Imaging-Based Structural Models of the Myocardium

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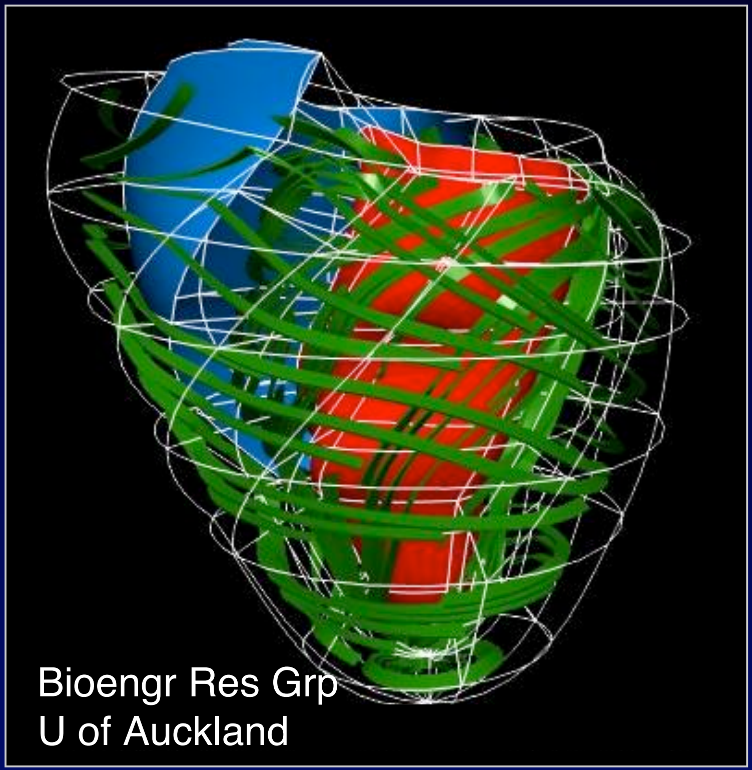
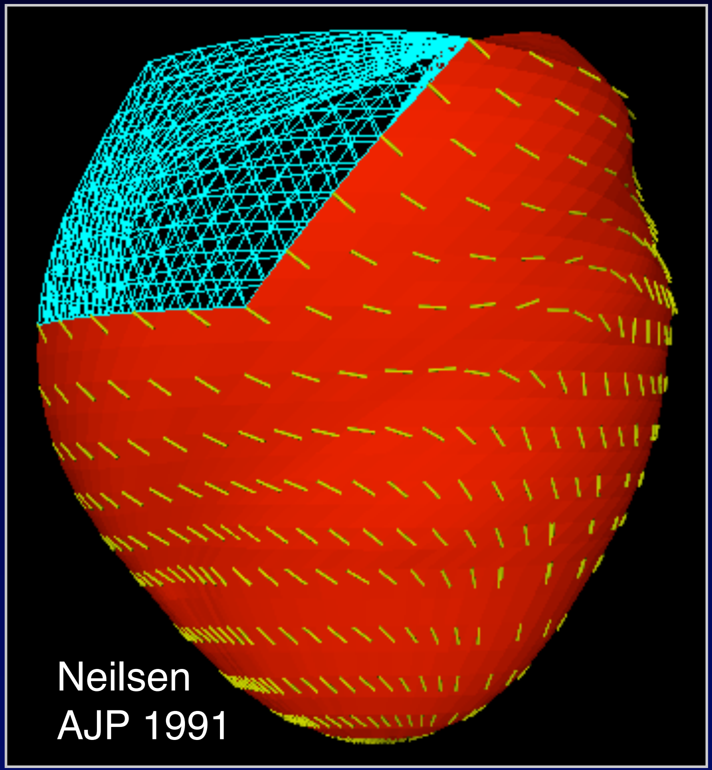
Department of Bioengineering

Small Animal Imaging Facility

Myocardial "Functional Anatomy"



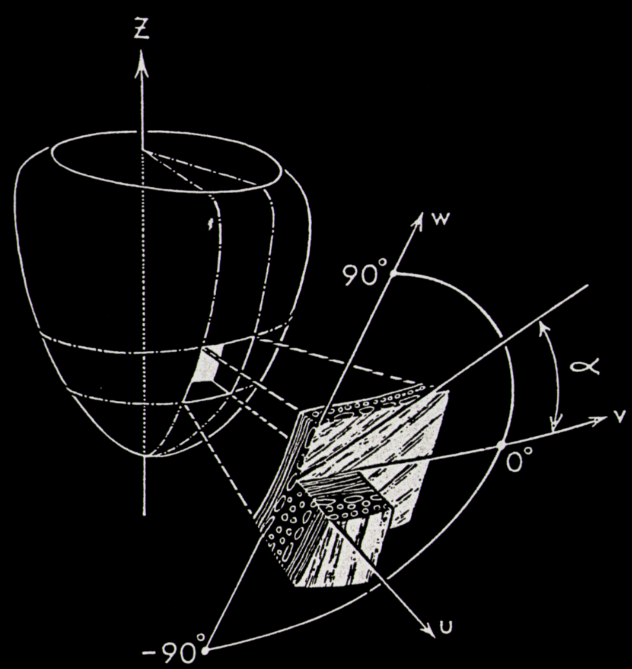


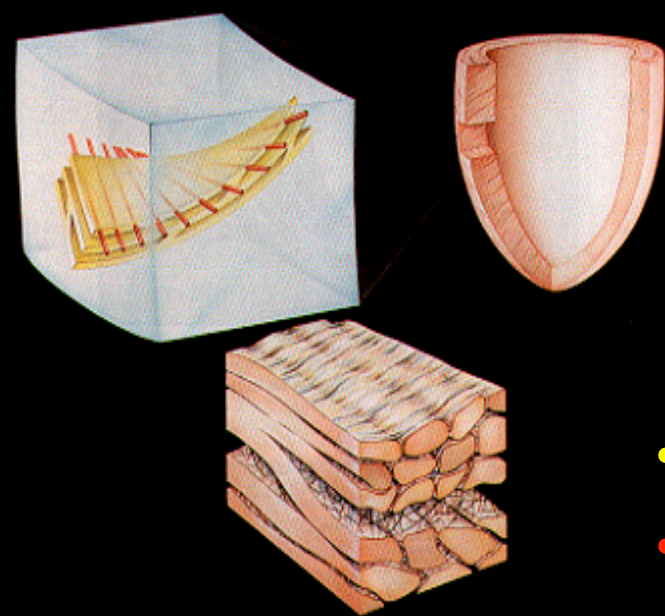
Modeling versus "morphologically accurate" modeling

Tissue Microstructure Histology

Myocardial structures

Fibers
Streeter et al., 1969





Sheets
LeGrice et al. 1995

Histology:

- "gold standard"
- destructive
- labor intensive
- prone to artifacts

Myocardial Structural Models /Atlases

Key Challenges

1. Fiber Orientation Measurement:
   - alternative to histology
   - suitable for the mouse

2. Statistics:
   - inter-species variability
   - intra-species variability
   - atlas?

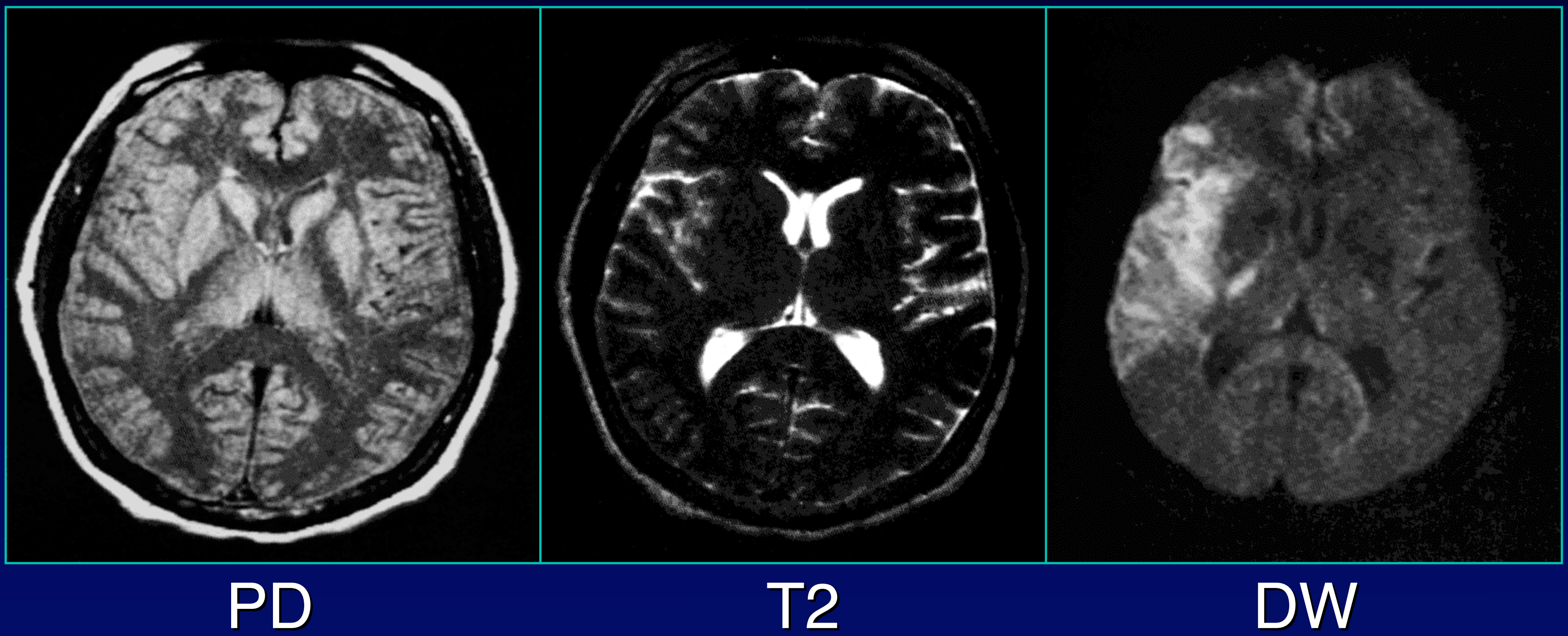
Imaging Based Alternatives

Requirements:

- noninvasive / nondestructive
- in vivo capable
- reasonable resolution
- intrinsic tissue contrast

MR Diffusion Imaging

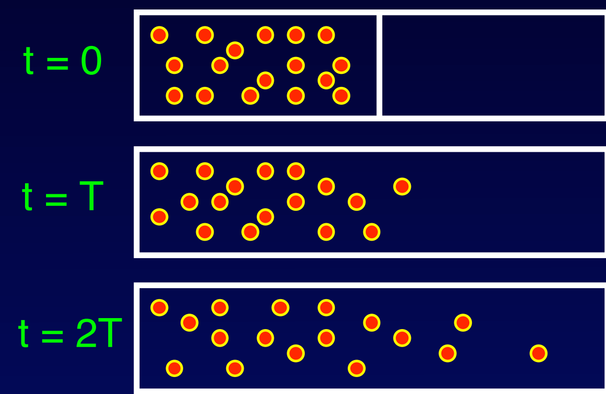
Detection of Early Stroke

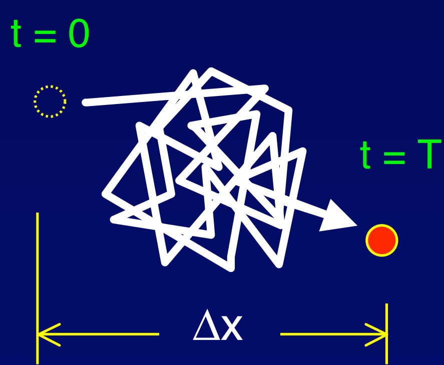


Diffusion is highly sensitive to tissue microstructure!

Diffusion in MRI

Conventional transport:

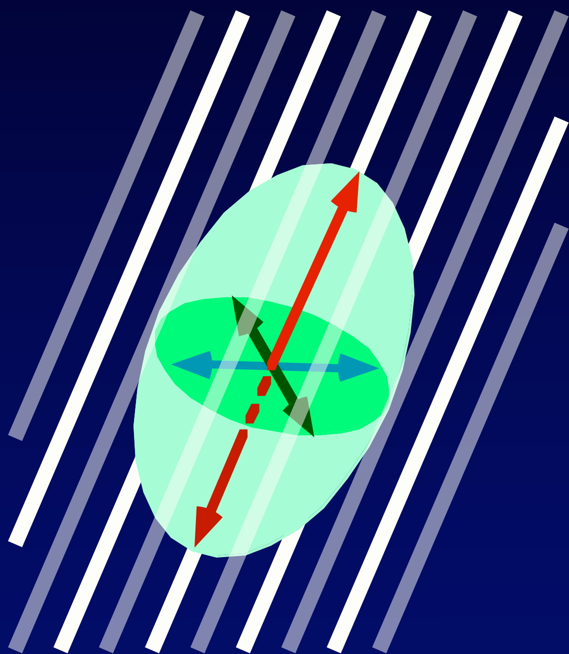




MRI:

- Random translational motion
- Diffusion in water versus diffusion of water

Diffusion in Anisotropic Tissues



examples:

- brain white matter
- myocardium
- cartilage …

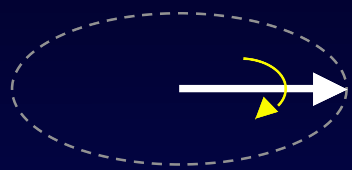
$$\mathbf{D} = \begin{bmatrix} D_{xx} & D_{xy} & D_{xz} \\ D_{xy} & D_{yy} & D_{yz} \\ D_{xz} & D_{yz} & D_{zz} \end{bmatrix}$$

MR diffusion tensor imaging
(MR-DTI)

Overview

- Principles and Methods of DTI
- Engineering Challenges
- Applications of Cardiac DTI
- Myocardial Structural Models and Atlases

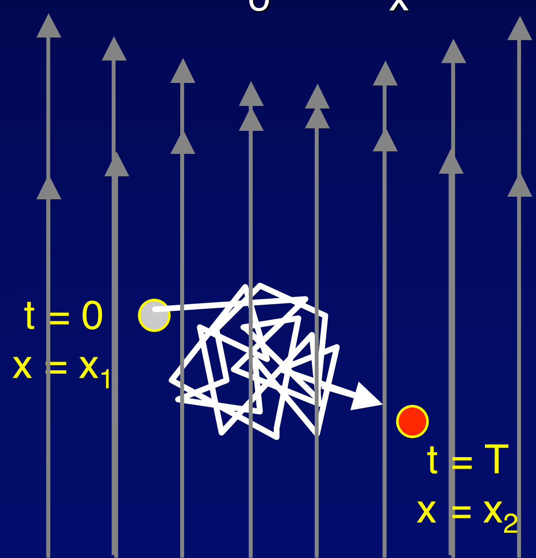
MR Diffusion Encoding

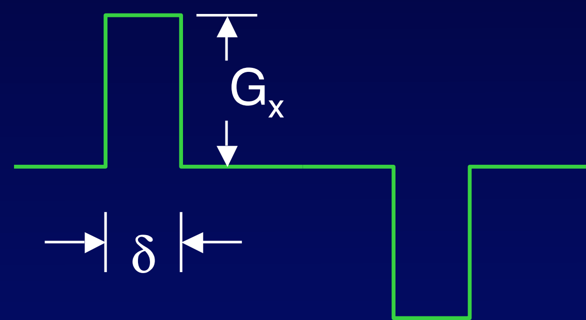


spin precession frequency

$$\omega = \gamma B$$

$$B = B_o + G_x \cdot x$$



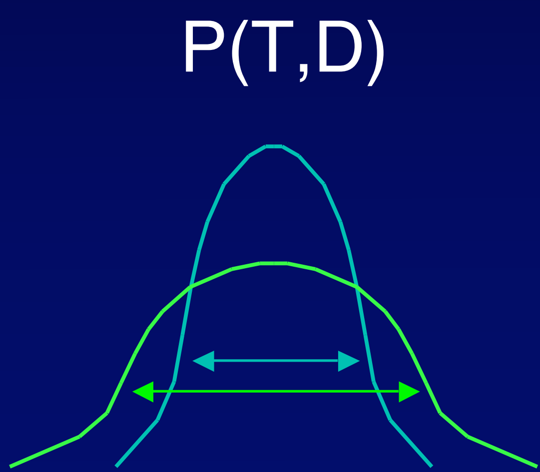


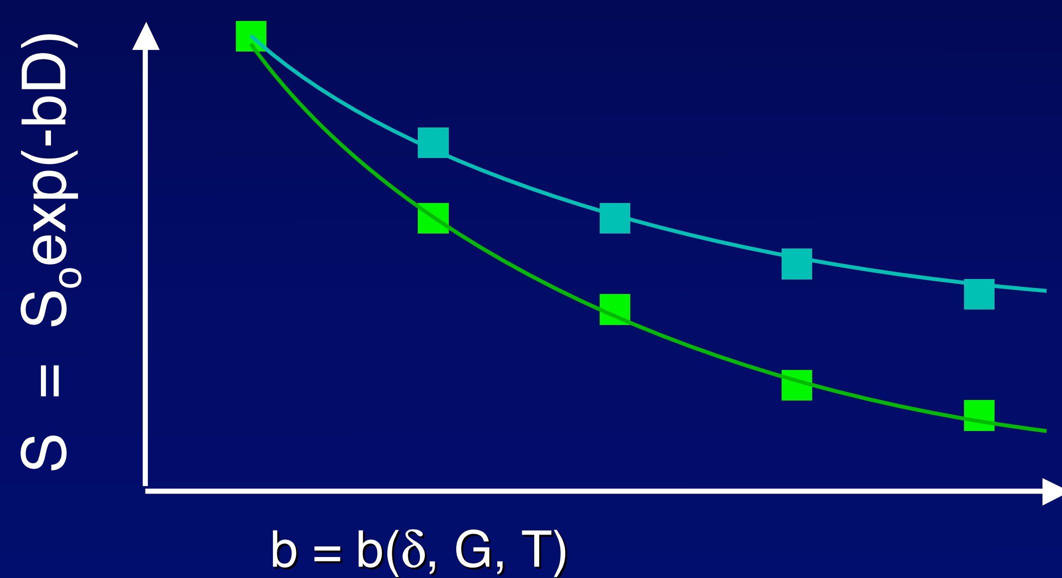
$$\left.\begin{aligned}\phi_1 &= \gamma\, \delta\, G_x\, x_1 \\ \phi_2 &= -\gamma\, \delta\, G_x\, x_2\end{aligned}\right\} \quad \Delta\phi = \gamma\, \delta\, G_x\, \Delta x$$

Diffusion Induced Signal Attenuation

$$S = S_o < \Delta\phi > = S_o \int \Delta\phi \, P(T, D) \, d\phi$$

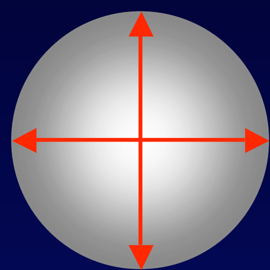
$$S = S_o \exp(-bD), \qquad b = \gamma^2 \int_0^{TE} \left[\int_0^{t} G_x(t')dt' \right]^2 dt$$



