

# Title Page with Authors

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Reconstruction and Visualization of Fiber and Lamellar Structure in the Normal Human Heart from Ex Vivo DTMRI Data

**(b) Authors:**

Damien Rohmer, *student assistant*; Arkadiusz Sitek, *PhD, scientist*; Grant T. Gullberg, *PhD, senior scientist*.

Ernest Orlando Lawrence Berkeley National Laboratory, Life Sciences Division, 1 Cyclotron Road, Berkeley, CA 94720, USA.

**(c-d) Corresponding Author :**

Grant T. Gullberg, Ph.D.  
Lawrence Berkeley Laboratory,  
1 Cyclotron Road, MS55R0121  
Berkeley, CA 94720, USA.  
Email: [GTGullberg@lbl.gov](mailto:GTGullberg@lbl.gov)  
Phone: 510-486-7483

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**Reconstruction and Visualization of Fiber and Laminar  
Structure in the Normal Human Heart from Ex Vivo DTMRI  
Data**

**Abstract:** (148 words)

**Objective:** The human heart is composed of a helical network of muscle fibers organized to form sheets that are separated by cleavage surfaces responsible for the orthotropic mechanical properties of cardiac muscle. The purpose of this study is the visualization of these structures in three dimensions.

**Methods:** Anisotropic least square filtering followed by fiber and sheet tracking techniques were applied to Diffusion Tensor Magnetic Resonance Imaging data of the excised human heart. The sheets were reconstructed by surfaces **that we defined locally from the second and third eigenvector of the diffusion tensor.**

**Results:** The fibers are shown to lie in sheets that have transmural structure which correspond to histological studies published in the literature. **Quantitative measurements show that the sheets are organized into laminar orientations of two dominant populations.**

**Conclusions:** A visualization algorithm **was developed to demonstrate the complex three-dimensional orientation of the fibers and sheets in human myocardium.**

**Key Words:** Cardiac Imaging, Diffusion Tensor MRI, Fiber Tracking, Laminar Structure.

## Introduction

The human heart is composed of a helical network of muscle fibers<sup>1,2</sup> organized to form sheets that are separated by a complex structure of cleavage surfaces.<sup>2</sup>

Understanding the three dimensional configuration of the fiber and sheet structure is of utmost importance for modeling the mechanical<sup>2-4</sup> and electrical properties<sup>5</sup> of the heart; and changes in this configuration may be of significant importance to understand the remodeling after myocardial infarction.<sup>6</sup> The visual comprehension of this anatomical structure is helpful to better understand the implications of the structure as to its relationship to the electrical, mechanical and biochemical properties of the heart. A comprehensive way to visualize these fibers is the use of three dimensional paths throughout the ventricle where the sheets are well represented by their cleavage surface.

It is known that **the principle eigenvector of the diffusion tensor obtained from diffusion tensor magnetic resonance imaging (DTMRI) can be used to determine the fiber direction.** However, the second and third eigenvectors of the tensor are also of interest and provide important information associated with the sheet geometry.<sup>7-11</sup>

The left ventricle is organized in a collection of three dimensional muscle fibers composed of myocytes (muscle cells) where each are 80 to 100  $\mu\text{m}$  in length and have a cylindrical shape with a radius of 5 to 10  $\mu\text{m}$ .<sup>4, 12</sup> To preserve the tissue architecture, especially during large deformations of contractile motion, cardiac fibers are embedded in an extracellular matrix called **endomysium** that consists of collagen where the type III collagen<sup>6, 13</sup> (highly deformable) has the highest proportion. Histological studies have shown that the orientation of the fiber angle varies continuously from **approximately**  $+60^\circ$  to  $-60^\circ$  across the wall,<sup>1</sup> **where from the apex to the base the fibers are a left-**

**handed spiral from the epicardium to the midwall, have a planar circular geometry in the midwall, and are a right-handed spiral from the midwall to the endocardium.**

The fibers in the heart form another three dimensional structure due to the alignment of the fibers in sheets.<sup>4, 12, 14, 15</sup> Histological studies show that the fibers are grouped in a volume of three to four cells thick within a laminar structure oriented transversally to the heart-wall.<sup>2</sup> **This laminar structure is bounded by cleavage planes** that are responsible for **some of the important** mechanical properties of the cardiac muscle.<sup>2, 16</sup> **These surfaces** exhibit an orientation which varies spatially showing a complex structure inside the heart.<sup>17</sup> The laminar structure can be roughly seen as **bounded by** twisted surfaces going across the wall and stacked from apex to base.<sup>14</sup> The sheets are physically separated by a coiled bundle of collagen fibers called perimysium.<sup>4, 12, 18</sup> This collagen consist mainly of type I (72%) (high tensile strength). The local geometry of the cleavage plane is characterized by the normal of the sheet at each position. Histological measurements have shown that this angle varies with the position across the wall (from +45° to -80°) and the distribution changes from the apical region (roughly convex variation across the wall) to the basal region (concave variation).<sup>17, 19</sup>

The diffusion tensor can be decomposed into eigenvalues and eigenvectors where the eigenvalues are sorted in decreasing order. Histology measurements have already validated the DTMRI measurement of the fiber direction with high precision.<sup>20, 21</sup> Based on the assumption that the water contained inside and outside the heart fiber cannot move freely, but is constrained to move in the direction of the fiber itself,<sup>22, 23</sup> it is confirmed that the first eigenvector corresponding to the largest direction of the diffusion is aligned with the direction of the fiber. **The information of the fiber angle for each voxel or for**

**a few nodes can be sufficient for mechanical studies of the motion of the heart,**<sup>24, 25</sup> **however, the anatomical structure of the fiber is not apparent unless the path of the fibers is followed to produce a three-dimensional visualization of its structure.** The fiber tracking method<sup>26</sup> helps the perception of this architecture by reconstructing the path followed by the fiber. With the visual information of the fiber linkage, a better comprehension of physical relationships between endocardium and epicardium and right and left ventricle is facilitated.<sup>27</sup> In addition, when a change occurs after cardiac remodeling<sup>6, 28-30</sup> due to infarct or surgery,<sup>31</sup> the visualization of the fiber path **may be helpful** for understanding the deformations induced.

The fiber tracking method is widely used in the brain to follow the white matter axons; however, some differences with the heart have to be taken into account. The white matter shows large differences of eigenvalues between the largest eigenvalue and the other two eigenvalues; and large variations of the ratio between these eigenvalues are present inside the brain as the grey matter is isotropic.<sup>32</sup> For the heart however, the ratio between the first and the second eigenvalue is roughly constant between 1.5 and 2. Therefore, techniques based upon the change of anisotropy are not appropriate for cardiac fiber tracking. Additionally, in the heart the fibers are organized in layers (sheets) separated physically by **cleavage planes**. This makes the diffusion smaller in the normal direction of the cleavage surfaces than diffusion inside the cleavage planes. The cleavage surface acts like a barrier to the diffusion. Because of that, the second eigenvector of the diffusion tensor is assumed to be positioned inside the sheet, and the third (the smallest one) is **assumed** locally **to be** normal to the sheet. These assumptions have been recently studied and a good correlation between histological measurements and analysis of

DTMRI data for both fiber and sheet structure has been shown.<sup>10, 20, 33</sup> The information of the sheet angle given at every position of the heart is of major interest for the mechanical modeling of the orthotropic distribution of strain and stress,<sup>12, 20</sup> but the perception of the real anatomical geometry is facilitated by the **three dimensional** visualization of the surfaces **within** the heart **wall**. This visualization is even more important for the sheet structure as the perception of a surface is more complex than a curve.

