Automatic 3D bi-ventricular segmentation of cardiac images by a shape-constrained multi-task deep learning approach

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Deep learning approaches have achieved state-of-the-art performance in cardiac magnetic resonance (CMR) image segmentation. However, most approaches have focused on learning image intensity features for segmentation, whereas the incorporation of anatomical shape priors has received less attention. In this paper, we combine a multi-task deep learning approach with atlas propagation to develop a shape-constrained bi-ventricular segmentation pipeline for short-axis CMR volumetric images. The pipeline first employs a fully convolutional network (FCN) that learns segmentation and landmark localisation tasks simultaneously. The architecture of the proposed FCN uses a 2.5D representation, thus combining the computational advantage of 2D FCNs networks and the capability of addressing 3D spatial consistency without compromising segmentation accuracy. Moreover, the refinement step is designed to explicitly enforce a shape constraint and improve segmentation quality. This step is effective for overcoming image artefacts (e.g. due to different breath-hold positions and large slice thickness), which preclude the creation of anatomically meaningful 3D cardiac shapes. The proposed pipeline is fully automated, due to network’s ability to infer landmarks, which are then used downstream in the pipeline to initialise atlas propagation. We validate the pipeline on 1831 healthy subjects and 649 subjects with pulmonary hypertension. Extensive numerical experiments on the two datasets demonstrate that our proposed method is robust and capable of producing accurate, high-resolution and anatomically smooth bi-ventricular 3D models, despite the artefacts in input CMR volumes.

Index Terms—Deep learning, bi-ventricular CMR segmentation, landmark localisation, non-rigid registration, label fusion, multi-atlas segmentation, shape constraint, cardiac artefacts.

I. INTRODUCTION

CARDIAC magnetic resonance (CMR) imaging is the gold standard for assessing cardiac chamber volume and mass for a wide range of cardiovascular diseases [1]. For decades, clinicians have been relying on manual segmentation approaches to derive quantitative measures such as left ventricle (LV) volume, mass and ejection fraction. However, manual expert segmentation of CMR images is tedious, time-consuming and prone to subjective errors. It becomes impractical when dealing with large-scale datasets. As such, there is a demand for automatic techniques for CMR image analysis that can handle the scale and variability associated with large imaging studies [2], [3]. Recently, automatic segmentation based on deep neural network has achieved state-of-the-art performance in the CMR domain [4], [5], [6], [7], [8], [9], [10], [11], [12], [13], [14]. For example, in the Automatic Cardiac Diagnosis Challenge (ACDC) [17], the 8 highest-ranked segmentation methods were all neural network-based methods.

For most 3D neural network-based segmentation methods, the size of cardiac images, especially that of high-resolution volumetric images [11], often presents a computational bottleneck at the training stage. To deal with this, shallow 3D network architectures [11] or fewer feature maps [5] are typically considered. Also, to reduce the computational burden, most methods extract the region of interest (ROI) containing the whole heart as a first step to reduce the volume size [8], [9], [10], [11], [14], [15], or train a 2D network to separately segment each short-axis slice in the volume [12], [13], [14]. However, there are fundamental problems associated with each of these workarounds. For example, the use of shallow 3D network architectures or fewer feature maps is known to compromise segmentation accuracy. The ROI extraction approach is carried out using ROI detection algorithms, whose robustness remains questionable [8]. In addition, as no 3D context is taken into account, 2D network-based methods suffer from lack of 3D spatial consistency between the segmented slices (leading to lack of smoothness in the long-axis direction), and may result in a false positive prediction at an image slice containing non-ventricular tissues that are similar to target ventricles [8].

Due to the limitations of standard clinical acquisition protocols, the raw volumetric CMR images acquired from standard scans often contain several artefacts [18], including inter-slice shift (i.e. respiratory motion), large slice thickness, and lack of slice coverage. Most deep learning methods do not routinely account for imaging artefacts [4], [5], [6], [7], [8], [9], [10], [12], [13], [14]. As such, these artefacts are inevitably propagated onto the resulting segmentations. An example is given in Fig 1c. The figure shows the segmentation of a 3D volume (whose short- and long-axis views are shown in Fig 1a and b) using a state-of-the-art CNN approach [13]. As can be seen, the segmentation Fig 1c inherits the misalignment and staircase artefacts present in the original volumetric image due to cardiac motion and large slice thickness. Further, holes exist at the apical region of the 3D model due to incomplete slice coverage of the whole heart. Different approaches have been proposed to tackle each artefact accordingly before building a smooth model. For example, misalignment was corrected using quadratic polynomials [15] or rigid registration [19]. Large slice thickness can be addressed by super-resolution techniques [20]. However, few studies have addressed different artefacts directly from an image segmentation perspective. To date, we are aware of only one deep learning segmentation...
method [11] that takes into account different cardiac artefacts, but the method was tested on only simulated images of the LV, whose anatomy is less complex than the bi-ventricular anatomy. It is thereby still an open problem as to how to build an artefact-free and smooth bi-ventricular segmentation model from real artefact-corrupted CMR volumes with novel image segmentation methods.

