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Abstract (for dissemination)	The aim of WP3 is to provide and develop models and software tools to determine the input for these computational models and to provide and evaluate the computational models themselves. The aim of this document is to define the work that is required to reach this goal.
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EXECUTIVE SUMMARY

The aim of EurValve is to develop and deploy a modelling-based decision support system for aortic and mitral valve disease that allows simulating, comparing and understanding the effects and risks of different treatment strategies. The decision support system will take all available information into account, in particular the results from different computational models.

The aim of WP3 is to provide and develop models and software tools to determine the input for these computational models and to provide and evaluate the computational models themselves. The aim of this document is to define the work that is required to reach this goal.

The main deliverable of WP3 is a workflow that gives information about the cardiac and cardiovascular haemodynamic characteristics, including those of the valves, of an individual patient. The following steps are required: The patient geometry is determined from a patient-individual medical image (Task 3.2). Simulation input parameters are determined from the electronic health record, from pervasive monitoring, from population data, from literature data, from the patient geometry, from machine learning (Task 3.1), from a parameter fitting/optimisation process on the computational model itself (Task 3.3/3.4) or from biopsy samples (Task 3.5). Then, the flow simulation can run according to a certain analysis protocol (Task 3.3). The results will be inputs for the decision support system.

To create a system that is clinically useful, the simulations need to be fast and the required input data must match the clinical routine. To evaluate how detailed the simulations need to be, simulations of different complexity are compared (Task 3.3). To reduce the computation time of the simulations, reduced order modelling is applied (Task 3.6). To find out which of the input parameters need to be tuned for individual patients, a variation and sensitivity analysis is conducted (Task 3.4). To infer missing parameters, machine learning is applied (Task 3.1).

According to the project proposal, a beta release of the software is planned for PM15 and a release version for PM30. In this specification document, the two overall deliverables have been broken down to individual deliverables for each task.

In Section 2, an overview of the envisioned system is given, and interaction and dependencies with other work packages are described. In Section 3, the different tasks as defined in the EurValve proposal are specified.

1 INTRODUCTION

The aim of EurValve is to develop and deploy a modelling-based decision support system for aortic and mitral valve disease that allows simulating, comparing and understanding the effects and risks of different treatment strategies. Clinical diagnosis and interventional planning for valve disease should be facilitated by interpreting and exploiting all available information, from personal clinical data, population data, clinical guidelines and from simulations. The decision support system will take all available information into account, in particular the results from different computational models. The computational models will offer more effective characterisation of the disease state, and will predict the effects of intervention.

The aim of WP3 is to provide and develop models and software tools to determine the input for these computational models and to provide and evaluate the computational models themselves.

Input parameters can be determined in different ways: besides parameters that are directly measured in the clinic for the individual patient, parameters can be determined from segmentation, from biopsy samples, from learning, from literature and from population data.

Different computational models will be employed, with different goals: characterisation of the valve haemodynamics, characterisation of the physiological envelope and quantification of the effect on cardiac physiology of valve disease and of potential interventions.

There are many sources of data and many potential analysis protocols, each of which might provide important information or insight into the patient's condition. EurValve must strike a balance between provision of a coherent and easy-to-operate diagnostic and prognostic analysis process and exploitation of state-of-the-art computational analysis tools.

The work of WP3 is divided into six tasks. To create the overall specification, each task leader constructed a task definition that included the inputs and outputs, and the dependencies on other tasks and work packages. The contributions of all task leaders are collected in this document.

In Section 2, an overview of the envisioned system is given, and interaction and dependencies with other work packages are described. In Section 3, the different tasks as defined in the EurValve proposal are specified.

2 WORK PACKAGE DEFINITION

The activities of this work package are divided into two categories, case processing and knowledge generation. The main deliverable of WP3 is a workflow that can be conducted for an individual patient; this is referred to as case processing. The workflow needs to be clinically feasible in terms of required input parameters and execution time, but also must be clinically meaningful. To achieve this workflow, tools for learning, for speed-up of simulations and for sensitivity analysis need to be developed, and simulations of different complexities must be compared; this is referred to as knowledge generation. Some of the developed tools will not be part of the final workflow but will be used only during the knowledge generation process.

2.1 Work package workflow

At a high level, the envisioned workflow can be described as follows: The patient's geometry is determined from their patient-specific medical images. Simulation input parameters are determined from the electronic health record, from pervasive monitoring, from population data, from literature data, from the patient geometry, from machine learning and from biopsy samples. Thereafter, the flow simulation can run according to a defined analysis protocol. An overview of this workflow is given in Figure 1.

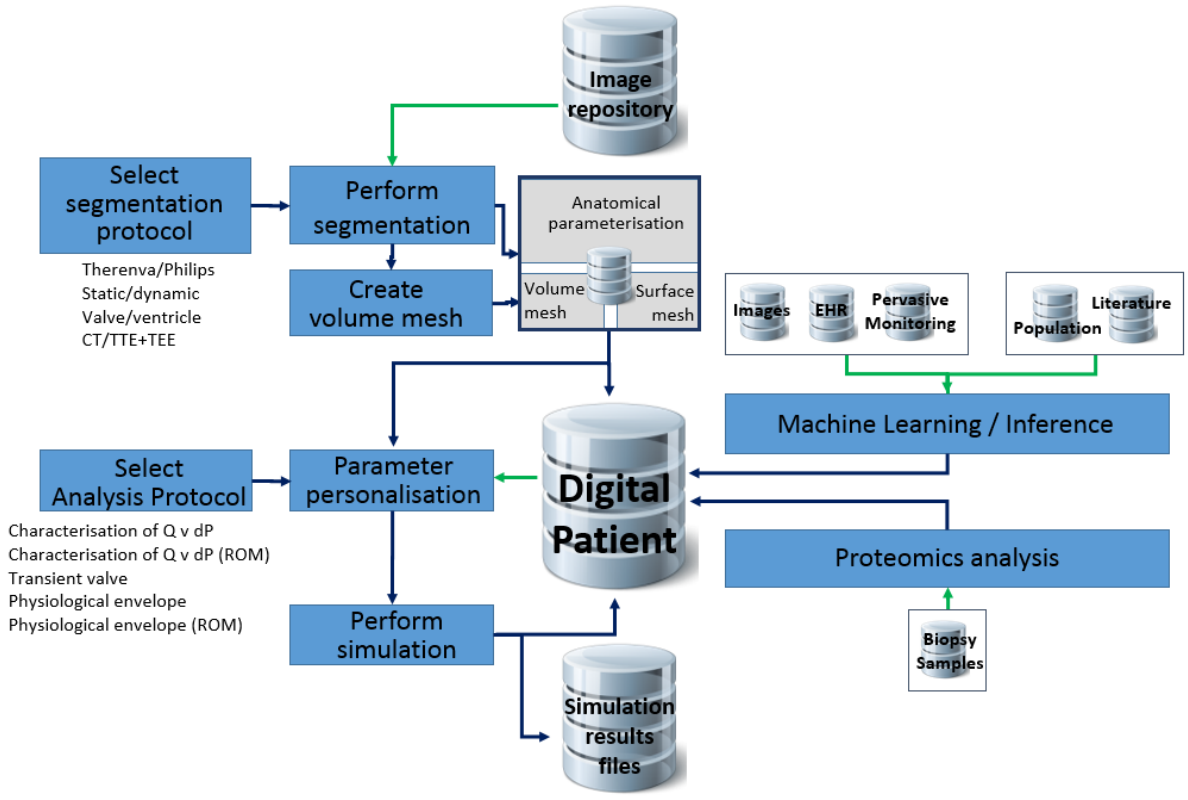

Figure 1: Workflow diagram of WP3

The central part of this workflow is the simulation. The detailed workflow and required input parameters depend on the selected analysis protocol for the flow simulation. The analysis protocols have different purposes as explained in the following.

Characterisation of the valve haemodynamics: The purpose of this analysis is to determine the haemodynamic characteristics of the valve in the open position (for pressure gradient computations) and in the closed position (for leakage/regurgitation computations). The primary interest is in the flow versus pressure drop relationship for the valve, although other characteristic haemodynamic measures may be computed. This requires a detailed anatomical/geometric representation of the open valve. It is hypothesised that an adequate representation of the valve haemodynamic characteristics could be achieved using a series of steady state flow analyses.

Characterisation of the physiological envelope and quantification of the effect on cardiac physiology of valve disease and of potential interventions: The purpose of this analysis is to determine the range of physiological operation for the individual patient. This is represented by specific values of analysis parameters from which, through the computational analysis protocols, the effect of the valvular disease on the system physiology is determined. It would be possible to analyse a wide range of physiological states, and once again a balance is needed between the capacity to produce analyses and the ability to provide meaningful representations of the patient's condition based on the relatively sparse physiological input data that will be available. Pragmatically, it is proposed that two physiological modes will be analysed, namely rest and exercise.

2.2 Work package tasks

The work in WP3 is divided into six different tasks as defined in the project proposal:

Task 3.1 Machine Learning: This task will infer data on a specific patient that is not available but required in order to execute the computational models.

Task 3.2 Segmentation Tools: To run a patient-individual 3D simulation, the patient-individual anatomy is crucial. The purpose of this task is to determine it from patient images, either CT or ultrasound.

Task 3.3 System models: This task will provide the computational models for the flow simulation. These can be 0D, and 3D model. Details were given in the previous section.

Task 3.4 Variation and Sensitivity Analysis Tools: There are very many parameters in these flow analyses and it will be impractical to tune all of them to the individual patient. This task will evaluate the sensitivity of the model outputs to the inputs. This in turn will determine which parameters will be tuned in the personalisation process.

Task 3.5 Proteomics Data Analysis Tools: This task will contribute models that use patient-specific data from tissue samples as input to allow the simulation of myocyte contractility and elastance in the united cell structures of a given patient. These parameters can be used as input for the flow simulation.

Task 3.6 Reduced Order Modelling Tools: It is important that the DSS is able to operate in time scales that are appropriate to support the clinical process. This task will develop a Reduced Order Model (ROM) that offers the potential for near real-time diagnostic and prognostic haemodynamic and physiological characterisation.

2.3 Interactions and dependencies

All tasks have certain inputs and outputs; these are described in detail in the next chapter. These lead to interactions between the different tasks and to interactions with other work packages. An overview is given in Figure 2. The dependencies of the individual tasks will be described in the individual task specifications. The dependencies with other work packages will be described here.

