King's Research Portal

DOI:

[10.1007/978-3-319-52718-5_7](https://doi.org/10.1007/978-3-319-52718-5_7)

Document Version

Peer reviewed version

[Link to publication record in King's Research Portal](#)

Citation for published version (APA):

Sinclair, M., Peressutti, D., Puyol Anton, E., Bai, W., Nordsletten, D., Hadjicharalambous, M., Kerfoot, E., Jackson, T., Claridge, S., Rinaldi, C. A., Rueckert, D., & King, A. (2017). Learning optimal spatial scales for cardiac strain analysis using a motion atlas. In *Lecture Notes in Computer Science (including subseries Lecture Notes in Artificial Intelligence and Lecture Notes in Bioinformatics)* (Vol. 10124 LNCS, pp. 57-65). (Lecture Notes in Computer Science (including subseries Lecture Notes in Artificial Intelligence and Lecture Notes in Bioinformatics); Vol. 10124 LNCS). SpringerVerlag Berlin Heidelberg. https://doi.org/10.1007/978-3-319-52718-5_7

Citing this paper

Please note that where the full-text provided on King's Research Portal is the Author Accepted Manuscript or Post-Print version this may differ from the final Published version. If citing, it is advised that you check and use the publisher's definitive version for pagination, volume/issue, and date of publication details. And where the final published version is provided on the Research Portal, if citing you are again advised to check the publisher's website for any subsequent corrections.

General rights

Copyright and moral rights for the publications made accessible in the Research Portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognize and abide by the legal requirements associated with these rights.

- Users may download and print one copy of any publication from the Research Portal for the purpose of private study or research.
- You may not further distribute the material or use it for any profit-making activity or commercial gain
- You may freely distribute the URL identifying the publication in the Research Portal

Take down policy

If you believe that this document breaches copyright please contact librarypure@kcl.ac.uk providing details, and we will remove access to the work immediately and investigate your claim.

Learning Optimal Spatial Scales for Cardiac Strain Analysis Using a Motion Atlas

Matthew Sinclair¹, Devis Peressutti¹, Esther Puyol-Antón¹, Wenjia Bai²,
David Nordsletten¹, Myrianthi Hadjicharalambous¹, Eric Kerfoot¹, Tom
Jackson¹, Simon Claridge¹, C. Aldo Rinaldi¹, Daniel Rueckert², and Andrew P
King¹

¹ Division of Imaging Sciences & Biomedical Engineering, King's College London, UK

² Biomedical Image Analysis Group, Imperial College London, UK

Abstract. Cardiac motion is inherently tied to the disease state of the heart, and as such can be used to identify the presence and extent of different cardiac pathologies. Abnormal cardiac motion can manifest at different spatial scales of the myocardium depending on the disease present. The importance of spatial scale in the analysis of cardiac motion has not previously been explicitly investigated. In this paper, a novel approach is presented for analysing myocardial strains at different spatial scales using a cardiac motion atlas to find the optimal scales for (1) predicting response to cardiac resynchronisation therapy and (2) identifying the presence of strict left bundle-branch block in a patient cohort of 34. Optimal spatial scales for the two applications were found to be 4% and 16% of left ventricular volume with accuracies of $84.8 \pm 8.4\%$ and $81.3 \pm 12.6\%$, respectively, using a repeated, stratified cross-validation.

1 Introduction

Cardiac motion is driven by the underlying electromechanics and perfusion, and has been increasingly assessed to predict the state and extent of cardiac disease. The comparison of cardiac motion across subject cohorts has been facilitated in recent years by the development of statistical motion atlases. A motion atlas entails the normalisation of subjects' cardiac geometry and motion both spatially and over time. Motion atlases have been used to identify abnormal cardiac motion [7,6,13], to predict scar location in the left ventricle (LV) [8,14], and to parcellate the LV based on motion as an alternative to AHA segments [1].

The importance of spatial scale in the analysis of cardiac motion has not been extensively investigated, despite the importance of scale in cardiac structure and function. As an example, the branching structure of the coronary vasculature follows power law relationships [3], and vessel generation has been shown to follow a power law in relation to downstream myocardial volume [12,17]. Disease in the coronary circulation is also known to manifest at different scales, both in the large coronary arteries and also at the microvascular scale [5]. Disease in the coronary circulation at different vessel scales entails different manifestations of perfusion abnormalities affecting function. This suggests that abnormal cardiac

motion may manifest at different spatial scales depending on the disease, and that by extension there may be a characteristic tissue spatial scale at which cardiac deformation may be most predictive for different applications.

