Cardiovascular Models for Personalised Medicine: Where Now and Where Next?

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Abstract

The aim of this position paper is to provide a brief overview of the current status of cardiovascular modelling and of the processes required and some of the challenges to be addressed to see wider exploitation in both personal health management and clinical practice. In most branches of engineering the concept of the Digital Twin, informed by extensive and continuous monitoring and coupled with robust data assimilation and simulation techniques, is gaining traction: the Gartner Group listed it as one of the top ten digital trends in 2018. The cardiovascular modelling community is starting to develop a much more systematic approach to the combination of physics, mathematics, control theory, artificial intelligence, machine learning, computer science and advanced engineering methodology, as well as working more closely with the clinical community to better understand and exploit physiological measurements, and indeed to develop jointly better measurement protocols informed by model-based understanding. Aspects of developments in physiological modelling, model personalisation, model outcome uncertainty, and the clinical decision support based on this, will be addressed and 'where-next' steps and challenges will be discussed.

Introduction

Cardiovascular models can be categorised by their purpose and by their dimensionality. Patient-generic models can be used for hypothesis creation, mechanistic understanding, device evaluation or educational purposes. Patient-specific models can be diagnostic, in that they can return characteristic, quantitative measures that might immediately be interpretable to categorise a physiological or pathophysiological state. They can also be predictive: they can forecast how the state will evolve, with or without an intervention. In this position paper, we will focus on the current-state-of-the-art and the future challenges when using cardiovascular models for personalised medicine. Figure 1 illustrates some of the considerations that need to be addressed when specifying and deploying a cardiovascular model depending on its purpose. There are several challenges in the integration of modelling into a clinical workflow. These include:

- Identification of direct inputs to models in data captured in the clinical process (contributing to model personalisation)
- Identification of direct outputs from models in data captured in the clinical process (contributing to model validation)
- Personalisation of model input parameters to reproduce model output parameters that are clinically observable in test cohort [optimisation processes]
- Association of personalised model parameters with wider data in clinical record (e.g. is resistance and/or compliance associated with age, or body mass index, or co-morbidities such as diabetes?) [exploitation of machine learning processes for model personalisation and model interpretation]
- Development of a principled approach to representation of the physiological envelope for individual patients

The above issues are specifically with regard to the challenges of model personalisation, but before this step there are many considerations at the pre-clinical stage. Issues like the selection of appropriate rheological models for blood and generic model and code verification are usually addressed before personailsation is attempted.

History

Zero-dimensional, or lumped parameter, models divide the system into compartments within which the fundamental variables are assumed to be uniformly distributed and vary only with time. The governing equations are ordinary differential equations. These models can be used to represent the whole cardiovascular system physiology or any portion of it. The physiological parameters of pressure, flow and volume can be considered equivalent to voltage, charge and current in electrical analogy models. A comprehensive review of the components of models of this type has been published by Shi et al [1]. These models are readily extended to include the representation of control mechanisms, chemical species concentrations and pharmacokinetics processes. Some of the oldest and most comprehensive systems physiology models are those published by Guyton[2]. More recently these types of models have been integrated with similar 0D systems biology models including the representation of biochemical and electromechanical processes at cellular level. Important early work to include control mechanisms, and to illuminate processes like haemorrhage, was published by Ursino [3]. A very comprehensive set of cardiovascular physiology models, including cellular and cardiac components and including the systems physiology models of Guyton, has been curated and made publicly available through the Cell-ML initiative of the ABI in Auckland[4]. This facility includes

tools for the solution of the ODEs and has been one of the most important initiatives of the last two decades in the context of standardisation, documentation, ontological representation, curation and portability of cardiovascular systems. There are currently many hundreds of models in the CellML repository, with over 50 circulation models ranging from the simplest with fewer than ten elements to high hundreds.

One dimensional models are used to describe vascular components in which distribution of quantities along the vessel axis are important, and are essential when wave effects, including transmission and reflection characteristics, are important. The vessels are represented by partial differential equations in time and one spatial dimension. It has been shown formally by Milišić and Quarteroni, [5] that in the limit an assembly of 0D models can approximate a 1D system. A comprehensive review of 1D modelling, including the fundamental mathematics and the major published vascular tree models (typically numbering of the order of 100 to 500 components), has been published by van de Vosse and Stergiopulos [6], complemented by a benchmark study of numerical schemes by Boileau et al [7]. Often these models are coupled with 0D representations of the heart (variable elastance or single fibre models) to produce closed-loop systems.

The first three-dimensional models of cardiovascular components were performed in the early 1980s when it became possible to solve the governing equations of fluid mechanics on large 3D meshes. Most commonly the solution processes were based on finite volume or finite element discretisations of the Navier-Stokes equations, using custom-written or commercial CFD code. In the earliest applications the 3D domains were often simplified and idealised but over three decades, in parallel with the development of increasingly powerful medical imaging, more and more detailed models were developed and published. More recently some groups used alternative mathematical representations, including for example Lattice Boltzmann formulations [8][9] that might have advantages for some domains, but overwhelmingly NS solvers have been dominant in cardiovascular applications.