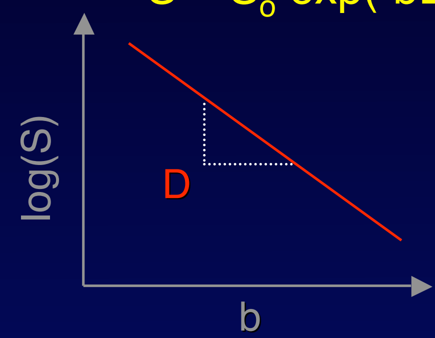


Beyond Isotropic Diffusion

isotropic



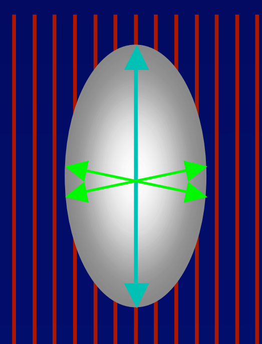
$S = S_o \exp(-bD)$

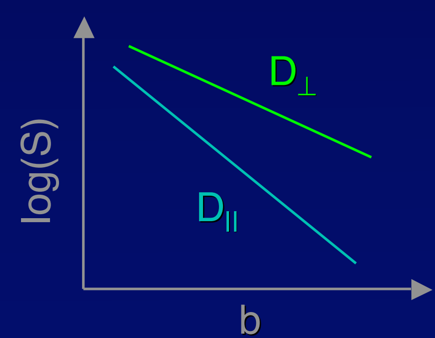


ADC independent of

$$\mathbf{g} = \begin{bmatrix} g_x \\ g_y \\ g_z \end{bmatrix}$$

axisymmetric anisotropy

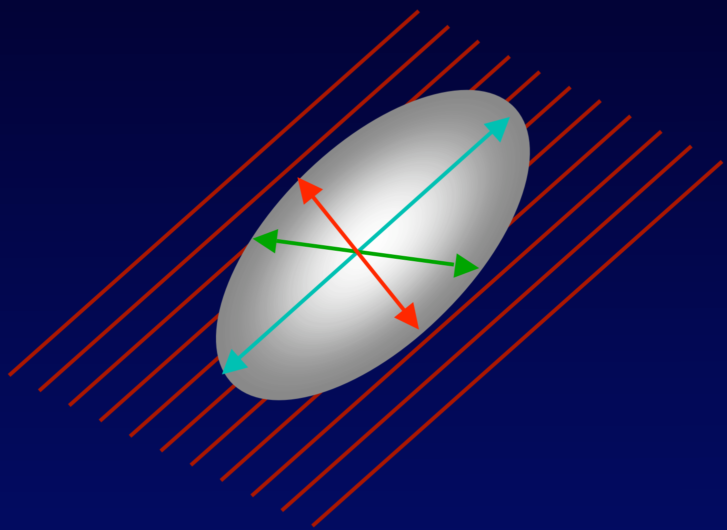




$$ADC = \mathbf{g}^T \bullet \begin{bmatrix} D_\perp & 0 & 0 \\ 0 & D_\perp & 0 \\ 0 & 0 & D_{||} \end{bmatrix} \bullet \mathbf{g}$$

$$S = S_o \exp(-b\mathbf{g}^T \cdot \mathbf{D}_\Lambda \cdot \mathbf{g})$$

Generalized Anisotropic Diffusion



Rotate G into local diffusion axes

$$\mathbf{g'} = \mathbf{R}\,\mathbf{g}$$

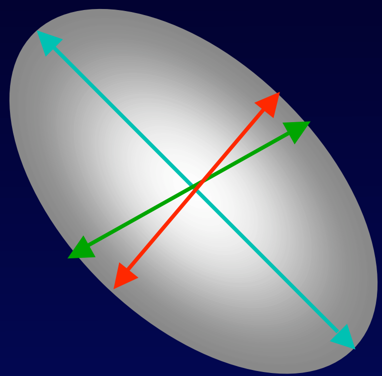
$$\mathrm{ADC} = \mathbf{g}^T \cdot \mathbf{R}^T \mathbf{D}_\Lambda \mathbf{R} \cdot \mathbf{g}$$

$$\mathbf{D} = \mathbf{R}^T \mathbf{D}_\Lambda \mathbf{R} = \begin{bmatrix} D_{xx} & D_{xy} & D_{xz} \\ D_{xy} & D_{yy} & D_{yz} \\ D_{xz} & D_{yz} & D_{zz} \end{bmatrix}$$

DTI strategy:

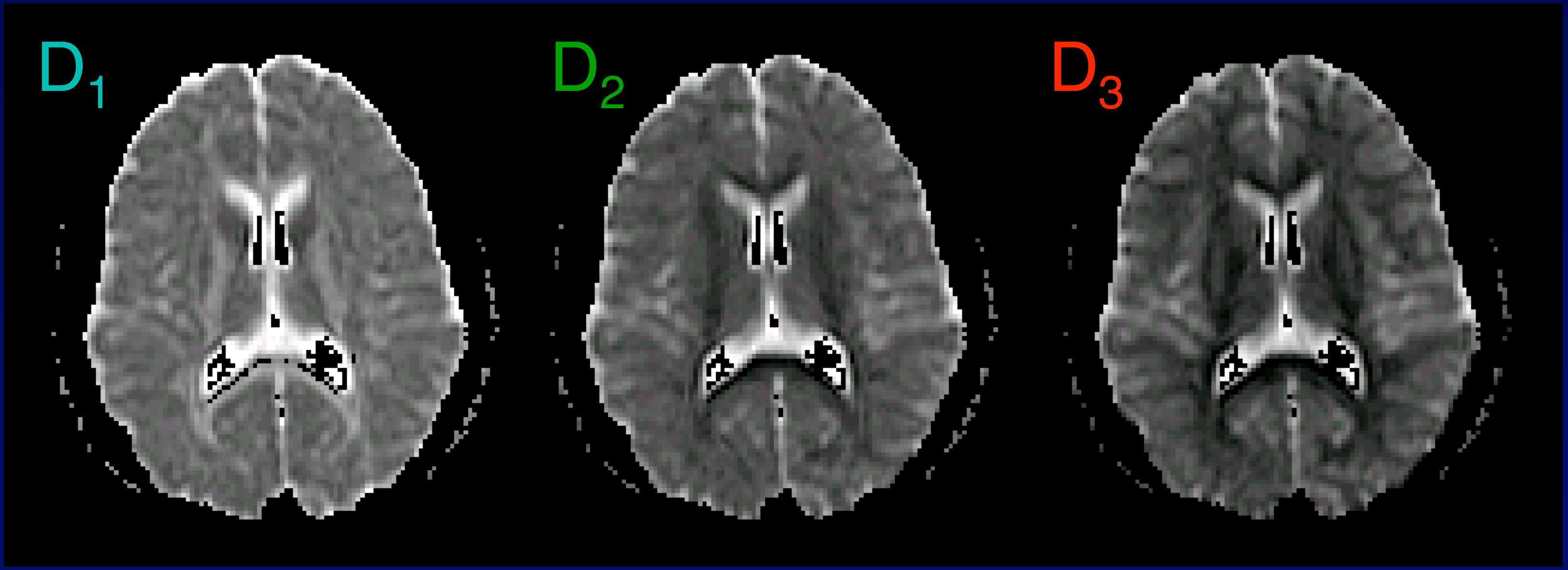
- use **g** to probe **D**
- encode in at least 6 non-colinear directions
- calculate **D**, then diagonalize

Tensor Diagonalization: Eigenvalues



diffusion along principal axes

$D_1 \geq D_2 \geq D_3$

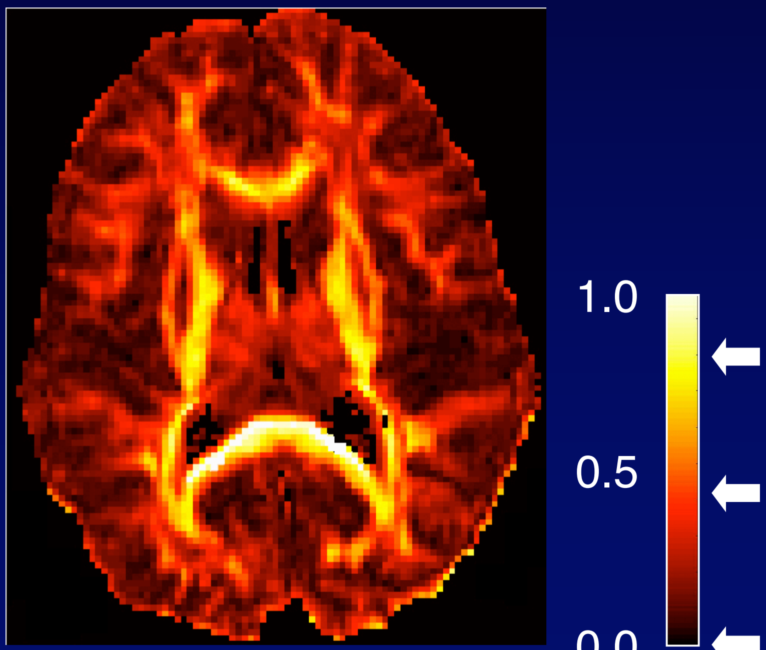


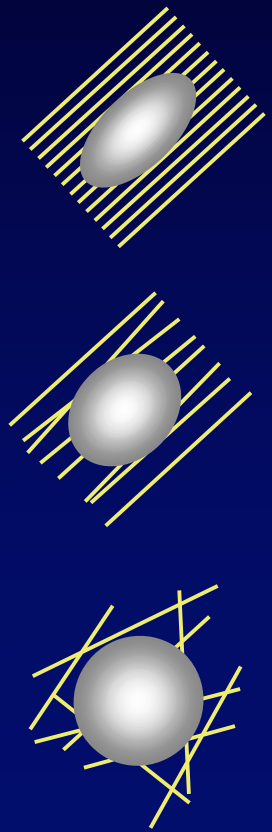
DTI: Scalar Anisotropy Index

Contrast for tissue microstructure

conventional T2

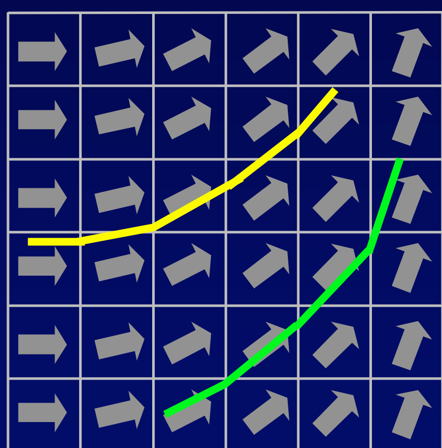
“fractional anisotropy”

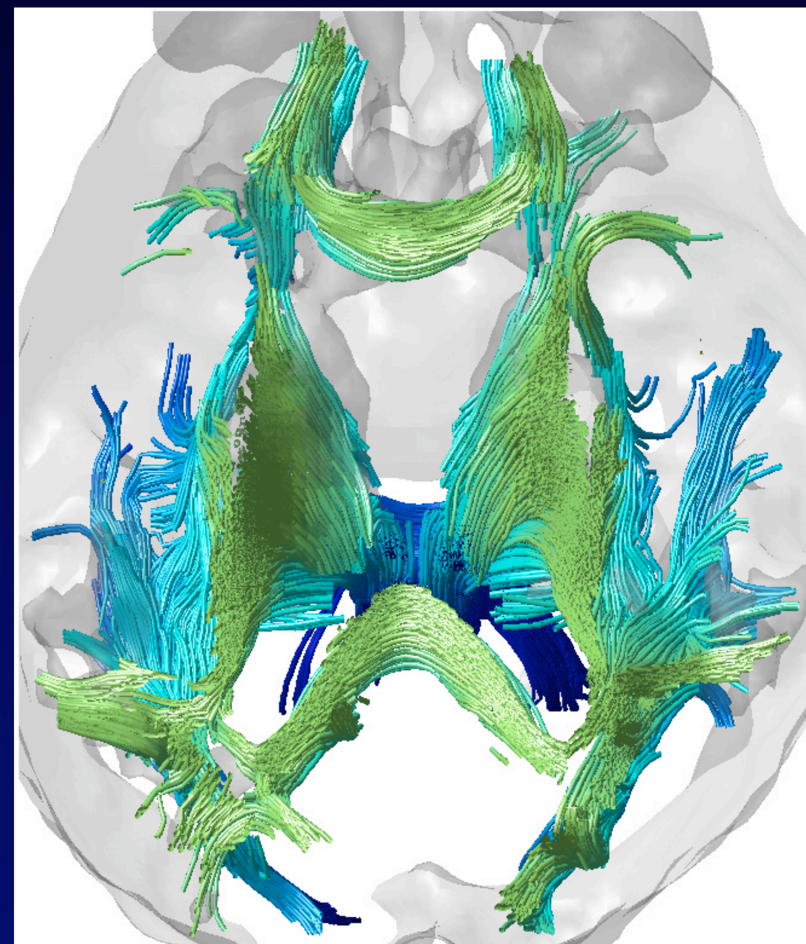




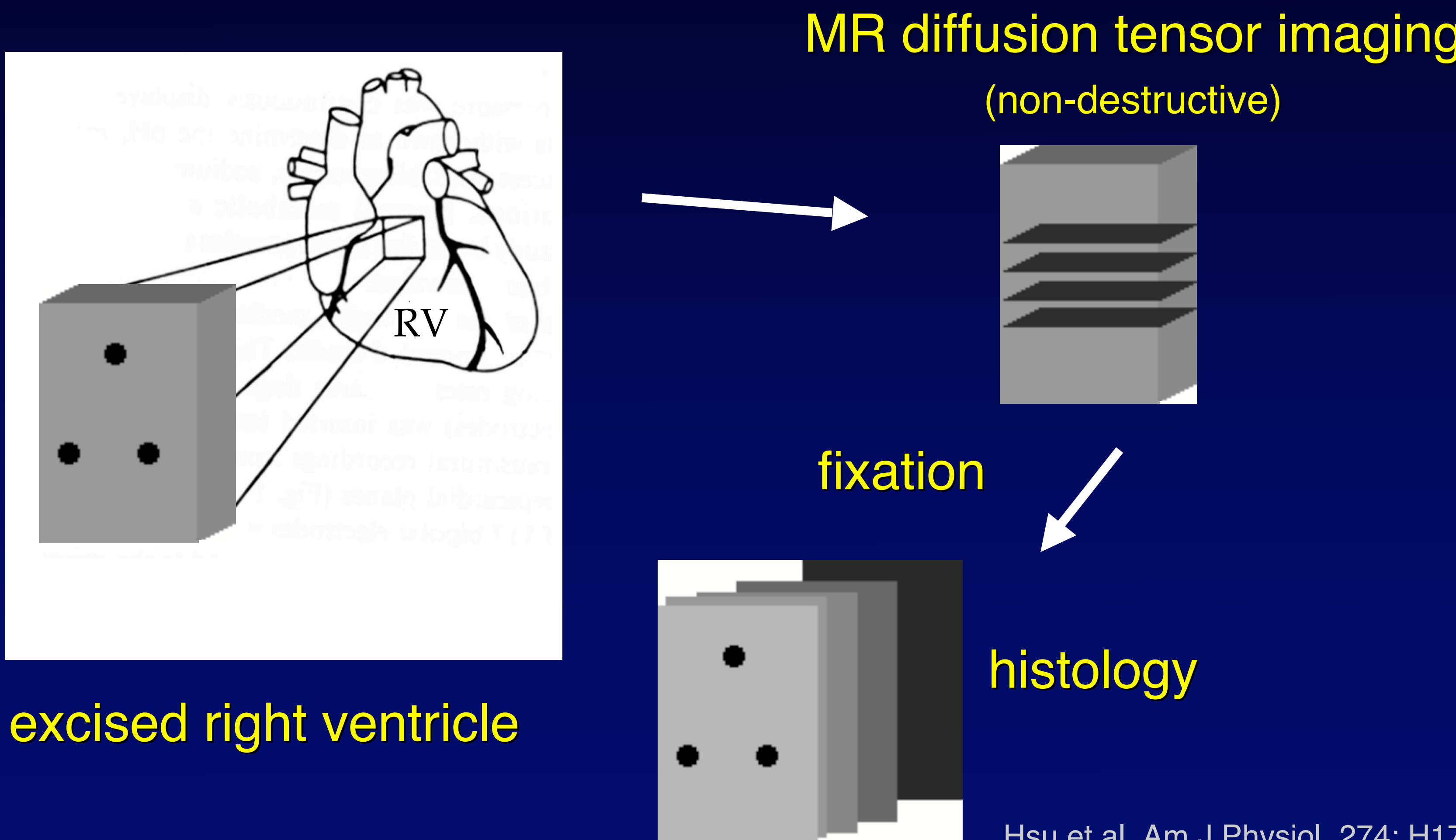
Tensor Diagonalization: Eigenvectors

primary eigenvector:
a proxy for tissue
fiber orientation





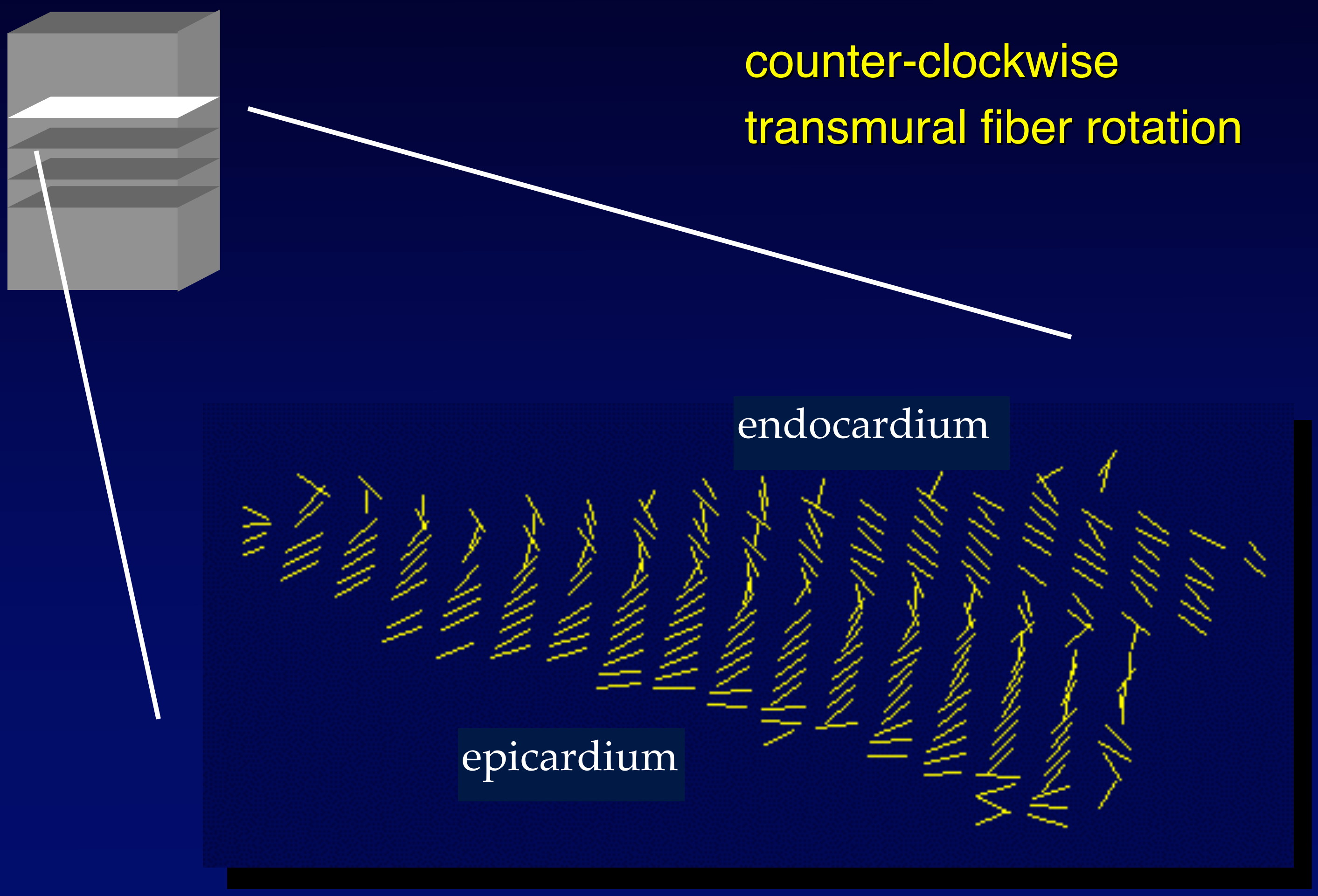
Validation in Cardiac DTI



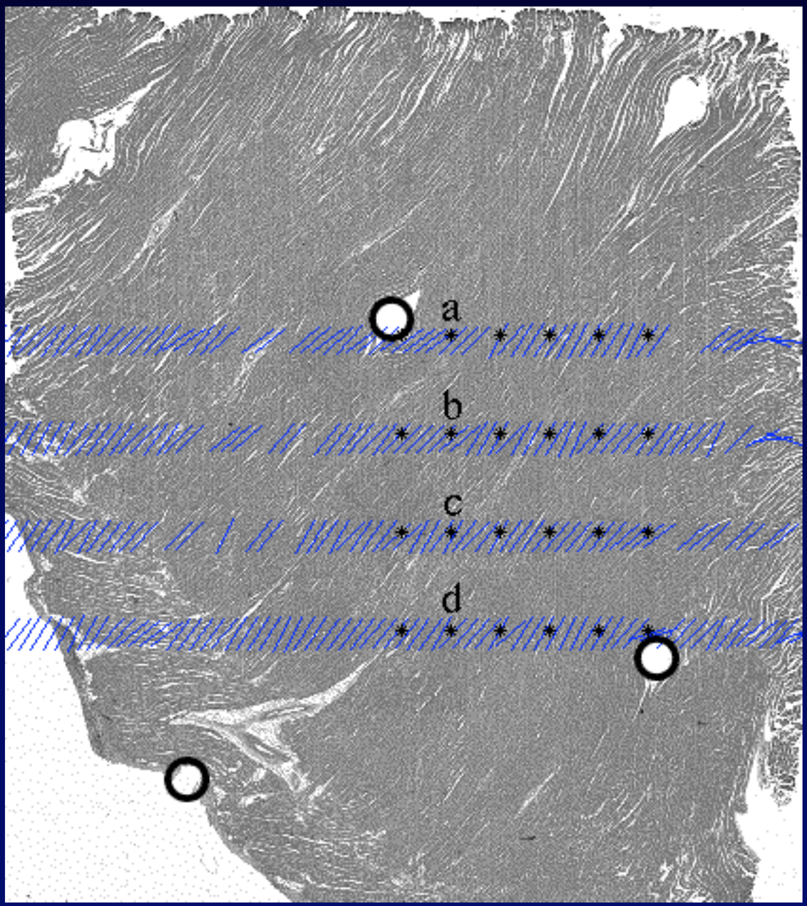
Hsu et al. Am J Physiol. 274: H1727, 1998