In this paper we present a novel framework based on computing strain at different spatial scales in the LV. This framework incorporates the use of a motion atlas with dimensionality reduction using principal component analysis (PCA) and classification using linear discriminant analysis (LDA) to identify the unique scale at which cardiac strain is most strongly predictive of different clinical parameters. We analyse myocardial strain due to its intrinsic link to tissue contractility, and due to its increased use in the clinical literature for the assessment of regional cardiac function (eg. [9]). In this study we apply our framework to the assessment of cardiac deformation at different scales in a cohort of cardiac resynchronisation therapy (CRT) patients, as detailed below.

2 Methods and Materials

2.1 Clinical Data

CRT is used to treat patients with electro-mechanical dyssynchrony which diminishes systolic function and can result in heart failure. Current clinical selection criteria for patients to undergo CRT include a NYHA functional class of II to IV, a QRS duration $>120ms$, and an LV ejection fraction (EF) $<35\%$ [11]. Response to CRT is defined as a decrease in end-systolic volume $\geq 15\%$. Under the current criteria, approximately 30% of patients undergoing CRT are non-responders, and improving on these criteria is an active field of research [11]. One factor influencing CRT response is the presence of strict left bundle-branch block (LBBB), defined by a longer QRS duration ($\geq 140ms$ in men and $\geq 130ms$ in women) and a mid-QRS notching [19], and characterised by dyssynchronous contraction of the septum relative to the LV lateral wall. While LBBB has a characteristic large-scale motion abnormality, it is yet unknown whether there is a particular scale of cardiac motion that distinguishes CRT responders' hearts from those of non-responders. A cohort of 34 CRT patients was considered in this study. LBBB was identified in 23/34 patients pre-CRT, and at a 6 month follow-up 26/34 patients were determined to be responders to CRT. The classification tasks considered in this study (see Section 3) are the identification of LBBB and the prediction of CRT response. Note that the prediction of CRT response was performed prospectively, i.e. using pre-CRT imaging data.

All patients underwent MR imaging before CRT using a 1.5T scanner (Achieva, Philips Healthcare, Best, Netherlands), with the acquisition of ECG-gated, breath-hold cine-MR and T-MR (3D-tagged) sequences. A single multi-slice short axis (SA) and three single-slice long axis (LA) cine-MR sequences were acquired. Slice thickness was $8mm$ and $10mm$ for SA and LA sequences respectively, with an in-plane resolution for both of $\approx 1.4mm$. Three orthogonal T-MR sequences were combined to produce a $3D+t$ image with $\approx 1.0mm$ isotropic resolution. The SA and LA cine-MR sequences were rigidly aligned to the T-MR coordinate system, compensating for motion occurring between sequential breath-holds. The T-MR sequence was chosen as reference as it was free from respiratory motion.

2.2 Spatio-temporal Motion Atlas

A motion atlas of the LV was formed to allow comparison of motion between patients. This process was based on frameworks proposed in a number of previous works (e.g. [6,13]). The main novelty in this study is the computation of myocardial strains at different spatial scales from a deforming LV point-cloud, and the investigation of application-specific scales for subsequent analysis. A framework for this approach is shown in Fig. 1, with the steps therein detailed below.

A) LV Geometry Definition. The LV myocardium was manually segmented in the end-diastolic (ED) SA stack and 3 LA slices, excluding papillary muscles. The segmentations from the SA and LA images were subsequently fused and manually smoothed at a $2mm$ isotropic resolution. Following the identification of anatomical landmarks, a statistical shape model (SSM) was optimised to fit to the endocardial and epicardial surfaces of the LV binary segmentation [2], providing point-correspondence between patient hearts. The overlap of the SSM with each patient’s LV geometry was visually assessed and the above process refined if necessary to ensure suitable overlap for subsequent motion tracking. In order to reduce the number of vertices of the SSM surface mesh (≈ 22000), a medial surface with regularly sampled vertices (≈ 3000) was generated via a combination of ray-casting and homogeneous downsampling followed by cell subdivision. Point-correspondence was retained by applying the same approach to each patient based on the initial point-correspondence of the SSM.

