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Clinical diagnostic biomarkers from the personalization of computational models of cardiac physiology

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Abstract

Computational modelling of the heart is rapidly advancing to the point of clinical utility. However, the difficulty of parameterizing and validating models from clinical data indicates that the routine application of truly predictive models remains a significant challenge. We argue there is significant value in an intermediate step towards prediction. This step is the use of biophysically based models to extract clinically useful information from existing patient data. Specifically in this paper we review methodologies for applying modelling frameworks for this goal in the areas of quantifying cardiac anatomy, estimating myocardial stiffness and optimizing measurements of coronary perfusion. Using these indicative examples of the general overarching approach, we finally discuss the value, ongoing challenges and future potential for applying biophysically based modelling in the clinical context.

Keywords: Cardiac Computational models, Clinical biomarker, anatomy, myocardial stiffness, coronary flow.

Introduction

The last 15 years has seen the intensification of efforts to develop clinically relevant computational models whose structure is directly linked to physiological mechanisms (Winslow et al. 2012). This work has been motivated by the objective of quantitatively predicting the behaviour of biological systems based on the integration of physiological understanding and clinical data. Based on general philosophies first formally organized and articulated in the IUPS sponsored Physiome Project (Hunter & Borg 2003), the VPH initiative has since sharpened the clinical focus of this community (Smith et al. 2011).

Within these programmes the heart has been, and arguably continues to be, the most advanced current exemplar of an integrated organ model for a number of reasons. Specifically, indicative of the relative simplicity of the heart is the well-characterized physiology of the cardiac system. This understanding has underpinned some of the very early exemplars of biophysically based models (DiFrancesco & Noble 1985) which, in turn, have provided a foundation on which many more complex frameworks have been developed (Clayton et al. 2011). Furthermore, while physiologically simple, the multi-physics function of the heart governed by nonlinear electrical-, mechanical- and fluid- dynamics has attracted a wide spectrum of researchers working at the interface between life and physical sciences. Finally, the links between health and heart function are direct and significant with cardiovascular disease remaining the number one cause of morbidity and mortality in the majority of western economies (Finegold et al. 2013).

In parallel with, and independently of, advances in the fields of experimental physiology and computational modelling, the extraction of novel diagnostic biomarkers has been driven by progress in biomedical signal acquisition and analysis (see Fig. 1), more predominantly in

medical imaging (Lamata, Casero, et al. 2014). In many cases the speed of development of large classes of imaging modalities has been remarkable with spatial and temporal resolution rapidly improving. In many situations these improvements have driven the rapid translation of a modality from the domain of the basic scientist to that of the practicing clinician. Specific cardiac examples mean that measurements of cardiac wall motion, chamber flow patterns and coronary perfusion are increasingly being used to provide high-resolution data sets for characterizing patients.

In addition to being directly visualized and qualitatively analysed, these data are also being examined using tools that extract a range of metrics including examples such as cardiac strain maps, regional metabolism and chamber flow rates. The impact from these technologies has been both immediate and clinically significant. Biophysically based studies successfully providing clinical metrics range from the imposition of modelling based constraints to detailed computational models. Specific examples include the use of the large deformation assumption of incompressibility to regularise deformation fields in image registration algorithms (Shi et al. 2012)) or with increased complexity, compartmental models to quantify perfusion parameters from dynamic studies (Tofts et al. 1999), computational fluid dynamics to compute the virtual fractional flow reserve (Min et al. 2012), and the electro-mechanical models to predict the outcome of cardiac resynchronization therapy (Sermesant et al. 2012).

However, in part because of the evidence-based focus of clinical medicine, the majority of extracted metrics continue to be analysed within phenomenological frameworks involving large patient cohorts. This practice arguably misses opportunities to extract the full value of information when integrated with established physiological understanding and patient-specific contexts.

Figure 1 about here

Efforts in parallel to apply biophysically based cardiac models in clinical contexts have also encountered other difficulties. In particular these include the critical development of a robust pipeline able to construct and solve models within clinical time scales. Embedded in this pipeline is also overcoming the challenge of deriving typically large nonlinearly related parameter sets from an individual's clinical data that, while increasingly comprehensive, continues to include significant variability and noise. Thus, despite significant work of a highly motivated community and many examples of progress, to date, instances of direct application of cardiac models in the clinic remain scarce.

This collective experience has revealed the size of a number of the challenges that remain to be overcome, and highlight that achieving this ultimate goal may still be some way off.

However, we argue that this evidence in no way devalues the goal of developing biophysically based models of whole organs and ultimately complete organisms in clinical contexts. In fact, what is now emerging from this work is a valuable set of tools that are increasingly being productively applied in a middle ground between image analysis and predictive computational modelling. Specifically this includes the application of geometric, physics and biophysically based computational modelling approaches to extract information embedded in clinical images but not directly assessable. In cases where this information has a strong link to clinical outcome, even if it is phenomenological rather than purely mechanistic, it has the potential to be valuable as a clinical biomarker. Furthermore, in many cases the extracted information is also valuable for informing the parameterization of fully predictive biophysically based models and/or defining boundary conditions. Specific examples include the calculation of pressure gradients from imaged fluid motion (Lamata,

Pitcher, et al. 2014), the determination of patterns of electrical activation from high temporal resolution cardiac motion maps (Rappaport et al. 2007), the estimation of vessel wall stiffness from velocity of pressure pulse wave transmission (Gaddum et al. 2015), and the computation of the fractional flow reserve without the need for catheterised measurements (Min et al. 2012; Morris et al. 2013).