The visualization of the fibers in the heart is still a new field of research. Only a few papers presenting graphical visualization of the heart fiber structure have been published for canine,<sup>8, 34</sup> mouse,<sup>35</sup> or porcine.<sup>36</sup> Some results showing the sheet orientation in canine heart has also been presented.<sup>36</sup> In the present paper, the representation is performed on a normal **excised** human heart. To the best of our knowledge, this is the first paper obtaining the three dimensional visualization of the sheet structure from DTMRI data.

In the present paper, first a method for anisotropic filtering is presented to regularize the available DTMRI data of a human heart. Then a fiber tracking algorithm and an algorithm for the reconstruction of the sheet structure are described. Based on the expected geometry of the sheet, the algorithm uses the smallest component of the tensor to reconstruct the sheet as a surface. Finally, a comprehensive visualization of fiber paths and sheet surfaces are presented using a high quality ray-tracer.

## Methods

### DTMRI Human Heart Data

The data were acquired at Johns Hopkins Medical Center using a normal excised human heart and was made available for downloading on the internet (<http://www.ccbm.jhu.edu/research/DTMRIDS.php>). The heart was placed in an acrylic container filled with Fomblin (**Ausimon, Thorofare, NJ**), a **perfluoropolyether** having a low dielectric effect and low MR signal to increase **tissue-fluid** contrast. This setup also eliminated unwanted susceptibility artifacts near the boundaries of the heart. Images were acquired with a 4-element phased array coil on a 1.5 T GE CV/I MRI Scanner (GE Medical System, Wausheka, WI) using an enhanced gradient system with 40mT/m maximum gradient amplitude and a 150 T/m/s slew rate. **The acquisition was performed similar to that performed in canine hearts<sup>9</sup> using a diffusion-weighted 3D fast spin-echo pulse sequence. The FOV was 10 cm. Gradient pulses were 20ms in duration with trapezoidal shape. The TR was set to 500 ms with 2 averages. The diffusion encoding was produced using a pair of gradient pulses placed symmetrically around the first 180° RF pulse. Nineteen diffusion weighted scans and 2 scans without diffusion gradients were performed with a b-value of 1500 s/mm<sup>2</sup>. The acquisition was performed over almost 60 hours of continuous imaging time.**

The data set was arranged in a 256×256×134 array where each voxel in the array consisted of the three eigenvalues and three eigenvectors. The size of each voxel was 429.7 μm × 429.7 μm × 1000 μm.

## Mathematical Model

The left ventricle is described with a cylindrical coordinate system with basis  $(\mathbf{e}_r, \mathbf{e}_\theta, \mathbf{e}_z)$  (bold letter refers to a vector), where  $\mathbf{e}_r$  is the radial component **orthogonal** to the wall,  $\mathbf{e}_\theta$  the circumferential and  $\mathbf{e}_z$  the axial component from apex to base. The fiber direction is denoted as  $\mathbf{e}_f$  and the unitary sheet normal is denoted as  $\mathbf{e}_n$  as seen in **Figure 1B and 1C**. The vector  $\mathbf{e}_s$  is chosen to lie inside the sheet so that the basis  $(\mathbf{e}_f, \mathbf{e}_s, \mathbf{e}_n)$  is orthonormal.

The fiber angle  $\alpha$  is defined as the angle between the projection of  $\mathbf{e}_f$  onto the plane  $(\mathbf{e}_\theta, \mathbf{e}_z)$ . As defined in the paper of Helm *et al.*,<sup>9</sup> the sheet angle  $\beta$  is defined as the angle between the projection of  $\mathbf{e}_n$  onto the plane  $(\mathbf{e}_r, \mathbf{e}_z)$ .

The diffusion tensor  $\mathbf{D}$  is decomposed into eigenvectors  $\mathbf{e}_1, \mathbf{e}_2$ , and  $\mathbf{e}_3$  with eigenvalues  $\lambda_1, \lambda_2$  and  $\lambda_3$ , such that  $\lambda_1 \geq \lambda_2 \geq \lambda_3$ . Denoting  $\mathbf{R}$  as the matrix of eigenvectors and  $\mathbf{A} = \text{diag}(\lambda_1, \lambda_2, \lambda_3)$  as the diagonal matrix of eigenvalues, the diffusion tensor can be decomposed as  $\mathbf{D} = \mathbf{R} \mathbf{A} \mathbf{R}^T$ . As in our previous discussion, it is hypothesized that  $(\mathbf{e}_1, \mathbf{e}_2, \mathbf{e}_3) = (\mathbf{e}_f, \mathbf{e}_s, \mathbf{e}_n)$ .

## Fiber Tracking Algorithm

A common way to render a continuous vector field is to use fiber tracking (streamline).<sup>34, 37-39</sup> Given an initial position within the myocardium, a particle moves within the vector field described by the first eigenvector  $\mathbf{e}_1$  of the diffusion tensor and its trajectory is parameterized. The mathematical formulation of the fiber tracking is to find the path  $\mathbf{s}$  which depends on the variable  $t$  where  $\mathbf{s}_0$  is the initial position:

$$\begin{cases} s'(t) = e_1(s(t)) \\ s(0) = s_0 \end{cases} . \quad (1)$$

This is a first order non linear ordinary differential equation (ODE). In this paper, **a fifth order Dormand-Prince Runge-Kutta method<sup>40</sup> with automatic error estimation is used to solve Equation 1.**

**The data provide the average of the fiber direction over a voxel which contains roughly 4600 fibers if we assume a voxel volume of  $(429 \times 429 \times 100) \mu\text{m}^3$  with 100% packing of myocytes with a volume of  $(20 \times 20 \times 100) \mu\text{m}^3$ .** We should then expect to see a smooth orientation along the heart without oscillations. However, oscillations can be noticed when computing fiber tracks directly from the DTMRI data without applying any method for smoothing. In order to minimize these effects, an anisotropic filtering method was used to smooth the directions of the fibers. We chose to implement the Moving Least Squares<sup>37</sup> (MLS) method which gives a point-to-point filter with respect to the local direction of the anisotropy. The method minimizes the following energy functional by constructing an approximate polynomial expression  $\tilde{\mathbf{D}}$  for the tensor field  $\mathbf{D}$  at each position  $\mathbf{p}$  inside the left ventricle:

$$E(\mathbf{p}) = \int_{\mathbf{p}' \in \text{heart}} G(\mathbf{p}' - \mathbf{p}) (\tilde{\mathbf{D}}(\mathbf{p}' - \mathbf{p}) - \mathbf{D}(\mathbf{p}'))^2 d\mathbf{p}' . \quad (2)$$

The integrand is weighted by a Gaussian function  $G$ .  $\tilde{\mathbf{D}}$  is the polynomial tensor estimated from the original tensor field  $\mathbf{D}$ . The product of tensors is understood to be the product of each individual component.