In the late 1990s and early 2000s there was increasing recognition that, as captured in the context of vessel mechanics by 1D models, the cardiovascular fluid domains are not geometrically frozen but are bounded, or separated, by flexible structures. This led to an explosion of 3D fluid-solid interaction models, based on a range of mathematical formulations for the coupling between solid and fluid domains. Stand-out applications for these methods included cardiac mechanics, with one of the first publications by Peskin [10], and heart valve mechanics, described by de Hart [11].

Apart from the physics involved and the way it is represented (0D, 1D or fully 3D) also material properties and especially the constitutive behaviour of blood and cardiovascular tissue is determinant for the outcome of the models. For vascular tissues important progress has been made recently [12].

Where Now?

The Virtual Physiological Human

A major impetus for computational physiology was provided by the European Commission's Virtual Physiological Human initiative, which saw the investment of over 250M€ over an eight year period. A White Paper, authored by opinion-formers in the community, was published in 2005 [13], and this was followed by the publication of the Roadmap to the Virtual Physiological Human [14][15] , which was based on widespread consultation with the contribution of over 300 active researchers. An overview of the goals of the VPH initiative was published in [16], with an update in 2012 [17].

In the context of vascular applications, a precursor to the VPH was the @neurIST project [18], which featured many of the elements that would become core parts of the community efforts. The focus was on diagnosis and treatment of aneurysms in the cerebral circulation, and one of the drivers was the increased incidence of detection of such aneurysms from advances in medical imaging. A workflow was developed to segment the medical image, to produce a mesh suitable for 3D computational fluid dynamics analysis to apply appropriate boundary conditions, based on coupling with a circulation model extended to include the neurovasculature, to solve the equations and to extract potential diagnostic measures from the 3D solutions [19]. This European initiative mirrored in several aspects the work of Cebral and his collaborators [20] in the United States. @neurIST also formalised the digital representation of all relevant aspects of the patient data in its Clinical Reference Information Model [21], incorporating over 2300 data items and the beginnings of an ontology for this application. It also produced a prototype clinical decision support system to present information to a clinical end user, integrating model outputs with clinical guidelines.

Some of the largest and most successful projects in the VPH initiative were focused on cardiac mechanics: euHeart [22][23] Health-e-child [24] and VP2HF [25] were notable examples. All of these were based on exquisitely detailed medical imaging of the heart, coupled with systems physiology models for boundary conditions, and targeted at the primary aims of the VPH; effective diagnosis, evaluation of individual prognosis and representation of the likely effects of potential interventions. Schievano et al [26] report an important and novel, first-in-man, valve application, and noted that their methodologies 'challenge the conventional stepwise pathway of bench and animal testing prior to human application, and may be safer and more relevant, potentially reducing the number of animal experiments necessary for testing new medical devices'.

Model Personalisation

Zero-dimensional models with personalised parameters might have clinical utility in their own right in the context of diagnosis and data interpretation. This was explored in an important series of papers by Hann and collaborators [27][28] who described processes for the assimilation of clinical measurements, including time-series physiological data, in an optimisation process to personalise parameters in relatively simple systems physiology models. Potential diagnostic application in heart failure was published by Sughimoto et al [29], who demonstrated the separation of systolic and diastolic dysfunction in heart failure based on the personalisation of elastance parameters in a simple systems physiology model.

The VPH initiative exemplified one critical aspect of model personalisation, namely the description of the individual anatomy based on medical image data. Despite recognition of the importance of the boundary conditions [30], the VPH projects generally had lesser focus on this issue. The projects that were funded often included some rudimentary personalisation of the boundary conditions to match a few clinical measurements. Sometimes measurements of pressure and/or flow at the domain boundaries were integrated explicitly in the 3D models, and sometimes they were used to tune parameters in lower dimensional model representations that were coupled at the boundaries. One of the most important projects to pioneer the latter process in the VPH initiative was the ARCH project in renal dialysis [31–34].

There is increasing recognition that model personalisation needs to be much more than anatomical personalisation, and it was evident that the tuning of integrated 3D/0D models to reproduce measured clinical data was a continuous and pervasive theme at the World Congress of Biomechanics in Dublin in 2018 [35]. This was presaged by the observation by Irene Vignon-Clemental, at the International Conference on CFD in Medicine and Biology in Albufeira in 2015

that ‘we are seeing a return to simpler models for clinical interpretation’. Marquis et al [36] have published a rigorous examination of the personalisation process as applied to a pulsatile cardiovascular model.

