Advances in computational modelling for personalised medicine after myocardial infarction

Kenneth Mangion,1,2 Hao Gao,3 Dirk Husmeier,3 Xiaoyu Luo,3 Colin Berry1,2

ABSTRACT
Myocardial infarction (MI) is a leading cause of premature morbidity and mortality worldwide. Determining which patients will experience heart failure and sudden cardiac death after an acute MI is notoriously difficult for clinicians. The extent of heart damage after an acute MI is informed by cardiac imaging, typically using echocardiography or sometimes, cardiac magnetic resonance (CMR). These scans provide complex data sets that are only partially exploited by clinicians in daily practice, implying potential for improved risk assessment. Computational modelling of left ventricular (LV) function can bridge the gap towards personalised medicine using cardiac imaging in patients with post-MI. Several novel biomechanical parameters have theoretical prognostic value and may be useful to reflect the biomechanical effects of novel preventive therapy for adverse remodelling post-MI. These parameters include myocardial contractility (regional and global), stiffness and stress. Further, the parameters can be delineated spatially to correspond with infarct pathology and the remote zone. While these parameters hold promise, there are challenges for translating MI modelling into clinical practice, including model uncertainty, validation and verification, as well as time-efficient processing. More research is needed to (1) simplify imaging with CMR in patients with post-MI, while preserving diagnostic accuracy and patient tolerance (2) to assess and validate novel biomechanical parameters against established prognostic biomarkers, such as LV ejection fraction and infarct size. Accessible software packages with minimal user interaction are also needed. Translating benefits to patients will be achieved through a multidisciplinary approach including clinicians, mathematicians, statisticians and industry partners.

INTRODUCTION
Ischaemic heart disease is the leading cause of premature disability and death in many countries worldwide.1 Despite reductions in age-standardised death rates, the incidence of heart failure after acute myocardial infarction (MI) remains persistently high.2 Left ventricular (LV) dysfunction after MI portends an adverse prognosis;3 however, LV dimensions change dynamically early post-MI making imaging-guided risk assessment challenging for clinicians2 (figure 1).

The clinician relies on medical imaging to provide global measures of LV systolic function, such as LV ejection fraction (EF), wall motion score and myocardial strain. These indices are indirect measures of LV pump function. In practice, therapeutic decisions are informed by an evidence base relating to LVEF.2 4 However, on an individual patient basis, risk prediction using LVEF is limited as the majority of patients who die prematurely have normal or mildly reduced LVEF.5

Another challenge is the lack of information on infarct size and pathology. Ideally, LV function should be registered with pathology to provide clinically relevant insights into salvaged myocardium and complications, including myocardial haemorrhage and contained myocardial rupture. Cardiac magnetic resonance (CMR) imaging provides multiparametric information in a single scan, and while CMR uniquely integrates function with pathology, CMR has limited availability in daily practice.

Computational heart modelling has potential to improve risk prediction in individual patients.6 7 For example, computed biomechanical parameters of LV function (table 1) may have the potential to provide new knowledge over and above conventional measures of pump function (eg, LVEF and myocardial strain).8–11 A number of modelling consortia have emerged since the international Physiome Project was first proposed at the International Union of Physiological Sciences Council in Glasgow in 1993. These consortia (table 2) have potential to push technical advances through to the clinic. Further integration of medicine with mathematics and statistics has potential to bring otherwise abstruse biomechanical parameters closer to the clinic, especially if novel inference techniques from machine learning and multivariate statistics are employed.

Biomechanical parameters of LV function (ie, contractility, stiffness, strain) are theoretically more tightly linked with LV pump performance (and thus prognosis) than global measures of systolic function such as LVEF. Measurement of these indices requires model personalisation, which presents a barrier translation to the clinic. Nonetheless, personalised heart modelling holds exciting potential for a diverse range of applications, from basic science to therapy development (including to replace, reduce and refine (3Rs) the need for animals in scientific research), and for risk stratification of individual patients after acute MI. In this review article, we provide the reader with a review of recent updates in modelling MI, including the challenges and future promise of computational heart modelling for personalised medicine.
The practice guidelines for ST-elevation myocardial infarction issued by the European Society of Cardiology assign the use of echocardiography with a class 1, level of evidence B indication for risk stratification based on assessment of infarct size and resting LV function. CMR imaging has a class 2a, level of evidence C, that is, indicated when echocardiography is not feasible, whereas routine CT is not recommended (class 3, level of evidence C). The North American guidelines give the assessment of LV function a class 1, level of evidence C, but do not specify the method used. The infarct territory is inferred by the presence of a wall motion abnormality and the standard