**In order to take into account the anisotropy,  $G$  is designed to promote the direction of the first eigenvector.** Equation 2 was implemented by taking into account a Gaussian function **with a standard deviation of 1 voxel in the fiber direction and 0.5**

in the other two directions. **A ratio of 2:1 was chosen recognizing the fact that the average diffusivity in the principal direction is larger than the diffusivity in the orthogonal direction.** The second and third eigenvectors which have very close corresponding eigenvalues were not differentiated for the purpose of filtering. **The term  $G$  serves to smooth local pixels according to the tensor components of its neighbors, but the extent to which it relies on its neighbors depends on the width of the Gaussian filter in each direction. In our case the direct neighbors (closest voxel) in the fiber direction had a weight of almost 1 and the neighbors that are located 3 voxels away from the center voxel has a weight of almost zero.** The linear system given by this method was solved by Gaussian elimination and numerical integration was realized by Gaussian quadrature of order four in a neighborhood of three voxels.

**Values of the tensor field were only known at discrete positions. The value of the tensor needs to be interpolated in the integration or in the regularization step in order to obtain the value of the vector field  $e_I(s)$  between sampling points. The component wise tensor interpolation was performed using trilinear interpolation. An interpolation polynomial of order 3 was chosen for  $\tilde{D}$  to eliminate spurious oscillations along the fiber track.**

For the case of a vector field the positive and negative directions along the current vector is specified. For the case of fibers, the diffusion tensor is symmetric as the diffusion occurs in both directions. Therefore the sign of the eigenvector is not meaningful. Thus in order to be consistent, a condition to invert or not to invert the sense of the displacement was needed before moving forward. This condition inverted the sign of the new direction if the angle between the new and old direction was greater than  $\pi$ .

### Sheet Tracking Algorithm

The diffusion tensor can also provide information about the laminar structure of the myocardium. For each position in the left ventricle, a tangent plane to the sheet was found. This plane was defined by the normal vector  $\mathbf{e}_3 = \mathbf{e}_n$ . In order to span a sheet surface, the direction  $\mathbf{e}_r$  was used. Since the sheet surface is supposed to cross the ventricular wall (Fig. 2), the best direction along which the plane could be defined is radially oriented across this wall. The sheet was tracked in this direction by projecting the desired direction  $\mathbf{e}_r$  onto the local plane defined by the fiber and sheet directions  $\mathbf{e}_f$  and  $\mathbf{e}_s$  (Fig. 3). The first spanned direction  $\mathbf{d}_1$  was determined by

$$\mathbf{d}_1 = (\mathbf{e}_r \cdot \mathbf{e}_f) \mathbf{e}_f + (\mathbf{e}_r \cdot \mathbf{e}_s) \mathbf{e}_s. \quad (3)$$

The vector  $\mathbf{d}_1$  was used to follow the surface in this direction using a first order Newton iteration.

In order to construct a 2D surface, the expansion in another perpendicular direction  $\mathbf{d}_2$  was performed. The vector  $\mathbf{d}_2$  was found by rotating the vector  $\mathbf{d}_1$  by a right angle around the normal of the sheet surface (Fig. 4):

$$\mathbf{d}_2 = (\mathbf{d}_1 \cdot \tilde{\mathbf{e}}_3) \tilde{\mathbf{e}}_3 - \mathbf{d}_1 \times \tilde{\mathbf{e}}_3, \quad (4)$$

where  $\tilde{\mathbf{e}}_3 = \pm \mathbf{e}_3$  depending on the convention. The sheet was also followed along the direction  $\mathbf{d}_2$  using a first order Newton iteration. This algorithm built the sheet surface from any starting point within the myocardium. The data were also filtered with the same MLS method that was used for the fibers. **For more details about this, please refer to our LBNL report.**<sup>27</sup>

### **Visualization of the Fiber and Sheet Tracking Results**

The fibers were represented as thin tube-like surfaces with a radius of roughly 400  $\mu\text{m}$ . Sheets defined as a set of parameterized points were triangulated creating meshed surfaces. The tubes and triangulated surfaces were displayed using the open source ray tracer POV-Ray (Persistence of Vision Raytracer) (<http://www.povray.org>). We chose the software to obtain a high quality rendering with lighting and shadowing which is much better than the triangle based render. The scene description in a POV-Ray script language was generated by fiber and sheet tracking routines.

### **Quantitative Measurement of Fiber and Sheet Angles:**

**The quantitative measurement of the fiber angle was performed by averaging the values of the angle  $\alpha$  across the wall in eight different regions as seen in Figure 3A. The regions were defined manually on a cylindrical model of the left ventricle. Each region was sampled from 1800 nodes across the wall. The width between the samples depended on the location in the wall of the ventricle and was expressed in percent of the total width. The histogram of the sheet angle was also plotted in eight different regions of the ventricle. The regions were defined similar to those defined by Helm *et al.*<sup>9</sup>**

## Results

Results of fiber tracking are presented in Figure 3. The visualization of the fibers in Figure 3 uses a color coding representation of the local fiber angle  $\alpha$ . **Left-handed spiraling fibers** are encoded with a blue color and **right-handed spiraling fibers** with a green color. The color intensity depends on the value of  $\alpha$ . The dark blue and dark green colors represent larger angles for the epicardium and endocardium, respectively. The light blue color in the midwall indicates fibers are located in the axial plane. On each picture the color intensity is scaled to its maximum angle. The fiber angles appear to vary smoothly across the wall. **A different structure is evident in the apex of the heart where** a twist of the fiber bundles is observed.

**Quantitative results for the fiber angle  $\alpha$  are shown in Figure 4. The fiber angle increases smoothly from  $-40^\circ$  to  $+60^\circ$ ,  $-20^\circ$  to  $+50^\circ$ , and  $-20^\circ$  to  $+60^\circ$  from epicardium to endocardium in the anterior, lateral, and posterior regions, respectively. The fiber angle varies linearly across the wall but becomes more non linear close to the epicardium and endocardium boundaries. The transmural gradients in the midwall are almost identical throughout the left ventricle, and are especially so for the basal region. The gradients in the epi- and endocardium regions show differences between regions and the variations within each region appear to be non-linear. One thing to note is that the curves for the fiber angles strictly decrease from epi- to endocardium. However, in some cases a minimum is found in the endocardium or a maximum in the epicardium that are not at the extreme boundary. It is possible that the segmentation incorrectly differentiated between myocardial and non myocardial tissue. Also, the noise is greater in the endo- and**

epicardial regions resulting in larger deviations and variance for the angle  $\alpha$ . The large fluctuations are especially seen in the apical region.

Our results in the one heart we studied showed some similarities but also some differences to those of Helm *et al.*<sup>9</sup> who applied DTMRI in excised canine hearts. They reported fiber angles ranging from epi- to endocardium from  $-35.7 \pm 8.6^\circ$  to  $38 \pm 6.1^\circ$ ,  $-41.0 \pm 8.0^\circ$  to  $29.7 \pm 6.6^\circ$ , and  $-57.0 \pm 6.2^\circ$  to  $39.5 \pm 10.6^\circ$  in the anterior, lateral, and posterior regions, respectively. Using DTMRI, fiber angles in excised hearts of goat have been reported by Geerts *et al.*<sup>11</sup> ranging from  $-75^\circ$  to  $+90^\circ$ ,  $-55^\circ$  to  $+85^\circ$ ,  $-40^\circ$  to  $+80^\circ$ ,  $-85^\circ$  to  $+50^\circ$  in the anterior, the intrapapillary muscle, the posterior, and the septal region, respectively. Both groups found that the helix angles were larger in the anterior region and significantly smaller in the posterior region and found a steeper slope of the transmural course of the helix angles in the anterior and septal regions.