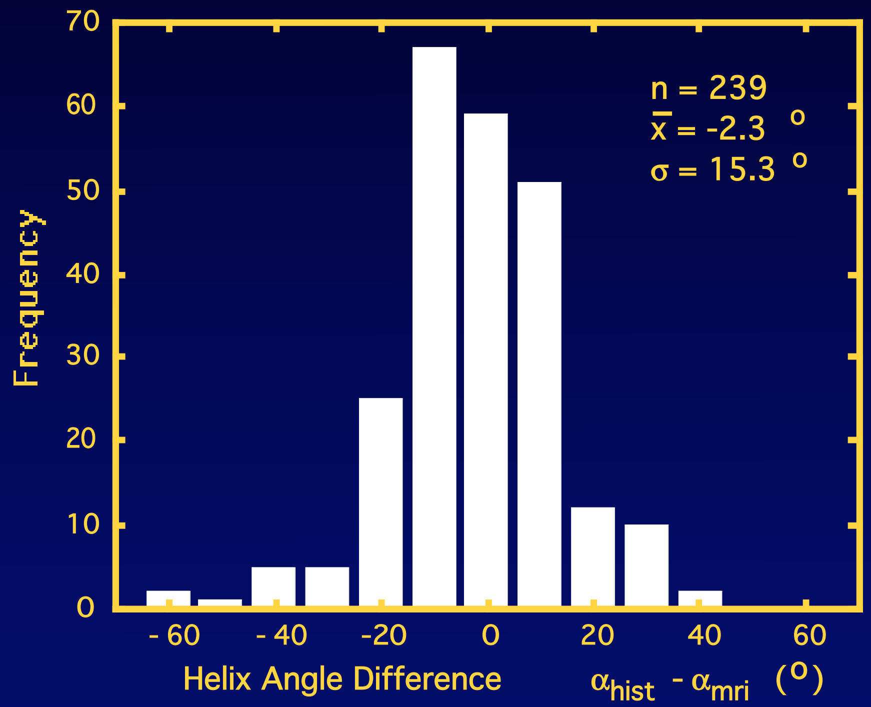
Diffusion Tensor Eigenvector

counter-clockwise
transmural fiber rotation



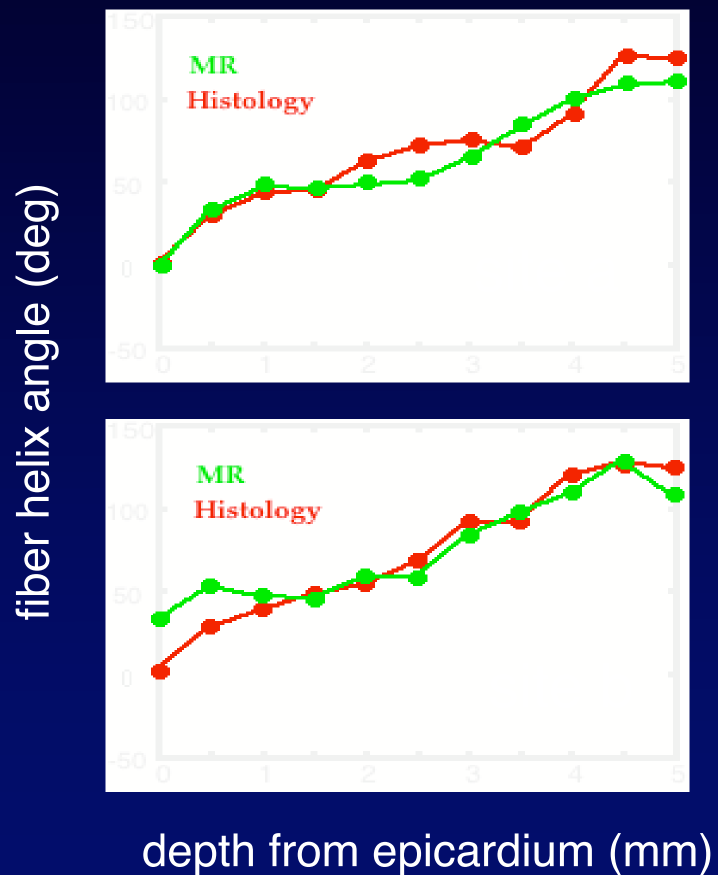
Point-by-Point Comparison

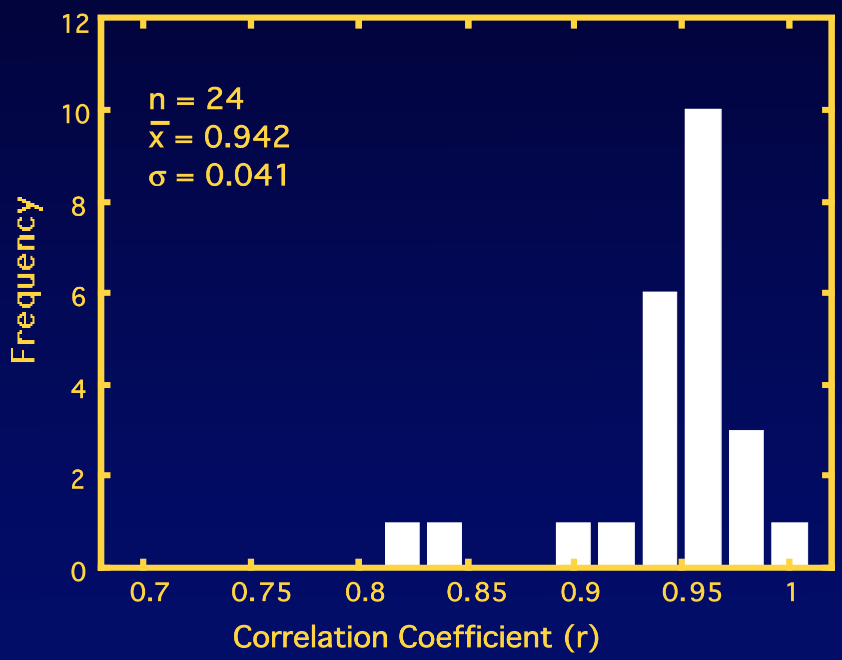




Depth: +2.0 mm

Transmural Fiber Rotation

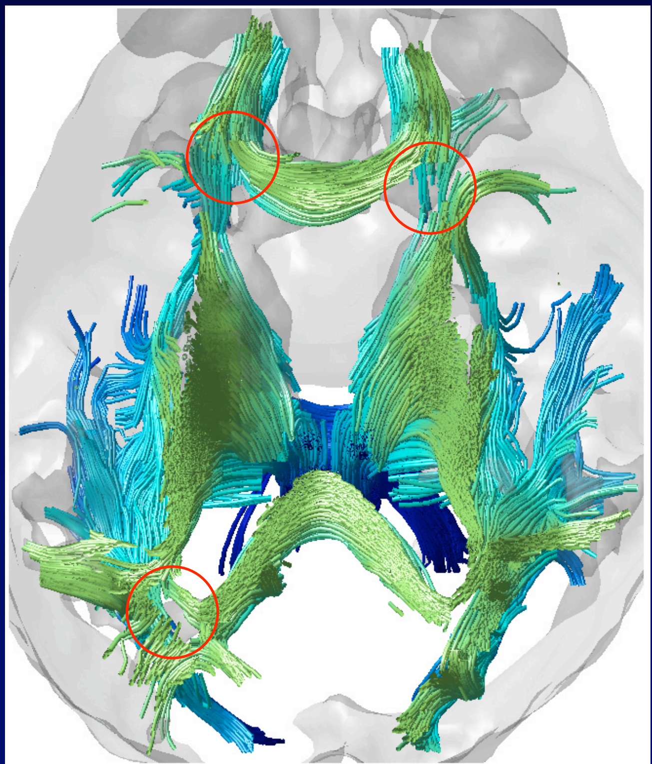




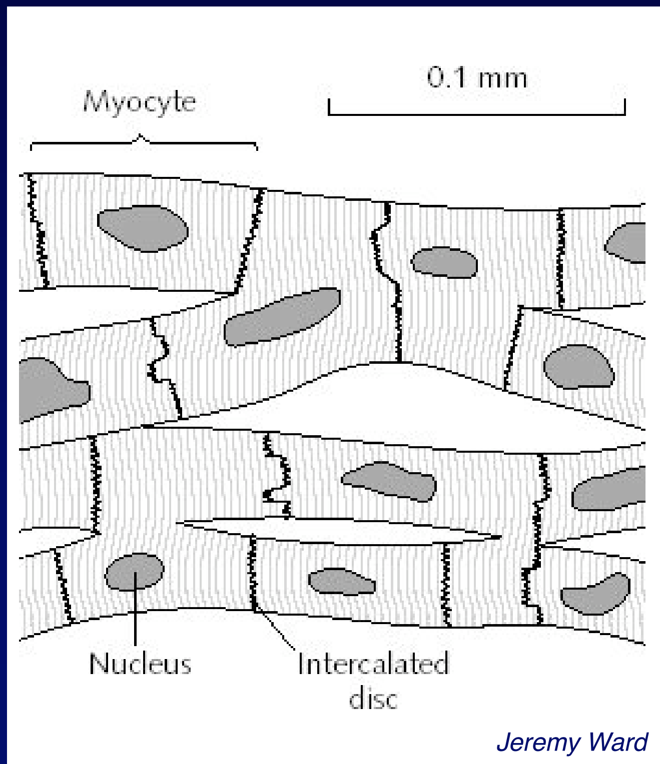
Is DTI Enough?

Assumption: Only One Diffusion Direction

1. Macroscopic merging or crossing fibers

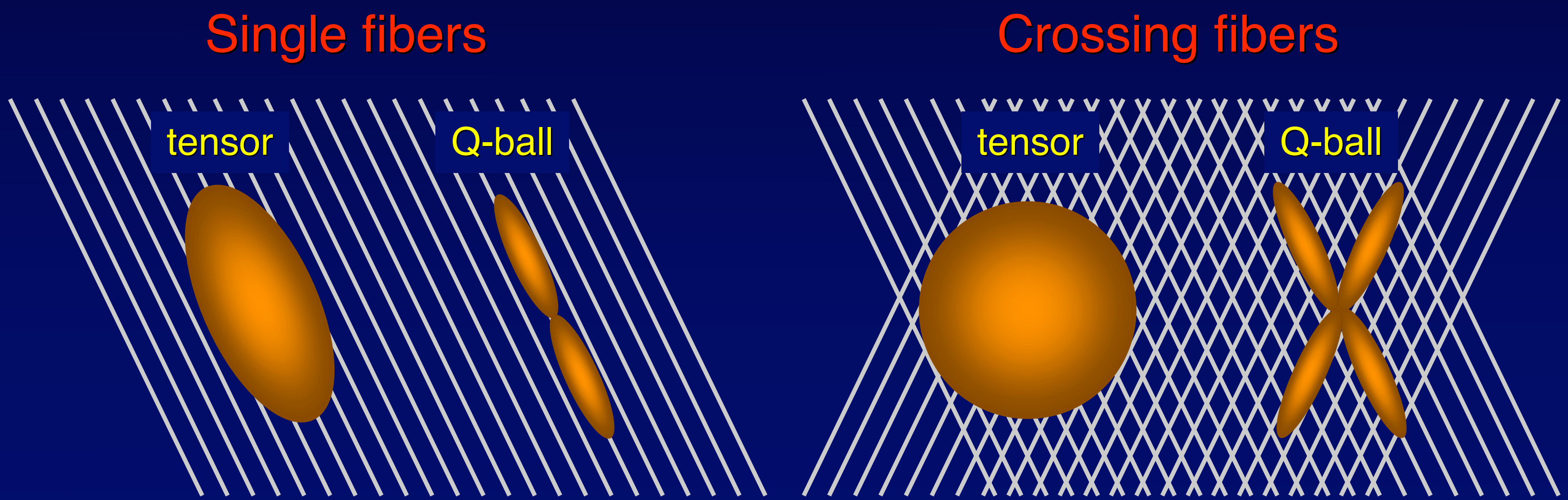


2. Myocyte cellular branching

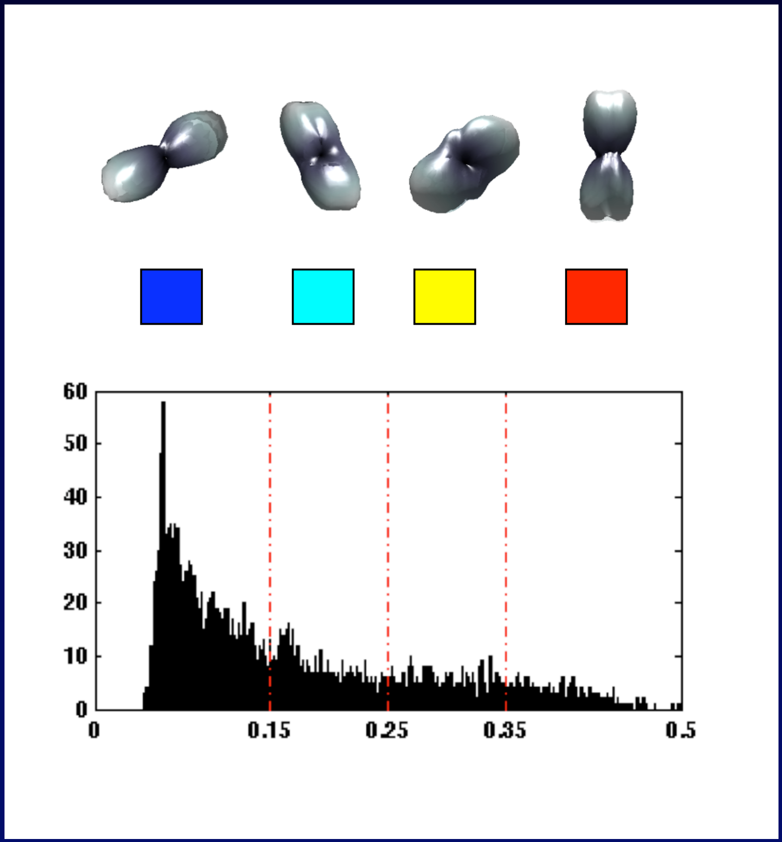


High-Angular Resolution Diffusion Imaging

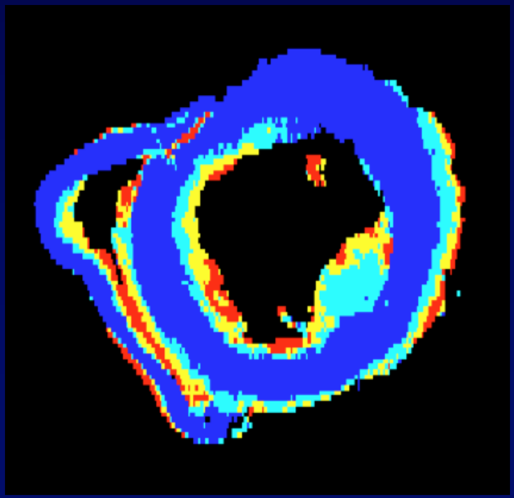
- More diffusion encoding directions:
- Non-tensor-based diffusion fitting:
  "Q-ball", generalized tensors, etc.



Q-ball Imaging of the Myocardium

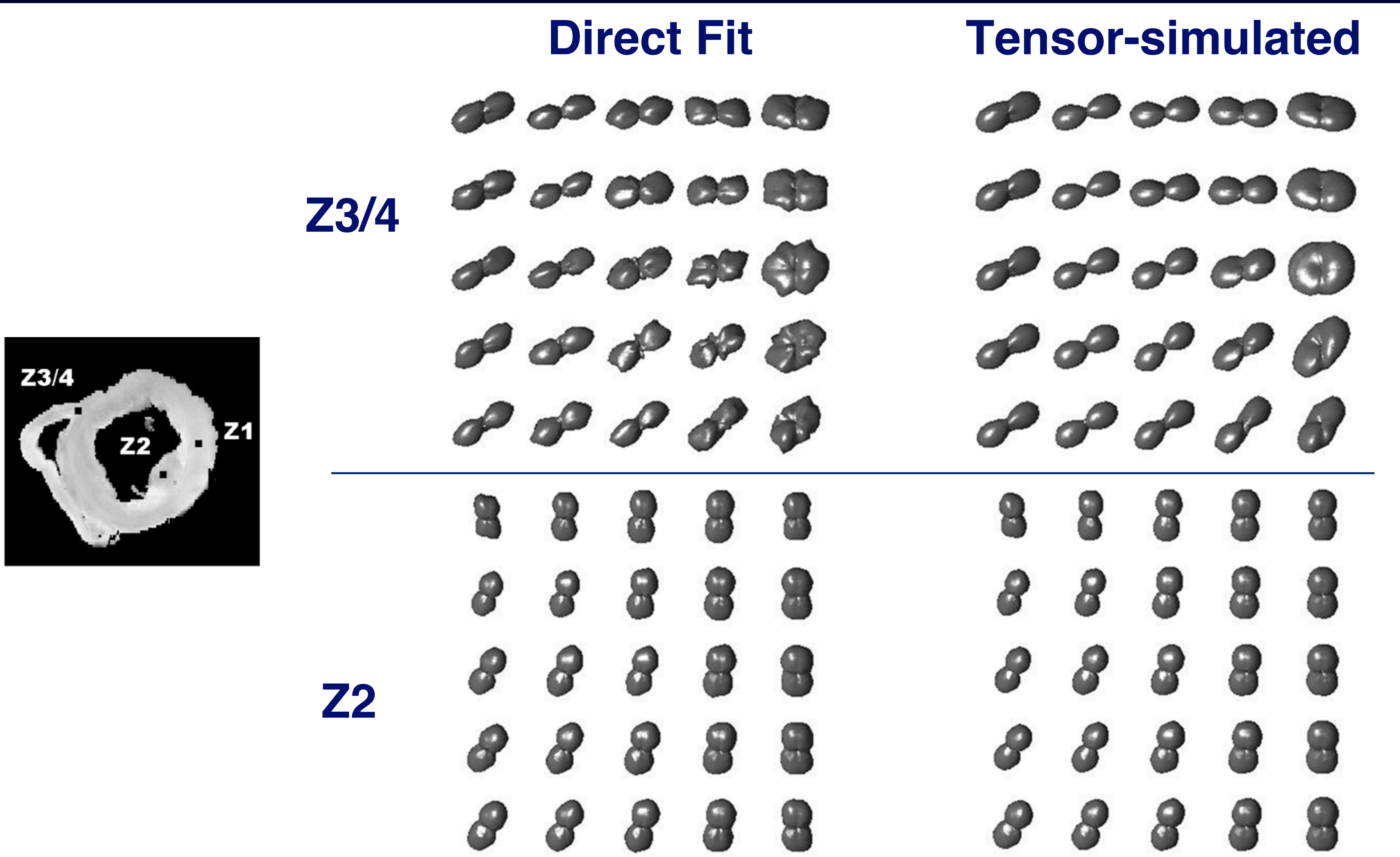


- Fixed canine heart
- Mid ventricular short axis
- 96 directions; b = 2000 s/mm^2



Shi et al. ISMRM 2007

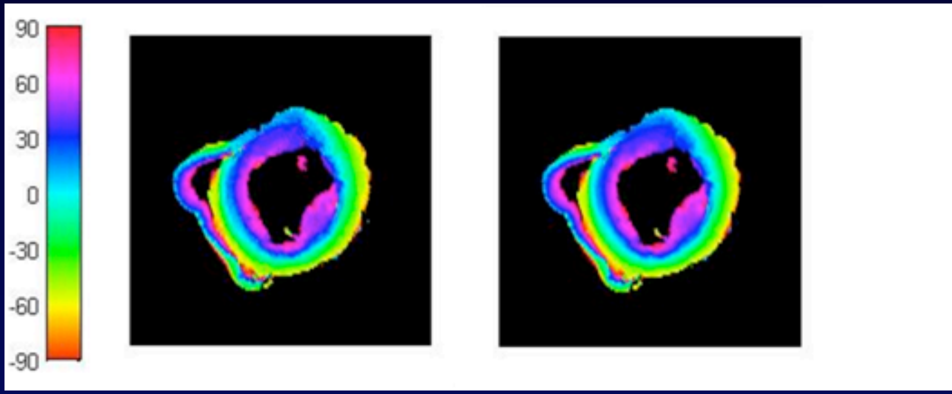
Trouble for DTI?