For clinical applications, segmentation algorithms need to maintain accuracy across diverse patient populations with varying disease phenotypes. In the existing literature, however, most methods [5, 6, 9, 11, 12, 13, 14, 15] have been developed and validated over normal (healthy) hearts or mildly abnormal hearts. Few studies have focused on hearts with very significant pathology with altered geometry and motion to healthy atlases. In addition, most methods [4, 5, 6, 7, 9, 10, 12, 14, 15] tend to use small image datasets. For example, four representative MICCAI challenges, namely the 2009 automatic LV segmentation challenge [1] (also known as Sunnybrook cardiac data), the 2011 LV segmentation challenge [2] (organized as part of the STACOM workshop), the 2015 RV segmentation challenge [21] and the 2017 ACDC, were tested on only 30, 100, 48 and 100 CMR datasets respectively. Given the small size of the datasets used for training and testing, whether the reported results can be generalised to larger cohorts remains questionable.

In this paper we propose a segmentation pipeline to address the aforementioned limitations of current approaches. Specifically, we make the following contributions: (1) We propose a multi-task deep learning network that simultaneously predicts segmentation labels and anatomical landmarks in CMR volumes. The network takes volumetric images as multi-channel vector images (2D representation), requires no ROI extraction, and contains up to 15 convolutional layers. As such, the network has the computational advantage of 2D networks and is able to address 3D issues without compromising accuracy and spatial consistency. This is the first work applying deep learning to CMR landmark localisation in a 3D context. (2) We introduce an anatomical shape constraint to refine the network segmentation, which is achieved using atlas propagation with a cohort of high-resolution atlases. As such, the pipeline is able to produce an accurate, smooth and clinically meaningful bi-ventricular segmentation model, despite the existing artefacts in the input volume. Moreover, due to the use of landmarks detected by the network, the proposed pipeline is entirely automatic. (3) We demonstrate that the proposed pipeline can be readily generalised to segmenting volumetric CMR images from subjects with pulmonary hypertension cardiovascular disease. We thoroughly assess the effectiveness and robustness of proposed pipeline using a large-scale dataset, comprising 2480 short-axis CMR volumetric images for training and testing. To our knowledge, this is one of the first CMR segmentation studies utilising a volumetric dataset of this size, and the technique introduced herein is the first automatic approach capable of producing a full high-resolution bi-ventricular model in 3D.

http://www.cardiacatlas.org/challenges/lv-segmentation-challenge/
http://www.cardiacatlas.org/studies/sunnybrook-cardiac-data/
Note that $|U_i| = |R_i| = |L_i|$ is the total number of voxels in a CMR volume. We then define all network layer parameters as $W$. In a supervised setting, we propose to solve the following minimisation problem via the standard (back-propagation) stochastic gradient descent

$$W^* = \arg\min_W L_D(W) + \alpha L_L(W) + \beta \|W\|_F^2,$$  \hfill (1)

where $\alpha$ and $\beta$ are weight coefficients balancing the three terms. $L_D(W)$ is the segmentation loss that evaluates spatial overlap with ground-truth labels. $L_L(W)$ is the landmark associated loss for predicting landmark locations. $\|W\|_F^2$, known as the weight decay term, represents the Frobenius norm on the weights $W$. This term is used to prevent over-fitting in the network. The training problem is to estimate the parameters $W$ associated with all the convolutional layers and by minimising (1) the network is able to simultaneously predict segmentation labels and landmark locations. The definition of $L_D(W)$ above is first given as follows

$$L_D(W) = - \sum_i \sum_{k,j} \mathbb{1}_{r_i^j = k} \cdot P(r_i^j = k | U_i, W),$$  \hfill (2)

where $\mathbb{1}_{\{\cdot\}}$ is an indicator function. $\epsilon$ is a small positive value used to avoid dividing by zero. $i$, $k$ and $j$ respectively denote the training sample index, the segmentation label index and the voxel index. $P(r_i^j = k | U_i, W)$ corresponds to the softmax probability estimated by the network for a specific voxel $x_j$ (subject to the restriction $r_i^j = k$), given the training volume $U_i$ and network weights $W$. Note that (2) is known as the differentiable Dice loss, in which the summations are carried out over all voxels, labels and training samples.

For landmark localisation in a CMR volume, the primary challenge is the extreme imbalance between the proportion of voxels belonging to landmark regions and the proportion
belonging to non-landmark regions (the 6 landmarks are represented by 6 voxels, while all the remaining voxels (numbering in the millions) represent background). To solve this highly imbalanced classification problem, we propose the class-balanced weighted categorical cross-entropy loss

\[ L_L(W) = -\sum_i \sum_k w_k \log P(l_j^i = k|U_i, W). \] (3)

Here \( k \) denotes the landmark label index, ranging from 1 to 7. \( Y_k^i \) represents the voxels in training sample \( i \) that belong to the region for which the value of landmark label index is \( k \). To automatically balance landmark and non-landmark classes, we use a weight \( w_k \) for \( Y_k^i \), where \( w_k = 1 - |Y_k^i|/|Y_i| \), \( k = 1, \ldots, 7 \). Here \(|Y_k^i|\) denotes the number of voxels in \( Y_k^i \), while \(|Y_i|\) represents the total number of voxels in training sample \( i \). Let us explain how the weighting process works intuitively. For the voxel falling in any one of the 6 landmark locations, \(|Y_k^i|\) is 1 and \(|Y_k^i|/|Y_i|\) is close to zero. Therefore, \( 1 - |Y_k^i|/|Y_i| \) is close to 1. On the other hand, \( \sum \log P(l_j^i = k|U_i, W) \) in (3) is very small as only one voxel contributes to this term. Therefore, the product \( w_k \sum \log P(l_j^i = k|U_i, W) \) ends up being a small value. In contrast, for a voxel falling in background area, \( 1 - |Y_k^i|/|Y_i| \) is a very small value close to zero. \( \sum \log P(l_j^i = k|U_i, W) \) is however very large as almost all voxels (excluding the 6 landmark voxels) contribute to this term. Therefore, the product \( w_k \sum \log P(l_j^i = k|U_i, W) \) becomes a small value. As such, the losses resulting from the landmark and non-landmark voxels are well balanced, which is crucial for successfully detecting merely 6 landmarks from a volume containing millions of voxels.

