

Chapter 5

Tissue segmentation using colour-based clustering

5.1 Introduction

Identification and quantification of connective tissue over the entire atria has generated considerable interest among researchers studying the relationship between atrial structure and electrical function (Nattel and Harada, 2014). Numerous experimental and clinical studies, have demonstrated a significant association between fibrosis and atrial rhythm disturbance, especially when the abnormality is accompanied by heart failure or atrial dilatation (Boixel et al., 2003; Hugh et al., 2015). Tissue specific modelling has been used to understand the role played by fibrosis in the initiation and maintenance of atrial electrical dysfunction (McDowell et al., 2013; Zhao et al., 2017). Accurate identification of tissue types is highly significant in the design of such modelling studies (McDowell et al., 2013; Smaill et al., 2013; Zhao et al., 2017).

The objective of this chapter is to develop a methodology, which allows intuitive separation of tissue type based on the colour it takes during the staining process, regardless of the slice to slice variations. In this dataset, three types of tissue are specifically identified by topical application of May-Grünwald stain.

- 1) Myocytes are coloured green.
- 2) Adipocytes are coloured yellow.

- 3) Collagen is coloured purple.

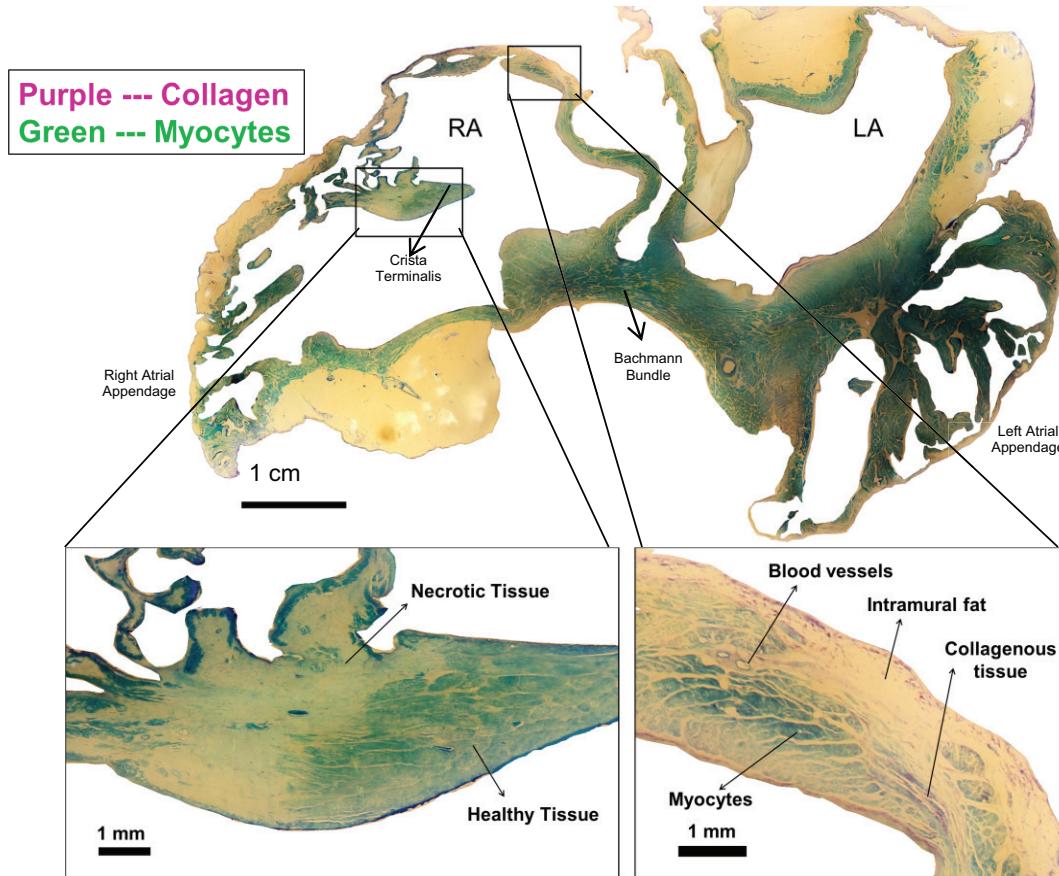


Figure 5.1: A representative slice from the image stack showing each of the three types of tissue identified by its colour – myocytes(green), adipocytes(yellow) and collagen(purple). Major parts of atrial section are also labelled.

Addition of colour-based segmentation to the image processing pipeline will enable us to identify and quantify the various types of tissue present in the image volume, where particular importance is assigned to the identification of fibrotic tissue.

Most organ-level datasets used for image-based atrial modelling are acquired with cardiac magnetic resonance (CMR) or CT imaging. Quantification of tissue types with these intensity-based imaging modalities is subject to considerable uncertainty and is labour intensive. While fibrosis can be detected with late gadolinium enhancement and T1 mapping CMR, spatial resolution is poor in the clinical setting (Dzeshka et al., 2015; Iles et al., 2015; Longobardo et al., 2014). For these reasons, histological imaging remains the gold standard in tissue type identification and techniques for identifying and segmenting

different tissue types on the basis of colour information are well established (Gavrilovic et al., 2013; Onder et al., 2014; Rabinovich et al., 2003; Ruifrok et al., 2001).