WP2: We rely on WP2 to provide the necessary infrastructure to run the segmentation, machine learning, and in particular the flow simulations and the infrastructure to store and exchange data. The different components will not exchange data directly but all data will be shared via a central database (see Figure 2). The data infrastructure is described in detail in (1) and the computing infrastructure is described in detail in (2). We assume that interaction between different components will be different in knowledge generation compared to case processing. For knowledge generation, the different components will only be coupled loosely. Some components will only run during the knowledge generation phase, like the generation of the ROM, some of the time consuming flow simulations, the sensitivity analysis, the learning part of the machine learning. Some components will be selected for case processing. The WP3 part of the case processing will adhere to the workflow described in 2.2. In the beginning, case processing will run in the central environment. At some point, it should migrate to the DSS, which should run locally in a hospital. However, we expect that there still will be a connection to the central environment.

WP4: We rely on work package 4 to provide us with data. Some will be patient-specific, like medical images, patient records, disease relevant measurements, or pervasive monitoring data (Task 4.4). Other will be more general like literature data or population data (Task 4.3). Medical images are required by Task 3.2 to determine the patient anatomy. Patient records, disease relevant measurements, and pervasive monitoring data will be used by Task 3.1 for the machine learning and by Task 3.3 for the flow simulations. Literature data and population data will be used for the training of the machine learning system and for the flow simulation if the sensitivity analysis shows low sensitivity. Same data is already required during the knowledge generation phase, for learning/training and for internal validation. We will mainly rely on retrospective data for this. In the case processing phase, we expect to receive prospective data.

WP5: We expect to provide an extensive amount of information to the DSS. All information derived by our work package can be used by the DSS. Which information is useful needs to be determined during development of the DSS. The derived information includes anatomical parameters, parameters that allow an effective characterisation of the disease state and parameters that will predict the effect of intervention.

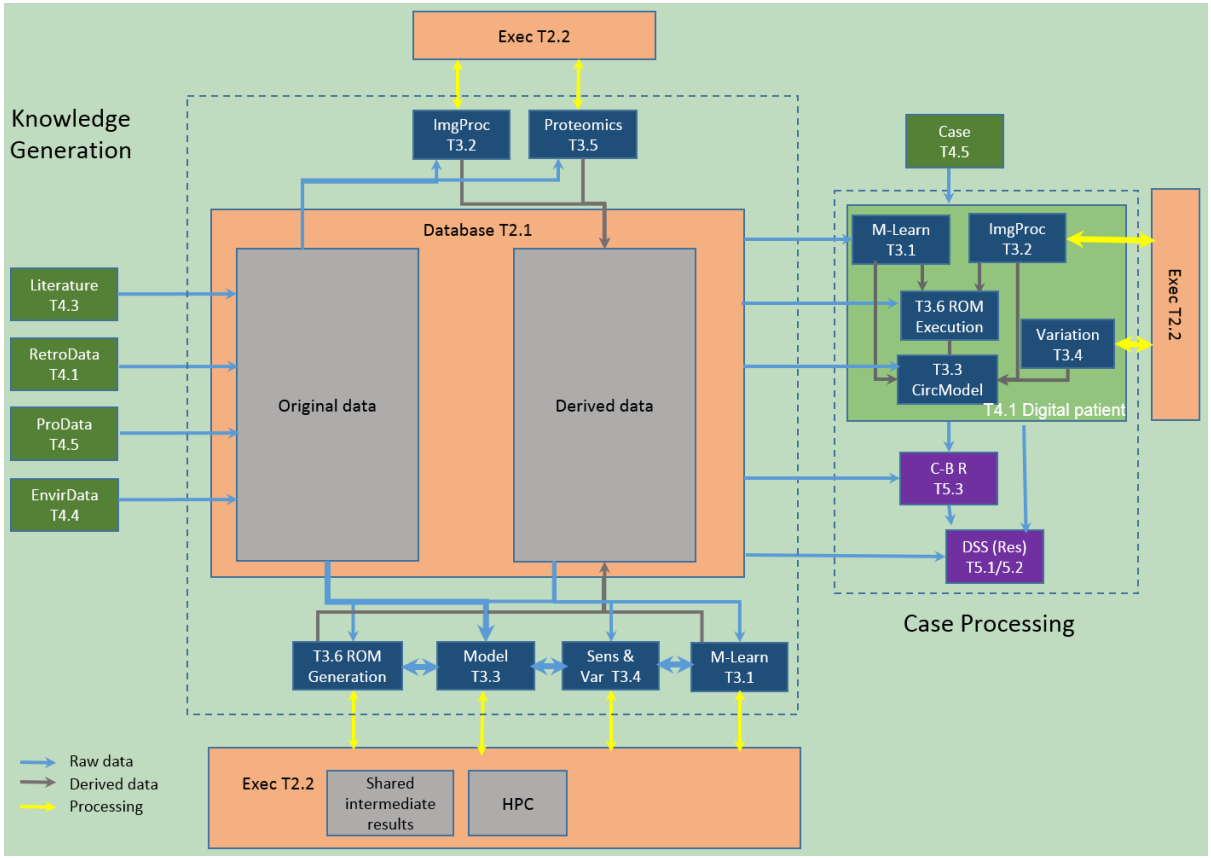

Figure 2: Overall EurValve workflow, illustrating sequence of analysis operations and communication with data repositories

2.4 Deliverables

According to the project proposal, we have committed a beta release of the software for PM15 and a release software for PM30. In this specification document, the two overall deliverables were broken down to individual deliverables for each task (at the end of each task specification). In addition to that, we decided that we would like to create a minimum viable product for PM9. For this internal goal, a common pipeline should be assembled, where each partner should contribute something. Depending on the matureness of the work of the individual tasks at the beginning of the project, this could also be a mock-up or a solution for a small sub-part. This will show the complexity of connecting the output of the different tasks and it should show whether the planned software and database structure is suitable.

3 TASK SPECIFICATION

3.1 Task 3.1 Machine Learning

Activity Leader: Philips Eindhoven

3.1.1 Task overview

As part of the personalised heart valve intervention decision support system to be developed by EurValve the machine learning module will infer data on a specific patient that is not available but required in order to execute the computational physiological models being used for making predictions. In particular, the project uses 0D models for modelling systemic aspects of a VHD patient (see Section 3.3 in this report) - these mechanistic models need for example values of various resistances as input in order to determine clinically relevant parameters such as pressure gradient or ejection fraction. The machine learning algorithm does not need to determine all input parameters needed by the computational physiological models being used: a selection of input parameters to be obtained by learning will be determined based on analyses of sensitivity of the model outputs with respect to their input parameters (see Section 3.4 in this report).

In addition to using patient data for learning required computational model parameters, we also intend to incorporate as part of the learning process, where possible and useful, information obtained from the literature. To this end, Task 3.1 interacts with Task 4.3 on Literature Data. To illustrate the possible use of information from the literature, note that it is often emphasised, in particular from example in guidelines for VHD (3), that as there are relatively many elderly VHD patients, often comorbidities play a role, while the specific pattern of comorbidities will influence the risks which need to be assessed in clinical decision making. As there are many different possible patterns of comorbidity, it would be hard to proceed by using only data: we do not expect to find data sets with significant numbers of patients for many relevant comorbidity patterns.

To summarise the requirements for Task 3.1 on a global level, we need to develop machine learning algorithms that are able to infer computational model input parameters by using patient data, preferably augmented with information obtained from the literature where that is useful. We will use these machine learning algorithms to support the use cases that will be pursued in the project, in particular the use case described above which aims at characterisation of blood flow versus pressure gradient over the aortic valve.
In this project, we will be using relatively simple computational physiological models. In the work on machine learning, we will seek to develop generic procedures for learning required model parameters, so that the results from the project could also be used with more complex computational models.

3.1.2 Task specific input and output

As inputs for machine learning we will use retrospective data that is available from within the project, from or via the clinical partners, and also prospective data that will be gathered by the project in clinical studies. An initial description of data that will be available for learning from within the project was given in the EurValve deliverable D4.1 (4). In particular, there will be data available on patient demographics, medication, risk factors, diagnoses, physiological and

laboratory measurements, electrocardiographically measurements, CT measurements, and operative data: for more information on specific attributes for these categories of data see Tables 2 to 9 in D4.1 (4).

In order to be able to optimise model parameter values with respect to interventional outcomes, we intend to use additional patient databases that have useful information on outcomes.

Outputs to be derived from machine learning will consist of computational measures and concepts, more specifically a subset of the list of these concepts that was given in Table 10 in D4.1 (4) – this table is also in Appendix 1, in extended form. As mentioned above, which exact subset of these concepts will need to be inferred by learning will be determined based on the outcome of sensitivity analyses. Generally speaking, computational parameters that will need to be obtained from learning will consist of various parameters describing resistances, capacitances and elastances and timing properties. These outputs from the machine learning algorithms will be used for executing computational physiological models in order to arrive at personalised decision support for VHD patients.

As was already mentioned, in addition to inputs from patient data we will also use inputs from the literature, in interaction with Task 4.3.

3.1.3 Task specific methods and workflow

The workflow specific to Task 3.1 is depicted in the following diagram.

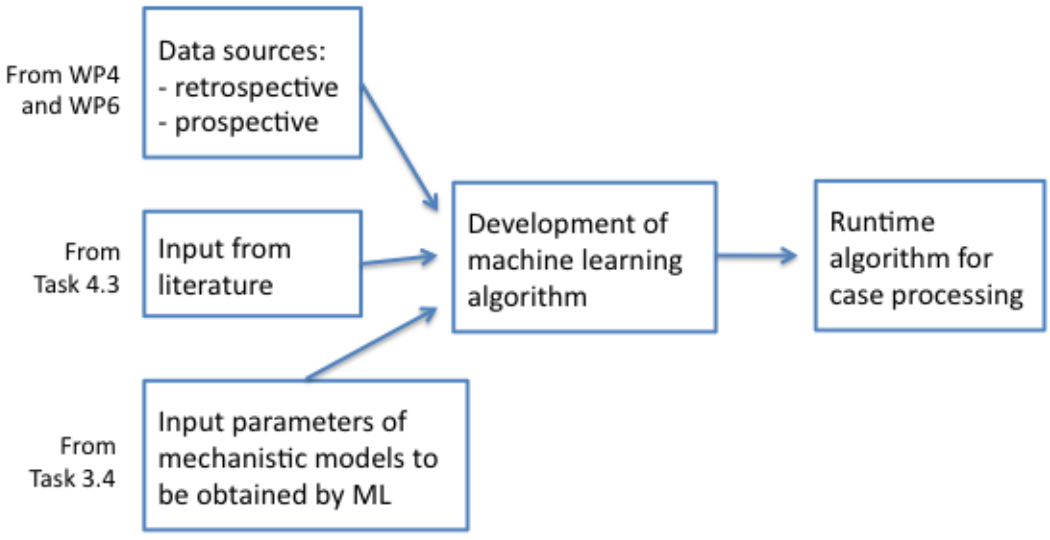

Figure 3: Workflow of Task 3.1

Figure 3 illustrates the approach we intend to pursue, using a "pipeline" where first sensitivity analysis is used (Task 3.4) to filter out certain input parameters of mechanistic models, as for example population means could be used as values for these model input parameters, and then machine learning is used to derive patient-specific values for the remaining model input parameters. Note that in cases where certain model outputs are available through patient

measurements there is subsequently an optimisation step where the mechanistic model is rerun in order to obtain improved values of model input parameters – for more on this see Figure 11 and accompanying text in Section 3.3 below. If this is feasible, we will also explore whether machine learning could play a role in this later process of parameter optimisation.

