Comparison of dMRI Models for Skeletal Muscle Microstructure Estimation with Numerical Simulations and Porcine Phantom

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Synopsis

Four models used to estimate skeletal muscle microstructure from dMRI signal are applied to a ex-vivo porcine phantom and provide physiologically reasonable parameter estimates. These models are then compared to numerical simulations of dMRI over a simplified repeating elemental volume. When the estimated parameters are compared to the true underlying parameters of the numerical model, the estimated parameters are found to be substantially inaccurate, motivating the need for more sophisticated models of dMRI in muscle.

Introduction

Estimating skeletal muscle microstructure from diffusion-weighted MRI (dMRI) requires models which accurately quantify the relationship. While numerically solving the governing equation of dMRI (the Bloch-Torrey equation) is possible, simplifying assumptions are commonly made to express the signal as an analytical function. A common assumption is treating the domain as separate homogenous compartments. Such models have been applied to muscle.[1-8] Attractive features of these models are their ability to analytically express the relationship between microstructure and dMRI signal while being physically motivated, thus allowing insight into underlying biophysical processes. However, such models require various assumptions about the underlying microstructure which may invalidate its ability to accurately relate changes in dMRI signal to the correct microstructural parameter. In this abstract we compare four analytical models of skeletal muscle dMRI with a direct numerical solution of the Bloch-Torrey equation to investigate each model's ability to accurately model microstructural changes.

Methods

Four different models which have been used in the literature to extract microstructural parameters were created: (1) a two-compartment model with exchange (also known as a Kärger model),[1,2] (2) a two-compartment model without exchange,[3-5] (3) a one-compartment model,[6] and (4) the Random Permeable Barrier Model (RPBM),[7,8] each of which have different assumptions and free parameters (Table 2). Using a numerical model based on a Lattice Boltzmann Method solution of the Bloch-Torrey equation,[9] dMRI signals were computed on the San Diego Supercomputing Center's Comet cluster[10] over a domain of periodically packed hexagonal cells surrounded by a permeable membrane and embedded in an extracellular matrix (Figure 1). The domain was parameterized by intra- and extracellular diffusion, cell diameter, membrane permeability, and volume fraction. Simulations were performed with a single microstructural parameter varied and all other parameters held constant (Table 1). PGSE sequences were simulated for 5 b-values (500, 750, 1000, 1500, and 2000 s/mm^2). At each b-value 5 diffusion times (Δ) were simulated (10, 25, 50, 75 and, 100 ms) with a gradient timing of 7.5 ms and the gradient strength adjusted to maintain a constant b-value. Six gradient directions were used to estimate a diffusion tensor from which fractional anisotropy, apparent diffusion coefficient, and the tensor's eigenvalues were extracted and used as inputs for the models. The Kärger, 2-compartment and 1-compartment models were fit to the numerical simulations using MATLAB's finsearch function while the RPBM was fit using nonlinear least squares. As a stand-in for skeletal muscle, experimental diffusion data was acquired from an ex-vivo porcine myocardium phantom imaged with a Siemens 3T TRIO scanner using a monopolar diffusion-weighted sequence with b-values of 800, 1500 and 2500 s/mm2, TR/TE/Δ/δ = 2930/94/44.35/22.93 ms, 2x2x2 mm resolution and 64 gradient directions.

Results and Discussion

In Figure 2 the models are fit to the phantom data. The models estimate physiologically reasonable microstructural parameters in similar ranges to each other. Figure 3 shows the fit of the models to the numerical data. While the models generally identify the parameter being varied, but also consistently estimate that parameters which were being held constant are instead widely varying. This means that without prior knowledge of which microstructural parameter is changing, it cannot be directly inferred from the model's results. Diffusion coefficients and cell diameters were the most consistently estimated, however, permeability and volume fraction were often misestimated by 50-100%. These results make two points about the applicability of the examined models. First, though they can estimate reasonable parameters from experimental data, predictions may not be reflective of the underlying microstructure. Second, more complicated models generally do not increase accuracy over simpler models, rather, they add additional free parameters allowing more spurious fits and sensitivity to initial guesses. These two points suggest that researchers should be careful of overinterpreting microstructural parameters estimated from such models, particularly extracellular parameters and demonstrates the need for a muscle-specific microstructural model of dMRI. Finally, the b-values and diffusion times used are taken as 'typical' values used in clinical studies, however, RPBM has been applied at longer diffusion times[8] which may increase the accuracy of all models, particularly in estimating diameter.