Rather than document an exhaustive list, the scope of this review is to provide further tangible examples in more detail of this approach using the cardiac models developed within our group. Through this, our goal is to demonstrate the value of these methodologies and discuss the opportunities and challenges of model-based parameter extraction. We will start this review with the simplest case of a purely anatomically based analysis of cardiac geometry. In the following section we will introduce the application of a physics model to extract mechanical parameters from cardiac motion data. Finally we will present a framework focused on capturing the biophysics across multiple scales to directly interpret, and ultimately optimise the acquisition of, the image data itself.

Computational anatomy reveals hidden shape changes

Cardiac remodelling refers to a change in size, shape or microstructure of our ventricles as a consequence of either exercise or a myocardial disease/injury. This is clinically demonstrated in Infarcted hearts that experience thinning and weakening of walls with necrosis, and they become larger, less elliptical and more spherical. In a progressive disease like heart failure, ventricles follow a similar remodelling path of larger size and sphericity (Helm et al. 2006; Fedak et al. 2005). Cardiac shape (remodelling) is thus an important indicator to stratify and monitor disease and therapy progression, and it is mainly characterized through changes in blood pool volume, sphericity or myocardial mass⁵⁷.

However, these metrics, although robust and well established, offer a limited representation of the variability of cardiac anatomy that is currently captured by conventional imaging modalities (US, MRI, CT).

The core concepts used for the extraction of shape biomarkers are framed within the field of research called Computational Anatomy (Grenander & Miller 1998), and the main tool is the statistical shape model (Heimann & Meinzer 2009). The central approach is to use a consistent description of the shape of an organ across a population, with anatomical correspondence between the different subjects. Construction of statistical shape models from medical images requires two conceptual steps, the delineation (image segmentation) and the codification (mesh personalization through registration) of the anatomy of interest. In general, as a result of these two processes, the anatomy will be described by a large number of variables (mesh nodes or degrees of freedom), and techniques of dimensionality reduction (such as principal component analysis commonly used after a seminal work with 2D images (Cootes et al. 1994)) are adopted to define the shape model (the average shape and the main modes of anatomical variation). As a result of this process, the anatomy of each case is described by a small set of shape coefficients that correspond to the modes of variation of the shape model: these are the potential new shape biomarkers.

In essence, shape analysis is the study of the variability of shape in a given population.

However, it is important to note that shape variability can also be caused by methodological limitations, such as human operator dependence at the acquisition stage, a lack of spatial resolution or image contrast, or a limited segmentation and meshing accuracy. Our recent advances have thus focused on the reduction of the impact of these limitations, proposing an automatic and robust mesh personalization strategy (Lamata, Sinclair, et al. 2014;

Lamata et al. 2011). The central approach in these studies is to regularise shape according to the assumption of a smooth ellipsoidal anatomy of the ventricles, formulated through meshes with high order interpolation and C_1 continuity (the geometry and its derivatives are continuous) using cubic Hermite basis functions (see Fig. 2).

(Figure 2 about here)

Progress in cardiac shape analysis is only possible due to the availability of images of sufficient resolution, quality and prevalence (Lamata, Casero, et al. 2014). 2D echocardiography is the most common in routine clinical practice, but it offers limited coverage of the anatomy with considerable inter-observer variability. For this reason Magnetic Resonance Image (MRI) is considered the gold standard for the quantification of cardiac morphology, and is thus the main focus of recent contributions in the field ⁴⁶. Specifically the following two examples are constructed from short axis MRI, the most common image MRI study.

In the specific example we focus on the application of statistical shape models to reveal anatomical changes in adulthood caused by a premature birth (Lewandowski et al. 2013). Shape metrics can predict the gestational age of an adult from the shape of its left ventricle with 93% specificity and 98% sensitivity (Gonzalez et al. 2015). Differences in this cohort were found in the six first modes of anatomical variation of the statistical shape model, encapsulating also subtle changes such as the relative position of the apex with respect to the ventricle that are missed by traditional metrics.

In summary, computational models of cardiac anatomy reduce the impact of acquisition noise and segmentation errors, and enable clinicians to stratify subjects according to the

remodelling pattern, and therefore make more accurate predictions of cardiovascular risks in later stages of life.

Mechanical models decouple diastolic biomarkers

Ventricular filling (diastole) is as important as ejection (systole) for an adequate pump function of our heart. Nevertheless, characterization of the diastolic function in clinical guidelines is currently based on indirect surrogates such as the displacement of the mitral valve, or a ratio between early and late filling (Members et al. 2012). The motivation of this work is to propose novel tools to assess the fundamental mechanisms that rule diastolic filling, and then enable a better understanding of the aetiology of cardiac disease processes and a better stratification of patients.

