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Abbreviations

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<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tr>
<td>DCM</td>
<td>Dilated cardiomyopathy</td>
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<td>DTI</td>
<td>Diffusion tensor imaging</td>
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<td>EA</td>
<td>Electrical axis</td>
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<td>ECG</td>
<td>Electrocardiogram</td>
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<td>EF</td>
<td>Ejection fraction</td>
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<td>Electromechanics</td>
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<td>EP</td>
<td>Electrophysiology</td>
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<td>GMM</td>
<td>Gaussian Mixture Model</td>
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<td>LBM</td>
<td>Lattice-Boltzmann</td>
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<td>LV</td>
<td>Left ventricle</td>
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<td>MCMC</td>
<td>Markov Chain Monte Carlo</td>
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<td>MRI</td>
<td>Magnetic resonance imaging</td>
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<td>NLS</td>
<td>Non-linear least square</td>
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<td>PCE</td>
<td>Polynomial Chaos Expansion</td>
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<td>PDF</td>
<td>Probability density function</td>
</tr>
</tbody>
</table>
Table of Contents

Executive Summary ........................................................................................................................................ 5

1. Introduction ............................................................................................................................................... 6
   1.1. Objective ............................................................................................................................................... 6
   1.2. Overview of the Modelling Pipeline ..................................................................................................... 6
       1.2.1. Cardiac Anatomy .......................................................................................................................... 6
       1.2.2. Electrophysiology .......................................................................................................................... 7
       1.2.3. Biomechanics ................................................................................................................................. 7
       1.2.4. Hemodynamic ................................................................................................................................... 7
   1.3. Technical Objectives of T8.2 .................................................................................................................. 7

2. Uncertainties in Model Parameters due to Data Noise .............................................................................. 7
   2.1. Inverse Uncertainty Quantification ......................................................................................................... 8
   2.2. Posterior Analysis under Uncertainty ......................................................................................................... 9
   2.3. Experiments and Results ......................................................................................................................... 9
       2.3.1. Precision of PCE Surrogate Model ............................................................................................... 9
       2.3.2. Estimation of Biomechanical Parameters and Comparison against State-of-the-Art ................... 10
   2.4. Empirical Evaluation of Estimated Uncertainty ..................................................................................... 11

3. Uncertainties in Anatomical Model Input .................................................................................................. 12
   3.1. Personalisation of Cardiac Models ........................................................................................................... 13
       3.1.1. Robust Segmentation of Myocardium from MRI ........................................................................ 13
       3.1.2. Personalised Cardiac Electrophysiology Model .......................................................................... 13
       3.1.3. Personalised Cardiac Mechanical Model ....................................................................................... 13
   3.2. Population-Based Uncertainty Quantification of Fibres ....................................................................... 14
       3.2.1. Variability Estimation in Atlas Space ............................................................................................ 14
       3.2.2. From Atlas to Patient Space .......................................................................................................... 14
   3.3. Propagation of Fibre Uncertainty on a Case Study .................................................................................. 15
       3.3.1. Clinical Background ....................................................................................................................... 15
       3.3.2. Goodness of Fit and Variability after Personalisation ..................................................................... 15
       3.3.3. Uncertainty on the Model Parameters and Discussion ................................................................... 17
Executive Summary

In paediatric cardiovascular disease, predicting how patients will respond to treatments, which treatments to use, and when to treat can be difficult to define due to small patient numbers and limited outcome data. Modelling of patient bioinformatic data may provide better insight into prognosis, which would help in patient management and in telling families how their child will progress. However, all modelling is affected by noise in measurements and inherent limitations of simplified (w.r.t. the real world) computational models. Simulation results for electrophysiology and biomechanics should therefore be presented together with estimated variance and confidence numbers.

In this report, we describe the progress towards this goal in the first 20 months of task T8.2. We present the developed pipeline and two studies of uncertainty. The first of these studies analyses the confidence of estimated model parameters due to noise in the input data. This becomes important when the model parameters in question are part of clinical decision making. The second study analyzes the differences in model output for varying cardiac fibre anatomies. This is especially interesting since fibre structure can currently not be measured in-vivo and simulations thus have to rely on prior models. The simulation pipeline for the second study combines modules from Siemens and INRIA, the two main partners involved in WP8. We present how this pipeline is connected and what possibilities this opens for the future of the project.
1. Introduction

1.1. Objective
In paediatric cardiovascular disease, predicting how patients will respond to treatments (operations, catheter interventions, pharmacology), which treatments to use, and when to treat can be difficult to define due to small patient numbers and limited outcome data. When children present with new onset heart failure, there are five possible outcomes: full recovery, dilated cardiomyopathy (DCM) requiring drug therapy, DCM requiring transplantation or mechanical support, another diagnosis (other forms of cardiomyopathy, metabolic disease) or death. At presentation, however, it is very difficult to predict which group any patient will end up in. Data suggests that good systolic function and younger age are good prognostic indicators for survival [1], but better prognosticators are necessary.

Over the last decade, there has been a huge investment into information technology and computer modelling to build models of the heart that are able to gather any kind of clinical information and produce realistic representations of the cardiovascular system. Modelling of patient bioinformatic data may provide better insight into prognosis of cardiomyopathies, which would help in patient management and in telling families how their child will progress. Would he/she recover completely or would he/she require heart transplant? These models have now reached high levels of reproducibility, opening new avenues for more efficient, safer, and cost-effective patient management. However, their comprehensive validation is still limited.