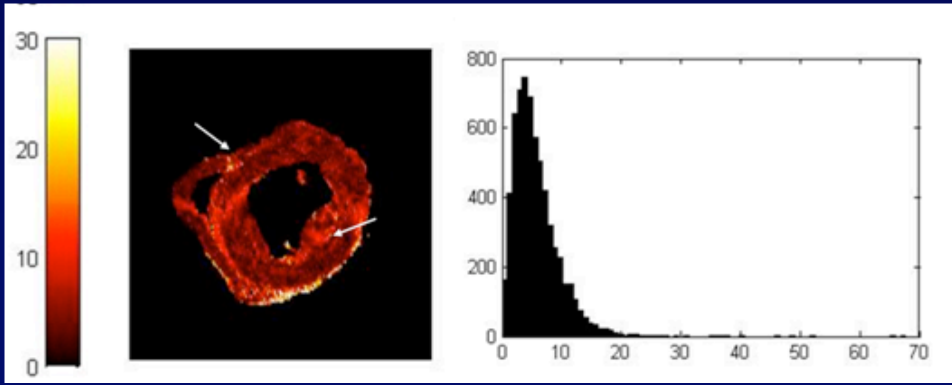
QBI vs DTI

Myocardial Fiber Orientation Mapping

Fiber
Helix Angle



Difference



QBI vs DTI: Implications

1. Small macroscopic differences exist

2. Little impact on fiber orientation mapping

3. Neither can resolve cellular branching

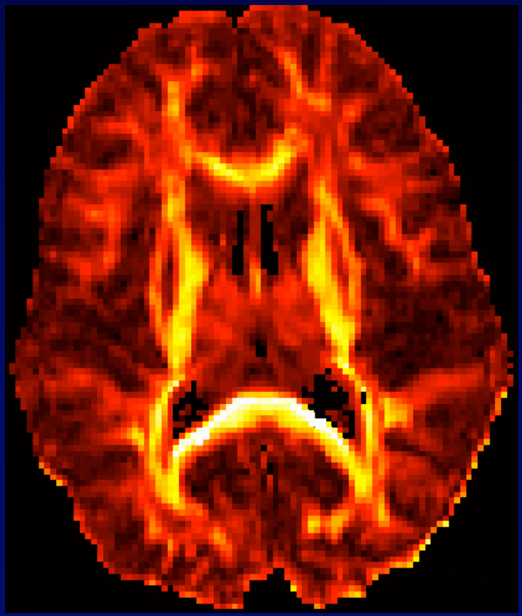
Overview

- Principles and Methods of DTI
- Engineering Challenges
- Applications of Cardiac DTI
- Myocardial Structural Models and Atlases

DTI: Engineering Challenges

- diffusion encoding via signal attenuation
- large dataset size -- minimum 7 images
- low spatial & temporal resolution, low quality

128 x 128
single shot DW-EPI
1.0 - 2.0 mm resolution
2.0 mm or larger slice
3D (multislice) scan in
~ 10 min

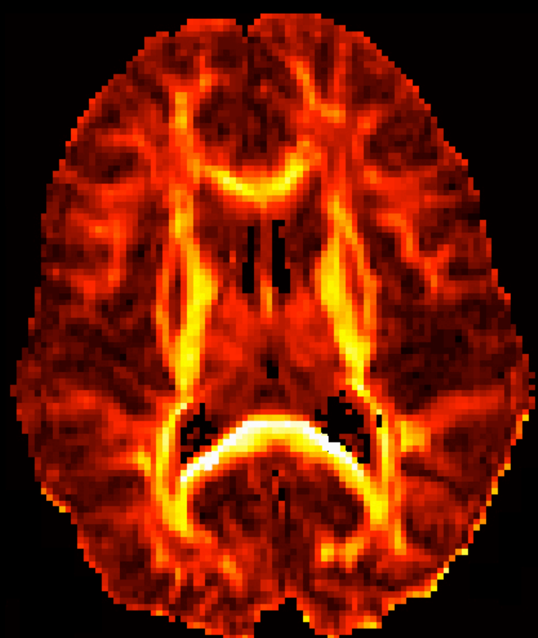


Areas of Development:

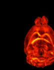
- acquisition efficiency
- distortion correction
- data de-noising

Diffusion Tensor "Microscopy"?

human brain
2.0 mm
10 min



mouse brain/heart
100 μm



$$\text{Scan time} \propto \left(\frac{1}{\text{Voxel}}\right)^2$$

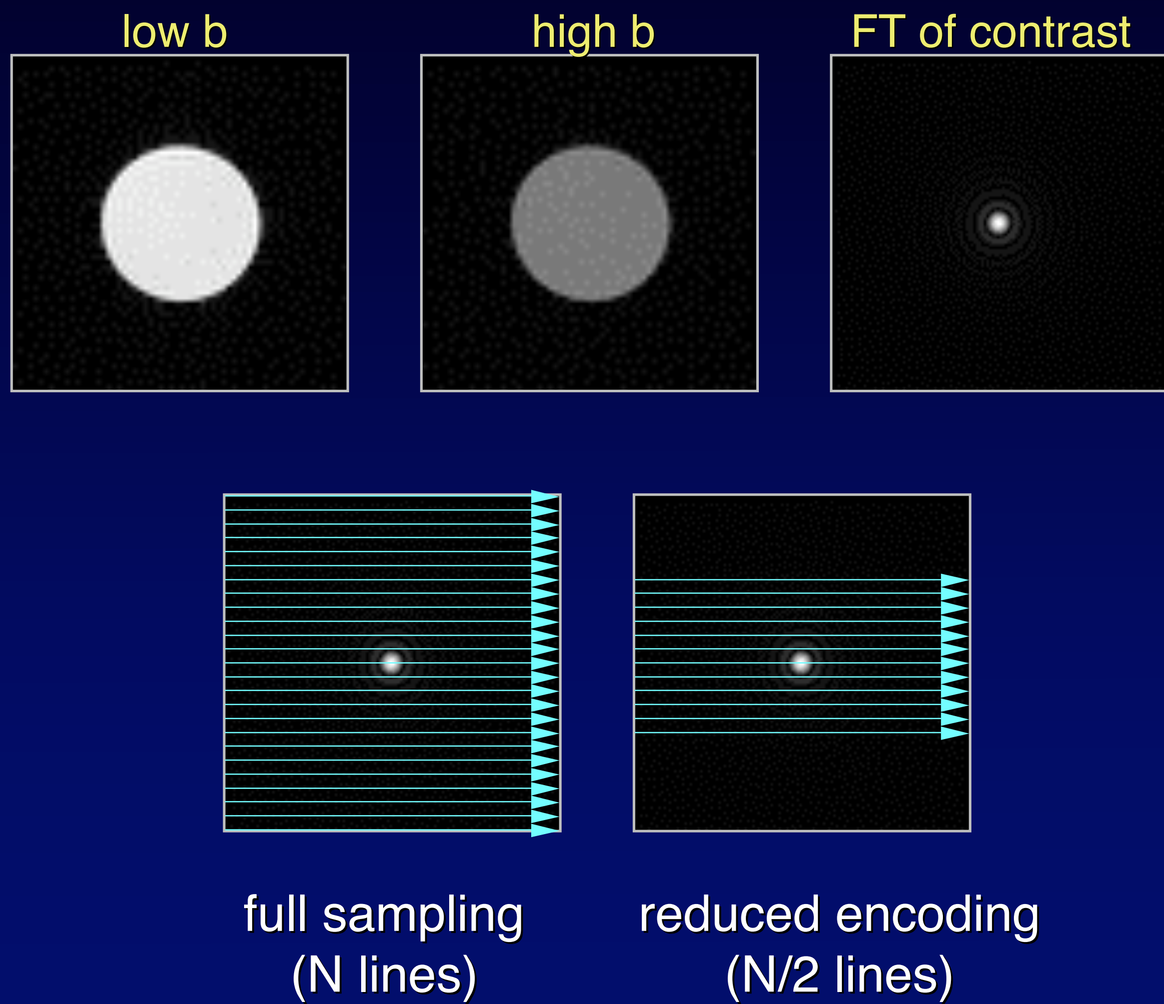
1200 YRS!!

Hardware Solutions for SNR

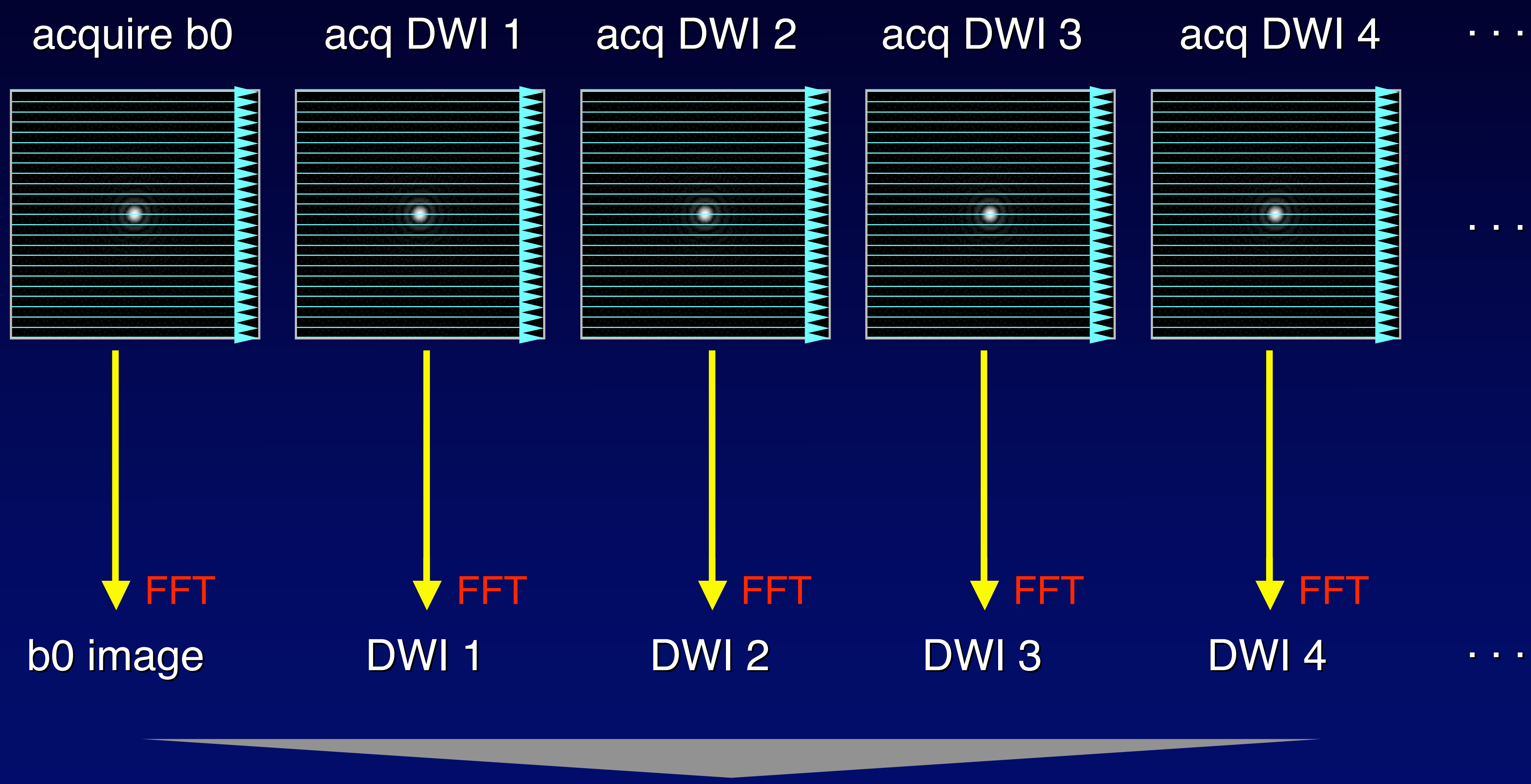
Factor	Change	Real Gain
Stronger magnet	2.3	2
Stronger gradient set	10	3.5
Smaller transceivers	10	10
Longer scans	200	14
Total		1000

