



Marina Strocchi¹

National Heart and Lung Institute,
Imperial College London,
London W12 0NN, UK
e-mail: m.strocchi@imperial.ac.uk

Christoph M. Augustin

Division of Medical Physics and Biophysics,
Medical University of Graz,
Graz 8010, Austria;
BioTechMed-Graz,
Graz 8010, Austria
e-mail: christoph.augustin@medunigraz.at

Matthias A. F. Gsell

Division of Medical Physics and Biophysics,
Medical University of Graz,
Graz 8010, Austria;
BioTechMed-Graz,
Graz 8010, Austria
e-mail: matthias.gsell@medunigraz.at

Christopher A. Rinaldi

School of Biomedical Engineering and Imaging
Sciences,
King's College London,
London SE1 7EH, UK;
Guy's and St Thomas' NHS Foundation Trust,
London SE1 7EH, UK
e-mail: aldo.rinaldi@kcl.ac.uk

Edward J. Vigmond

IHU Liryc, Heart Rhythm Disease Institute,
Fondation Bordeaux Université,
Pessac 33604, France;
IMB UMR 5251,
Université Bordeaux,
Talence 33400, France
e-mail: edward.vigmond@u-bordeaux.fr

Gernot Plank

Division of Medical Physics and Biophysics,
Medical University of Graz,
Graz 8010, Austria;
BioTechMed-Graz,
Graz 8010, Austria
e-mail: gernot.plank@medunigraz.at

Chris J. Oates

School of Mathematics, Statistics and Physics,
Newcastle University,
Newcastle upon Tyne NE1 7RU, UK
e-mail: chris.oates@newcastle.ac.uk

Integrating Imaging and Invasive Pressure Data into a Multiscale Whole-Heart Model

Cardiovascular diseases are the leading cause of death. Clinical data used to decide treatment are hard to integrate and interpret, making optimal treatment selection difficult. Personalized models can be used to integrate clinical data into a physics and physiology-constrained framework, but their clinical application faces limitations due to complex calibration and validation. In this study, we present a novel systematic calibration method for a whole-heart, multiscale, electromechanics model using emulators, sensitivity analysis, and history matching. Using cardiac motion derived from ECG-gated computed tomography (CT) and invasive left ventricular (LV) pressure data, we calibrated 25 model parameters to match the LV end-diastolic (ED) and peak pressure, ED and end-systolic (ES) volumes (EDV and ESV), right ventricle EDV, and the left atrium EDV, ESV, and the maximum volume during venous return. After calibration, all features were fit within [0.8, 10.8]% of the mean target value, and fell within 1.4 experimental standard deviations from the target values. We validated the model by comparing CT-derived and simulated atrioventricular plane displacement (AVPD) (8.2 versus 8.1 mm) and the ED and ES configurations against the CT images. The model replicated the measured acute hemodynamic response to biventricular (BIV) pacing (simulated: 222 mmHg/s versus clinical: 213 ± 65 mmHg/s). This study provides a systematic method to integrate clinical data into a whole-heart, multiscale electromechanics framework. The validation shows that the model replicates local heart motion and response to therapy, demonstrating potential in assisting clinical decision-making. [DOI: 10.1115/1.4069497]

Keywords: multi-scale model, clinical data, electromechanics model, patient-specific model, whole-heart model, calibration

¹Corresponding author.

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Richard D. Wilkinson

School of Mathematical Sciences,
University of Nottingham,
Nottingham NG7 2RD, UK
e-mail: rich.d.wilkinson@gmail.com

Steven A. Niederer

Imperial College London,
National Heart and Lung Institute,
London W12 0NN, UK;
The British Library,
The Alan Turing Institute,
London NW1 2DB, UK
e-mail: s.niederer@imperial.ac.uk

Introduction

Cardiovascular diseases are the leading cause of death globally. Currently, the treatment course of a patient with heart disease is informed by guidelines, which are in turn based on evidence from clinical trials performed on heterogeneous and often unbalanced patient populations [1]. This decision-making process often leads to suboptimal treatment response, increased risk for the patient, and unnecessary costs on the healthcare system [2]. Precision medicine, where the treatment is directly tailored to a specific patient rather than based on generalized guidelines, has the potential to improve cardiac patients care and quality of life [3]. However, currently available techniques to collect data from a patient provide limited information on the underlying mechanisms leading to that patient's heart function. In order to deliver precision medicine and link this data together, the clinical measurements need to be integrated with advanced computational and/or statistical techniques to provide a common representation of a patient's heart.

Computational models of the heart offer a physics-based framework capable of incorporating anatomical and multiscale functional information [4,5]. When personalized to replicate the available functional clinical data collected from a patient, a cardiac, patient-specific computational model provides a noninvasive tool to infer underlying mechanisms and test different treatments, to assist clinical decision-making, ultimately determining the outcome of that specific patient. Despite the contribution of previously developed models in improving our understanding of cardiac disease and therapy response mechanisms [6–10], these models only consider one or two chambers, neglecting the interaction mechanisms between the atria and the ventricles. Furthermore, these models are often based purely on images, calibrate a limited number of *a priori* selected parameters, or rely on phenomenological models.

The need to understand how the atria and the ventricles affect each other's function has motivated cardiac modelers to transition from single or dual chamber to whole-heart models [11–13]. The majority of the whole-heart models published to date are only anatomically personalized, with limited functional personalization to the left ventricular (LV) volume transient or ejection fraction from the imaging data [14–16] or the literature [17,18]. Nevertheless, these models have improved our understanding of the interaction between the atria and the ventricles, and have highlighted the importance of including the effect of the pericardium in the simulations to achieve physiological motion [13,15,16,19] and to account for different contraction properties between the atria and the ventricles [18]. However, before whole-heart models can progress to clinical applications, more thorough calibration involving dynamics for both the atria and the ventricles has to be performed, together with a rigorous validation process in order to build confidence in the model predictions [20].

In this study, we present a systematic method to constrain the parameters of a multiscale whole-heart model, built on our previous

work on global multiscale sensitivity analysis (GSA) with Gaussian processes emulators (GPEs). We applied this method to generate a patient-specific model of a female patient with atrial fibrillation (AF) and heart failure (HF), using volume and pressure biomarkers extracted from computed tomography (CT) imaging and invasive LV pressure data. The calibrated model was validated against the CT anatomy at end diastole and end systole and additional clinical data collected during pacing, which were not used in the calibration procedure. The validation shows that the model provides reliable predictions of function and response to treatment, demonstrating the potential of cardiac electromechanics model to assist the clinical decision-making process.

Methods

In the sections below, we first provide a description of the calibration method. Then, we summarize the available clinical data and the multiscale, whole-heart electromechanics framework the calibration method was applied. Finally, we describe how the fitted model was validated using clinical data that were not used during the calibration procedure.

Calibration Method. We break the calibration up into three steps (Fig. 1): (1) We determine, given the current plausible range of each parameter, which parameters are important or explain the greatest variance in simulation outputs. (2) We use history matching to fit the subset of important parameters, while all other parameters are held fixed to their default value. (3) After restricting the range of the important parameters, we update their plausible range and default value. We then repeat step 1, identifying new parameters to fit.

