A Framework for Personalized Cardiovascular Models in Hypertrophic Cardiomyopathy

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Abstract

Hypertrophic cardiomyopathy (HCM) is a genetic cardiovascular disease with a complex and heterogeneous phenotype. Longitudinal strain, assessed by speckle-tracking echocardiography (STE), is a reliable marker of left ventricle (LV) function and is significantly reduced in HCM patients. This work presents a framework for personalized HCM cardiovascular modeling. The retrospective database included 50 HCM patients, enrolled in Rennes University Hospital, who underwent 2D-STE. The cardiovascular model included multi-segment ventricles, atrias, systemic and pulmonary circulations. Morris sensitivity analysis determined the set of 85 parameters to be identified. Evolutionary algorithms were used to fit the model parameters to longitudinal strains and LV outflow track (LVOT) pressure gradients data. A total of 50 HCM personalized models were obtained, with a mean strain $RMSE$ *of* $4.0 \pm 0.6\%$ *and a mean LVOT pressure gradient absolute error of 2.8 ± 4.1 mmHg. Patient-specific model parameters provided mechanistic interpretation of the observed strain patterns. This work paves the way towards the proposition of HCM digital twins to improve risk stratification.*

1. Introduction

Hypertrophic cardiomyopathy (HCM) is a genetic cardiovascular disease, characterized by unexplained left ventricle (LV) hypertrophy, myocardial disarray and increased myocardial stiffness. It has a reported prevalence ranging from 1 in 200 to 1 in 500 and is associated with an increased risk of sudden cardiac death, particularly in young adults [1]. Longitudinal strain, assessed by 2D speckle-tracking echocardiography (STE), is a reliable marker of LV function and it is significantly reduced in HCM patients [2]. Its potential role in individual risk assessment has been demonstrated [3].

The mechanisms underlying myocardial deformation, however, are complex and challenging to characterize, highlighting the potential of computational models to provide mechanistic insights into the observed strain patterns.

Patient-specific computational models integrate clinical data into mathematical models based on fundamental physical and physiological laws. Virtual patient representations can support risk stratification, therapy optimization, and drug response prediction [4]. This is particularly relevant in HCM, given its intrinsic phenotypic heterogeneity and complexity. Mechanistic approaches include 3D cardiac models [5] and 3D cardiac models coupled with 0D circulatory models [6]. However, their scalability remains challening due to their high computational cost. In contrast, 0D cardiovascular models are computationally efficient and can be parameterized using non-invasive clinical data [7]. Their integration with optimization pipelines for patient-specific modeling has been demonstrated [8]. To the best of our knowledge, however, no previous study has applied this approach to personalized cardiovascular modeling in a large cohort of patients with HCM.

The objective of this paper is to present a framework for building personalized HCM cardiovascular models using patient specific longitudinal strain curves and LV Outflow Track (LVOT) pressure gradient data.

2. Methods

2.1. Experimental data

The retrospective database included 50 HCM patients, enrolled in Rennes University Hospital and who underwent 2D-STE using a Vivid 7, E9 or E95 ultrasound system (GE). Left ventricle longitudinal strain was obtained from apical 2-,3- and 4- chamber views at a frame rate of at least 60 fps (EchoPAC v204; GE). Additionally, a set of clinical features, including the LVOT pressure gradient at rest, was acquired for each patient.

2.2. Cardiovascular model description

Building upon our group's previous work [8,9], the proposed model included: i) the cardiac electrical system, ii) the right and left atria, iii) the multi-segment right and left ventricles, iv) the systemic and pulmonary circulations, v) the heart valves and the representation of the LVOT obstruction [10]. A comprehensive description can be found in [8]. The computational model was developed using the Multi-formalism Modeling and Simulation Library (M2SL) framework described in [11].

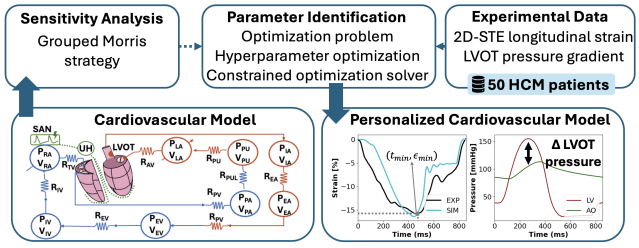

Figure 1: Pipeline for the personalization of 50 HCM cardiovascular model. Parameters were selected based on sensitivity analysis. Cardiovascular model parameters were then fitted to experimental data using evolutionary algorithms.

2.3. Sensitivity analysis

Sensitivity analysis was conducted to identify the most influential parameters on the LVOT pressure gradient, the diastolic and systolic volume and pressure and the mean and dispersion of the global peak strain and its timing [12]. Following [8, 12], a grouped Morris screening method was employed to qualitatively rank parameter importance, based on the Elementary Effect measure [13,14]. Here, the sampling strategy proposed in [15] was adopted to maximize the coverage of the parameter space while maintaining low computational costs. All parameters were varied within $\pm$ 20% of their nominal values. Only the ventricular segment function parameters corresponding to different LV segments were grouped together as in [12]. In total, 29 parameter groups were analyzed, of which 7 corresponded to the LV segment function parameters and the remaining 22 to individual hemodynamic parameters.

