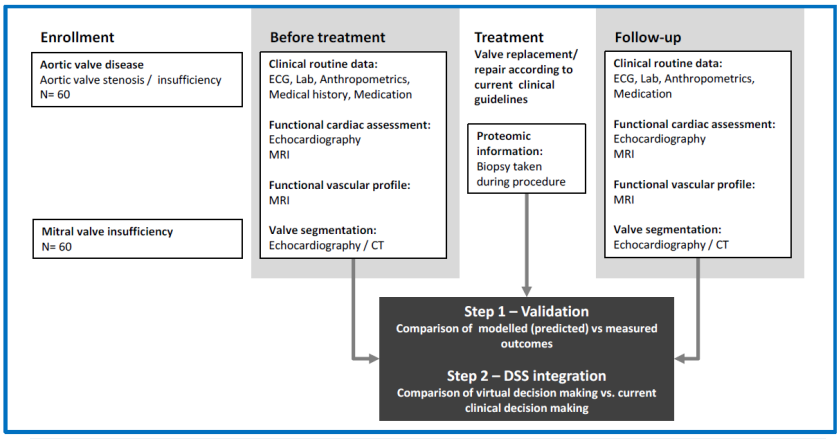
EurValve Project Newsletter June 2017

Project Update

EurValve Clinical Trials now fully initiated

In the EurValve project we will implement and validate a Clinical Decision Support System (CDSS) for aortic and mitral valve replacement and repair. The evaluation phase will involve a prospective clinical study with 120 patients enrolled across three clinical centres, in Berlin, Eindhoven and Sheffield. All three centres have now achieved approval for their clinical studies and have begun to recruit patients.

Patients attending hospital for valve replacement or repair will be extensively imaged both before and after surgery. Some patients will also be equipped with wearable devices to monitor aspects of their activity and physiology over three sessions (see page 6) and perform other activity tests both before and after surgery.

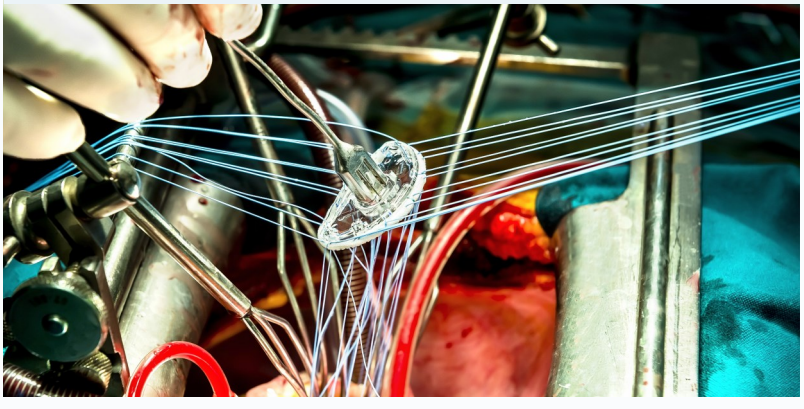


General Assembly

EurValve's second General Assembly took place in Berlin in June 2017. Major topics covered included ethics and dissemination.

Project Milestone #3

The project successfully passed its important third Milestone in June 2017: The Component Assembly phase has been achieved.



Inside this Issue

WWW

Check out the EurValve website at eurvalve.eu

Beneficiary Profiles

Each edition of the EurValve newsletter will contain profiles on selected beneficiaries. In this edition, we feature Catharina Hospital, the Technical University Eindhoven and ANSYS, Lyon.

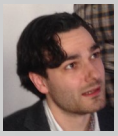
Beneficiary Profile – Catharina Hospital, Eindhoven

Catharina Ziekenhuis, founded in 1843, is a teaching hospital in Eindhoven, Netherlands.

Catharina's Heart Centre treats the largest volume of cardiac patients in the Netherlands. More than 100 percutaneous aortic valve implantations (TAVI) are performed annually, and the Centre also has a percutaneous mitral valve treatment programme; in all, over 2500 percutaneous coronary interventions are performed annually (elective and urgent). The Centre performs both clinical and basic scientific research and has a strong scientific partnership with the Technical University of Eindhoven (TU/e, also a EurValve beneficiary). The main task of the Centre in EurValve is the collection of data for the DSS.

Pim Tonino is Catharina's senior EurValve representative, and an interventional cardiologist in Catharina Hospital. He has over 10 years' experience in basic and clinical research and is currently the steering committee member for international randomised clinical interventional trials. His PhD degree from TU/e included the 'FAME' clinical study which examined Fractional Flow Reserve versus Angiography for Multivessel Evaluation. Pim specialised in percutaneous heart valve interventions (TAVI, mitraclip and mitral valve) and FFR. He has published more than 30 articles in international journals and his current research activities comprise membership of the FAME 2 steering committee and several studies on the subject of TAVI.