Conclusion

We utilized four microstructural models found in literature to estimate microstructural parameters from ex-vivo porcine myocardium. We showed that these models do not accurately predict the underlying microstructure when compared with numerically simulated data, sometimes being off by over 100%, suggesting that though reasonable values are predicted when applied to experimental data, predictions from such models should be interpreted with caution. This work motivates further development of more advanced models, particularly in determining extracellular structure which is of interest in understanding mechanical force transmission of the muscle.

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Figures

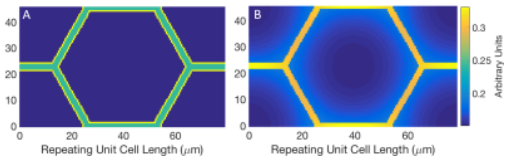

Figure 1: A) Typical geometry of periodic unit cell used for simulations and B) signal map for b=750 s/mm^2, = 50 ms and microstructural parameters all at their constant value (c.f. Table 1).

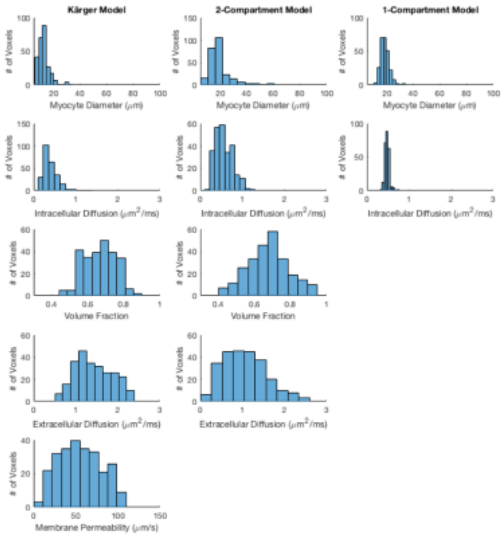

Figure 2: Comparison of compartmental models with phantom data for the combination of four different ROI's of 4x4x4 voxels taken from two different porcine hearts (2 ROIs each). The Kärger, 2-compartment, and 1-compartment were fit to the acquired DTI data, RPBM was not fit as it requires multiple diffusion times which was not acquired. Estimated microstructure values are in agreement between models, though the 1-compartment model has a smaller distribution for its parameters while the extra parameters of the Karger and 2-compartment models tend to be widely distributed indicating poor fitting.

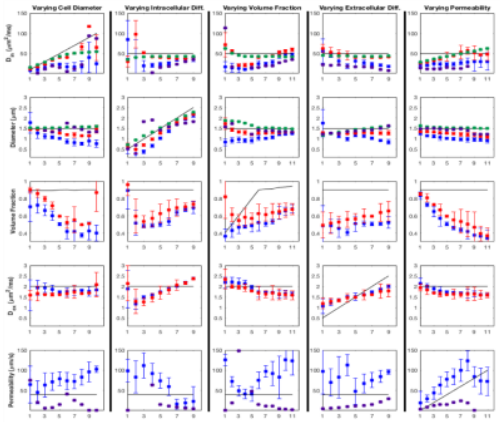

Figure 3: Comparison of analytical models with numerical simulations. Each column corresponds to the varying of a single microstructural parameter while all other parameters are held constant. Rows relate to the estimated microstructural parameter, not every model has all the displayed free parameters (Table 2). For each case 50 different initial guesses were used, error bars denote the standard deviation of the fitted values for the different guesses illustrating the robustness and stability of the fit for that parameter. Blue is 2CE, Red is 2-compartment, Green is 1-compartment, Purple is RPBM.

Parameter	Constant Value	Range	Units
Intracellular Diffusion (D_{in})	1.5	$0.50 - 2.50$	$\mu m^2/ms$
Intracellular Diffusion (D_{ex})	2.0	$0.50 - 2.50$	$\mu m^2/ms$
Myocyte Diameter	50	$5.0 - 100$	μm
Membrane Permeability	40	$1.0 - 100$	$\mu m/s$
Myocyte Volume Fraction	0.90	$0.40 - 0.95$	

Table 1: Parameter values used for numerical simulations when the parameter was held constant as well as the range over which the parameter was varied.

	Myocyte Diameter	Intracellular Diffusion	Volume Fraction	Extracellular Diffusion	Membrane Permeability
Kärger	X	X	X	X	X
2-Compartment	X	X	X	X	—
1-Compartment	X	X	—	—	—
RPBM	X	X	—	—	X

Table 2: Free parameters for different models