In Fig 4 we show the architecture of the proposed SSLLN. There are two major differences between our network architecture and existing 2D or 3D ones, which we highlight as two novelties of this work. First, 2D networks [4] [5] [6] [7] [9] [10] [12] [13] [14] [15] [16] are often trained using 2D short-axis slices separately. Therefore, there is no 3D spatial consistency between the resulting segmented slices. 3D networks [5] [6] [7] [11] often rely on 3D convolutions, which in practice leads to 5D tensors (e.g. batch size \( \times \) [3D volume size] \times classification categories) during forward and backward propagations and requires far more GPU memory than their 2D counterparts. Workarounds such as subsampling [23] or use of small batch size and fewer convolutional layers [5] [7] [11] are often considered when training 3D networks, but these either complicate the training process or cause loss of information and accuracy. Unlike 2D networks, our network treats each input CMR volume as a multi-channel vector image, known as ‘2.5D’ representation. In this sense, 3D volumes rather than 2D short-axis slices are used to train our network. As such, our network accounts for the spatial consistency between slices. Retaining the 3D spatial relationship is crucial for landmark localisation as landmarks encode spatial information. Unlike 3D networks, our network only involves 4D tensors (excluding the last layer). After the input volume passes through the first convolutional layer, the subsequent convolutional operations (excluding the last layer) in our network function exactly the same as those in 2D methods. Hence, the proposed network has the computational advantage of 2D networks, and also handles the input explicitly as a 3D volume (rather than a series of 2D slices), thus retaining accuracy and spatial consistency. This will be demonstrated later in Section III-C. Second, our network predicts segmentation labels and landmark locations simultaneously as we integrate the two problems into a unified image classification method for which we tailored a novel loss function \( \Phi \). We are not aware of any previous approach that detects cardiac landmarks using a deep learning-based classification method. This is also the first work that focuses on segmentation and landmark localisation simultaneously.

After the network is trained, given an unseen CMR volume \( f : \Omega \to \mathbb{R}^{N} \) (\( #S \) is the number of short-axis slices in the volume) defined on the domain \( \Omega \subset \mathbb{R}^2 \), we deploy the network on it and obtain the probability maps of segmentation (\( P_S \)) and the probability maps of landmarks (\( P_L \)) from the last convolutional layer. The binary segmentation and landmark labels are the indices of the maximum values of their probability maps along the channel direction, i.e. \( S = \arg \max_{k=1,\ldots,N} P_S^k \) and \( L = \arg \max_{k=1,\ldots,N} P_L^k \).

C. Introducing anatomical shape constraint

Due to limitations of cardiac MR imaging, low-resolution (LR) volumetric training dataset often contains artefacts, such as inter-slice shift, large slice thickness, lack of slice coverage, etc. Inevitably, the deployment of SSLLN-LR trained from such a dataset leads the propagation of these artefacts to the resulting segmentation. An example can be found in Fig 5D and F. In this section, we introduce an explicit anatomical shape constraint through atlas propagation to overcome such artefacts in SSLLN-LR segmentation. In Fig 5 we outline the proposed shape constraint framework, including initial affine alignment, atlas selection, deformable registration and label fusion. The framework involves using a cohort of high-resolution (HR) atlases produced from SSLLN-HR, each of which consists of an HR CMR volume (1.25 \( \times \) 1.25 \( \times \) 2.0 mm), and its corresponding landmarks and segmentation labels. Next, we go over the framework in full detail.

Due to individual differences, the scanned heart often shows marked variations in size, pose and shape (as shown in Fig 5A and D). This poses difficulty for existing image registration algorithms due to their non-convex nature. For this, the landmarks detected from SSLLN-HR and -LR were used to initialise the subsequent non-rigid algorithm between target and each atlas. An affine transformation with 12 degrees of freedom was first computed between the target landmarks (predicted by SSLLN-LR) and the atlas landmarks (predicted by SSLLN-HR). In addition to initialising the non-rigid image registration, the resulting affine transformations were used to warp segmentations in all atlases to the target space for atlas selection. According to the normalised mutual information (NMI) scores between the target segmentation and each of affinely warped atlas segmentations, \( L \) most similar atlases can be selected to save registration time and to remove dissimilar atlases for label fusion.