Jo Zelis is a clinical researcher within the cardiovascular team in Catharina Hospital. He is responsible for many of the practical activities associated with the conduct of the EurValve clinical trial in Eindhoven. His research interests span the full range of clinical activities that relate to cardiovascular care.



"The **target user** of this Decision Support System is the **healthcare professional**, in this case the surgeon or cardiologist, who will make the decision on the nature and timing of the intervention."

Beneficiary Profile – TU/e

The Eindhoven University of Technology, TU/e, is located in Eindhoven, Netherlands, and specialises in engineering, science & technology. To ensure that research responds flexibly to dynamic external developments and to strengthen the societal and economic impact of the research, TU/e concentrates on strategic areas around the major societal issues, Energy, Smart Mobility, and Health, and emphasises knowledge utilisation.

TU/e is also one of the first universities in Europe with a Department of Biomedical Engineering that features a dedicated and complete undergraduate and graduate program. The Cardiovascular Biomechanics (CVB) group of the Department of Biomedical Engineering focuses on numerical and experimental modelling of the cardiovascular system, with the aim to improve and develop diagnostic methods and therapeutic protocols. Special attention is given to the complex constitutive behaviour of biological tissues, including their ability to adapt to changing environment. In addition to computational studies, ex vivo experimental techniques that enable temporary cultivation of animal arterial segments and hearts are developed. The group has considerable experience in the inclusion of sensitivity and uncertainty analysis in patient specific modelling. TU/e's main task in EurValve is the provision and deployment of software tools that perform variation and sensitivity analysis.

Frans van de Vosse graduated in physics and is now professor of Cardiovascular Biomechanics at TU/e. He specialises in computational fluid dynamics and fluid-structure interaction, experimental verification, and cardiovascular physiology. His current research relates to the computational and experimental biomechanical analysis of the cardiovascular system and its application to clinical diagnosis and intervention.

Marcel Rutten received his MSc degree in mechanical engineering on the topic of wave propagation in large arteries, and his PhD on fluid structure interaction in large arteries, both from the Technical University of Eindhoven. Since then, he has been a Lecturer in cardiovascular mechanics in the Department of Biomedical Engineering, also at TU/e.

> "Aortic Stenosis (AS) is the most common valvular heart disease in both the EU and the USA and it is predominantly a disease associated with calcification of the aortic valve in old age (estimated 2% - 7% of the population over 65)."

Beneficiary Profile – ANSYS

Founded in 1970, ANSYS now employs nearly 3,000 technical professionals, many of whom are expert MSc and PhD level engineers in finite element analysis, computational fluid dynamics, electronics, semiconductors, embedded software and design optimisation. ANSYS is the global leader in engineering simulation, helping the world's most innovative companies deliver radically better products to their customers. By offering the best and broadest portfolio of engineering simulation software, they help them solve the most complex design challenges and engineer products limited only by imagination. Uses of ANSYS include creation of complete virtual prototypes of complex products and systems – comprised of mechanical, electronics and embedded software components – which incorporate all the physical phenomena that exist in real-world environments.

Michel Rochette is Director of Research at ANSYS. He graduated from the University of Nice in 1990, where he subsequently obtained his PhD degree in mathematics. He founded CADOE, a mathematics company specialising in 3D parametric simulation, in 1994. He has been leading ANSYS research on two main topics: Patient-Specific Simulation, and Reduced Order Modelling. His research team has 2 senior research engineers and 5 PhD students mainly focused on patient specific simulation. As leader of the ANSYS medical initiative he manages partnerships with academic labs, University hospitals, medical software vendors, medical devices companies and medical imaging specialists. He is also responsible for the development and validation of vertical medical applications developed with external partners.

Valéry Morgenthaler is the principal researcher in ANSYS Lyon, responsible for the design and implementation of the EurValve Reduced Order Model that will enable the rapid solution of complex 3D pressure and flow fields in the left ventricle. Working closely with the modelling team in Sheffield he is optimising the ROM design to ensure satisfactory performance across the entire physiological envelope.

> "The **specific challenge of EurValve** is to develop a digital patient, specifically in the context of heart valve disease, which integrates heterogeneous patient data, complemented by population data where appropriate."

