SIMCor

In-Silico testing and validation of Cardiovascular IMplantable devices

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First version of the definition of the input space

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Lead beneficiary	Technische Universiteit Eindhoven (TUE)
Author(s)	Wouter Huberts (TUE)
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Executive summary

The deliverable describes the first version of the definition of the input space that will be used to feed the virtual cohort generators. Accurate definition of the input space depends on available clinical data, the model used for virtual cohort generation and model parameter prioritization based on advanced sensitivity analysis techniques. The final models to be used will be part of future deliverables, which also holds for the sensitivity analysis. In this document we will describe the envisioned strategy for input space definition and how this strategy will result in an input distribution that captures realistic aortic valve disease and heart failure patients. The feasibility of the input space definition as envisioned by the project methodology will be supported by preliminary results of virtual cohort generation of aortic valve patients. Here we also discuss how clinical data is transformed into data that can be fed into our virtual cohort generator. This preliminary use case nicely demonstrates our approach but is not yet completely validated. However, it is already integrated into the Virtual Research Environment as a typical example. How integration is done will also be shown. Moreover, we present preliminary results on the geometric input definition of porcine pulmonary arteries.

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Acronyms

Acronym	Full name
TAVI	Trans aortic valve implantation
PAPS	Pulmonary artery pressure sensor
HF	Heart failure
CFD	Computational fluid dynamics
0D	Lumped parameter model
VRE	Virtual research environment
LDDMM	Large deformation diffeomorphic metric mapping
SSM	Statistical shape model

Introduction

This deliverable describes the first version of the definition of the input space that will be used to feed the virtual cohort generators.

First, the document describes the envisioned strategy for input space definition, and how this strategy will result in an input distribution that captures realistic aortic valve disease and heart failure patients.

Then, it presents preliminary results of virtual cohort generation of aortic valve disease, and on the geometric input definition of porcine pulmonary arteries.

Approach envisioned for input space definition

In SIMCor, we use an approach in which we define a N-dimensional input space based on available clinical data that has been post-processed to serve as input for a validated physiological model (i.e., the digital representation of the real patient). The process can be summarized as follows:

- The input space is spanned by the upper and lower limits of model parameters and boundary conditions, which are inferred from the available data.
- Subsequently, we assume that all parameter values within the input space are uniformly distributed, and new samples are randomly selected from the defined input space.
- These newly generated samples are then fed into the physiological model to simulate the outputs of interest (see *D7.1 – Definition of model output (TUE, M6)*). To reduce computational cost, we use a surrogate model that is a fast equivalent of the real physiological model.
- Finally, a filter (acceptance criteria) is implemented to compare the simulation results with real population output data, hereby removing the models with non-physiological outcomes. The complete set of inputs of all realistic simulations defines a region (or multiple regions) of the initial sparse N-dimensional input space. Samples generated from these regions together with the physiological model define the virtual patients.

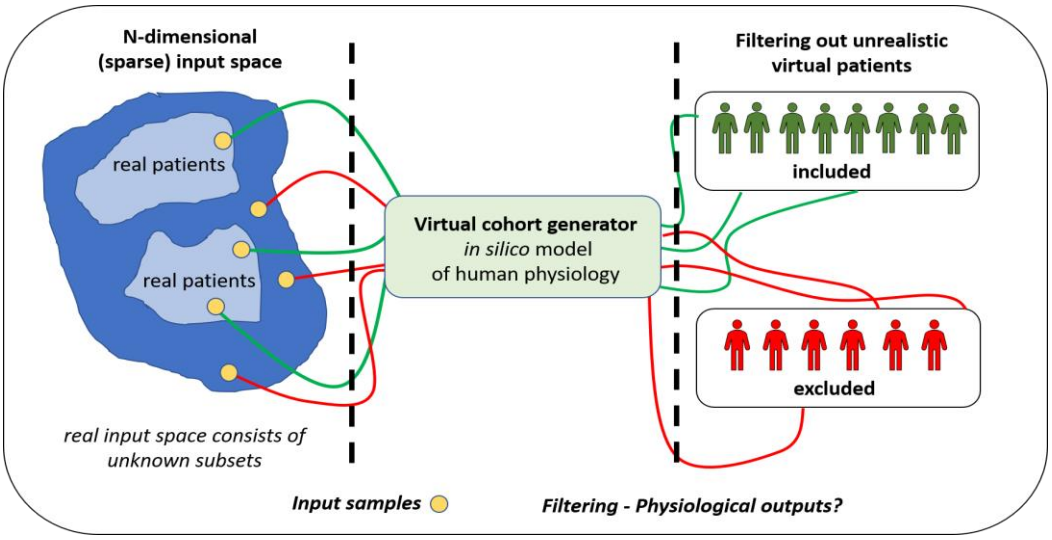

Figure 1: Schematic overview of the SIMCor methodology for virtual cohort generation.