We conclude this section with a few comments related to machine learning techniques. With an eye to transparency of the results, we are especially interested in the development of interpretable machine learning algorithms for determination of parameters necessary for running computational mechanistic models.
We will explore the use of multiple methods to obtain suitable machine learning algorithms. For example, we will explore the use of ensemble techniques. We also intend to explore the use of similarity measures in learning algorithms. It is too early to indicate preferred options yet.
In addition to using data attributes that are directly available in machine learning algorithms, we will also explore the use of additional features that can be derived from the available data using various techniques, for example involving signal processing.
Whereas machine learning algorithms typically work only with data, in this project we will seek to augment data by incorporating also knowledge, in particular by incorporating as mentioned also information relevant for decision support obtained from the clinical literature.
In our work on machine learning we will pay special attention to validation, in order to ensure that our algorithms will be applicable to new data.

3.1.4 Task deliverables

Table 1: Deliverables of Task 3.1

D	Lead	Title	Due
D 3.2.1	PEN	Initial machine learning algorithm for learning required aortic valve model input parameters	PM14
D 3.3.1	PEN	Validated machine learning algorithms for learning required aortic valve and mitral valve model input parameters	PM29

3.2 Task 3.2 Segmentation Tools

Activity Leader: Philips Hamburg

3.2.1 Task overview

Within the EurValve project, different flow simulations are planned as described above. The 3D flow simulations need a static patient specific geometry (mesh representing the anatomy) generally at the point in time when the relevant valve is open. The 4D flow simulations need a dynamic segmentation (mesh for each time in the cardiac cycle). Whereas as the 0D simulation would benefit from information like cardiac output, or time dependent chamber volume curves, or myocardial mass or aortic valve opening. The models and software to yield detailed anatomical segmentations of the mitral and aortic valves, left ventricle, left atrium and aorta from medical images or image sequences will be provided by this task.

3.2.2 Task specific input and output

The input for this task are 3D or 4D medical images of the patient as provided by the clinical partners through WP4 and WP6. To extract all relevant information either a gated CT image sequence with contrast or TEE sequence + TTE sequence is required. CT can be used to segment the chamber and the valves. Therefore, it could give all required information. TEE can be used to segment the valves. TTE can be used to segment the chambers. Therefore, the combination could give all required information. MR can be used to segment the chambers. MR is not really suitable to segment the valves. At least, no MR images have been seen that show an open valve sufficiently detailed for automatic segmentation. Therefore, MR can probably not give all relevant information. The outputs of this task will feed Tasks 3.3, 3.5., and 3.6, where they will drive the flow simulations.

For different applications, different models are required. The following models are of interest in the context of EurValve:

CT dynamic valve model

Input:	Multi phase CT, gated with contrast agent
Components:	Open and closed mitral valve and aortic valve, left ventricle, left atrium, potentially myocardium
Outputs:	Aortic valve area, outflow tract diameters, bulbus diameters, centreline aorta, dynamic LV volume, dynamic LA volume. Potential outputs: Measure to characterise roundness of bulbus, ellipsoid of outflow tract, angle between aorta and ventricle, mitral valve annulus circumference, mitral valve opening
Scope:	Adult patients, tricuspid aortic valve, (if bicuspid is required this would have to be developed within the EurValve project), no aortic aneurism
Status:	In progress, in particular the dynamic mitral valve is under development

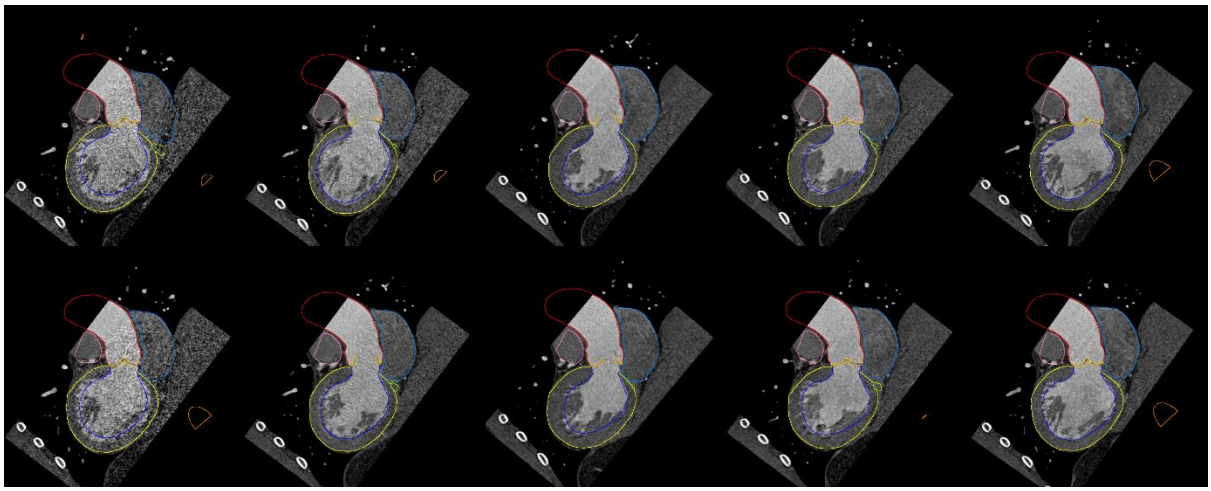

Figure 4: Example of a dynamic valve segmentation

3D TTE dynamic chamber model

Input:	TTE sequence
Components:	4 chambers
Outputs:	Time dependent volume curves for chamber volumes
Scope:	Adult patients, no detailed valves (the valves are difficult to see in TTE images), no aorta (also difficult to see), only the chambers that are well visualised in the image can be quantified.
Status:	Prototype, needs to be updated if it should be used within EurValve

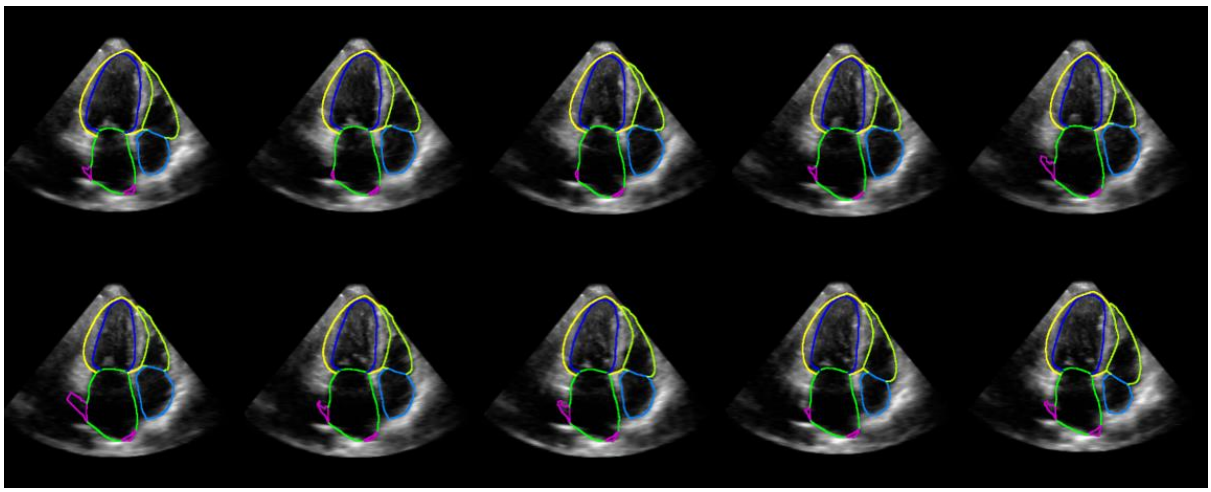

Figure 5: Example of dynamic chamber segmentation

3D TEE dynamic valve model

Input:	TTE sequence with AV/MV and LV in image
Components:	Aortic valve + Mitral valve + aortic bulbus + left ventricle + left atrium
Potential outputs:	Annulus diameter, aortic valve area, time dependent left ventricle volume, MV open area, LVOT diameter,
Scope:	Adult patients, tricuspid aortic valve, no aorta, only the parts that are visualised well can be quantified
Status:	Not existent yet, needs to be developed in EurValve, if required

3D MR static chamber model

Input:	3D SSFR MR
Components:	4 chambers
Outputs:	Chamber volumes and aorta
Scope:	Adult patients, not dynamic, no detailed valves (the valves are difficult to see in MR images), only the chambers that are well visualised in the image can be quantified.
Status:	Prototype, needs to be updated if it should be used within EurValve

Cine MR dynamic chamber model

Input:	Cine MR (short axis + 4 Chamber)
Components:	4 chambers
Outputs:	Time dependent volume curves for chamber volumes
Scope:	Adult patients, no detailed valves (the valves are difficult to see in MR images), only the chambers that are well visualised in the image can be quantified. Images need to be pre-registered.
Status:	Under development

3.2.3 Task specific methods and workflow

The work will build upon previously developed model-based segmentation technology that enables segmentation of the heart and aortic and/or mitral valve by adapting a generic mesh model with trained boundary detectors to images (5). The segmentation environment is divided in two parts: algorithms and model. The algorithms are independent of the application. All the application depended parameters are encoded in the model, i.e. which components are available, how detailed the segmentation should be, how the image looks like. With an approach like this, multi-modality segmentation within one framework is possible (6). Details

of the heart and valve anatomy may be captured by additional post-processing steps that are configured by the model and that depend on the model-based segmentation result (7).

A segmentation task generally consists of four steps:

1. Localisation of the heart in the image
2. Rigid and affine adaption of the mesh to the image
3. Deformable adaptation of the mesh to the image
4. Post-processing: Extraction of information based on the segmentation results (chamber volumes, aortic valve area, myocardial mass, annulus diameter, …)

This is independent of the model. However, which information is provided in the end, depends on the model as described in the previous section. In the context of the overall workflow, the workflow of Task 3.2 is shown Figure 6: Workflow of Task 3.2Figure 6.