1.2. Overview of the Modelling Pipeline
Modelling cardiac electromechanical activity has been an active research area for several decades. Within the MD-Paedigree project, the models used were selected based on three criteria: 1) the computational efficiency of the simulation at the organ scale, in order to enable model personalization and interaction with the model; 2) the observability of their parameters from clinical data and 3) their predictive power for the clinical question addressed.

A computational heart model is described by four components: anatomy, electrophysiology, biomechanics, and hemodynamic. These components were already described in deliverables D8.1 and D9.1. For convenience, we repeat this section here, but the knowledgeable reader might skip it to go directly to Section 1.3.

1.2.1. Cardiac Anatomy
Cardiac anatomy is usually modelled from medical images such as computed tomography (CT) or magnetic resonance images (MRI). Image segmentation algorithms have been developed in the past to (semi-) automatically segment the cardiac chambers [2][3][4]. For ventricular modelling, both endocardia and the heart epicardium are segmented and then merged to form a volumetric mesh of the heart. Cardiac fibres are then mapped to this volumetric mesh. Several choices are available:

- rule-based approach, where fibres elevation angle are user-defined at the endocardia and epicardium and then interpolated elsewhere [5][6][7];
- ex-vivo atlases generated from diffusion tensor MRI (DTI) of animals [8] or more recently of humans [9];
- or in-vivo DTI, although this modality is still not available in clinical routine [10].
1.2.2. Electrophysiology
For the electrophysiology (EP), phenomenological models of trans-membrane potential propagation, based on 2 or 3 variables and reaction-diffusion partial differential equations (PDE) already provide a good representation of cardiac electrical behaviour \[11, 12\]. These equations are traditionally solved using finite element models \[13\],[14] but recently Lattice-Boltzmann approaches have been proposed \[15\], which are naturally suited for parallel architectures and provide near real-time electrophysiology computations. Cardiac EP models can be coupled to electrical conductivity in torso for the simulation of electrocardiograms \[6, 16\], making their clinical interpretation easier.

1.2.3. Biomechanics
For the biomechanics, models mainly use the Hill-Maxwell representation of muscles, with an active contractile part in parallel with a passive part. The active part models the contractile mechanisms of the myofilament \[5, 17, 18\]. The passive part models the behaviour of the myocardium tissue (its constitutive law). Thanks to recent advances in numerical schemes \[19, 20\], it is recommended to use hyper-elastic materials to capture the non-linear behaviour of the tissue. Models can then be either transverse isotropic \[21\] or orthotropic \[22, 23\]. Finally, an additional series element is sometime added to the active one to capture the effects of the Z-discs for instance \[17\]. These models incorporate few parameters for the contraction-relaxation behaviour and few others for the passive stress-strain relationship.

1.2.4. Hemodynamic
Finally, the hemodynamic can be either modelled through detailed computational fluid dynamics equations including potentially the fluid-structure interaction \[24\], or lumped models at a larger spatial scale. The choice is made depending on the data and the parameters of interest for the clinical question \[25, 26, 27\].

1.3. Technical Objectives of T8.2
Task T8.2 combines two modelling steps of the presented simulation pipeline; electrophysiology (EP) and biomechanics. Based on results from previous projects as Sim-e-Child, both models need to be set up and personalised. During personalisation, parameters of the model (e.g. tissue diffusivity for EP or stiffness for biomechanics) need to be estimated so that the model output best fits the specific patient data.

As all measurements contain a certain amount of noise, and some data are not possible to measure at all, the uncertainty of the model and its result is one of the main topics of this task. It should be studied both from a theoretical point of view and experimentally by a consensus framework that integrates results of models from different partners. Final result of the task will be the calculation of certainty or agreement maps, which can be used to show to clinicians significant simulation outcomes.

2. Uncertainties in Model Parameters due to Data Noise
In order to provide clinically useful information for a specific patient, MD-Paedigree’s cardiac models must first be personalised, i.e. the parameters of the model need to be estimated from clinical data. However, uncertainty in data and model assumptions are known to increase the non-identifiability of parameters. In particular, solution uniqueness is not guaranteed and multiple solutions or entire manifolds of solutions with equal level of confidence may exist. As a result, the clinical value of a single estimate can be questioned. Yet, to the best of our knowledge, only little work exists in the cardiac modelling community which addresses these challenges.
We developed a novel stochastic method for the robust estimation of biomechanical parameters of the myocardium, which gives additional insight by providing uncertainty measures of the estimated model parameters due to noisy data. The workflow is sketched in Figure 1. A standard sensibility analysis requires thousands of model runs, which is not feasible in practice when models require several minutes to compute. To make the problem tractable, we first estimate a surrogate model of our electromechanical model by using Polynomial Chaos Expansion (PCE), which is then used in a Bayesian inference framework to estimate posterior probabilities of model parameters. We then apply the mean-shift algorithm on the posteriors to find the optimal parameter value by integrating the space of measurements uncertainties. It should be noted that the framework is not limited to a particular model or model parameterization.