Whether personalised 0D models are used independently or as part of multi-scale models, it is often the case, especially in a routine clinical pathway, that physiological measurements that might support a model personalisation process are sparse (e.g. [37]). It is generally true that a personalisation strategy will be most robust when the number of parameters to be personalised is relatively small, perhaps fewer than ten, and even the most parsimonious systems model has many more parameters. An important element of a personalisation strategy is the identification of the model input parameters to which the target output parameters are most sensitive. In this context the target outputs include both those that are measured and used for personalisation (to improve the robustness of the personalisation step) and those that are used for diagnostic interpretation. In practice sensitivity analysis must be an integral part of a personalisation process.

A special type of measured data is time-series data, when a parameter is measured at multiple time points in the cardiac and/or respiratory cycle. These are often collected in clinical research protocols, and are much richer in information than the extrema (e.g. systolic and diastolic pressure) that are more usually collected in routine clinical pathways. Time series volume and flow data is increasingly available from modern dynamic medical imaging protocols. There has been enormous progress on the mathematical and theoretical underpinning of the process of data assimilation of rich, time series, clinical data. A very promising approach uses unscented Kalman filtering to personalise the parameters in systems physiology models, including in the context of boundary conditions for 3D models [38–41]. This can be extremely important in situations in which a computational model is used to represent accurately the haemodynamics in the measurement state, perhaps to extract additional parameters that are not directly measured. It might also be very valuable when the aim is to personalise model parameters for subsequent use in simulations of predicted changes under an intervention.

Recognition of Model Uncertainty

One of the major advances for the cardiovascular modelling community in the last decade has been the formal evaluation of model sensitivity and uncertainty [42–45]. Increasing recognition of the importance of this topic, and the transatlantic community effort to address the challenges, was underlined at the INI Fickle Heart workshop held in June 2019 at the Newton Institute in Cambridge [46]. It has been suggested that ‘1) if you don’t acknowledge any uncertainty in the model predictions, why would anyone take you seriously? 2) Model predictions are useless without a quantification of their uncertainty ‘.

Clinicians are used to dealing with uncertainty in their decision processes, but often model-based applications return quantitative parameters based on deterministic simulations with no indication of the effects of propagation of uncertainties in the clinical data that underpins the model through to the model measurements and predictions. This needs to become an integral part of the modelling process, and part of any reported results in a decision support system.

Acute v Long-Term Outcome

One of the primary benefits of modelling is its predictive capacity. It is able to predict how a state will evolve both with and without an intervention. Generally, although not without challenges including the representation of the body’s homeostatic mechanisms, the prediction of the short-term response to an intervention is massively easier than prediction of the longer-term response.

The latter inevitably includes biological remodelling processes that produce profound additional layers of complexity. There are many challenges in the representation of biological pathways, and it is in this sector of research that we need to do much more to recognise the influence of the genotype and the way that it governs many of the responses to physiological states. The patient phenotype is a combination of all information that is known about an individual, layering physiological characterisation on top of the underlying genotype. Our society is increasingly conscious of the benefits of improved lifestyles, and we believe that modelling can play a critical role in understanding the evolution of the phenotype under all types of intervention. Phenotypic plasticity is often measured in large-scale trials, for example of the benefits of exercise, including at public health levels, but modelling has the capacity to promote understanding of causative associations. We are seeing real progress in the representation of the underlying processes of remodelling of the vascular wall [45,46], and even some examples in patient geometries [49], but there is much to do to integrate more personalised structural and genotypic data into the process.

Clinical Decision Support

A review of the challenges of clinical translation of cardiovascular models was published by Huberts et al [50]. These included:

- the identification of the calculations that are of most direct interest to the medical doctor,
- the identification of the right level of complexity of a model for a particular purpose,
- the importance of verification and validation,
- the need to work in a complex legal and regulatory framework.

The importance of the latter points, as well as the recognition by the regulatory authorities of the potential of simulation, is emphasised by the leadership and engagement of the US Food and Drug Administration with the ASME V&V40 initiative [51]. An excellent review of many of the relevant issues is presented in [52]

One of the important issues to consider in designing a clinical decision support system is that of resource, both in terms of man-time and compute time. There is always a trade-off between level of automation and robustness, although of course automation can eliminate intra- and inter-observer variability. Compute resource is often not the limiting step in the modern world, although still the execution time for a full fluid-solid interaction analysis might take many days even on high performance computing resource. What is acceptable depends on the clinical scenario. If decisions are taken over a period of days or weeks then a remote service might be appropriate, such as that commercialised in the context of coronary FFR by HeartFlow (https://www.heartflow.com/) in perhaps the most prominent and successful application of model-based predictive clinical decision support in the cardiovascular sector.