Fig. 1: An illustration of the proposed framework, with reference to relevant sections.

B) Motion Tracking. The high resolution $3D+t$ T-MR sequence was then used for motion tracking. DICOM header information was used to determine the fraction of the cardiac cycle over which each $3D+t$ T-MR sequence was acquired, and temporal normalisation was performed for each patient, so that $t \in [0, 1)$, with 0 being ED and 1 being the end of the cardiac cycle. A $3D$ GPU-based B-spline free-form deformation (FFD) registration was used [16] to estimate LV motion between consecutive frames of the T-MR sequence. Subsequently, the inter-frame transformations were composed to estimate motion between each

time frame and the ED time frame, producing a $3D + t$ B-spline transformation, ψ . In order to compare cardiac phases between patients, the reference ED medial surface was warped using ψ over $t \in [0, 1]$ at 30 equally spaced cardiac phases. The typical available fraction of the cardiac cycle from each T-MR sequence was 80%, so the first 24 frames of each transformation were used, $t \in [0, 0.8]$. The motion of each patient's LV was therefore fully represented by 24 deformed meshes.

C) Multiscale Strain Calculation. In addition to producing a medial surface, the myocardial volume enclosed by the fitted SSM was sampled in a regular grid with half the resolution of the T-MR images (i.e. with an isotropic spacing of $\approx 2mm$). This produced point-clouds with ≈ 30000 points for each patient LV. The $3D + t$ motion transformation ψ was applied to the point-cloud to transform it to each of the cardiac phases at times, t , for each patient. At time $t=0$, at each point, i , on the medial surface, $P_{i,t=0}^m$, a neighbourhood of K nearest-neighbour points in the point-cloud, $\{P_{i,k,t=0}^{pc}\}, k = 1, \dots, K$, were selected. These points were selected based on a percentage volume of the LV, representing a spatial scale. Six spatial scales were chosen following a power law, namely $V_s = 2^s\%$, $s \in [0, 1, 2, 3, 4, 5]$, (i.e. 1%, 2%, 4%, 8%, 16%, 32%) of the total LV volume, corresponding to approximately $K_s = 300 \times 2^s$, $s \in [0, 1, 2, 3, 4, 5]$ points in a neighbourhood at each respective scale. The method for computing strain at each $P_{i,t}^m$ from its deforming neighbourhood $\{P_{i,k,t}^{pc}\}, k = 1, \dots, K$ is described below.

From large deformation mechanics, the deformation gradient tensor $\mathbf{F}$ maps the relative spatial position of two neighbouring particles before deformation ($d\mathbf{X}$) to their relative spatial position after deformation ($d\mathbf{x}$) [4]. The mapping from the relative position at the ED time frame ($d\mathbf{X}$) to that at every other time frame ($d\mathbf{x}_t$) in the cardiac cycle can be expressed as $d\mathbf{x}_t = \mathbf{F}_t d\mathbf{X}$. Considering a point on the medial surface $P_{i,t=0}^m$ and its point-cloud neighbourhood at a given scale (s), $\{P_{i,k,t=0}^{pc}\}, k = 1, \dots, K_s$, the vector $d\mathbf{X}_{i,k} \in \mathbb{R}^3$ expresses the $[x, y, z]$ distance between the pair of points $P_{i,t=0}^m$ and $P_{i,k,t=0}^{pc}$ at the undeformed ED time frame, $t = 0$. Stacking these vectors for all k neighbours gives a matrix of distances at ED, $d\hat{\mathbf{X}}_i \in \mathbb{R}^{K_s \times 3}$. At each consecutive time point, t , computing the distances between the deformed medial surface point $P_{i,t}^m$ and the same (as at ED) but deformed neighbours $\{P_{i,k,t}^{pc}\}, k = 1, \dots, K_s$, we get the deformed distance matrices $d\hat{\mathbf{x}}_{i,t} \in \mathbb{R}^{K_s \times 3}$. The deformation gradient $\mathbf{F}_{i,t} \in \mathbb{R}^{3 \times 3}$ satisfying $d\hat{\mathbf{x}}_{i,t} = \mathbf{F}_{i,t} d\hat{\mathbf{X}}_i$ at medial surface point, i , and time, t , is then computed from the least-squares minimisation of $\sum_k \left\| d\hat{\mathbf{x}}_{i,t} - \mathbf{F}_{i,t} d\hat{\mathbf{X}}_i \right\|^2$. Neighbourhood strain is computed using the Green-Lagrange strain tensor, $\mathbf{E}_{i,t} = \frac{1}{2}(\mathbf{F}_{i,t}^T \mathbf{F}_{i,t} - \mathbf{I})$. For each patient, this computation was performed for every time frame, at every medial surface vertex and for neighbourhoods at each spatial scale V_s . Compute time for strain at all medial surface vertices for a given patient for a single frame ranged from approximately 3s at $V_0 = 1\%$ to 100s at $V_5 = 32\%$ on 8 CPUs.

