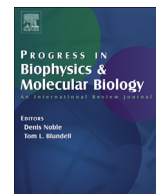




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Images as drivers of progress in cardiac computational modelling

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ABSTRACT

Computational models have become a fundamental tool in cardiac research. Models are evolving to cover multiple scales and physical mechanisms. They are moving towards mechanistic descriptions of personalised structure and function, including effects of natural variability. These developments are underpinned to a large extent by advances in imaging technologies. This article reviews how novel imaging technologies, or the innovative use and extension of established ones, integrate with computational models and drive novel insights into cardiac biophysics. In terms of structural characterization, we discuss how imaging is allowing a wide range of scales to be considered, from cellular levels to whole organs. We analyse how the evolution from structural to functional imaging is opening new avenues for computational models, and in this respect we review methods for measurement of electrical activity, mechanics and flow. Finally, we consider ways in which combined imaging and modelling research is likely to continue advancing cardiac research, and identify some of the main challenges that remain to be solved.

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1. Introduction

From the first models of single cell electrophysiology (Noble, 1960, 1962) the field of cardiac modelling has experienced remarkable progress. Current models incorporate multi-physics phenomena (Hunter et al., 2003; Kohl and Noble, 2009; Nordsletten et al., 2011), combining electrophysiology (Trayanova, 2011), mechanics (Nash and Hunter, 2000), mechano-electric interactions (Hermeling et al., 2012; Hales et al., 2012), fluid flow (Taylor and Figueroa, 2009) and tissue perfusion (Lee and Smith, 2012). They characterize processes across scales, from nano to macro. Cardiac models increasingly incorporate subject-specific information, from ventricular anatomy to electrical and mechanical material properties (Ranjan et al., 2012; Sermesant et al., 2012; Krishnamurthy et al., 2013; Xi et al., 2013). Having proved their value for advancing our insight into mechanisms of (patho)-

physiology (Hunter et al., 2001), models are now moving to applications in the clinic (Burnes et al., 2000; McDowell et al., 2012).

Healthy cardiac function depends on the interplay of multiple biophysical phenomena. The elucidation of mechanisms and their complex interrelations is particularly challenging when using a purely experimental approach. Mechanistic description, quantitative analysis, identification of causal interrelations, consideration of dynamic behaviour, and – in particular – prediction, are domains where computational modelling has started to play a prominent role in cardiac research. In this context, models enable one to integrate and interpret experimental data, to form and test hypotheses about cardiac function, and to assess physiological variables that may not be open to direct measurement due to their invasiveness or for technical reasons (e.g. lack of techniques to measure local stress *in situ*).

Electrophysiologically, cardiac cells can be divided into excitable (mainly cardiomyocytes; note that intra-cardiac neurons are generally excluded from cell-based cardiac modelling) and non-excitable (mainly fibroblasts, endothelial, immune and fat cells). In healthy myocardium, cardiomyocytes occupy ~75% of tissue volume. The remainder is dominated by fibroblasts, accounting for ~60–70% of all cardiac cells (Camelliti et al., 2005). The heart is

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an organ with built-in pacing and conduction capability, from the sinoatrial node, via the atrio-ventricular node and the specialised Purkinje system, to ventricular cardiomyocytes. The generated electrical wavefront triggers well-coordinated contraction of the muscle. On the cellular level, a wide range of cardiac EP models have been developed for the various cell sub-types involved in this process (e.g. (Zhang et al., 2000; Li and Rudy, 2011; Noble, 2011; Britton et al., 2013)), and the introduction and use of cell-level mark-up languages (like CellML) and associated tools are improving model exchange and re-use (Lloyd et al., 2004; Pitt-Francis et al., 2006; Garny et al., 2009; Gianni et al., 2010; Kerfoot et al., 2013). At the tissue level, cardiac EP models have traditionally considered the myocardial wall as a continuum (Garny et al., 2003; Clayton et al., 2011; Cooper et al., 2011), typically introducing anisotropy through conductivity tensors.

From a mechano-anatomical model perspective, the heart can be decomposed into active and passive components. The mechanically active component is formed by the contractile cardiomyocytes, while the mechanically passive component comprises intra-cellular visco-elastic structures (both in cardiomyocytes and non-myocytes) and the extra-cellular matrix which provides the deformable skeleton of the heart (Weber et al., 1994). Similarly to EP models, cardiac mechanical models traditionally represent this microstructure as a continuum, encoding microstructure in the anisotropy of the contractile and material properties (Hunter et al., 2003). More recent attempts have tried to incorporate the hetero-cellular nature of heart muscle (Xie et al., 2009), and the feedback from mechanical to electrical behaviour of the heart (Kohl et al., 1999, 2006; Li et al., 2004).