2.4. Parameter identification

Optimization problem: The mono-objective function $J_{error} = J_{strain} + J_{gradient}$ was defined as the sum of the strain error J_{strain} and LVOT pressure gradient error $J_{gradient}$. J_{strain} represents the mean relative error between the experimental and simulated longitudinal strain curves across the 16 segments and was defined as:

$$J_{strain} = \frac{1}{16}\sum_{s=1}^{16}\left[\gamma\sqrt{\frac{1}{N}\sum_{t_i=0}^{N}\left(\frac{\epsilon_{s,sim}(t_i)-\epsilon_{s,exp}(t_i)}{mean_{GLS}}\right)^2} + \frac{|\epsilon_{s,sim}(t_{s,min,sim})-\epsilon_{s,exp}(t_{s,min,exp})|}{|\epsilon_{s,exp}(t_{s,min,exp})|} + \frac{|t_{s,min,sim}-t_{s,min,exp}|}{t_{s,min,exp}}\right] \quad (1)$$

where $\epsilon_{s,exp}$ and $\epsilon_{s,sim}$ correspond to the experimental and simulated longitudinal strain curves for each LV segment s. The mean global longitudinal strain ($mean_{GLS}$) was used as the normalization value. The relative error $J_{gradient}$ between the experimental $\Delta^{exp}_{p,rest}$ and simulated $\Delta^{sim}_{p,rest}$ LVOT pressure gradient was defined as:

$$J_{gradient} = \frac{|\Delta^{exp}_{p,rest} - \Delta^{sim}_{p,rest}|}{\Delta^{exp}_{p,rest}} \quad (2)$$

The possible solutions were constrained to ensure that they fall within the physiological range. Specifically, the systolic and diastolic blood pressure were limited to vary within 20% of their baseline values, set at 120 mmHg and 80 mmHg, respectively.

Hyperparameter optimization: The hyperparameter γ was fixed after a grid search. A total of 10 patients (5 with obstructive phenotype) were selected from the entire database. For each patient, γ was varied between 1 and 30.

Constrained optimization solver: Evolutionary algorithms were used for parameter optimization, combining self-adaptive constraint handling [16] with differential evolution [17]. A population of 100 individuals was evolved over 150 generations, with hyperparameters and penalty terms adaptively recalculated at each generation. Performance was assessed using the mean strain RMSE and the LVOT pressure gradient absolute error. Parameter identification was performed using the Pygmo Python library within the M2SL C++ framework , with GNU Guix for package management [18].

3. Results

Sensitivity analysis: Morris sensitivity analysis is presented in Figure 2 for the dispersion of global peak strain. For readability, only the 12 most influential parameters are shown. Although not all model outputs are presented, they were all analyzed to determine the set of parameters to be identified. While the relative ranking of the parameters varied across outputs, most of the influential parameters were common to all outputs.

Parameter influence was distributed between hemodynamic, obstructive and LV segment electrical and mechanical parameters. The main hemodynamic parameters were

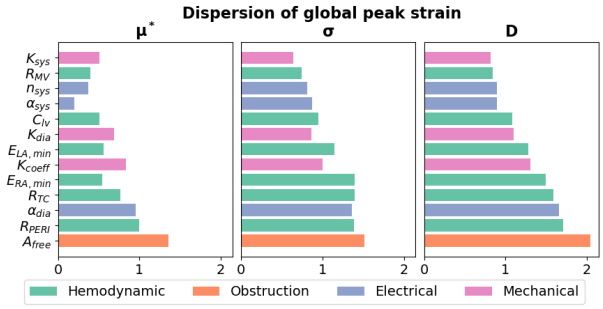

Figure 2: Morris sensitivity analysis results for dispersion of global peak strain. The mean μ^* and standard deviation σ of the elementary effect associated with each parameter are presented [13]. Parameters are sorted according to the euclidean distance D in the μ^*-σ plane. Each color indicates to which physiological category parameters belong.

the systemic resistance (R_{PERI}), right and left atrial minimum elastance ($E_{LA,min}$, $E_{RA,min}$), LV chamber compliance (C_{LV}), and mitral and tricuspid valve resistance (R_{MV}, R_{TC}). The obstructive parameter was A_{free}. The main LV segment parameters were related to active relaxation decay (α_{dia}, n_{dia}), segment geometry (K_{coeff}), active contraction shape (n_{sys}, α_{sys}), and systolic (K_{sys}) and diastolic (K_{dia}) function.