Doable, but not practical

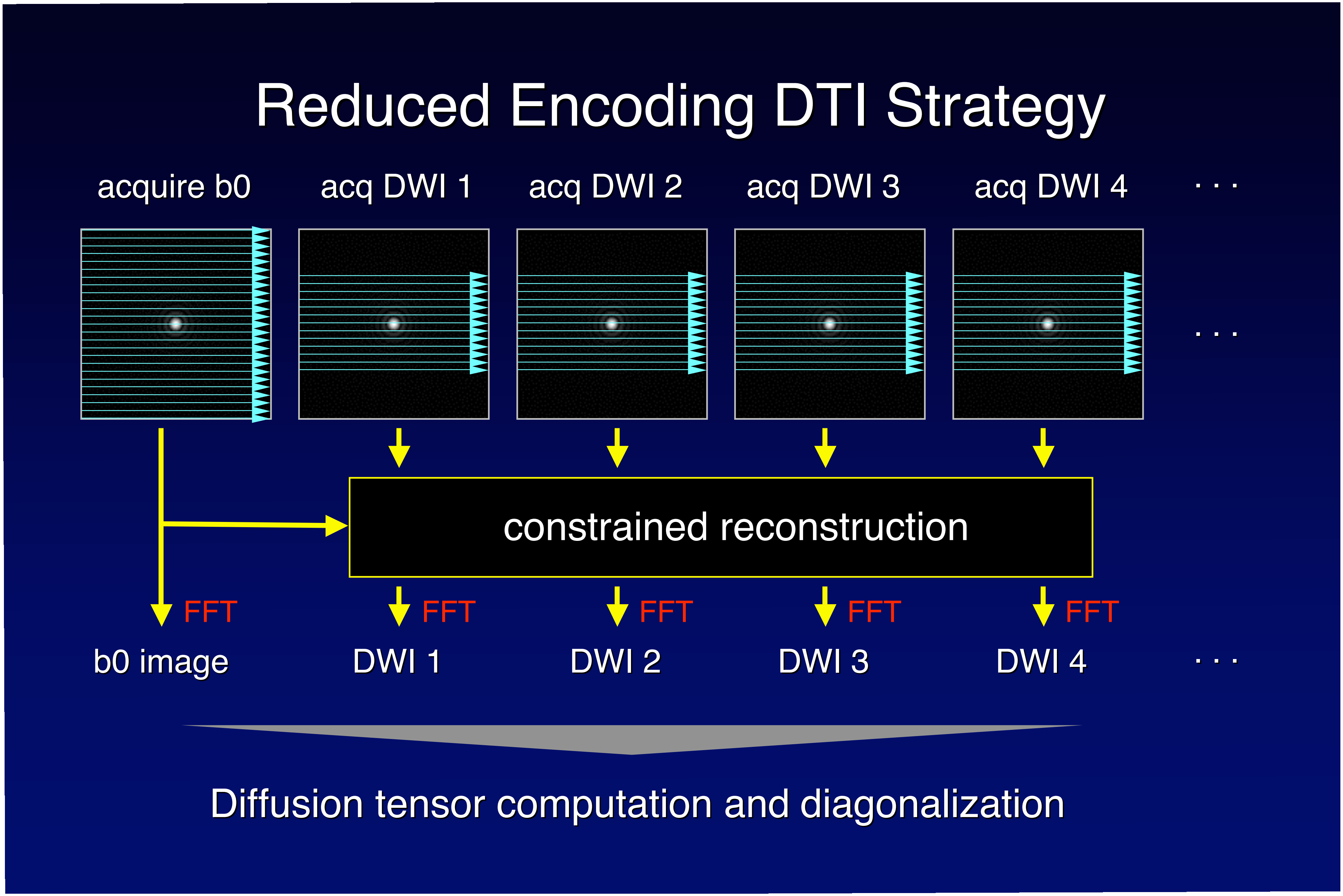
Reducing DTI Scan Time



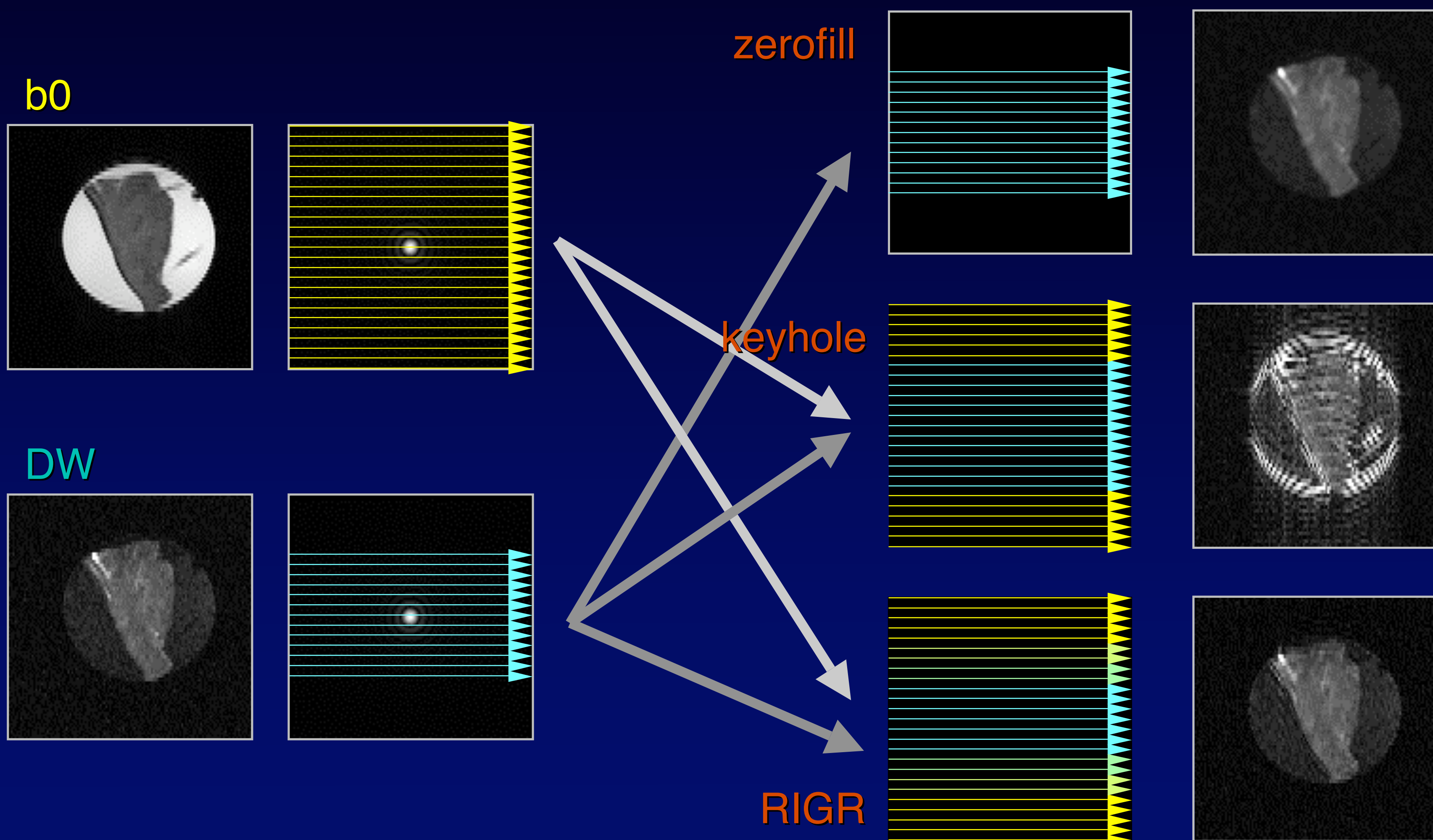
Conventional DTI Strategy



Diffusion tensor computation and diagonalization

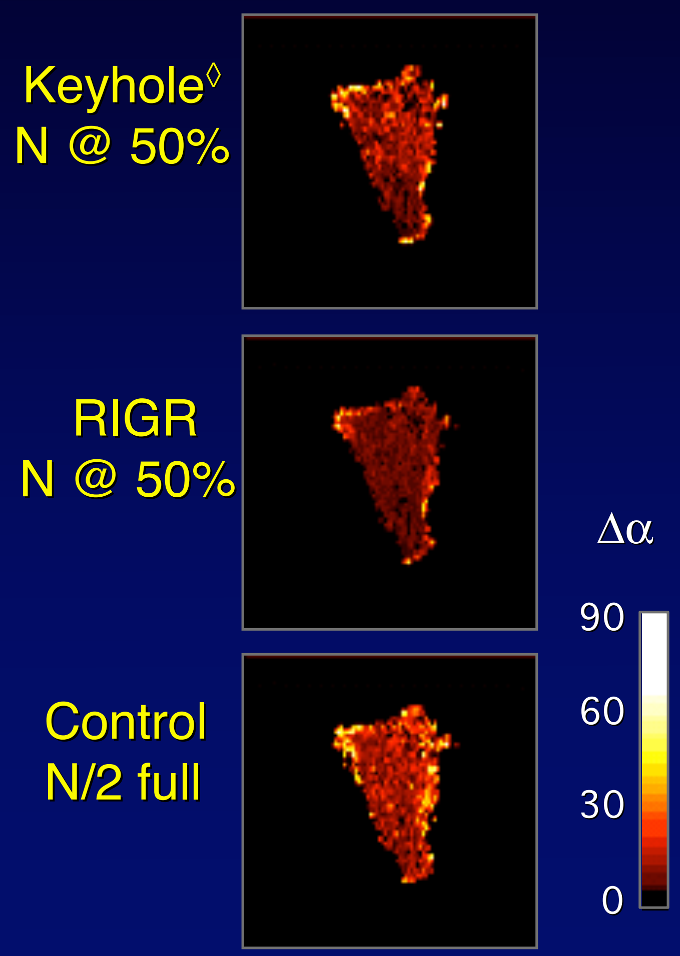

Reduced Encoding DTI Strategy
acquire b0
acq DWI 1
acq DWI 2
acq DWI 3
acq DWI 4
. . .
. . .
constrained reconstruction
FFT
FFT
FFT
FFT
FFT
b0 image
DWI 1
DWI 2
DWI 3
DWI 4
. . .
Diffusion tensor computation and diagonalization

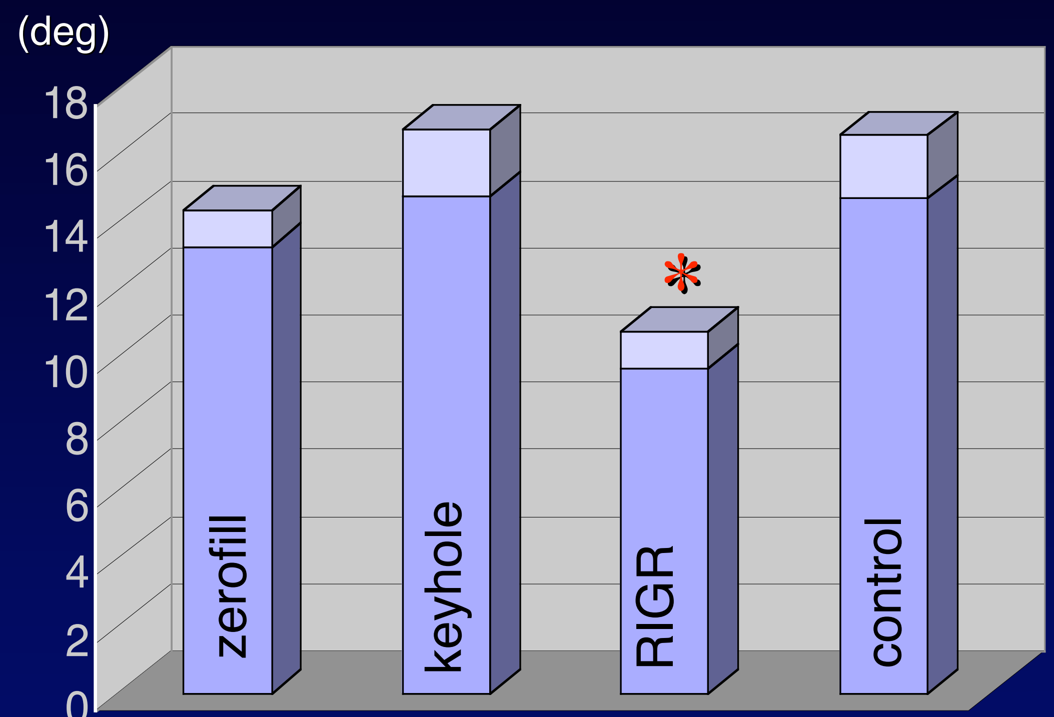
Constrained Reconstruction Methods



Fiber Orientation Mapping Accuracy

Fiber orientation angle vs "gold standard"





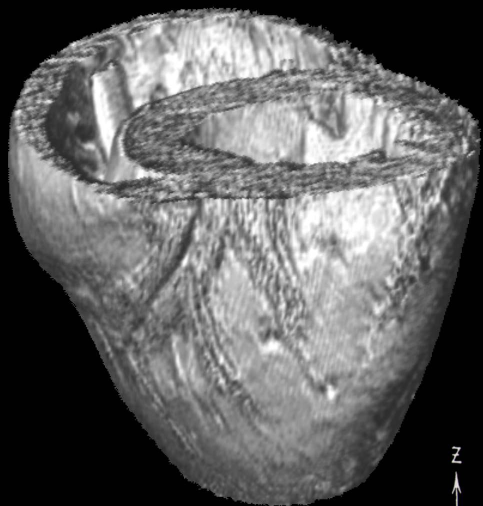
3D DTI: 256 x 128 x 128 matrix size
9 hr vs. 30 hr scan time

Hsu & Henriquez. J Cardiovasc Magn Reson. 3: 339, 2001

3D Myocardial Fiber Orientation Mapping

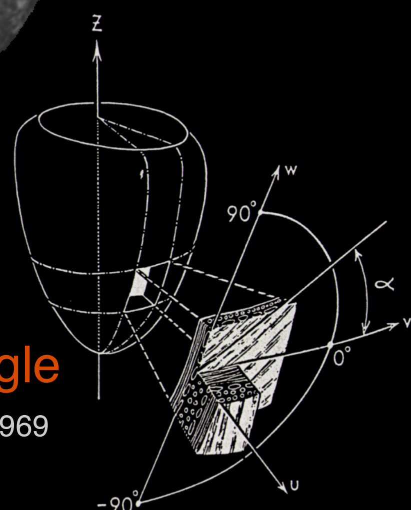
dog heart

10 cm



fiber helix angle

Streeter et al., 1969



MR-DTI
selected short-axis slices

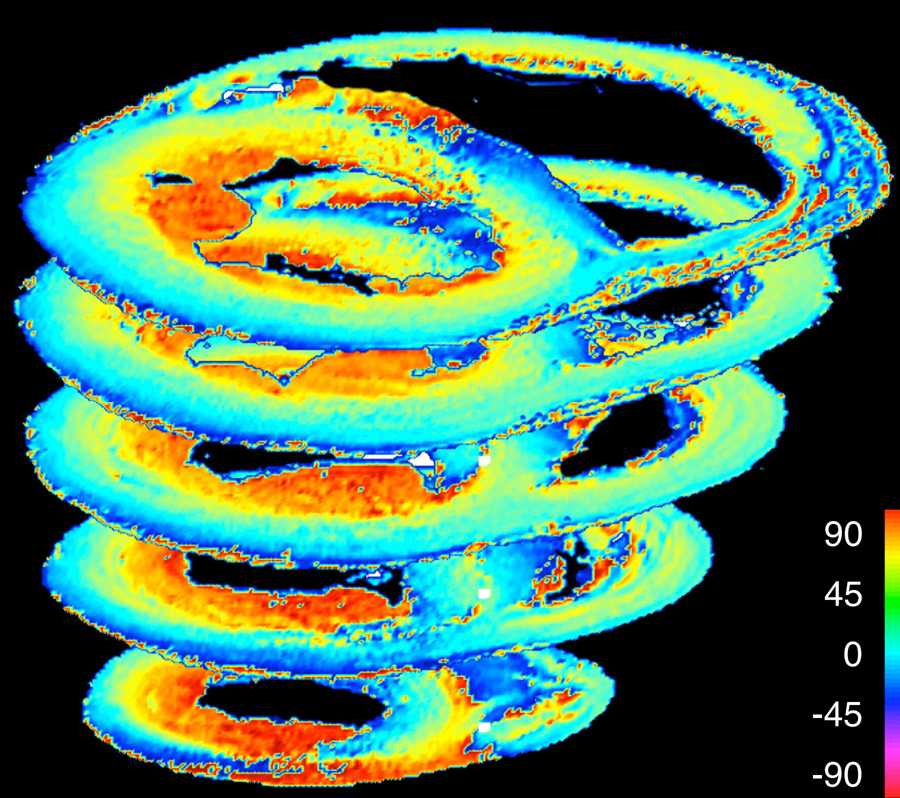
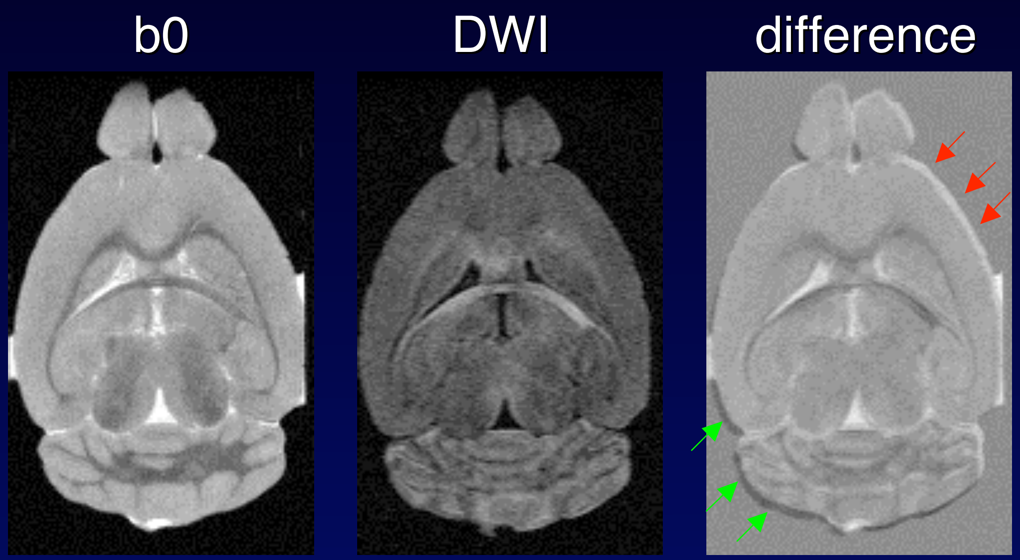


Image Registration

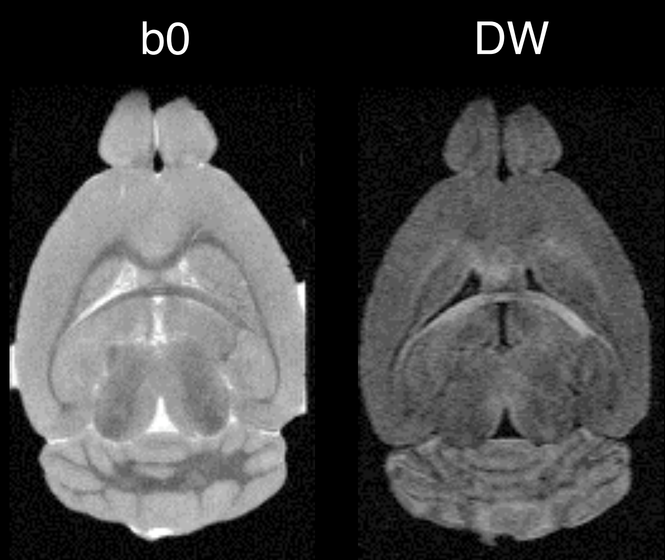


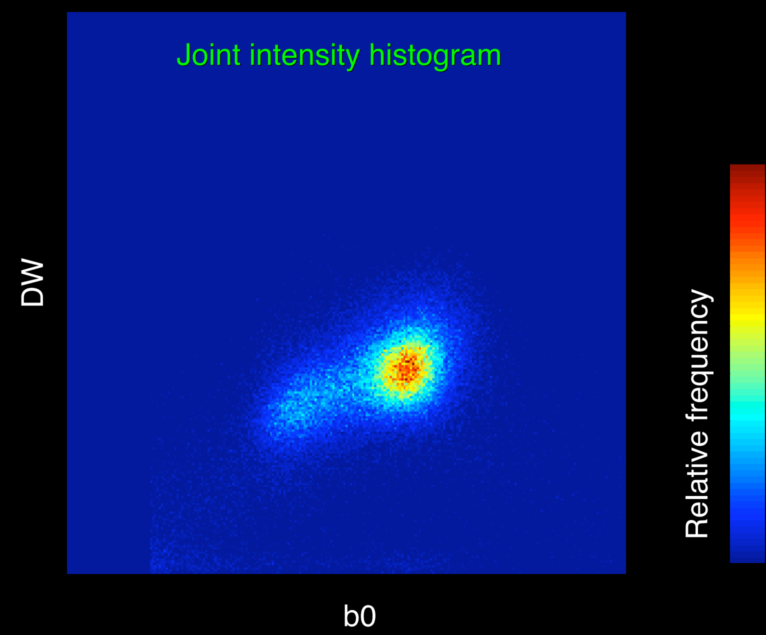
- Diffusion gradient direction dependent
- Causes: eddy-currents, field inhomogeneity, motion, etc
- DT estimation errors at borders
- Loss of fine structures

Registration of DW/DT Images

Challenges:

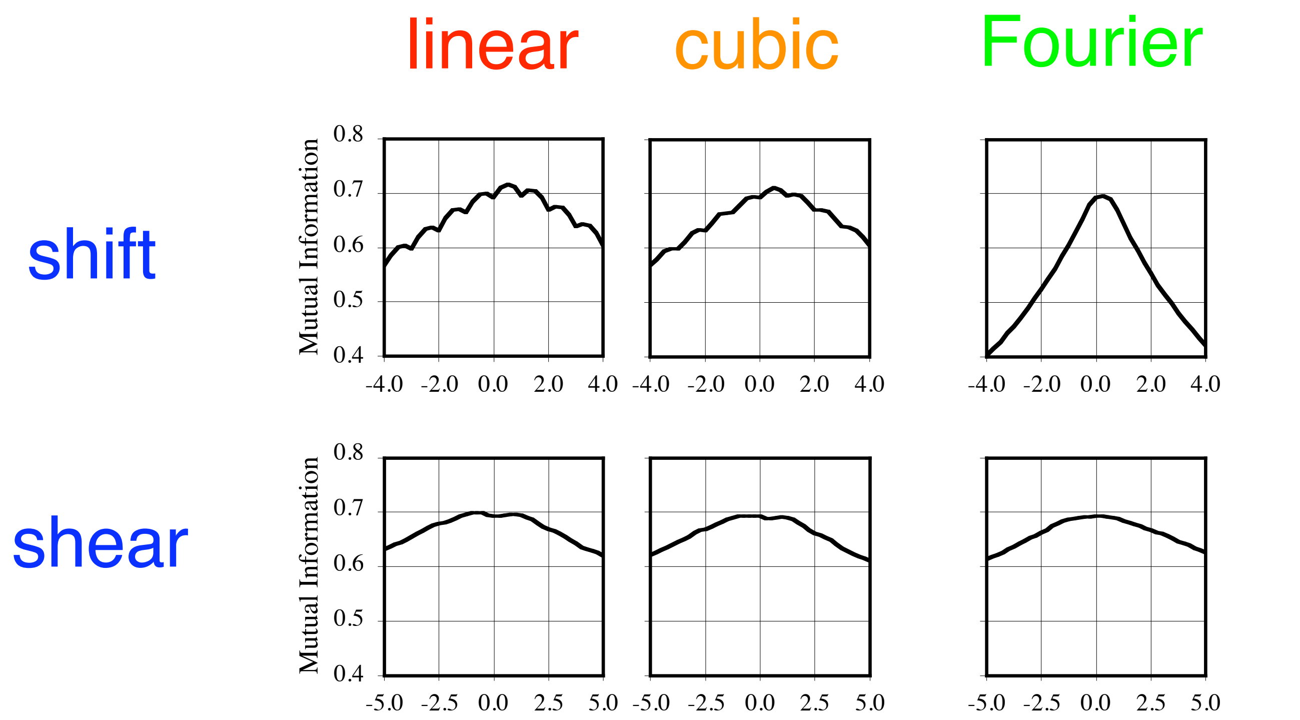
- 3D landmarks difficult
- No exact one-to-one intensity correlation