From a fluid dynamics perspective, the ventricles are chambers whose inflow and outflow tracks are controlled by valves. Blood can be accurately represented as an incompressible fluid, and inside the cardiac chambers and big vessels its constitutive behaviour can be approximated by a Newtonian model.

Depending on the specific research question addressed, a cardiac model can represent a combination of the aforementioned three physical domains: EP, mechanics and fluidics. The two most common combinations are electro-mechanical (Trayanova, 2011) and fluid–solid interaction models (Taylor and Figueroa, 2009) for the study of the ventricles and main vessels, respectively.

The synergy between experimental methods (e.g. data from images and functional maps) and theory (computational models) is key in the generation of novel insight in cardiovascular science (Quinn and Kohl, 2013). The availability of novel imaging technologies, and the innovative use or extension of established ones, are main drivers of this progress. Recent years have seen dramatic improvements in imaging capabilities, and a rapid expansion of their application. Images cover most of the scales relevant to cardiac modelling, from subcellular structures (Iribe et al., 2009) to whole organs (Pope et al., 2008; Trayanova, 2011). Images have moved from characterizing static structures to providing dynamic measures of function (Townsend, 2008), including electrophysiology, mechanics and blood flow, and modern techniques even probe different aspects of metabolic activity (Taegtmeier and Dilsizian, 2013). Image analysis methods, allowing the combination of images from multiple subjects, are gradually enabling the transition from individual to population studies (Young and Frangi, 2009).

For these reasons, imaging and modelling are increasingly linked. Development of computational models relies on information acquired from images. Image data have become drivers of progress in cardiac computational modelling in three general areas (Fig. 1). First, they capture **anatomy**, providing the **structural information** necessary to run simulations (MacLeod et al., 2009). Secondly, images provide **functional information** used to build,

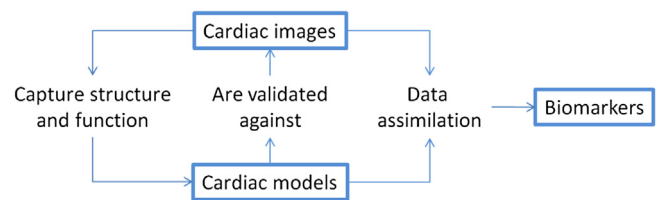


Fig. 1. Conceptual scheme of how cardiac images interact with computational models to generate novel insight and drive research progress.

adjust and validate models (Carusi et al., 2012). When models are not able to reproduce the data contained in images, model limitations are identified, and new mechanisms may be unveiled (Kohl et al., 2010). Thirdly, images are used to estimate model parameters by **data assimilation** (Sermesant et al., 2006b), finding the model parameters that best explain the observed data. These parameters can then be fed back to experimental investigations, or be used as biomarkers. Models also feedback onto imaging methodologies providing a framework for integrating images across multiple scales, for interpreting measurements introducing the biophysics of the system and for linking data across different imaging platforms.

In this review, we concentrate primarily on the scales from tissue to whole organ. Subcellular structures rely on a separate set of imaging technologies (Iribe et al., 2009; Wong et al., 2013) and modelling approaches (Winslow et al., 2006; Gaur and Rudy, 2011), and while there are relevant conceptual similarities, these merit a review on their own. Rather than presenting an exhaustive list of papers, we aim at providing a consideration of the main trends in the field, highlighting in particular how the use of novel imaging technologies is opening up new possibilities for innovation. We illustrate this by offering representative examples covered in previous publications. We do not provide details about modelling, but instead refer the reader to recent reviews and original sources.

Following this introduction, the paper is organized as follows. Section 2 provides an overview of imaging modalities that have become established in clinical cardiac assessment, and of the ways in which they have been applied in combination with computational models. Sections 3 and 4 focus on more experimental imaging techniques, illustrating specific areas in which progress in modelling has been made possible through advances in imaging technologies, and/or in which new imaging developments have been motivated by the needs of modelling research. This is separated into new imaging technologies currently pushing the boundaries of structural (Section 3) and functional (Section 4) characterization of the heart. Section 5 discusses current and future challenges and opportunities involving the combination of images and models in cardiovascular science and medicine.

2. Established clinical imaging technologies: An overview

Imaging has become an integral part of cardiac health and disease assessment. Several cardiac imaging modalities are now widely available in the developed world, and are used as part of standard procedures recommended by the relevant medical societies. As models evolve towards clinical application, data from these imaging modalities are commonly available to build personalised models. Understanding strengths and limitations (including those arising from clinical constraints) of the various techniques is fundamental for successful interrelation with computational modelling. This Section provides an overview of several well-established imaging technologies that have been used in combination with computer models, and discusses

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