In a mechanical analysis of the ventricular chamber, an impaired diastolic function is caused by two main characteristics of the myocardium: its capacity to relax, and its stiffness. These two physiological parameters are coupled, and are difficult to assess *in vivo*. As a consequence, the criterion to diagnose diastolic dysfunction is guided by indirect surrogates and is subject to many limitations and controversies (Maeder & Kaye 2009). This is especially relevant for the management of heart failure with a preserved ejection fraction (HF-PEF), which affects half of patients with HF, and is a significant and growing clinical problem (Borlaug & Paulus 2011). The hypothesis is that computational models of cardiac mechanics can improve the assessment of diastolic performance by a direct estimation and uncoupling of the biomarkers of stiffness and relaxation. Then, the access to these fundamental metrics, and not indirect surrogates of diastolic filling, will enhance the management of diseases such as HF-PEF.

The core methodological concept applied to estimate the diastolic biomarkers is called data assimilation (Sermesant et al. 2006), and refers to the process of optimization of model parameters in order to reproduce the clinical information available. In our problem we have data of the deformation and the pressure of the left ventricle, and the model parameters are the material stiffness, the decaying active tension, and the reference configuration (the resting mechanical state - the stress and strain free condition of the ventricle that is used as a reference in the mechanical simulation). In this approach, the simultaneous optimization of all unknowns with redundant information of several frames or heart beats achieves the uncoupling between stiffness and decaying tension, as described in ⁸².

The estimation of stiffness and relaxation requires additional assumptions, since the number of unknowns is larger than the number of equations: each pair of pressure and deformation data represents an equation to be fulfilled, but with an additional unknown, the amount of remaining active tension at that time, in addition to the unknowns of stiffness and reference configuration. A common assumption is that there is no remaining active tension at the last diastolic frame (Xi et al. 2013; Wang et al. 2009), and it is also reasonable to consider the decaying active tension as a monotonically decaying function. With these two conditions all the parameters can be identified (Xi et al. 2013).

A computational ventricular model to reproduce cardiac deformation and pressure can include a wide range of components, with different levels of physiological realism. The key aspects to consider are: a personalized geometry (reconstructed as described in the previous section), a material constitutive law to account for the passive mechanics (including non-linear and non-isotropic properties), a contractile decaying active tension, and a formulation of the mechanical equilibrium between forces (where different

assumptions can be taken, such as the incompressibility of the material, or a quasi-static formulation that neglects inertial effects). The model simulates an inflation of an elliptical geometry driven by the decay of the active tension and the increase of the loading (filling) pressure in the cavity. As a result, the deformation of the ventricle is predicted by defining the remaining components of the simulation, including the mechanical boundary conditions (see Fig.3).

(Figure 3 about here)

The core component in the estimation of parameters is the definition of the metric, the functional that compares the clinical data to the predicted inflation by the simulation. Common choices are the volume of the cavity (a single bulk metric, though robust), or the deformation field (much more detailed, but subject to errors finding the material point correspondence). Recent works have also explored the personalization constrained by velocities (thus including also mechanical inertial effects in the model), reporting an improved performance in the estimation of regional contractile parameters (Wong et al. 2015).

The current methodological limitation for the clinical translation is the need for catheterized pressure data (Xi et al. 2014). Research is also needed to uniquely identify material parameters, a problem that can be reduced by an adequate choice of the constitutive law (Hadjicharalambous et al. 2014; Nasopoulou et al. 2015). Other methodologically critical aspects are the choice of a mechanical reference configuration, and the correct temporal alignment of pressure and deformation data. Since the seminal work where materials stiffness was estimated from clinical data (Wang et al. 2009), computational models have been shown to be able to decouple active and passive mechanics, obtaining results that

correlate with the disease status of subjects (Xi et al. 2013), and to be more robust to offset errors in pressure recordings (Xi et al. 2014).

Models reveal regions of perfusion defects

The maintenance of coronary blood flow to cardiac tissue is not only critical for heart function but also remarkable. The modelling of coronary perfusion in the heart is an inherently multi-physics problem requiring the integration of anatomical models with myocardial mechanics and coronary perfusion. A number of modelling efforts have developed anatomical models focused on representing coronary blood flow and/or the interaction with cardiac mechanics either in lumped parameter (Spaan et al. 1981) or anatomically detailed (Smith 2004) models (see Fig. 4). However, while informative in terms of physiology the complex and highly variable nature of coronary anatomy poses a significant challenge for developing personalized models that can be applied in the clinic.

(Figure 4 about here)

Specifically, measuring flow below the largest coronary vessels introduces fundamental challenges. One modality used to overcome this issue is contrast-enhanced magnetic resonance perfusion imaging, in which injected contrast agents (CAs) provide an indication of regions that are perfused without having to determine flow at the vessel level. This approach has been shown to be effective, and combined with its non-invasive, non-ionising nature means perfusion protocols are being rapidly adopted in many clinical centres. However, in addition to the spatial temporal resolution issues, the transport and MR properties of these CAs means that their concentration (or contrast) is only a proxy for blood flow. In particular, the CAs are often freely diffusive, that is they diffuse through the

vessel walls into the cardiac tissue, and into regions that are under-perfused. In addition, the signal response curve is highly nonlinear, saturating after a threshold concentration. These effects confound absolute quantification of the blood flow and complicate the goal of developing model-based clinical metrics.

