Advances in computational modelling for personalized medicine after myocardial infarction.

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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. These scans provide complex datasets 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 post-MI patients. 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. Whilst 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 post-MI patients, whilst 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[2], however, LV dimensions change dynamically early post-MI making imaging-guided risk assessment challenging for clinicians [3] (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 multi-parametric information in a single scan, and while CMR uniquely integrates function with pathology, CMR has limited availability 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 (e.g. LVEF & 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 (i.e. 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 personalization, which presents a barrier translation to the clinic. Nonetheless, personalized 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 myocardial infarction, including the challenges and future promise of computational heart modelling for personalised medicine.

Imaging myocardial function

The practice guidelines for STEMI issued by the European Society of Cardiology[2] 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, i.e., indicated when echocardiography is not feasible, whereas routine computed tomography is not recommended (class 3, level of evidence C). The North American guidelines[4] 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[12] and the standard 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 post-MI patients[2]. CMR, however, has superior accuracy and precision for imaging LV and RV function when compared with echocardiography[13]. CMR is multi-parametric, thus a single scan provides information on tissue characteristics[3], infarct pathology[14] 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 [6].

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[2,4,14], however, it varies with heart rate, blood pressure and inotropic state[15]. 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 e.g. mineralocorticoid receptor antagonist, implantable defibrillator device, may be sub-optimal if based on a single LVEF value.

Most imaging derived prognostic markers in MI patients have some limitations. Considering CMR, infarct size may be overestimated in the acute phase due to oedema[16], and microvascular obstruction and intramyocardial haemorrhage vary dynamically during the first week following MI[3]. 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[2]. CMR methods continue to evolve balancing diagnostic utility (e.g. 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 e.g. LV thrombus, myocardial haemorrhage, and LV volumes and infarct complications evolve over time[3,16]. Infarct characteristics are generally stable from 7–10 post-MI permitting longer-term risk stratification. Adverse remodelling typically becomes established from 3 months. Therefore, multi-parametric 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 e.g. 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 (i.e. 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 (e.g. LV function by echocardiography), partially (i.e. cardiac conduction using the surface electrocardiogram), or not at all (i.e. tissue pathology and 4D-flow, unless CMR is used). Multi-scale/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 multi-scale/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, etc.) 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 (i.e. contractility, stiffness).

Personalised modelling in myocardial infarction

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[17]. Cardiac models are usually implemented using computer languages that produce outputs (deformation, stress, etc.) from inputs (clinical data etc.) which are run on high performance computers[18].

Cardiac dynamics are complex multi-physics problems that involve myocardial tissue mechanics, haemodynamics, electrophysiology, biochemistry and their interactions, spanning from sub-cellular to organ levels[18], as listed in Figure 1. Cardiac models have been developed over the past decades, ranging from single myocyte models[19], to two-dimensional approximation[20], three-dimensional models[21], and multi-scale/physics systems[18]. A biomechanical cardiac model encompasses various components to capture ventricular dynamics[7], including geometrical representation (numerical mesh), mathematical representation (i.e. finite element methods), boundary conditions (motion constrain 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 personalized 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 personalized 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, i.e. 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 minimizing 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[7] or by warping idealized ventricular geometry, e.g. an ellipsoid, into patient data[22].

Personalized modelling not only depends on anatomically accurate geometry, but also 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 myocardium[23] have progressed from linear material to nonlinear material laws by considering myocyte organization 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 minimizing the difference between in-vivo measurements (displacement, strain, pressure-volume curve) and the modelling results with respect

206 to those unknown parameters[20,24–27](Figure 4). However, due to the excessively
207 large number of potential parameter combinations, and their non-linear influence on
208 predictions, the practical realisation of this task is not trivial, and depends on the
209 execution of computer-intensive optimisation algorithms. Recently, more advanced
210 techniques from computational statistics and machine learning, such as Bayesian
211 optimisation and statistical emulation, are being used[28].

212 Predicting myocardial systolic stress also requires further parameterisation of the
213 active contraction model, which usually complements a myocardial passive response
214 model[7]. Most of myocardial active models are based on '*the sliding theory'* at
215 cellular level and up-scaled to tissue level (Table 1). At cellular level, the active
216 tension can be described as a function of intracellular calcium, sarcomere length, and
217 contraction velocity. At tissue level, active tension is a function of myocyte
218 organization and individual myocyte contractility. Due to the large set of unknown
219 parameters in the active contraction model, parameterisation is usually carried out at
220 tissue level, by scaling cellular active tension so that myocardial motion in systole
221 matches in-vivo measurements[21] (Figure 4).