Mutual Information Image Registration

Sub-pixel Interpolation



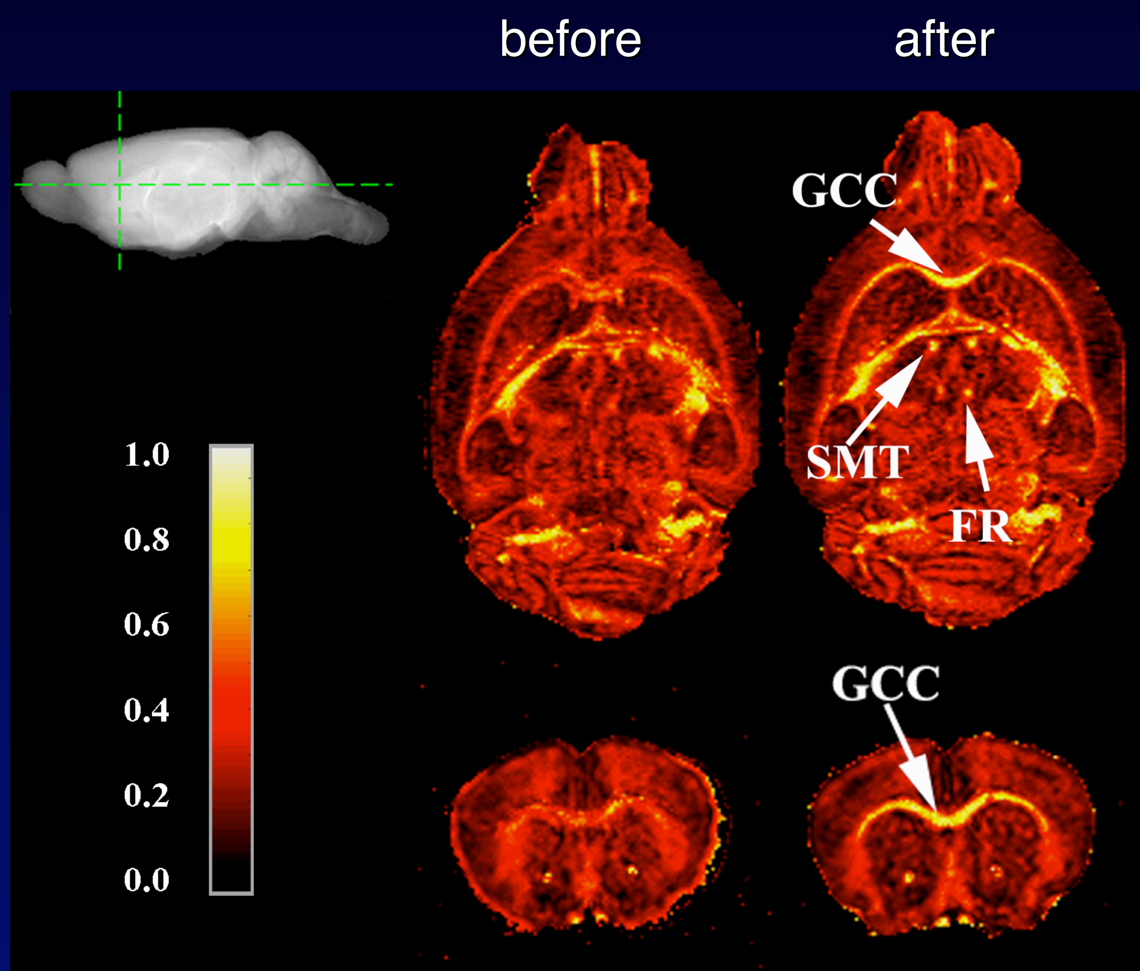
Mistry et al. Magn Reson Med. 56: 310, 2006

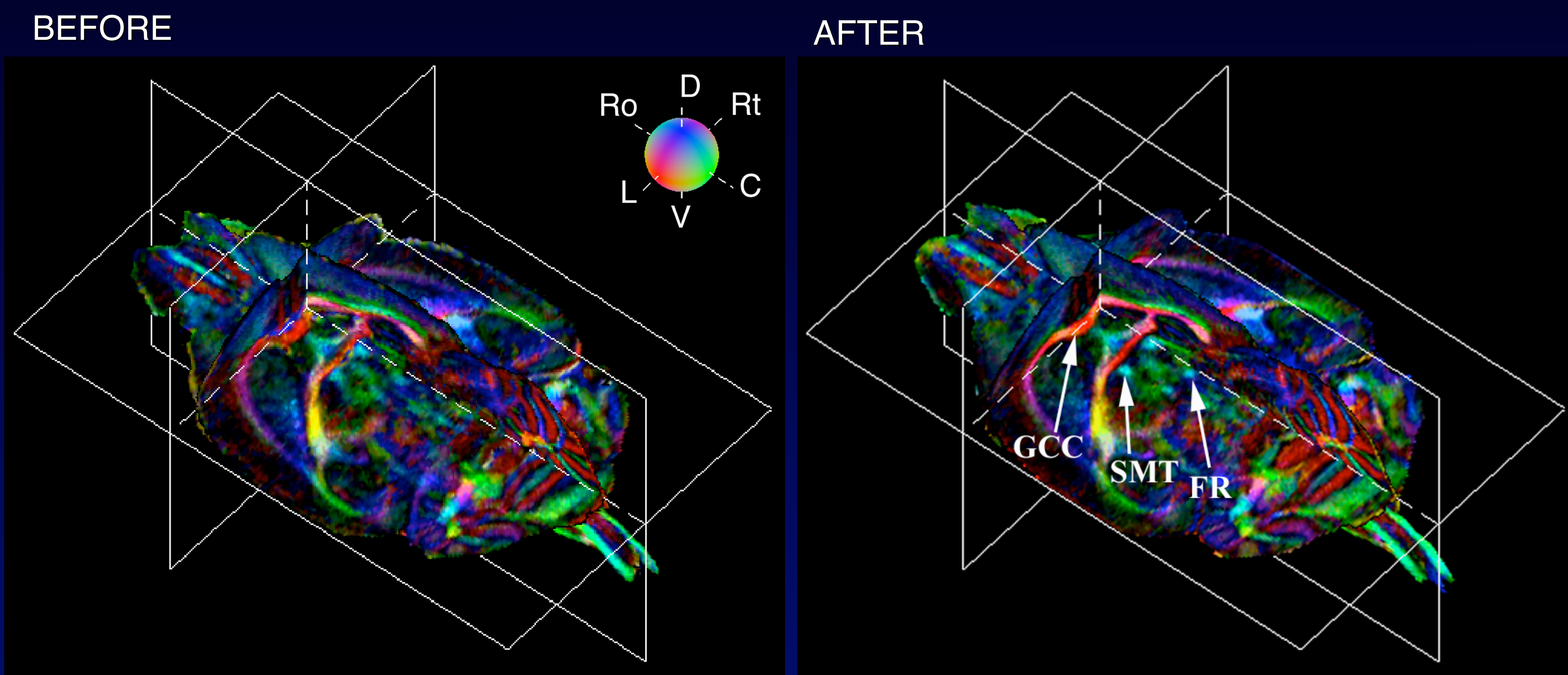
Mutual-Information Registration

12-dimensional
search space:

shift_x*
shift_y*
shift_z*
scaling_x
scaling_y
scaling_z
shear_xy*
shear_yx*
shear_yz*
shear_zy*
shear_xz*
shear_zx*

*Fourier deformation




BEFORE
AFTER
D
Ro
Rt
L
C
V
GCC
SMT
FR

Overview

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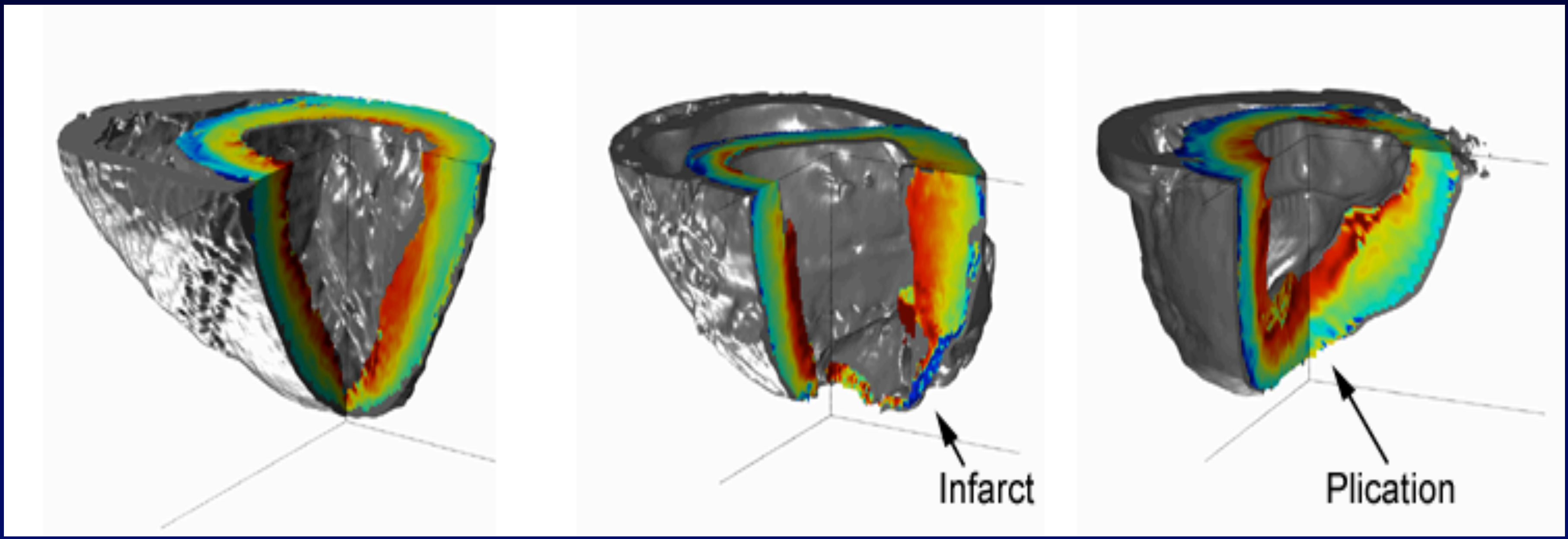
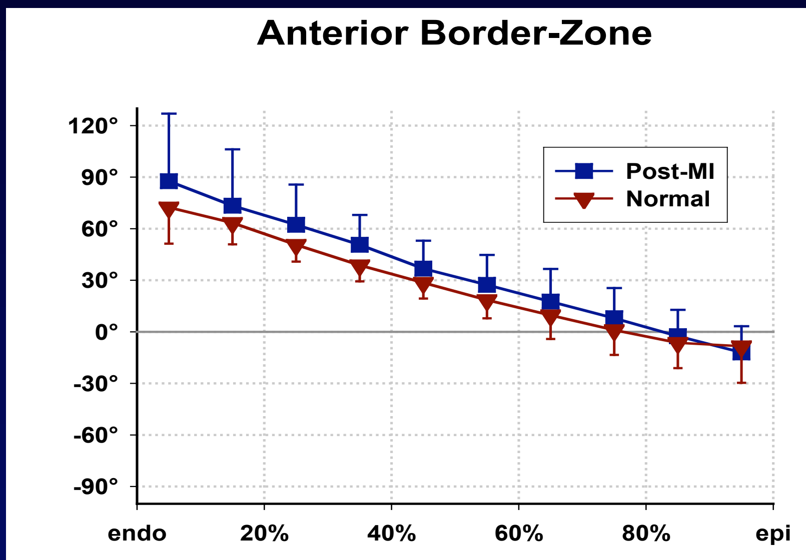
Post-Injury / Surgery Remodeling

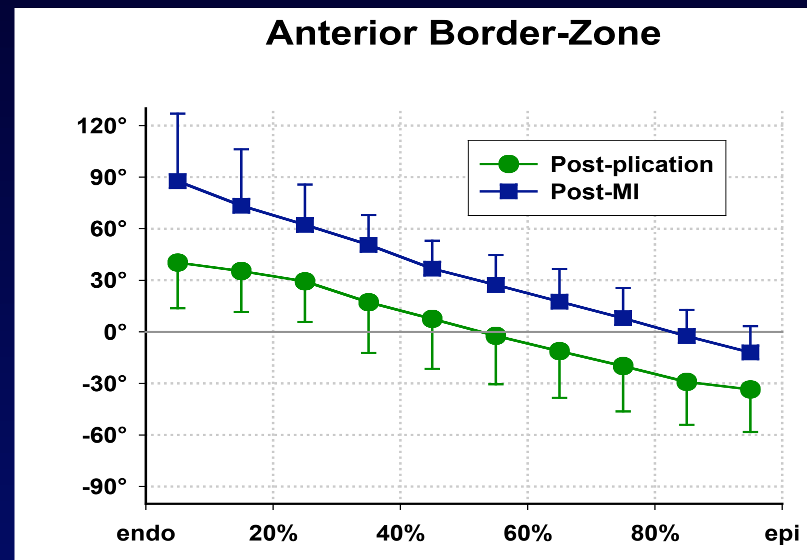


Sheep hearts
2T, 256 x 128 x 128 acq
10 cm FOV
Scan time: 9.1 hr

Walker et al. J. Thoracic Cardiov Surg. 129: 382, 2005

Regional Comparison

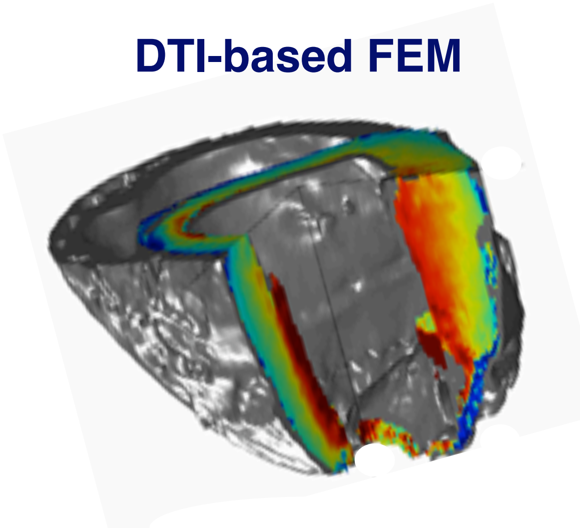


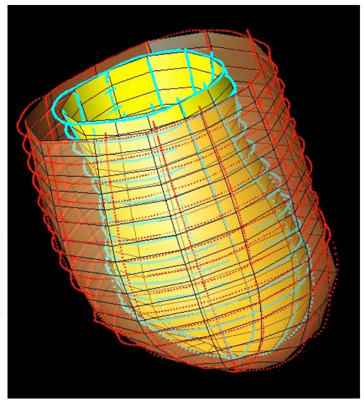


- No change after infarction!!
- Post-plication changes in adjacent regions

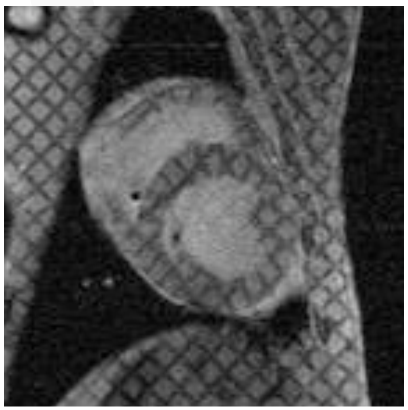
Cardiac Mechanics of LV Aneurysm

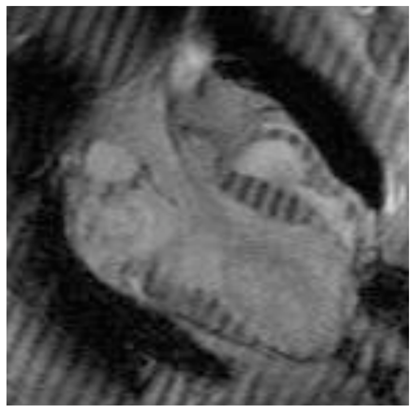
DTI-based FEM



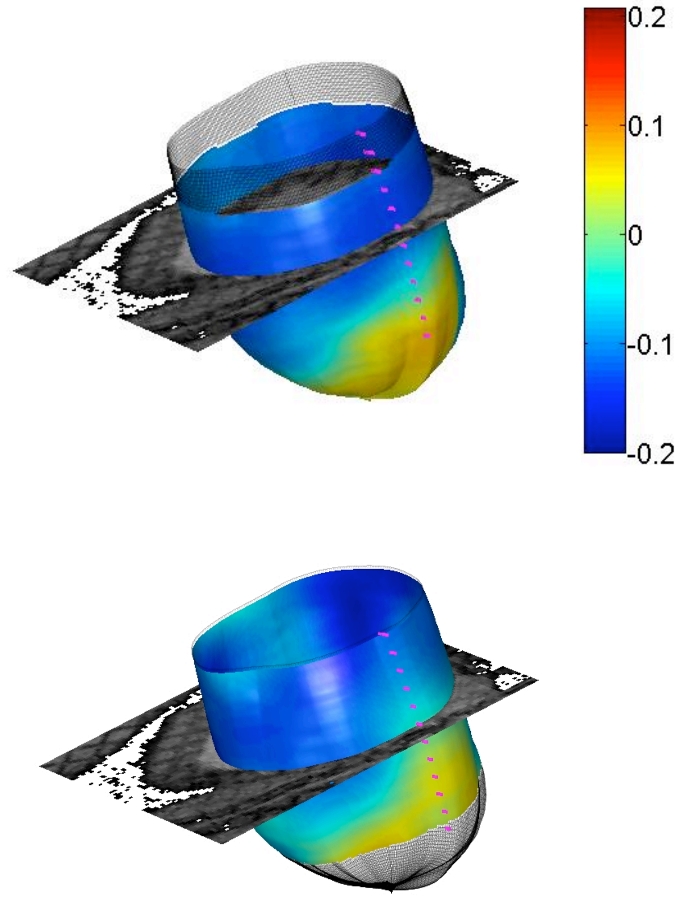


In Vivo Tagging





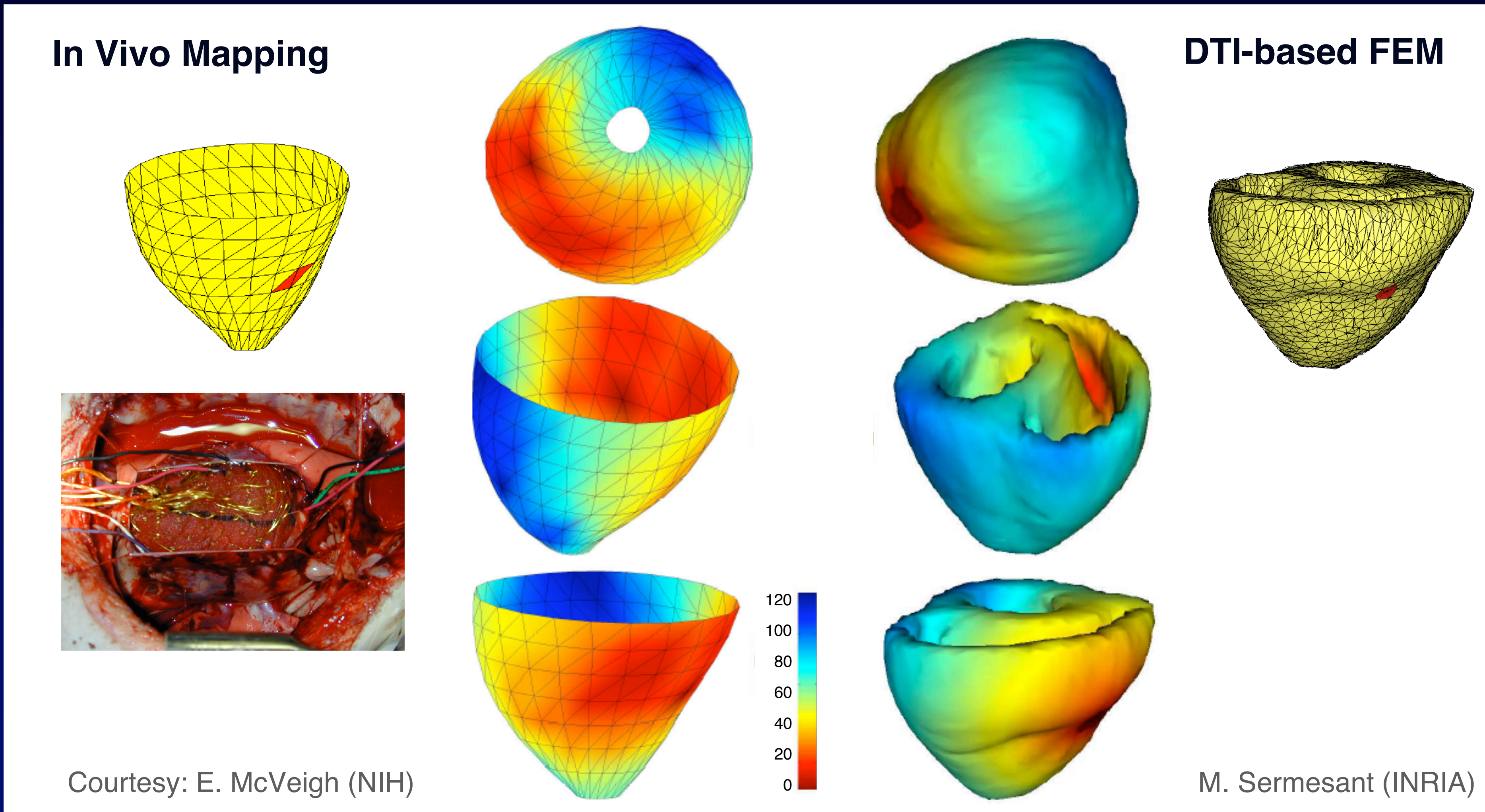
Circumferential Strain



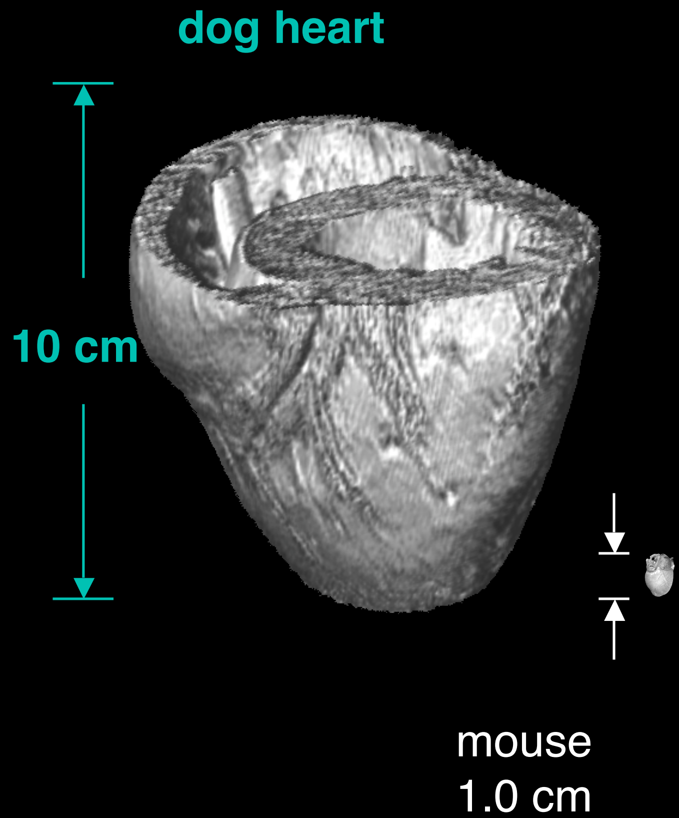
Walker et al. Am J Physiol. 289: H692, 2005