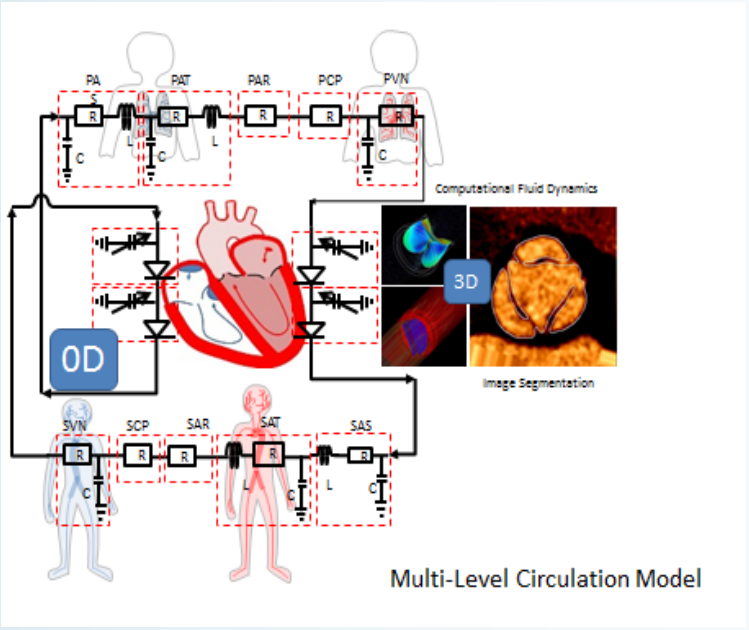
Concept of the Computer Model

The physiological status of a patient can be described, to any desired level of precision, by a computer model. This would typically be attempted for two significant reasons:

- The model can provide otherwise unobtainable quantitative measures that are able to characterise the physiological status and contribute to diagnosis.
- Changes in any of the elements that make up the system, such as the patency of a heart valve, give rise to physiological changes that can be determined by the model. So the benefits of prospective interventions, such as valve replacement, can be simulated.

If it can be assumed that there is an association between physiological status and biological response, such as the 'remodelling' of the heart as a reaction to load, such a response might be described by the characterisation of specific pathways of causality, which in turn might be described by personalised mechanistic models, offering a significant improvement in patient assessment compared with propensity to particular outcomes based on population studies.

The computational models at the core of this project are a series of published compartmental models that describe the distribution of flow and pressure in the cardiovascular system, combined with anatomically accurate models based on 3D and 4D imaging of the patient. Specifically for the diagnosis of heart valve disease and for valve interventional planning it is important to be able to assess the pressure gradient across the valves, any leaks through the valves (the focus is on mitral and aortic valves) and their contribution to the loads on the chambers of heart and their effectiveness in supplying blood to the circulation. The novelty of this proposal lies not simply in the computational models (where the partners have strongly established expertise) but in the combination of these models with heterogeneous clinical and population data.



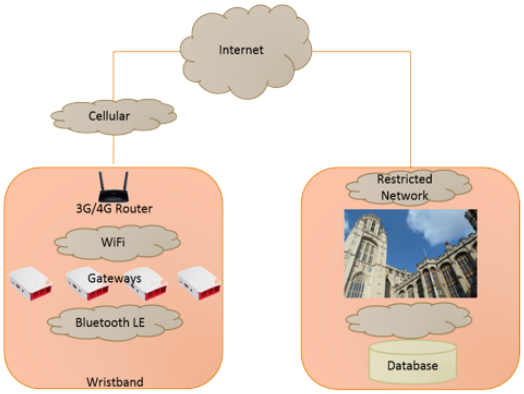
The model is fundamentally multilevel. The anatomical region of the valve is described in accurate detail, based on medical imaging of the patient. The circulation is described in terms of compartmental electrical analogue models that are able to represent the variations of pressure and flow throughout the system as a function of the compliance and impedance of the vessels. The figure above indicates which of the anatomical elements is represented by each part. A specific implementation of the digital patient that includes all data, measured or derived, that is relevant to this patient, and to this disease process, will be developed.

Activity Monitoring - Update

An exciting part of the clinical work in EurValve is the possible utility of patient activity data in the assessment of health status, both before and after intervention. In EurValve two wearable devices are in use.

University of Bristol 'Sphere' Activity Monitor

The University of Bristol's 'Sphere' wearable device is a purpose-built research tool that is being used to measure the activity level of enrolled participants in the Sheffield arm of the prospective trial. The system monitors physical activity using accelerometers, and can pinpoint the patient's location within their home using signals from multiple base stations. Various measures of agility, including threshold-crossing, are being investigated to determine their relevance to heart valve disease.



An overview of the kit operating at a participant's home (above) and the communication networks involved between kit components and the University of Bristol (right).