One successful focus in the literature has been the use of models to assess myocardial perfusion reserve from clinical images. Myocardial perfusion reserve (MPR) is the ratio of baseline blood flow to hyperaemic flow, representing the ability of the heart to cope with increased oxygen demand. It is known that during exercise or under pharmaceutically induced stress, blood flow may increase by a factor of 3-4 (Cullen et al. 1999) and therefore a measured MPR of 3-4 indicates a healthy condition. Extracting a quantitative estimate of MPR from MR perfusion imaging therefore provides a useful biomarker with which to diagnose and assess the functional severity of a coronary stenosis.

Several different methods have been proposed in the literature for calculating this metric, which designate it as either MPR or myocardial perfusion reserve index (MPRI). An early theoretical treatment of CA transport in the coronary circulation was the central volume principle analysis by Zierler, which showed that, under the assumption of constant flow, estimates of flow and volume could be extracted from a concentration time profile (Zierler 1962). Jerosch-Herold et al (Jerosch-Herold et al. 1998) built on the central volume principle to represent each voxel in the myocardium by a transfer function, in this case a Fermi function. An estimate of myocardial blood flow was then obtained by performing a

deconvolution of the perfusion signal and the input signal taken from the left ventricular cavity. This was done under both rest and stress conditions to directly calculate an MPRI.

Cullen et al (Cullen et al. 1999) used an ordinary differential compartment model to represent the flux of CA through the myocardium (see Tofts et al (Tofts et al. 1999) for further refinements of these models). From the measured signals they estimated a parameter K , which is proportional to perfusion, and which, under certain assumptions, can be used to calculate a ratio that is representative of MPR. Nagel et al. (Nagel et al. 2003), building on the insight that signal upslope relates to flow (Al-Saadi et al. 2000), proposed that an MPRI could be more simply computed via the ratio of normalized peak signal upslopes taken under rest and stress conditions. Though advocating this method for its simplicity, Nagel et al. concede that the freely diffusive behaviour of the CA appeared to confound the index. Furthermore, Jerosch-Herold (Jerosch-Herold et al. 2004) demonstrated that this method of calculating MPRI underestimates flow reserves in healthy cases when compared with other accepted quantitative modalities such as PET. They verified this behaviour computationally using MMID4, the multi-path, multi-indicator, four-region organ model developed by Bassingthwaite (now part of the JSIm environment (Butterworth et al. 2013)).

(Figure 5 about here)

Therefore to investigate the metric's sensitivity to freely diffusive CA properties, a porous medium model of CA transport in the myocardium (Cookson et al. 2014) is used to perform a parameter space study. This more complex approach treats the blood flow (Cookson et al.

2012; Chappelle et al. 2010; Michler et al. 2013), CA transport (Cookson et al. 2014; Sourbron 2014; Nolte et al. 2013), and imaging physics (Cookson et al. 2014) separately. Specifically, porous medium models – which can represent spatially heterogeneous tissue properties and blood flow – form the input to a scalar transport model of a freely diffusive CA through the blood and extra-cellular space, represented schematically in Fig. 5. The porous flow models are parameterised as a continuum using a volume-averaging of discrete vessel characteristics (Hyde et al. 2012; Hyde et al. 2014). The CA concentration given by the transport model is then post-processed using an empirically derived signal response function (Ishida et al. 2010).

The effect of the freely diffusive behaviour is demonstrated in the point-wise perfusion signal traces extracted from the model shown in Figure 6. Comparing results for a blood pool CA in Figure 6c and a freely diffusive CA in Figure 6d, effect of the trans-vascular diffusion is to extend the signal's tail and slow the decay rate, due to the storage of CA in the extra-cellular space and its subsequent slow clearance. Consequently the concentration and signal are no longer directly related to the blood flow at a given point in time. Figure 7 shows the variation of these signals' upslope with changing transport properties of the CA. Specifically the Peclet number, Pe , which characterises the extent to which transport of the CA occurs through blood flow relative to molecular diffusion, and the Damköhler number, Da , which describes how quickly the CA diffuses into the extravascular space relative to transport by the blood velocity. Under a stress protocol, when velocity may triple, Pe will triple, while Da reduces by a third.

(Figure 6 about here)

(Figure 7 about here)

These results show that a CA with Da in the range 0.1 to 10 will be most sensitive for calculating MPRI. For $Da < 0.1$, the change in upslope is due solely to changes in Pe , as indicated by the arrows in Fig 7. However, for $Da > 10$, the increase in upslope due to increasing Pe is counteracted by the reduction due to decreasing Da , rendering MPRI insensitive and susceptible to noise in this region. This implies that some degree of freely diffusive behaviour may actually be favourable when calculating MPRI, making the metric more sensitive. Modelling therefore provides a valuable contribution to evaluating the suitability of a particular CA for use with a desired image analysis metric.

As these models and the data assimilation pipeline continue to mature, including the introduction of a poroelastic formulation of the CA transport model (Cookson et al. 2012; Cookson et al. 2015; Lee et al. 2014) that captures perfusion, mechanics, and perfusion imaging in the beating heart, it will be possible to create realistic simulations of clinical perfusion images. Using the perfusion simulation as a gold standard reference of the underlying blood flow, the imaging protocol can be computationally optimized to provide the best representation of this flow. Potential applications where this extra spatial and physical fidelity will prove crucial include refining perfusion gradient based analysis (gradientograms) (Hautvast et al. 2011) and directly comparing 2D perfusion imaging with 3D (Motwani et al. 2014).