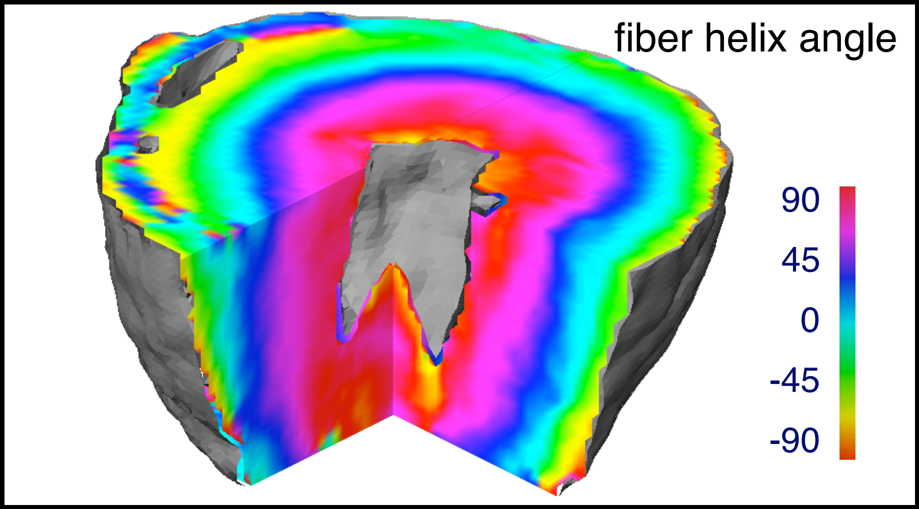
Myocardial Electrophysiology

Canine Ectopic Pacing Action Potential Wave Front



DT Microscopy of Mouse Hearts

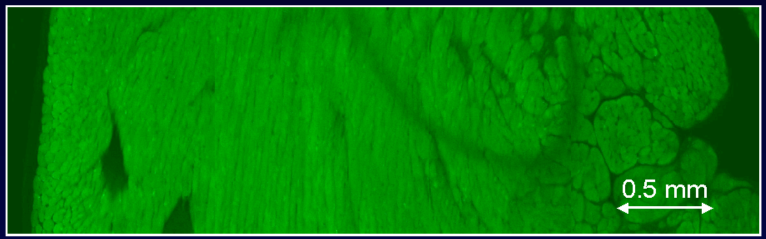




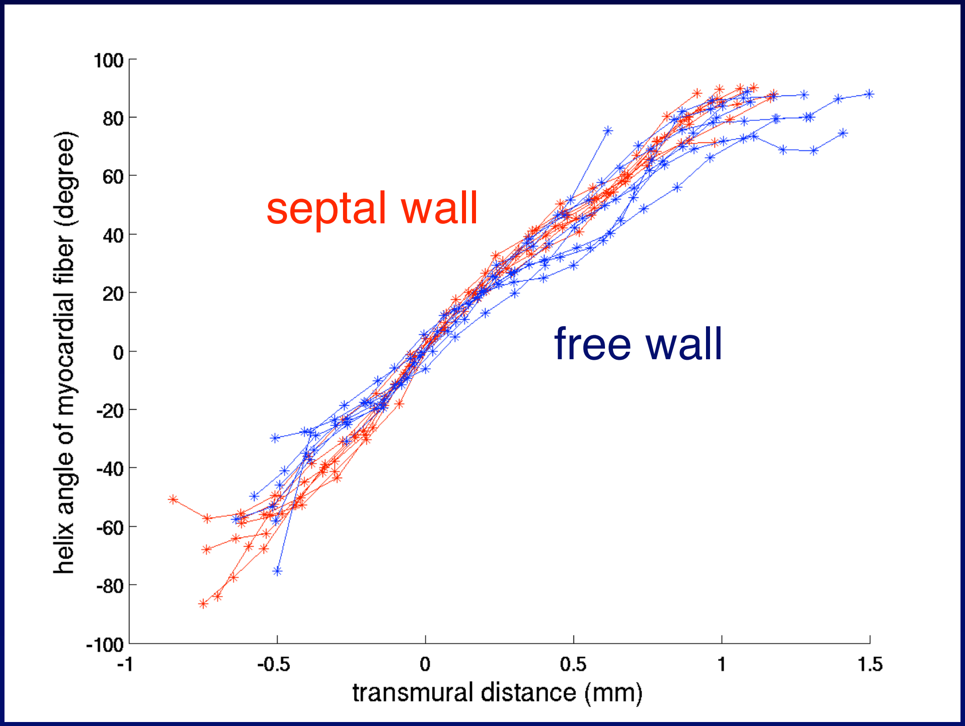
9T, 100 μm isotropic resolution
200,000+ measurement points

Jiang et al. Magn Reson Med. 52: 4453, 2004

LV Transmural Fiber Helix Angles



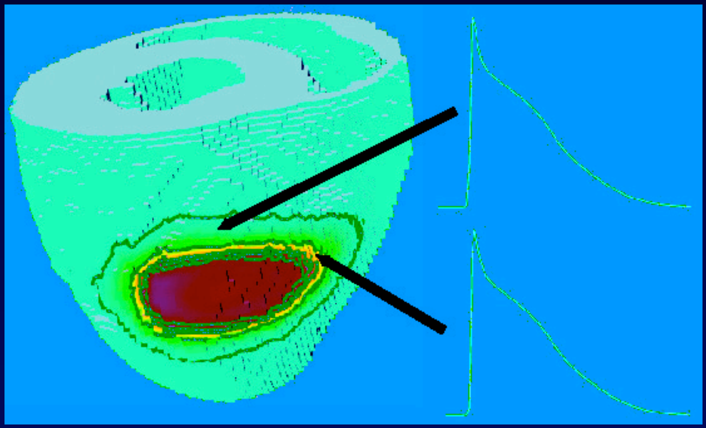
Courtesy: K. Pandya (UNC-CH)



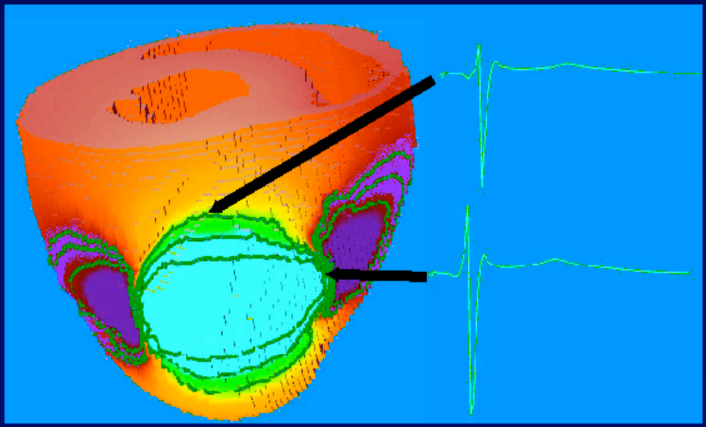
Fiber Angle Mapping
Accuracy: ± 5°

Mouse Heart Electrophysiology

transmembrane
potential
5 ms post pacing



extracellular
potential
5 ms post pacing



Collaborators:
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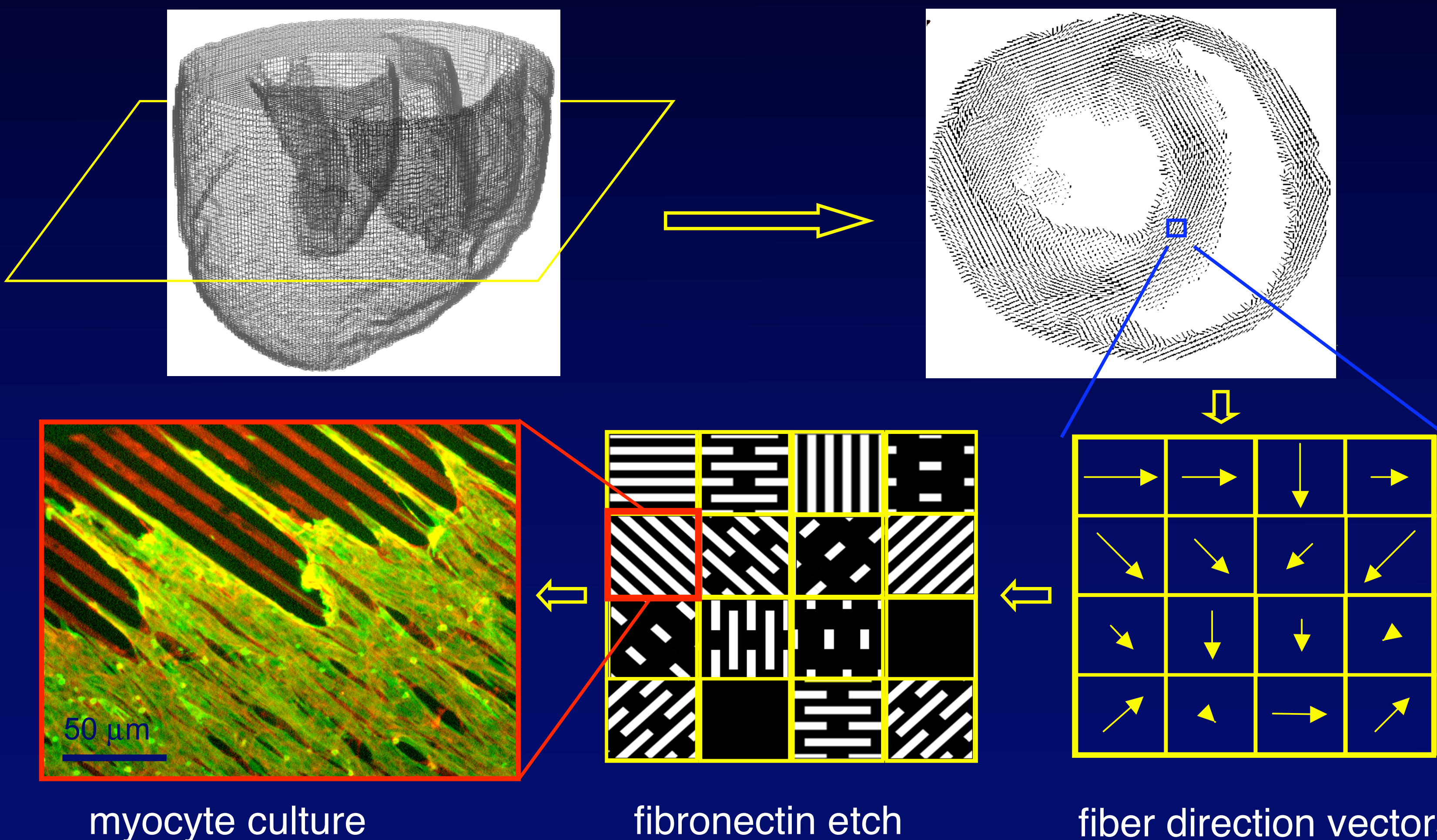
C. Henriquez
D. Weinstein (Utah)
G. Kindleman

DTI and Tissue Engineering

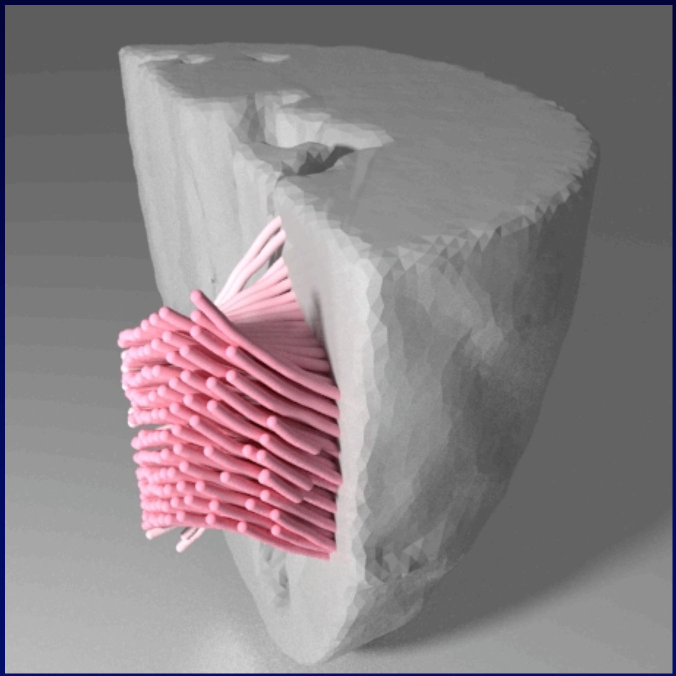
“Biologically Inspired” 2D Heart Slice

N. Bursac (Duke)



Myocardial Fiber Visualization

DTI-based renderings of a rat LV

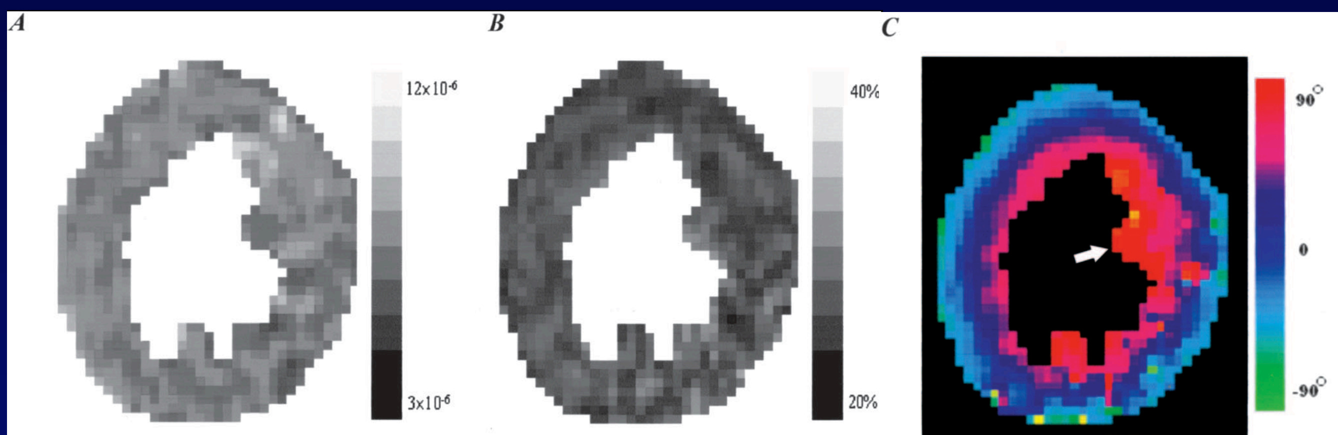


G. Gullberg, LBNL

In Vivo Cardiac DTI?

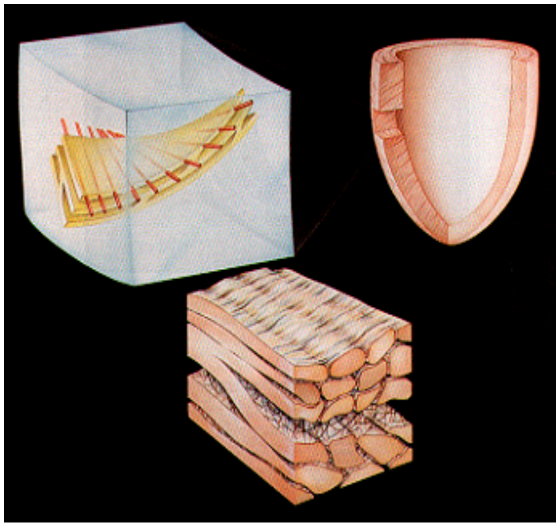
Possible, but . . .