If results are required during the course of a single clinical visit or procedure then it is likely that the computations might need to be performed locally, perhaps on the clinical workstation. Such scenarios are commonplace in the clinical environment, and this makes it a fertile area of application for reduced order models. In the last few years there have been tremendous advances in the application or reduced-basis models. A comprehensive introduction to the reduced-basis approach is published by Lassila et al. [53]. Other approaches that might fall under the general terminology of a reduced order model include lower order (0D or 1D) models, which have underpinned systems physiology models for many years, and meta-models, which seek to capture the model behaviour in a simpler model that is fitted to data produced by the full moel . Gaussian

process emulators have also seen an upsurge of interest in the cardiovascular sector in the last five years [54]

Coronary Fractional Flow Reserve as an Exemplar of Personalised Physiological Modelling

Perhaps the most successful penetration of cardiovascular modelling tools into clinical application is in coronary modelling. Coronary fractional flow reserve (FFR) [55] is a measure of the capacity to increase flow to an affected area of the myocardium by removing the blockage caused by a coronary stenosis. It is based on a very simple ratio of the pressure distal to the diseased segment to the proximal pressure. The computation of this parameter exemplifies many of the issues in personalised physiological modelling and its translation to clinical application.

- The importance of FFR is that it does not simply characterise the local anatomy in isolation. It is a physiological measure. It has long been known that tighter lesions, characterised by a greater percentage blockage of the artery, generally have greater effect on the patient and cause more symptoms. However for the same anatomical blockage, some patients see more benefit from the treatment of the lesion than others. The reason is that the flow to the myocardium is determined not only by the resistance of the artery in which the lesion is observed but also by the resistance of all of the distal arterial and microvascular structures that it supplies. In the simplest representation, for steady flow, there are two resistances in series, and the important question is how significant the first resistance, that of the diseased artery, is to the overall resistance. This very simple model leads to the hypothesis that the ratio of distal to proximal pressure, under hyperaemic conditions, might be indicative of the capacity to restore flow by removal of the resistance in the coronary artery. Measurement of the pressure ratio requires passage of a pressure wire through the lesion, a process that is invasive and not completely without risk. If the coronary artery can be segmented from medical image data, and an estimate of the personal myocardial resistance can be made, then FFR can be computed. This requires the coupling of a local three-dimensional model (or, indeed, a one dimensional model [56][57]) of personal coronary anatomy coupled to a personalised model of the distal resistance. Morris et al [58] review the challenges and limitations of the computation of FFR, including the question of the estimation of distal resistance in an individual.
- Noninvasive computational estimation of FFR is an example of the diagnostic capacity of a model. It produces a measure of the consequence of the disease in the reduction of flow. It is also predictive: the same measure is used to estimate the ratio by which the flow might be improved under an intervention. Because the model describes the system more comprehensively than the simple two-resistor model on which the concept is based, it can more accurately estimate the capacity for flow improvement. Inevitable there is some residual local resistance in the artery after treatment, and this can be simulated in the same way as the diseased artery. It is possible to include a very detailed model of the intervention, for example the deployment of a stent and the interaction with the wall [59–62], including the contact mechanics in the deformable system if this is justified for the application.
- A major challenge in clinical translation is that very often the model produces measures that are hypothesised to be important, but there simply is not the clinical trial basis to prove the association between the model measurement and clinical diagnosis or outcome. This was very apparent in the @neurIST project outlined earlier. @neurIST produced a series of morphometric, structural and haemodynamic characterisations of a cerebral aneurysm that, based on our understanding of the physics and biology, ought to be associated with the risk of rupture of an individual aneurysm. For example complex, undulating shape, local wall stress

concentrations and physiologically abnormal wall shear stress might all be indicative of risk. @neurIST spent 15M€ to develop a comprehensive computational process to estimate indices derived from these parameters, and characterised of the order of 300 aneurysms using these tools. However the incidence of rupture is low, and the investment in the computational workflow is very small relative to what needs now to be invested to cement the associations between these novel indices and clinical sequalae. In contrast, there is a wealth of clinical trial data [63][64] that has proven that clinical outcome is improved if a coronary fractional flow reserve is used to guide the decision on intervention. This has made computation of FFR a real low-hanging fruit for computational physiology. It did not have to be proved that a new computational measure had value, only that a computational measure could serve as an adequate surrogate for an invasive measure that was already recognised. Several studies have reported this association for models derived from CT [65][66] and angiographic [67][68] image data.

- A further challenge in the invasive measurement of FFR is that, at least in its original concept, for diagnostic interpretation the pressure measurements should be made when the effect of the disease is most apparent – i.e. during hyperaemia (maximal flow). This is induced by administration of a drug, also not without potential drawbacks or complications. If the effect of the drug can be simulated adequately then this can also be included in the modelling process. This also raises the more general issue of simulation of non-rest conditions in all sorts of applications. This was recognised by Marsden et al [69] over a decade ago, who proposed that respiration and exercise should be incorporated into CFD simulations for realistic evaluation of system performance in congenital heart defects [70–72], but outside this application there is relatively little literature on the systematic extrapolation of personalised models to multiple physiological states.