Discussion

It can be argued that the interpretation of clinical data from the perspective of a model is as old as medical practice itself. By “model” here we refer to the representation of our understanding of human physiology. The step taken by the VPH community is the deployment of computational technologies to expand the integrative scope of these models, thus enabling quantitative analysis of complex data across multiple scales. The examples presented above are indicative of this type of significantly wider community effort to translate computational modelling of the heart into the clinic. In this paper we have argued that a key staging point in producing ultimately predictive models is first the use of these frameworks to extract more robust and accurate diagnostic biomarkers, focusing thus the scope on the *explanatory* rather than *predictive* application of models. The value in pursuing this goal is in more rapidly delivering clinically useful tools while simultaneously developing a foundation from which to extend the same modelling techniques for prediction.

However, while in many ways using models to derive biomarkers is a less ambitious objective, a number of central challenges remain. Specifically, the extraction of a novel biomarker requires the balancing of model complexity with the quality and availability of data. Historically biophysically based cardiac models have often embedded detailed representations of established mechanisms that are in tension with the identifiability of model parameters given the available resolution and accuracy of clinical data (Audoly et al. 2001; Kirk et al. 2013). This means that there remain highly sophisticated modelling frameworks that continue to be too detailed to be directly translated to a clinical context. The reason for this mismatch between complexity and clinically available data is that often models have been developed as part of controlled *ex vivo* or animal experimental studies

(Niederer et al. 2009; Li et al. 2010). This approach has provided a solid foundation to advance our knowledge of physiology (see vertical arrow in Fig. 1). However, it is important to note that clinical translation requires the reduction of the complexity of the modelling framework so that it encapsulates the behaviour of physiological variables that are observable or inferable from clinical data alone. As argued in (Garny et al. 2005), the ideal model is as simple as possible, and as complex as necessary for the particular question raised. This principle is demonstrated specifically in the example of the estimation of diastolic biomarkers, which is limited by the low identifiability of the material constitutive parameters (Xi et al. 2013) but where the choice of an adequate model for the constitutive relationship can alleviate the impact of this limitation (Hadjicharalambous et al. 2014).

It is also important to note that the extraction of diagnostic biomarkers does not require a perfect match between model and data. As outlined above both model and data have limitations and as such they are both sources of uncertainty about the physiological variable that is being assessed. Analysis of the sensitivity of results to model assumptions and to noise and artefacts in the data, and how the uncertainty is propagated (Pathmanathan & Gray 2013), are critical steps for the efficacy of novel biomarkers. As argued, the key is to choose the right model for the clinical question, with the addition of minimal complexity. There is significant evidence that you do not need a fully realistic, validated and predictive model to make a clinical impact. Even a very simplified model can provide significant diagnostic value, such as the non-invasive estimation of the pressure drop through a stenosed cardiac valve through the peak blood velocity applying the Bernoulli principle (Firstenberg et al. 2000).

Given the often practical and sometimes ethical constraints around collecting clinical data, testing and validating novel ideas and methods to extract clinical biomarkers through computational models is often difficult. In this context, a valuable first step is the testing of a technique through *in silico* experiments. If successful, an initial proof of concept with simulation results is provided, and additional insights about the requirements in data availability and quality are generated. An example is the definition of the number of frames required to constrain the identification of myocardial stiffness (Augenstein et al. 2005), and the possibility to reveal regional myocardial stiffness by recording a number of heart beats (Xi et al. 2011). However, it is important to note that such a result, while necessary, is far from being a sufficient finding of positive evidence for working with real clinical data.

As argued above, computational models also have the capability to unveil metrics that otherwise are not measurable directly from the data. Stiffness or permeability as described above are extracted when clinical data is explained through a fundamental physics law formulated in a model. This brings the potential of an additional mechanistic understanding of the disease process, offering a closer link to the pathophysiological causes. The opportunities here are clear but again there are also risks. The incorporation of sparse sources of data also introduces errors in the temporal synchrony or spatial alignment of the different pieces. This means that the new model-driven biomarkers can be very sensitive to these errors, and thus reduce any potential clinical translation. Robust and reliable biomedical signal analysis algorithms are needed to mitigate this risk.

A collateral benefit of the approach outlined in this study is that the disagreement between even incomplete/simplified models and noisy/limited data presents opportunities to gain additional insights. Specifically, a mismatch between the model and the data provides the

ability to challenge assumptions, revealing the relevance of a model component not included, and to eventually improve the realism of the model (Smith et al. n.d.). This mismatch can also originate in the data limitations guiding researchers and/or clinicians to optimise acquisition protocols, to reconsider the adoption of better constraints or assumptions to reconstruct or extract the relevant information, and to eventually improve the quality of the data. The interaction between experiment and simulation is important for the generation of advances and novel insights. An example of this process was the inclusion of the decaying active tension in the estimation of diastolic biomarkers: the necessity of this model component was made clear when trying to find the evidence in real data of a better parameter identifiability by the use of sequential frames (Xi et al. 2013).

The ultimate value of a diagnostic biomarker is provided when a correlation is found with clinical outcomes. Accordingly, clinical guidelines for the management of cardiac diseases are frequently based on indirect surrogates that render the needed predictive value to guide decisions. In this context, computational models bring the opportunity to improve existing biomarkers, and to propose novel ones, based on the fundamental mechanisms and physiological laws, rather than indirect surrogates.