Sensitivity analysis techniques can be used to determine which model inputs are mainly responsible for model output realisations in the output range of interest. This insight can be used to optimize the filtering criteria and only filter those virtual patients out that produce model realisations in specific (sub)regions of the output interest, hereby allowing for the generation of (sub)sets of the virtual cohort.

Preliminary results aortic valve disease patients

In this section, we demonstrate the feasibility of the envisioned strategy by presenting preliminary results of generating virtual patients suffering from *aortic valve disease* (AVD). We start by defining the N-dimensional sparse input space, that is needed to feed the physiological model serving as basis for the virtual cohort generator. Thereafter, we describe how this input space is converted to virtual patients.

Input space definition

The physiological model used for virtual cohort generation was previously developed within our group by Hoeijmakers et al.[1,2] and replicated by one of our MSc. students (Damian Suasso de Lima de Prado, BSc.) to create the results presented in this deliverable. The physiological model consists of a stenotic aortic valve geometry in the systolic phase, a prescribed systolic flow at the inlet**,** and a zero-pressure boundary condition at the outlet. The model can calculate realistic pressure drops and velocity fields as observed in the clinic and during in-vitro experiments. However, the patient-specific validation still needs to be done and is one of the aims of SIMCor (*Deliverable 7.8 – Validated virtual cohorts for in-silico trials (TUE, M36)*).

Geometric input

The geometric subspace of the N-dimensional input space is based on 74 iso-topological geometries of aortic valve stenoses collected during an earlier project on aortic valves (EurValve[3]) and converted to iso-topological meshes by PHI. Subsequently, statistical shape modelling is performed to transform this database of real patients into a range of shape modes and scaling factors.

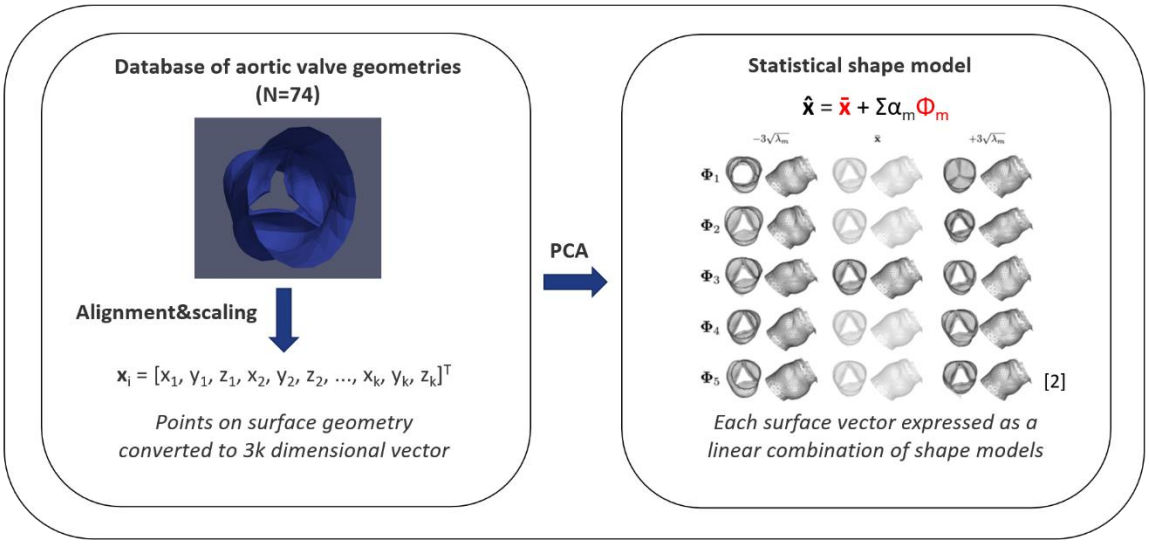

Figure 2: Typical aortic valve geometry and the conversion to a statistical shape model. References in the figures are aligned with references in the text.