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

230 The underlining myocyte architecture and collagen network also play an essential role

in determining pump function. Diffusion tensor MRI (DT-MRI) reveals fibre organization[31]. However, it is still a work-in-progress due to challenges presented by cardio-respiratory motion. Therefore, most cardiac models used rule-based approaches to describe their organizations[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[8].

Biomechanical findings from personalized 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 models[25,27,33,35–38] have been developed for estimating myocardial passive stiffness in both healthy subjects and patients with heart failure. These models were constructed utilising CMR imaging (cine, 3D tagging and flow imaging)[27,33] or a combination of CMR imaging (cine, tagging) and invasive LV end-diastolic pressure measurements[25]. 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 to healthy hearts.

Post-MI passive stiffness is highest at 1 week followed by improvements with remodelling by 12 weeks[39]. From animal and human studies, Guccione's group[9–11] has reported that the infarcted region not only has a higher passive stiffness and higher wall stress when compared to 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[40] have disclosed that remote myocardial contractility increases at 10 days and 38 days post-MI. Several computational studies have reported that maximal active tension is much higher in patients with heart failure when compared to normal subjects[7,33], and in patients with MI[21], 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 inter-individual 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[41]. 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[42](Table 3). Further work is needed to investigate the effect of sex, age and anthropometry on myofibre stress.

Recently, we utilised an "*extreme case-control*" study design, with cardiac modelling undertaken in 27 healthy controls and 11 post-MI patients[8]. By combining computational modelling with machine-learning approaches, we reported that myofibre active tension is much higher in MI patients compared to healthy volunteers, and myocardial contractility correlated negatively with the observed recovery in LV pump function at six 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 post-MI patients as compared to 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[43]. 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, nonlinear) and boundary conditions; (6)model abstraction from subcellular to organ levels; (7)multi-physics domains e.g. electrophysiology[44,45]. These uncertainties may be either directly measured, i.e. 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, utilizing methods such as Bayesian filtering[46], Markov chain Monte Carlo[47] and Gaussian process emulators[28]. Uncertainty quantification in cardiac models should be a high priority to ensure successful future clinical translation[43].

Validation and verification

Some validation has been achieved to date through comparisons with experimental benchmark data[48], computational models[49], 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 magnetic

resonance elastography[50] and DTI[31] hold promise for assessing the mechanical properties of tissue in-vivo. Recently, there has been growing interest in the development of methodologies and frameworks for verification, validation and uncertainty quantification (VVUQ) in order to improve model credibility[44].

Clinical Perspective and Future Directions

Computational modelling is currently operative mainly within the domain of cardiac science. Recent advances support a forward-looking view, and personalized computational heart modelling has realistic potential to provide clinicians with new predictive tools, that currently are not available in daily practice[7].

Bringing models into the clinic for patient benefits presents an exciting challenge (please see Online Supplement). In the future, modelling applications for risk stratification should ideally exploit echocardiography (since this is the standard of care) or CMR. Machine learning and statistical emulation techniques will be necessary to enable software applications for near real-time use in the clinic.

Further work should establish a minimum-dataset of what imaging to acquire in post-MI patients, the timing of the imaging scans, validate novel biomechanical parameters against more established prognostic markers, such as LVEF, e.g. in multicentre studies. Technical innovations should lead to software packages that require minimal user interaction. Our view is that adoption in the clinic is most likely through incremental steps with adoption of software tools (patches, programmes, etc.) that build on existing clinical workflows. To this end, clinicians, mathematicians, statisticians, and industry partners must work collaboratively.

Conclusion

Imaging-derived heart models have a number of potentially useful applications. Novel biomechanical parameters including myocardial contractility, stiffness, stress, and their distribution, have potential as novel surrogates in therapeutic studies and for risk stratification of individual patients. Multi-scale/physics models that integrate multiple forms of information hold promise for personalised medicine.