In this chapter, we outline a novel clustering approach that enables fast and reliable identification of tissue types in large volume cardiac datasets. The input to this system is the segmented 3D geometry generated in the previous chapter. We then separate the volume bounded by this surface geometry into three clusters based on their colour, with each cluster representing myocytes, adipocytes and collagen.

5.2 Colour based segmentation of histological images: *Background*

Colour-driven tissue segmentation is usually the first step towards quantitative histological image analysis (Cheng et al., 2001; Garcia-Lamont et al., 2018; Ivanovici et al., 2013; McCann et al., 2014). Typically, approaches developed first to process monochrome images have been extended to the RGB colour space (Azevedo Tosta et al., 2017; Moghadamzadeh et al., 1997; Oger et al., 2012; Zorman et al., 2007). However, RGB is a non-optimal colour space for computation of colour differences, because colour characteristics like chromaticity and intensity cannot be separated from each other in this model. For this reason, colour spaces like La^{*}b^{*} (Luminance and two colour channels, a^{*} and b^{*}) and HSV (Hue, Saturation and Value) (Huang et al., 2011; McDermott et al., 2012; Paschos, 2001) were designed with colour differences that correspond better to human perception. Intensity is decoupled from chromaticity in these colour spaces. Hence these properties can be studied separately. It is now clear that the same processing technique can give different results in different colour spaces and it follows that the choice of colour space depends on the processing application. Also, it can be useful to combine the properties of images in various colour spaces. In certain cases, such hybrid approaches provide more robustness (Azevedo Tosta et al., 2017; Garcia-Lamont et al., 2018; Vandenbroucke et al., 2003; Vantaram et al., 2012).

Numerous supervised and unsupervised methods have been proposed for extracting information from histochemically stained images. Supervised methods range from traditional analyses based on colour histogram (Healey, 1992; Kolesnik et al., 2005; Lezoray et al., 2002; Mccann, 2015; Shafarenko et al., 1998; Tsai et al., 2002) to the more

recent approaches based on deep learning techniques (Fu et al., 2018; Komura et al., 2018; Litjens et al., 2017). The rising popularity of these supervised techniques calls for faster generation of accurately labelled data which can be used as training data to systems implementing neural networks. Unsupervised methods like clustering are good at finding structures in data when prior labels are not given. Although hundreds of algorithms have been used to organise unlabelled data into sensible groupings, the most popular are hierarchical clustering, k-means clustering, fuzzy c-means clustering, mean shift clustering and graph theory based clustering. The general goal of all clustering algorithms (Jain, 2010) is to find K groups from a given representation of N objects based on some similarity measure such that similarity of objects from same group is maximised while similarity between objects from different groups is minimised. In the case of colour images, pixels are the objects to be clustered.

K-means algorithm (Macqueen, 1967) has been very popular due to its simplicity and efficiency. In particular, it has been highly successful in segmenting colour images in perceptually uniform colour spaces like La^*b^* by minimising the Euclidean distance based similarity measure (Jain, 2010; Lucchese et al., 1999; Sertel et al., 2008; Sertel et al., 2009; Shashar et al., 2016). However, for robust implementation of k-means it is necessary to 1) specify the number of clusters beforehand and 2) to account for the inherently high sensitivity to initialisation (Jain, 2010). With the latter, the most common approach is to uniformly initialise with random points. This is repeated with different sets of initial centroids in an attempt to avoid getting stuck at local minima(Fu et al., 2018). The approach works well with simple two dimensional clustering problems. However, when dealing with large scale colour images, it is less robust and can behave erratically resulting in slow convergence or failure to converge at all. K-means++ algorithm was introduced (Arthur et al., 2007) as an automatic way to provide robust initialisation to k-means. It seeks to spread out the centres as much as possible, but is not computationally efficient. There is a scalable version (Bahmani et al., 2012) of this method, which is known as k-means||(read as k-means parallel) and is useful when k is very large.

K-means is a hard clustering approach where one data point is assigned to a specific group. Fuzzy clustering approaches (Bezdek et al., 1984) extends this notion to soft clustering by providing the option for each data point to belong to more than one group, but with different membership values. Fuzzy c-means is an equally popular approach and both are widely used in combination where a coarse segmentation using k-means

is refined by fuzzy c-means (Etehadtavakol et al., 2010; Moghaddamzadeh et al., 1997). Clustering approaches based on graph theory, also known as spectral clustering methods represent objects in data as nodes in a weighted graph. The normalised cut algorithm introduced by Shi and Malik (Shi et al., 2000) is the most notable such clustering method. However, it has a hard constraint based on the cluster size and performs poorly on large images in its original form. Mean shift clustering (Comaniciu et al., 2002) is another method which can group the data arbitrarily when the number of clusters is not specified. It works by kernel density estimation where the only parameter used is kernel bandwidth value. A faster version of mean shift algorithm developed in the La^*b^* colour space was used by Wu et al (Wu et al., 2015) for segmentation of histological images. Various improvements to standard clustering approaches have been suggested. These include incorporation of constraints based on spatial information, density of data points, number of clusters, purpose of grouping and scale of the problem (Baykan et al., 2018; Illea et al., n.d.; S. Khan et al., 2004; Shinnou et al., 2008; Wagstaff et al., 2001; Woelker, 1996). Few of these refinements have been extended to colour image processing.