Since the correspondences of structures across both target and atlas volumes are explicitly encoded in their segmentations, we
only use segmentations for the following non-rigid registration. Let \( S \) and \( l_n \) \((n = 1, \ldots, L)\) be the SSLLN-LR segmentation and the \( n \)th atlas segmentation, respectively. Let \( P_{S,l_n}(i,j) \) be the joint probability of labels \( i \) and \( j \) in \( S \) and \( l_n \), respectively. It is estimated as the number of voxels with label \( i \) in \( S \) and label \( j \) in \( l_n \) divided by the total number of voxels in the overlap region of both segmentations. We then maximise the overlap of structures denoted by the same label in both \( S \) and \( l_n \) by minimising the following objective function

\[
\Phi_n^* = \arg \min \Phi_n(C(S, l_n(\Phi_n)))
\]

where \( \Phi_n \) is the transformation between \( S \) and \( l_n \), which is modelled by a free-form deformation (FFD) based on B-splines \([23]\). \( C(S, l_n) = \sum_{i=1}^{N} P_{S,l_n}(i,i) \), representing the label consistency \([25]\). \( C \) in \([4]\) is a similarity measure of how many labels of all the labels in the atlas segmentation are correctly mapped into the target segmentation. With the affine transformation as initialisation, a multi-scale gradient descent was then used to minimise the objective function \([4]\). After the optimal \( \Phi_n^* \) is found, the segmentations and volumes in the \( n \)th atlas are warped to the target space. The process is repeated until \( n = L \).

Lastly, we perform non-local label fusion to generate an accurate and smooth bi-ventricular model \( \hat{S} \) for the imperfect SSLLN-LR segmentation \( S \). Let us first denote the warped atlas volumes and segmentations as \( \{(f_n,l_n')|n = 1, \ldots, L\} \), respectively. Here, \( n \) denotes the warped atlas index and \( L \) is the number of selected atlases. For each voxel \( x \) in the target LR volume \( f \), a patch \( f_x \) centred at \( x \) can be constructed. The aim of the label fusion task is to determine the label at \( x \) in \( f \) using \( \{(f_n,l_n')|n = 1, \ldots, L\} \). For each voxel \( x \) in \( f_n \), we define \( \{(f_{n,y},l_{n,y})|y \in N(x)\} \), where \( y \) denotes a voxel in the search window \( N(x) \), \( f_{n,y} \) denotes the patch centred at voxel \( y \) in the \( n \)th warped atlas, and \( l_{n,y} \) denotes the corresponding label for voxel \( y \). The resulting label at voxel \( x \) in the target volume \( f \) can be calculated as

\[
S_x = \arg \max_{k=1,\ldots,N} \sum_{y \in N(x)} e^{-\frac{h}{\left| f_{x-\frac{1}{2},y}-l_{n,y} \right|^2}} \cdot \delta_{l_{n,y},k}
\]

where \( h \) denotes the bandwidth for the Gaussian kernel function and \( \delta_{l_{n,y},k} \) denotes the Kronecker operator, which is equal to one when \( l_{n,y} = k \) and equal to zero otherwise. The equation \([5]\) can be understood as a form of weighted voting, where each of the patches from each of the atlases contributes a vote for the label. It is a non-local method because it uses patch similarity formulation (i.e. Gaussian kernel function), which is inspired from the non-local means for image denoising \([26]\).

In a Bayesian framework, \([5]\) has been shown in \([27]\) essentially a weighted \( K \) nearest neighbours (KNN) classifier, which determines the label by maximum likelihood estimation. By aggregating high-resolution atlas shapes in this way, an explicit anatomical shape constraint can be inferred. The artefacts in the SSLLN-LR segmentation can thus be resolved, as shown in Fig. \([5]\) \( J \).

III. EXPERIMENTS

In this section, we cover extensive experiments to evaluate (both qualitatively and quantitatively) the performance of the proposed pipeline on short-axis CMR volumetric images. Dice index and Hausdorff distance \([13]\) were employed for evaluating segmentation accuracy. Dice varies from 0-1, with high values corresponding to a better results. The Hausdorff distance is computed on an open-ended scale, with smaller values implying a better match. We also validate the performance using clinical measures (ventricular volume and mass) derived from the segmentations. In experiments, each component in the pipeline is studied separately: 1) the proposed SSLLN-SR network is evaluated using HR CMR volumes in Section \( \text{III-C} \) 2) the proposed SSLLN-LR network and shape constraint (i.e. SSLLN-LR+SC) are evaluated using simulated and real LR CMR volumes in Section \( \text{III-D} \) and \( \text{III-E} \) respectively.
A. Clinical datasets

**UK Digital Heart Project Dataset:** This dataset (henceforth referred to as Dataset 1) is composed of 1831 cine HR CMR volumetric images from healthy volunteers, with corresponding dense segmentation annotations at the end-diastolic (ED) and end-systolic (ES) frames. The ground-truth segmentation labels were generated by a semi-automated process which included a manual correction step by two experienced clinical experts. For each volume at ED, 6 landmarks, as shown in Fig. 3 middle, were manually annotated by one clinician. The raw volumes were derived from healthy subjects, scanned at Hammersmith Hospital, Imperial College London using a 3D cine balanced steady-state free precession (b-SSFP) sequence [22] and has a resolution of $1.25 \times 1.25 \times 2\, \text{mm}$. As introduced in Section II-A, HR imaging technique does not produce cardiac artefacts which are often seen in LR imaging acquisition [18].