Contributorship statement:

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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Competing interests

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References

1 GBD 2013 Mortality and Causes of Death Collaborators. Global, regional, and national age–sex specific all-cause and cause-specific mortality for 240 causes of death, 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013. *The Lancet* 2015;**385**:117–71. doi:10.1016/S0140-6736(14)61682-2

2 Ibanez B, James S, Agewall S, *et al.* 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevationThe Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). *Eur Heart J* doi:10.1093/eurheartj/ehx393

3 Carrick D, Haig C, Ahmed N, *et al.* Temporal Evolution of Myocardial Hemorrhage and Edema in Patients After Acute ST- Segment Elevation Myocardial Infarction: Pathophysiological Insights and Clinical Implications. *J Am Heart Assoc Cardiovasc Cerebrovasc Dis* 2016;**5**. doi:10.1161/JAHA.115.002834

4 O'Gara PT, Kushner FG, Ascheim DD, *et al.* 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: executive summary: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines: developed in collaboration with the American College of Emergency Physicians and Society for Cardiovascular Angiography and Interventions. *Catheter Cardiovasc Interv Off J Soc Card Angiogr Interv* 2013;**82**:E1-27. doi:10.1002/ccd.24776

5 Dagres N, Hindricks G. Risk stratification after myocardial infarction: is left ventricular ejection fraction enough to prevent sudden cardiac death? *Eur Heart J* 2013;**34**:1964–71. doi:10.1093/eurheartj/eht109

6 Chabiniok R, Wang VY, Hadjicharalambous M, *et al.* Multiphysics and multiscale modelling, data–model fusion and integration of organ physiology in the clinic: ventricular cardiac mechanics. *Interface Focus* 2016;**6**:20150083. doi:10.1098/rsfs.2015.0083

7 Wang VY, Nielsen PMF, Nash MP. Image-Based Predictive Modeling of Heart Mechanics. *Annu Rev Biomed Eng* 2015;**17**:351–83. doi:10.1146/annurev-bioeng-071114-040609

8 Gao H, Aderhold A, Mangion K, *et al.* Changes and classification in myocardial contractile function in left ventricle following acute myocardial infarction. *J R Soc Interface* Published Online First: 2017. doi:10.1098/rsif.2017.0203

9 Walker JC, Ratcliffe MB, Zhang P, *et al.* MRI-based finite-element analysis of left ventricular aneurysm. *Am J Physiol Heart Circ Physiol* 2005;**289**:H692-700. doi:10.1152/ajpheart.01226.2004

10 Wenk JF, Sun K, Zhang Z, *et al.* Regional left ventricular myocardial contractility and stress in a finite element model of posterobasal myocardial infarction. *J*

Biomech Eng 2011;**133**:044501. doi:10.1115/1.4003438

11 Wenk JF, Klepach D, Lee LC, *et al.* First evidence of depressed contractility in the border zone of a human myocardial infarction. *Ann Thorac Surg* 2012;**93**:1188–93. doi:10.1016/j.athoracsur.2011.12.066

12 Tennant R, Wiggins CJ. The effect of coronary occlusion on myocardial contraction. *Am Heart J* 1935;**10**:843–4. doi:10.1016/S0002-8703(35)90365-9

13 Bellenger NG, Burgess MI, Ray SG, *et al.* Comparison of left ventricular ejection fraction and volumes in heart failure by echocardiography, radionuclide ventriculography and cardiovascular magnetic resonance; are they interchangeable? *Eur Heart J* 2000;**21**:1387–96. doi:10.1053/euhj.2000.2011

14 Carrick D, Berry C. Prognostic importance of myocardial infarct characteristics. *Eur Heart J Cardiovasc Imaging* 2013;**14**:313–5. doi:10.1093/ehjci/jes296

15 Bull SC, Main ML, Stevens GR, *et al.* Cardiac toxicity screening by echocardiography in healthy volunteers: a study of the effects of diurnal variation and use of a core laboratory on the reproducibility of left ventricular function measurement. *Echocardiogr Mt Kisco N* 2011;**28**:502–7. doi:10.1111/j.1540-8175.2010.01380.x

16 Dall'Armellina E, Karia N, Lindsay AC, *et al.* Dynamic Changes of Edema and Late Gadolinium Enhancement after Acute Myocardial Infarction and Their Relationship to Functional Recovery and Salvage Index. *Circ Cardiovasc Imaging* 2011;**4**:228–36. doi:10.1161/CIRCIMAGING.111.963421

17 Holzapfel GA. Nonlinear Solid Mechanics: A Continuum Approach for Engineering. 2000.http://www.wiley.com/WileyCDA/WileyTitle/productCd-0471823198.html (accessed 19 Jul 2017).

