient model is computationally more demanding and may take up to 100 times longer. Hence, for many steady simulations, or individual transient simulations, the use of an HPC infrastructure is recommended.

Stage of development: The model, and various variations thereof, have been published[55] and has had several levels of validation. First, the simulation results are qualitatively corroborated against literature and similar pressure drops were found for similar aortic valve areas. Second, the model has been validated with an experimental *in-vitro* setup[56]. Here it was found that the evolution of the aortic valve pressure drop in pulsatile flow conditions is captured sufficiently, although it was also shown that the agreement between CFD and experiments is not guaranteed. In fact, the CFD models tended to underestimate steady and peak systolic pressure drops but did capture the pressure drop waveform in pulsatile flow conditions. It was also found that unsteadiness becomes more important when the aortic valve area increases and may become important for intermediate stenoses.

Intended use:

- For the creation of surrogate models that will be used for virtual cohort generation
- For the validation of surrogate models

Isogeometric Analysis Model of TAVI deployment

Model description: This model is intended to demonstrate the capabilities of the Isogeometric Analysis (IGA) paradigm for simulating the deployment of TAVI devices. The developed model should capture the geometric features of the devices essential for the understanding of the deployment behaviour, as well as the essential mechanical behaviour, including device-vessel interactions. To focus on these aspects, established models for the mechanical behaviour of the vessel will be considered.
In the first part of the project, the focus in the IGA model development will be on the construction of the device's IGA model, for which computer-aided design (CAD) formats will form the basis. The analysis-suitability of these IGA models will be tested using benchmark simulations for large-displacement mechanical behaviour. In this phase, a surrogate model for the vessel will be considered.
In the second part of the project, the IGA model will be enriched with contact mechanics capabilities. This will commence with the consideration of the contact mechanics between a rigid device and a deformable vessel. Subsequently, both the device and the vessel will be deformable.

Input:

- CAD models of the devices (e.g., IGES, STEP), or alternatively STL or BREP (which require additional pre-processing to be made analysis-suitable).

[56]Hoeijmakers et al., M.J.M.M. Hoeijmakers, M.C.M. Rutten, F.N. van de Vosse. Experimental validation of the simulated transvalvular pressure-drop of healthy and stenosed heart valves in steady and pulsatile flow conditions.Chapter 6, PhD thesis, 2021 - https://research.tue.nl/files/165209705/20210108_Hoeijmakers.pdf

- Description of the anatomy of the vessel before and after insertion of the device. This can be patient-specific but is not strictly required for the development of this model.

Output:

- Deformations and stresses of the device and the surrounding vessel
- Characterization of the contact between the device and vessel (e.g., contact stresses, contact area)

Numerical implementation: The idea is to integrate the developments in existing (commercial) software, creating the experience that the simulation is directly performed on the CAD model. To this end use will likely be made of software-coupling tools and IGA-compatible open-source finite element libraries (e.g., Nutils, http://www.nutils.org/en/stable/).

Computational costs: The developed model is adaptive in the sense that it can be used for very coarse calculations (taking minutes) to very much refined simulations (taking multiple hours).

Intended use: TAVI getting a quick/initial estimate of the mechanical behavior of the device under deployment, directly based on the geometric CAD model. This allows designers to understand the impact of their design decisions on the mechanical behavior of the device.

Models by UCL

Finite Element Analyses of TAVI implantation

Model description: We have a computational framework to simulate the implantation of TAVI devices based on FE analyses. Geometrical results of FE analyses can be post-processed to derive measurements of *paravalvular leakage* (PVL). Please note that TAVI simulations are proposed by other partners in the consortium, which needs close collaboration and fine tuning within WP9.