D) Spatial Normalisation. Differences in patient-specific LV geometries result in a biased comparison of motion between patients, which spatial normal-

isation is used to correct. Strains were reoriented from the patient-specific to the atlas coordinate space, similarly to how displacements [15] and velocities [6,7] have previously been reoriented. For each patient n , strain in atlas space, $\mathbf{E}_{i,t,n}^{\text{atlas}}$, was computed via the Green-Lagrange strain tensor from the reoriented deformation tensor $\mathbf{F}_{i,t,n}^{\text{atlas}} = \mathbf{J}_{i,\phi_n,t} \mathbf{F}_{i,t,n}^{\text{pat}} \mathbf{J}_{i,\phi_n,t}^{-1}$, where $\mathbf{J}_{i,\phi_n,t}$ is the Jacobian at time t of the patient-to-atlas transformation ϕ_n . Finally the reoriented strain $\mathbf{E}_{i,t,n}^{\text{atlas}}$ was projected into a local atlas coordinate system in radial, r , longitudinal, l , and circumferential, c , directions. The maximum eigenvalue of strain in each direction was used to produce local strain magnitudes, $\mathbf{e}_{i,t,n}^{\text{atlas}} = [e_{i,t,n}^r, e_{i,t,n}^l, e_{i,t,n}^c]$, for each patient, n , cardiac phase, t , and medial surface point, i , consistent with a clinically used coordinate system [9]. Figure 2 illustrates the scale-dependent strain magnitudes (i.e. the norm of $\mathbf{e}^{\text{atlas}}$ at each vertex) at an end-systolic time frame for a patient with LBBB.

Fig. 2: Strain magnitude displayed at different spatial scales on the LV medial surface at end-systole for a patient with LBBB (and septal flash), in a SA view (top) and a posterior LA view (bottom). Positive strains (stretching) are observed more distinctly in the septal region (red arrow) and negative strains (compression) are observed in the LV lateral wall (blue arrow), most strongly at $V_s = 16\%$.

2.3 Dimensionality Reduction and Classification

The local strains in atlas space $\mathbf{e}_{i,t,n}^{\text{atlas}}$ were concatenated into a single row vector such that for patient n , $\hat{\mathbf{e}}_n \in \mathbb{R}^M$, where $M = (3 \times T \times N_m)$, T is the number of cardiac phases and N_m is the number of points in the atlas medial surface mesh. The row vector for each patient was then stacked to produce a matrix $\mathbf{X} = [\hat{\mathbf{e}}_1^T, \dots, \hat{\mathbf{e}}_{N_p}^T]^T \in \mathbb{R}^{N_p \times M}$, where N_p = number of patients. PCA was used to reduce the dimensionality of $\mathbf{X}$ to form $\tilde{\mathbf{X}} \in \mathbb{R}^{N_p \times D}$ ($D \ll M$). LDA was used to classify patients from this low dimensional embedding $\tilde{\mathbf{X}}$. Different numbers of PCA dimensions, D_j , were considered in the analysis.

In order to quantify accuracy as well as its standard deviation (SD) from this dataset, a repeated, stratified cross-validation (RSCV) was performed on $\tilde{\mathbf{X}}_{j,s} \in \mathbb{R}^{N \times D_j}$, for each scale V_s and number of dimensions D_j . This involved dividing $\tilde{\mathbf{X}}_{j,s}$ into training and validation data by randomly sampling from $\tilde{\mathbf{X}}_{j,s}$ without replacement, while ensuring balanced classes in both training and validation datasets ('stratified'), and repeating this process to obtain a range of accuracy

values at each D_j and V_s . A stratified approach to sampling was used since there are imbalanced classes in the data for the classification tasks.