18 Quarteroni A, Lassila T, Rossi S, *et al.* Integrated Heart—Coupling multiscale and multiphysics models for the simulation of the cardiac function. *Comput Methods Appl Mech Eng* 2017;**314**:345–407. doi:10.1016/j.cma.2016.05.031

19 Hunter PJ, McCulloch AD, ter Keurs HEDJ. Modelling the mechanical properties of cardiac muscle. *Prog Biophys Mol Biol* 1998;**69**:289–331. doi:10.1016/S0079-6107(98)00013-3

20 Guccione JM, McCulloch AD, Waldman LK. Passive material properties of intact ventricular myocardium determined from a cylindrical model. *J Biomech Eng* 1991;**113**:42–55.

21 Gao H, Carrick D, Berry C, *et al.* Dynamic finite-strain modelling of the human left ventricle in health and disease using an immersed boundary-finite element method. *IMA J Appl Math* 2014;**79**:978–1010. doi:10.1093/imamat/hxu029

22 Lamata P, Sinclair M, Kerfoot E, *et al.* An automatic service for the personalization of ventricular cardiac meshes. *J R Soc Interface* 2014;**11**:20131023. doi:10.1098/rsif.2013.1023

23 Holzapfel GA, Ogden RW. Constitutive modelling of passive myocardium: a structurally based framework for material characterization. *Philos Trans R Soc Lond Math Phys Eng Sci* 2009;**367**:3445–75. doi:10.1098/rsta.2009.0091

24 Dokos S, Smaill BH, Young AA, *et al.* Shear properties of passive ventricular myocardium. *Am J Physiol Heart Circ Physiol* 2002;**283**:H2650-2659. doi:10.1152/ajpheart.00111.2002

25 Xi J, Lamata P, Niederer S, *et al.* The estimation of patient-specific cardiac diastolic functions from clinical measurements. *Med Image Anal* 2013;**17**:133–46. doi:10.1016/j.media.2012.08.001

26 Gao H, Li WG, Cai L, *et al.* Parameter estimation in a Holzapfel–Ogden law for healthy myocardium. *J Eng Math* 2015;**95**:231–48. doi:10.1007/s10665-014-9740-3

27 Hadjicharalambous M, Asner L, Chabiniok R, *et al.* Non-invasive Model-Based Assessment of Passive Left-Ventricular Myocardial Stiffness in Healthy Subjects and in Patients with Non-ischemic Dilated Cardiomyopathy. *Ann Biomed Eng* 2017;**45**:605–18. doi:10.1007/s10439-016-1721-4

28 Shahriari B, Swersky K, Wang Z, *et al.* Taking the Human Out of the Loop: A Review of Bayesian Optimization. *Proc IEEE* 2016;**104**:148–75. doi:10.1109/JPROC.2015.2494218

29 Park J-H, Marwick TH. Use and Limitations of E/e' to Assess Left Ventricular Filling Pressure by Echocardiography. *J Cardiovasc Ultrasound* 2011;**19**:169–73. doi:10.4250/jcu.2011.19.4.169

30 Chen WW, Gao H, Luo XY, *et al.* Study of cardiovascular function using a coupled left ventricle and systemic circulation model. *J Biomech* 2016;**49**:2445–54. doi:10.1016/j.jbiomech.2016.03.009

31 Toussaint N, Stoeck CT, Schaeffter T, *et al.* In vivo human cardiac fibre architecture estimation using shape-based diffusion tensor processing. *Med Image Anal* 2013;**17**:1243–55. doi:10.1016/j.media.2013.02.008

32 Genet M, Lee LC, Nguyen R, *et al.* Distribution of normal human left ventricular myofiber stress at end diastole and end systole: a target for in silico design of heart failure treatments. *J Appl Physiol Bethesda Md 1985* 2014;**117**:142–52. doi:10.1152/japplphysiol.00255.2014

33 Asner L, Hadjicharalambous M, Chabiniok R, *et al.* Estimation of passive and active properties in the human heart using 3D tagged MRI. *Biomech Model Mechanobiol* 2016;**15**:1121–39. doi:10.1007/s10237-015-0748-z

34 Zile MR, Baicu CF, Gaasch WH. Diastolic heart failure--abnormalities in active relaxation and passive stiffness of the left ventricle. *N Engl J Med* 2004;**350**:1953–9. doi:10.1056/NEJMoa032566

35 Xi J, Shi W, Rueckert D, *et al.* Understanding the need of ventricular pressure for the estimation of diastolic biomarkers. *Biomech Model Mechanobiol*