**Pulmonary Hypertension Dataset:** This dataset (henceforth referred to as Dataset 2) was acquired at Hammersmith Hospital National Pulmonary Hypertension Centre, and composed of 649 subjects with pulmonary hypertension (PH) - a cardiovascular disease characterised by changes in bi-ventricular volume and geometry. PH subjects often have breathing difficulties, therefore HR imaging was impractical for the majority of patients in this cohort due to the relatively long breath-hold time required. Within the cohort, 629 of the 649 patients were scanned using conventional LR image acquisition, and this manner of image acquisition (over multiple short breath-holds) often leads to lower-resolution volumes and inter-slice shift artefacts. In contrast, the remaining 20 subjects managed to perform a single breath-hold, and therefore HR volumes could be acquired for these subjects. Coupled with these HR volumes, LR volumes were also acquired during scanning, forming 20 pairs of LR and HR cine CMR volumes. The resolutions for LR and HR volumes are $1.38 \times 1.38 \times 10\, \text{mm}$ and $1.25 \times 1.25 \times 2\, \text{mm}$, respectively. For all 649 subjects, the manual ground-truth segmentation labels at ED and ES were generated, and 6 landmarks at ED were also annotated.

B. Preprocessing and augmentation

Image preprocessing was carried out to ensure: 1) the size of each volumetric image fits the network architecture; 2) the intensity distribution of each volume was in a comparable range so that each input could be treated equally importantly. As such, each of the HR volumes in Dataset 1 was reshaped to common dimensions of $192 \times 192 \times 60$ with zero-padding if necessary, while each of LR volumes in Dataset 2 was interpolated to $1.25 \times 1.25 \times 2\, \text{mm}$ and then reshaped to $192 \times 192 \times 60$. For the best visual effect, the figures shown in experiments may be cropped manually. However, no ROI detection algorithm (for localisation of the heart) was used in image preprocessing. The intensity redistribution processes for both HR and LR volumes are the same. After reshaping, we first clipped the extreme voxel values (i.e. outliers) in each HR/LR volume. We defined outliers as voxel values lying outside of the 1st to 99th percentile range of original intensity values. Finally, the resulting voxel intensities of each volume were scaled to the $[0, 1]$ range.

Since our network takes volumetric images as inputs, we performed 3D data augmentation on-the-fly during training. At each iteration, augmentation included rescaling of voxel intensities in the input volume, and a 3D random affine transformation of the volume and corresponding label and landmarks. For simplicity, the affine transformation only involved in-plane translation, isotropic scaling and rotation along one random direction ($x$-, $y$- or $z$-axis) at the central voxel of the volume. Neither shearing nor volume flipping was used. Data augmentation enables the network to see a large and diverse array of inputs by the end of training, and was implemented using the SimpleITK library in Python. With an Nvidia Titan XP GPU, training (50 epochs) took approximately 20 and 10 hours for Datasets 1 and 2, respectively. For inference, segmentation (without shape refinement) of an HR/LR volume for a single subject at ED took $<1s$.

C. Experiments on high-resolution volumes

First, we conducted experiments using Dataset 1, which includes 1831 HR CMR volumes. We randomly split the dataset into three disjoint subsets of 1000/600/231. The first subset was used to train SSLLN-HR, and the second and third subsets were used for testing the accuracy of segmentation and landmark localisation, respectively. During training, we only used ED instances (volumes, landmarks and segmentation labels). Note that the proposed SSLLN-HR is a multi-task network that simultaneously outputs segmentation labels and landmarks. Next we segmented a cardiac volume into 5 disjoint regions: the left ventricular cavity (LVC), right ventricular cavity (RVC), left ventricular wall (LVW), right ventricular wall (RVW) and background. We note that the technique introduced herein is the first one capable of producing a full HR bi-ventricular segmentation (i.e. LVC+LVW+RVC+RVW) in 3D.

In Fig. 6, we compare SSLLN-HR with the 2D FCN proposed in [13], where the authors trained a network using each short-axis slice in the volume separately. As c, f and i show,

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\[ \text{Code is publicly available at } \text{https://github.com/baiwenjia/ukbb_cardiac} \]
2D FCN produces very similar results compared with the proposed method and ground truth for the short-axis view image. However, 2D FCN results in a jagged appearance as shown in the long-axis view image, and there are ‘cracks’ in the corresponding 3D model as shown in e. This problem is due to the fact that the 2D method does not consider the 3D context of the volumetric image, leading to a lack of spatial consistency between the segmented slices. In contrast, the proposed SSLLN-HR is a 2.5D network that treats each input CMR volume as a multi-channel vector image. 3D volumes rather than 2D short-axis slices are fed to train SSLLN-HR and as a result, the network accounts for the spatial consistency between slices, enabling smooth results.

Table I

| Dice Index (%) | 2D FCN | SSLLN-HR | p-value | Hausdorff Dist. (mm) | 2D FCN | SSLLN-HR | p-value |
|----------------|--------|----------|---------|---------------------|--------|----------|---------|
| LVC            | 0.956±0.019 | **0.960±0.015** | p<0.001 | 3.567±0.558 | **3.396±0.555** | p<0.001 |
| LWV            | 0.873±0.036 | **0.879±0.030** | p<0.001 | 3.879±0.635 | **3.686±1.306** | p<0.003 |
| RVC            | 0.921±0.030 | **0.929±0.025** | p<0.001 | 4.679±1.382 | **4.550±1.860** | p<0.019 |
| RVW            | 0.669±0.092 | **0.662±0.103** | p=0.110 | 5.236±3.165 | **5.464±2.701** | p<0.001 |

Table I provides a summary of quantitative comparison between SSLLN-HR and 2D FCN, with statistics derived from 600 subjects. Statistical significance of the observed differences in the evaluation metrics (Dice index and Hausdorff distance) between the two methods is assessed via the Wilcoxon signed-rank test. The results in the table demonstrates excellent agreement between automated and manual segmentations. For SSLLN-HR, the mean Dice values of LVC, LVW and RVC are respectively 0.96, 0.88 and 0.93, which are better than 2D FCN results. However, 2D FCN performs slightly better on segmenting RVW, and both methods achieve a relative low Dice score on this anatomy. This is due to the thinness of RVW (only three or four voxels in thickness) and Dice index is more sensitive to errors in this structure.