A comparison of fiber tracking results from filtered and unfiltered data is presented in Figure 5. Fibers were tracked throughout the entire ventricle without filtering and after filtering. It can be noticed that the filtered data provide fibers that appear to be more parallel and the fiber bundles are easier to distinguish. The measurement of the angle  $\alpha$  is also plotted comparing the result for both cases. The plot shows that filtering doesn't impact the statistical average of the fiber angle in the midwall. However, small differences in value can be noticed in the epicardial regions.

The surfaces of the sheet structures for the midwall are presented in Figure 6 and for the apex in Figure 7. These surfaces were built starting with seed points positioned in

the midwall and were grown in four orthogonal directions perpendicular to the normal of the surface (Fig. 2C). The histogram of the sheet angle  $\beta$  for the regions in Figure 3A is also plotted in Figure 8. The histogram results show some similarity between regions, especially for the lateral wall. The epicardium, endocardium, and apex regions show more variation.

Our results from one human heart are difficult to compare with those of other investigations who obtained measurements from several hearts. There are some similarities but also differences. Helm *et al.*<sup>9</sup> reported several observations from canine data that we need to investigate in more detail. We find as they that the majority of regions contained a dominant angle within the distribution of sheet angles. These findings are similar to histological results reported by others<sup>2, 16, 19, 41</sup> indicating that there are dominant muscle layers. Also, our dominant populations seem to be located at  $50^\circ$  and  $100^\circ$  which are close to but not exactly equal to  $45^\circ$  and  $117^\circ$  observed by Helm *et al.*<sup>9</sup>. Histology measurements of Dokas *et al.*<sup>3</sup> identified a dominant midwall muscle layer at  $\sim 45^\circ$  and another at  $\sim 135^\circ$  in pigs, and Ashikaga *et al.*<sup>16</sup> observed angles at  $36^\circ$  and  $\sim 70-90^\circ$  apart in canines. Dominant angles have also been observed by Harrington *et al.*<sup>19</sup> applying DTMRI to hearts excised from sheep. They identified two families of sheets with sheet angles of approximately  $-45^\circ$  and  $+45^\circ$ . These were angle measurements of the second eigenvector whereas our measurements of  $\beta$  were based upon measurements of the third eigenvector. Therefore, their measurements would correspond to a  $\beta$  of  $+45^\circ$  and  $+135^\circ$ .

## Discussion

A method was presented for generation of **qualitative computer visualization** of fiber and laminar structures in the normal human heart from ex vivo DTMRI data. In our implementation, the fibers were represented as shaded 3D tubes to improve the depth perception of the structure. The fiber angles are shown to vary smoothly across the wall from a negative (epi) to positive (endo) angle. Fibers lie within sheet surfaces (cleavage planes), but the knowledge of fiber directions is not sufficient to create visualization of the cleavages planes. This implies that the surfaces need parameterizations which are not related to the fiber directions. Our work helps **demonstrate** the relationships between fiber directions and laminar structure by providing high quality visualizations of both of these structures.

**As it has been reported in the literature the fiber angles are shown to vary smoothly as a linear function across the wall but become more non-linear near the endo- and epicardial walls with significant increase in the gradients. Also, the variance is greater in these regions. This increase in noise may be due to both statistical effects of data acquisition and deterministic effects caused by the difficulty of segmenting the edges of the myocardium. This may be the reason for the actual minimum or maximum in the measured angle before the endo- or epicardial boundary.**

**The process of fiber tracking is sensitive to noise. High frequency oscillations in the angle make the fibers have a noisy irregular path. Therefore, the path followed by a bundle of fibers might change from one bundle to a neighboring bundle. One could reduce this noise by averaging over more fibers, however, in our**

**work we depended upon the regularization to provide the averaging. After the numerical solution of the differential equations (Eq. 1), an anisotropic filtering with preferential weighting in the fiber direction was performed at every position to enable the reduction of data errors.**

In our work there were two possible sources of bias. One, the solution to the differential equations can introduce bias due to interpolation. Therefore, **in order to minimize large errors in following the fiber over long distances, the Dormand-Prince Runge-Kutta method<sup>40</sup> with automatic error estimation was used to reduce the errors in the numerical solution of the differential equations. Two, we only had access to diffusion tensor data and did not have access to the original raw data used to reconstruct the diffusion tensor. In our algorithm it was necessary to interpolate the matrix components of the tensor field. However, there is a non-linear transformation between a representation of the interpolation of the original data and the interpolation of the tensorial components. Therefore, a further improvement of our method, which needs to be investigated, may be to perform interpolation of the original data from which the tensor is calculated instead of interpolating the tensorial values.**

The fiber direction was obtained based only on the largest eigenvectors which had amplitudes that were significantly greater and less sensitive to noise than the other two eigenvectors. **The diffusion tensor in the heart has ratios of 1.46 and 1.74 between first and second and between the first and third eigenvalues, respectively. (Compare this with the brain which has a difference of a factor of ten between the first and the second and third eigenvalues.)** It was fairly easy to distinguish the first eigenvector

from the other two eigenvectors. However, it was more difficult to determine the sheet structure which was obtained based on the second and third eigenvectors which had magnitudes that were closer in value. Thus a small amount of noise can easily invert the ordering of the second and third eigenvectors. Also the two smallest eigenvectors have lower amplitudes than the first component and therefore the signal to noise is much less. This is especially appreciated close to walls of the epicardium and endocardium where some surfaces of the cleavage planes appear to be very noisy (Fig. 6C, E, F).

A **better** criterion to verify the correct interpretation of the two smallest eigenvectors **may be needed** to avoid misclassification by providing **better** a priori constraints on the orientation of the sheet normal. **The current algorithm follows the radial direction and assumes that that the structure of the sheet goes mainly across the wall.** If this is not correct, the projected vector does not sufficiently control the directionality of the tracking and can lead to arbitrary directions for the sheet construction with amplitude that could approach zero. This problem appears specifically in the midwall of the anterior wall where the normal directions of the sheets are almost transverse to the wall. **Also, if in some region the radial direction becomes perpendicular to the sheet, more a priori information may be needed to correctly visualize the sheet structure in this region.** More robust methods may also be needed to enable the possibility of reconstructing surfaces in regions with interdigitating sheets oriented with a relative angle of about 70-90 degrees.<sup>2, 15, 19</sup> The tensor model is unable to detect sheet crossings because the diffusion distribution at the crossing does not correspond to a Gaussian distribution. **In this case a different model of diffusion would have to be taken into account.**<sup>42</sup>

Since the precise structure of the sheet surfaces is not well known, it is difficult to conclude if fine structure of the surface is real or is due to noise. The sheet tracking algorithm was performed with the same regularization that was used for the fiber tracking. This constrained the tracked fibers to lie exactly inside the surface. However, another type of MLS regularization could also be implemented to filter more in the direction of the sheet than in the direction normal to the sheet.