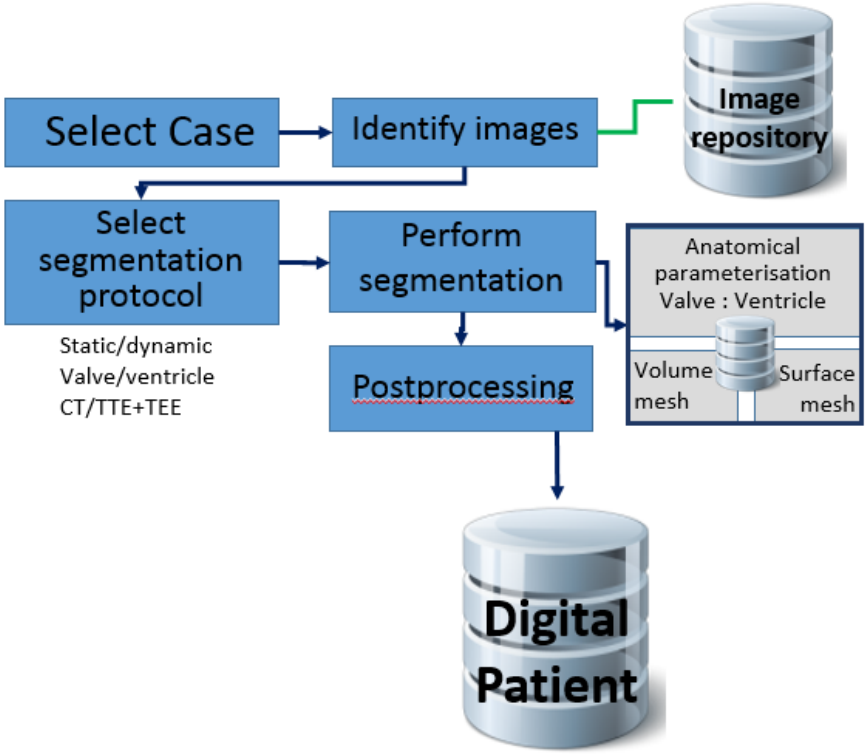

Figure 6: Workflow of Task 3.2

Although the general segmentation environment is available and mature, the models as they are required for EurValve are not all available. In particular, the dynamic mitral valve model and the Cine-MR model are under development and the TEE dynamic valve needs to be developed within EurValve. All other models need to be adapted for the usage within EurValve. Additionally, the segmentation algorithm and in particularly the relevant measurements will be validated quantitatively based on manual measurements that should become available through WP4. Which models will finally be made available, depends on the images that will become available within EurValve.

3.2.4 Task deliverables

Table 2: Deliverables of Task 3.2

D	Lead	Title	Due
D 3.2.2	Ph HH	CT dynamic mitral valve model TEE dynamic valve model (in progress version)	PM14
D 3.3.2	Ph HH	Validated and fine-tuned models	PM29

3.3 Task 3.3 Systems Models

Activity Leader: USFD

3.3.1 Task overview

The aim of this task is to produce the software components and toolkits that underpin the computational characterisation of the haemodynamics of the individual patient, including the effect of valve disease and the predicted changes under candidate interventions. In line with the guidance text of Call PHC-30-2015, to which this project was submitted, we proposed a multi-scale approach including zero-dimensional and three dimensional components. The former represents the overall haemodynamic system, including representations of the heart chambers, the heart valves and the vessels, and the latter represents the detailed anatomy of the heart valves that are the clinical target of EurValve. The types of model, together with a brief indication of purpose, are illustrated in Figure 7.

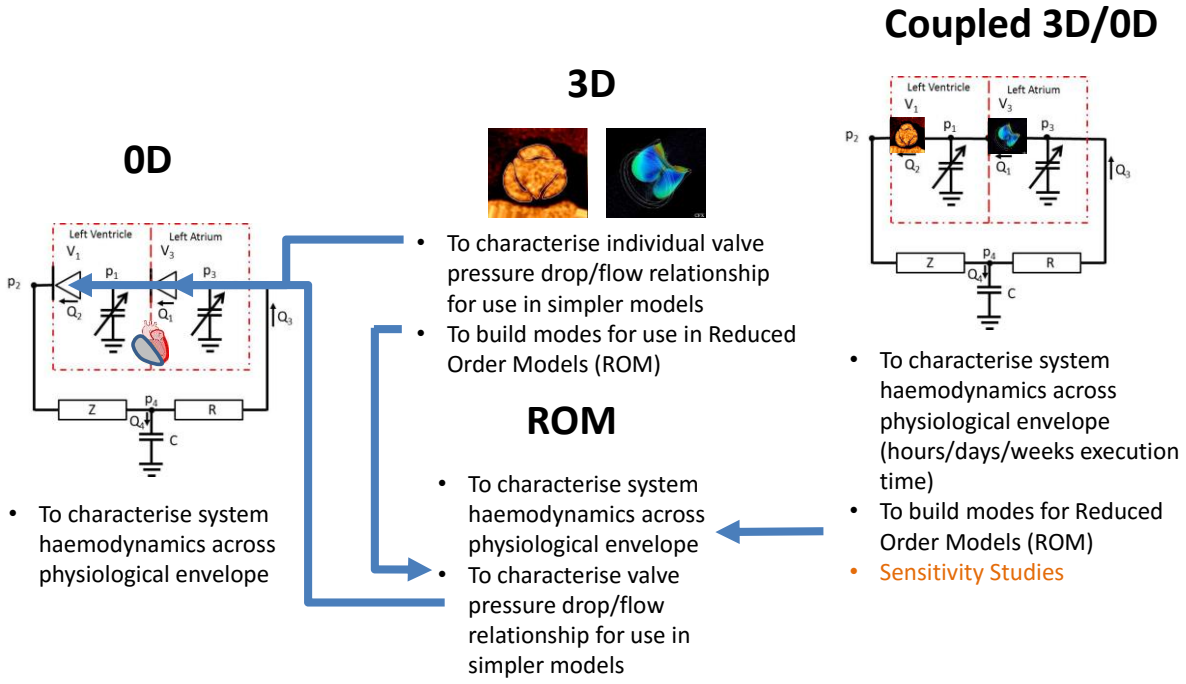

Figure 7: Overview of multi-dimensional models, interactions and purpose

3.3.2 Task specific input and output

The haemodynamic characterisation of the influence of valve disease and/or of intervention in an individual patient requires essentially three types of input. The first is a representation of the overall haemodynamic system, the second a representation of the local anatomy of the valve and the third is the description of the constitutive equations that describe the behaviour of the material components (including, for example, the rheological properties of blood).

An overview of the models themselves is presented in the following section, 3.3.3. The analysis concepts were summarised in Table 10 of D4.1, the description of the patient avatar for

EurValve. This is reproduced in Table 7, Annex 1, extended in this report to include an indication of which concepts are inputs to the model, and the source of these data, and which are outputs. The outputs include the haemodynamic characterisations that are of direct interest to the clinician in the evaluation of the status of the valve disease. Most of these outputs correspond to clinical concepts with which the clinical user is already familiar, and as part of the evaluation exercise the computed measures will be compared where possible to measurements that have been made in the patient cohort. It is important to note, though, that the motivation for the computation is to provide characterisations under physiological states that have not been measured in the clinic and to predict the effects of interventions, not simply to reproduce computationally measurements that are already made in the clinic. There are a few concepts, such as ventricular work, that might be important clinically but are not routinely measured, and it is anticipated that these will provide additional insight into the patient physiology.

3.3.3 Task specific methods and workflow

Again to conform to the requirements of Call PHC-30-2015, the strategy for EurValve is built on the re-use of existing models rather than on the development of new models or on research in the context of modelling *per se*. This section provides a brief overview of the models that EurValve will operate. As indicated in Figure 7, EurValve will operate zero-dimensional, three dimensional and coupled (multi-scale) models.

The focus of EurValve is on the evaluation of the effect of heart valve disease on an individual. Conceptually the simplest model is a 3D model in which the geometry of the valve is represented explicitly. A typical 3D computational fluid dynamics (CFD) analysis workflow, in this case for the characterisation of the pressure drop versus flow relationship for the aortic valve in the open configuration, is illustrated in Figure 8. Our working hypothesis is that the pressure drop across the valve can be adequately characterised by a series of steady flow analyses at different flow rates, and that, when coupled with a lower dimensional system model (next paragraphs), these can be used to represent transient flow characteristics over the cardiac cycle, at least with respect to the computation of important clinical indices. An analysis protocol based on this hypothesis is computationally fast, and efficient in terms of implementation. This hypothesis will be evaluated and tested in EurValve.

A candidate protocol for the valve characterisation, indicating the decisions that need to be made to standardise the analysis, is outlined in Annex 2: A Candidate Steady-Flow Protocol for Valve Characterisation. The fall-back position, should this representation prove insufficiently accurate for clinical purpose, is a fully transient CFD analysis, also discussed below, but, due to long run times and high computational cost, this would limit the exploitation pathways. A similar workflow will operate to characterise and to quantify the regurgitant flow over a leaky valve in the closed configuration. This does not capture the swept volume associated with the process of closure itself, which would necessitate a fully transient analysis. The conditions under which a transient analysis might be necessary will be established as part of EurValve's validation process.

In EurValve all 3D CFD models will be performed in ANSYS Fluent. The selection of this software component is based on its credibility for immediate application and exploitation as a

central component of EurValve's DSS. ANSYS Fluent has been an acknowledged leader in CFD for more than 30 years. ANSYS Fluent by the wide choice of its models, its versatility, its robustness and simplicity has become one of the major players in CFD for biomedical applications. The most effective implementation in the EurValve DSS is ensured by the membership of ANSYS as a full partner in the EurValve Consortium.

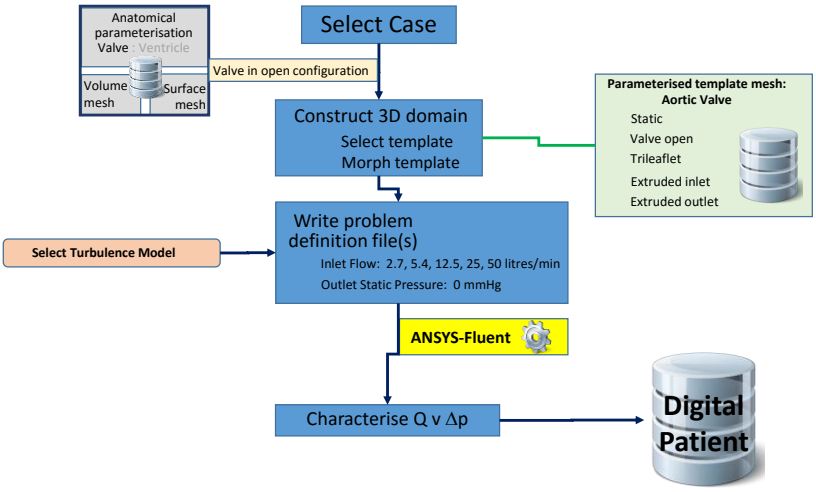

Figure 8: Typical 3D analysis workflow – characterisation of pressure flow relationship for aortic valve

The 3D model described above produces a haemodynamic characterisation of the valve, described by a pressure-flow relationship. In order to interpret this in the broader context of the physiological impact of the patient this needs to be integrated with a model of the rest of the haemodynamic system. A 0D model is the lowest order model that simulates the interaction between the heart valves and the rest of the cardiovascular system. A comprehensive review of 0D models and their applications is presented by Shi et al (8).