As outlined above, the long-term vision of the research community developing computational cardiac models is to inform clinical decisions based on personalized models with increasing levels of personalization, and eventually with the capability to predict the outcome of different treatment options. Initial evidence of the predictive capability of models has been provided in several clinical decision processes, such as the risk assessment of ventricular tachycardia¹, bone fracture (Schileo et al. 2008) or aneurysm rupture (Cebra

et al. 2005), or the patient selection for cardiac resynchronization therapy (Sermesant et al. 2012; Niederer et al. 2010).

We have argued, with demonstration cases, that the first step towards clinical translation is the explicative, and not the predictive, application of models, and that the adoption of novel model-based diagnostic biomarkers will be achieved through the adaptation of model complexity, assumptions and information relevant to the clinical context.

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Figure Captions

Fig. 1: Conceptual diagram illustrating how the field of computational modelling interacts with experimental physiologists and the field of biomedical signal analysis. Laws, models of our understanding of physiology are built from experimental data (vertical orange arrow), and these models are used to interpret clinical data and reveal novel personalized biomarkers (horizontal blue arrow).

Fig. 2: Personalization of anatomical models using computational meshes with high order interpolation (Lamata, Sinclair, et al. 2014; Lamata et al. 2011). (a) Segmentation of a stack of short axis slices of the left ventricle, showing an acquisition limitation, a slice shift. (b) The reconstructed smooth geometry of the left ventricle, which has been implicitly regularized to the template shape of a truncated ellipsoid, reducing the impact of acquisition and segmentation errors.

Fig. 3: Personalization results of mechanical models to reveal the parameters of decaying active tension and myocardial stiffness. Three instants of diastolic filling phase are shown, and illustrate the good match found between the simulated meshes and the original medical images.

Fig. 4: Anatomically based model from (Smith 2004) computing blood flow within a coupled model of coronary flow and large deformation myocardial contraction. The colour coding shows the force of compression on the embedded coronaries during diastole (left) and mid systole (right) ranging from blue (0 KPa) to red (10 KPa).

Fig. 5: Simulation setup used in (Cookson et al. 2014), to model the passage of CA through the capillaries. The permeability tensor K can be made spatially heterogeneous to simulate a

regional perfusion defect. Contrast agent diffuses from the blood into the tissue, and vice versa, at a rate proportional to the concentration difference that exists between the two phases. Originally published in (Cookson et al. 2014), reproduced here in modified form under the Creative Commons License 3.0 (<http://creativecommons.org/licenses/by/3.0/>).

Fig. 6: a 2D perfusion image of the mid-third of the heart exhibiting a perfusion defect (indicated by arrows) (a), with time series extracted in healthy and defect regions (b), simulated time series data for a blood-bound contrast agent in both healthy and diseased regions (c), simulated time series data for a freely-diffusing contrast agent in both healthy and diseased regions (d), concentration contour plots taken at several time points for the freely-diffusing contrast agent (e). For data sampled in the healthy region of the myocardium, dashed dark blue represents the contribution to the signal from the fluid, dashed green represents the contribution from the tissue and the solid light blue curve is the total, observed signal. In the defect region, total signal is shown by the solid red line.

Fig. 7: The variation of signal upslope with Da and Pe illustrating the behaviour of perfusion reserve index for three indicative contrast agents, which have varying degrees of freely-diffusing behaviour. CAs in Zone 2 are most sensitive to changes in velocity and therefore most suited for use with the perfusion reserve index, whereas CAs in Zone 3 are unsuited to this metric due to the upslope varying only slightly with changes in velocity. Originally published in (Cookson et al. 2014), reproduced here in modified form under the Creative Commons License 3.0 (<http://creativecommons.org/licenses/by/3.0/>).