Figure 1: Inverse uncertainty quantification framework

2.1. Inverse Uncertainty Quantification

We reformulate the utilized forward model as a statistical forward problem \( f(\theta) = d^c \) where \( \theta \) and \( d^c \) are random input (model parameters) and output (model responses) variables. Bayesian calibration is used to infer the values of \( \theta \) and to quantify their uncertainty due to noisy measurements \( d^m \). The goal now is to compute the posterior PDF \( p(\theta|d^m) \) by forward propagation of uncertainty [28]. Following Bayes’ rule,

\[
p(\theta|d^m) \propto p(d^m|\theta)p(\theta) = \exp \left( -\frac{1}{2} \epsilon(d^c, d^m)^T S^{-1} \epsilon(d^c, d^m) \right) p(\theta)
\]

\( p(d^m|\theta) \) is the likelihood, describing how well each set of parameters is supported by the data. \( p(\theta) \) is the prior, representing the knowledge on the parameters independently from the measurements, and is modelled here using a uniform distribution. The likelihood is expressed in terms of the error between responses and measurements, \( \epsilon(d^c, d^m) = d^c - d^m \), modeled as a normal distribution with zero mean and diagonal covariance matrix \( S \). All sources of error are aggregated under \( \epsilon \). The posterior is then sampled using the Markov Chain Monte Carlo (MCMC) method [29].

To make the MCMC sampling computationally tractable, we use Polynomial Chaos Expansion (PCE) to estimate a surrogate model \( \hat{f}(\theta) \approx f(\theta) \). \( \hat{f} \) provides an efficient functional mapping from model input to individual response [30]. For each response \( r \in d^c \), the finite PCE approximation \( \hat{f}_r(\theta) \) corresponds to expressing that model response \( f_r(\theta) \) in terms of linear combinations of multivariate Legendre polynomials, where the total number of coefficients \( P + 1 = (q + 1)^{\text{dim}\theta} \) is defined by a user-specified maximum polynomial order \( q \) (the higher \( P \), the more fidel the approximation). The coefficients of the polynomials are obtained using spectral projection, which requires \( P + 1 \) forward model runs. We refer to [28][30] for theoretical details. The PCE surrogate of our forward model is finally used to efficiently generate MCMC samples of the posterior \( p(\theta|d^m) \), instead of the full forward model.
2.2. Posterior Analysis under Uncertainty

We now have a PDF of the model parameters knowing the noise in the data, \( p(\theta|d^n) \). Coming back to the original objective (model personalization), we now need to derive an estimate of the model parameters and their confidence interval (see Figure 1). We want to estimate the parameters \( \theta^* \) that are most robust to varying level of noise in the data, since that level is often difficult to precisely estimate. To that end, we propose to aggregate the posteriors calculated for different levels of noise into one PDF, from which we will estimate the most likely value of the model parameters.

More precisely, in a first step, we estimate the number of modes \( k_i \) in the posterior using the mean-shift algorithm for a given level of noise \( S \) (Eqn. on p. 8), on which we fit a Gaussian Mixture Model (GMM) with \( k_i \) components \( G_i \). This step is repeated \( n_S \) times with distinct levels of measurement noise uncertainty by varying the error variances of the individual responses in \( S = S_i \) of the likelihood. At the end of this process, \( n_S \) mixture models \( G = G_1, ..., G_{n_S} \) are generated.

In a second step, the \( G_i \) are aggregated into one robust mixture model \( \hat{G} \), which forms an explicit representation of uncertainty and includes the final robust estimate \( \theta^* \). In brief, for all modes \( \mu \) of the GMMs in \( G \), the combined support for \( \mu \) from all \( G_i \) that do not contain the current mode is computed by summation of the respective log-probabilities \( \log(G_i(\mu)) \). Based on the computed support, weighted k-means clustering is performed to separate all modes into \( k^* \) clusters, where \( k^* \) is determined by voting among the \( k_i \) of the individual \( G_i \). The centroid of the cluster with the highest combined support is the final estimate \( \theta^* \). The final aggregated mixture model \( \hat{G} \) is computed by merging the information from all \( k^* \) clusters, where covariance matrices of each cluster are merged using a weighted linear combination to become robust to noise.

2.3. Experiments and Results

Since the described procedure was developed in year 1 of the project, there was no MD-Paedigree data available to evaluate the method at that time. For this reason, we used 8 DCM patients from another study for evaluation. The main objective was to investigate the uniqueness and level of confidence of biomechanical parameter estimates given measured volume and pressure curves affected by unknown noise. The proposed approach was applied to estimate the LV maximum active force and passive biomechanical tissue parameters \( \theta = (\sigma_0, \beta) \). The responses \( r \) chosen in that study were the minima, maxima and means of pressure and volume curves. PCE surrogates for the patient-specific electromechanical models were computed with maximum polynomial order \( q = 4 \), if not stated otherwise. Therefore, 25 true model evaluations on a 5x5 isotropic grid were performed, where both \( \sigma_0 \) and \( \beta \) varied within [150, 330] kPa and [0.2, 1.5], respectively, to represent physiological ranges. The mean-shift based posterior analysis was carried out using \( n_S = 15 \) random noise levels. Intermediate GMMs were estimated based on 50,000 MCMC samples each. The level of noise for the specific responses was modelled as a Gaussian distribution with mean 0 and standard deviation \( SD \), where \( SD \) is drawn from a uniform distribution \( SD_r \sim U(r^l, r^u) \). Lower and upper bound \( r^l = 1 \) and \( r^u = 3 \) (units are kPa or mL, depending on the response) were chosen heuristically to model plausible levels of noise in the data.