5.3 The proposed method

From an overall qualitative assessment of the current image volume, we estimated the general trend in the proportional quantities of the three tissue types. Myocytes and adipocytes make up the lion's share of the structure, although their distribution may vary unpredictably between slices. In this data set, purple-stained fibrotic tissue represents a small proportion of the total tissue volume. This is a common trend in most of the scientific/medical datasets where the most significant class turns out to be the minority class. Efficient ways of grouping this type of data are actively studied in the clustering literature under the tag of class imbalance problems. Severely skewed distributions are notoriously known for damaging the efficacy of machine learning based workflows, particularly when the available data holds the key (Japkowicz et al., 2002; Krawczyk, 2016; Weiss et al., 2001). In this context, the stark imbalance between fibrotic tissue and the other two tissue types needs to be treated with due seriousness. More importantly in this dataset, the collagen does not form concentrated patches, but is scattered across the atria as very fine lines or diffuse spots.

In addition to issues associated with extreme class imbalance, the colour information carried by each of the tissue types varies due to differences in staining and lighting conditions. Although resultant artefact is reduced by pre-processing steps including image normalisation described in chapter 3, the three tissue types are characterised by various shades of green, yellow and purple. Also, due to the imbalance between the groups, it is necessary to work out how to solve the clustering problem at the best available resolution. Finally, because the volume of the image dataset is large, it is desirable to use a simple and fast clustering approach to speed up the tissue type identification workflow. We therefore decided to optimise the popular K-means based tissue segmentation in the La^*b^* colour space.

As stated previously, proper initialisation and prior knowledge about the expected number of clusters are pre-requisites for a robust implementation of k-means using colour images (Jain, 2010). The importance of appropriate initialisation is demonstrated in Figures 5.2 and 5.3 where random and kmeans++ initialisations, respectively, are used with La^*b^* colour space. None of the clusters give an adequate representation of fibrosis (purple colour).

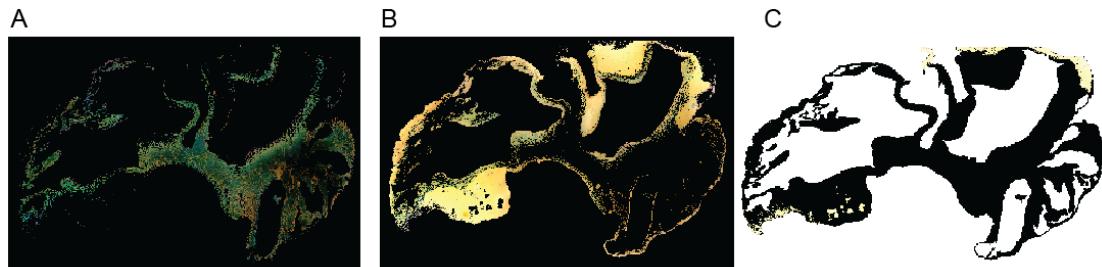


Figure 5.2: Clustering results from k-means in La^*b^* colour space with random initialisation: (A) Cluster 1 (B) Cluster 2 (C) Cluster 3.



Figure 5.3: Clustering results from k-means in La^*b^* colour space with k-means++ initialisation: (A) Cluster 1 (B) Cluster 2 (C) Cluster 3.

For robust definition of the approximate centroids of the three dominant colour clusters, it is necessary to integrate the plethora of colour related information within this dataset.

This led to the development of a balanced representation of the images where dominant colours in each slice are visualised as a colour histogram. We developed a novel two dimensional representation of the three dimensional colour gamut by efficiently quantizing the entire range of colours. All the groups, including the minority class, get equal importance under this representation. Colour variability between various groups was maintained while scaling down the complexity of the clustering problem. The colour quantization approach was guided by the relative density of various combinations of RGB values with respect to a particular chromaticity plane in the La^*b^* colour space. This density based binning mechanism proved to be an effective means of extracting the distinct chromatic information carried by these histological images. The two-dimensional representation enabled easier analysis of the large image dataset by aiding automated implementation of colour guided k-means clustering.

Specifically the approach provided:

- 1) Better visual control over the data through the low-dimensional balanced representation of the three distinct colours in each image.
- 2) Automatic identification of perfect seed points for initialising k-means clustering in each slice, thereby improving the robustness of the approach over the entire dataset.
- 3) Easy visual transformation between colour specific components in 3 different colour spaces - La^*b^* (a^* , b^* co-ordinates), HSV (Hue component) and RGB (R, G, B channels).

5.4 A balanced visualisation of colour distribution

The easiest way of visualising the distribution of colours present in the image is to plot a 3D colour histogram. In Figure 5.4, we present colour distributions in 3 different colour spaces - RGB, HSV and La^*b^* - using the colour inspector app in ImageJ. These figures compare the colours extracted from the same slice under their respective transformations. In RGB and HSV distributions, colour information is less uniformly distributed than in the La^*b^* representation. The three significant colours - purple, yellow and green - are each distinctly visible with much less variations, especially in the a^*-b^* plane. However, it is difficult to navigate this 3D space as the colour clusters are continuous and plotting itself is computationally expensive due to the large number of voxels in the volume image. A two dimensional mapping of this colour distribution would be useful in this case.