To derive a statistical shape model[4] all real patient geometries are represented by a vector consisting of points that are defined on the valve surface geometries, also known as the vertices. Thereafter, all geometries are aligned and scaled to filter out shape variation due to translation, rotation, and scaling.

[1] Hoeijmakers et al. (2019): https://doi.org/10.1016/j.jbiomech.2019.07.010

[2] Hoeijmakers et al. (2021): https://doi.org/10.1002/cnm.3518

[3] https://www.eurvalve.eu/.

[4] Heimann et al. (2009): https://doi.org/10.1016/j.media.2009.05.004

This alignment is done by using Generalized Procrustes Analysis[5] in which the mean squared distance between two shapes is minimized. This method is used to iteratively determine a mean shape to which all shapes in the training set have minimum distance. After subtracting the mean shape from each shape vector, a covariance matrix can be made. Hereafter, an eigendecomposition can be performed to obtain and the main modes of variation, the shape modes (eigenvectors) and eigenvalues. Each shape mode describes one of the possible variations within the geometry. Each patient geometry can thus be described by the following equation:

$$\hat{x_i} = \bar{x} + \sum_{m=1}^{N_m} \alpha_{i,m}\phi_m, \quad i \in \{1,2,\dots,N_s\}.$$

Herein $\hat{x_i}$ describes each reconstructed patient *i*, $\bar{x}$ is the mean shape, $\alpha_{i,m}$ describes the shape coefficient for each patient *i* and each mode m, ϕ_m describes the shape mode for each mode m, N_s is defined as the number of patients used to derive the statistical shape model, and N_m defines the number of modes.

After reconstructing the patient geometries using different numbers of shape modes, we have conducted 3D simulations to calculate the pressure drops across the valve stenoses. Based on these analyses, we have found that geometric reconstructions based on 5 shape modes are sufficient to accurately calculate the pressure drops. Therefore, we need five shape coefficients to properly parameterize each patient geometry. To define the upper and lower limits of the different shape coefficients, we will consider geometries that are within three standard deviations with respect to the mean geometry. The lower bound of the shape coefficients are then defined as $\alpha_m = -3\sqrt{\lambda_m},\ m = (1,2,3,4\ or\ 5)$ where α describes the shape coefficient, *m* the mode number and λ the eigenvalue that is representative for the variance. The upper bound is defined as $\alpha_m = +3\sqrt{\lambda_m}\ m = (1,2,3,4\ or\ 5)$. In addition to these shape modes, we also introduce a scaling parameter s to allow for creating geometries with different patient sizes. The range of the scaling parameter is set to 0.8 to 1.2 times the original size based on the available data.

The resulting new patient geometry is a new vector consisting of vertices that have been manipulated by the shape modes, shape coefficients and scaling parameter. These vertices can finally be transformed into a mesh that can be used for CFD or TAVI deployment simulations.

Physiological boundary conditions

Following parametrization of the geometry, we only need an inlet flow boundary condition and a zero-pressure condition at the outlet. Our physiological model uses a peak systolic inflow and the lower- and upper limits are set to respectively 50 and 650 ml/s [6]. This range is based on literature in which peak flows around 600 ml/s, systolic flow of 400 ml/s and diastolic flow of 0 ml/s are reported. The inflow completes our 7-D input space.

[5] Gower et al. (1975), "Generalized Procrustes Analysis", Psychometrika, vol. 40, pp. 33–51

[6] Hoeijmakers et al. (2020): https://doi.org/10.1002/cnm.3387

Virtual cohort generation and integration into the VRE

Surrogate model development

To develop a surrogate model, we generate multiple samples from the input space defined above and obtain the corresponding virtual geometries using the statistical shape model. These virtual geometries are subsequently used for accurate 3D CFD simulations to generate the pressure drop across the aortic valve stenosis. The calculated pressure drops, together with the corresponding shape modes, coefficients, scaling parameter and peak systolic flow, are used to train a genetic-aggregation model[7] in ANSYS fluent R2021R1 (ANSYS Inc, Canonsburg, Pennsylvania, United States).