2.3.1. Precision of PCE Surrogate Model

We verified that the selected PCE order of \( q = 4 \) was enough to model the posterior PDF of the forward model. Therefore, we compared the responses computed with that PCE model with those obtained using a
high-fidelity PCE model of order $q = 10$. 1000 sets of parameters were sampled randomly per patient and all model responses were calculated using both models. We observed very low mean errors of 1.61 mL and 0.56 kPa respectively, two orders of magnitude less than their absolute values. These results suggest that PCE of order $q = 4$ is enough to reliably estimate the model posterior.

2.3.2. Estimation of Biomechanical Parameters and Comparison against State-of-the-Art

We then estimated $\sigma_0$ and $\beta$ for all cases using our approach and verified the goodness of fit by comparing LV EF and LV SV computed by the true forward model with the measurements. Strong goodness of fit was achieved with mean absolute EF error of 2.3% +/- 1.3% and SV error of 8.6mL +/- 3.6mL over the population. NLS-based (BOBYQA) solutions yielded equivalent goodness of fit, while usually requiring about 14 iterations to converge, which is in the same order as the number of forward model runs to build the surrogate PCE model for our approach. However, it should be stressed that our approach yields significantly richer information by providing uncertainty estimates. Figure 2 reports estimated parameters and confidence intervals of our approach, and estimated parameters for the NLS approach. As one can see, noise in the data can have significant impact on the confidence of estimated parameters, with intervals of up to +/- 25 kPa for $\sigma_0$ and 0.5 for $\beta$. Such estimates could be employed as indicator of model fitting quality. Furthermore, as shown in Figure 3, our method is robust to varying noise levels and multimodal PDFs are captured correctly. The difference in EF and SV based on the two modes (left panel) is only 0.2% and 1.6mL, respectively.

![Figure 2: Left: 95% confidence intervals (bold lines) of the GMM mode with highest support for both parameters. Red, filled dots and blue circles represent our estimate and the NLS solution, respectively. Right: LV volume and pressure over one heart cycle from forward simulation with estimated robust parameters for one patient.](image)

![Figure 3 Left: Example posterior PDF (80%, 95%, and 99% confidence regions) estimated by our approach. Red and blue dot represent our estimate and the NLS-based estimate, respectively. However, as one can see, the solution is not unique, since the PDF is multimodal. Both modes give equivalent goodness of fit. Right: 95% confidence intervals for contractility parameter with increasing measurement noise level. Confidence intervals get larger (higher uncertainty), yet the parameter estimate (red dot) remains robust.](image)
2.4. Empirical Evaluation of Estimated Uncertainty

In an empirical experiment on one dataset, we investigated the “meaningfulness” of the estimated uncertainty by analyzing how the goodness of fit of the model responses $d^c$ to the measured data $d^m$ varies between regions of high confidence and regions of low confidence. To that end, we computed the forward model with parameters $\theta$ taken along a line of the parameter space (Figure 4, left panel) and compared the computed LV EF to the measured one. The results are plotted as “error profiles” in Figure 4, mid and right panel.

![Figure 4: Empirical evaluation of estimated uncertainty. Left panel: Automatically estimated posterior PDF overlaid by black lines depicting the one-dimensional subspaces A and B that were analyzed in this experiment. Mid & Right panels: LV EF error profiles of A and B, overlaid by vertical lines representing the intersections of the 1D subspaces with the 80% (light green), 95% and 99% (blue) confidence regions of the estimated posterior.](image)

As one can see from the error profile A in Figure 4, mid panel, the absolute LV EF error is significantly lower for parameter values within the marked regions (high confidence), while outside the 99% (blue contours) confidence region, errors drastically increase. The further away from these regions, the larger the error. In Figure 4, right panel, the underlying 1D subspace connects the two modes of $\tilde{\theta}$. In this case, all points on the resulting line are inside regions of high confidence. LV EF errors are consistently low (note the different ranges of the y-axis in mid and right panel of Figure 4), while the two modes (solution and alternative solution) mark points that are local minima of the error profile. These empirical findings suggest that the proposed aggregation method is meaningful.
3. **Uncertainties in Anatomical Model Input**

Uncertainties in model parameters, as presented in the previous section, are only one of several sources of uncertainty in cardiac simulation. Another source of uncertainty comes from the lack of knowledge on cardiac fibres for a given patient. Indeed, it is still difficult to obtain measurements on the fibre architecture for a given patient in-vivo, therefore we have to rely on prior knowledge. In order to propagate the inherent uncertainty, it first needs to be quantified. This was done by computing statistics on a small population of healthy hearts (details in Sec. 3.2). Second, the personalisation pipeline has to be efficient enough so that a sampling of this uncertainty can be propagated. Finally, we obtain a sampling of the distribution of the parameters and personalised simulations (see Figure 5).