Input:

- Anatomical models of the aortic valves, annulus, left ventricular outflow tract and aortic root (stl)
- Geometrical model of the TAVI device
- The positioning of the TAVI device
- Boundary and contact conditions

Output:

- Post-implantation geometries, stresses, and contact pressures
- Estimations of paravalvular leakage

Numerical implementation: An FE model is set up to simulate the implantation of TAVI devices in patient-specific anatomies or population derived geometries. A streamlined workflow is implemented to optimize and standardize the computational procedures. FE input will include meshed geometry, tissue material properties, and TAVI device model. The workflow will include setup of the FE simulations, such as positioning, boundary conditions and contact conditions. Simulation output will include geometry of the expanded device, deformed LVOT, stresses and contact pressures, which will be related to the acute performance of TAVI. Moreover, we have validated a geometric model as a valid surrogate for fluid flow model to estimate the PVL risk. Using this approach, we will avoid computationally expensive fluid simulations. The FE analyses are carried out with Abaqus (Dassault Systemes), while the PVL model is implemented in MATLAB.

Computational costs: The computational costs are considered high.

Stage of development: The models are ready to be used[57,58,59,60,61].

Intended use: TAVI effect simulations

[57]Bosi et al., A validated computational framework to predict outcomes in TAVI. Scientific Reports 10, 2021 - https://doi.org/10.1038/s41598-020-66899-6

[58]Bosi et al., Patient-specific finite element models to support clinical decisions: A lesson learnt from a case study of percutaneous pulmonary valve implantation. Catheterization and Cardiovascular Interventions 86, 2015 - https://doi.org/10.1002/ccd.25944

[59]Bosi et al.,Population-specific material properties of the implantation site for transcatheter aortic valve replacement finite element simulations. Journal of Biomechanics 71: 236-244, 2018 - https://doi.org/10.1016/j.jbiomech.2018.02.017

[60]Schievano et al., First-in-man implantation of a novel percutaneous valve: a new approach to medical device development. EuroIntervention 5, 745-750, 2010 - https://doi.org/10.4244/eijv5i6a122

[61]Schievano et al., Patient specific finite element analysis results in more accurate prediction of stent fractures: application to percutaneous pulmonary valve implantation. Journal of Biomechanics 43: 687-693, 2010 - https://doi.org/10.1016/j.jbiomech.2009.10.024

Models for heart failure patients in a non-acute setting

Models by BIO

PAPS – 3D Structural Mechanics Model

Model description: The model represents the PAPS device, consisting of the implant body and fixation elements at two faces of the body. The model should be able to compute accurate patient-specific responses regarding mechanical issues. In detail, retention force and contact force with the vessel need to be simulated for further assessment of migration and perforation risk. The model will require patient-specific information on the anatomy of the pulmonary artery. Further material models of the vessel wall and of the fixation elements, which are made of the shape memory alloy nitinol, are needed.
The simulation target is to determine the mechanical parameters for assessing the clinical endpoints, migration of the sensor and perforation of the vessel wall by the fixation elements, for the PAPS use case. Detailed mechanical simulations of the vessel implant interaction are then conducted using a commercial finite element software.

Input:

- Device geometry with implant body and relaxed fixation elements.
- Patient-specific anatomy of the pulmonary artery.
- Constitutive models of the vessel wall and the fixation elements (shape memory).
- Implantation site and device orientation.

Output:

- Position and displacement of sensor device and fixation elements after deployment.
- Deformation of the pulmonary artery.
- Strain / stresses in the fixation elements.
- Normal contact stresses and forces between fixation elements and pulmonary artery.
- Maximal axial retention force on sensor.

Numerical implementation: The commercial explicit time integration finite element (FE) solver ANSYS LS-DYNA is used. Limited parallel solving licenses are available (35 parallel processes). Vessel implant interaction at least at states of minimum and maximum blood pressure in the pulmonary artery is planned.

Computational costs:

- The numerical effort of the simulation including sensor release in the pulmonary artery is moderate, using 35 cores parallel the computation time will be less than 8 hours.
- Depending on the generated geometries the meshing and geometry preparation step could be demanding, and manual effort could be needed. Full automation of the simulations is challenging, and may be not possible.

Intended use:

- Migration - Due to the calculated retention forces and quantification of axial loads acting on the device body, the risk of sensor migration can be quantified.
- Perforation - The calculated contact stresses and forces between fixation elements and vessel wall will help to assess the risk of perforation.