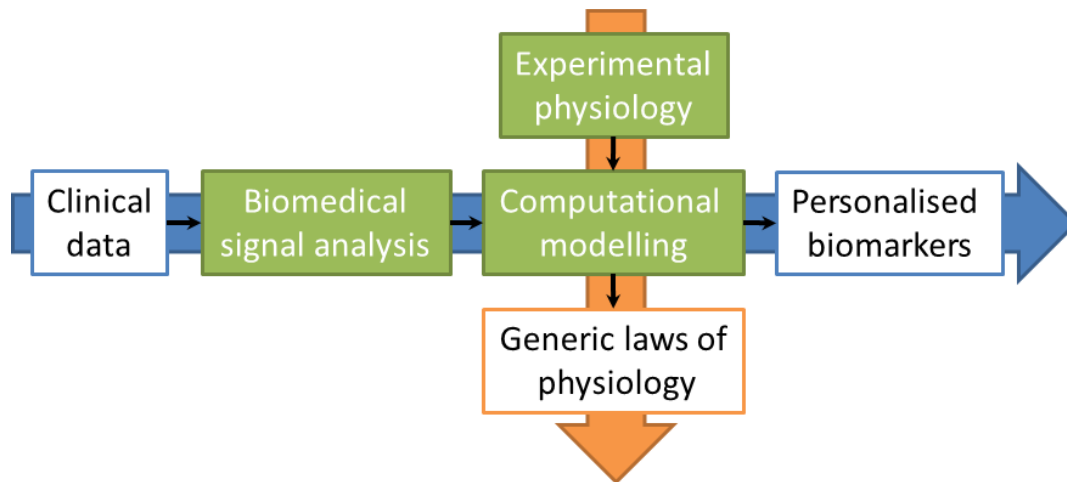
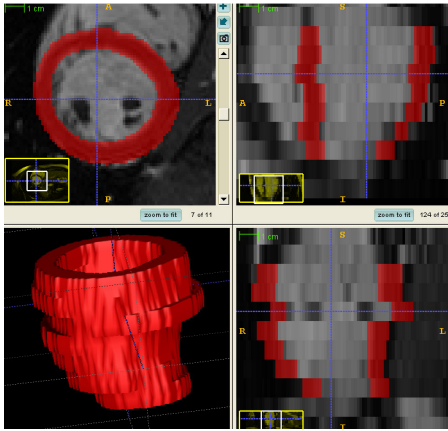
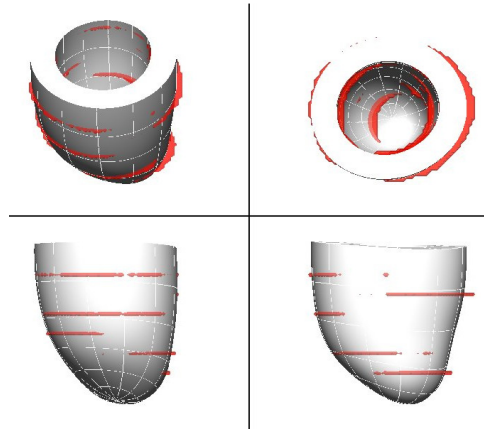


Figure 1



(a)



(b)