![Figure 5: Global scheme of fibre variability propagation along personalisation pipeline.](image.png)

We illustrated this method on a paediatric dilated cardiomyopathy case (details in Sec. 3.3). From a clinical standpoint, it is very difficult to predict the dramatic evolution of such rapidly-evolving case, even with advanced imaging. The aim of the project is to test if parameters derived from biophysical models could help predicting the outcome of such cases.
3.1. Personalisation of Cardiac Models

3.1.1. Robust Segmentation of Myocardium from MRI
Patient-specific heart morphology is obtained from short-axis cine magnetic resonance images (MRI). To that end, a robust, data-driven machine learning approach is employed [31] to estimate surface meshes of the left endocardium, left outflow tract, left epicardium, right endocardium, right outflow tract and right inflow tract. Each surface is estimated using marginal space learning and probabilistic boosting trees, constrained by a shape model learned from a database of hundreds of cases, thus ensuring inter-patient point correspondence. Next, each surface is tracked over the entire cine sequence using a combination of tracking by detection and tracking by registration. Finally, the surface meshes at mid-diastole are selected to generate a closed surface of the biventricular myocardium, which is transformed into a tetrahedral volume mesh for simulation. This part of the pipeline has been described in detail in deliverable D8.1.

3.1.2. Personalised Cardiac Electrophysiology Model
Cardiac electrophysiology (EP) is modelled using the approach presented in [32]. Cardiac transmembrane potentials are calculated according to the mono-domain Mitchell-Schaeffer (MS) model as it offers a good compromise between model observability and fidelity. In this study, we are mostly interested in two parameters: the time during which the ion channels are closed $\tau_{\text{close}}$, which captures action potential duration and is directly linked to the QT duration; and tissue diffusivity $c$, which determines the speed of the electrical wave propagation and is directly linked to the QRS duration. We model fast regional diffusivity for the left $c_{\text{LV}}$ and right $c_{\text{RV}}$ endocardium to mimic the fast conducting Purkinje network, and slower diffusivity $c_{\text{myo}} \leq c_{\text{LV}}$, $c_{\text{myo}} \leq c_{\text{RV}}$ for the myocardium. Transmembrane potentials are calculated using LBM-EP, a Lattice-Boltzmann method, which is coupled to a boundary element method approach to calculate the 12-lead cardiac electrocardiogram (ECG) resulting from the cardiac potentials [32]. The model is finally personalised like in [33, 34]. BOBYQA, a constrained gradient-free optimization method is used to estimate tissue diffusivity and $\tau_{\text{close}}$ such that computed QRS duration, QRS electrical axis (EA) and QT duration match the measurements.

3.1.3. Personalised Cardiac Mechanical Model
The cardiac mechanical model is based on the Bestel-Clement-Sorine (BCS) model [35]. This model describes the heart as a Mooney Rivlin material and models the stress along the cardiac fibres according to microscopic scale phenomena. Particularly, this model is compatible with the laws of thermodynamics and is able to model the Starling Effect. In this pipeline, it integrates a circulation model representing the four phases of the cardiac cycle (aortic pressure modelled by a four-parameter Windkessel model), and takes the depolarization times and the action potential durations in each point of the mesh as an input to compute the mechanical contraction and relaxation of the myocardium.

As in [36], we only personalize the most influential and independent parameters which are the maximal contraction $\sigma$, the viscosity coefficient $\mu$, the Bulk Modulus $K$ and the Aortic peripheral resistance $R_p$. The calibration is performed following [36]: after performing 9 simulations using some specific parameter values that lie in a range of acceptable values, an algorithm runs and finds (in one iteration) the set of parameters that best fit the observations using the Unscented Transform Algorithm. In our case, the observations are the minimal LV volume and the time between the two moments the LV is at 50% of its contraction volume, both calculated from the cine MRI.

\footnote{http://www.cgal.org -- computational geometry algorithms library}
3.2. Population-Based Uncertainty Quantification of Fibres

3.2.1. Variability Estimation in Atlas Space

One often characterizes the variability of a random vector by its mean and covariance matrix, since these two first moments completely characterize the Gaussian distribution. For more complex distributions, one can compute Polynomial Chaos Expansion (PCE) as performed in the previous section. However, in more than a few dimensions, the covariance matrix is too large to be computed robustly from only a few data observations, and higher order expansions are even more complex. An alternative is to draw just a few samples from the population distribution, either by choosing randomly a number of points from the data observations, or more rationally by selecting a few points that describe the main subspace of variation in the data, for instance through Principal Component Analysis (PCA). Within this subspace, one could describe the variability using a minimal number of points thanks to the so-called sigma-points at the vertices of a minimal simplex, originally designed for the Unscented-Kalman Filter [37]. However, it is often empirically observed that using symmetric points on all axes is significantly more accurate for underlying symmetric distributions. This is the approach we took in this study to quantify the variability of the fibre architecture.

We used N=10 ex-vivo DTI acquisitions of healthy human hearts, registered in the atlas space [38]. Both left and right ventricle images were generated with this atlas, but due to the lower resolution of the right ventricle, we chose to use this atlas only for the left ventricle part. On the right ventricle, we instead use a single DTI heart acquisition with high resolution done by Johns Hopkins University (JHU) [39]. Therefore we have no variability estimation of the fibres for the right ventricle.

To compute the mean DTI over the population and quantify the variability, we work in the Log-Euclidean space [40] rather than the standard Euclidean space. The mean DTI is \( \bar{D} = \exp \left( \frac{1}{N} \sum_{i=1}^{N} \log(D^{(i)}) \right) \) and the data matrix of centred observations is \( X = \left[ \text{vect}(\log D^{(1)} - \log \bar{D}); \ldots; \text{vect}(\log D^{(N)} - \log \bar{D}) \right] \). The PCA is obtained by diagonalizing the large covariance matrix \( \Sigma = XX^T/(N-1) \). More efficiently, we chose to compute the singular-value decomposition (SVD) of the data matrix \( X = U\Lambda V^T \), where the NxN diagonal matrix \( \Lambda \) encloses the square root of the eigenvalues of \( \Sigma \). We choose to only study the first 3 eigenmodes \( U_{1,2,3} \), because they already explain 59% of the variation of the log-tensors seen in the population. For each mode, we compute two symmetric images representing the range of variation along the mode at plus or minus one standard deviation as: \( M_{i, \pm}(x) = \exp(\log(\bar{D}(x)) \pm \sigma_i U_i(x)) \).