The calibration procedure aims at restricting the parameters $\mathbf{x} = (x_1, \dots, x_D)$ of a simulator or model $\mathbf{y} = f(\mathbf{x})$ so that the model outputs (or features) are as close as possible to a set of target clinical measurements $\boldsymbol{\mu}$ with associated uncertainty $\boldsymbol{\sigma}$. Here, D is the number of parameters, N_o is the number of outputs, and $\mathbf{y} = (y_1, \dots, y_{N_o})$, $\boldsymbol{\mu} = (\mu_1, \dots, \mu_{N_o})$ and $\boldsymbol{\sigma} = (\sigma_1, \dots, \sigma_{N_o})$ are the vectors of scalar outputs, clinical target values and standard deviations, respectively. In this study, given the extensive cost of the simulations, we use GPEs to approximate the model [21]. GPEs provide a statistical model $f_{\text{emul}}(\mathbf{x})$ to approximate how a scalar simulator output $y_j = f(\mathbf{x})$ changes as a function of the model parameters $\mathbf{x}$ (see Sec. 1 of the Supplemental Methods available in the Supplemental Materials on the ASME Digital Collection for details). In this study, we trained an independent GPE for each scalar model output of interest (Fig. 1, step 1 a–c). After being trained on a set of training points obtained from the simulator, the GPEs provide a prediction $\mathbb{E}[f_{\text{emul}}(\mathbf{x})]$ with an associated uncertainty $\text{Var}[f_{\text{emul}}(\mathbf{x})]$.

The first step of the calibration procedure is a GSA to identify the important parameters we want to restrict (Fig. 1, step 1d). A

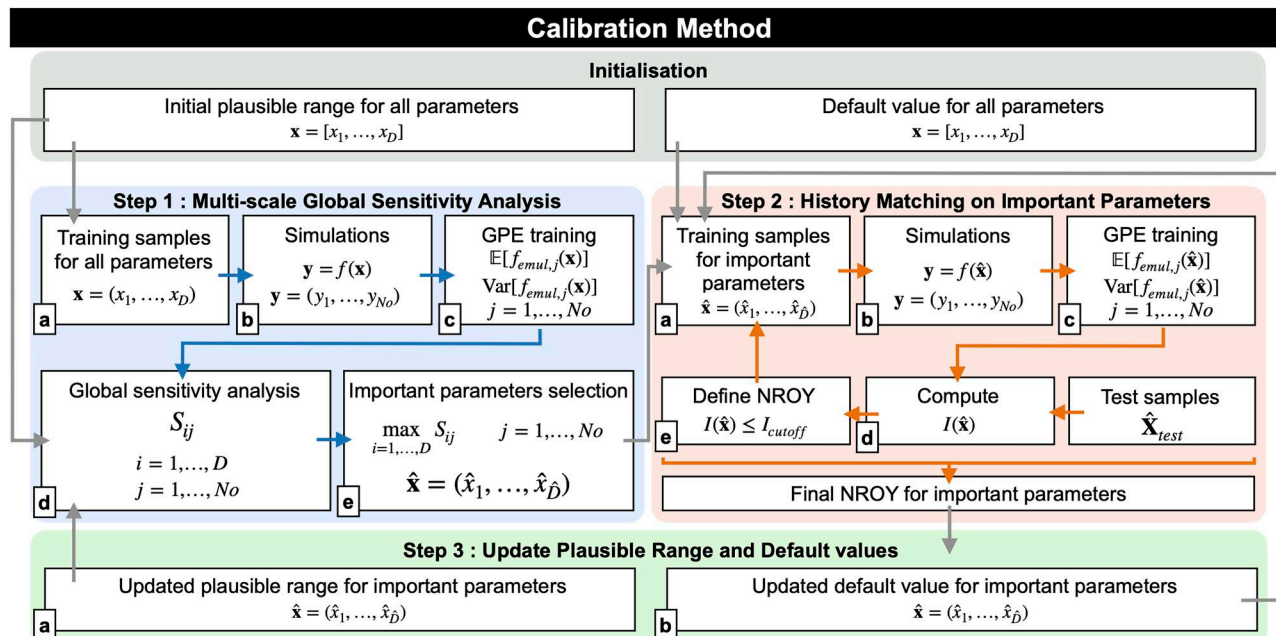


Fig. 1 Calibration method. GPE were trained with simulations run varying all D parameters (step 1(a)–(c)). The trained GPEs were used to perform a global sensitivity analysis to get sensitivity indices S_{ij} (step 1(d)), which were used to select a subset of important parameters $\hat{D}$ (step 1(e)). History matching was used to restrict the important parameters (step 2). Using the final not-ruled-out-yet (NROY) from the history matching, the plausible range and default value of the important parameters were updated (step 3(a) and 3(b)). Finally, the sensitivity analysis was repeated with the important parameters restricted to the NROY region from the history matching.

sensitivity analysis provides a matrix of sensitivity indices S_{ij} for every j -th output to every i -th model parameter, and it expresses how sensitive y_j is to x_i . We used the GPEs to compute the sensitivity indices using a Sobol sensitivity analysis as described in our previous study [22]. The important parameters were identified by taking the parameter with the maximum sensitivity for each output (Fig. 1, step 1e). This resulted in a subset of $\hat{D} < D$ important parameters $\hat{\mathbf{x}} = (\hat{x}_1, \dots, \hat{x}_{\hat{D}})$ to restrict (step 2), where the important parameters are varied within their range, while all the others are fixed to a default value. In the sections below, vectors and quantities defined on the subset of important parameters are denoted with $\hat{\cdot}$.

In the second step of the calibration (Fig. 1, right), we use history matching to restrict the range of the $\hat{D}$ important parameters from step 1 so that the model outputs $\mathbf{y}$ are as close as possible to the target values $\boldsymbol{\mu}$. History matching aims at iteratively dividing a set of test samples $\hat{\mathbf{X}}_{test}$ into implausible and nonimplausible (or not-ruled-out-yet, NROY) by computing an implausibility measure $I(\hat{\mathbf{x}})$:

$$I(\hat{\mathbf{x}}) = \max_{j=1, \dots, No} I_j(\hat{\mathbf{x}}), \quad I_j^2(\hat{\mathbf{x}}) = \frac{(\mathbb{E}[f_{emul,j}(\hat{\mathbf{x}})] - \mu_j)^2}{\text{Var}[f_{emul,j}(\hat{\mathbf{x}})] + \sigma_j^2} \quad (1)$$

given the GPE predictions and uncertainty, and the clinical target values and standard deviation for each output. By defining a cutoff on $I(\hat{\mathbf{x}})$, the test points can be divided into NROY ($I \leq I_{cutoff}$), that is, points that are within uncertainty bounds from the clinical data, and implausible ($I > I_{cutoff}$). New training samples from the NROY are added, the GPEs are retrained (Fig. 1, step 2a–c), and the implausibility measure is computed (step 2d). We refer to each history matching iteration as a *history matching wave*. Each wave results in a nonimplausible region, where the important parameters provide predictions that are within uncertainty bounds defined by the threshold I_{cutoff} (step 2e). In step 3, we update the default value of the important parameters (step 3b) and their plausible range based on the last history matching wave (step 3a). The new default value for each important parameter was found by taking the parameter combination (or test sample) with the minimum $I(\hat{\mathbf{x}})$, therefore

providing the sample where the predictions are as close as possible to the target values.

To find new important parameters, the GSA (step 1) is repeated with the important parameters from the previous iteration restricted to the plausible region from step 2, providing new sensitivity indices and therefore a new set of important parameters to restrict. Steps 1, 2, and 3 are repeated until all model outputs are within a desired cutoff from the target clinical values, or until a sufficient number of parameters have been restricted. In the application outlined below, a cutoff of 1.4 on the implausibility measure ensured that all target features of interest fell within the clinical uncertainty. This required restricting 25 out of the 48 model parameters. This method provides a systematic and flexible framework to iteratively restrict a model with a large number of parameters and multiple model outputs at the same time. Below, we apply this calibration method to a whole-heart model using clinical data collected from a patient with heart failure and atrial fibrillation.