Some other limitations are linked to the choice of POV-Ray software used for visualization. The visualization is done by ray tracing and because of that is very slow compared to other libraries such as OpenGL. Therefore, at the current stage of our **development**, interactive viewing of the results of the fiber and sheet tracking is not possible. **More work is needed to make the visualization interactive.**

Even with these difficulties the structure and orientation of the **sheets** constructed in our work compares well with **qualitative visualization** of histological measurements in transmural sections obtained from apex to base in the literature.<sup>14</sup> **At the epicardium it was difficult to obtain a smooth sheet surface because the difference between second and third eigenvalues for this region is smaller than for other regions of the myocardium. Thus, the variances associated with the directions of the second and third eigenvectors are increased in that region. This finding is consistent with Helm *et al.*<sup>9</sup> who found no significant difference between second and third eigenvalues of the diffusion tensor in the epicardium. At the apex one observes a twist of the sheet around the apex (Fig. 7).**

**However, several problems are encountered when using the current MRI technology to acquire in vivo human DTMR images of the human heart with the**

same high resolution and high signal to noise as that used in this paper. The first is the long acquisition time. The data were acquired continuously for approximately 60 hours on a 1.5T clinical scanner using a standard diffusion tensor acquisition protocol. This would be totally impossible for imaging the in vivo human heart. The signal noise is improved when going to higher field strengths.<sup>43-45</sup> However, there are several issues that need to be solved before high field DTMRI is feasible. The second problem is that the DTMRI approach which assumes a Gaussian diffusion model has difficulty to track interdigitating sheets. This could possibly be solved by using q-space imaging<sup>46</sup> though this again would increase acquisition time. Q-space imaging has been applied to the spinal cord<sup>47</sup> and has also been applied ex vivo to study the complex fiber structure of the bovine tongue.<sup>47</sup> The third problem relates to performing any in vivo DTMRI of the moving heart. There is virtually only one group of researchers that have successfully accomplished this task.<sup>7, 48-51</sup> The moving heart with its nonlinear deformation presents a significant challenge in our ability to perform DTMRI.

The technique presented here may have important implications for the in vivo study of heart structure in health and disease. For example it may be useful for visualizing the reorganization of sheets over the cardiac cycle. Chen *et al.*<sup>41</sup> showed using DTMRI in excised rat hearts that sheet reorientation within the subepicardial to subendocardial region is a primary determinant of myocardial wall thickening. This information could be helpful in developing more advanced electromechanical models of the heart that are used in the study of the basic principles of cardiac function.

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### List of Figures:

**Figure 1.** Representation of the fibers in the heart. (A) The long oval structures correspond to the fibers. (B) The laminar structure in the heart is represented with the cylindrical basis  $(e_r, e_\theta, e_z)$  and the sheet basis with the basis  $(e_f, e_s, e_n)$ . (C) **Simplified visualization of the sheet and fiber spatial arrangement with the associated coordinate system. ( $e_f=e_1$ ) is the fiber direction, ( $e_s=e_2$ ) is the sheet direction and  $e_n$  is the normal to the sheet, where  $e_1, e_2$  and  $e_3$  are eigenvectors of the diffusion tensor.** (D) **Definition of the fiber angle  $\alpha$  and sheet angle  $\beta$ .**

**Figure 2.** (A) Projection of the desired radial direction  $e_r$  onto the sheet surface defined by the normal  $e_n$ . Vector  $e_f$  is the fiber direction and  $e_s$  is the sheet direction.  $d_1$  is the projection of  $e_r$  onto the plane spanned by the vectors  $e_f$  and  $e_s$ . (B) Reconstruction in the radial direction (**First step used for the construction of the sheet**). At each position (blue spheres), the fiber direction  $e_f$  and the sheet direction  $e_s$  are determined from the data. The projected desired radial directions  $d_1$  are in transparent white. (C) Reconstruction in the circumferential direction. The yellow vectors  $e_n$  are normal to the surface and the perpendicular directions  $d_2$  (shown in magenta) are the reconstructed circumferential directions.

**Figure 3.** Visualization of the fiber structure of the left ventricle. (A) The visualization was created by using a cylindrical mesh of 1000 seed points throughout the entire volume. **Left-handed to right-handed rotation** of the fibers going from the epicardium to endocardium can be seen. The nearest wall is the septum. (B) The heart is displayed

with the posterior wall on the bottom. (C) Short section of the left ventricle which illustrates the smooth variation of the fiber angle and its sign inversion across the wall from epi- to endocardium. (D) Orientation of the fibers by sections in the anterior wall from septal to lateral wall. For each section, the fibers are plotted closer to the endocardium. The smooth change of direction can be seen while the fiber bundle wraps around the endocardium. (E) Helical visualization of the fibers from apex to base. (F) Fiber tracks close to the apex. The twist around the apex can be appreciated. It is worth noticing the smooth continuity of some bundles of fibers going down from the endocardium (green), pass the midwall (in light blue) and going up again (dark blue). The large variations between green and blue in the middle of the apex are due to the fast change **from left-handed to right-handed** rotation. In the center, the comparison between **left-handed and right-handed** rotation is not accurate as the fibers become more aligned with the central axis of the left ventricle.

**Figure 4. Quantitative distribution of the fiber angles  $\alpha$ . (A) Regions of the ventricle that are used for sampling the fiber angle. (B) Plot of the fiber angle from epicardium to endocardium in percent of the wall thickness. The values correspond to the average over 1800 nodes and the error bars correspond to the standard deviation of the samples.**

**Figure 5. Comparison between unfiltered and filtered data. (A) Comparison of the result of the fiber tracking for the entire ventricle. The left part represents the fiber track for the unfiltered case where some noisy oscillation can be seen in the**

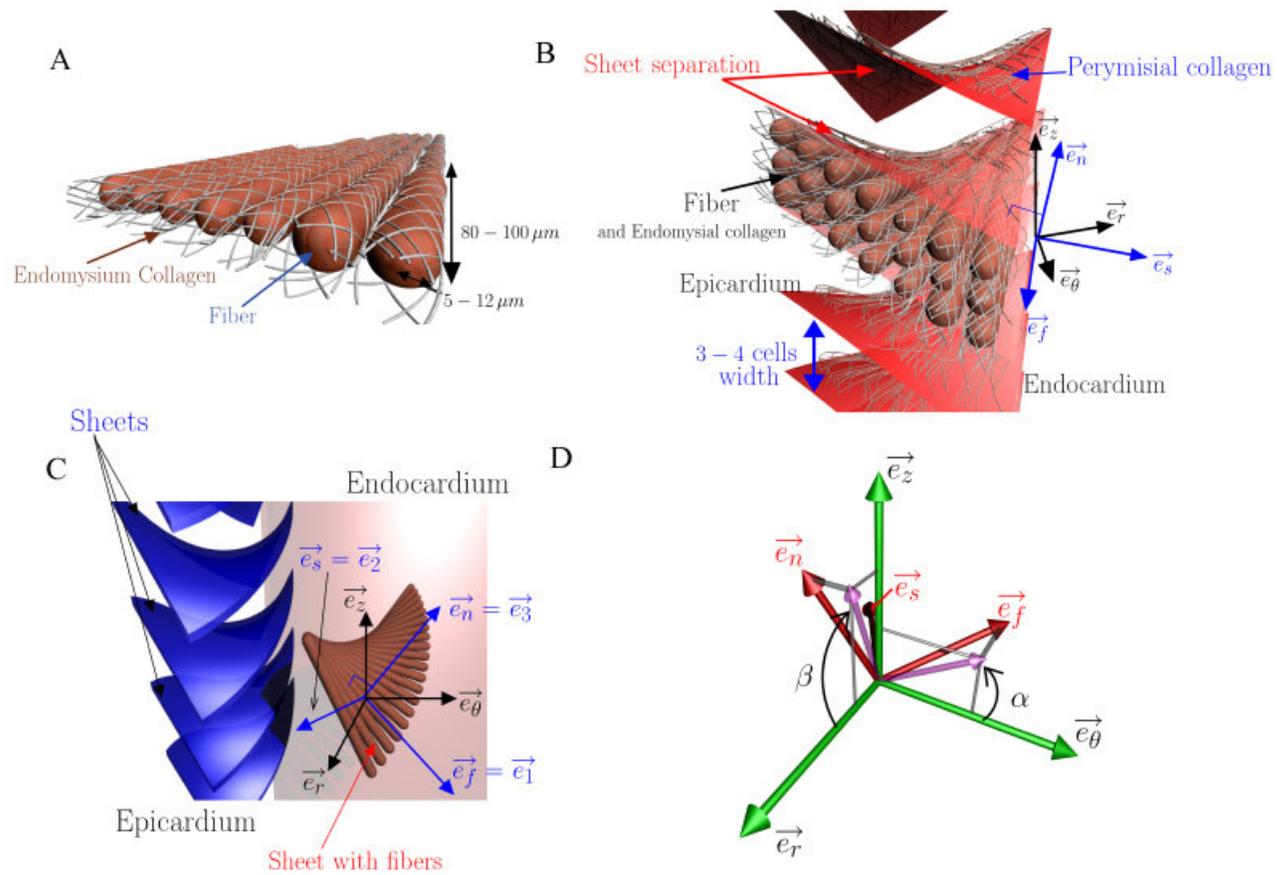
**epicardial regions, while the right part show the result for the filtered data. The color encoding is the same as for the previous pictures. (B) Comparison of the fiber angle in the filtered and unfiltered data. The black line is the fiber angle after the filtering, while the gray line is the fiber angle before applying the filter.**