The trained surrogate model is subsequently validated by comparing the results on 74 geometries of stenotic aortic valves from real patients against highly accurate 3D CFD calculations with different prescribed flows, i.e., 100, 200, 400 and 600 ml/s. In the 3D simulations the peak systolic flow is obtained by prescribing a plug-velocity profile. Moreover, the outflow boundary is extended with 3.5 times the ascending aorta diameter.

It is demonstrated that the differences (root mean squared error) in transvalvular pressure drop between the CFD simulations and the surrogate model trained by using 250 or more training points, are smaller than ~4% for all cases and flow regimes.

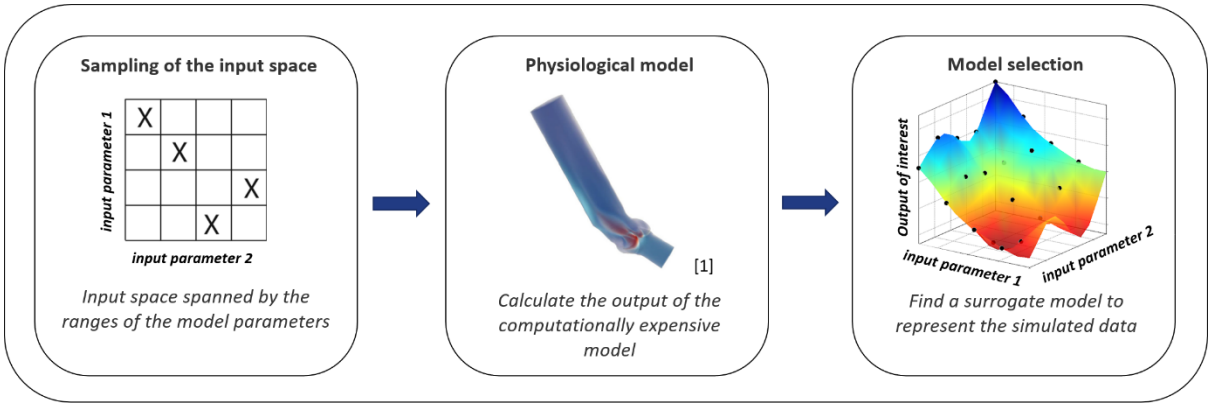

Figure 3: Generation of a surrogate model. References in the figures are aligned with references in the text.

Filter design and cohort generation

In this preliminary analysis we have chosen to set a calculated pressure drop across the stenotic valve larger than 300 mmHg as a non-physiological simulation. In future studies this can and will be adapted to the specific needs of the filter. The exact filter will later be based on physiological or physical constraints but also based on (regional) sensitivity analysis techniques that identify the regions in the model input space that are responsible for model realizations in the preferred (sub)regions of the output space[8]. The latter gives the flexibility to create virtual patients that fulfill some specific criteria, for example, only patients with mild stenoses.

After proper definition of the input space, the development of the surrogate model and proper filter design, the virtual patients can be created. This is done by sampling the model input space by Latin HyperCube sampling[9] to ensure proper distribution of the input samples throughout the full input domain. Each sample thus consists of shape parameters (shape coefficients, scaling factor) and a peak systolic flow. These parameters are used as input of our surrogate model that subsequently calculates the pressure drop across the stenotic valve. Thereafter, the filter removes all non-physiological realisations of the model (in this typical example a pressure drop >300 mmHg). All input samples of

[7] Ben Salem and Tomaso (2018): https://doi.org/10.1007/s00158-018-1925-3
[8] Pianosi et al. (2016): http://dx.doi.org/10.1016/j.envsoft.2016.02.008
[9] McKay et al. (1979): https://doi.org/10.2307/1268522

the realistic simulations are stored and form the new virtual patient input distribution. The 3D valve geometry can be derived by using the statistical shape model and the shape parameters of the input sample. Together with the physiological model, the reconstructed geometry and the boundary condition represent a realistic virtual patient.

VRE integration

The approach for virtual cohort generation is designed to be integrated into the Virtual Research Environment of SIMCor. In this deliverable, we demonstrate the feasibility of our approach and present a first use case example.