Patient Data and Anatomical Model. The clinical data used in this study were collected as part of a clinical trial (REC number 14/WM/1069) approved by the West Midlands Coventry & Warwick ethics committee. The study was conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

The patient used in this study was selected for cardiac resynchronization therapy (CRT) upgrade from RV pacing to biventricular (BIV) pacing. Ten frame electrocardiogram (ECG)-gated CT images were acquired prior to the upgrade procedure. The end-diastolic (ED) frame was used to build an anatomical model of the patient's heart [23], inclusive of the atria, the ventricles, and a proximal portion of the aorta and the pulmonary arteries. Valve planes were used to close the endocardial surfaces of all four chambers, and rings were defined at the opening of the pulmonary veins, the LA appendage, and superior and inferior venae cavae. Fibers in the ventricles and the atria were defined with the Bayer method, with endocardial and epicardial fiber angles of ± 60 deg [24] and by mapping the Labarthe fibers using the universal atrial coordinates [25,26], respectively.

Table 1 Pressure and volume metrics estimated from the clinical data

Feature		μ_j	σ_j
LV peak pressure	mmHg	125.3	7.9
LV end-diastolic pressure	mmHg	7.0	3.0
LV end-diastolic volume	mL	180.4	2.1
LV end-systolic volume	mL	112.9	3.9
RV end-diastolic volume	mL	146.9	2.1
LA volume precontraction	mL	130.4	3.9
LA end-systolic volume (a wave)	mL	125.2	3.9
LA maximum volume (v wave)	mL	147.5	3.9

For each feature, we provide the target mean and standard deviation extracted from the data (see Sec. 2 of the Supplemental Methods available in the [Supplemental Materials](#) on the ASME Digital Collection). Abbreviations: LV = left ventricle, RV = right ventricle, LA = left atrium.

During the upgrade procedure, invasive hemodynamic recordings of the LV endocardial pressure were performed. Baseline (RA-RV pacing) and BIV pacing recordings were alternated. Only the baseline recordings were used in the calibration procedure, while hemodynamic recordings during BIV pacing were used to validate the model. We tracked the motion of the patient's heart using a motion-tracking algorithm [27–29] to derive a time-varying deformation field over the CT volume. The anatomical patient-specific model was embedded in this field and deformed to track the endocardial surfaces of the LV, RV, and the LA. The endocardial surfaces were then used to compute an image-derived volume transient for these chambers and derive values for the LV end-diastolic volume (EDV), end-systolic volume (ESV), RV EDV, LA EDV (volume prior to active contraction), LA ESV during active contraction (a wave) and LA maximum volume during the venous return (v wave). Because the local motion derived from the CT was not used in any other way to inform the calibration procedure, we used it to independently validate the kinematic model after the calibration. The RA could not be tracked due to image artifacts and poor image contrast. In Sec. 2 of the Supplemental Methods available in the [Supplemental Materials](#), we provide a detailed description of how we derived the LV pressure features and the volume features for the LV, RV, and LA from the data. This provided the vectors $\mu = (\mu_1, \dots, \mu_{N_0})$ and $\sigma = (\sigma_1, \dots, \sigma_{N_0})$ of target values and uncertainties for the model outputs (Table 1).

Whole-Heart Electromechanics Model. The modeling framework and numerical settings used in this study have been described previously [22] and in Sec. 3 of the Supplemental Methods available in the [Supplemental Materials](#). Briefly, a reaction-Eikonal model was used to simulate the propagation of the stimulus in the myocardium. The activation was initiated at the location of the RA and of the RV pacemakers' leads identified from the patient's CT. The local activation time computed with the reaction-Eikonal model was used to trigger local activation of the cell action potential, simulated with the Courtemanche [30] and the ToR-ORd [31] models for the atria and the ventricles, respectively. The calcium transient computed by these models was used to couple them with the Land model for the contraction of human myocytes [32]. This model provides a local active tension transient in the atria and in the ventricles and accounts for both length and velocity dependence of cellular contraction.

Passive mechanics of the atrial and ventricular myocardium were simulated with a transversely isotropic Guccione model [33], while all other tissues were represented with a Neo-Hookean model, with stiffnesses set according to previous studies [22]. Near incompressibility of all tissue types was enforced using a penalty method [34,35]. The local passive stress from the Guccione model and the local active stress computed with the Land model for human myocyte contraction provided the total stress of the system, used to solve the momentum equation to find the displacement of the heart

over time. The motion of the heart was constrained by applying spatially varying normal spring boundary conditions at the epicardium of the atria and the ventricles to represent the effect of the pericardium on the heart [13,22]. We also applied omnidirectional springs to the right pulmonary veins and at the superior vena cava rings. Finally, the mechanics model was coupled with a circulatory system model based on CircAdapt [36], discarding the adaptation rules. The monolithic 3D solid–0D fluid coupling method was described in detail by Augustin et al. [37]. All simulations were run with the Cardiac Arrhythmia Research Package [37–39].

We retrieved the stress-free configuration for the mechanics simulation using the method described in Ref. [40]. All four chambers in the end-diastolic configuration were unloaded from the end-diastolic pressure (EDP) of the right and the left heart, and the stress-free configuration was re-inflated to the end-diastolic pressure to achieve their original volumes before starting the simulation. The ToR-ORd-Land and Courtemanche-Land models were initialized by running an isometric simulation with no stretch for 500 beats. All simulations were carried out at a basic cycle length of 854 ms (70 bpm) based on the patient's heart rate during the invasive LV pressure recordings.

The calibration method was applied to a whole-heart electro-mechanics framework to build a personalized model of the patient's heart. Based on the clinical data available for this patient (Table 1), the model outputs $y = (y_1, \dots, y_{N_0})$ we calibrated were the LV peak pressure, EDP, EDV, ESV, RV EDV, LA EDV (volume prior to active contraction), LA ESV during active contraction (a wave) and LA maximum volume during the venous return (v wave). The parameters included in the calibration procedure were selected based on GSA carried out on different model components, based on our previous study [22]: ventricular cell model (13 parameters), atrial cell model (13 parameters), tissue electrophysiology (4 parameters), passive mechanics and boundary conditions (6 parameters), and circulatory system model (7 model parameters). The GSA on the circulatory system model was extended compared to our previous study to include the valve areas (see Sec. 4 of the Supplemental Methods available in the [Supplemental Materials](#) on the ASME Digital Collection). In addition, we included the atrioventricular delay, the unloading pressures for the left heart and the right heart, and two factors to scale the LV bulk stiffness and reference active tension and define a higher stiffness and a lower tension development in the RV myocardium compared to the LV myocardium, to account for the higher collagen content and lower myocyte density of the RV compared to the LV [41]. This led to $D = 48$ model parameters $x = (x_1, \dots, x_D)$ included in the calibration. In Table 1 in the Supplemental Methods available in the [Supplemental Materials](#) on the ASME Digital Collection, we provide all model parameters included in the analysis, their symbol, meaning, and range of variation. The parameter space was sampled as described in Ref. [22] and in Sec. 2 of the Supplemental Results available in the [Supplemental Materials](#) to build a training set for the GPEs over the whole parameter space. These GPEs were then used to perform the GSA and identify important parameters to restrict at each iteration of the calibration procedure.

To calibrate the whole-heart model, we carried out seven iterations of the calibration procedure until all model outputs fell within the acceptable range defined by the clinical data (Table 1). This allowed us to constrain the bounds of 25 of the 48 input parameters. In Sec. 1 of the Supplemental Results available in the [Supplemental Materials](#), we use a simulation study to verify that our history matching approach is able to recover true synthetic parameter combinations.