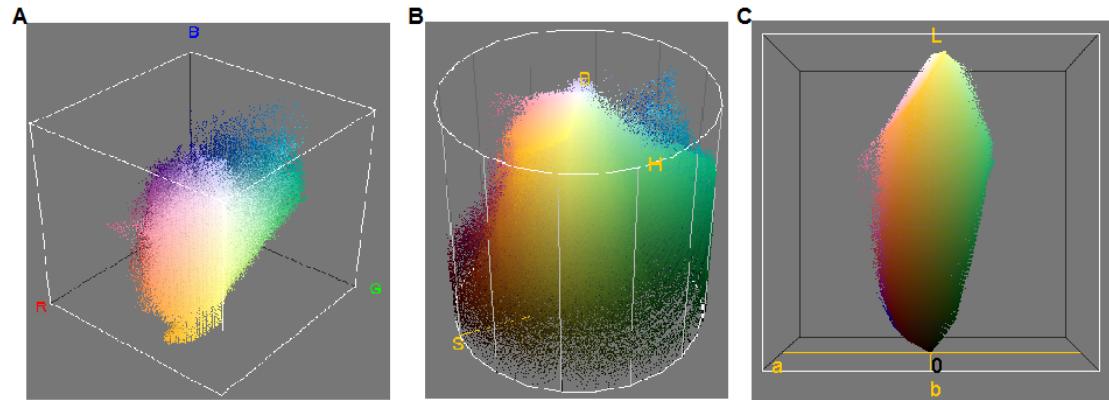


Figure 5.4: 3D colour histograms in different colour spaces visualised by colour inspector app in ImageJ. Visualisations in (A) RGB colour space (B) HSV colour space (C) La^{*}b^{*} colour space.

A two dimensional representation of the 3D colour gamut was generated in the form of a scatter plot with a^* and b^* as the two co-ordinates as shown in Figure 5.5. Instead of becoming an equivalent lower dimensional representation of the 3D histogram, this initially results in a misleading representation of the colour gamut (Figure 5.5 (A)). We developed a density based filtering method to make it more meaningful. This was done by ensuring that only one point is generated in the scatter plot for a particular a^* - b^* combination. For any particular a - b combination, all the combinations of RGB values are identified and averaged separately. The averaged values are used to colour that (a, b) location. Thus any (a, b) point in the plot is coloured with most frequent R, G, B combination corresponding to that a, b combination. This procedure is illustrated in Figure 5.5(B). The resulting two-dimensional representation is shown in Figure 5.5(C). In a single figure, it captures the colour specific components from three different colour spaces. The co-ordinates are the chromatic components in La^{*}b^{*} space - a^* and b^* . The colour values are R, G, B components from RGB colour space. Also, the linear hue (H in HSV colour space) variation is represented by the angle subtended at the centre. The following section describes how this representation is used to locate the approximate colour cluster centroids for proper initialisation of k-means clustering.