The current workflow for the VRE is designed as follows (all steps are summarized in *Figure 4*). We let the user define the ranges of the input space (i.e., the ranges of the shape coefficients, scaling factor and flow). Moreover, the user must indicate the number of "virtual patient candidates" that should be evaluated by the virtual cohort generator. Note that the initially selected number of "virtual patient candidates" will be larger than the number of resulting virtual patients after filtering. In future releases, we will change this so that the user can insert the number of realistic virtual patients that should be produced by the generator. The number of candidates is equal to the number of samples taken from the input space. These samples are then automatically evaluated by our surrogate model which results in a pressure drop estimation for all input samples. The surrogate model was developed in ANSYS fluent R2021R1 (ANSYS Inc, Canonsburg, Pennsylvania, United States) but converted to an executable that can be run without the need to install ANSYS and to have a license.

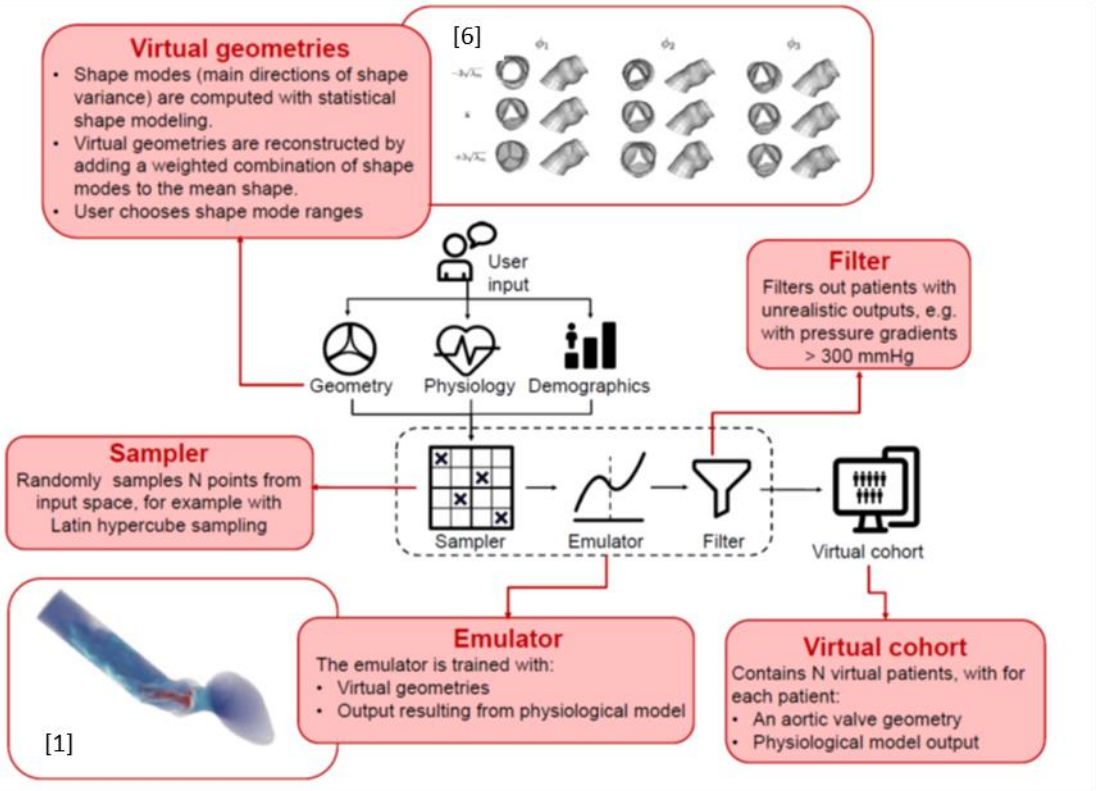

Figure 4: Workflow of virtual cohort generation of aortic valve disease patients as implemented in the VRE. References in the figures are aligned with references in the text.

After obtaining the calculated pressure drops physiologically unrealistic candidates are automatically removed based on the user-defined acceptance criteria. The filtering procedure results in a database with input samples that result in realistic virtual patients. The definition of virtual patients used here

is adopted from Chase et al.[10] and Viceconti et al.[11] (*Figure 5*). The shape parameters (α_m *and s*) and the SSM are finally used to reconstruct 3D geometries that can then be used, together with the corresponding flow *Q* and the physiological model, to test the TAVI device.