Model Validation. To validate the final fitted model, we compared model predictions and clinical data that were not used in the calibration. The final fitted model was selected as the parameter combination with the minimum implausibility measure from the last history matching iteration, namely, where the predicted outputs were closest to the mean of the clinical data. We will refer to this to as the *fitted* or *calibrated model*. First, we compared the

simulated motion resulting from the fitted model against the end-diastolic and the end-systolic (ES) CT images, noting that in the calibration we only fitted to the EDV and not the end-diastolic shape. We also compared the LV atrioventricular plane displacement (AVPD) derived from the CT and from the simulation. Second, we used the BIV pacing data ($N = 6$ beats) to verify that the model was able to predict acute response to pacing for this patient. We computed the acute hemodynamic response from the clinical data as the difference between baseline (964 ± 43 mmHg/s) and paced (1176 ± 49 mmHg/s) maximum pressure derivative (213 ± 65 mmHg/s). We performed BIV pacing simulations by adding an LV epicardial stimulus simultaneous to the RV pacing stimulus. The location of the LV lead at the time of the recording was not available. We accounted for this uncertainty in our paced model by defining a grid of 12 points around the LV latest activated area (Fig. 2, right), which is where the lead is aimed to be implanted during a pacemaker implantation procedure [42].

Results

First, we present results for the multiscale GSA and for the model calibration procedure, showing that we were able to restrict the parameters to areas where all model outputs were within the target clinical ranges. Then, the results for model validation are shown, to demonstrate the validity of the calibrated model in predicting the baseline motion of the patient's heart and acute response to pacing therapy.

Model Calibration. The 441 successful simulations performed over the whole parameter space were used to train GPEs to predict all model outputs of interest as a function of all $D = 48$ parameters x . In Sec. 2 of the Supplemental Results available in the [Supplemental Materials](#) on the ASME Digital Collection, we show the results for a 5-fold cross-validation performed during GPE training for each scalar model output of interest. All coefficient of determinations (R^2 scores) and independent standard errors were above 0.86 and 81%, respectively, indicating that the GPEs were able to accurately predict all model outputs over the parameter space, and that the observations fell within the GPE uncertainty.

Using the trained GPEs, we performed an initial GSA and used the Sobol total order effects to identify the parameters to restrict (or infer) at each iteration. Figure 3 shows the parameters ranked according to their maximum total order effect, normalized between

0 and 1 for each output. Each column in the top section represents the parameter ranking at each GSA iteration, with the bigger circles at the top highlighting the important parameters identified in that iteration. The lines show the trajectory of the ranking of each parameter as the important parameters get restricted with history matching. At the bottom, the restricted parameter ranges are shown. The initial range was normalized between 0 and 1, and the final restricted range is shown relative to the initial normalized range. For instance, in the first iteration, the important parameters were identified to be the unloading pressure for the left heart ($p_{\text{unload}}^{\text{left}}$), the systemic (R_{sys}), and the pulmonary (R_{pulm}) resistances. Through history matching, these parameters were restricted down to 8.4%, 3.9%, and 6.3% of their initial ranges, respectively. Repeating the GSA with the restricted ranges caused the ranking of these three parameters to drop from the three most important down to 42nd, 43rd, 44th out of 48, showing how the GSA depends on the parameter ranges it is performed on. In Sec. 3 of the Supplemental Results available in the [Supplemental Materials](#) on the ASME Digital Collection, we show the model parameters, their initial range, and the restricted ranges. We also describe which parameters were fitted in each iteration, the heat map of the GSA at each iteration, as well as the final nonimplausible area for each subset of important parameters. In summary, we have used an iterative GSA approach to identify different subsets of important parameters to robustly restrict their ranges with the use of GPEs and history matching.

The iterative GSA and history matching allowed us to bring the simulated outputs close to the target values extracted from the clinical data (Fig. 4). Figure 4(a) shows the simulated values for each feature, with the colored points from blue to red indicating the GSA-history matching iteration. The multiple vertical lines of the same color indicate different history matching waves over the same parameters. The shaded areas indicate the target ranges for each feature, computed as $\mu_j \pm 3\sigma_j$ following the 3-sigma rule [43] (Table 1). The parameter inference procedure restricted the parameters to areas where all output features were within the target clinical ranges. For instance, the initial simulated LV peak pressure (Fig. 4(a), top-right) ranged between 49 mmHg and 118.5 mmHg (blue dots on the left). At the end of the first history matching performed on the first three important parameters, the best achievable range for the LV peak pressure was [93, 95] mmHg, which was outside the target range of [101.6, 149.0] mmHg. On the other hand, at the last wave of the last history matching iteration (Fig. 4(a), red dots), the simulated LV peak pressure range of [118.2, 119.7] mmHg was within the

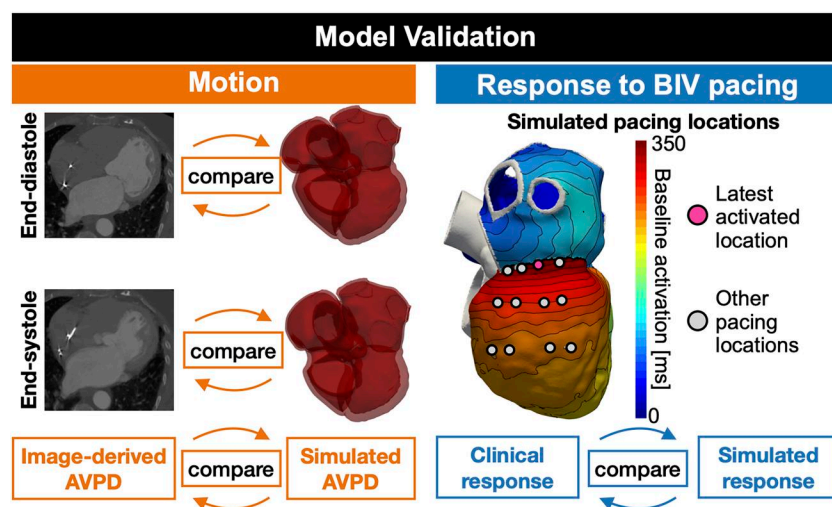


Fig. 2 Validation method. The simulated end-diastolic and end-systolic configurations were validated against the CT images (left). The acute response to biventricular (BIV) pacing computed as the change in maximum pressure derivative from baseline was validated against the clinical response. Twelve different LV pacing locations were simulated to include the uncertainty on the LV pacing location in the model (right).

target clinical range (125.3 ± 7.9 mmHg, range [101.6,149.0] mmHg). The same holds for all other features, which were restricted to be within their target clinical ranges (see Sec. 3 of the Supplemental Results available in the [Supplemental Materials](#)). Figure 4(b) shows the pressure and volume traces for the LV, RV and LA (black) for the first set of simulations of the calibration procedure. The shaded areas show the target ranges the curves should fall within as defined by the clinical data. Finally, Fig. 4(c) depicts the pressure–volume loops simulated for the best parameter combination resulting from the parameter inference procedure (see Sec. 3 of the Supplemental Results available in the [Supplemental Materials](#), Table 4 for the final values). These results demonstrate

that our parameter inference procedure successfully restricts the parameter ranges to areas where all features of interest for the LV, RV, and LA fall within the targets defined from the clinical data.