EurValve: Applying the Lessons Learned

The recently-completed EurValve project [73][74] reflects many of the lessons that we have learned are important for cardiovascular modelling in clinical decision support. The aim was improved clinical decision support for aortic and mitral valve disease. The disease targets were aortic stenosis and mitral regurgitation. In either case the heart works harder to maintain flow. The underpinning hypothesis (echoing the philosophy of coronary FFR) was that it is not the local anatomical severity of the disease that is important but rather its effect on the overall physiology. Left ventricular work and/or peak power might be important diagnostic measures. These parameters can be estimated from a personalised systems physiology model. A prediction of the reduction in these measures associated with an intervention might represent a clinically-relevant quantitative measure of the potential benefit. Furthermore the derived personalised parameters might have diagnostic or prognostic capacity in their own right. An overview of the components of EurValve, highlighting the integration of a core data and compute infrastructure with computational modelling and clinical elements, is illustrated in Figure *2*.

The current diagnostic process was reviewed, cataloguing all of the measurements that are made, under what conditions. A series of tables was assembled to list the parameter, or concept, and its units. Snapshots are illustrated in Figure 3. This immediately clarified very obvious issues, such as the fact that blood pressure might be measured very many times under variable conditions. Other measurements, for example volume or flow measures, were often made under very different physiological states, and there is a recognised inconsistency between measures made using different imaging modalities. A similar table of computational concepts was generated and mapped onto the clinical concepts.

The analysis steps in EurValve exploited many of the methods referenced previously. The most parsimonious model that was able to represent the most important clinical concepts, including cardiac energetics parameters, was identified and a tuning process was developed to personalise the parameters. The primary protocol was based on a characterisation of the valve from 3D computational fluid dynamics analysis based on segmented medical image data. The decision was taken that the decision support system, including valve and system characterisation, should be operable within a single clinical visit. The first operation was segmentation of the valve and local portions of the chambers and aorta as appropriate. Then a series of steady state simulations was run (with an open, stenotic, aortic valve or a closed, regurgitant, mitral valve) to characterise the relationship between pressure drop and flow in the appropriate state for the disease process. This characterisation was integrated with the personalised systems model to 'measure' the pressure, volume and flow distribution. The total execution time was of the order of fifteen minutes. EurValve also pursued a novel approach that we believe might be the future for integration of sophisticated modelling into clinical decision support systems at the point of care. This exploited Reduced Order Modelling (ROM) technology from ANSYS, based on a reduced basis re-formulation of multiple CFD analysis results. The valve and local geometry was parameterised, so that the full 3D geometry could be reconstructed from something of the order of ten or twenty parameters. The solution space was characterised by performing very many simulations across the parameter space and using sophisticated methods to interpolate within this space for any new geometry. With this method the primary computational burden is moved off line, and in this case the simulations were performed on the Prometheus supercomputer in Cracow in Poland. The resulting ROM was installed on a local machine and could return the flow for a given pressure gradient for a new case, as part of the simulation process, in less than one second.

The next step was to decide what simulations to run for an individual. We would argue that the most appropriate boundary conditions for a simulation are not necessarily, indeed not likely to be, those that are measured in the clinic. Most clinical measurements and images are collected in a rest state and/or supine, which might have very little to do with the conditions under which the disease is manifest, especially for cardiovascular conditions in which symptoms are usually associated with exertion. In the EurValve clinical cohort the individuals were monitored, using the Philips Health Watch, over a period of up to two weeks prior to the valve intervention to determine their maximum heart rate as they went about their lives. The model was personalised to the clinical measurements in the rest state, but a process was developed to extrapolate to the exercise state based on published literature for the association between parameters such as LV elastance and heart rate. The model prediction included the reductions in these measures under intervention in both rest and exercise states. There is primary clinical interest in whether these predictions might be reflected in improvement of current outcome measures, such as improvements in the six-minute walk test.

The ultimate goal of EurValve was to produce a comprehensive decision support tool, and this included further components that are out-of-scope for this article but important in the global context. These included presentation of the clinical guidelines interpreted for the individual and a module for Case-Based Reasoning so that the user could find similar cases and examine the decisions that were taken and the outcomes. The efficient computational supported the routine operation of the modelling process, including model personalisation (integrating heart rate data), characterisation of rest and exercise states, and prediction of the physiological effect of a candidate intervention. Analysis was performed for over 120 individual patients, from three clinical centres. Typical 0D model execution time for one case was under five minutes. Detailed reporting of the results is out-of-scope for this overview article, but a summary of statistics for personalised

elastance parameters at rest is presented in Figure *4*. It is immediately apparent that there is greater variation in the mitral cohort, and that the values for the aortic cohort are closer to the normal range. It remains to be seen whether these integrated model-based characterisations are diagnostic of the severity of the disease or prognostic of outcome, but it has been proven that they can be performed in a relatively routine process in tractable timescales.