Models by CHA

3D Computational Fluid Dynamics Model

Model description: This model will be developed for the purpose of SIMCor. The aim of this model is to calculate patient-specific haemodynamics within the pulmonary artery before and after implantation of a pulmonary pressure sensor. The model will require patient-specific information on the anatomy of the pulmonary artery. Regarding hemodynamic boundary conditions, a volume flow waveform will most likely be specified at the inlet of the main pulmonary artery. Boundary conditions for the branching vessels of the left and right pulmonary artery will have to be determined throughout the Project. Ideally, simple pressure-boundary conditions or very simple resistance models can be used that do not require much personalization. Elasticity of the pulmonary artery wall will also be neglected in this model. However, as material properties of the vessel will be considered during implantation of the pulmonary artery pressure sensor, deformations caused by this implantation and thus also hemodynamic changes due to these deformations will be accounted for by the model. The aim of the model is to calculate all relevant hemodynamic parameters that are relevant for estimation of the three clinical endpoints identified for the PAPS use case: thrombosis, perforation of the vessel wall by the struts and displacement of the sensor.

Input:

- Patient-specific anatomy of the pulmonary artery before and after implantation of the PAPS.
- Volume flow waveforms at the main pulmonary artery either modelled from 4D-VEC-MRI measurements or taken from literature.

Output:

- Spatially resolved information on velocities and pressures within the aortic lumen as well as wall shear stresses at the aortic wall.
- Forces acting on the sensor:
    - change in forces at the fixation wires;
    - change in forces in normal direction (displacement);
    - size and shape of recirculation regions;
    - oscillating shear indices at the sensor as well as the vessel;
    - washout.

Numerical implementation: A commercial solver (STAR-CCM+, v15.02) is used. Unlimited academic research licenses are available. Therefore, licensing is not prohibiting large numbers of simulations.

Stage of development: Must be developed throughout the project. However, the model is rather simple and several aspects from other models can be reused.

Computational costs:

- Direct numerical costs are moderate: simulation of three full heart cycles requires three days per case on a local workstation. Running simulations on a cluster with 4 nodes and 96 cores per node allows computation in less than 10 hours.
- Manual costs for setting up the model will be reduced to a minimum. If geometries and boundary conditions are generated using virtual cohort generation and/or statistical shape modelling, full automation of simulations becomes feasible. Thus, also large virtual cohorts can be simulated.

Intended use:

- PAPS – Thrombosis: Here, recirculation regions, regions with stationary flow and wall shear stresses and oscillating shear indices at the sensor surface as well the vessel will be calculated as those are known to be associated with thrombosis.
- PAPS – Displacement: Here, the forces in flow direction will be calculated. These include the pressure as well as shear forces.
- PAPS – Perforation: For perforation, the FE models used for implantation will be more important, as those allow quantification of stresses in the vessel wall. However, using this model additional forces at the contacts between vessel and fixation wire can be quantified which might add to the risk for perforation.

Models by IIB

No models of PAPS available.

Models by PHI

No models of PAPS available.

Models by TUE

3D Computational Fluid Dynamics Model coupled to a 0D model of the heart

Model description: Now the TUE does not have a specific model to simulate pulmonary haemodynamics. However, to generate realistic boundary conditions for our virtual cohort we aim to develop a 3D CFD of the pulmonary circulation coupled to a 0D model of the heart before PAPS implantation. The parameters of the heart model will be set so that the heart represents the heart of a heart failure patient. This model will also be used to validate and feed the surrogate models that will be used for virtual cohort generation. A close collaboration with CHA and BIO is likely anticipated for here as these partners also aim to develop (or already have) 3D models of pulmonary artery haemodynamics.

Input:

- Patient-specific anatomy of the pulmonary artery before implantation of the PAPS.
- Volume flow waveforms at the main pulmonary artery modelled by the 0D model of the heart.
- Cardiac heart parameters adapted to heart failure patients, either by means of parameter estimation using clinical data, or based on literature.

Output: Spatially resolved information on velocities and pressures within the aortic lumen as well as wall shear stresses at the vascular walls of the pulmonary arteries.

Numerical implementation: A commercial solver (ANSYS 2021 R1) will be used. Unlimited academic research licenses are available. Therefore, licensing is not prohibiting large numbers of simulations. We also have a 3D-0D coupled model available in the open-source finite element package FEniCS (https://fenicsproject.org/).