Figure 7. Testing 3D spatial consistency of the 2D FCN and SSLLN-HR methods. 1st column: target segmentation volumes with zero-filled gaps of different sizes; 2nd and 3rd columns: 2D FCN results; 4th and 5th columns: SSLLN-HR results.

In Fig 7 we further compare the proposed SSLLN-HR with the 2D FCN. We selected batches of k consecutive short-axis slices in a volumetric image, with multiple settings of k (=5, 13, and 20). In each case, we set intensities in the selected slices to zero, as shown in the 1st column. The two methods under comparison were then applied to these partially zero-filled volumes, and the results are given in 2nd-5th columns. As is evident from the results, 2D FCN fails to segment the zero-filled slices, thus leaving gaps in the resulting 3D segmentations. In contrast, SSLLN-HR demonstrates robustness to missing slices and has the capability of ‘inpainting’ these gap regions. However, as the gap (number of zero-filled slices) increases (from k=5 to k=20), the segmentation performance becomes worse. These results further illustrate that the proposed network retains 3D spatial consistency, which the 2D FCN is unable to achieve. Our method thus outperforms the 2D approach in this regard.

Figure 8. Statistical plots of landmark localisation errors. On the top, each blob denotes a point-to-point distance error of one landmark at one specific testing sample. The dark black line represents the mean error of all 6 landmarks across all subjects. The gray shaded narrowband shows the error region associated with the standard deviation of landmark distance errors. On the bottom, the cumulative error distribution curves for each landmark are given.

To enable automatic alignment for subsequent non-rigid registration, we also predicted landmark locations (together with the segmentation) for each input volume using the proposed SSLLN-HR. 1000 out of 1831 subjects were used to train
the SSLLN-HR and the trained model was then tested on 231 unseen subjects. The automatically detected landmarks were compared with the manual ones using the point-to-point Euclidean distance.

The statistics of each landmark localisation error are summarised in Table II which includes the median, average, and standard deviation (SD) values derived from 231 test subjects. The median/mean point-to-point distance errors vary between 4.93/5.56 mm for the landmark-I to 9.06/10.24 mm for the Landmark-II. Fig 8 provides a simple visualisation of the relative error distribution in the sample. The top plot shows that the mean distance error of the 6 landmarks for all subjects is around 7 mm, and the continuous shaded error region indicates that our method produces results that are robust to inter-subject variation. The bottom plot shows the cumulative distribution of point-to-point distance error for each landmark. From this plot, we see that for all landmarks, about 90% of test volumes had point-to-point distance error of <17 mm. Of note, for Landmark-I, error distance was less than 10 mm in more than 90% of the cases, indicating superior accuracy.

Fig 9 shows a visual comparison of automated and manual landmarks. b shows the landmark locations predicted by our SSLLN-HR. As is evident, each landmark is represented by a few locally clustered voxels. The central gravity (represented by a single voxel) of each landmark in b can be computed by averaging the positions of the voxels forming the true landmark. The corresponding results are shown in c, where the two type of landmarks are superimposed. The respective colour-coded single-voxel landmarks are shown in d, which were used for initial point-to-point affine registration, as shown in Fig 5. In f, we superimposed the automated detected landmarks and manual landmarks (e). As can be seen, f demonstrates very good consistency between the automated and manual landmarks. Fig 9 together with Table II and Fig 8 provide ample evidence that the proposed SSLLN-HR has the capability of detecting landmarks robustly and accurately.

D. Experiments on simulated low-resolution volumes

To quantitatively assess the performance of SSLLN-LR and shape constraint (SSLLN-LR+SC) in the pipeline (bottom path in Fig 2), we developed a method to simulate the types of artefacts seen in LR cardiac volumes. Specifically, in Fig 10 an HR volume and its manual segmentation were first downsampled from 1.25 x 1.25 x 2 mm to 1.25 x 1.25 x 10 mm, as shown in the 1st and 2nd columns. The downsampling produces a staircase artefact due to reduction in long-axis resolution. Moreover, the segmentation (d) around the apical region is now incomplete due to the lack of slice coverage of the whole heart. We further simulated inter-slice shift artefact by randomly translating each 2D short-axis slice horizontally. This step produced misalignment in the cardiac volume and its segmentation, as shown in the 3rd column.

Next, for training the SSLLN-LR, the LR volume e and its segmentation f were used as inputs. Note that our method is capable of producing an HR smooth segmentation model even from misaligned inputs such as the example in f. Since we have the smooth ground truth b for the simulated e, we can quantitatively assess the ability of our method to recover the original smooth shape. For these simulation experiments, we used split subsets (1000/600/231) described in Section III-C.

The first two subsets were corrupted with the simulated artefacts described above, which were used for training the SSLLN-LR and evaluating the proposed shape constraint (SC) component of the pipeline. The HR atlas shapes (segmented by SSLLN-HR) in the last cohort (n = 231) were used to infer the shape constraint for refinement of SSLLN-LR segments.