EurValve will support the operation of two zero-dimensional models. The first model implemented by EurValve, illustrated schematically in Figure 9, is based on a model of the left heart and systemic circulation published to the CellML model repository (9), which is itself a simplification of the models described by Korakianitis and Shi (10), (11). Although it appears very simple, the most basic version of this model, as implemented in CellML, features 23 input parameters. Further details, including the governing equations for the zero-dimensional models, are presented in Annex 3: Governing Equations for 0D Model (uncontrolled).

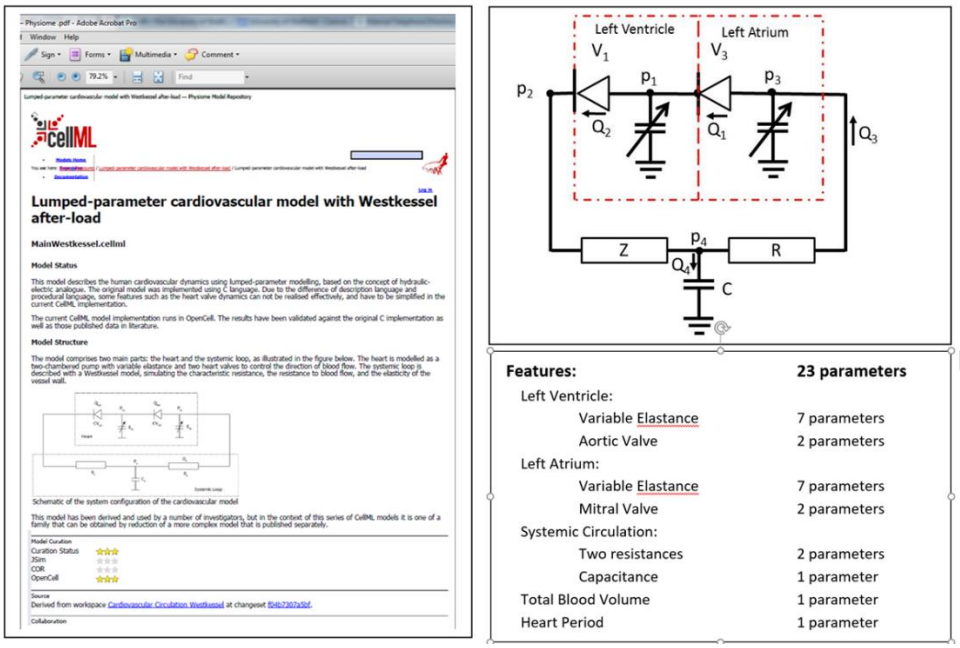

Figure 9 Schematic of the basic (uncontrolled) 0D model

EurValve will also implement and test the potential of Shi's 2006 valve models for personalisation and clinical exploitation.

The second model to be implemented in EurValve builds on the first to represent the barocontrol mechanisms, based on a subset of the regulation effectors described and modelled by Ursino (12). The controlled version of the model features 47 input parameters. It is most unlikely that there will be sufficiently rich physiological clinical information to support the personalisation of all of these parameters, and it will be important to devise a strategy, based on a combination of literature review, experimentation, formal sensitivity studies and learning and optimisation operations, to select an appropriate subset of these parameters for personalisation. These models together will be used to characterise the physiological effect of the valve disease under rest and exercise conditions, and the prospective acute changes under candidate interventions.

An analysis protocol for the operation of the 0D model, using the image-based CFD valve characterisation together with personalised inputs from the machine learning operations, is illustrated in Figure 10.

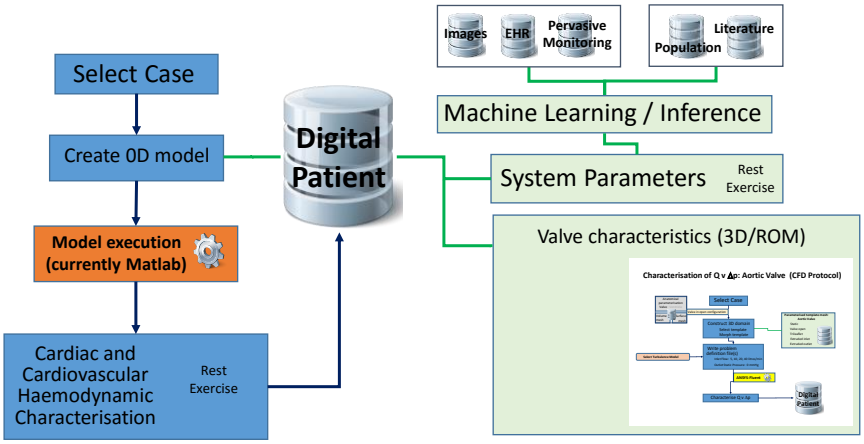

Figure 10: 0D Analysis workflow - patient specific haemodynamic characterisation

In some cases, particularly in the rest state, some of the output parameters from the haemodynamic characterisation might have been measured clinically. In these cases, an optimisation process will update the model parameters to fit the observations. This is illustrated in Figure 11.

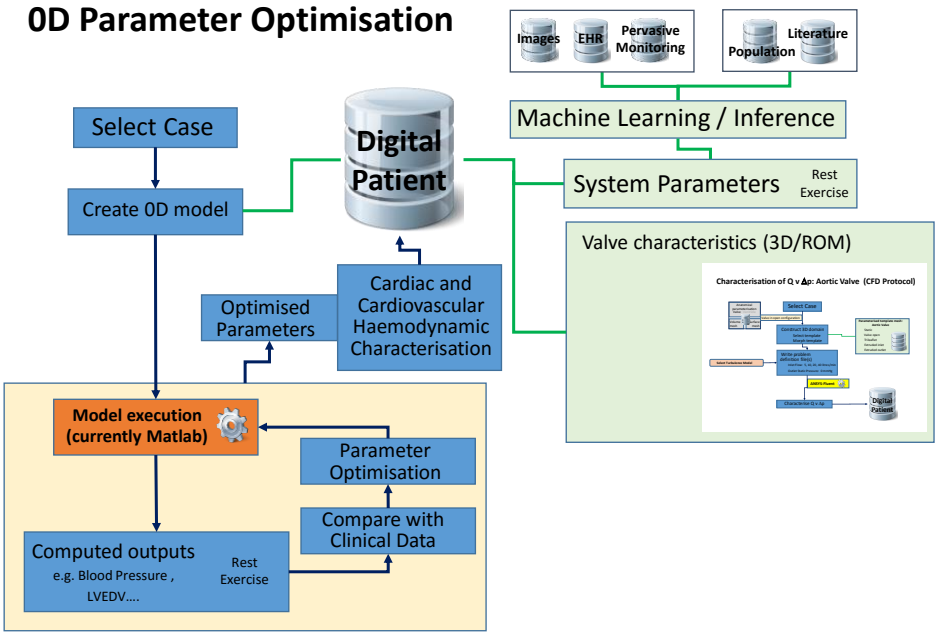

Figure 11: Extended 0D Analysis workflow including parameter optimisation loop

Although the focus of EurValve is on the characterisation of system haemodynamics and prediction of acute responses to intervention, we will also investigate the use of models to represent the longer-term processes such as ventricular re-modelling, and appropriate models for this component will be investigated.

A comprehensive review of the mathematical models of growth and remodelling has been published by Bovendeerd (2012) (13). The focus of the review is on the fibre orientation in the ventricular wall, which is out-of-scope for EurValve models, but nevertheless it contains useful background information on the mathematical representation of the process of remodelling including model optimisation and adaptation. Of direct relevance to EurValve are the clinical reviews of ventricular remodelling following aortic valve interventions published in 2006 by Villa et al (14) and in 2014 by Kim et al (15) Similarly, clinical reports of remodelling following valve repair for mitral regurgitation are available in the literature, e.g. Song et al 2010 (16). The 0D/1D model has been used earlier by Kroon et al (17) to investigate remodelling of the heart in patients who underwent surgery to create an arterio-venous fistula for dialysis purpose. A similar strategy could be adapted for remodelling after valve replacement.

The state-of-the-art in the haemodynamic assessment of valve-system interactions is a fully-coupled 3D-0D model in which the valve(s), atrium (or atria) and ventricle(s) are described by 3D models, coupled at their boundaries to 0D representations of the circulations. These models can extend to the representation of the electrophysiology, including wave propagation in the myocardium, and of the resulting ventricular contraction. In the opinion of the EurValve analysis partners there are major challenges in the implementation in a clinical tool of the complex workflows that result from these coupled, multi-physics, multi-scale systems, not least in the personalisation of the many parameters that are required to support the analysis. EurValve aims to prove that simpler models can be effectively tuned (personalised) using the data in our Digital Patient, and will provide important data to support the clinical decision on timing and nature of interventions. Nevertheless, EurValve plans to operate two types of fully-coupled models for the purpose of validation of the accuracy of the proposed analysis protocol. These are:

- Coupled transient analysis (but with valve fully open or fully closed, the latter for study of regurgitation) with idealised representation of heart chambers in 3D domains.
- Coupled transient analysis, again with valve fixed in the open position, of the haemodynamics in the region of the aortic valve when the 3D motion of the ventricle is explicitly described in the 3D model.

In all cases the analysis is limited to the fluid mechanics. EurValve will not model electrophysiology or mechanical contraction, except for the latter as it is described by a prescribed wall motion. A workflow for the 3D-0D coupled analysis is illustrated in Figure 12. The 0D components will be implemented with User-Defined Functions using standard C within the ANSYS Fluent software. Should the accuracy of the proposed steady-flow based protocol prove inadequate for clinical purpose, EurValve will implement the coupled, transient, analysis protocol though the DSS.