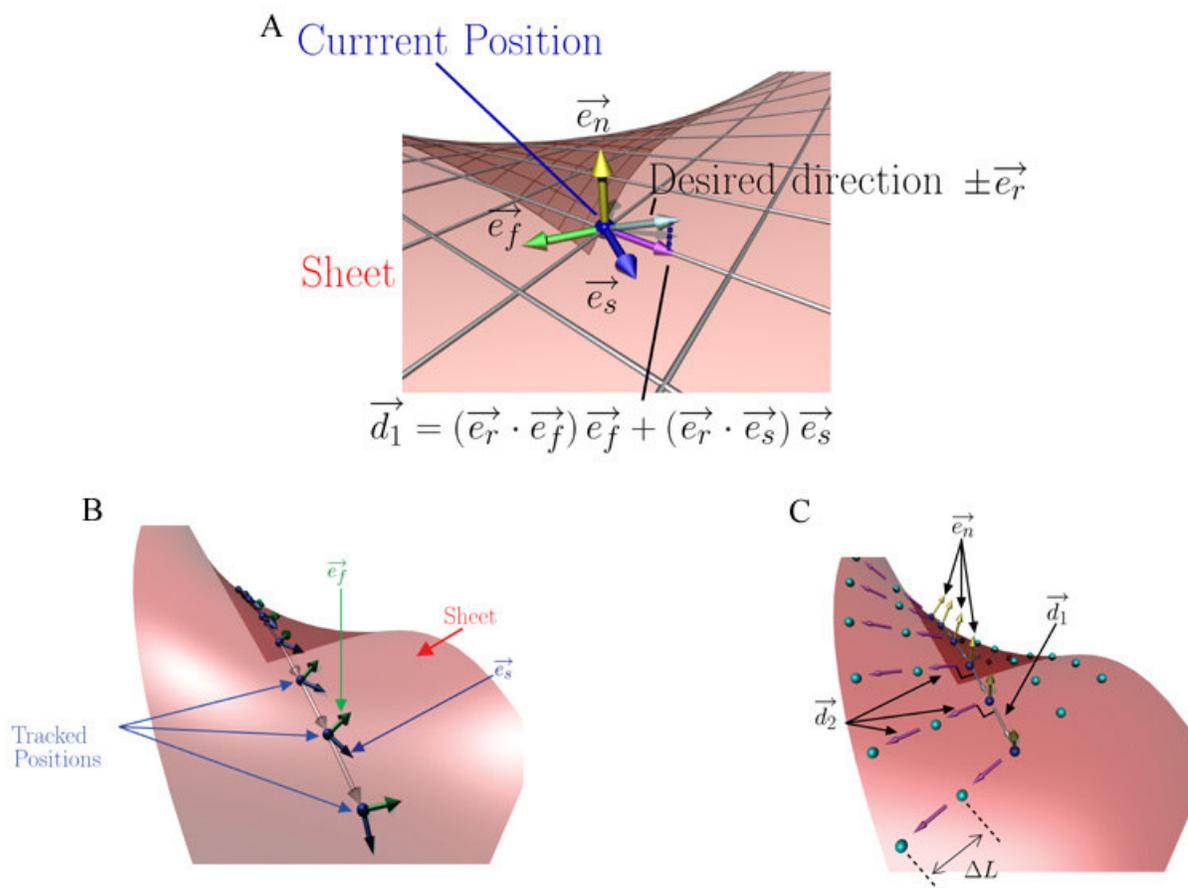
**Figure 6.** Visualization of the sheet structure of the left ventricle. (A) One sheet reconstructed by our method. The line traveling left from the closest corner corresponds to the epicardium. The concave shape in the z coordinate is characteristic of a region close to the base of the LV. (B) The fibers are shown embedded in the sheet surface. It can be noticed that the fibers lie completely on the surface. The color on the surface shows the third component of the fiber direction (red: small z component, blue: large z component). The surface **twist** clockwise with the fibers in the epicardial region, has a local maximum in the midwall where some circumferential fibers lie on it, and then goes down, twisting in the opposite direction with the fibers. (C) and (D) present sheets stacked crossing the ventricular wall. The twist of the sheets is noticeable with a concave curvature in the transverse section of the heart wall. The color of the sheet is only used to differentiate them. In (D), the endocardium corresponds to the red surface and the epicardium is shown by the mesh. (E) Large sheets around the left ventricular positioned closer to the basal region. The color of the sheets encodes the z component of the fiber direction (blue: planar fiber, red: fiber going up or down). Some irregular structures can be seen close to the epicardium due to noise. The color of the endocardium encodes the z component of the sheet normal. The green color indicates a large z component (the sheet is almost in the radial plane); while the white transparent color indicates a more vertical