In Table III we compare the Dice index and Hausdorff distance between the SSLLN-HR and SSLLN-LR+SC results. SSLLN-HR was directly evaluated on 600 artefact-free HR volumes at ED in Section III-C while SSLLN-LR+SC was tested on the 600 corresponding simulated LR volumes where

Table III

| Dataset | Dice Index (%) | Hausdorff Dist. (mm) |
|---------|----------------|----------------------|
|         | LVC            | RVC                  | DVC |
| LOW     |                |                      |     |
| SSLLN-HR | 0.906 ± 0.015 | 0.912 ± 0.033        | 0.662 ± 0.103 |
| SSLLN-LR+SC | 0.950 ± 0.015 | 0.963 ± 0.040        | 0.662 ± 0.103 |

In Table III we compare the Dice index and Hausdorff distance between the SSLLN-HR and SSLLN-LR+SC results. SSLLN-HR was directly evaluated on 600 artefact-free HR volumes at ED in Section III-C while SSLLN-LR+SC was tested on the 600 corresponding simulated LR volumes where
cardiac artefacts exist, as shown in Fig 10. Although SSLLN-HR performs better than SSLLN-LR+SC, the performance gap between two approaches is minor. For LVC, LVW and RVC, the Dice index of SSLLN-HR is only about 0.2 higher than that of SSLLN-LR+SC. The Hausdorff distance of SSLLN-HR is about 0.5 mm smaller than that of SSLLN-LR+SC for all 4 regions. Again due to the thin structure of RVW, the mean Dice values of the two methods are relatively low: 0.662 and 0.557, respectively. This table shows that SSLLN-LR+SC achieves good segmentation results for imperfect LR input volumes, and the results are comparable to direct segmentation of artefact-free HR results.

In Table IV, we report the mean and standard deviation of the measurements derived from the two automated methods and manual segmentation. The table further demonstrates SSLLN-LR+SC results are comparable to SSLLN-HR results, proving that our proposed method can produce comparable to direct segmentation of artefact-free HR volumes, even though target segmentation volumes are of low resolution and contain artefacts. Moreover, the RVM measurement derived from the two methods is consistent with the manual RVM measurement, confirming adequate segmentation of RVW using the two methods despite relatively lower lower Dice scores, as shown in Table IV.

### Table IV

**Comparison of clinical measures between SSLLN-HR, SSLLN-LR+SC and manual measurements on 600 volumetric cardiac images.** SSLLN-HR was validated on high-resolution volumes from Dataset 1, whilst SSLLN-LR+SC was validated on 600 low-resolution volumes, simulated from the corresponding high-resolution volumes.

|               | SSLLN-HR | SSLLN-LR+SC | Manual |
|---------------|----------|-------------|--------|
| LVV (ml)      | 148.392±34.352 | 151.048±35.016 | 147.638±34.711 |
| LVM (gram)    | 123.028±24.123 | 124.240±24.383 | 119.278±25.685 |
| RVV (ml)      | 168.638±37.144 | 174.383±39.480 | 171.553±38.622 |
| RVM (gram)    | 35.466±8.121  | 32.290±7.381  | 33.704±7.261  |

Next, we compare the proposed SSLLN-LR+SC with the current 3D network-based approaches, including 3D-seg model 11, 3D-UNet model 28, and cascaded 3D-UNet and convolutional auto-encoder model (3D-AE) 29, as well as 3D anatomically constrained neural network model (3D-ACNN) 11. To ensure a fair comparison, we used the same 20 CMR volumes as in 11 and the quantitative results are presented in Table V. Since 3D-ACNN only segments the left ventricle (LV) of the heart, the table only shows the results for the endocardium and myocardium of the LV. Among the 3D methods compared, 3D-seg and 3D-UNet do not use shape information, while 3D-AE and 3D-ACNN infer shape constraints using an auto-encoder during network training. As is evident, shape-based models outperform those without shape constraints. Our SSLLN-LR+SC outperforms the other two shape-based methods. We propose two main reasons for this: 1): SSLLN-LR+SC uses atlas propagation to impose a shape constraint explicitly while 3D-AE and 3D-ACNN impose shape constraints in an implicit fashion. When the initial segmentation by SSLLN-LR is of sufficiently adequate quality, such an explicit shape constraint is able to produce more accurate segmentation. 2): SSLLN-LR+SC is a 2.5D-based method which allows the use of deeper network architectures than the 3D-based methods (e.g. ACNN-seg only uses 7 convolutional layers while SSLLN-LR+SC has 15), leading to improved segmentation accuracy.

### Table V

**Comparison of Dice index and Hausdorff distance between the proposed SSLLN-LR+SC and 4 state-of-the-art 3D approaches.** These methods were tested on 20 simulated LR volumes (~200 CMR images). The ground-truth labels were obtained from high-resolution volumes acquired from same subjects, which do not contain cardiac artefacts.

|               | Endocardium | Myocardium |
|---------------|-------------|------------|
|               | Dice Index (%) | Hausdorff Dist (mm) | Dice Index (%) | Hausdorff Dist (mm) |
| 3D-UNet       | 0.925±0.019  | 10.28±6.25  | 0.773±0.038  | 10.15±10.58  |
| 3D-AE         | 0.926±0.019  | 9.94±9.02   | 0.764±0.045  | 9.81±11.77   |
| 3D-ACNN       | 0.939±0.017  | 7.89±3.85   | 0.811±0.027  | 7.31±3.98    |
| SSLLN-LR+SC   | 0.943±0.020  | 4.09±0.69   | 0.854±0.042  | 4.37±1.04    |

