Fascicle Ellipticity as an Explanation of Transverse Anisotropy in Diffusion MRI Measurements of Skeletal Muscle

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Synopsis

Diffusion MRI of skeletal muscle exhibits a transverse anisotropy, the source of which has yet to be conclusively determined. To explore this, histological images were segmented into intracellular and extracellular domains and used to inform a direct numerical simulation of the Bloch-Torrey equation. Histology images were examined at the myocyte and fascicle scale and it was found that results from the fascicle images exhibited increased transverse anisotropy. These results suggest that fascicle organization may pay a hereunto unrecognized role in affecting dMRI in skeletal muscle.

Introduction

Diffusion MRI in skeletal muscle exhibits anisotropic diffusion behavior with three distinct eigenvalues (λ_1/ λ_2/ λ_3).[1] While the explanation for the difference in the primary and secondary values is well established to relate to diffusion in the axial direction of the muscle cell, the origin of the difference in λ_2 and λ_3 has not been conclusively determined. Myocardium also exhibits transverse anisotropy which is associated with its sheet-like structure,[2] however, skeletal muscle does not exhibit such sheet-like organization. Skeletal muscle has a hierarchical organization of organized bundles (fascicles) surrounded by a connective collagen tissue (perimysium). These fascicles are in turn made up of individual muscle fibers (myocytes) and are also surrounded by connective tissue (endomysium). Most investigations of skeletal muscle structure's effect on dMRI signal focus on this myocyte level because its length scale relates to the diffusion distance typical in dMRI experiments. The length scale of fascicles is much larger than this diffusion distance and so not expected to influence the signal. Myocyte ellipticity has been proposed as an explanation for the transverse anisotropy,[3] however, such ellipticity would need long-range organization for its cumulative effect to appear at the voxel level which has not been observed. Contrary to this, ellipticity of fascicles can be readily observed in histological images (Figure 1). Though the fascicle is larger than the diffusion distance, the perimysium thickness is on the order of the diffusion distance and occupies enough voxel volume (~10%) to affect the dMRI signal. In this abstract, histological images of myocyte and fascicle structures are used to numerically simulate dMRI experiments to examine how realistic structures at these different spatial scales affect dMRI signal.

Methods

Histological images of fascicle and myocytes from different muscle groups and species were collected and processed with ImageJ[4] which segmented the image into intra- and extracellular domains. These domains related either to the perimysium and fascicle space or the endomysium and myocyte space. Three histology images at the fascicle level[5-7] and four at the myocyte level[7-10] were obtained. These images were used as the basis of a periodic domain over which the Bloch-Torrey equation was numerically solved[11] for an applied PGSE pulse with b = 800 s/mm^2 and δ/Δ/TE=10/60/70 ms applied in 10 gradient directions. The intracellular space had a diffusion coefficient of 1.5 μm^2/ms and T2 of 40 ms while the extracellular space had a diffusion coefficient of 2.0 μm^2/ms and T2 of 80 ms. Surrounding the cell is a sarcolemma membrane with permeability of 40 μm/ms. Parameters were chosen in keeping with reported literature values. The simulated signals were used to estimate a diffusion tensor using custom code written in MATLAB from which eigenvectors, eigenvalues, FA and ADC were determined.

Results

Representative cases of the original histology image, segmented image, and the simulated signal for fascicle and myocyte structures are shown in Figures 1 and 2 respectively. Figures 1 and 2 are from the same high-resolution histology image at different levels of magnification.7 Within each fascicle the domain is assumed to be homogeneous and isotropic to avoid effects of myocyte structure on the signal. Table 1 shows the computed DTI metrics of the simulations and DTI measurements from a previous dataset of the vastus medialis as a reference of typically measured values.[12]

Discussion and Conclusion

It has been hypothesized that skeletal muscle's transverse anisotropy is due to structural similarity to myocardium[1] or due to ellipticity of the muscle fibers,[3] but such structures have not been observed in histology. Combining these hypotheses, fascicle ellipticity partially explain the observed transverse anisotropy. Though the fascicle is much larger than the diffusion distance, its elongated organization leads to a perimysium pathway along which diffusion is unrestricted. This pathway has a large enough volume fraction of the domain to materially influence the signal. Under this interpretation, the larger λ_2 is reflective of this perimysium pathway. The origin of this fascicle ellipticity is unknown and needs to be carefully investigated to ensure it is not an artifact of histology preparation, though differences in the ellipticity of fascicles and myocytes have also been examined in determining effective mechancial properties.[13] The secondary eigenvectors' directions are macroscopically organized and can be tracked,[14] and examination of this transverse anisotropy could be a new avenue of using dMRI to understand muscle organization beyond tractography. Additionally, these results challenge the common assumption of modeling skeletal muscle as a system of packed myocytes with no regard for larger structural features. Explaining this transverse anisotropy may require sophisticated multiscale models of diffusion in muscle which incorporate both myocyte and fascicle level structural information.