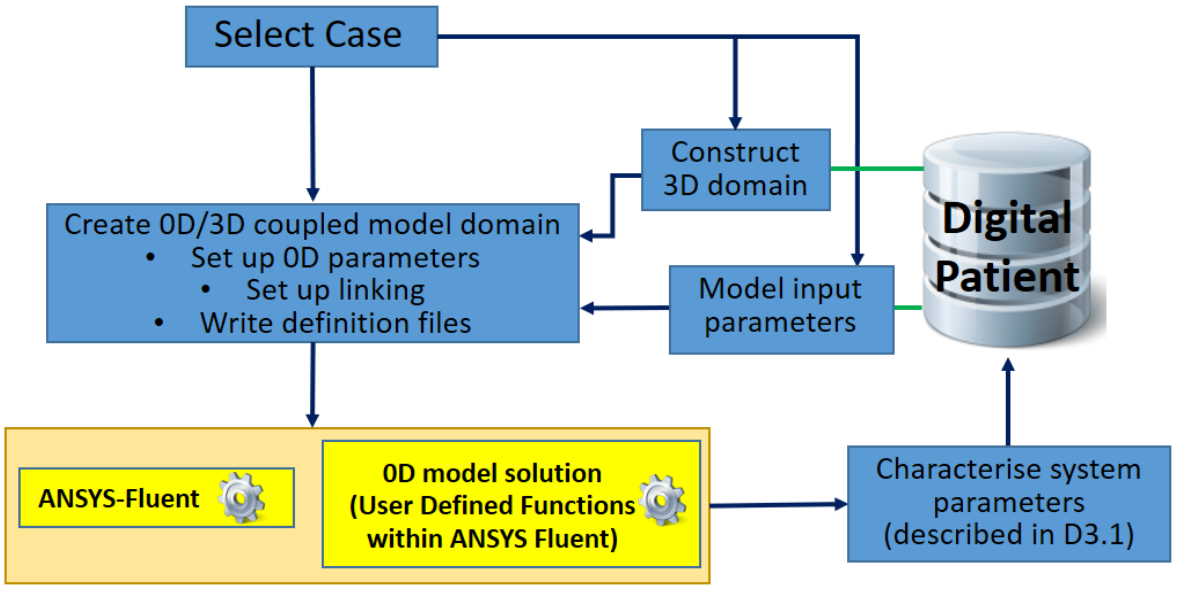

Figure 12: Coupled 3D-0D Analysis workflow with User Fortran – characterisation of systemic circulation

3.3.4 Task deliverables

Table 3: Deliverables of Task 3.3

D	Lead	Title	Due
D 3.2.3	USFD	0D controlled, 0D uncontrolled, 3D models	PM14
D 3.3.3	USFD	Refined 0D controlled, 0D uncontrolled, 3D models (or 0D/3D if necessary depending on validation)	PM29

3.4 Task 3.4 Variation and Sensitivity Analysis Tools

Activity Leader: TUE

3.4.1 Task overview

The analysis tools that will be made available in this task will provide means to assess the boundary conditions and model parameters that are most worthwhile to be obtained patient-specifically and which ones can be based on population averages. This will allow us to improve clinical diagnosis and interventional planning exploiting all available information, from personal clinical data, population data, clinical guidelines and other sources on the basis of those parameters that are relevant for the specific output deemed to be important to provide a specific decision in the DSS. The same analysis tools can also be used to guide model simplification and verify applicability of model reduction methods. Finally, the tools will provide quantification of the uncertainty of model predictions, such that appropriate interpretation of their significance for a specific decision in the DSS can be made.

To determine how each fraction of the total uncertainty in a specific output of a model corresponds to input uncertainties of each model parameter (or to each possible interaction between parameters),

- In a first step, the models that will be used (0D, 3D, ROM or coupled 0D/3D) need to be defined in Task 3.3.
- Next, candidate model outputs relevant for decision support need to be identified. An approach that starts with a reduced order model that will be expanded step-by-step with input that decreases output uncertainty of the prediction will be used. In this way, the impact of reduced order modelling on the output parameter of interest can be investigated.
- After this, input uncertainty ranges need to be set, based on population variations or measurement inaccuracies. The tools provided in this task will use these ranges to produce the individual samples in the input space of the model.
- Also the difference of taking the boundary conditions for in- and outflow from directly assessed flow assessment and boundary conditions derived from 1D wave propagation or distributed 0D models for impact of valve disorders on the coronary circulation and myocardial contraction will investigated. Relate to the different use cases described above. The use cases will be similar to those that are defined in Task 3.1 and 3.3.

3.4.2 Task specific input and output

In this task the clinical data that will be needed is exactly the same as the clinical data that will be used in the models that will be used and are presented in Task 3.3, (and implicitly 3.5 and 3.6) provided that also (either known or estimated) variations due to measurement inaccuracies or population variations should available.

The derived data will be equivalent to the derived data that is obtained from each of the models used and will be extended with uncertainty ranges that follow from the uncertainties in input parameters or boundary conditions. In addition, derived data from Task 3.1 can be used to extend the parameter input space with available information, from population data, clinical guidelines and other sources.

This task will provide quantitative insight in and knowledge of those parameters that are worthwhile to determine more accurate (factor prioritisation) and those that can be determined from population average data (factor fixing). These results will be made available via the derived-data part of the EurValve database and will be used by the machine learning and case processing services of EurValve.

The model personalisation (i.e. prioritisation and fixing of parameters) will not be a one-step process and will require an iterative interaction with the machine learning and systems modelling tasks. Especially, the way in which assimilation of data can be used to derive relevant replacement of missing or incomplete data will rely on this interaction between these tasks. Data will be shared via the EurValve database.

3.4.3 Task specific methods and workflow

This task will add the tools needed to perform a sensitivity analysis and to provide model output together with quantification of output uncertainty given the uncertainty in input parameters and boundary conditions. Sobol (main and total) sensitivity indices will be used (18). These indices will be derived analytically from a meta-model, based upon generalised polynomial chaos expansions that expands the model output space with multidimensional polynomials that dependent on the input parameters. These expansions will be obtained using least square regression. A screening method of Morris will be applied prior to the meta-model construction to reduce the dimensionality ingoing to a subset of important parameters (19). Once the quantification of the sensitivity of a specific model output to its input parameters is available, suggestions for parameter reduction and directions for new machine learning targets can be made.

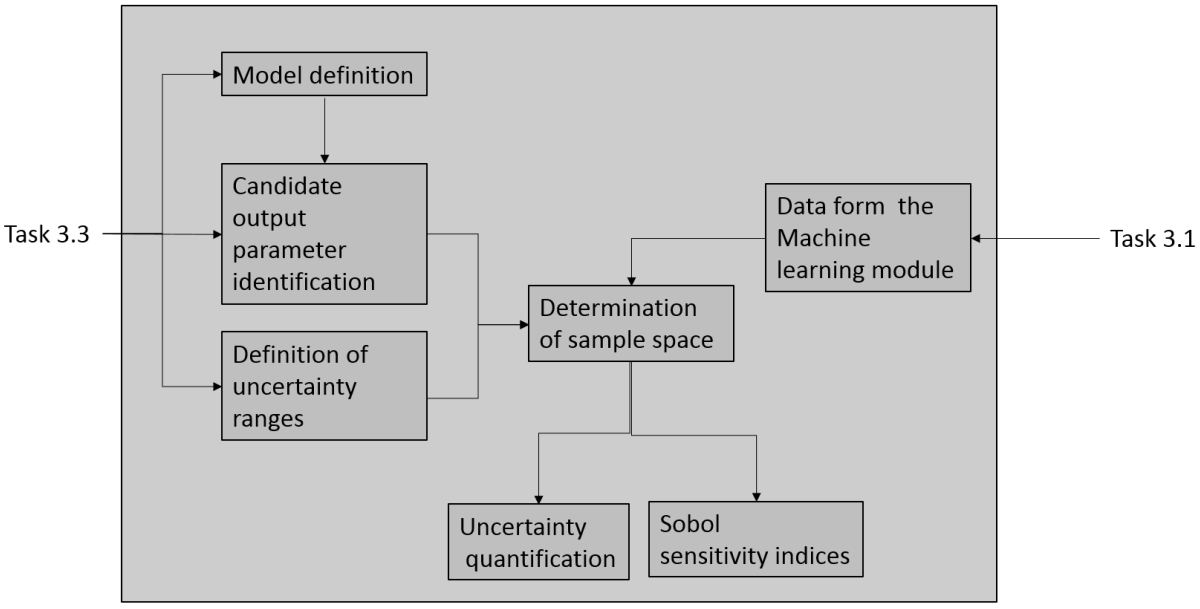

Figure 13: Overview of Task 3.4

3.4.4 Task deliverables

Table 4: Deliverables of Task 3.4

D	Lead	Title	Due
D 3.2.4	TUE	Operational sensitivity tool for 0D controlled, 0D uncontrolled, 3D models	PM14
D 3.3.4	TUE	Operational sensitivity tool for refined 0D controlled, 0D uncontrolled, 3D models (or 0D/3D if necessary depending on validation)	PM29

3.5 Task 3.5 Proteomics Data Analysis Tools

Activity Leader: MDC

3.5.1 Task overview

To improve insight into the course of myocardial remodelling we will integrate information that is collected on the tissue as well as cell level. Tissue samples that are excised during surgery will be used for proteomics of the cardiac tissue. For cellular data, cell culture models will be employed. Models that use patient-specific proteomics as input parameters allow the simulation of myocyte contractility and elastance in the united cell structures of a given patient. This information can be integrated back to the models at an organ level. This is an important step for illuminating the complex interplay of the medical, physiological and biological processes that determine the prognosis for each individual patient.

3.5.2 Task specific input and output

In this task we will use patient tissue samples obtained during surgery at the German Heart Centre Berlin or myocytes from cell culture. The output will be a list of protein copy numbers characterising the copy numbers of the 3000 most abundant proteins for each patient. These copy numbers will serve to parameterise mathematical models in Task 3.6.

3.5.3 Task specific methods and workflow

The Max Delbrück Centre has a state-of-the-art mass-spectrometry based proteomics setup. For the EurValve project a specialised work-flow will be setup, which generates data in close collaboration with the group for mathematical cell physiology. As a new aspect in EurValve the proteomic data will be used for model parameterisation in the group of the Mathematical Cell Physiology of the MDC. Mathematical models will comprise membrane potential dynamics, intracellular Ca^{2+} dynamics and the sarcomere.