2014;**13**:747–57. doi:10.1007/s10237-013-0531-y

36 Genet M, Chuan Lee L, Ge L, *et al.* A Novel Method for Quantifying Smooth Regional Variations in Myocardial Contractility Within an Infarcted Human Left Ventricle Based on Delay-Enhanced Magnetic Resonance Imaging. *J Biomech Eng* 2015;**137**:0810091–8. doi:10.1115/1.4030667

37 Wang VY, Young AA, Cowan BR, *et al.* Changes in In Vivo Myocardial Tissue Properties Due to Heart Failure. In: *Functional Imaging and Modeling of the Heart*. Springer, Berlin, Heidelberg 2013. 216–23. doi:10.1007/978-3-642-38899-6_26

38 Land S, Park-Holohan S-J, Smith NP, *et al.* A model of cardiac contraction based on novel measurements of tension development in human cardiomyocytes. *J Mol Cell Cardiol* 2017;**106**:68–83. doi:10.1016/j.yjmcc.2017.03.008

39 McGarvey JR, Mojsejenko D, Dorsey SM, *et al.* Temporal Changes in Infarct Material Properties: An In Vivo Assessment Using Magnetic Resonance Imaging and Finite Element Simulations. *Ann Thorac Surg* 2015;**100**:582–9. doi:10.1016/j.athoracsur.2015.03.015

40 Chabiniok R, Moireau P, Lesault P-F, *et al.* Estimation of tissue contractility from cardiac cine-MRI using a biomechanical heart model. *Biomech Model Mechanobiol* 2012;**11**:609–30. doi:10.1007/s10237-011-0337-8

41 Mann DL, Bristow MR. Mechanisms and Models in Heart Failure. *Circulation* 2005;**111**:2837–49. doi:10.1161/CIRCULATIONAHA.104.500546

42 Lee LC, Wenk JF, Zhong L, *et al.* Analysis of patient-specific surgical ventricular restoration: importance of an ellipsoidal left ventricular geometry for diastolic and systolic function. *J Appl Physiol Bethesda Md 1985* 2013;**115**:136–44. doi:10.1152/japplphysiol.00662.2012

43 Mirams GR, Pathmanathan P, Gray RA, *et al.* Uncertainty and variability in computational and mathematical models of cardiac physiology. *J Physiol* 2016;**594**:6833–47. doi:10.1113/JP271671

44 Pathmanathan P, Shotwell MS, Gavaghan DJ, *et al.* Uncertainty quantification of fast sodium current steady-state inactivation for multi-scale models of cardiac electrophysiology. *Prog Biophys Mol Biol* 2015;**117**:4–18. doi:10.1016/j.pbiomolbio.2015.01.008

45 Johnstone RH, Chang ETY, Bardenet R, *et al.* Uncertainty and variability in models of the cardiac action potential: Can we build trustworthy models? *J Mol Cell Cardiol* 2016;**96**:49–62. doi:10.1016/j.yjmcc.2015.11.018

46 Xi J, Lamata P, Lee J, *et al.* Myocardial transversely isotropic material parameter estimation from in-silico measurements based on a reduced-order unscented Kalman filter. *J Mech Behav Biomed Mater* 2011;**4**:1090–102. doi:10.1016/j.jmbbm.2011.03.018

47 Murphy KP. *Machine Learning: A Probabilistic Perspective*. MIT Press 2012.

514 48 Zhu Y, Hardy CJ, Sodickson DK, *et al.* Highly parallel volumetric imaging with a
515 32-element RF coil array. *Magn Reson Med* 2004;**52**:869–77.
516 doi:10.1002/mrm.20209

517 49 Land S, Gurev V, Arens S, *et al.* Verification of cardiac mechanics software:
518 benchmark problems and solutions for testing active and passive material
519 behaviour. *Proc R Soc A* 2015;**471**:20150641. doi:10.1098/rspa.2015.0641

520 50 Elgeti T, Sack I. Magnetic Resonance Elastography of the Heart. *Curr Cardiovasc*
521 *Imaging Rep* 2014;**7**:9247. doi:10.1007/s12410-013-9247-8

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Figure Legends

Figure 1. Similar presentations yet divergent outcomes. Two male patients presented with anterior ST elevation MI and had primary angioplasty to their proximal left anterior descending artery. They were enrolled in the British Heart Foundation MR-MI study (ClinicalTrials.gov identifier NCT02072850). Patient A was a 56 year old male, who had a symptom to balloon time of 209 minutes. MRI on day 2 revealed a LV ejection fraction of 47.4%, and indexed LV end-diastolic volume of 85.6 ml/m2. Infarct size (A.2, yellow arrows) at baseline was 34.9% LV mass. Microvascular obstruction (A.2, red thin arrows) was 2.89% LV mass. At 6 months follow-up (A.3), his LV ejection fraction improved to 56.1%, with no significant change in indexed LV end-diastolic volume (88.3ml/m2).