Based on the sensitivity analysis and prior knowledge, the set of obstructive and hemodynamic parameters included A_{free}, R_{PERI}, C_{LV}, E_{PU} (pulmonary elastance), and E_{IA} (aortic elastance). The set of electromechanical segment parameters comprised α_{dia}, n_{dia}, n_{sys}, K_{sys}, and K_{dia}, corresponding to five parameters for each of the 16 segments. Thus, a total of 85 parameters were included in the optimization pipeline.

Hyperparameter optimization: Figure 3 shows the mean strain RMSE and absolute LVOT pressure gradient error as a function of γ. A value of $\gamma > 1$ was required for a satisfactory strain fit, with γ between 10 and 30 providing the best trade-off between the two errors. We selected $\gamma = 19$ as it yielded the smallest spread in mean strain error while maintaining an acceptable LVOT pressure gradient error of approximately 6 mmHg.

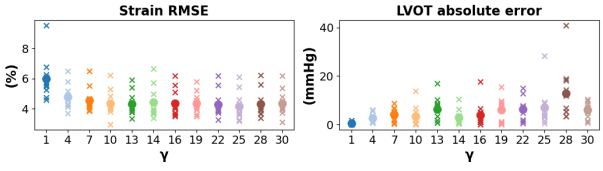

Figure 3: Mean strain RMSE (*left*) and absolute LVOT pressure gradient error (*right*) for values of γ ranging from 1 to 30. Crosses indicate individual errors; circles indicate the population mean.

Personalized cardiovascular models: The optimization pipeline was applied on 50 HCM patients. The mean strain RMSE was 4.0 $\pm$ 0.6% and the mean LVOT pressure gradient absolute error was 2.8 $\pm$ 4.1 mmHg. Personalized cardiovascular model simulations for one obstructive patient are presented in Figure 4. Specifically, increased diastolic function parameter values were observed in the basal–mid septal, apical–inferior, and mid-anterior segments. A gradient in systolic function was also observed, with increasing values from the basal septal toward the basal lateral region. The active relaxation parameter showed a similar pattern.

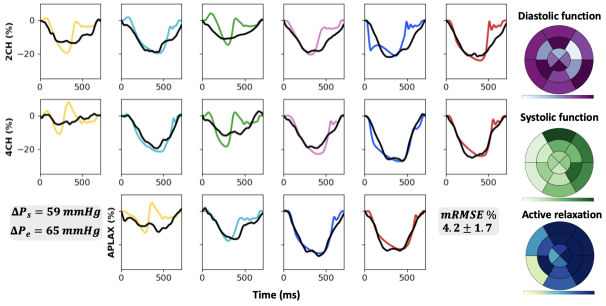

Figure 4: Personalized cardiovascular model simulations for an obstructive HCM patient. Experimental (black) and simulated (colored) strain curves (*left*). Bull-eye's plot for the identified parameters (*right*). The mean strain RMSE and the experimental (e) and the simulated (s) LVOT pressure gradients are also indicated.

4. Discussion

In this work, we proposed a framework for building personalized HCM cardiovascular models by identifying the most influential and physiologically relevant model parameters and optimizing them using evolutionary algorithms.

Parameters were selected based on their influence on the LVOT pressure gradient and strain morphology (A_{free}, α_{dia}, n_{dia}, n_{sys}, K_{sys}, and K_{dia}). Given the effects of myocardial remodeling on ventricular compliance [19], C_{LV} was also included. Finally, R_{PERI}, E_{IA}, and E_{PU} were included to constrain diastolic and systolic pressure.

The proposed optimization pipeline successfully personalized 50 HCM cardiovascular models, as shown by the low errors between experimental and simulated strain curves and LVOT pressure gradients and illustrated in Figure 4. The simulated strain patterns can be related to patient-specific model parameters, providing a mechanistic interpretation of the observed deformation patterns. Particularly, for the example of one HCM patient displayed in Figure 4, the impaired diastolic function could be associated with increased stiffness, which is consistent with the markedly reduced strain observed in the same regions. The observed systolic function gradient illustrates the spatial heterogeneity of ventricular dysfunction, where higher

values correspond to greater contractile force and, consequently, increased deformation, particularly in the basal anterior and lateral regions. The active relaxation parameter characterizes post-contraction relaxation, with larger values indicating slower relaxation. The anterior, lateral, and inferior segments show abnormal relaxation, with no rapid relaxation phase and persistent contractile activity throughout the cardiac cycle. These impaired mechanisms are consistent with functional alterations in HCM described in [20]. Future work will investigate the integration of patient-specific models with machine learning approaches to assess their potential to improve HCM risk stratification in a larger patient cohort.

In this study, the main limitations are the lack of additional functional data (e.g., volume and pressure measurements), which may limit the estimation of circulatory parameters, and the use of longitudinal strain alone, without accounting for the other dimensions of myocardial deformation. Finally, the reproducibility of the method remains to be assessed, which is a key step toward clinical implementation and will be addressed in future work.

5. Conclusion

This work proposed a framework for HCM personalized cardiovascular modeling and it represents a first step towards a Digital Twin Support System within the SMASH-HCM project.

Acknowledgments

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