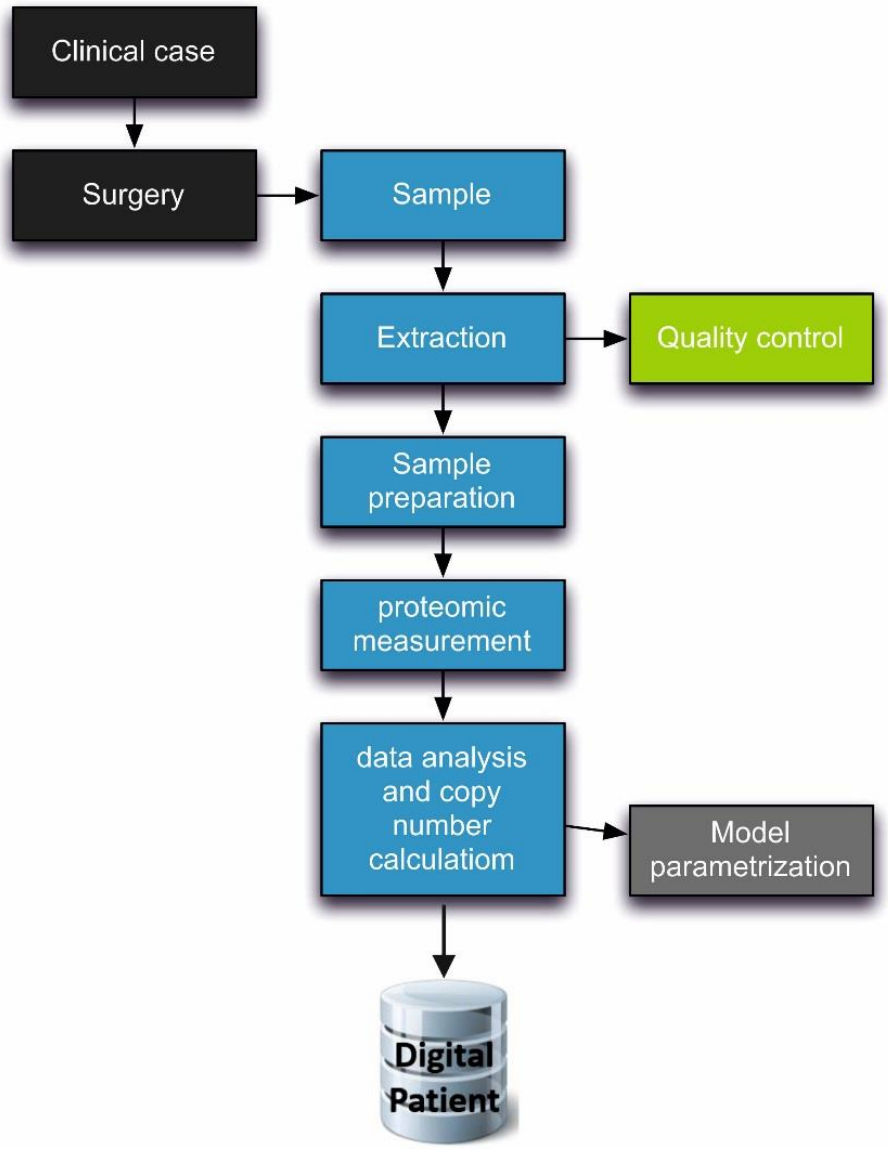

Figure 14 Workflow of Task 3.5

3.5.4 Task deliverables

Table 5: Deliverables of Task 3.5

D	Lead	Title	Due
3.3.4	MDC	Proteome analysis Cell model	PM30

3.6 Task 3.6 Reduced Order Modelling Tools

Activity Leader: ANSYS

3.6.1 Task overview

Within the EurValve project steady (3D) and transient (4D) flow simulations (CFD) for each patient are considered. These CFD simulations are highly time consuming. Many input parameters could be analysed: inlet boundary conditions, outlet boundary conditions, patient anatomy through a surface mesh and eventually the variation of that mesh during the cardiac cycle. The goal of Reduced Order Modelling Tools (ROM) is to reduce the computational complexity of 3D steady-state or transient problems (20). ROM as a technique to replace very time-consuming 3D calculations by real-time computations giving very accurate results including fields as velocities on cells (21). There are several ROM tools associated to different types of simulation (steady or transient eventually including a coupling with a 0D model) and to different types of parameters (boundary conditions or patient anatomy). Globally we will consider two steps: (i) off-line simulation step where we launch various computations to learn the variation of the output results with respect to the input parameters (ii) on-line simulation (in quasi real time) that could be embedded into the Decision Support System. For each haemodynamics analysis protocol we need to consider those two steps.

3.6.2 Task specific input and output

The main inputs for this task are the several 3D steady and transient simulation workflows proposed by the Task 3.3. For each simulation model the other inputs are the parameter definition (boundary conditions and patient anatomy) mainly provided by the Task 3.2. The creation of a ROM with respect to the patient variability could need a large collection of surface meshes (and eventually the variation of those meshes in the cardiac cycle) extracted from a database of patients using tools provided by the Task 3.2. Moreover, the simulation workflow will include the definition of simulation results. Those results could be a single scalar or the time variation of a scalar during the cardiac cycle. We could also consider results on a mesh (e.g. velocity on each cell) and time variation of those field results.

In the specific case of variable patient anatomy, the output is the database of surface meshes enriched by morphing and indexation techniques to extract the main shape parameters. In addition to this database, we will deliver some software components to compute for a new patient represented by his surface mesh (Task 3.2) the closest virtual patient which is represented by a set of shape parameters (22). These shape parameters are the inputs of the model ROM databases associated to the several 3D simulation workflows.

Then, for each 3D simulation workflow, we consider two outputs. First, the ROM database created after the off-line step. Secondly, the ROM simulation software able to deliver accurate simulation results for a new set of input parameters.

All the results of the ROM task will be used by the Decision Support System tool.

3.6.3 Task specific methods and workflow

The research team of ANSYS in France has been developed a full set of ROM tools that could be used to drastically accelerate 3D steady and transient CFD simulations. This includes the steady ROM tool for parametric studies and the dynamic ROM tool for transient simulations. In addition of the ROM tools able to replace heavy CFD simulations by a very quick solve, we also propose a set of methods for shape statistical analysis including mesh morphing and indexation techniques.

The main limitation of ROM for parametric studies is the number of input parameters we could efficiently manage. The challenging application of these ROM techniques is to accurately parameterise simulation results with respect to the human variability in terms of anatomy. The additional development will mainly concern the accuracy of our ROM models compared to the corresponding 3D simulation workflow.

In the context of the overall workflow, the workflow of Task 3.6 is shown in Figure 15.

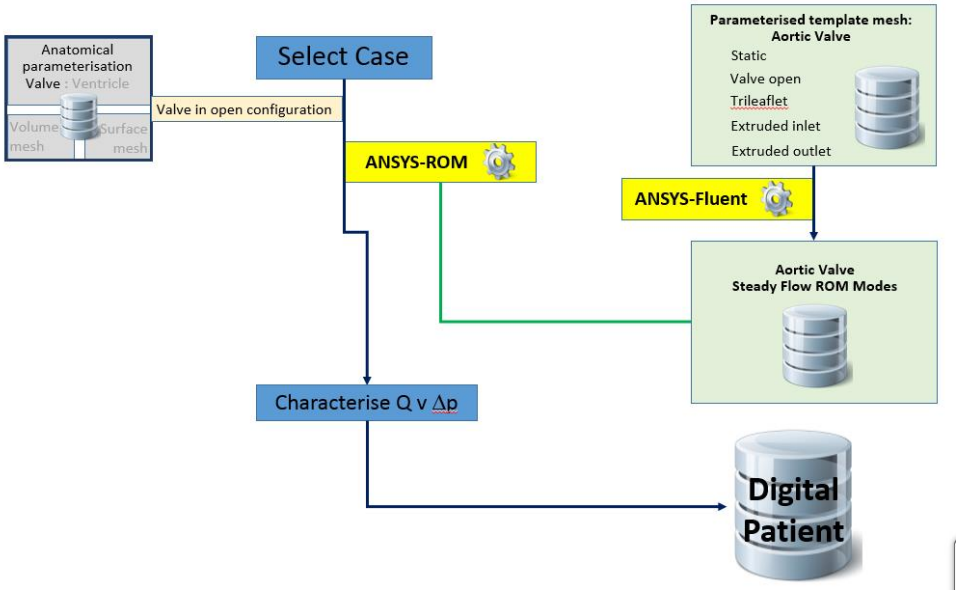

Figure 15: Workflow of Task 3.6

3.6.4 Task deliverables

Table 6: Deliverables of Task 3.6

D	Lead	Title	Due
D 3.2.6	ANSYS	First shape statistical analysis of patients First database of offline simulations with shape parameters Initial online simulations for static and dynamic aortic valve	PM14
D 3.3.6	ANSYS	Final, validated ROM for aortic and mitral valve	PM29

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LIST OF KEY WORDS/ABBREVIATIONS

AV	Aortic valve
CFD	Computational fluid dynamics
CT	Computer tomography
DSS	Decision support system
LA	Left atrium
LV	Left ventricle
ML	Machine learning
MR	Magnetic resonance
MV	Mitral valve
PM	Project month
ROM	Reduced order modelling
TTE	Trans-thorax echocardiography
TEE	Trans-oesophageal echocardiography
VHD	Valvular heart disease
WP	Work package

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ANNEX 1: TABLE OF COMPUTATIONAL ANALYSIS CONCEPTS

Field Label	Field Name	Data Type	Code/Unit/Comment	Input or Output	Data Source
Aortic Flow/dP characterisation coefficients	com_aQdPcoeff	OrderedMap < Double>	[mixed]	Output (3D) Input(0D)	
Barocontrol afferent signal parameters	com_baro_cp	OrderedMap <Double>	*{fmin [s-1], fmax [s-1], Pn [mmHg], kn [mmHg]}*	Input	Lit/ML/ Pop*
Barocontrol efferent sympathetic signal parameters	com_baro_es	OrderedMap <Double>	*{fes0 [s-1], fesinf [s-1], kes [s]}*	Input	Lit/ML/ Pop*
Barocontrol efferent vagal signal parameters	com_baro_ev	OrderedMap <Double>	*{fes0 [s-1], fesinf [s-1], kev [s]}*	Input	Lit/ML/ Pop*
Barocontrol regulation effectors	com_baro_reg	OrderedMap <Double>	*{gain, time constant and time delay for each effector}*	Input	Lit/ML/ Pop*
Baroreceptor pressure control time parameters	com_baro_ti	OrderedMap <Double>	{τ_p [sec], τ_z [sec]}	Input	Lit/ML/ Pop*
Left Atrium Elastance Offset parameters	com_elaoff	OrderedMap <Double>	[p0 mmHg, V0 ml]	Input	Echo
Left Atrium Elastance timing parameters	com_elatimepar	OrderedMap <Double>	[Dimensionless, fraction]	Input	Echo
Left Ventricle Elastance Offset parameters	com_elvoff	OrderedMap <Double>	[p0 mmHg, V0 ml]	Input	Echo
Left Ventricle Elastance timing parameters	com_elvtimepar	OrderedMap <Double>	[Dimensionless, fraction]	Input	Echo
Maximum Left Atrium Elastance	com_elamax	Double	[mmHg/ml]	Input	Echo
Maximum Left Ventricle Elastance	com_elvmax	Double	[mmHg/ml]	Input	Echo
Minimum Left Atrium Elastance	com_elamin	Double	[mmHg/ml]	Input	Echo
Minimum Left Ventricle Elastance	com_elvmin	Double	[mmHg/ml]	Input	Echo
Mitral Flow/dP characterisation coefficients	com_mQdPcoeff	OrderedMap <Double>	[mixed]	Output (3D) Input (0D)	
Systemic compliance	com_sysresdis	Double	[ml/mmHg]	Input	Machine learning