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Figures

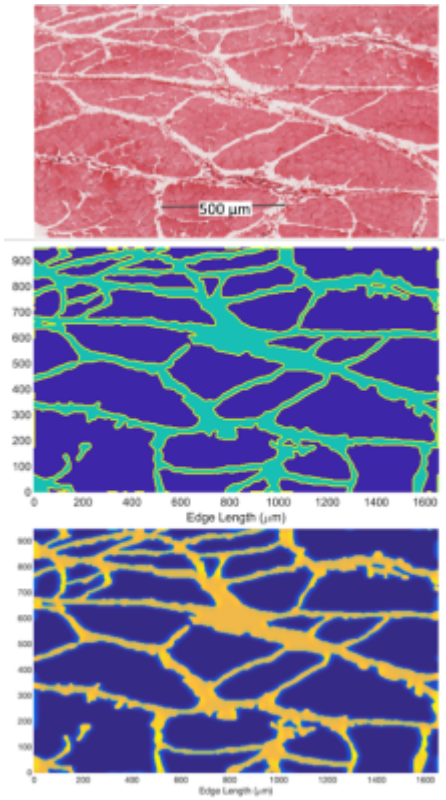

Figure 1: Histology, segmented domain, and map of signal distribution in arbitrary units for one of the fascicle geometries taken from the image in reference 7. Ellipticity of the fascicles is clearly evident, with the major axis oriented in the longitudinal direction.

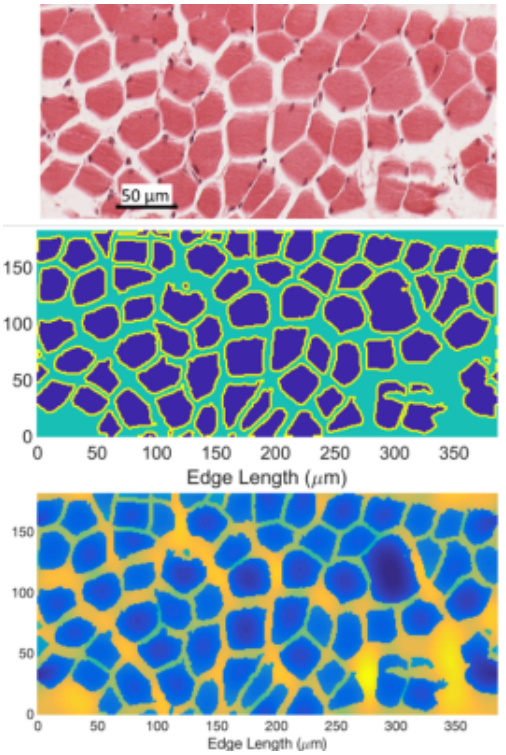

Figure 2: Histology, segmented domain, and map of signal distribution in arbitrary units for one of the myocyte geometries taken from the image in reference 7. Myocytes do not exhibit ellipticity nor any overall organizational structure which would give rise to transverse anisotropy.

	FA	ADC	λ	λ	λ	Transverse Anisotropy	
Fascicle Length Scale	0.158	1.473	1.717	1.454	1.247	14.2%	5
	0.115	1.498	1.674	1.492	1.328	11.0%	6
	0.149	1.502	1.708	1.536	1.261	17.9%	7*
Average	**0.141**	**1.491**	**1.699**	**1.494**	**1.279**	**14.4%**	
Muscle Length Scale	0.323	1.182	1.635	1.012	0.899	11.1%	8
	0.398	1.119	1.661	0.872	0.822	5.7%	9
	0.330	1.259	1.756	1.039	0.981	5.6%	7+
	0.421	1.078	1.634	0.833	0.766	8.1%	10
Average	**0.368**	**1.159**	**1.671**	**0.939**	**0.867**	**7.6%**	
Clinical Data Set	0.20 ± 0.03	1.63 ± 0.07	1.96 ± 0.08	1.57 ± 0.08	1.36 ± 0.08	13.0%	

Table 1: DTI metrics from the seven numerical simulations. Figure 1 results are denoted by * and Figure 2 results are denoted by $^{+}$. Transverse anisotropy is defined as $1-\lambda_3/\lambda_2$. While there is anisotropy in the simulations at the myocyte length scale, there is greater anisotropy at the fascicle length scale, which also matches the observed anisotropy in the clinical data. FA of the clinical data is between the two groups, likely because it is a combination of effects at both spatial scales. Diffusion coefficients in the clinical data are higher, suggesting that larger intrinsic diffusion coefficients are necessary.