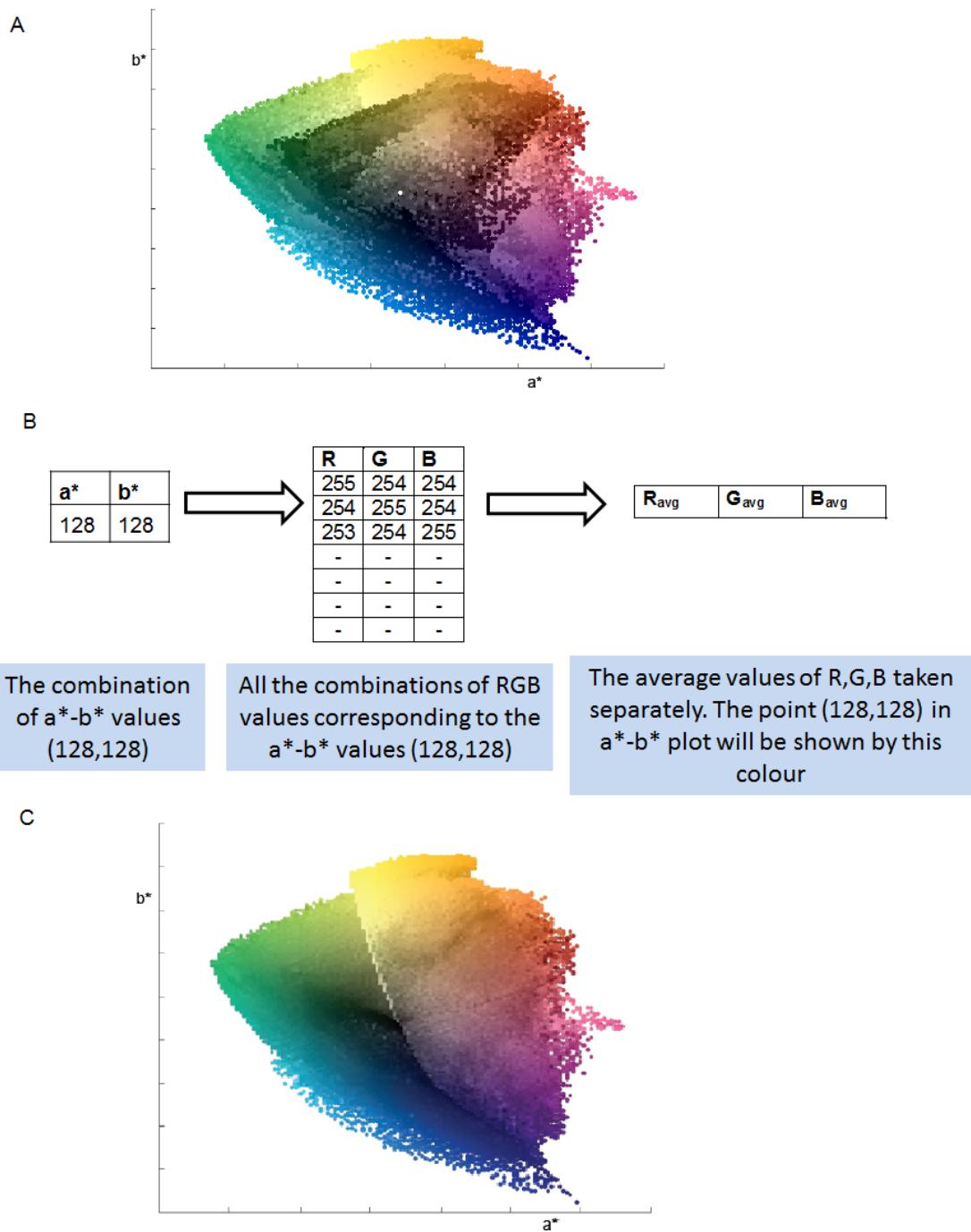


Figure 5.5: Generation of a balanced two dimensional visualisation of colour distribution by filtering the a^* - b^* plot. (A) Colour distribution before filtering. (B) Filtering procedure (C) Final distribution after filtering.

5.5 Locating the initial centroids and k-means clustering

The two-dimensional colour distribution diagram in its filtered form displays three sectors representing the three tissue types. The sectors for these tissue types which are roughly identified based on their respective hue values are shown in the Figure 5.6. Although they overlap at their boundaries, three intersecting regions showing the characteristic colours provided by May-Grünwald stain - purple, yellow and green - are clearly visible. We hypothesized that a^* and b^* values corresponding to the centres of these sectors can be used as the centroid values for initialising a k-means clustering in La^*b^* colour space. At this stage, these centres can be located simply by visual analysis. However, we developed a more robust method to automate this process.

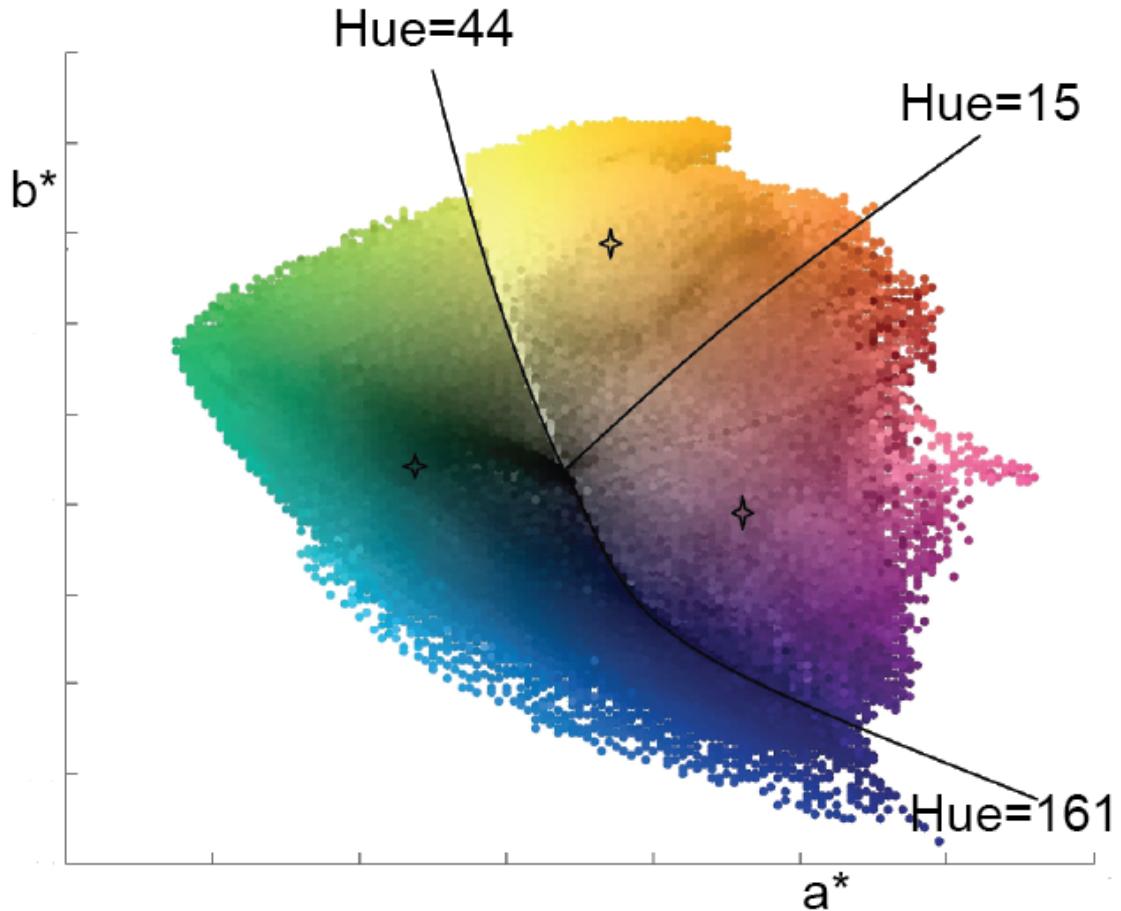


Figure 5.6: Three sectors representing the three tissue types identified based on their respective hue values. The computed sector centers are also shown. These centers are used as centroids to initialise k means clustering.