3.2.2. From Atlas to Patient Space

In order to relate the atlas space to the geometry of our target patient, we register the mesh of our patient to the mask of both the atlas (for the LV) and the JHU heart (for the RV) with a three-steps framework. First, the mask of the patient is aligned with the mask using a rigid landmark based registration method. Correspondences between the atlas and the target heart are manually checked. Secondly, we perform a similarity registration with five coarse levels and one fine level, each of which are composed of 10 iterations. Finally, we perform a diffeomorphic registration using diffeomorphic demons algorithm with 15x10x5x5 iterations (from coarsest to finest level), a Gaussian smoothing factor of 2 in the regularization phase, and an interpolation for the moving image done with B-splines [41]. We then get the full diffeomorphic transformation for each one of our two initial atlases to the target patient mask.
We apply the transformation found in the previous step to the mesh of the patient. For each of the vertices, if the correspondence lies within the RV we use the JHU DTI-image whereas we use the mean or the sampled images of the Lombaert atlas if it lies within the LV. We take the mean (in the Log-Euclidean space) of the tensors of the 5-nearest voxels. The tensor value is then reoriented using the Finite Strain method, and the fibre orientation is taken as its first eigenvector [8]. The results of the fibres personalisation are 7 sets of fibres shown in Figure 6.

3.3. Propagation of Fibre Uncertainty on a Case Study

3.3.1. Clinical Background
The patient analysed in this case study is a 16 years old male who had no family history of cardiac disease. After being admitted at OPBG hospital for chest pain, evidence of reduced ejection fraction and dilated left ventricle led to a first diagnosis of myocarditis. A detailed echocardiographic examination performed 3 month later showed evidence of markedly increased trabeculae of the left ventricular apical and lateral walls, possibly suggesting the presence of left ventricular non-compaction. The MRI study did not confirm this diagnosis but only the idiopathic dilated cardiomyopathy. After 9 month of follow-up in the clinic, the patient was put on the national heart transplant list due to worsening conditions. The patient is now doing well at follow-up after transplant, and the pathology and histology testing at the hospital confirmed the diagnosis of idiopathic dilated cardiomyopathy.

3.3.2. Goodness of Fit and Variability after Personalisation
For each of the 7 tested fibre architectures we personalised EP and EM parameters as described in Sec. 3.1. High goodness of fit between observations and simulations were achieved for all instances: for the ECG, the maximum obtained errors after personalization are 0.2ms for QRS, 2.9ms for QT and 0.3° for EA, which is well below 1% of the measured values for QRS (96ms) and QT (413ms), and below 1% of the maximum possible error (180°) for EA (5°), respectively. Similarly in terms of mechanics, the error between simulated and measured minimal volume and the time at 50% contraction are below 3%.

After this step, we can observe the spatial variability of EP depolarisation times and end-diastolic strain between modes in Figure 6. Although the main features of the ECG are the same, variations in local depolarization times can be up to 10ms from one set of fibres to the mean fibre set due to the difference in current propagation. Interestingly, for some of the sets we can notice a correlation between the peaks and zones of the variations of the depolarization times and the variations of fibre orientation, which would be interesting to investigate deeper.
Figure 6: Top left: Mean fibres. Top right: modes of variation plus (top) / minus (bottom) σ coloured by angular variation w.r.t. the mean (from 0° blue to 20° red). Middle left: Mean depolarisation times after EP personalization; from blue (early) to red (late ~100ms). Middle right: Variation from mean depolarisation times colouring from blue (-10ms) to grey (0ms) to red (+10ms). Bottom left: Local strain at end-systole range from blue (high) to red (low). Bottom right: Variation for each different fibre modes after mechanical personalisation (blue: more contraction, red: less than on mean fibre).
3.3.3. Uncertainty on the Model Parameters and Discussion

Table 1 shows the values of the parameters after calibration for the mean fibre model, and their relative variation for each fibre set (Mx and Px are the two fibre sets representing the mode x as described in Sec. 3.2, for x = 1, 2 or 3).

For the EP parameters, we first note that $c_{RV}$ varies the most, although fibres are fixed on this ventricle. This might be explained by the large changes in direction of depolarisation on the LV due to changes in fibre orientation, which would require the conductivity of the RV to vary as well to match the same $EA$. Logically, $\tau_{close}$ varies very little, since it is directly linked to the QT duration, which is not much affected by fibre orientation. Finally, one should notice the observed variabilities with the intrinsic uncertainty due to the parameter estimation process (which was for instance quantified as high as 45% for $c_{RV}$ in some cases) [32].