### E. Experiments on pathological low-resolution volumes

In Section III-D, we have quantitatively studied the performance of the proposed SSLLN-LR+SC using simulated LR cardiac volumes. In this section, we will use real LR volumes. In particular, we test SSLLN-LR+SC on volumetric data in patients with pulmonary hypertension (PH) in Dataset 2. PH leads to a progressive deterioration in cardiac function and ultimately death due to RV failure. As such, it is critical to accurately segment different functional regions of the heart in PH so as to study PH patients quantitatively. Fig 11 shows the difference in two CMR volumes from a representative healthy subject and a PH subject. In health, the RV is crescentic in short-axis views and triangular in long-axis views, wrapping around the thicker-walled LV. In PH, the dilated RV pushes onto the LV causing deformation and loss of its circular shape. The abnormal cardiac morphology of PH heart poses challenges for existing segmentation algorithms.

![Figure 11: Illustrating the difference between a healthy subject (first wo) and a PH subject (last two) from short- and long-axis views. Both subjects were scanned using low-resolution acquisition.](image-url)
with over five years’ experience of CMR imaging and judged satisfactory in all cases. In Fig [12] a–h and Fig [13] we show an exemplary bi-ventricular segmentation of a cardiac volume in PH. We visually compare SSLLN-LR+SC with 2D FCN [13] and two approaches (nearest neighbour interpolation (NNI) and shape-based interpolation (SBI) [25, 40]) that interpolate the 2D FCN results. Both 2D FCN and interpolation methods do not use anatomical shape information, so they performed worse than SSLLN-LR+SC in the long-axis view, as confirmed in Fig [12] f–h. Due to the high in-plane resolution, similar results in the short-axis view were achieved by different methods, as shown in Fig [12] b–d. Moreover, we observed from Fig [13] that SSLLN-LR+SC gives a better 3D phenotype result which is smooth, accurate and artefact-free.

Figure 12. Bi-ventricular segmentation of volumetric images from two PH patients. a and e: original low-resolution volume (two views) from patient I; b and f: 2D FCN+NNI results; c and g: 2D FCN+SBI results; d and h: SSLLR-LR+SC results. i and m: original low-resolution volume from patient II; j and n: SSLLN-LR+SC results; k and o: original high-resolution volume from patient II; l and p: ground truth. The proposed SSLLN-LR+SC is not only insensitive to cardiac artefacts (inter-slice shift, large slice thickness, and lack of slice coverage), but also robust against the change of cardiac morphology due to pathology.

Table VI

|                      | SSLLN-LR+SC | Manual | p-value |
|----------------------|-------------|--------|---------|
| LVV (ml)             | 120.098 ±20.822 | 114.815 ±25.099 | p ≈0.119 |
| LVM (gram)           | 125.989 ±34.639 | 124.237 ±25.271 | p ≈0.855 |
| RVV (ml)             | 221.514 ±64.534 | 204.293 ±58.534 | p ≈0.001 |
| RVM (gram)           | 51.621 ±14.938 | 49.877 ±14.166 | p ≈0.501 |

Lastly, we test SSLLN-LR+SC using 20 pairs of LR and HR cardiac volumetric images. In Fig [12] i–p, we first demonstrate a segmentation example on a pair of LR and HR volumes acquired from a same patient with PH. The original low-resolution volume (1.38 × 1.38 × 10 mm) was segmented by SSLLN-LR+SC into a HR smooth model (1.25 × 1.25 × 2 mm). The smooth segmentation is then visually compared with the ground truth, obtained directly from segmenting the corresponding HR volume of the patient. As is evident, the paired segmentation results show a very good agreement in terms of their cardiac morphology. Further, Table [VI] is provided, which shows a quantitative comparison between the SSLLN-LR+SC results and the ground-truth segmentations. It can be seen that the automated measurements are quantitatively consistent with the manual measurements. Further, comparing Table [VI] with Table [IV], we observed PH patients tend to have a bigger RVC and a smaller LVC than healthy subjects, and that the RVV of PH patients is thicker than that of healthy subjects. These observations are in line with previously reported description of the anatomical differences between PH and healthy hearts, as shown in Fig [11]. Note that p values in Table [VI] are relatively large. This is likely due to the relatively low sample size of the dataset used in this experiment, in addition to the fact that automatic and manual measurements are not substantially different.

IV. Conclusion

In this paper, we developed a fully automatic pipeline for shape-constrained bi-ventricular segmentation of short-axis CMR volumes. In the pipeline, we proposed a network that learns segmentation and landmark localisation tasks simultaneously. The proposed network combines the computational advantage of 2D networks and the capability of addressing 3D spatial consistency issues without loss of segmentation accuracy. The pipeline also includes an explicit shape constraint, thus allowing accurate, smooth and anatomically meaningful bi-ventricular segmentations despite artefacts in the cardiac volumes. Extensive experiments were conducted to validate the effectiveness of the proposed pipeline for both healthy and pathological cases.

V. Acknowledgements

The research was supported by the British Heart Foundation (NH/17/1/32725, RE/13/4/30184); National Institute for Health Research (NIHR) Biomedical Research Centre based at Imperial College Healthcare NHS Trust and Imperial College...
London; and the Medical Research Council, UK. We would like to thank Dr Simon Gibbs, Dr Luke Howard and Prof Martin Wilkins for providing the CMR image data. The TITAN Xp GPU used for this research was kindly donated by the NVIDIA Corporation.

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