Philips Health Watch

To provide data on heart rate, the commercially-available Philips Health Watch will be used in all three clinical centres (Berlin, Sheffield and Eindhoven). To enable analysis of data from the watch in EurValve, Philips has specially developed an iPod app for retrieval of data from the watch. This app is not available to the public. The Health Watch continuously tracks heart rate and acceleration, from which can be computed measures of activity and energy expenditure. Normally, consumers can monitor their metrics and receive personalised health guidance using a publicly available smartphone app. This consumer use includes monitoring of steps and heart rate. The watch also provides automatic activity recognition (cycling, running, walking), a heart rate "zone" indication, and a sedentary-behaviour alert for wellness purposes.

Herman ter Horst (Philips Eindhoven) explains to members of the clinical teams how data can be retrieved from the watch.

In EurValve, by contrast, detailed data from the watch will be made available for analysis via the specially developed app, and the clinical intent is to examine heart rate and movement data to identify marker characteristics of physiological state. It is hoped the measures can be derived from this data to support the information from clinical investigations and interviews - known to be influenced by the circumstances of data-collection - ultimately to enhance clinical judgement.

Linking the Activity Data

The opportunity to link the two data sets from the Bristol and Philips wearable sensors is extremely exciting, and investigation is continuing regarding the practicalities of data collection, the burden on the participants, ethical compliance, data security and in the development of appropriate analytical protocols.

Researcher Profile

My name is Roel Meiburg, and I come from Eindhoven in the Netherlands. I've completed both a Bachelor's and a Master's degree in BioMedical Engineering at Eindhoven University of Technology (TU/e). I started working as a Research Associate on the EurValve project at TU/e in June 2016, allowing me to complete my PhD on the patient-specific modelling of cardiac valve disease for the Clinical Decision Support System.

What is your role with EurValve?

My role is mainly to perform sensitivity analyses and uncertainty quantification on the circulation models. This means that, using smart statistical techniques, we can find which model parameters are the most important for any of the model's outputs of interest. Using this knowledge, we can prioritise the parameters that must be determined patient-specifically, and identify the others where it is appropriate to set them at a population-average. Once a patient-specific model is made, the clinicians can perform multiple digital 'treatments' to assess their respective outcomes. However, since there is always a degree of uncertainty in the input parameters, this also leads to a degree of uncertainty in the output of interest. This output uncertainty must be quantified and reported to the clinicians to inform them fully of the predictive capabilities of the model.

What are the challenges of your work?

While sensitivity analysis and uncertainty quantification are powerful tools, they require a significant level of knowledge of the system to which they are applied, if they are to perform correctly. Furthermore, the results are not always easy to interpret and can therefore be hard to explain correctly and clearly.

What do you do in your free time?

I love sports and exercising. I exercise 5/6 days week, and am currently training to run a half marathon. I also love to travel, and going hiking/camping. But fortunately I know how to relax as well, and like going for a beer with friends or staying at home and watching movies and series on Netflix.

Dissemination

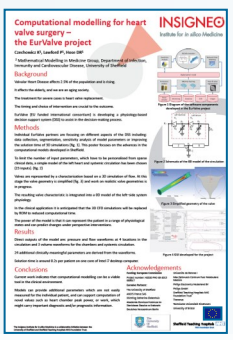
Insigneo Institute Showcase, Sheffield May 2017

Marco Viceconti, Executive Director cutting the "birthday cake"

Over two hundred people attended Insigneo's fifth birthday as Europe's largest academic institute devoted entirely to the development of *in silico* medical technologies. The event was celebrated in May this year at the Octagon Centre, The University of Sheffield.

The day featured:

- Displays of the high-quality research carried out at the Institute;
- An Industrial Village showcasing *in silico* medicine's latest commercial applications;
- Talks covering the full scope of our research, from fundamental science to translation and from clinical implementation to industrial development.



EurValve was represented both by a poster by Krzysztof Czechowicz entitled: *Computational Modelling for Heart Valve Surgery* and an oral presentation by Professor Pat Lawford entitled: *Modelling of Diseased Heart Valves*.

EurValve Information

Project title	**EurValve—Personalised Decision Support for Heart Valve Disease**
Project Number	**689617** **Total cost: €4 998 012,51**
Start date	**01/02/2016** **End Date: 31/01/2019**
Coordinator	**The University of Sheffield**
Partners	**ANSYS**
	Catharina Hospital
	Cyfronet AGH Krakow
	The German Heart Institute Berlin
	University of Rennes 1 - LTSI
	Philips Eindhoven
	Max Delbrück Centre for Molecular Medicine
	Philips Hamburg
	Sheffield Teaching Hospitals NHS Foundation Trust
	Therenva
	Technical University of Eindhoven
	University of Bristol

Find out more about EurValve on our website: **www.eurvalve.eu**

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https://ec.europa.eu/digital-single-market/ehealth