Regarding the mechanical parameters, we can easily explain the variations of the $Rp$ and the $\sigma$. It is indeed well known that the fibre architecture has a strong influence on the stroke volume and when we fix all the parameters, we see that the ejection fraction is maximal for the mean fibre, with the largest variations along the mode 2. To achieve the same level of ejection fraction with a less efficient set of fibre, the peripheral resistance must be lowered and the maximum contraction increased, which is what we observe for all the modes, (and in a larger range for the mode 2). The variations of $K$ and $\mu$ are more challenging to interpret directly. They impact directly the slopes of contraction and relaxation phases, thus ensuring the fitting of the time at 50% contraction.

<table>
<thead>
<tr>
<th>Parameter Unit</th>
<th>$c_{omy}$</th>
<th>$c_{LV}$</th>
<th>$c_{RV}$</th>
<th>$\tau_{close}$</th>
<th>$\sigma$</th>
<th>$\mu$</th>
<th>$K$</th>
<th>$Rp$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>1.21e3</td>
<td>4.70e3</td>
<td>1.83e4</td>
<td>2.09e2</td>
<td>4.74e6</td>
<td>2.29e5</td>
<td>2.01e7</td>
<td>1.9e7</td>
</tr>
<tr>
<td>P1</td>
<td>-17.2%</td>
<td>-14%</td>
<td>-14.7%</td>
<td>-0.48%</td>
<td>+2.71%</td>
<td>-5.84%</td>
<td>-5.21%</td>
<td>-26.7%</td>
</tr>
<tr>
<td>M1</td>
<td>+11.5%</td>
<td>+10.6%</td>
<td>+6.06%</td>
<td>+0.14%</td>
<td>+4.2%</td>
<td>-8.54%</td>
<td>-11.4%</td>
<td>-30.9%</td>
</tr>
<tr>
<td>P2</td>
<td>-0.82%</td>
<td>+2.34%</td>
<td>+24.2%</td>
<td>-0.14%</td>
<td>+2.4%</td>
<td>-20.1%</td>
<td>+4.86%</td>
<td>-54.6%</td>
</tr>
<tr>
<td>M2</td>
<td>+3.28%</td>
<td>+2.55%</td>
<td>-30.9%</td>
<td>-0.14%</td>
<td>+0.86%</td>
<td>-2.02%</td>
<td>+10.6%</td>
<td>-35.8%</td>
</tr>
<tr>
<td>P3</td>
<td>+3.28%</td>
<td>+7.02%</td>
<td>-11.4%</td>
<td>-0.14%</td>
<td>+3.75%</td>
<td>-2.87%</td>
<td>-7.64%</td>
<td>-34.4%</td>
</tr>
<tr>
<td>M3</td>
<td>-0.82%</td>
<td>-7.66%</td>
<td>+9.06%</td>
<td>-0.57%</td>
<td>+0.75%</td>
<td>-12.6%</td>
<td>-0.98%</td>
<td>-20.7%</td>
</tr>
</tbody>
</table>

Table 1: Variability in estimated EP and EM model parameters after personalisation.
4. Case Studies for Electrophysiological and Biomechanical Simulation

In addition to the patient case from OPBG which was presented in the previous section, we have run the combined pipeline on cases from the other two clinical partners in WP8. This is an important step to verify that the data acquired by the clinical partners in WP3 follows the correct protocols and can actually be processed. Before presenting results for these cases further below, we will describe the simulation pipeline used for these experiments.

This pipeline (see Figure 7) is peculiar in that modules from Siemens and INRIA are called alternatingly to produce the final results: patient data from various clinical partners is analyzed by Siemens to extract the heart anatomy, which is passed on to INRIA. INRIA then generates multiple possible fibre architectures for this anatomy and passes them back to Siemens, where they are used in the computation of electrophysiology. These results are again sent to INRIA for a subsequent biomechanics simulation, which computes the dynamic heart motion. This set-up with multiple exchanges of data and results is made possible by the highly modular simulation frameworks of MD-Paedigree, which have been developed in close collaboration with all partners. By specifying compatible data formats for intermediate results as cardiac chamber anatomy or fibre structure, modules from INRIA or Siemens can be plugged in for individual modelling steps with minimal effort, allowing maximum flexibility.

Figure 7: Modelling pipeline used to generate results for electrophysiology and biomechanics. Data is exchanged between partners after every step, showing the modularity of the framework.
4.1. Results for a Patient from UCL

The processed case from UCL (ID 010) is a male patient. At time of cine MRI acquisition, he was 7-years old and weighed 28 kg. Figure 8 shows the results of anatomical modelling performed at Siemens based on cine MRI images. Personalisation of fibres including the main modes of variation was computed from the atlas with the method described in Sec. 3.2 (see Figure 9). The large differences in size and shape between the 7-year old patient and the atlas (which is based on adult hearts) led to some difficulties during personalisation. Since the proposed method relies on a registration between the atlas and the patient, large differences in geometries, as is the case here, can make an accurate registration difficult. Moreover, due to the fact that the atlas does not contain information for the heart base, the resulting fibre orientations in this area are not as accurate. We plan to review our pipeline in order to compensate for these challenges and develop a personalisation method that can be adapted to hearts with different geometries and sizes, as required by the young patients in MD-Paedigree.

Figure 8: Segmentation results for UCL 010 from cine MRI. Green: LV endocardium, violet: LV epicardium, orange: RV epicardium.

Figure 9: Personalised fibre structure for UCL case, generated from adapted atlas. Mean fibres are shown on the left and the three largest modes of variation (from left to right) for plus (top row) and minus (bottom row) sigma are shown on the right. Colours at the fibre level correspond to the angular difference to the mean from 0 degrees (blue) to 20 degrees (red).