According to this method, the sector centres are computed as the centre of mass of the sector. Considering the distribution in each sector as a system of particles P_i (for $i = 1, \dots, n$), each with mass m_i that is located in space with coordinates r_i (for $i = 1, \dots, n$), then the coordinates R of the centre of mass satisfy the condition

$$\sum_{i=1}^n m_i(r_i - R) = 0 \quad (5.1)$$

Solving this equation for R gives,

$$R = \frac{1}{M} \sum_{i=1}^n m_i r_i \quad (5.2)$$

where $m_i = 1$ for all points, $M = \text{sum}$ of all m and $r_i = [x_i, y_i]$, the x and y coordinates for $i = 1, \dots, n$.

The resulting sector centres computed for the representative slice following this method are marked in the Figure 5.6. Images are converted to La^*b^* colour space before the grouping of pixels. Then k-means clustering (number of clusters=3) is initialised with the computed sector centres as the initial centroids. Based on the Euclidean distance criterion, each pixel from the image is associated with its nearest cluster centre. Means are recomputed and the process is repeated until convergence. The algorithm converges when the cluster centres (means) remain unchanged over two successive iterations. Three panels in the Figure 5.7 show the three distinct clusters representing the three tissue types, separated by our approach. We developed the application in Python/MATLAB.

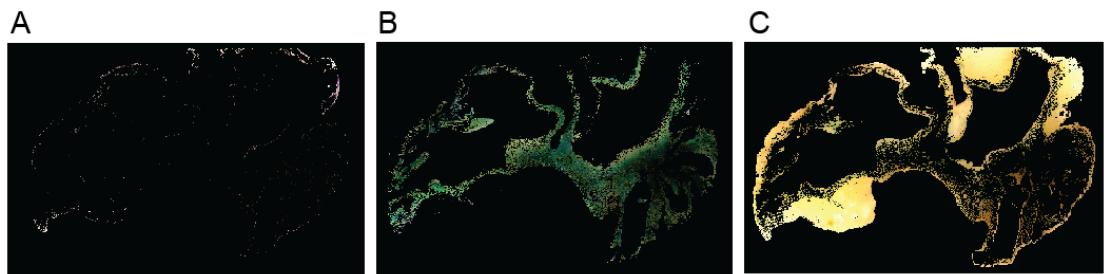
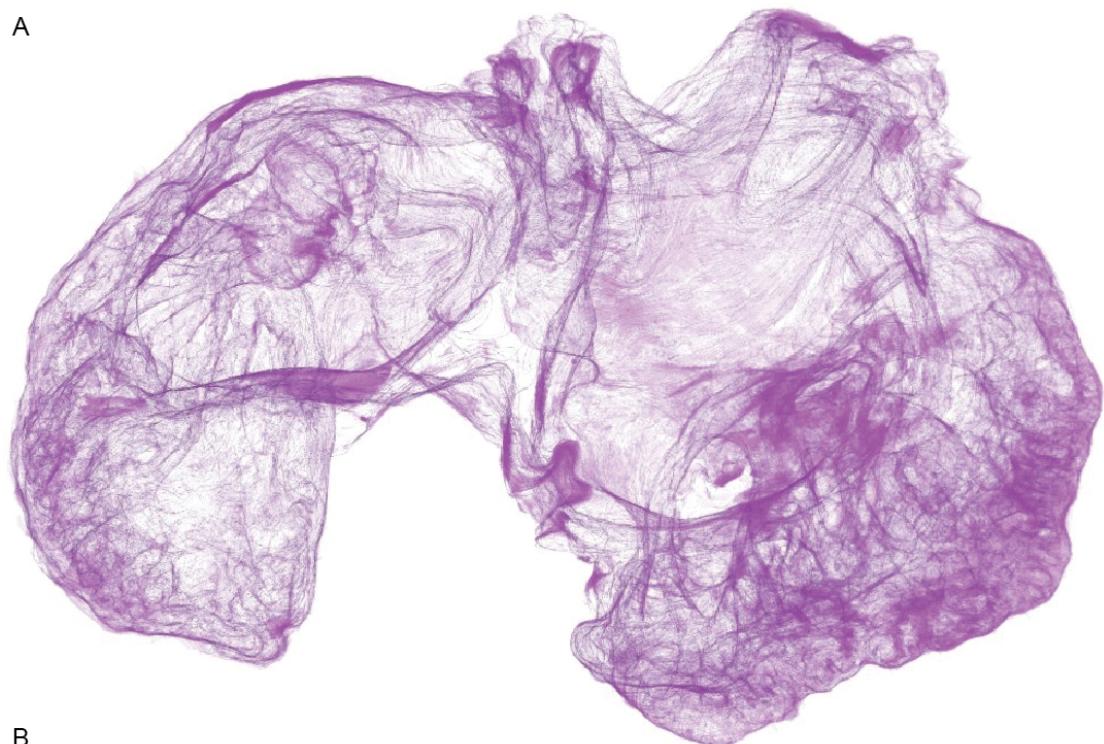


Figure 5.7: Three distinct clusters representing the three tissue types – (A) Connective tissue, (B) Myocytes and (C) Adipocytes - separated using the proposed method.