Stage of development: Must be developed throughout the project. However, several aspects from other models can be reused.

Computational costs: Direct numerical costs can be high but need to be defined during the project. However, to get an idea of the computational cost, a 3D simulation of the aorta with 1.5 million Taylor-Hood elements, coupled to a 0D model of the heart and peripheral circulation, and implemented in

FEniCS took approximately50 CPU hours per simulated second on an ordinary laptop with 9th generation i7 processor and 16 GB RAM.

Intended use:

- For the creation of surrogate models that will be used for virtual cohort generation;
- For the validation of surrogate models;
- For the definition of realistic boundary conditions in case of heart failure patients.

Isogeometric Analysis Model of PAPS implantation

The description of this model is similar to the IGA model for TAVI deployment but now the PAPS device will be evaluated. Therefore, we refer to the section in which the TUE models of aortic valve disease patients are discussed.

Models by UCL

No models of PAPS available.

Candidates for surrogate modelling

Multiple surrogate modelling techniques (also called metamodels or emulators) are available in scientific literature, but the models are far from being fully exploited as replacement for computationally demanding cardiovascular models. In this section, we will briefly describe a selection of surrogate modelling techniques that we will evaluate during SIMCor, and from which we believe that they have potential to serve as a fast counterpart of our models that have a large computational burden. In this section we will not discuss reduced-order modelling techniques such as 0D and 1D models as these models were already discussed in the previous section.

Before we start our elaboration, we would like to stress that the biggest challenge of surrogate modelling is proper parameterization of the geometries and the number of simulations required to feed the surrogate models. The former is dealt with in WP5 and WP6, whereas the latter will be an integrated part of the research that will take place related to virtual cohort generation and validation. The optimal design of experiment and the best suitable surrogate models are important project outcomes of WP7.

Polynomial chaos expansion techniques

Surrogate or metamodelling based on polynomial chaos expansion are typically used for uncertainty and sensitivity analysis[62,63,64.] Uncertainty analysis quantifies the uncertainty in model output due to uncertainties in the input factors (e.g., parameters, boundary conditions and/or model assumptions), whereas sensitivity analysis attributes each fraction of the output uncertainty to individual input factors and their uncertainties, or to interactions of these uncertain factors[2].

The basic idea of this modelling technique is that a stochastic output space is spanned by orthogonal polynomials that are dependent on stochastic inputs. Depending on the distribution of the input specific polynomials are selected. For example, Hermite polynomials are used for Gaussian input distributions, whereas Legendre polynomials are used for uniform distributions. However, mixed formulations are also possible. As soon as a proper surrogate model has been found, statistical metrics to quantify the model output uncertainty can be found analytically. In addition, the so-called Sobol sensitivity indices can be derived analytically. The Sobol indices are still considered as best available practice for sensitivity analysis[2].

We have used polynomial chaos expansion for multiple uncertainty and sensitivity analyses of cardiovascular models[65,66,67]. For this, we most often applied an adaptive implementation in which the most relevant basis functions are added step-by-step based on the quality of the model fit through simulation data of high computationally demanding models[68]. The predictive power of the resulting metamodel is determined by means of leave-one-out cross validation method. This *adaptive*

[62]Xiu et al., Parametric uncertainty analysis of pulse wave propagation in a model of a human arterial network. Journal of Computational Physics 226(2): 1385-1407, 2007 - https://doi.org/10.1016/j.jcp.2007.05.020

[63]Sudret et al., Global sensitivity analysis using polynomial chaos expansion. Reliability Engineering and System Safety 93(7): 964-979, 2008 - http://dx.doi.org/10.1016/j.ress.2007.04.002

[64]Huberts et al., Applicability of the polynomial chaos expansion method for personalization of a cardiovascular pulse wave propagation model. International Journal of Numerical Methods in Biomedical Engineering 30(12), 2014 - https://doi.org/10.1002/cnm.2695

[65]Donders et al., Personalization of models with many model parameters: an efficient sensitivity analysis approach. International Journal of Numerical Methods in Biomedical Engineering 31(10), 2015 - https://doi.org/10.1002/cnm.2727