Patient B was a 58 year old male, who had a symptom to balloon time of 132 minutes. MRI on day 2 revealed a LV ejection fraction of 46.4%, and indexed LV end-diastolic volume of 98.2 ml/m^2. Infarct size at baseline was 32.4% LV mass. Microvascular obstruction (A.2, red thin arrow) was 0.08% LV mass. At 6 months follow-up (A.3), his LV ejection fraction deteriorated to 36.9%, with adverse remodelling (indexed LV end-diastolic volume 126.4 ml/m^2). He proceeded to have an internal cardiac defibrillator implanted for primary prevention.

Figure 2. The distinct components of a mathematical cardiac model.

Figure 3. Stage 1 involves patient enrolment and diagnosis, and cardiac imaging such as magnetic resonance imaging (MRI). The MRI images are all co-registered at the same position and depict a short axial mid-left ventricular position. (a.1): cine image, (a.2): T2-weighted image for oedema (red arrow) (a.3, a.4): late gadolinium enhanced

image for myocardial infarction (red arrow), (a.5) circumferential strain map. Stage 2 involves image analysis and model construction. (b.1, b.2) ventricular wall boundary segmentation, (b.3) pathological region identification, (b.4) 3-dimensional LV geometry, (b.5) AHA-17 segmental mapping. Stage 3 depicts mathematical modelling. (c.1) mesh representation, (c.2, c.3) cardiac dynamics simulation at end-diastole and end-systole, (c.4) systolic stress distribution, (c.5) ventricular flow in diastolic filling.

Figure 4. Schematic illustration of inversely estimating unknown parameters in modelling myocardial passive stiffness and active contraction.

Figure 5. Examples of biomechanical models of left ventricular function for a healthy left ventricle (a, b), and a MI heart (c, d) from the authors' group, adapted from[8]. (a) is the LV geometry from a healthy volunteer, and (b) shows the systolic stress along myocytes, in general, systolic stress is homogeneous throughout the whole ventricular wall. (c) is the LV geometry from a MI patient, red to blue colour suggests the MI extent from 1 to 0, which means blue (0) is functional myocardium, red (1) is the infarct region; (d) is the systolic stress along myocyte in the MI model, high stress regions can be found in the MI region, and less homogeneous compared to the healthy heart model in (b).

563 **Table 1.** Examples of biomechanical parameters of left ventricular pump function

564 derived from mathematical modelling.

Myocardial biomechanics parameter	Definition
1. Passive stiffness	⇒ The relationship between myocardial stress and myocardial strain. Stiffness represents the hyper-elastic properties of myocardium, and is a passive component of diastolic function.
2. Required contractility	⇒ 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. It is different from the maximum contractile function, the difference between the maximum contractile function and the required contractility is the contractile reserve.
3. Systolic stress pattern	⇒ The sum of active stress + passive stress in systole, it can be normalized by systolic blood pressure, denoted as normalized 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 resulted 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.
4. Systolic myofilament kinetics	⇒ 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, etc. Systolic myofilament kinetics reflects the quantity of binding sites formed between myosin and actin in systole.

565 **Table 2.** Research consortia on mathematical modelling of the cardiovascular system.

Cardiac modelling consortium	Organization and funding body	Aims	Related heart research	Output and application examples
The Physiome Project (www.physiomeproject.org)	Started from the International Union of Physiological Sciences council in 1993	To develop a multi-scale modelling framework for understanding physiological function, allowing models to be combined and linked in a hierarchical fashion.	Electromechanical models of the heart, myocardial ion channels, myofilament mechanics and signal transduction pathways, tissue mechanics, coronary blood flow, etc.	1. Standardized mark-up languages for encoding models 2. Model repositories for sharing and collaborating 3. the physiome modelling framework
The EUheart project (www.euheart.eu)	Funded by FP7 with 16 industrial, clinical and academic partners	To develop individualized, computer-based human heart models for improving the diagnosis, therapy planning and treatment of cardiovascular disease	Focusing on model personalization, arrhythmias, coronary disease, heart failure, etc.	Cardiac resynchronisation therapy