Using our calibration method, we were able to restrict parameters spanning different scales of heart function to replicate clinical data collected from the LV, RV, and the LA (Fig. 3):

- *Ventricular cell properties*, restricted to replicate the patient's LV pressure and volume: steady-state duty ratio of the cross-bridges ($r_{s,v}$), the reference isometric tension ($T_{ref,v}$), the calcium bound to the troponin when 50% of cross-bridges are blocked ($TRPN_{50,v}$), the cross-bridges cycling rate (μ_v), the

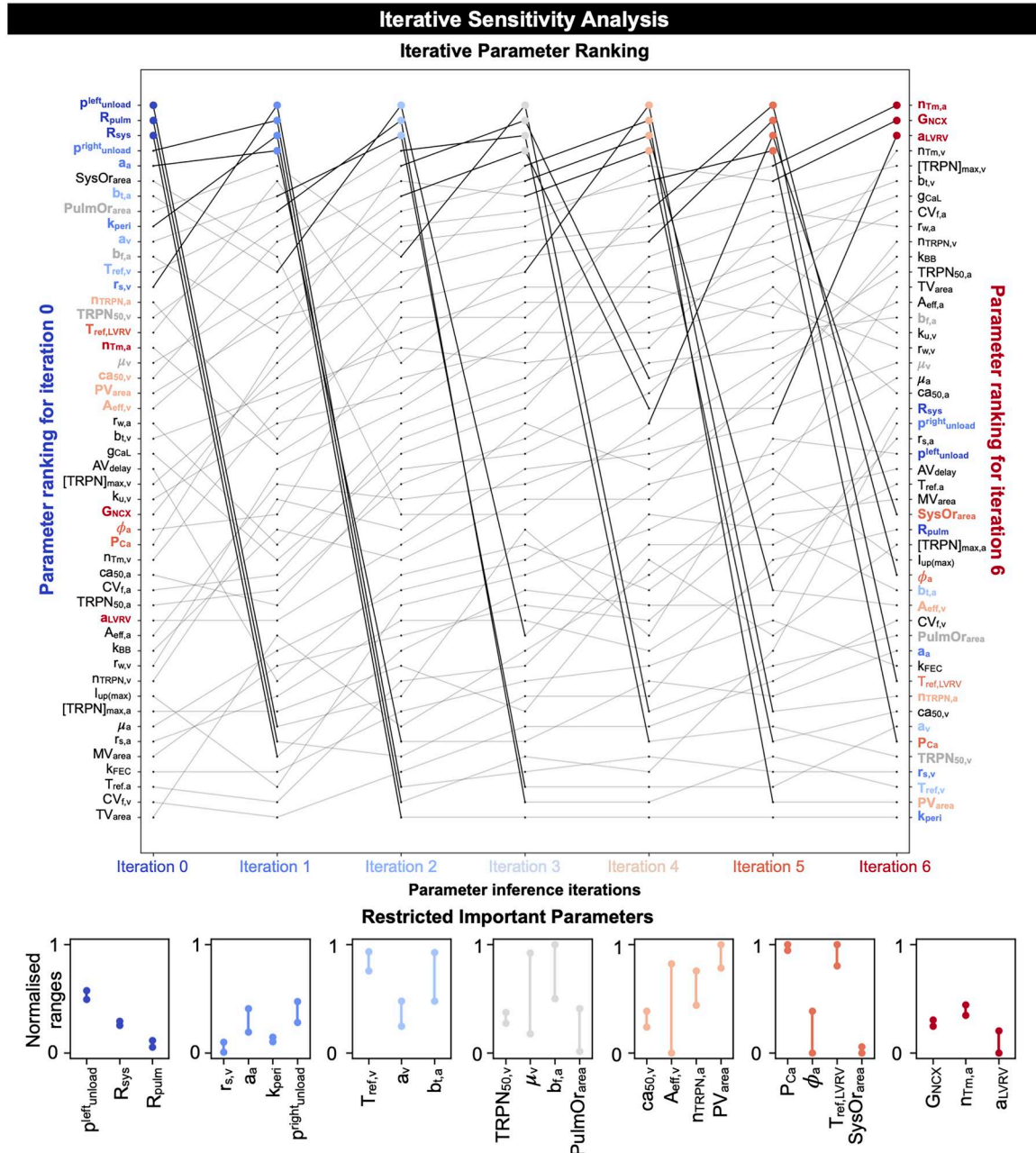


Fig. 3 Sensitivity analysis results. We used the sensitivity analysis to rank the parameters according to their normalized total effect. The image at the top shows the ranked parameters at each sensitivity analysis iteration going from left (initial sensitivity analysis) to right (last iteration). Each dot represents the ranked position of a parameter and the lines show the trajectory of the ranking of each parameter as the parameter space gets restricted through history matching. The bigger dots show the important parameters selected at each iteration, and the colors of the parameter names on the y axis indicate the iteration at which the parameters were restricted. The parameters with a black label were never selected. The plots at the bottom show the normalized ranges of the important parameters, and how they get restricted with history matching.

calcium sensitivity ($ca_{50,v}$), the cross-bridge distortion due to velocity of contraction ($A_{eff,v}$), the conductance of the L-type calcium channels (P_{Ca}), and the conductance of the sodium-calcium exchanger (G_{NCX})

- *Atrial cell properties*, restricted to replicate the atrial volumes: calcium-troponin cooperativity ($n_{TRPN,a}$), the decay of the cross-bridges distortion (ϕ_a), the Hill coefficient for calcium-troponin and the unblocked cross-bridges ($n_{Tm,a}$)
- *Passive stiffness parameters*, restricted for both atria (a_a , $b_{t,a}$, $b_{f,a}$) and ventricles (a_v) to replicate ventricular and atrial volumes, together with boundary conditions for the pericardium (k_{peri}) and the unloading pressures (p_{unload}^{left} and p_{unload}^{right})
- *Circulatory system* parameters for the peripheral resistances (R_{sys} and R_{pulm}) and the valve areas (PV_{area} , $SysOr_{area}$,

$PulmOr_{area}$) were calibrated to replicate ventricular and atrial volumes and the LV pressure

- *The RV scaling parameters* a_{lvrv} and $T_{ref,lvrv}$ were inferred to calibrate the LV and the RV volumes

The complexity of the calibration procedure we presented allowed us to infer properties from all scales (from protein to tissue and circulatory system) and chambers (atria and ventricles). As discussed below, this has the potential to provide patient-specific cell and tissue properties that remain elusive to clinical measurements.

Model Validation. After the parameter inference procedure, we identified the value for each parameter that allowed us to achieve the best fit (Fig. 4(c)). This parameter combination was then used to