Where next?

We believe that the fundamental engineering and imaging technology will continue to develop apace. The balancing of the timescales of clinical pathways with computational and quality assurance requirements when presenting clinical decision support is very problem specific. Where the clinical pathway allows there is great merit in a service model in which the clinical team uploads data for remote analysis (already relatively routine in clinical service for radiological reporting of medical image data and now offered by Heartflow for model-based clinical decision support for a coronary application). The potential of reduced-basis ROMs, developed offline using major computational resource but implemented on local infrastructure (including potentially on imaging hardware in the hospital), has already been introduced, and it can be imagined that a new service sector could develop to produce ROMs for all types of clinical applications in the future.

Many of the attempts to personalise system parameters in cardiovascular models have used optimisation or filtering techniques from the engineering community. Most recently there have been increased efforts to deploy machine learning techniques from the artificial intelligence community. Essentially these seek to learn the model from the data rather than to apply a model to compute outputs from inputs. We believe that the integration of these methodologies will produce major breakthroughs in model personalisation, perhaps by using a model to reduce the machine learning challenge and perhaps by learning model parameters form large clinical datasets. This latter function might be particularly useful in situations in which associations exist between observations or parameters, but they are not clearly quantified. An example is the influence of co-morbidities such as diabetes on parameters including microvascular resistance. Although AI and hybrid methods can be extremely powerful, and offer huge potential, it is recognised that the ‘black box’ nature poses additional challenges in the context of verification and validation.

A major deficiency in the whole field of personalised modelling is the capacity to decide on the most appropriate set of simulations for an individual, and the capacity to interpret the results. When designing an aircraft there is a fundamental process of specification of the flight or service envelope. It is known what challenges that aircraft will be subjected to, and the stresses, strains and fatigue life are evaluated accordingly. We do not seem to have any similar concept of a ‘physiological envelope’ to represent formally the excursions that an individual might make, in what proportions, as they go about their lives. These considerations are included intuitively, and sometimes implicitly or explicitly in clinical guidelines, in the clinical decision process but not in any formal sense in the modelling process. We believe that the characterisation of this envelope will be a significant step forwards in the exploitation of the power of personalised computational cardiovascular models. There is much to do to evaluate how different states accumulate to produce change, for example the difference between intense exercise interval training and more moderate continued exercise, and to develop algorithms to represent the biological processes of remodelling, whether negative or positive. These do exist, but they are not mature. For engineering materials we have cumulative damage rules that can be applied over a duty cycle [75], but generally there is not the data to support physiological system equivalents.

The concept of the digital twin is already becoming reality in applications such as the continuous monitoring, data assimilation and simulation of aircraft engines. We can imagine a future in which a personal digital twin continuously assimilates data streamed from wearable devices [76]and other pervasive instrumentation to produce characteristic and diagnostic measures and to underpin predictive simulations of the effects of all types of interventions, from lifestyle through to medical and surgical options. There are special challenges for clinical application with respect to the consistency and accuracy of medical data. As discussed previously, often the same parameter is measured multiple times and under different protocols: it is recognised that many clinical measurements are very dependent on the details of the modality and of the measurement protocol, which can be different across clinical centres (with variable degrees of calibration), and are often subject to inter- and intra-observer variability. It is not unusual that the modelling community produces excellent and predictive results using data from carefully designed research trials using state-of-the-art measurement technology, but the benefits do not cascade to clinical practice because of the practicalities of routine clinical measurements constrained by economic and time considerations. We would suggest for successful model-based clinical decision support it is imperative that data accuracy and reproducibility, or data certification [77], is considered when developing the processes for interpretation and presentation to clinical end users – and that part of this is the propagation of measurement uncertainty through the predictive models.

The modelling of cardiovascular physiology is just one part of a broader perspective, but it is representative in many ways. The community is moving towards a causally cohesive multiscale and multiphysics representation of human physiology that will capture what we know at a given time, and will continuously evolve as it is confronted by huge amounts of experimental, genotypic and phenotypic data. This digital twin will run, eat and age. It will integrate enormous amounts of empirical data and physiological insight into a functional and causal whole across scale, space and time, thereby functioning as a highly efficient synthesiser of intellectual capital from various disciplines.