A



B

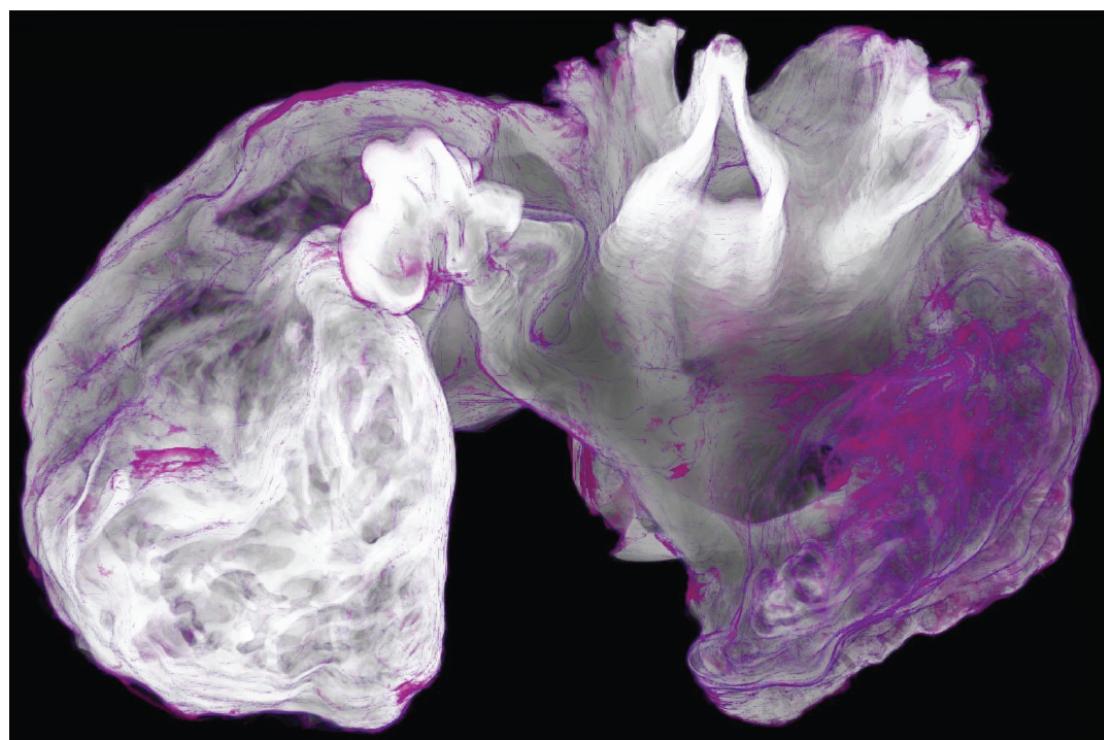


Figure 5.8: Connective tissue organization mapped over the whole atria . (A) Isolated connective tissue network. (B) Connective tissue network superimposed on the geometry

5.6 Results

The colour based process outlined in this chapter enabled efficient separation of tissue types. Connective tissue organisation over the entire atria was mapped as shown in Figure 5.8.

Furthermore, an objective local analysis of connective tissue organisation was conducted at two particularly significant sites identified from the global visualisation as shown in Figure 5.9. One section was from the lateral wall of RA, while the other was from the left superior PV sleeves. These sections were selected for local analysis as they showed significant presence of connective tissue. This is shown in the segmented 3D blocks .

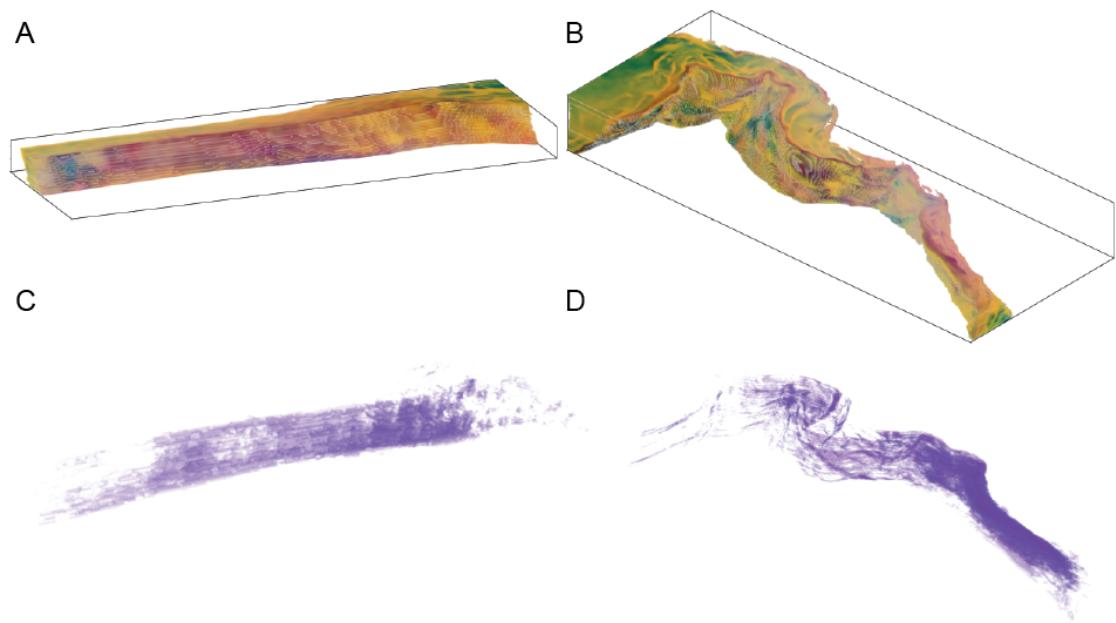


Figure 5.9: Objective local analysis of connective tissue organisation at two significant sites. A-B) 3D block of tissue from Lateral RA and PV sleeves respectively. C-D) Connective tissue isolated from (A) and (B) respectively. PV: Pulmonary Vein. RA: Right Atrium.