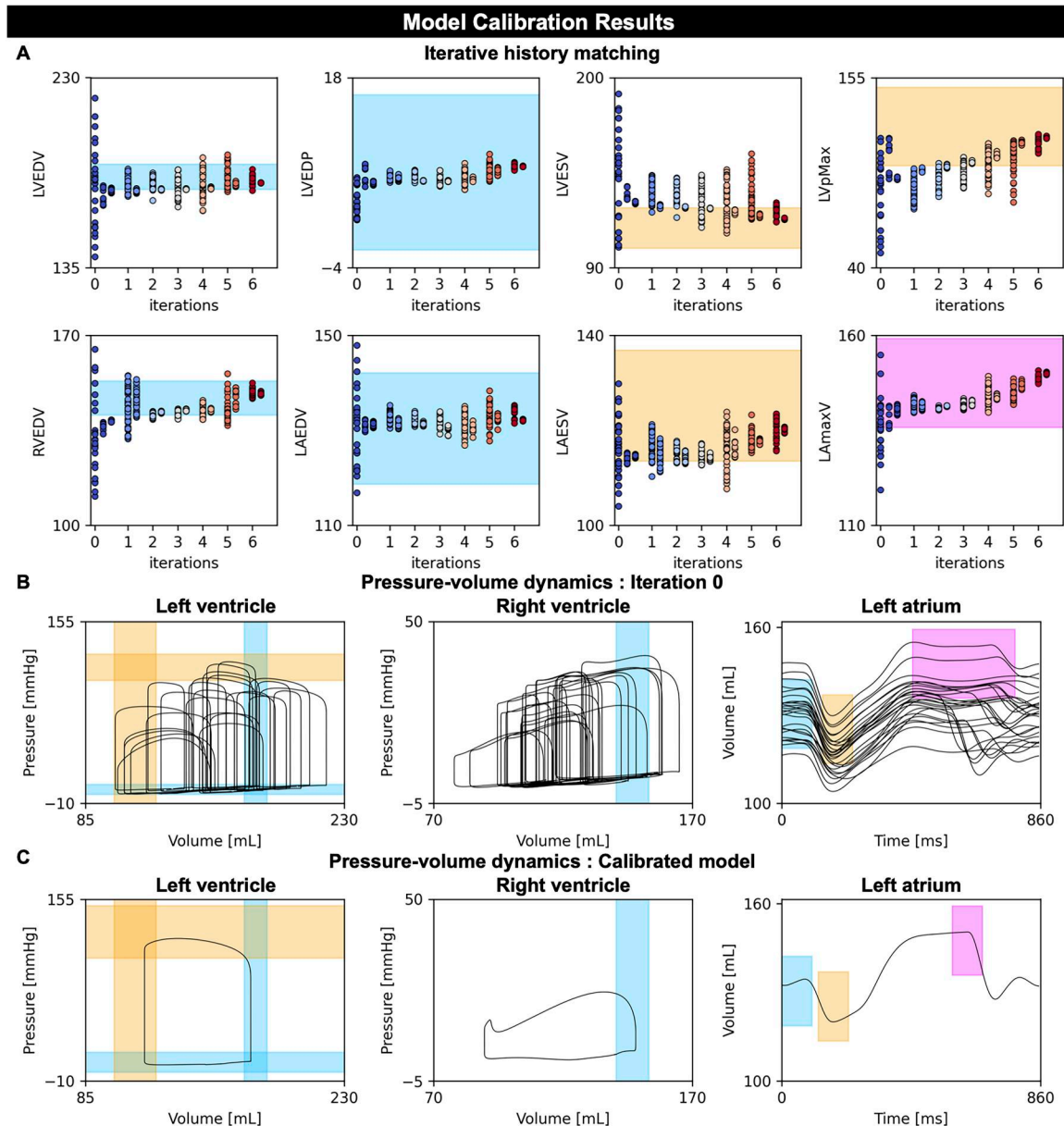


Fig. 4 Model calibration results. (a) Iterative history matching: each plot represents a feature, and the shaded areas show the ranges derived from the clinical data. Each dot shows the features extracted from one simulation and the colors represent an iteration of the calibration (global sensitivity analysis + history matching). The multiple lines with dots of the same color present a history matching wave. (b) First iteration of history matching: the black dynamics show the simulated pressure and volume transients for the LV and the RV, and the volume transient of the LA for the first iteration of history matching compared to the clinical data ranges (shaded areas). These simulations correspond to the first blue dots in panel A. (c) Calibrated model: simulated dynamics for the best sample in the last history matching wave. This is the model we will use for model validation.

perform model validation against clinical data that was not used in the parameter inference procedure.

We compared the local motion predicted by the model at end diastole and at end systole against the end-diastolic and the end-systolic CT. Figure 5 shows the predicted end-diastolic and end-systolic configurations (red outlines) overlaid to a four-chamber (4ch), two-chamber (2ch), ventricular and atrial short axis (SA) of the CT. These images show that the simulation is able to replicate the motion of the patient's heart during baseline. The simulated AVPD was also similar to the CT-derived AVPD (8.1 mm versus 8.2 mm). This first validation demonstrates that the baseline model fitted to pressure and volume features from the LV, RV, and the LA was also able to predict the local motion from the patient's cardiac CT, despite this information not being used in the calibration procedure.

We wanted to verify the validity of the model in predicting acute response to therapy. To achieve this, we simulated BIV pacing and compared the predicted acute hemodynamic response (that is the absolute change in the maximum LV pressure derivative from baseline to BIV pacing) against the clinically measured response. When simulating BIV pacing at the latest activated point, the predicted acute hemodynamic response was 222 mmHg/s, which was similar to clinically measured values (213 ± 65 mmHg/s, Fig. 5, bottom). When accounting for the uncertainty in the LV pacing location, the model simulated an acute hemodynamic response of 179 ± 79 mmHg/s. The best response was achieved when the LV was paced closest to the latest activated area (light purple, Fig. 5), and it

got worse when the LV was paced further away from the late activated area (dark purple). These results show that the model is able to replicate measured acute response to pacing therapy, showcasing its validity in performing reliable *in silico* predictions.

Discussion

In this study, we propose a novel systematic method to infer parameter ranges in complex high computational cost models. We then applied this method to infer patient-specific multiscale model parameter ranges that allow us to recapitulate emergent organ scale clinical measurements in a detailed four-chamber heart model. GPEs were trained to predict whole-organ biomarkers (e.g., LV peak pressure) and to perform a GSA by varying 48 model parameters across different scales (from protein to whole-organ) and physics (from electrical to mechanical and hemodynamic properties). The GSA informed which parameters were the most important for each model output of interest. The important parameters were restricted using history matching to bring the simulated biomarkers as close as possible to the ranges derived from the clinical data. Biomarkers for the LV pressure and volume, and the RV and LA volume were used in the calibration. The GSA was repeated to account for the new, restricted ranges and to identify a new subset of important parameters. This iterative GSA and history matching procedure allowed us to restrict 25 of the 48 parameters, and to bring all the biomarkers for the LV, RV and the LA within clinical ranges. The

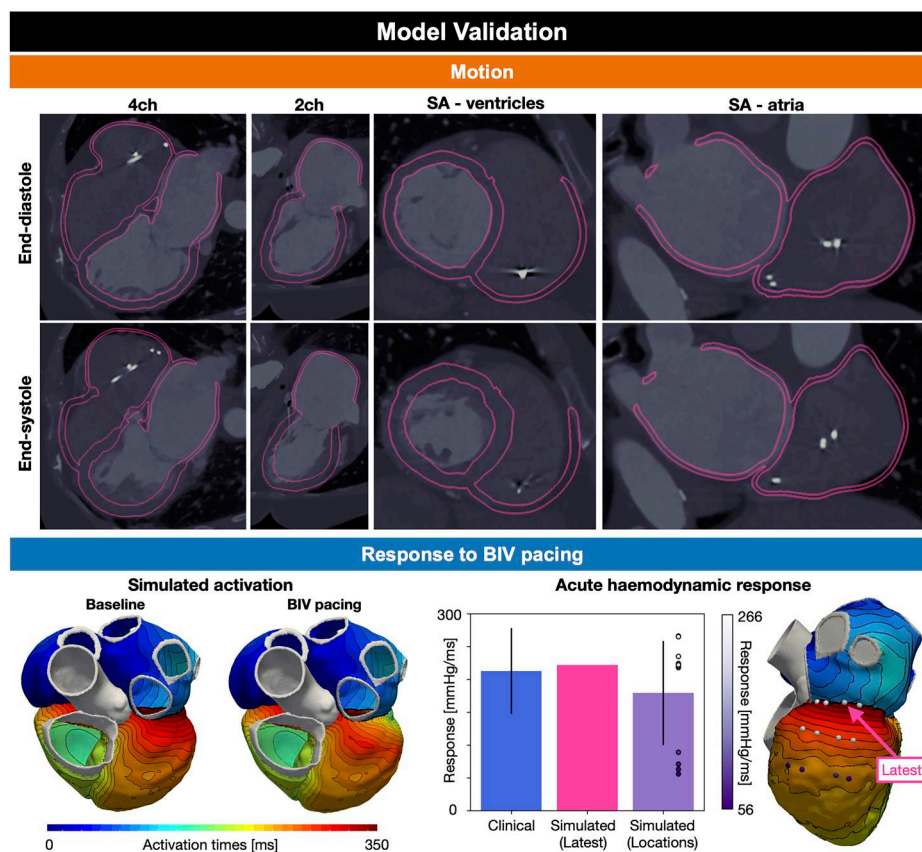


Fig. 5 Model validation results. We validated the simulated motion against the CT images at end-diastole (top) and at end-systole (bottom). The pink outline shows the simulated geometry. The comparison is shown for a four-chamber slice (4ch, first column), a two-chamber slice (2ch, second column), the short axis of the ventricles (SA-ventricles, third column) and of the atria (SA-atria, last column). BIV pacing was simulated by introducing an additional stimulus at the LV epicardium (bottom section, left) at different locations. The acute hemodynamic response was computed as the change in maximum LV pressure derivative from baseline to pacing. The clinical response is represented by the blue bar, while the pink bar represents the simulated response achieved by pacing the latest activated point in the model. The third purple bar shows the mean response simulated by pacing at different locations with dark and light purples showing lower and higher response, respectively.