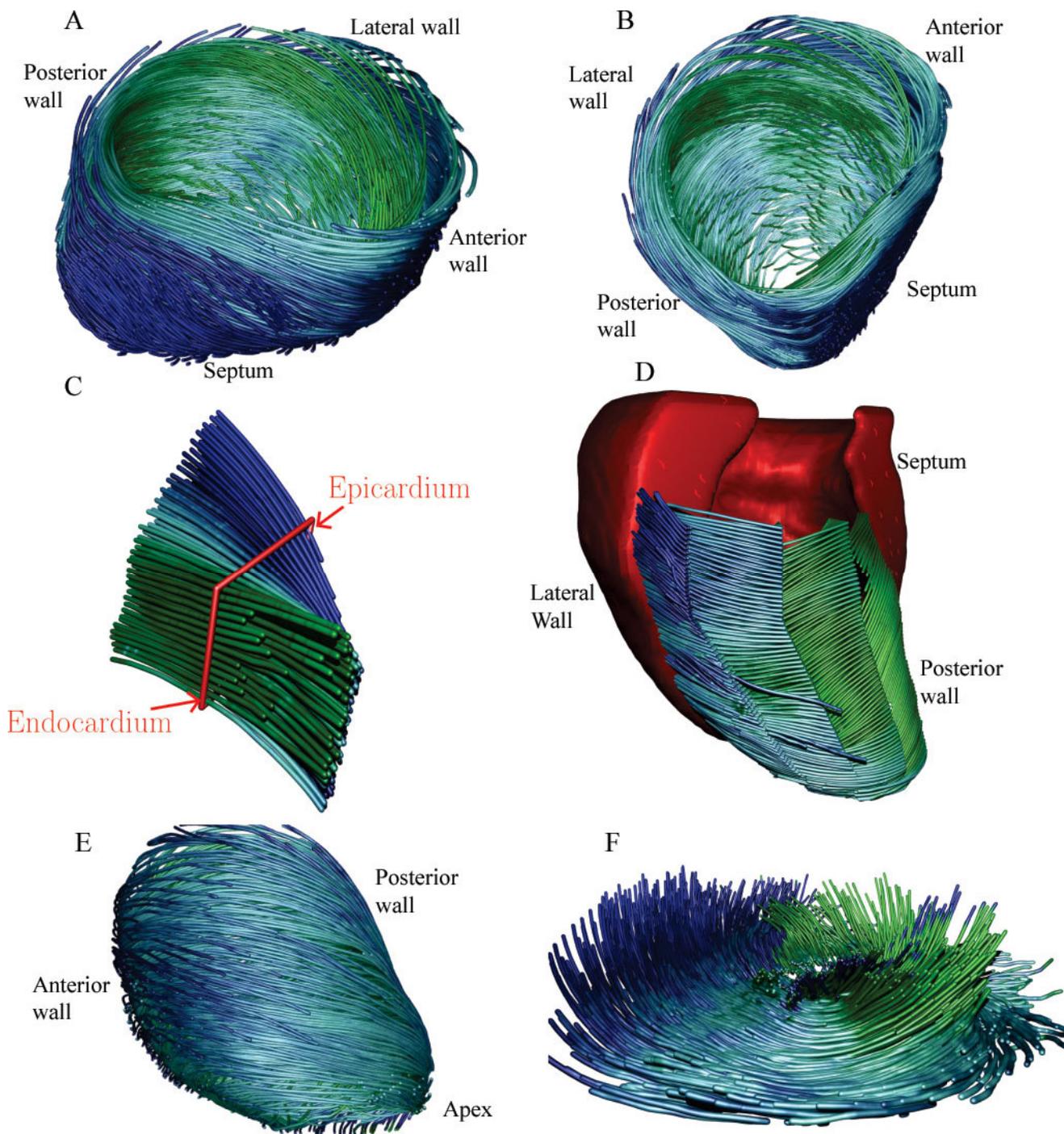
direction (less planar sheets). (F) Small sheet surfaces distributed over the entire left ventricle. The spatial variation shows a complex global structure. The color coding of the endocardium is the first and second component of the fiber direction and the color coding of the sheets is the same as in (E).

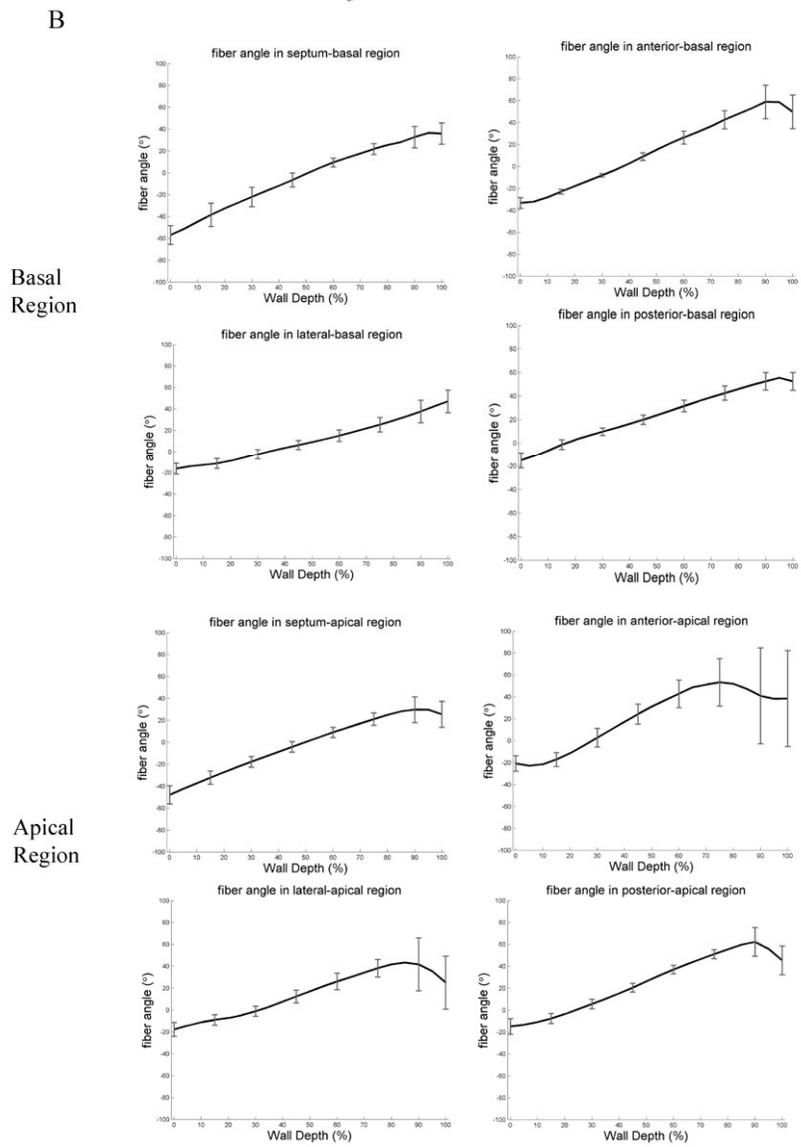
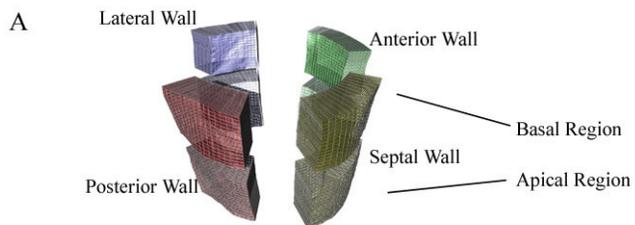
**Figure 7.** Reconstruction of the sheets in the apex. These sheets smoothly join the epicardium to the endocardium. The color of the surface encodes the third component of the fiber direction. In the region where the **fiber angle is almost zero** (red regions), the surface has very little twist and is almost planar. For the other case where the fibers have a larger z component, the curvature of the sheet is greater. The structures in the septal wall are not shown. This is because at this region the heart is linked with the right ventricle. The algorithm does not perform well due to the assumptions of how the surfaces cross the left ventricle which probably differ from surfaces embedded in the right ventricle. **The orientation of the view is labeled on the figure.**