**Table 1** Examples of biomechanical parameters of left ventricular pump function derived from mathematical modelling

<table>
<thead>
<tr>
<th>Myocardial biomechanics parameter</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Passive stiffness</td>
<td>The relationship between myocardial stress and myocardial strain. Stiffness represents the hyperelastic properties of myocardium, and is a passive component of diastolic function.</td>
</tr>
<tr>
<td>2. Required contractility</td>
<td>Active tension generated by the sarcomere, the basic contractile unit in myocytes, at its resting length, it is the required minimum contractile function to meet the body's blood demand.</td>
</tr>
<tr>
<td>3. Systolic stress pattern</td>
<td>The sum of active stress+passive stress in systole, it can be normalised by systolic blood pressure, denoted as normalised stress. Stress is the force per unit area at any point, active stress means the force is generated by myocyte contractile units triggered by intracellular calcium, whereas passive stress is the force resulting from resistance to myocardial deformation, which does not involve energy consumption, for example, when collagen is stretched, there is a force inside collagen to counterbalance the external stretching force.</td>
</tr>
<tr>
<td>4. Systolic myofilament kinetics</td>
<td>The ratio between systolic active stress and the required contractility. Systolic active stress is the actual myocardial active force, which is a function of contractility, myocardial deformation, and so on. Systolic myofilament kinetics reflects the quantity of binding sites formed between myosin and actin in systole.</td>
</tr>
<tr>
<td>Cardiac modelling consortium</td>
<td>Organisation and funding body</td>
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<tr>
<td>The Physiome Project (<a href="http://www.physiomeproject.org">www.physiomeproject.org</a>)</td>
<td>Started from the International Union of Physiological Sciences council in 1993</td>
</tr>
<tr>
<td>The euHeart project (<a href="http://www.euheart.eu">www.euheart.eu</a>)</td>
<td>Funded by FP7 with 16 industrial, clinical and academic partners</td>
</tr>
<tr>
<td>The Sim-e-Child project (<a href="http://www.sim-e-child.org">http://www.sim-e-child.org</a>)</td>
<td>Funded by FP7, as a follow-up to Health-e-Child project</td>
</tr>
<tr>
<td>CARDIOPROOF (<a href="http://www.cardioproof.eu">www.cardioproof.eu</a>)</td>
<td>Funded by FP7, a proof of concept of model-based cardiovascular predictions from VPH</td>
</tr>
<tr>
<td>The virtual rat physiology (<a href="http://www.vph-institute.org">www.vph-institute.org</a>)</td>
<td>An international non-profit organisation to ensure the realisation of the virtual physiological human project</td>
</tr>
<tr>
<td>The EPSRC centre for multiscale soft tissue mechanics (<a href="http://www.softmech.org">www.softmech.org</a>)</td>
<td>Funded by EPSRC UK with School of Mathematics and Statistics, University of Glasgow</td>
</tr>
<tr>
<td>The Virtual Physiological Rat Project (<a href="http://www.virtualrat.org">http://www.virtualrat.org</a>)</td>
<td>Funded by NIH USA focusing on the system biology of cardiovascular disease</td>
</tr>
</tbody>
</table>

All websites were accessed on 23 April 2017. This is not an exhaustive list of groups on computational cardiac modelling, other research groups include MD-Paedegree (http://www.md-paedegree.eu), LifeV (http://www.lifev.org), Continuity (http://www.continuity.ucsd.edu), CMiSS (http://www.cmis.org), Chaste (http://www.cs.ox.ac.uk/chaste), GlasgowHeart (www.glasgowheart.org) and CHeart (http://cheart.co.uk). EPSRC, Engineering and Physical Sciences Research Council; NIH, National Institutes of Health; VPH, Virtual Physiological Human.
assessment of LV function post-MI consists of LVEF and wall motion scoring.