model was validated against the baseline end-diastolic and the end-systolic CT, and the patient's acute hemodynamic response to BIV pacing. This study provides a systematic and flexible method to integrate clinical data into a complex whole-heart electromechanics simulation framework to build a patient-specific, whole-heart model. The validation shows that the model is able to replicate the patient's local heart motion as well as acute response to therapy, demonstrating that it is a reliable representation of the patient's heart.

Comparison to Previous Whole-Heart Models. The complexity of a whole-heart compared to mono or dual-chamber frameworks widens the spectrum of pathologies and treatments that can be simulated. Four-chamber frameworks can simulate scenarios where AV interaction is important, thanks to the realistic representation of the mechanical interaction between chambers modulated by the pericardium and the circulatory system. For this reason, in the last decade, an increasing number of whole-heart models have been developed [11–18,38,44–46]. Most of the studies employing whole-heart frameworks, however, lack calibration to real-world clinical data from multiple chambers and independent model validation. Part of the reason of this is the lack of clinical data from the subject the heart model was generated from, as most of these studies focus on a healthy volunteer. To cite a few examples, Moss et al. [44] used a strongly coupled whole-heart model to investigate the effect of cardiac motion on the 12-lead ECG, and used the healthy volunteer's 12-lead ECG to validate the simulated ECG, but the mechanics model was not validated. Pfaller et al. [15] and Fritz et al. [16] used the clinical magnetic resonance imaging (MRI) images to validate the predicted motion and the AVPD. However, the pressure transients produced by the model were not validated. Finally, like many other studies, Land et al. [18] used literature data for the LV peak pressure and stroke volume to calibrate the model and achieve physiological pressure and ejection. This was however not supported by clinical data from the patient. In this study, we calibrated a whole-heart model to image-derived volume features from the LV, RV and LA, as well as LV invasive pressure recordings. Similar to previous whole-heart models [15,16], we used the end-diastolic and end-systolic clinical images and image-derived AVPD to validate the predicted motion. In addition, we validated the predicted response to BIV pacing against invasively recorded hemodynamic response, showing that our model is able to replicate acute response to therapy.

Previous whole-heart models calibrated a small number of user-defined, preselected parameters. Pfaller et al. [15] adapted five circulatory system parameters and the reference contractility for the ventricles to achieve physiological pressures and an LV ejection fraction compatible with the patient's MRI. Similarly, Fritz et al. [16] modified the ventricular reference contractility and the stiffness of the pericardium to achieve physiological ejection and motion compatible with the patient's MRI, and Land et al. [18] scaled the circulatory system parameters from a dog model to simulate physiological LV pressure and ejection. Fitting subjective parameters based on known physiological relationships between model inputs and outputs is a commonly used in cardiac electromechanics models, as it offers a low-cost calibration procedure owing to the fact that only a few parameters are adapted to achieve the target dynamics. However, this might introduce bias in the fitting procedure. In this study, we used a systematic and unbiased approach to select the parameters to fit. Among the 25 parameters we calibrated, circulatory system parameters (e.g., systemic and pulmonary resistances in iteration 0, Fig. 3), stiffness of the pericardium (k_{peri} in iteration 1), and reference contractility ($T_{\text{ref},v}$ in iteration 2) were fitted, similarly to the studies mentioned above. However, we selected these parameters with an unbiased method with clear assumptions rather than relying on known physiological relationships.

Although our method is systematic and unbiased, it introduces a significant computational cost compared to previous whole-heart electromechanics studies [15,16,18]. The desired level of accuracy

of the calibration procedure should always be guided by the application the model is intended for, and by the clinical data available for that patient. In this study, we wanted to demonstrate the capability of our method to calibrate a wide range of model parameters to fit both pressure and volume dynamics for multiple chambers, made possible by the rich dataset we had available for this patient. Fitting features for only one chamber of interest would considerably reduce the number of fitted parameters and therefore the computational cost. Furthermore, the simulations performed to train the GPEs used for the multiscale GSA constitute half of the total computational cost of the calibration procedure. In Sec. 4 of the Supplemental Results available in the [Supplemental Materials](#) on the ASME Digital Collection, we show that GPE performance is maintained when training the GPEs with 90%, 80%, and 70% of all 441 available data points, saving significant computational cost. Nevertheless, the cost of the GSA remains large. Using a less complex sensitivity analysis method like a one-at-a-time approach, where the model parameters are varied at their minimum and their maximum, would require 96 simulations (twice the number of parameters) rather than more than 400–500. However, this type of sensitivity analysis would only account for first-order sensitivity indices, while discarding interactions between model parameters. Alternatively, using known physiological relationships between model parameters and features of interest to select parameters to calibrate, similar to previous studies [15,16,18] rather than a GSA, allows for a much simpler and still widely used approach owing to the significantly smaller computational costs required by the calibration.

Compared to previously published whole-heart electromechanics models, our study calibrated a large number of model parameters (25 versus a maximum of 6 in other models), selected with a systematic and unbiased method. Our approach constitutes an example of a more extensive, although computationally demanding, calibration procedure involving pressure and volume features from multiple chambers, 25 model parameters across different scales and physics, as well as model validation, combining clinical data, machine learning, GSA and complex heart electromechanics simulations.

Inferring Non-Clinically Observable Heart Properties. When designing the treatment of cardiac patients, clinicians rely on clinical data, spanning from genetics and blood samples up to detailed cardiac imaging and invasive pressure data. Although recent advancements in genetic testing and imaging have improved the information clinicians obtain from these data, the mechanisms underlying the pathology and/or response to therapy often remain elusive to clinical observations. Computational models of the heart can quantify the effect of anatomy as well as cell and tissue properties on the patient's heart function and on response to treatment, and link these properties to observable clinical biomarkers. By coupling a model for sarcomere contraction with CircAdapt, a zero-dimensional model for the cardiovascular system, Lumens et al. were able to show that cross-bridge cycling rate worsens response to pacing [47]. Other computational studies have been able to show that response to cardiac resynchronization therapy is also affected by the effectiveness of length dependence of tension [48] and by heart size [49]. Multiscale models of the heart have been used to identify ablation targets for ventricular tachycardia [50,51] and to predict recurrence of AF after ablation [8]. Finally, detailed biventricular models have been used to infer passive and active properties in the infarcted [52] and pulmonary hypertensive [53] rat heart. These studies constitute examples of the potential of computational models in assisting the clinical decision-making process, by either estimating material properties in different disease scenarios, providing mechanistic insight into response to therapy, or by guiding therapy delivery based on clinically derived patient-specific properties (e.g., scar and anatomy). However, these studies consider only the ventricles or the atria, therefore lacking AV interaction, and they present different levels of personalization, from calibration to literature data [47], to anatomical [8,50,51] and/or functional personalization [48,49]. The patient-specific whole-