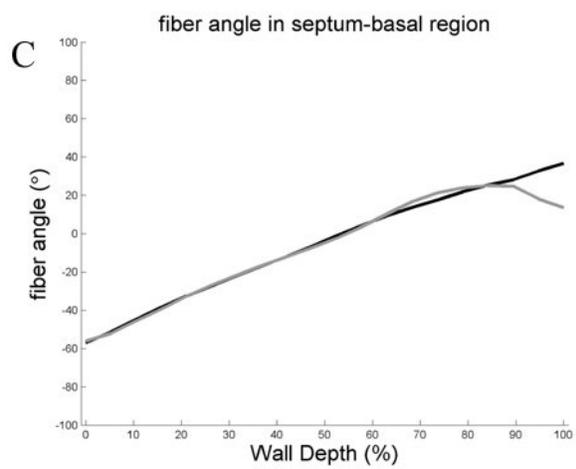
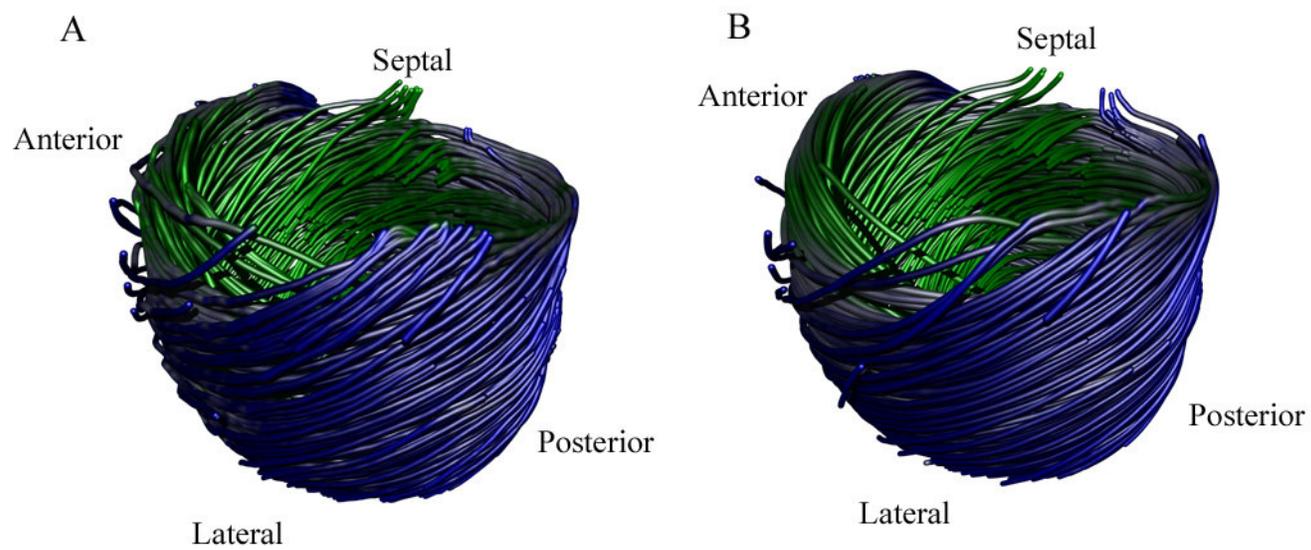
**Figure 8. Quantitative distribution of the sheet angles. Histograms of the sheet angle  $\beta$  for the regions as defined in Figure 4A. Each region is separated in three sections across the wall where the sampling is performed: epicardium, midwall and endocardium region.**



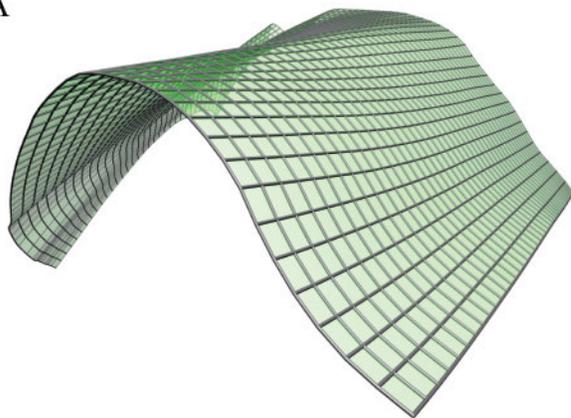




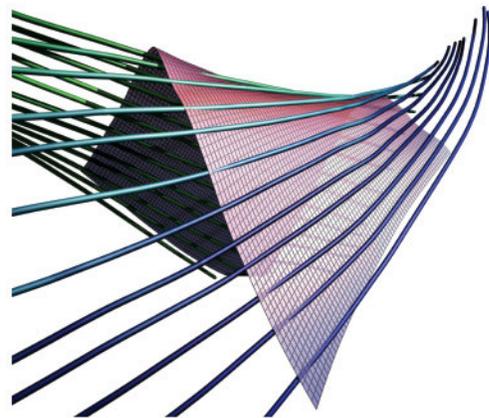




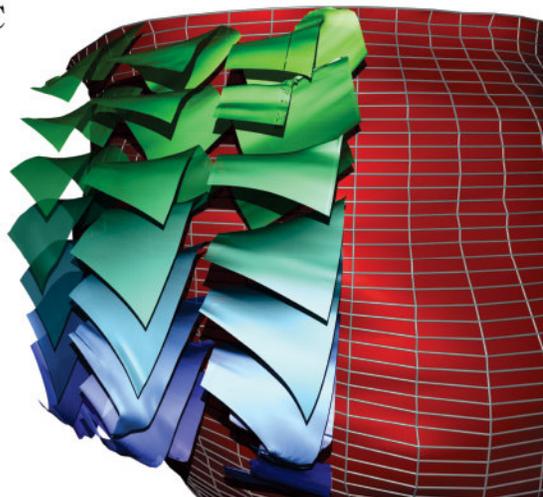
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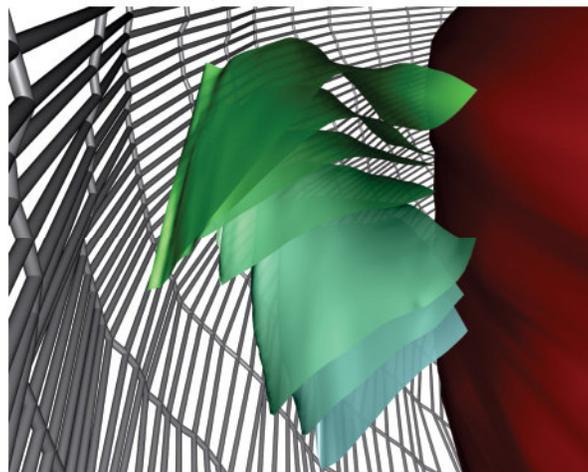
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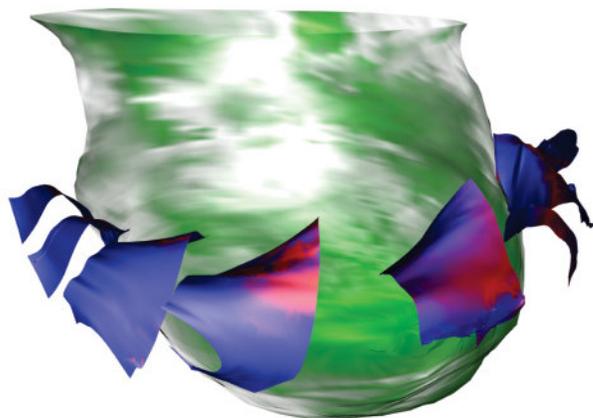
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