Field Label	Field Name	Data Type	Code/Unit/Comment	Input or Output	Data Source
Systemic resistance distal	com_sysresdis	Double	[mmHg/ml]	Input	Machine learning
Systemic resistance proximal	com_sysresprox	Double	[mmHg/ml]	Input	Machine learning
Total Blood Volume	com_tbv	Integer	[ml]	Input	
Heart Rate	com_hr	Integer	[beats/minute]	Input (uncont.) /Output (cont.)	ECG
Aortic Flow/dP characterisation	com_aQdP	OrderedMap <Double>	[Q l/min, dP mmHg]	Output	
Aortic Valve dPcurve	com_dp_curve	OrderedMap <Integer, Double>	{*TimePoint*, *Measurement*}	Output	
Aortic Valve dPmax	com_dpmax	Integer	[mmHg]	Output	
Aortic Valve dPmean	com_dpmean	Integer	[mmHg]	Output	
Cardiac output	com_co	Integer	[mL/min]	Output	
Doppler A-Wave	com_echo_pw_a	Double	[cm/sec]	Output	
Doppler E-Wave	com_pw_e	Double	[cm/sec]	Output	
Left Atrium volume at ED	com_laed	Integer	[mL]	Output	
Left Atrium volume at ES	com_laes	Integer	[mL]	Output	
Left Ventricle Ejection fraction	com_lvef	Integer	[%]	Output	
Left Ventricle volume at ED	com_lvved	Integer	[mL]	Output	
Left Ventricle volume at ES	com_lvves	Integer	[mL]	Output	
Left Ventricular Peak Power	com_lvwork	Double	[Watts]	Output	
Left Ventricular Work	com_lvwork	Double	[Joules]	Output	
Mitral Flow/dP characterisation	com_mQdP	OrderedMap <Double>	[Q l/min, dP mmHg]	Output	
Mitral Valve Effective Regurgitant Orifice Area	com_mi_eroa	Integer	[mm²]	Output	
Mitral Valve Pressure Half Time	com_mi_pht	Integer	[msec]	Output	
Mitral Valve Regurgitation	com_mi	Integer	{0,1,2,3,4}	Output	

Field Label	Field Name	Data Type	Code/Unit/Comment	Input or Output	Data Source
Mitral Valve Regurgitation Volume	com_mi_rvol	Integer	[mL/beat]	Output	
Mitral Valve Vena contracta	com_mi_vc	Integer	[mm]	Output	
Pulmonary Vein Flow	com_pulmonary	Character	{systolic dominance, blunting, flow reversal}	Output	
Right Ventricle Ejection Fraction	com_lvef	Integer	[%]	Output	
Right Ventricular Systolic Pressure	com_rvsp	Integer	[mmHg]	Output	
Systemic Oxygen Consumption	com_O2_rate	Double	[ml/min]	Output	
Tricuspid Valve Regurgitation	com_ti	Integer	{0,1,2,3,4}	Output	
Volume curve left atrium	com_la	OrderedMap <Integer,Double >	{*TimePoint*, *Measurement*}	Output	
Volume curve left ventricle	com_vc_lv	OrderedMap <Integer,Double >	{*TimePoint*, *Measurement*}	Output	
Aortic Valve Regurgitation	com_ai	Integer	{0,1,2,3,4}	Output	

* Lit/ML/Pop: From Literature, Machine Learning or Population Means

Table 7: Computational Analysis Concepts (extended from D4.1 Table 10)

ANNEX 2: A CANDIDATE STEADY-FLOW PROTOCOL FOR VALVE CHARACTERISATION

The most complex mode of operation is a 3D local representation of the valve and some proportion of the atrium, ventricle and/or aorta coupled with a 0D circulation model. It is hypothesised that an adequate representation of valve characteristics might be achieved using a simple steady-flow protocol. For aortic valve stenosis this analysis has a single purpose: it is to compute the pressure gradient across the aortic valve as a function of the flow. This has great merit for implementation in a clinically-oriented workflow. This annex describes a precise protocol by which such an analysis can be performed, thus describing the operations that are required for implementation of a CFD-based workflow in the decision support system. Note that if the reduced order modelling approach of Task 3.6 is successful it will only be necessary to perform these analyses off-line to build the reduced order models on which the DSS will operate. The purposes of this annex are:

- To provide a basis for iteration and communication between the analysis partners to develop and to refine the process.
- To assist WP2 in the evaluation of the computational and infrastructural requirements associated with 3D CFD analyses.
- To assist WP4 in the understanding of how the clinical data will be interpreted in the context of the setting of boundary conditions for the CFD analyses.

The **analysis domain** will comprise:

- an inlet chamber which is created by the extrusion of a proximal plane of the segmented ventricular inflow tract, by a distance of one equivalent diameter along the local tangent to the centre line.
- the 3D representation of the ventricular inflow tract, the aortic valve, the aortic root and a portion of the ascending aorta. This portion of the domain will be created from a segmentation of the medical image. Potential imaging modalities are
    - CT dynamic valve model (3.2.2 1 in the deliverable)
    - 3D TEE dynamic valve model (3.2.2 3 in the deliverable)
- an outlet section which created by the extrusion of a distal plane of the segmented ascending aorta, by a distance of six equivalent diameters along the local tangent to the centre line.

The **inlet boundary condition** will be the flow, or the point-by-point velocity normal to the inlet plane (zero velocity in plane), at each position on the proximal boundary. For the latter the assumption of plug flow will be made (zero velocity at the ‘wall’ boundary, constant velocity at all other nodes). The flow, or the equivalent velocity, will be prescribed at five flow rates, chosen to span the range of likely flow rates over the cardiac cycle. These are:

- 2.7 litres/min, one half of a typical cardiac output
- 5.4 litres/min, a typical cardiac output
- 12.5 litres/min, one half of a typical peak flow rate
- 25.0 litres/min, a typical peak flow rate
- 50.0 litres/min, and extreme peak flow rate

The **outlet boundary condition** will be a static pressure of zero applied at the distal plane.

Rheological properties. For the purposes of these analyses blood will be assumed to be a Newtonian fluid with a density of 1060 kg/m^3 and a viscosity of 0.004 Pa.s.

Turbulence. The Reynolds number will be estimated using the equivalent diameter at the minimum area of the valve, and where this is less than 1000 laminar flow will be assumed. Where the Reynolds number exceeds this, a normalised SST (shear stress transport) turbulence model will be employed.

Output. The operation of these models will produce the distribution of pressure and velocity, and where relevant turbulence parameters, throughout the solution domain. Typically, the full results file, containing the complete distribution of pressure and flow throughout the domain for a steady state analysis of the region around the valve, will be of the order of 1GB. These results will be stored in a separate EurValve database for the duration of the project, but only a reduced representation will be written to the Digital Patient. Post-processing will be carried out to extract:

- The static pressure at one hundred equally-spaced points along the centre line;
- The static pressure drop from a position on the centre line one diameter proximal to the valve plane to three diameters distal to the valve plane [or a criterion based on the rate of pressure recovery at the location], where the diameter is defined as the equivalent diameter at the root of the valve.

It is also possible to record other haemodynamic characteristics, including for example measures of wall shear stress and/or of vorticity and vortex structures. The clinical utility and interpretation of these measures is uncertain, but candidates will be explored with the clinical centres when typical analysis results are available to form the basis of discussion.

These reduced output measures are regarded as characteristic of the valve, and will be written to the digital patient definition.

ANNEX 3: GOVERNING EQUATIONS FOR 0D MODEL (UNCONTROLLED)

The 0D model describes the circulation in the left heart and the systemic circulation. It consists of the heart represented by 2 heart chambers, the mitral and aortic valves, and the systemic circulation modelled by 2 resistances and 1 capacitance. There are several options for the representation of the performance of the heart chambers and of the valves, and indeed of the systemic circulation. The equations presented below are based on a variable elastance description of the heart chambers and a nonlinear forward flow, perfect diode representation of the valve, but other representations including the single fibre model of the ventricle and a CFD-based representation of the valve characteristics will be implemented and tested in EurValve.

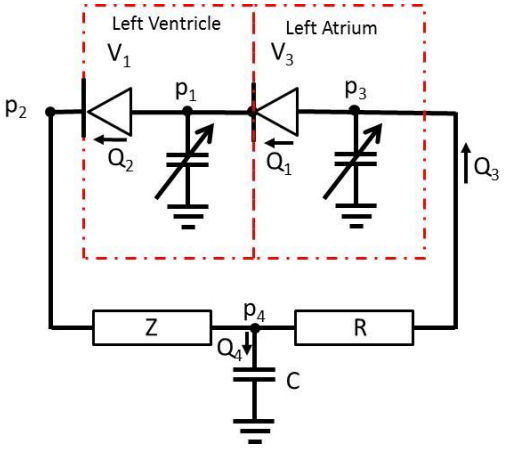

Figure 16 Schematic of the 0D model

The 0D model is governed by 10 equations describing the systemic circulation:

$$\frac{dV_1}{dt} = -Q_2 + Q_1$$

$$0 = p_1 - p_{LV,0} - e_{LV}(t) \cdot (V_1 - V_{LV,0})$$

$$0 = Q_2 - \{CV_{ao} \cdot \sqrt{p_1 - p_2}\}$$

$$0 = ZQ_2 - p_2 + p_4$$

$$0 = RQ_3 - p_4 + p_3$$

$$\frac{dp_4}{dt} = \frac{1}{C} Q_4$$

$$0 = Q_2 - Q_3 - Q_4$$

$$\frac{dV_3}{dt} = Q_3 - Q_1$$

$$0 = p_3 - p_{LA,0} - e_{LA}(t) \cdot (V_3 - V_{LA,0})$$

$$0 = \mathrm{Q}_1 - \left\{\mathrm{CV}_{\mathrm{mit}} \cdot \sqrt{\mathrm{p}_3 - \mathrm{p}_1}\right\}$$

where Q_i are p_i is flow and pressure at point i located as seen in Figure 1. V_1 is the volume of the ventricle, V_3 is the volume of the Atrium. $\mathrm{p}_{\mathrm{LV},0}$ and $\mathrm{V}_{\mathrm{LV},0}$ are the initial pressure and volume of the left ventricle. $e_{\mathrm{LV}}(t)$ is the left ventricle elastance. Z is the proximal systemic resistance, C is the systemic capacitance, R is the distal systemic resistance. . $\mathrm{p}_{\mathrm{LA},0}$ and $\mathrm{V}_{\mathrm{LA},0}$ are the initial pressure and volume of the left atrium. $\mathrm{CV}_{\mathrm{mit}}$ and $\mathrm{CV}_{\mathrm{ao}}$ are characterisation coefficients describing the mitral and aortic valve.