Echocardiography has several attributes including portability, high temporal resolution, shorter scanning time and lower cost. For these reasons, echocardiography is the standard of care for cardiac imaging in patients with post-MI. CMR, however, has superior accuracy and precision for imaging LV and right ventricular function when compared with echocardiography. CMR is multiparametric, thus a single scan can provide information on tissue characteristics, infarct pathology and myocardial viability. CMR does not involve ionising radiation and can be safely repeated. For these reasons, CMR is the modality of choice for computational modelling of human hearts.

CLINICIAN’S VIEW OF THE NEED FOR HEART MODELLING

The LVEF is the ratio of blood ejected during systole to the LV volume at the end of diastole. LVEF is one of the strongest predictors of mortality post-MI to date, however, it varies with heart rate, blood pressure and inotropic state. Wall motion scoring is a qualitative, subjective approach for the assessment of LV function. Assessments of LV function by echocardiography may be imprecise, and potentially decisions about therapy, for example, mineralocorticoid receptor antagonist, implantable defibrillator device, may be suboptimal if based on a single LVEF value.

Most imaging-derived prognostic markers in patients with MI have some limitations. Considering CMR, infarct size may be overestimated in the acute phase due to oedema, and microvascular obstruction and intramyocardial haemorrhage vary dynamically during the first week following MI. The natural temporal evolution of LV function and infarct characteristics raises the question of the optimal timing of a scan post-MI. CMR utility for risk stratification post-MI is identified in updated guidelines from the European Society of Cardiology. CMR methods continue to evolve balancing diagnostic utility (eg, T2*-CMR for myocardial haemorrhage) against patient-level considerations (scan duration). The optimal timing of a CMR scan depends on the clinical question. CMR is useful early post-MI (<3 days) for immediate assessment of risk, for example, LV thrombus, myocardial haemorrhage, and LV volumes and infarct complications evolve over time. Infarct characteristics are generally stable from 7 to 10 post-MI permitting longer term risk stratification. Adverse remodelling typically becomes established from 3 months. Therefore, multiparametric CMR helps answer different questions according to the time point post-MI.

Risk prediction in individual patients is problematic, and improvements are needed to reliably identify those patients at greatest risk who may benefit from targeted interventions, for example, defibrillator therapy.

This gap is a target for computational modelling which has potential to define more informative prognostic biomarkers for stratification of individual patients. Further, computational modelling has the potential to integrate multiple domains of information including electrophysiology (ie, conduction throughout myocardial tissue), biomechanics, blood flow (4D flow within the LV cavity), myocardial perfusion and infarct pathology. This approach is termed ‘multi-scale/physics modelling’. Usually, these domains of information are considered in isolation (eg, LV function by echocardiography), partially (ie, cardiac conduction using the surface ECG), or not at all (ie, tissue pathology and 4D flow, unless CMR is used). Multiscale/physics heart modelling holds exciting potential to bring together key domains of information in one temporally and spatially resolved form. These concepts are beyond theoretical, and the field of multiscale/physics modelling is making important advances towards personalised medicine in the clinic.

Towards clinical translation

Considering the practical challenges, progress is likely to be made with incremental steps. For example, infarct size and myocardial salvage are not routinely measured with CMR in clinical practice mainly because of time constraints. Standardised workflows for CMR imaging post-MI should be developed in parallel with computational modelling approaches. In an environment as complex as an infarcted heart, there are a variety of factors that will influence the success of clinical treatments. However, reliable computational models based on longitudinal patient-specific CMR imaging can inform the best timing for treatment, monitoring and baseline selection. Future advances in personalised medicine are anticipated to lead to integration of multiscale data (anatomy, pathology, physiology, genomics, and so on) into a scaled, patient-specific report.

Advances in software and machine learning could make this task more accessible for clinicians. Beyond this, future advances could lead to registration of these pathologies with parametric maps of novel biomechanical parameters (ie, contractility, stiffness).