3 Experiments and Results

A $\approx 75/25$ split was deemed suitable for the training data $\tilde{\mathbf{X}}_{j,s}^{\text{train}}$ (26/34 patients) and validation data $\tilde{\mathbf{X}}_{j,s}^{\text{val}}$ (8/34 patients), to allow for at least 2 observations from the smallest class (CRT non-responders, 8/34) to be represented in the validation set of each RSCV repetition. Experiments showed that accuracies and SDs stabilised after around 100 repetitions of the RSCV, which has been used for all results below. The optimal scale and number of dimensions for prediction of CRT response and identification of LBBB was selected as the combination of V_s and D_j that maximised the classification accuracy from the RSCV. Given the small size of the patient cohort (34 subjects), only up to the first 5 PCA dimensions were assessed to avoid over-fitting, specifically $D_j \in [2, 3, 4, 5]$. Accuracies, sensitivities and specificities are visualised in grids with respect to V_s (y-axis) and D_j (x-axis), as shown in Figure 3.

Application 1: Predicting CRT response. The cohort included 26 responders (class 1) and 8 non-responders (class 0). The prediction outcomes at different values of D_j and V_s are shown in Fig. 3 (top row). The optimal spatial scale for predicting CRT response was $V_s = 4\%$ at $D_j = 2$, producing a prediction accuracy = $84.8 \pm 8.4\%$ (1SD), sensitivity = $94.0 \pm 8.1\%$ and specificity = $52.5 \pm 34.2\%$.

Application 2: Identifying LBBB. The cohort included 23 patients with strict LBBB (class 1) and 11 without it (class 0). LBBB identification outcomes at different values of D_j and V_s are shown in Fig. 3 (bottom row). The optimal spatial scale for classifying LBBB presence was $V_s = 16\%$ at $D_j = 3$, producing an accuracy = $81.3 \pm 12.6\%$, sensitivity = $90.2 \pm 12.9\%$ and specificity = $63.7 \pm 25.9\%$. This large spatial scale shows correspondence to the strong signal at 16% in the ED medial surface strain maps in Figure 2.

4 Discussion

We have proposed a novel method for analysing strain at different spatial scales in the LV to identify an optimal scale for the classification of clinical parameters. Myocardial strain has not previously been analysed in the context of a motion atlas, nor has it been applied to the prediction of CRT response in the literature to the authors' knowledge. The accuracy achieved with our approach is comparable with the current state-of-the-art, where a volume-change systolic dyssynchrony index reported in [18] produced 85% sensitivity and 82% specificity. A 76% sensitivity and 100% specificity was reported in [10] by identifying a type II activation pattern.

Our results reveal that CRT response and LBBB are best predicted and identified, respectively, at different spatial scales. The larger optimal spatial scale of 16% for LBBB identification is consistent with the expected motion abnormality,

i.e. septal flash. Figure 2 also illustrates that at end-systole, for a patient with LBBB, a visibly distinct difference in strains in the LV free wall and the septum becomes apparent at the larger scales. This distinct pattern is present in most of the patients with LBBB, and contributes to the high sensitivity ($90.2 \pm 12.9\%$) of LBBB identification, whereas the lower specificity ($63.7 \pm 25.7\%$) may be due to the presence of more varied deformation patterns amongst patients without LBBB. Similarly, the high CRT response prediction sensitivity ($94.0 \pm 8.1\%$) suggests responders are generally easily distinguishable by small scale strain patterns, whereas correctly predicting the non-responders remains a challenge given the low specificity ($52.5 \pm 34.2\%$), and may also be due to the small number of non-responders in the cohort.

Fig. 3: Accuracy (left), sensitivity (middle) and specificity (right) of the RSCV for CRT response (top) and LBBB (bottom) classification. CRT response prediction has the best accuracy at a spatial scale of 4%, showing high sensitivity at lower scales, and peak specificity at 4%. LBBB identification has peak accuracy, sensitivity and specificity at a scale of 16%, performing best at lower D_j values.