Figures and Tables

Aims	**Anatomy**	**B.Cs**	**Challenges**
Fundamental Understanding	Idealised, Generic or Individual	Population or Individual	Accurate physics, chemistry, biology, … Segmentation (3D, 4D (?)), Ethics, data access, data sharing (anonymised?)
Device Design	Idealised, Generic or Individual	Population or Individual	As above
Establish Associations for Clinical Interpretation	Individual	Individual	Representation of physiological envelope, how to extrapolate from measurements/clinical record data to physiological risk states & how to accumulate information from multiple states (physiological/biological Miner's Law ….)
Diagnosis and Interventional Planning (not time critical)	Individual	Individual	**Efficiency (man time)** Efficiency (computer time)… optimal accuracy ? & available computational resource, if remote resource - data security (pseudonymised?)
Diagnosis and Interventional Planning (time critical)	Individual	Individual	**Efficiency (man time)** **Efficiency (computer time)… *sufficient* accuracy ?** & available computational resource, if remote resource - data security (pseudonymised?)

Figure 1: Considerations in Model Specifications for Cardiovascular Simulation (the most important considerations are shown in **bold**)

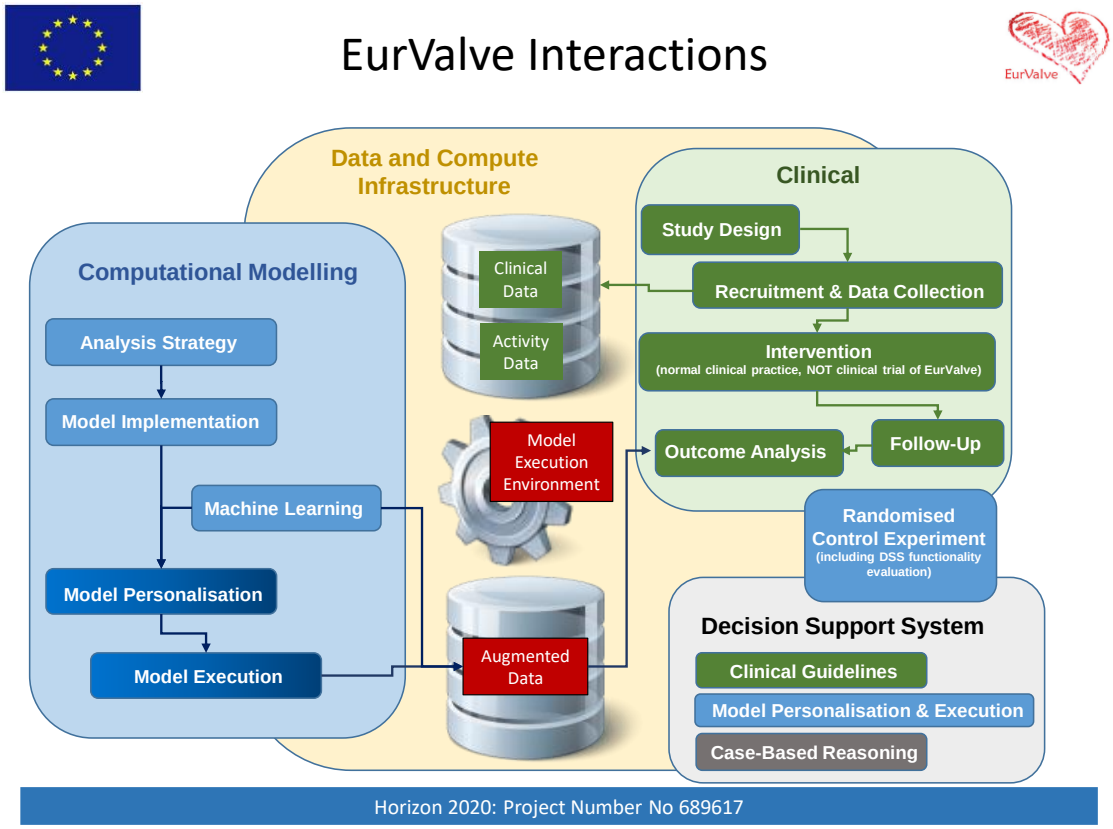
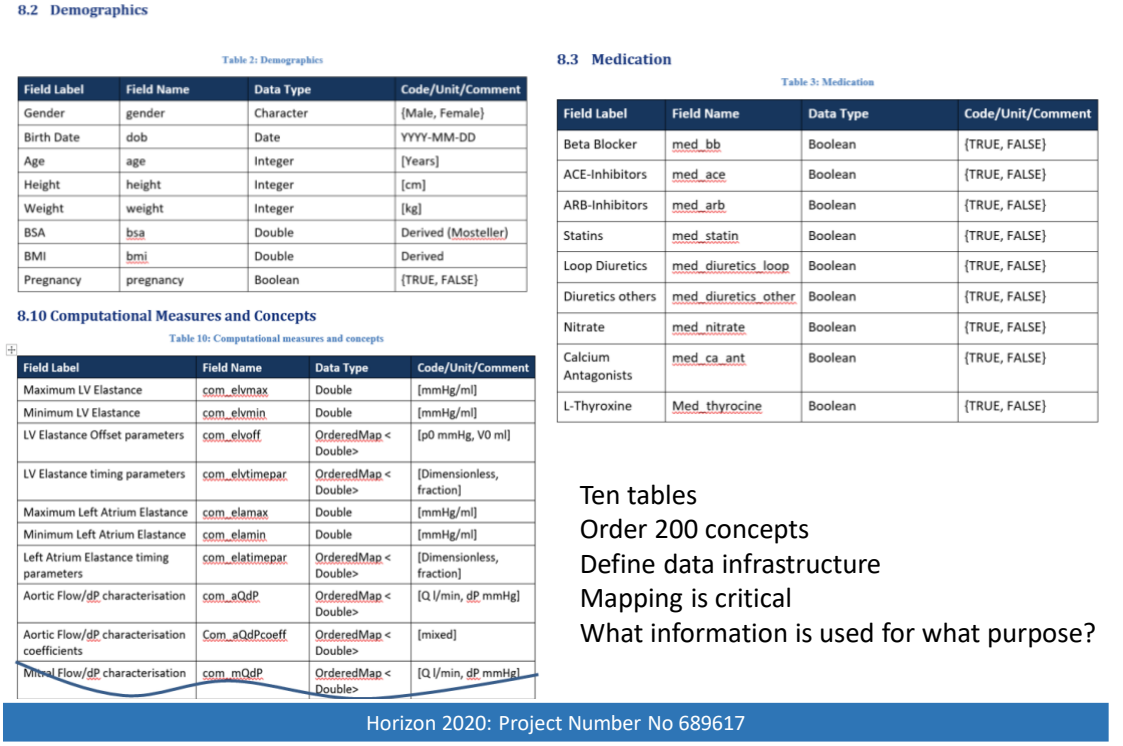