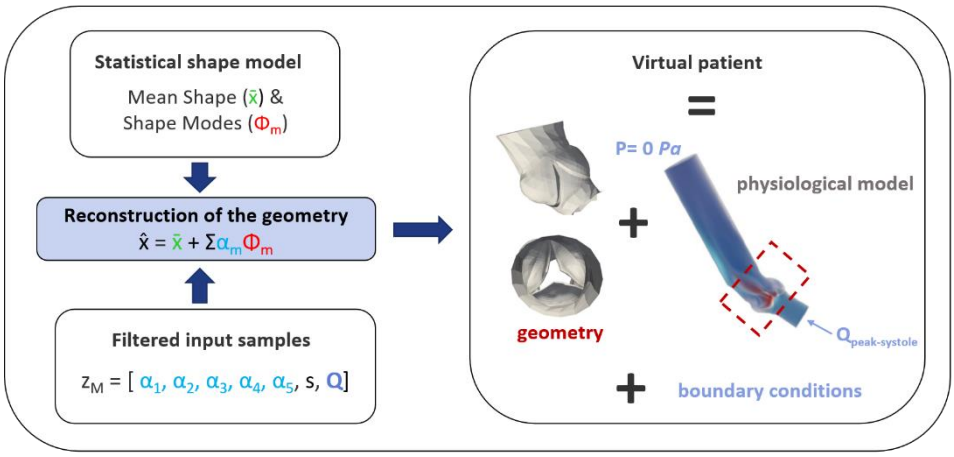

Figure 5: Resulting virtual patient, i.e., a geometry, boundary conditions and a physiological model

[10] Chase et al. (2018): https://doi.org/10.1186/s12938-018-0455-y
[11] Viceconti et al. (2017): https://doi.org/10.1177/0954411917702931

Preliminary results heart failure patients

Virtual cohort generation of heart failure patients is not yet at the same stage of development as the aortic valve disease patients. To date, we have made a preliminary geometric input definition, here presented.

Geometric input

A first iteration of a statistical shape model describing the porcine pulmonary was developed using a centreline-based approach, as successfully used for human aortic geometries[12]. Here, the main vessel and all branches of the vascular structure are described by the respective centrelines as well as the local radius information. The patient- or animal-specific geometry can be then described following the assumption of circular cross-sections. This assumption was found to be valid for porcine pulmonary arteries. However, a relevant constraint of this shape model specification is, that the topology of the vascular tree is identic among all cases. Variants with 2 or 4 branching vessels instead of 3 are rather common, so the assumption was shown to be not valid for the porcine pulmonary artery. In humans, the heterogeneity of vascular trees of human pulmonary arteries was even more pronounced.

Nonetheless, a subset of 15 porcine pulmonary arteries with similar numbers of branching vessels on the left and right pulmonary artery was identified. From this subset, a statistical shape model was generated to describe the shape variance. Using this shape model, virtual pulmonary artery geometries were generated (see Figure 6) to assess the feasibility of the method.

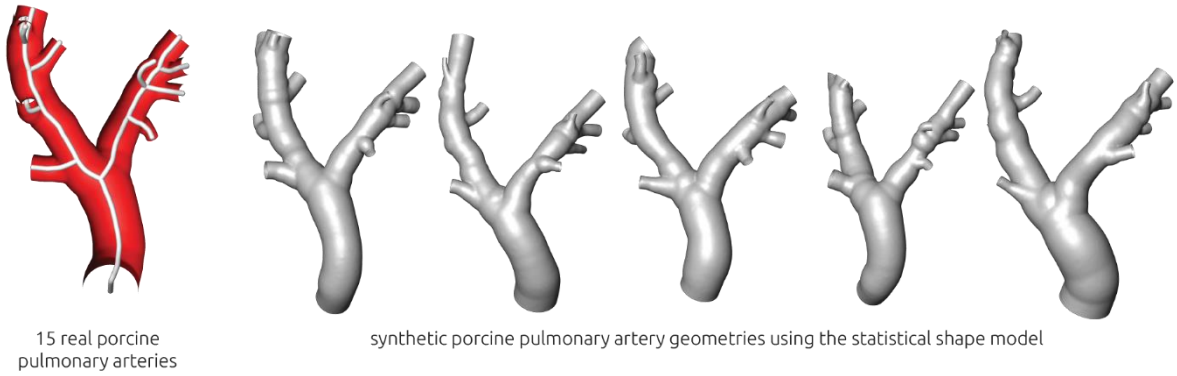

Figure 6: Examples of synthetically created porcine pulmonary artery geometries using a statistical shape model.