Figure 2

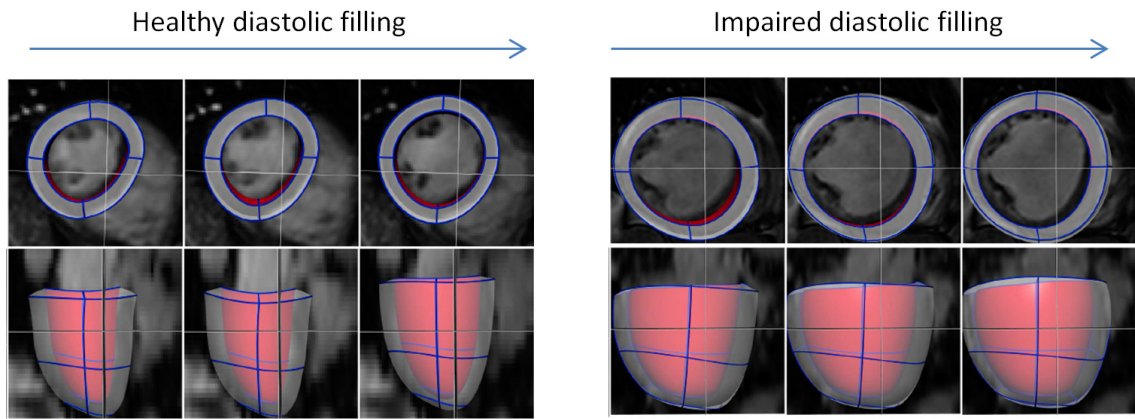


Figure 3

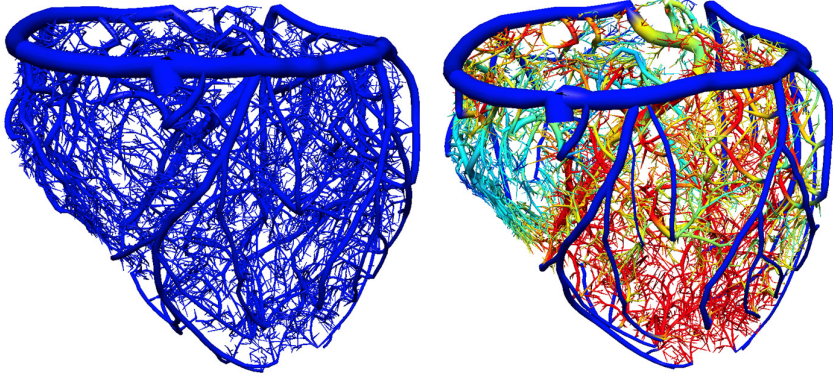


Figure 4

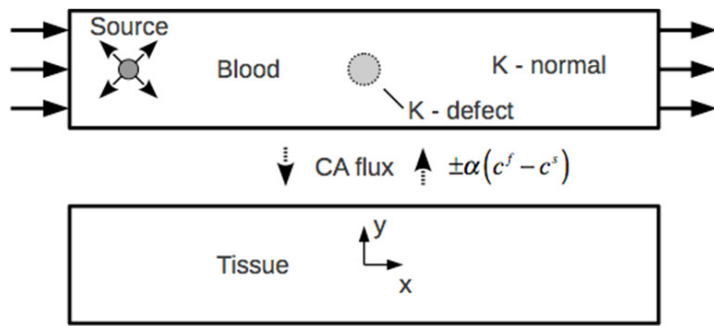


Figure 5

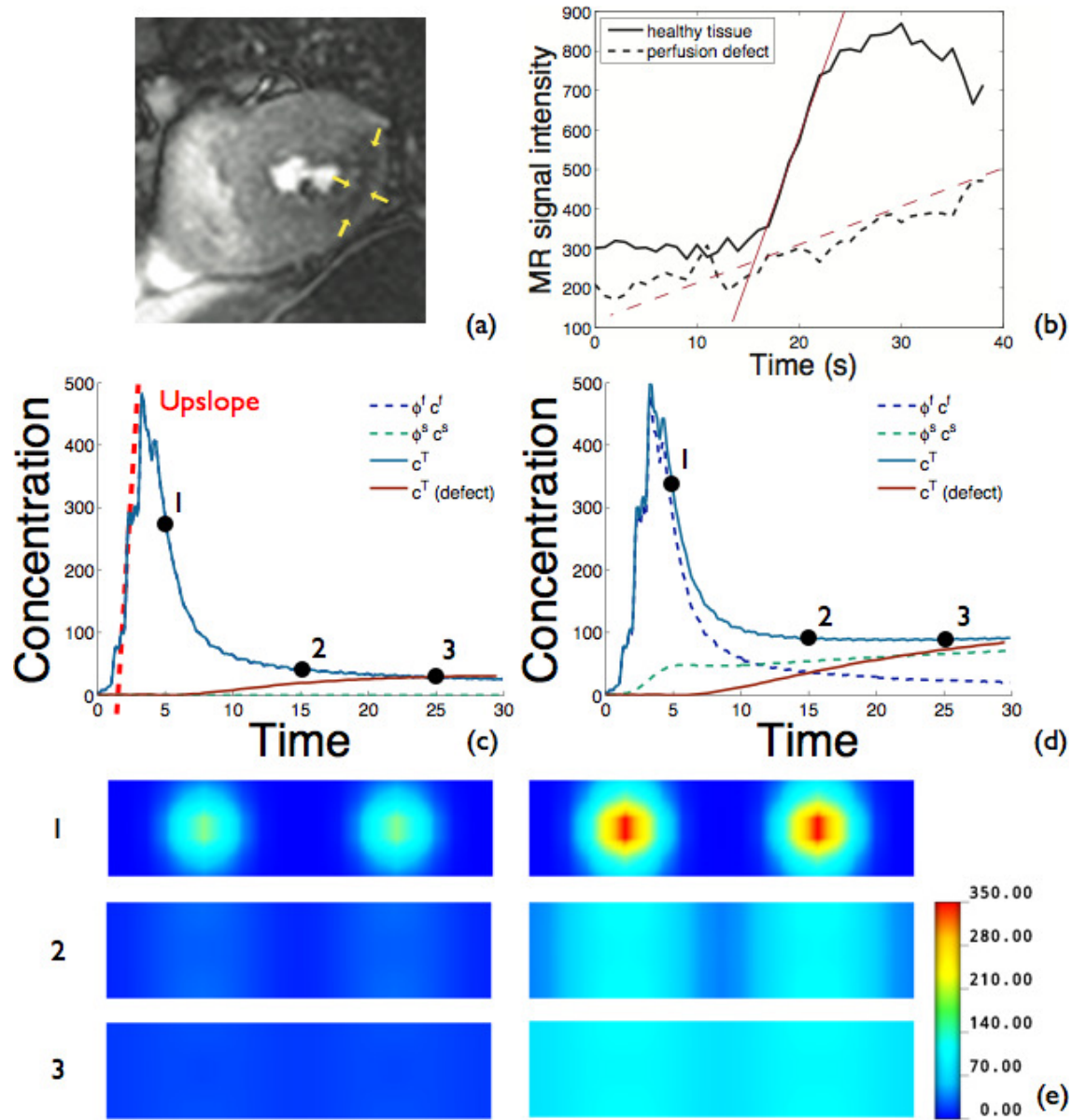


Figure 6

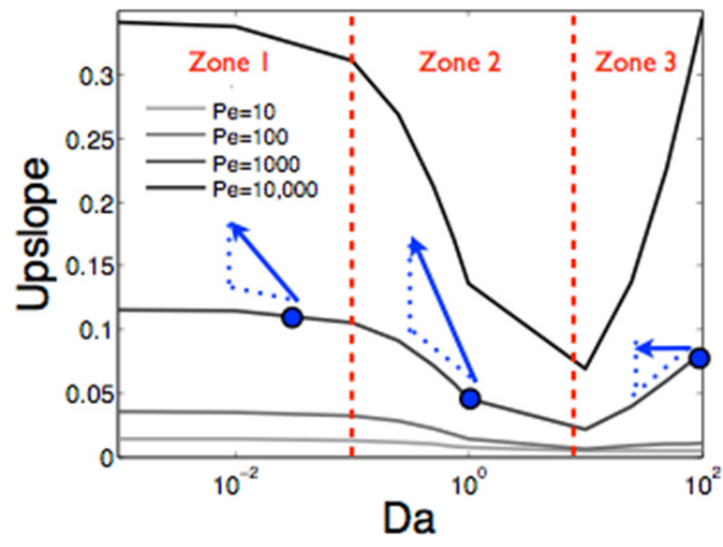


Figure 7