With the limited cohort size of 34, we restricted the learning techniques employed to simple methods (PCA and LDA) which would limit over-fitting by minimising the number of parameters. A larger cohort would permit use of more advanced techniques with more parameters, such as manifold learning and non-linear classifiers (e.g. SVMs), as well as reduce the variance in our results.

Our framework could also be applied to other cardiac pathologies for which abnormal deformations might be expected, and could be assessed with respect to a healthy subject motion atlas, and in conjunction with clinical indicators to predict disease occurrence or treatment outcome in the future.

References

1. Bai, W., Peressutti, D., *et al.*: Beyond the AHA 17-Segment Model: Motion-Driven Parcellation of the Left Ventricle. In: MICCAI STACOM Workshop (2015)
2. Bai, W., Shi, W., *et al.*: A cardiac atlas built from high resolution MR images of 1000 + normal subjects and atlas-based analysis of cardiac shape and motion. *Med. Image Anal.* 26(1), 133–145 (2015)
3. Bassingthwaite, J., van Beek, J.: Lightning and the Heart: Fractal Behavior in Cardiac Function. *Proceedings of the IEEE* 76(6), 693–699 (2002)
4. Bonet, J., Wood, R.: *Nonlinear Continuum Mechanics for Finite Element Analysis*. Cambridge University Press, Cambridge (2008)
5. Camici, P., Crea, F.: Coronary microvascular dysfunction. *N. Engl. J. Med.* 356(8), 830–40 (2007)
6. De Craene, M., Duchateau, N., *et al.*: SPM to the heart: Mapping of 4D continuous velocities for motion abnormality quantification. *Proceedings - International Symposium on Biomedical Imaging* pp. 454–457 (2012)
7. Duchateau, N., De Craene, M., *et al.*: Constrained manifold learning for the characterization of pathological deviations from normality. *Med. Image Anal.* 16(8), 1532–1549 (2012)
8. Duchateau, N., Sermesant, M.: Prediction of infarct localization from myocardial deformation. In: STACOM. vol. 9534, pp. 51–59 (2015)
9. Gotte, M., Germans, T., *et al.*: Myocardial Strain and Torsion Quantified by Cardiovascular Magnetic Resonance Tissue Tagging. *Studies in Normal and Impaired Left Ventricular Function. J Am Coll Cardiol* 48(10), 2002–2011 (2006)
10. Jackson, T., Sohal, M., *et al.*: A U-shaped type II contraction pattern in patients with strict left bundle branch block predicts super-response to cardiac resynchronization therapy. *Heart Rhythm* 11(10), 1790–1797 (2014)
11. Kirk, J., Kass, D.: Electromechanical dyssynchrony and resynchronization of the failing heart. *Circulation Research* 113(6), 765–776 (2013)
12. Marxen, M., Sled, J., Henkelman, R.: Volume ordering for analysis and modeling of vascular systems. *Ann Biomed Eng* 37(3), 542–551 (2009)
13. Peressutti, D., Bai, W., *et al.*: Prospective Identification of CRT Super Responders Using a Motion Atlas and Random Projection Ensemble Learning. In: MICCAI (2015)
14. Peressutti, D., Bai, W., *et al.*: Towards Left Ventricular Scar Localisation Using Local Motion Descriptors. In: STACOM (2015)
15. Perperidis, D., Mohiaddin, R., Rueckert, D.: Construction of a 4D statistical atlas of the cardiac anatomy and its use in classification. *MICCAI* 3750, 402–410 (2005)
16. Rueckert, D., Sonoda, L., *et al.*: Nonrigid registration using free-form deformations: application to breast MR images. *IEEE Trans Med Imaging* 18(8), 712–21 (1999)
17. Sinclair, M., Lee, J., *et al.*: Microsphere skimming in the porcine coronary arteries: Implications for flow quantification. *Microvascular Research* 100, 59–70 (2015)
18. Sohal, M., Duckett, S., *et al.*: A prospective evaluation of cardiovascular magnetic resonance measures of dyssynchrony in the prediction of response to cardiac resynchronization therapy. *J Cardiovasc Magn Reson* 16, 58 (2014)

19. Tian, Y., Zhang, P., *et al*: True complete left bundle branch block morphology strongly predicts good response to cardiac resynchronization therapy. *Europace* 15(10), 1499–1506 (2013)