In general, the centreline-based shape model seems feasible for description of the shape variance of the main, left and right pulmonary artery. For the branching vessels another approach must be pursuit. This is especially true for the human pulmonary artery anatomy. Currently, different methods are discussed and will be evaluated. The most promising approach is describing the branching vessels independently from the main vessel by heuristic description of their location as well as rotation and inclination angle. This seems feasible, as the detailed path of the branching vessel is not necessary for either hemodynamic or structural mechanical simulations.

[12] Gundelwein et al. (2018): http://dx.doi.org/10.1007/978-3-030-04747-4_7

Future work

Regarding the input space definition several important steps will be considered in the coming period. First, we will use a statistical shape modelling approach that is more generally applicable than the method used so far. Second, we will re-evaluate the complexity of our physiological models with respect to the output of interest and the required accuracy in the prediction. It is evident that changes in model complexity will also change the required model input and thus the input domain. In the remainder of this deliverable, we will elaborate a little bit on our future plans regarding this issue.

Geometric input

For the statistical shape modeling method that is currently used, point-to-point correspondence between all geometries is required. However, not all geometries that result from imaging segmentations are iso-topologic. Therefore, a new statistical shape modeling framework proposed by Durrleman et al.[13], for which no point-to-point correspondence is required, will be implemented. This framework relies on control-points-based *large deformation diffeomorphic metric mapping* (LDDMM). The idea behind it is that statistical shape modeling is applied to the deformation vectors that deform a certain template geometry towards each patient (target) geometry. These vectors are called momenta and are located at certain control points. Each point (x) of the template shape is transformed by these momenta as follows[14]:

$$\phi(x) = x + \sum_{k=1}^{n_{cp}} K_V(x, q_k) \cdot \beta_k,$$

with $\phi(x)$ the transformed point x, n_{cp} the number of control points, q_k the k'th control point, and β_k the momentum located at control point q_k. The Gaussian kernel K_V is defined as[14]:

$$K_V(x, q_k) = e^{\frac{-\|x-q_k\|^2}{\lambda_V^2}},$$

with kernel width λ_V the distance between the control points. In other words, the contribution of each momentum to the deformation of a template point is weighted by this Gaussian kernel. The momenta β_k and the template shape are calculated alternately. The momenta are computed by minimizing the distance between the initial template and the target shape, using a correspondence-less similarity metric[14]. The template is updated by deforming it towards each target with the computed momenta and afterwards computing the average. The momenta are calculated again, now based on the new template. This process is repeated until the difference between the deformed template and the target shape is below a certain threshold. This results in a set of vectors for each target shape. Since these vectors are defined at predefined control points, we now have an iso-topologic description of all geometries (Figure 7). The statistical shape modeling method that was used in the previous section for the aortic valve geometries can be applied to these resulting vectors.

The control-points-based LDDMM method was tested on aortic valve geometries. A template geometry was deformed towards one target geometry, and the results are shown in Figure 8. In Figures 8a and 8b it is visible that the leaflets of the template geometry are deformed towards a more closed position, as in the target shape. Furthermore, Figures 8c and 8d show that the aortic diameter of the template is decreased such that it matches the aortic diameter of the target shape. This result shows that this method is applicable for aortic valve geometries, which makes it a very promising statistical shape modeling tool.

[13] Durrleman et al. (2014): doi: 10.1016/J.NEUROIMAGE.2014.06.043
[14] Bône et al. (2021): https://hal.inria.fr/hal-01874752v2

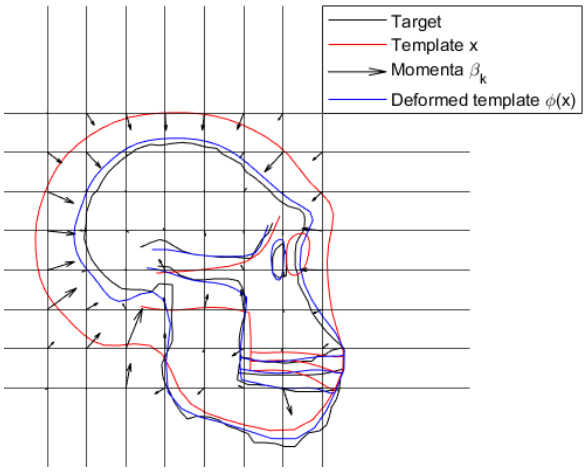

Figure 7: Control-points-based LDDMM applied to a 2-D skull geometry. Adapted from http://www.deformetrica.org.