PERSONALISED MODELLING IN MI

Cardiac modelling and technical considerations

Cardiac biomechanical models are a set of mathematical relationships which describe myocardial motion and deformation under various loading conditions and constrains, as governed by the continuum mechanics theory. Cardiac models are usually implemented using computer languages that produce outputs (deformation, stress, and so on) from inputs (clinical data, and so on) which are run on high-performance computers. Cardiac dynamics are complex multiphysics problems that involve myocardial tissue mechanics, haemodynamics, electrophysiology, biochemistry and their interactions, spanning from subcellular to organ levels, as listed in figure 2. Cardiac models have been developed over the past decades, ranging from single myocyte models, to two-dimensional approximation, three-dimensional models and multiscale/physics systems. A biomechanical cardiac model encompasses various components to capture ventricular dynamics, including geometrical representation (numerical mesh), mathematical representation (ie, finite element methods), boundary conditions (motion constraint imposed by surrounding tissue and organs, blood pressure and flow rates), material properties (myocardial passive stiffness and contractility) and model output analysis (figure 2). The development of personalised heart models is complex and involves multidisciplinary involvement and collaboration (figure 3). These include: stage 1: patient enrolment, cardiac imaging and clinical assessment by healthcare staff; stage 2: image analysis and personalised model construction, requiring collaborative work between modellers and cardiologists; stage 3: mathematical model implementation, calibration, inference and result interpretation, mainly performed by mathematical modellers and statisticians.

MODEL PERSONALISATION

An accurate, fast and reliable heart geometry reconstruction is the first step in clinical translation. To reconstruct cardiac geometry from in vivo data, endocardial and epicardial boundaries are delineated from images, that is, segmentation. At this point, the
endocardial and epicardial borders which are represented by a 3D 'cloud' of points will undergo surface fitting, where a smooth surface is constructed by minimising the difference between the points and the fitted surface. The next step is volumetric meshing, where the LV wall is divided into polyhedrons as small representative solids. Different methods are being developed for cardiac geometry reconstruction including user iterative interventions for reconstruction or by warping idealised ventricular geometry, for example, an ellipsoid, into patient data.22

Personalised modelling depends on anatomically accurate geometry and relies on mathematical formulation and patient-specific material properties as shown in figure 2. Knowledge of myocardial passive and active material properties is essential to accurately predict cardiac function as well as to design and evaluate new treatment based on those models. Much research has been carried out to estimate myocardial property from in vivo data, and to understand heart dysfunction based on the changes of myocardial mechanical properties.

Mathematical descriptions of passive myocardium23 have progressed from linear material to non-linear material laws by considering myocyte organisation and its associated collagen networks.6 However, non-invasively estimating material parameters remains a great challenge. Inverse approaches for determining myocardial material parameters have attracted much interest, in which one can estimate the unknown parameters by minimising the difference between in vivo measurements (displacement, strain, pressure-volume curve) and the modelling results with respect to those unknown parameters6 24-27 (figure 4). However, due to the excessively large number of potential parameter combinations, and their non-linear influence on predictions, the practical realisation of this task is not trivial, and depends on the execution of computer-intensive optimisation algorithms. Recently, more advanced techniques from computational statistics and machine learning, such as Bayesian optimisation and statistical emulation, are being used.30

Predicting myocardial systolic stress also requires further parameterisation of the active contraction model, which usually complements a myocardial passive response model.7 Most of myocardial active models are based on ‘the sliding theory’ at cellular level and upscaled to tissue level (table 1). At cellular level, the active tension can be described as a function of intracellular calcium, sarcomere length and contraction velocity. At tissue level, active tension is a function of myocyte organisation and individual myocyte contractility. Due to the large set of unknown parameters in the active contraction model, parameterisation is usually carried out at tissue level, by scaling cellular active tension so that myocardial motion in systole matches in vivo measurements21 (figure 4).

LV pressure is a loading condition, and when LV pressure is not available, computational estimates of cardiac dynamics become less certain. The ratio between early mitral inflow velocity and mitral annular early diastolic velocity has been used to estimate the ventricular filling pressure, but this can be unreliable in certain situations.29 Systolic ventricular pressure may be inferred from non-invasive cuff-measured blood pressure or by measuring flow in large arteries through coupling circulation models.30 Non-invasively measuring the absolute blood pressure is challenging, though pressure gradients can be estimated from flow measurements.