Figure 2: Illustration of Component Interactions in Development of a Model-Based Clinical Decision Support Environment



8.2 Demographics

Table 2: Demographics

Field Label	Field Name	Data Type	Code/Unit/Comment
Gender	gender	Character	{Male, Female}
Birth Date	dob	Date	YYYY-MM-DD
Age	age	Integer	[Years]
Height	height	Integer	[cm]
Weight	weight	Integer	[kg]
BSA	bsa	Double	Derived (Mosteller)
BMI	bmi	Double	Derived
Pregnancy	pregnancy	Boolean	{TRUE, FALSE}

8.10 Computational Measures and Concepts

Table 10: Computational measures and concepts

Field Label	Field Name	Data Type	Code/Unit/Comment
Maximum LV Elastance	com_elvmax	Double	[mmHg/ml]
Minimum LV Elastance	com_elvmin	Double	[mmHg/ml]
LV Elastance Offset parameters	com_elvoff	OrderedMap < Double>	[p0 mmHg, V0 ml]
LV Elastance timing parameters	com_elvtimepar	OrderedMap < Double>	[Dimensionless, fraction]
Maximum Left Atrium Elastance	com_elamax	Double	[mmHg/ml]
Minimum Left Atrium Elastance	com_elamin	Double	[mmHg/ml]
Left Atrium Elastance timing parameters	com_elatimepar	OrderedMap < Double>	[Dimensionless, fraction]
Aortic Flow/dP characterisation	com_aQdP	OrderedMap < Double>	[Q l/min, dP mmHg]
Aortic Flow/dP characterisation coefficients	Com_aQdPcoeff	OrderedMap < Double>	[mixed]
Mitral Flow/dP characterisation	com_mQdP	OrderedMap < Double>	[Q l/min, dP mmHg]

8.3 Medication

Table 3: Medication

Field Label	Field Name	Data Type	Code/Unit/Comment
Beta Blocker	med_bb	Boolean	{TRUE, FALSE}
ACE-Inhibitors	med_ace	Boolean	{TRUE, FALSE}
ARB-Inhibitors	med_arb	Boolean	{TRUE, FALSE}
Statins	med_statin	Boolean	{TRUE, FALSE}
Loop Diuretics	med_diuretics_loop	Boolean	{TRUE, FALSE}
Diuretics others	med_diuretics_other	Boolean	{TRUE, FALSE}
Nitrate	med_nitrate	Boolean	{TRUE, FALSE}
Calcium Antagonists	med_ca_ant	Boolean	{TRUE, FALSE}
L-Thyroxine	Med_thyrocine	Boolean	{TRUE, FALSE}

Ten tables
Order 200 concepts
Define data infrastructure
Mapping is critical
What information is used for what purpose?

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Figure 3: Snapshot of Data Tables supporting EurValve Information Model [78]

	Elvmin		Elvmax	
	Aortic	Mitral	Aortic	Mitral
Median	0.10	0.15	1.55	2.90
Mean	0.11	0.17	1.71	3.32
STDEV	0.03	0.09	0.75	2.05

Figure 4: Statistics for Personalised Elastance Parameters in Left ventricle Model for Aortic Stenosis and Mitral Regurgitation Cohorts (120 individuals in total)

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