The Sim-e-Child project (http://www.sim-e-child.org)	Funded by FP7, as a follow-up to Health-e-Child project	To integrate innovative disease models and complex data with knowledge discovery applications to support clinical decisions in paediatrics diseases	Developments and application cardiac models for congenital heart diseases using grid-enabled platform for largescale simulations	Personalized virtual child heart modelling framework
CARDIOPROOF (www.cardioproof.eu/)	Funded by FP7, a proof-of-concept of model-based cardiovascular predictions from VPH	To consolidate and check the applicability and effectiveness of existed predictive modelling tools, and validate in clinical trials	Focusing on patients with aortic valve disease and aortic coarctation	Integration of software technologies into clinical decision making and treatment planning systems, for example, the virtual stenting solution
The virtual rat physiology (www.vph-institute.org)	An international non-profit organization to ensure the realization of the virtual physiological human project	To develop new methods and technologies to make possible the investigation of the human body as a whole by integrating knowledge from different fields	Activities and facilities to promote collaborative research of the human body as a single complex system.	Development of standards for models and data, establish model and data repositories, and associated toolkits

The EPSRC centre for multiscale soft tissue mechanics (www.softmech.org)	Funded by EPSRC UK with School of Mathematics and Statistics, University of Glasgow	To develop a multi-scale soft tissue models for heart diseases by integrating mathematicians, clinicians, experimentalists, and modellers to elucidate the chain of events from mechanical factors at a subcellular level to cell and tissue response	Novel multiscale mathematical models and computer-intensive statistical inference techniques applicable to heart diseases, in particular myocardial infarction	Personalized models in patients following acute ST-segment elevation myocardial infarction, three potential biomechanical parameters were identified using machine learning approaches
The Virtual Physiological Rat Project (http://www.virtualrat.org)	Funded by NIH USA focusing on the system biology of cardiovascular disease	To understand how disease phenotypes apparent at the whole-organism scale emerge from molecular, cellular, tissue, organ, and organ-system interactions	Developing a theoretical/computational understanding of cardiovascular system dynamics and the aetiology of hypertension	Developing multi-scale models to construct and assess competing hypothesis across different species

Note: all websites were accessed on 23rd April 2017. This is not an exhaustive list of groups on computational cardiac modelling, other research groups include MD-Paedigree (http://www.md-paedigree.eu/), LifeV (http://www.lifev.org), Continuity (http://www.continuity.ucsd.edu), CMISS (http://www.cmiss.org), Chaste (http://www.cs.ox.ac.uk/chaste/), GlasgowHeart (www.glasgowheart.org), CHeart (http://cheart.co.uk).

569 **Table 3.** Summary of estimated myocardial contractility from computational models derived from in vivo cardiac imaging.

Studies	Imaging modality	Number of subjects	Ventricular pressure	Myocardial contractility
Genet et al, 2014 [32]	Tagged MRI	5 HVs	Assumed pressure	143 kPa
Genet et al, 2015 [36]	3D cine, 3D tagged, 2D LGE MRI	1 MI patient	Assumed end-diastolic and cuff-measured end-systolic pressure	146.9 kPa
Wenk, et al, 2012 [11]	Tagged and LGE MRI	1 MI patient	Direct, invasive measurement	109.5 kPa
Wang et al, 2013 [37]	Cine MRI	6 HVs, 5 hypertrophic HF 9 non-ischemic HF	Assumed pressure	88 kPa (HV) 160 kPa (hypertrophic) 124 kPa (NI- HF)
Gao et al, 2014 [21]	Cine MRI	1 HV 1 MI patient	Assumed end-diastolic and cuff-measured end-systolic pressure	168.6 kPa (HV) 309.1 kPa (MI)
Asner et al, 2015 [33]	Cine, 3D tagged, and 4D flow MRI	1 HV 2 patients with DCM	Non-invasively estimated pressure	139 kPa (HV) 168 kPa (patients)
Land et al, 2017 [38]	CT imaging	3 patients with preserved heart function	Assumed pressure	120 kPa

570 DCM – dilated cardiomyopathy, HF: heart failure, HV: healthy volunteer, LGE: late gadolinium enhancement, kPa: kilo Pascal.