The complete anatomical model including the mean fibres was then sent back to Siemens, where electrophysiology personalisation was performed. A very good match between measured ECG and computed ECG could be achieved by automatic tuning of model parameters as described previously. The goodness of fit in terms of errors between measured and computed QRS duration, QT duration and electrical axis were as low as 0.1ms, 4.8ms and 4.1°, which is below clinical variability. Figure 10 shows a visualisation of the resulting depolarisation times.
Personalisation of the biomechanical model proved to be challenging for this case, probably due to the problems encountered during fibre adaptation. The described inaccuracies in fibre orientation led to a strongly increased contractility which did not fit the measured ejection fraction. Even though we ultimately captured the minimal volume correctly, the simulated relaxation is too slow compared to the cine MRI data (see Figure 11). As for the fibre modelling, we plan to improve the personalisation of biomechanics for future cases.

<table>
<thead>
<tr>
<th>$\sigma$</th>
<th>$\mu$</th>
<th>$K$</th>
<th>$R_p$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pa</td>
<td>Pa/s</td>
<td>Pa</td>
<td>Pa m^3/s</td>
</tr>
<tr>
<td>32.75e6</td>
<td>1.43e5</td>
<td>10.3e6</td>
<td>25.3e6</td>
</tr>
</tbody>
</table>
4.2. Results for a Patient from DHZB
The patient selected from DHZB is also male (ID Patient-1). At the time of data acquisition his age was 15 years and 4 months, and his weight was 54 kg. The segmentation result for his MRI data is shown in Figure 12. The atlas-based personalisation of fibres for this case is displayed in Figure 13.

We followed the same modelling workflow as with the other patients. However, at the time of writing this report, no clinical ECG information was available for this case. Hence, ECG-based electrophysiology personalisation could not be performed. Instead, standard parameters were used. The resulting depolarisation maps are shown in Figure 14.
For the biomechanics personalisation of this patient, we captured the minimal volume correctly and could reproduce the contraction part of the heart cycle relatively accurately. However, the relaxation part still deviates from the observed movement (see Figure 15 for all results). Parameter values for this simulation are coherent and lie in the range of the ones found for the OPBG case.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\sigma$</td>
<td>6.87e6 Pa</td>
</tr>
<tr>
<td>$\mu$</td>
<td>1.5e5 Pa s</td>
</tr>
<tr>
<td>$K$</td>
<td>13.3e6 Pa</td>
</tr>
<tr>
<td>$R_p$</td>
<td>26.1e6 Pa m$^3$ s</td>
</tr>
</tbody>
</table>

Figure 14: Depolarisation times for the DHZB case, based on standard ECG parameters.

Figure 15: Biomechanical simulation results for the DHZB case. Top: the modelled cardiac parameters. Bottom: comparison of simulated volume curve (black) in comparison to measured data from MRI (red).
5. Conclusions and Outlook

5.1. Achievements
In Sec. 2, we explored the impact of data noise on the estimated biomechanical parameters. The presented approach relies on stochastic parameter estimates and aggregates the probabilities estimated under different noise levels to derive a robust parameter estimate without explicitly knowing the level of noise in the data. First results on 8 cases showed that not only our approach is as effective as well-established deterministic inverse method algorithms, but that it is also as computationally efficient while providing uncertainty estimates. Furthermore, we could demonstrate the non-uniqueness of the inverse problem by reporting different solution spaces, which can be automatically identified through the estimated posterior PDFs. Our approach could therefore provide precious insights when analyzing the clinical relevance of estimated parameters and personalised model predictions.

In Sec. 3, we have detailed how a quantified uncertainty on myocardial fibres could be propagated along an efficient model personalisation pipeline. We presented the need to comprehensively quantify the influence of the parameters on the final output, and reversely to quantify their uncertainty when personalising models in order to fit clinical data. Atlases with mean and principal modes of variations are a good way to hierarchically represent the main directions of variability on quantities with many parameters such as vector or scalar fields. We used that method for the uncertainty on local fibre orientation in each point of the heart, and assessed the variations of personalized parameters according to those uncertainties. Interestingly, if we have prior knowledge on some parameters of the heart, this method could reciprocally give us information on the fibre set with the highest probability.

Finally, in Sec. 4, we presented the modular simulation pipeline spanning anatomy, electrophysiology, and biomechanics, which was tested on cases from all three clinical partners of WP8.

5.2. Outlook and Future Work
While the presented achievements are large steps towards the final goals of WP8, a number of challenges still lie ahead.

The planned consensus framework, which will be able to integrate results from Siemens and INRIA, is one of the next steps that will be tackled. With our modular simulation pipeline, much of the ground-work is already laid, so that focus can be put on the calculation of certainty and agreement maps.

Several aspects of the pipeline in Sec. 3 could be further improved for a more general assessment of uncertainty, in particular with a better personalisation from clinical data (evolution of regional volumes, the whole flow curve) and an extension of the Atlas method to regional parameters such as conductivity or stiffness maps.

Last but not least, our personalisation approach needs to be adapted further to work reliably with data from young patients, as the presented case studies have shown.

Overall, task T8.2 will continue to push forward electrophysiological and biomechanical modelling for clinical applications in Cardiomyopathies. With 24 months remaining to work on the project and data from WP3 flowing in at a steady pace now, exciting times are lying ahead of us.
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