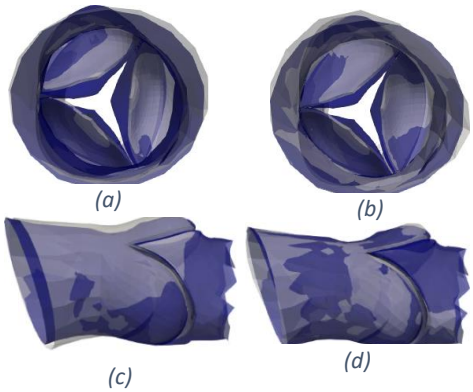

Figure 8: Aortic valve template (white) before (a and c), and after (b and d) deformation towards target geometry (blue), by control-points-based LDDMM.

This framework will be applied to 100 non iso-topologic aortic valve geometries, originating from CHA. The idea is to extract the main directions of shape variance (shape modes) within the sets of momenta. Virtual geometries will be reconstructed by deforming a template by a weighted combination of these shape modes. The same method will be used to reconstruct virtual pulmonary artery geometries. The virtual geometries will be used to train an emulator, such that it can generate the desired physiological output, for shape modes and boundary conditions as input.

Model for virtual cohort generation

Aortic valve disease patients

The physiological model that we have used so far is only focusing on the pressure drop. For this output of interest Hoeijmakers et al. demonstrated that this simplified model with stationary peak systolic flow is sufficiently accurate when the pressure drops exceed 10 mmHg. However, when we aim to evaluate also other hemodynamic metrics and/or the situation after TAVI deployment we need to assess again the required level of model complexity and the surrogate model to be used. Moreover, we need to provide boundary conditions that are representative for both the situation before and after TAVI deployment.

Properly parameterized reduced order 0D models that mimic the heart and vascular structures distal to the 3D aortic valve geometry can potentially be used to obtain boundary conditions that can adapt to the changing haemodynamics after the TAVI procedure. How we can do this and how these models need to be parameterized to realistically represent our aortic valve disease patients will be part of our future work.

All clinical data collected within SIMCor will help us by reaching these objectives.

Heart failure patients

Regarding heart failure patients we aim to follow a similar strategy as the one described in this deliverable. However, we are not yet at this level because we are still working on the development of the physiological model. In contrast to the aortic valve disease patients, we could not build on previous modelling work and/or existing databases. The SIMCor database is now sufficiently mature to make the same steps for the heart failure patients. In addition, we must determine the best surrogate model to serve as virtual cohort generator.

Like the work discussed before, also for the HF patients we aim to develop an accurate 0D model to serve as boundary condition model. Here we will include the left and right side of the (sick) heart, the pulmonary and the systemic circulation (*Figure 9*).

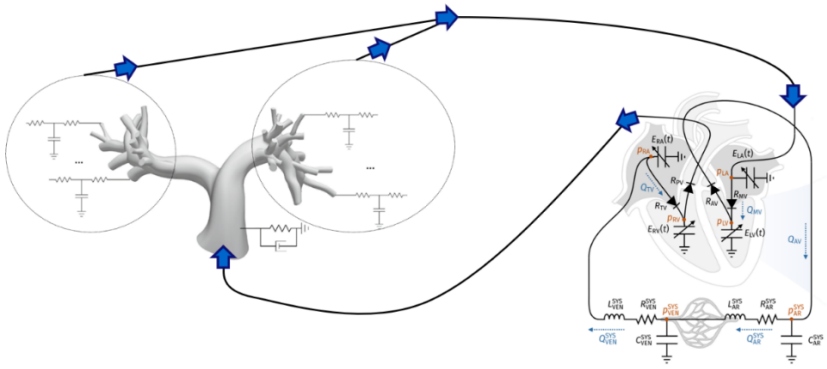

Figure 9: A schematic picture of the pulmonary artery in 3D coupled to 0D boundary models. Right part of the figure adapted from Regazzoni et al.[15]

[15] Regazzoni et al. (2021): https://www.biorxiv.org/content/10.1101/2020.06.23.166421v2