[66]Keijsers et al., Global sensitivity analysis of a model for venous valve dynamics. Journal of Biomechanics 49(13): 2845-2853, 2016 - https://doi.org/10.1016/j.jbiomech.2016.06.029

[67]Heusinkveld et al., Complementing sparse vascular imaging data by physiological adaptation rules. Journal of Applied Physiology 130: 571-588, 2021 - https://doi.org/10.1152/japplphysiol.00250.2019

[68]Quicken et al., Application of an Adaptive Polynomial Chaos Expansion on Computationally Expensive Three-Dimensional Cardiovascular Models for Uncertainty Quantification and Sensitivity Analysis. Journal of Biomechanical Engineering-Transactions of the ASME 138(12), 2016 - https://doi.org/10.1115/1.4034709

polynomial chaos expansion (agPCE) was introduced by Blatman et al.[69] and significantly increased the speed of the analysis for expensive cardiovascular models[68].

More recently, we have adopted this agPCE approach for the optimization of an arteriovenous graft by using the surrogate model for predicting how different helical graft design parameter settings translate to hemodynamic graft performance[70]. This approach performed very-well and has the advantage, due to its nature as a sensitivity tool, that it provides information about the design parameters that are most rewarding to optimize, and how these parameters interact. Moreover, we have used the agPCE method to define a surrogate model for fast and accurate calculations of pressure differences across iliac artery stenoses in peripheral arterial disease patients[71].

In SIMCor we will also evaluate the agPCE method as a surrogate model for virtual cohort generation. Our current agPCE implementation allows for scalar outputs that can be calculated much faster than the same scalar values when using the computationally demanding model. Of course, this is only possible when the surrogate model has been trained properly with sufficient data points of the computationally expensive models. The creation of multiple models is needed with our implementation when multiple scalar outputs are considered. Similarly, vector-valued outputs like time signals of pressure and flow are theoretically feasible but require the development of metamodels for each vector component. Note however that for the development of these different meta-models, the same simulation data can be reused. Moreover, there are possibilities to create one single metamodel based on PCE for vector-valued (multidimensional or time-dependent) outputs[72,73]. This will be further explored in SIMCor.

Genetic-aggregation technique

The use of surrogate models instead of computational expensive simulation has become very popular in engineering design problems. Multiple surrogate model families, such as amongst others regression, kriging, and neural networks, are available in literature. One single model family can be used but also a combination of individual models is possible, i.e., a weighted average of different types of models, referred to as aggregation or ensemble models. On forehand, it is often difficult to decide which combination of models is most suitable for a given problem. Consequently, automatic selection algorithms are required to find the optimal aggregation weights and metamodels.

The genetic-aggregation technique introduced by Salem et al.[74] is an aggregation technique that explores the space of surrogate models by using an evolutionary (genetic) algorithm in which each surrogate model is considered an individual. The aggregation weights of the ensembled surrogate model are optimized by means of a universal criterion, i.e., the penalized predictive score (PPS)., that quantifies the quality of the ensembled surrogate model.

This genetic-aggregation technique was successfully applied to obtain a surrogate model for the calculation of pressure drops across aortic valve stenoses[75], and is therefore also highly suitable for virtual cohort generation in the SIMCor project. Once trained by means of high-fidelity but