5.7 Evaluation

The performance of the proposed tissue segmentation method is evaluated using the Dice similarity coefficient (DSC) (Dice, 1945). DSC is an overlap-based evaluation metric widely used in validation of medical volume segmentation (Fu et al., 2018; Zou et al., 2004; Zijdenbos et al., 1994). It compares two binary sets of segmentation results

- ground truth and automatic - and provides a score between 0 and 1. DSC score is computed based on the confusion matrix components - True positives(TP), False positives(FP) and False negatives(FN) - as indicated below :

$$DSC = \frac{2.TP}{2.TP + FP + FN}$$

A DSC score of 1 represents complete spatial overlap between the two sets while 0 represents no overlap.

From the current dataset, we selected five slices (numbered 380, 480, 580, 680, 780 from top), well separated from each other, for evaluation. Ground truths are generated by manually segmenting each of the five slices into three tissue classes. Class-wise DSC was computed for each of the slices and the averaged results are summarised in Table 5.1. The overall segmentation performance which is computed as the average of mean class-wise similarity coefficients is 0.9683. Figure 5.10 shows a set of automatic and manual versions of the segmentation. The composite outputs show the representative slice (Refer to Figure 5.1 - slice number 580) clustered into the constitutive tissue types at high resolution. It is observed that the result of automatic segmentation is almost identical to the manually segmented ground truth as expected from the relatively high DSC score.

Tissue class	DSC
Myocytes	0.9815
Adipocytes	0.9819
Collagen	0.9416

Table 5.1: Mean class DSC

Mean DSC = 0.9683

5.8 Discussion

The tissue segmentation problem discussed in this chapter involved challenges due to the unconventional image size, extreme class imbalance and unpredictable changes in class distributions across the image stack.

We developed a fast and automatic method to address most of these problems efficiently. The colour-based tool runs through the entire dataset producing robust segmentation

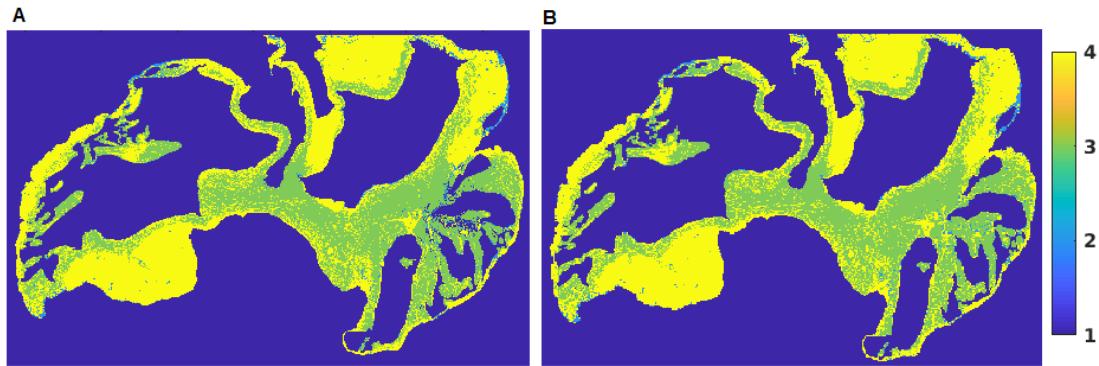


Figure 5.10: Composite outputs generated by A) automatic and B) Manual segmentations of the representative slice shown in Figure 5.1. Various tissue types are labelled according to the following legend.

Label 1: Background **Label 2:** Fibrosis **Label 3:** Myocytes **Label 4:** Fat

of the three tissue types. At first, a balanced representation of the colours distributed in each slice is generated. Initial points are then identified on this colour distribution diagram for the widely used k-means segmentation in CIELa*b* colour space. This type of initialisation ensures the robustness of the segmentation outputs across the entire image volume, without any further operator intervention.

There are certain limitations to this approach which may be addressed at a later stage. First, the only parameter used here for separating the tissue types is colour. Hence the results produced by this method are not accurate when the tissue types are not well separated in terms of their colours. For instance, the necrotic tissue regions as well as the wax background in this dataset are represented by yellowish colour which is highly similar to the colour of adipocytes. They cannot be easily separated from each other just based on colour. Other parameters like tissue texture may need to be considered. On the other hand, healthy tissue and collagen are represented by unique colours which makes them identifiable based on colour alone. Furthermore, the validation process appears to be limited as it is based on as selection of slices. There is no practical solution to this limitation due to the human effort involved in generating more manual annotations. However, the performance of the tool was consistent throughout the dataset and this has been visually validated. Also, as noted earlier in chapter 4, manual segmentations are based on human interpretation and need to be treated as close approximations to ground truth.

In the general context of fibrosis assessment ,the problem of class imbalance might not

be as severe as experienced by us in this particular case. Most of the cases requiring segmentation and quantification of fibrotic tissue carry heavy fibrosis so that the tissue classes present a more balanced picture.

In addition to the longstanding problem of fibrosis quantification, there are more recent studies focusing on the significance of atrial adipocytes in severity and recurrence of AF (Hatem et al., 2016; Wong et al., 2016). The development of more accurate tissue segmentation methods like the one discussed in this chapter will definitely impart more momentum to these arrhythmia studies. Being an unsupervised method, the approach used here also has the potential for generating accurate training data for more advanced segmentation algorithms based on supervised learning techniques.

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