The underlining myocyte architecture and collagen network also play an essential role in determining pump function. Diffusion tensor MRI reveals fibre organisation.31 However, it is still a work in progress due to challenges presented by cardiorespiratory motion. Therefore, most cardiac models used rule-based approaches to describe their organisations,9 21 32 33 which inevitably contribute to model uncertainty for predictive modelling. Our recent modelling study demonstrated that myocyte architecture is an important factor for estimating myocardial contractility.9

BIOMECHANICAL FINDINGS FROM PERSONALISED HEART MODELS

Clinically, increased passive myocardial stiffness is a major cause of impaired LV pump function due to inadequate diastolic filling and subsequent increased end-diastolic pressure.34 Image-based cardiac models25 27 33 35-37 have been developed for estimating myocardial passive stiffness in both healthy subjects and patients with heart failure. These models were constructed using CMR imaging (cine, 3D tagging and flow imaging)37 31 or
a combination of CMR imaging (cine, tagging) and invasive LV end-diastolic pressure measurements. Nevertheless, although different myocardial constitutive laws are used in the above studies either with invasively or non-invasively measured or population-based ventricular pressure, the findings from computational cardiac models seem consistent. The myocardium from diseased hearts is stiffer compared with healthy hearts. Post-MI passive stiffness is highest at 1 week followed by improvements with remodelling by 12 weeks. From animal and human studies, Guccione’s group has reported that the infarcted region not only has a higher passive stiffness and higher wall stress when compared with remote myocardium, but the myocardial contractility in the border zone is reduced as well, correlating with the area at risk. They suggested that adverse remodelling post-MI could be due to an altered myocardial stress pattern. Porcine biomechanical heart models have disclosed that remote myocardial contractility increases at 10 and 38 days post-MI. Several computational studies have reported that maximal active tension is much higher in patients with heart failure when compared with normal subjects, and in patients with MI, suggesting an increased dependency on myocardial contractile reserve. However, computationally estimated myocardial passive stiffness and contractility vary considerably between healthy and diseased hearts (table 3). The reasons for this variability are unclear but may be related to interindividual variations, sample size or technical factors. Ventricular wall stress and its inhomogeneous distribution could also lead to adverse remodelling, including myocardial hypertrophy, and heart failure. Figure 5 shows the LV systolic stress patterns in a healthy control and a patient post-MI. Clearly, there is a more homogenous distribution of LV stress in health, and restoring ventricular stress to a normal stress distribution could be a potential therapeutic target (table 3). Further work is needed to investigate the effect of sex, age and anthropometry on myofibre stress.

Recently, we used an ‘extreme case-control’ study design, with cardiac modelling undertaken in 27 healthy controls and 11 patients with post-MI. By combining computational modelling with machine learning approaches, we reported that myofibre active tension is much higher in patients with MI compared with healthy volunteers, and myocardial contractility correlated negatively with the observed recovery in LV pump function at 6 months post-MI. By contrast, LVEF was not associated with LV outcomes at 6 months. We observed moderately strong predictive associations for the biomechanical parameters despite the sample size being limited. Future prospective studies should evaluate whether novel biomechanical parameters (table 1) have superior prognostic value in patients with post-MI as compared with standard indices such as LVEF.

**CHALLENGES IN PERSONALISED MODELLING**

Model uncertainty and metrology

Uncertainty quantification in heart models is essential to support the use of these techniques as tools to aid clinical decision-making. Specific topics for uncertainty evaluation include (1) in vivo imaging acquisition (noise, incomplete heart structure representation); (2) image segmentation; (3) model construction; (4) model simplification (heterogeneity); (5) material laws assumptions (linear, non-linear) and boundary conditions; (6) model abstraction from subcellular to organ levels; and (7) multiphysics domains, for example, electrophysiology. These uncertainties may be either directly measured, that is, imaging noise, or indirectly inferred such as material laws. Increasingly, computer-intensive statistical inference is being used to quantify uncertainty in parameter estimation, model selection and model prediction, using methods such as Bayesian filtering, Markov chain Monte Carlo and Gaussian process emulators. Uncertainty quantification in cardiac models should be a high priority to ensure successful future clinical translation.
Validation and verification
Some validation has been achieved to date through comparisons with experimental benchmark data, computational models and clinical images. However, substantial challenges exist, as directly validating stress and myocardial contractility in vivo is next to impossible. Novel non-invasive techniques such as imaging-derived heart models have a number of potentially useful applications. Novel biomechanical parameters including models that integrate multiple forms of information hold promise for personalised medicine.

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Contributors CB conceived the idea for the review. KM and HG drafted the manuscript. DH, XYL and CB were involved in revising this manuscript critically for important intellectual content. KM and HG were responsible for designing the figures. All authors (KM, HG, DH, XYL and CB) gave final approval of the version to be submitted and any revised version. CB is responsible for the overall content as guarantor.

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