[69]Blatman et al., Adaptive sparse polynomial chaos expansions for uncertainty propagation and sensitivity analysis. PhD thesis 2009 - https://sudret.ibk.ethz.ch/research/publications/doctoralTheses/g--blatman.html
[70]Quicken et al., Haemodynamic optimisation of a dialysis graft design using a global optimisation approach. International Journal of Numerical Methods in Biomedical Engineering 37(2), 2020 - https://doi.org/10.1002/cnm.3423
[71]Heinen et al., A metamodeling approach for instant severity assessment and uncertainty quantification of iliac artery stenoses. Journal of Biomechanical Engineering 142(1), 2020 - https://doi.org/10.1115/1.4044502
[72]Xiu et al, Parametric uncertainty analysis of pulse wave propagation in a model of a human arterial network. Journal of Computational Physics 226(2): 1385-1407, 2007 - https://doi.org/10.1016/j.jcp.2007.05.020
[73]Blatman et al., Sparse polynomial chaos expansions of vector-valued response quantities. Conference Proceedings of the 11th Conference on structural safety and reliability, New York, USA, 2013 - http://dx.doi.org/10.1201/b16387-469
[74]Salem and Tomaso, Automatic selection for general surrogate models.Structural and Multidisciplinary Optimization 58:719–734, 2018 - https://doi.org/10.1007/s00158-018-1925-3
[75]Hoeijmakers et al., Combining statistical shape modeling, CFD, and metamodeling to approximate the patient-specific pressure-drop across the aortic valve in real-time. International Journal of Numerical Methods in Biomedical Engineering 36(10), 2020 - https://doi.org/10.1002/cnm.3387

computationally expensive CFD simulations, the surrogate model was able to provide an accurate estimate of the pressure drop-flow relationship in real-time. The input of the surrogate model consisted of flow rate and statistical shape models that were used to describe the aortic valve geometry.

Vectorial Kernel Orthogonal Greedy Algorithm

An interesting surrogate modelling technique that will be considered and applied during virtual cohort generation and validation will be the Vectorial Kernel Orthogonal Greedy Algorithm (VKOGA, Santin et al.[76]). The VKOGA method approximates the input-output functional by means of a linear combination of kernel functions, whereas a Greedy Algorithm is used to obtain a sparse surrogate model. A nice property of this method is that you can easily create a surrogate model for vectorial outputs such as for example time signals.

The VKOGA method was successfully used as a surrogate model of a 1D pulse wave propagation model by Koeppl et al.[77], who used the resulting surrogate model for parameter estimation based on pressure and flow waveforms. Koeppl et al.[77] also showed the enormous increase in computational efficiency by reporting that the calculation of one full cardiac cycle was a factor 10^6 faster when using the surrogate model instead of the full model. A first exploration of these methods on a similar model by TUE also showed the potential computational benefits of this surrogate modelling approach.

Reduced-basis modelling

Reduced-basis methods represent a very efficient approach for the numerical approximation of pressure and velocity fields in fluid dynamic problems[78,79]. The basic idea of the reduced-basis method is as follows. After proper parameterization of the governing equations of the problem, the parameterized solutions lie on a low dimensional manifold. The solution manifold is a set of solutions that will be obtained after running the computationally expensive model for a suitably chosen set of model parameterizations (i.e., the offline phase). Each solution of the manifold is called a snapshot. Thereafter, each member of the solution manifold is approximated with a low number of basic functions, i.e., the reduced basis which has a much lower dimension than the original problem. Now, for any new set of parameters, an approximated solution can be found by expressing it as a linear combination of the problem-dependent reduced-basis functions. The latter, so-called online phase, can be done in a time frame close to real-time. This fast evaluation potential makes this method very well suited for the virtual cohort methodology used in SIMCor. Moreover, it can facilitate our sensitivity and uncertainty analyses of the 3D models that we are planning to use.

Though reduced-basis techniques have already demonstrated their large potential to increase the computational efficiency of cardiovascular models, an important challenge remains for SIMCor: The full potential of the method can only be fully exploited if we will be able to find a proper shape transformation to map the parameterized governing equations applied to complex cardiovascular geometries on a parameter-independent domain. The latter is of importance to ensure the beneficial efficiency of the method as it allows to separate the parameters and the operators within the formulation[78,80]. This will be one of the objectives of WP7.

[76]Haasdonk et al., Greedy kernel approximation for sparse surrogate modeling. In: Keiper W, Milde A, Volkwein S eds. Reduced-Order Modeling (ROM) for Simulation and Optimization: Powerful Algorithms as Key Enablers for Scientific Computing. Springer International Publishing; 2018:21-45. https://doi.org/10.1007/978-3-319-75319-5_2

[77]Koeppl et al., Numerical modelling of a peripheral arterial stenosis using dimensionally reduced models and kernel methods. International Journal of Numerical Methods in Biomedical Engineering 34(8), 2018 - https://doi.org/10.1002/cnm.3095