heart electromechanics model presented in this study is able to capture AV interaction mechanisms, and was personalized to clinical data from multiple sources and chambers. The calibration procedure allowed us to restrict 25 parameters, spanning from ventricular and atrial ion currents, contractile properties and myocardial stiffness, up to properties of the circulatory system. While myocardial stiffness and circulatory system resistances could be estimated in vivo through imaging [54] and hemodynamic measurements, clinical data are unable to quantify cell properties (e.g., cell contractility). Furthermore, some of the parameters we inferred are associated with specific genes. For instance, G_{NCX} , representing the density of the sodium-calcium exchanger in the ventricles, is associated with gene NCX1 or SLC8A1 [55]. This could facilitate establishing genotype-phenotype links, that is the connection between a patient's genetic information and their observable characteristics. By creating cohorts of patient-specific models (for instance, healthy controls versus heart failure), we would be able to compare the calibrated parameters to identify heart properties that differ between groups. In the context of therapy optimization, when applied to cohorts of responders and non-responders to a specific therapy, the calibration procedure could unveil intrinsic tissue and/or cell properties that affect response. The calibration method presented in this study has the potential to provide patient-specific information that remain elusive to clinical measurements alone. This could ultimately assist and optimize the patient-selection process for therapy delivery.

Limitations. Although our study constitutes the first multiscale, whole-heart electromechanics model calibrated to clinical data from the atria and the ventricles, it has some limitations.

The simulation framework used in this study was very complex and the resulting simulations were very computationally expensive. Due to this complexity and to reduce the overall computational cost of the model calibration procedure, we did not run a fully converged Newton solution by constraining the maximum number of Newton iterations to 2. We have previously shown that this allows us to speed up the simulations by up to 3 times, but also that it introduces small errors in the simulated pressure and volume features (below 3%) [22]. This significantly reduced the computational cost of our study, making it possible to run more than 800 simulations to calibrate 25 out of the 48 model parameters we considered in the initial GSA. The computational cost of this study is still very large, and possibly prohibitive if applied to large cohorts of patients. This could be addressed in future with more efficient high-performance computing facilities or better statistical methods requiring less model evaluations to be trained [56].

In our simulations, we assumed that the mechanical deformation does not affect the ion channels and the electrical properties of the tissue, as the electrophysiology and the mechanics were solely coupled through the calcium transient. However, there are known mechanisms in which stretch induces changes in the electrical activity of the heart through, for instance, stretch-activated ion channels [57]. These mechanisms might play a role in some pathologies, such as arrhythmogenesis initiation [58]. Depending on the application, the effect of these mechanisms might need to be included in the simulations to provide a more reliable representation of the patient's heart.

Following our previous study [22], we used a GSA on each submodel to exclude the unimportant parameters based on their effect on the submodel outputs of interest. This was done under the assumption that these parameters would also be unimportant for whole-organ biomarkers. This allowed us to reduce the computational cost significantly as we were able to exclude 76 of the initial model parameters. However, this approach might fail to capture interactions between the parameters we excluded from the submodels. Since the parameters we excluded had small, if any, effects on submodel outputs, we expect the combined effects between unimportant parameters of different submodels to be small as well. Additionally, in our GSA and history matching, we discarded any potential correlation between different model outputs.

Training a GPE for each output separately provided us the flexibility to fit the hyperparameters for each GPE independently. This could have been accounted for by training a multi-output GPE instead [59], where the GPE degrees-of-freedom are estimated for all outputs at the same time rather than independently. Alternatively, more advanced machine learning techniques such as latent neural ordinary differential equations [60,61] or physics-informed neural networks [62–65], could be used to further reduce the computational cost of the calibration procedure and/or to approximate pressure and volume time transients rather than only scalar quantities. These techniques have already been used to predict cardiac activation of the LA [62] and pressure–volume relationships in an LV [61,64] and whole-heart electromechanics model [60] and LV strains [64].

In our GSA, we did not formally account for the uncertainty of the GPEs when computing the total order effects. However, we sampled the posterior distribution of the GPEs 1000 times for each GSA and computed the average total order effects across these samples. How the GPE uncertainty is incorporated in the GSA might affect the ranking of the parameters, and therefore which parameters are selected at each iteration. However, performing 7 iterations of the calibration procedure, leading to 25 out of the 48 model parameters being selected and restricted, attenuates this effect as, for example, a potentially important parameter that was not selected in the first iteration will be selected in the second. In applications where less iterations of the calibration procedure are required or performed due, for example, to computational cost, the method used to compute the sensitivity indices and to incorporate GPE uncertainty is more likely to impact the final set of parameters that are restricted. In future studies, the uncertainty of the GPE prediction could be accounted for by using alternative approximations of the sensitivity indices that directly include GPE standard deviation as well as the expected value.

Our method relies on the availability of patient-specific clinical data, comprising an ECG, an ECG-gated CT and invasive LV pressure measurements. ECG-gated CT provides submillimeter resolution images of the patient's heart, [66] but it requires ionizing radiation and contrast, therefore preventing its use on healthy controls and patients with, for example, poor kidney function. Our calibration procedure could have been applied using volume features derived from MRI. Compared to CT, cardiac MRI has lower spatial resolution, but it is widely available, provides superior temporal resolution, and does not require ionizing radiation [66]. Our study also relies on invasive LV catheterization to get LV peak pressure and LV EDP, which carries risk of complications. This type of data is therefore not available for the majority of subjects (e.g., healthy controls). Alternatively, noninvasive cuff pressure measurements could be used as an estimate for LV peak pressure and be used as a target in the calibration procedure. Furthermore, there is an increased availability of large datasets such as the UK Biobank, [67] where cardiac MRI, ECG and cuff pressure measurements are provided for more than 50,000 healthy controls and patients with a range of cardiac pathologies, and the multi-ethnic study of atherosclerosis, [68] providing cardiac MRI, ECG and blood pressure in 6500 subjects of different ethnicity. These datasets provide access to imaging, to derive the patient-specific geometry and volume features at different phases of the cardiac cycle, and noninvasive blood pressure measurements, making it possible to apply our calibration procedure for research groups without access to clinical data.

Due to the high computational cost and high dimensional parameter space, by necessity we had to use approximations and make assumptions. Despite this, our framework allowed us to integrate imaging and invasive pressure clinical data from the LV, RV, and the LA into a whole-heart electromechanics framework. The model validation shows that the parameter values resulting from the history matching constitute a reliable representation of the patient's heart motion and of the acute response to pacing therapy.

Conclusions

We have presented a method to calibrate multiscale model parameters of a multiscale, whole-heart model using real-world

clinical data from multiple chambers. This study provides a systematic framework to integrate imaging and pressure data into a complex multiscale model, employing emulators, sensitivity analysis and history matching. The validation demonstrates the validity of the model in predicting the patient's heart motion and response to pacing therapy, and showcases its potential in providing reliable in-silico predictions. Furthermore, our iterative method follows three steps, outlined in Fig. 1 (parameter restriction and updating the default values), that are generalizable to any computational modeling framework with a large number of parameters and different outputs to be fitted at the same time.

Author Contribution Statement

M.S. and S.A.N. conceptualized the study. M.S., C.M.A., M.A.F.G., E.J.V. and G.P. contributed developed the software used in this study. M.S., S.A.N., C.J.O., and R.D.W. designed the experiments. C.A.R. collected and managed the clinical data used in this study. M.S. performed the simulations and the analysis, interpreted the results and drafted the paper. All authors revised the paper and approved its final version.

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Data Availability Statement

The datasets generated and supporting the findings of this article are obtainable from the corresponding author upon reasonable request.

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