[78]Quarteroni et al., Reduced Basis Methods for Partial Differential Equations. Springer, 2016 - 0.1007/978-3-319-15431-2

[79]Hesthaven et al., Certified Reduced Basis Methods for Parametrized Partial Differential Equations. SpringerBriefs in Mathematics, 2016 - 10.1007/978-3-319-22470-1

[80]Ballarin et al., Reduced order models for patient-specific haemodynamics of coronary artery bypass grafts", PhD Thesis, Politecnico di Milano, 2015 - https://www.politesi.polimi.it/handle/10589/102804

Physics-constrained Neural Networks and deep learning

Other interesting surrogate models that are worth evaluating for virtual cohort generation in SIMCor are based on *physics-informed neural networks* (PINNs). Physics-informed neural networks integrate physics-based governing equations into neural networks. The integration of these governing equations overcomes the large data requirement in classical deep learning methods, and simultaneously efficiently combines data and physical knowledge.

PINNs can be very interesting for virtual cohort generation and validation because it might help to extract more accurate inlet and outlet boundary conditions for flow simulations by assimilating sparse measurements. Arzani et al.[81] was able to calculate accurate wall shear stresses without full knowledge of the boundary conditions by using sparse velocity measurements away from the wall. In SIMCor, we will evaluate whether this approach can also be applied to non-idealized vessel or valve geometries.

Within the Project, the potential use of PINNs might not be limited to deal with data sparsity but could also be suitable for surrogate modelling during virtual cohort generation and validation. Recently, Sun et al.[82] introduced a physics-informed deep neural network that can be used as a surrogate model and does not rely on simulation data for training. Consequently, we do not need to perform computationally expensive CFD models to feed our surrogate models, and not for virtual cohort generation. However, whether this approach is suitable for our applications with complex geometries, pressure and flow fields need to be determined. TUE is planning to examine the feasibility of this method for its use in SIMCor.

[81]Arzani et al., Uncovering near-wall blood flow from sparse data with physics-informed neural networks. Physics of Fluids 33, 2021 - https://doi.org/10.1063/5.0055600

[82]Sun et al., Surrogate modeling for fluid flows based on physics-constrained deep learning without simulation data. Computer Methods in Applied Mechanics and Engineering 361, 2020 - https://doi.org/10.1016/j.cma.2019.112732

Integration into the virtual research environment (VRE)

The generation of the virtual cohort will be done by evaluating the fastest available models (e.g., the surrogate models) for multiple inputs. The inputs are sampled uniformly from an *a priori* distribution based on real patient data (see WP5 and WP6). The outputs of the models are subsequently used to remove non-physiological combinations of inputs. The resulting inputs that are not removed are considered as realistic virtual patients.

We anticipate integrating the following components of the virtual cohort generator to the VRE. First, we will give the user the possibility to define the input space that will be used for sampling by indicating the maximum and minimum values for each input. Then an integrated sampling strategy will generate multiple inputs for our models used for virtual cohort generation (most likely the surrogate models). The surrogate models will also be part of the VRE and will be used to calculate the outputs that are used to select physiologically realistic virtual patients. The filter will also be an integrated component of the VRE. The outcome of the virtual cohort generator that will be implemented in the VRE is thus a set of virtual patients (i.e., a geometry and realistic boundary conditions).

Future work

With respect to the models that are presented in this deliverable, we will further develop these models for their intended use. For example, models of TAVI deployment and PAPS implantation will be developed in WP8 and WP9, whereas WP7 will apply and validate existing models, and/or will develop and validate surrogate models that will be used for virtual cohort generation.

Another important step that needs to be done is to use the virtual cohorts generated in WP7 for device effect simulations in WP9. Finally, we also need to consider how we can map our engineering metrics to clinical outcomes of clinical trials. This is especially important for Task 7.6 in which the virtual cohorts developed for the evaluation of TAVI and PAPS will be used for prediction of clinical-trial related parameters (e.g., sample size, outcome criteria, inclusion and exclusion criteria for the real patient population). This is required for the evaluation and quantification of the effectiveness of *in-silico* workflows in the design of real clinical trials, to be carried out in WP10.