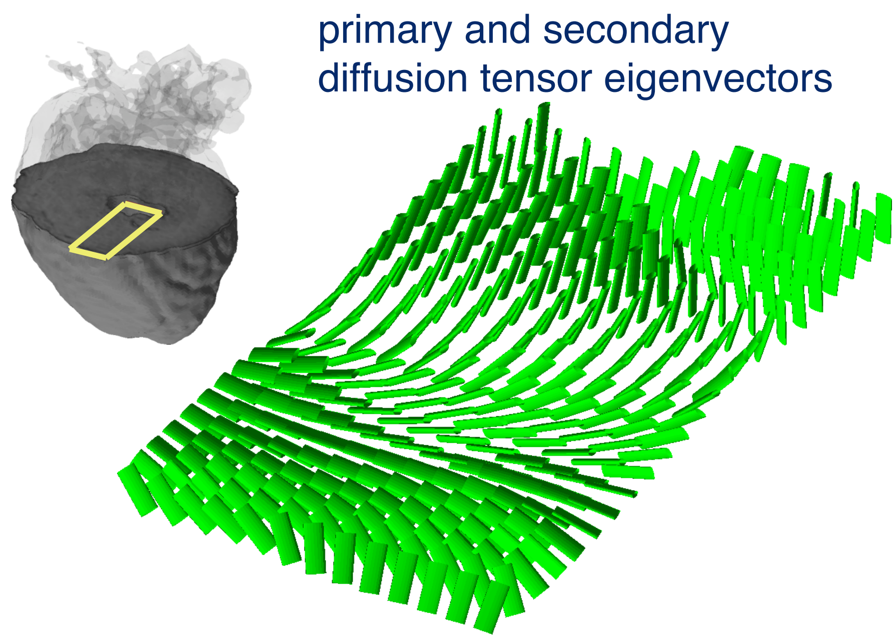
MD FA α_H



Wu et al. Circulation. 114: 1036, 2006

Myocardial Sheet Structure





- Morphologically consistent
- Not fixation artifact
- Biophysical origin still unknown

Overview

- Principles and Methods of DTI
- Engineering Challenges
- Applications of Cardiac DTI
- Myocardial Structural Models and Atlases

Myocardial Structural Models /Atlases

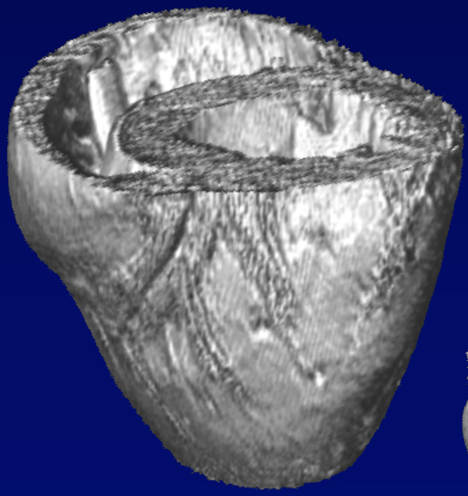
Key Challenges

1. Fiber Orientation Measurement:
   - alternative to histology
   - suitable for the mouse

2. Statistics:
   - inter-species variability
   - intra-species variability
   - atlas?

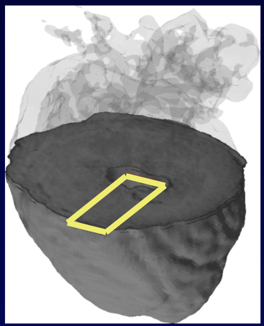
Myocardial Fiber Orientation:
Inter-Species Variability

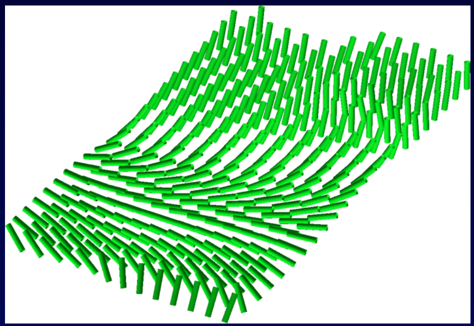
Species	N	Scanner	FOV	SNR
Sheep	5	2.0 T	10 cm	125
Rabbit	6	7.0 T	4.0 cm	102
Mouse	10	9.4 T	1.2 cm	95

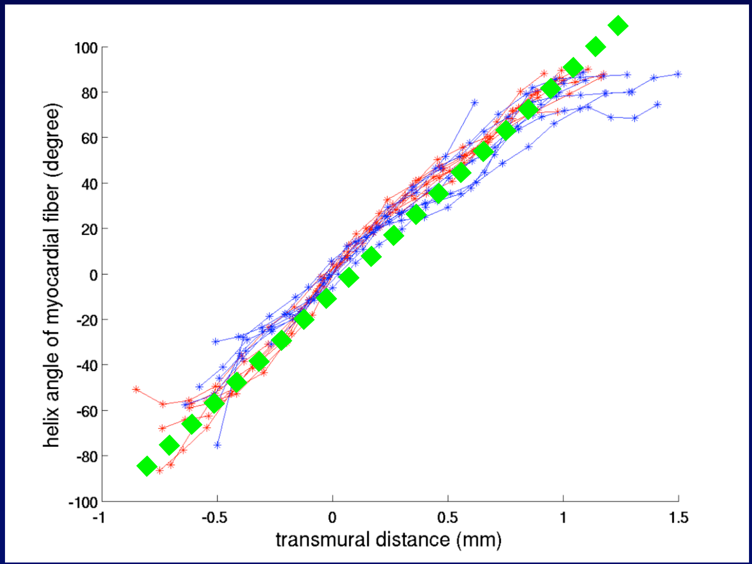


3D DTI:
- normal, fixed in end-systole
- 128 x 128 x 128 matrix
- b0 + DWI in 12 optimized directions
- 9.1 hr acquisition

Myocardial Fiber Orientation:
Inter-Species Variability

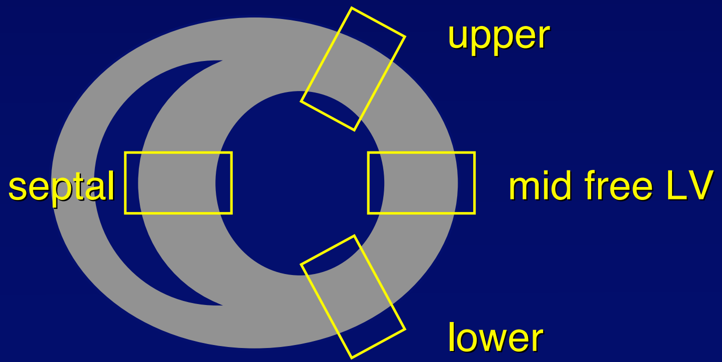






- subepicardial helix angle
- epi-to-endocardial range
- linearity

2-way ANOVA comparing across species and myocardial zones



	Species	Septal	Mid Free wall	Upper Free wall	Lower Free wall
Range	Mouse	69.0 ± 17.8	68.9 ± 17.4	75.3 ± 17.1	72.4 ± 22.4
	Rabbit	44.0 ± 11.3	48.9 ± 10.5	47.6 ± 11.7	39.4 ± 9.70
	Sheep	38.0 ± 9.92	54.5 ± 7.27	54.4 ± 10.8	51.7 ± 10.7
Subepicardial Helix Angle	Mouse	-58.6 ± 9.53	-50.2 ± 14.7	-35.9 ± 14.6	-46.9 ± 14.4
	Rabbit	-42.6 ± 14.9	-29.9 ± 14.6	-27.7 ± 11.4	-23.7 ± 13.9
	Sheep	-28.2 ± 19.2	-30.2 ± 8.74	-24.3 ± 9.64	-26.6 ± 9.26
Linearity	Mouse	0.98 ± 0.011	0.99 ± 0.011	0.97 ± 0.025	0.98 ± 0.017
	Rabbit	0.93 ± 0.14	0.94 ± 0.038	0.94 ± 0.050	0.97 ± 0.028
	Sheep	0.91 ± 0.070	0.95 ±0.044	0.95 ± 0.055	0.94 ± 0.052

No significant zonal difference detected,
but species-species differences are significant

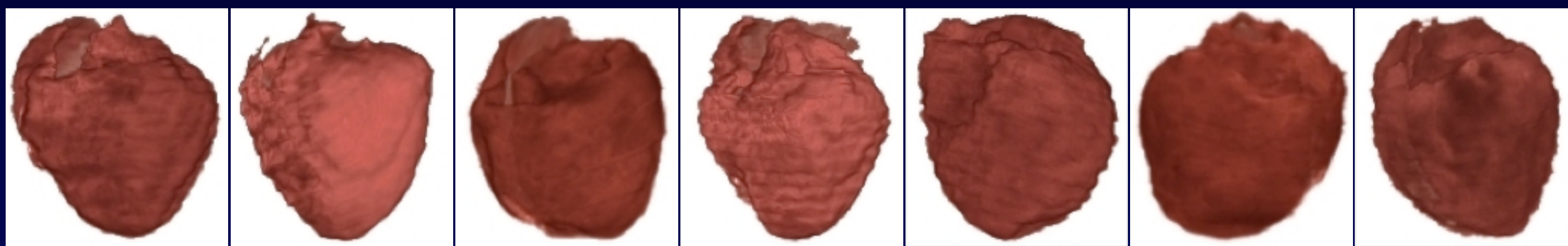
	Range	Sub-epi α_H	Linearity
mouse-sheep	YES	YES	YES
mouse-rabbit	YES	YES	YES
rabbit-sheep	YES	YES	NO

Inter-Species Variability: Implications

1. Biomechanics:
   - fewer myocyte in smaller hearts
   - steeper transmural angle = higher torsion?

2. Myocardial modeling:
   - cannot scale across species
   - at least hearts of different sizes

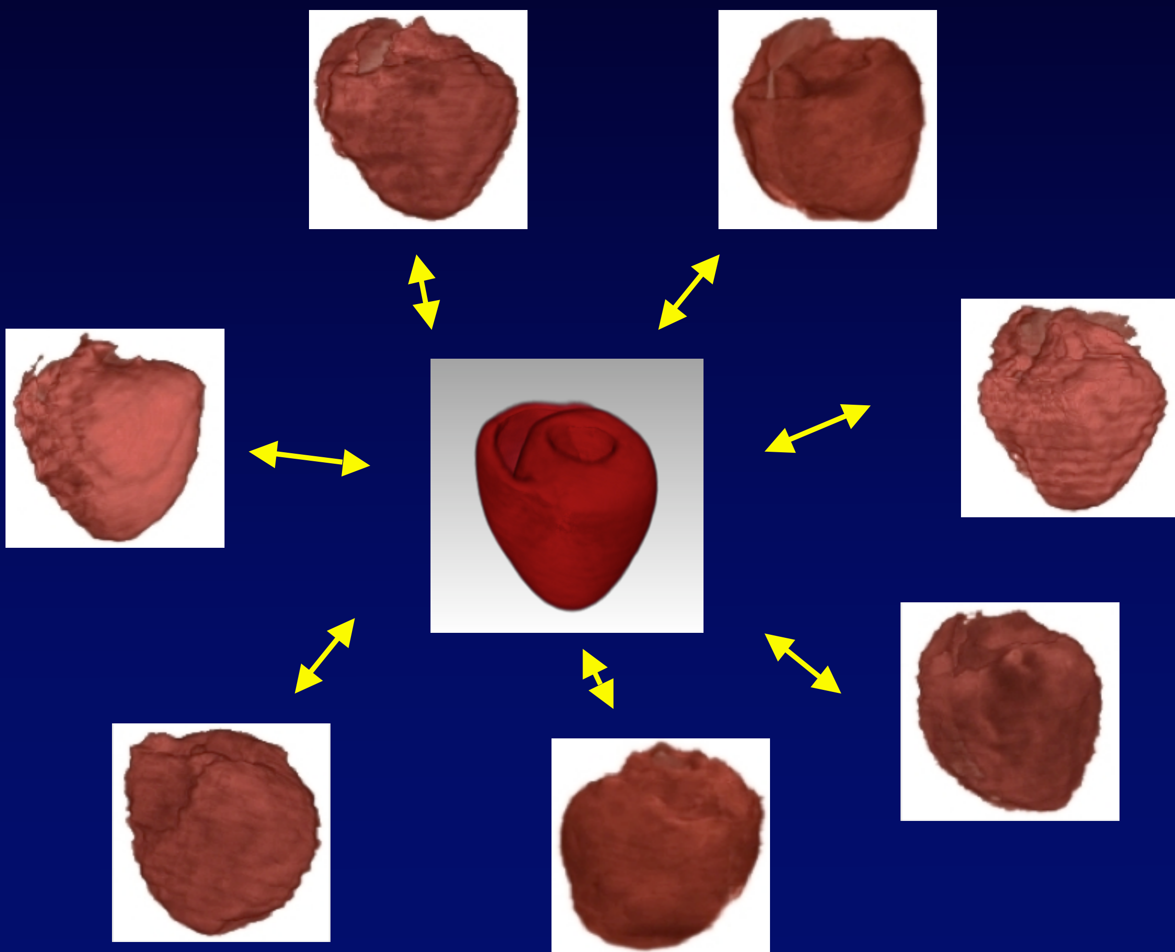
Myocardial Fiber Orientation:
Intra-Species Variability



Areas of Development:

- define anatomically-equivalent points
- quantitative comparison of tensor fields

Large Deformation Diffeomorphic Metric Mapping (LDDMM)

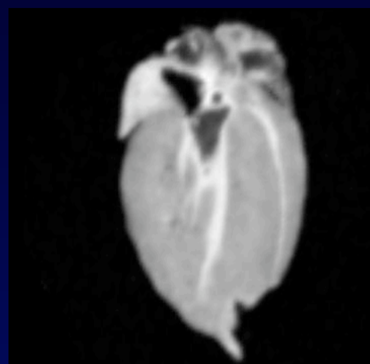


- infinite DOF
- invertible

Image Processing Pipeline

original

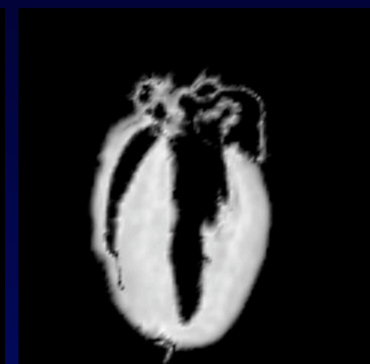
align



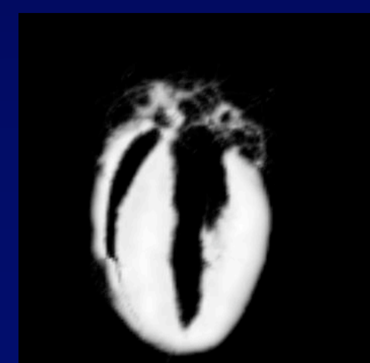
segment

affine

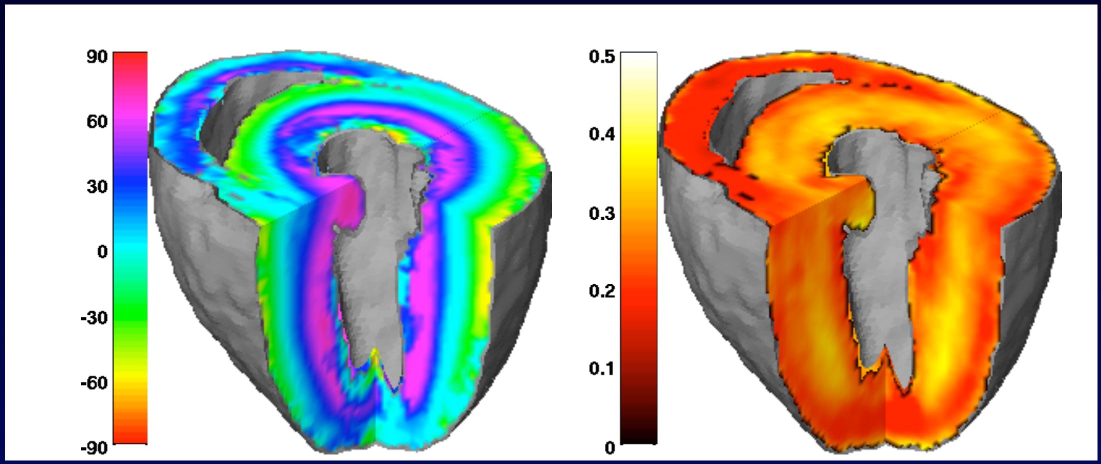
LDDMM



atlas



Statistics of Group Averages



α_H Anisotropy

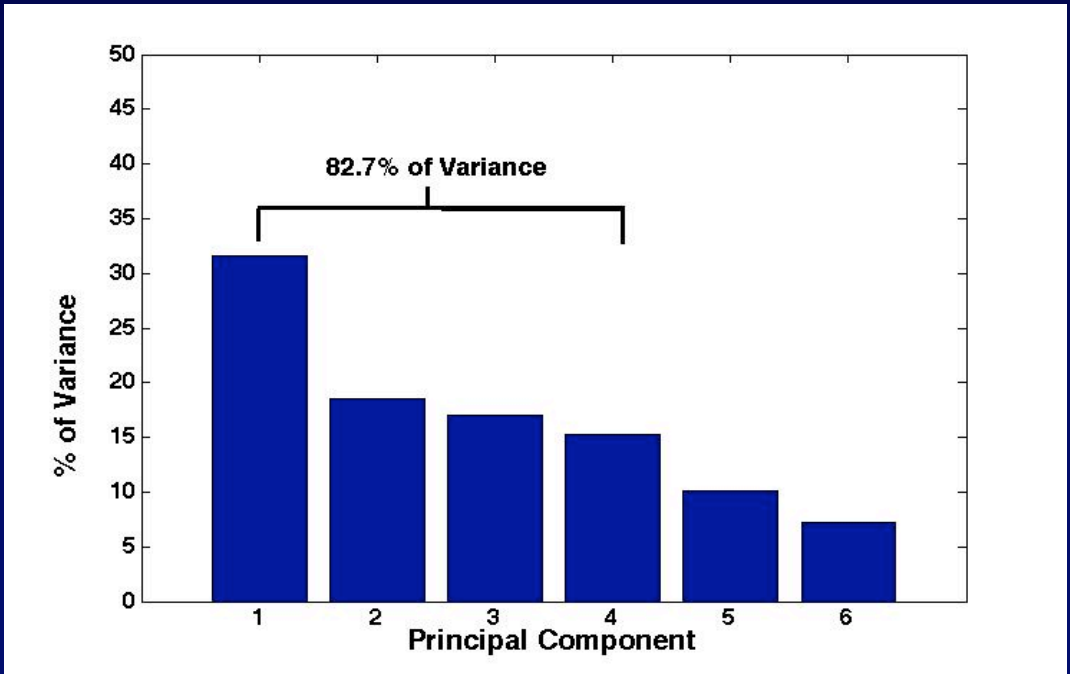
- averages scalar of quantities vs. tensor
- pixel-wise vs. whole-heart comparison

Principal Component Analysis

- reduces 10,000s to (N-1) DOF
- scalar measurements
- whole-heart comparison

Group of 11 mouse hearts

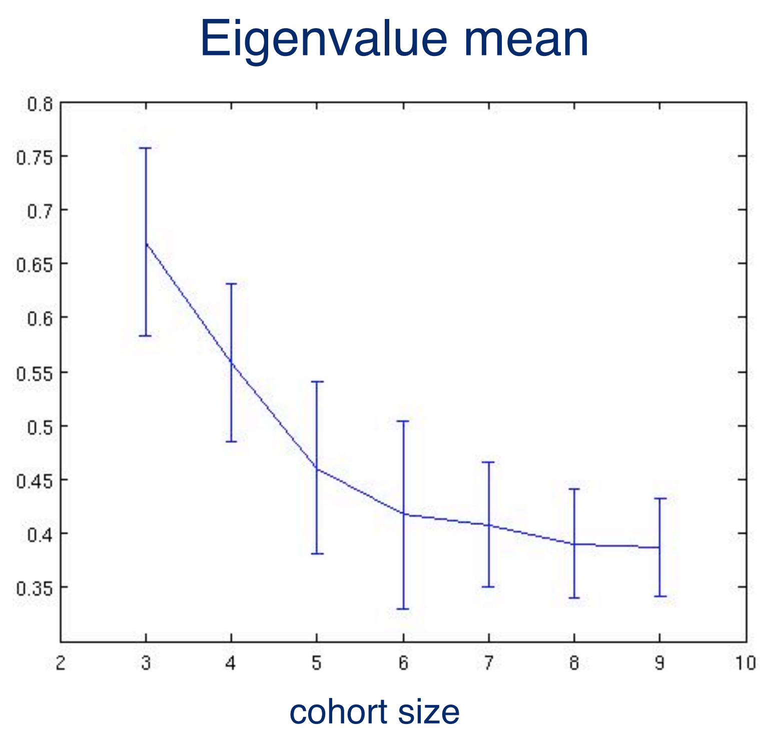
helix angle

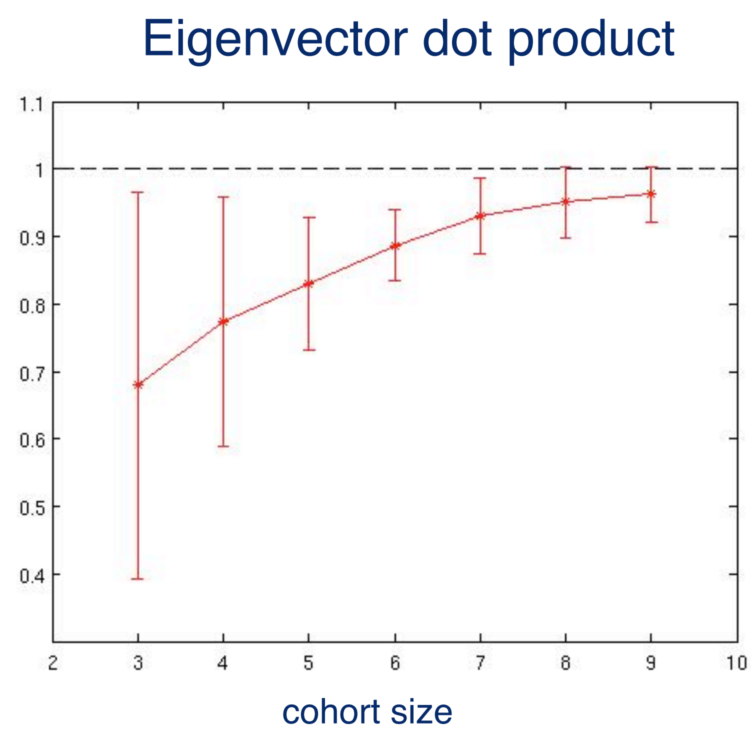


Statistical Power:

First Help Angle Component

Mean ± SD of 20 sub-samples

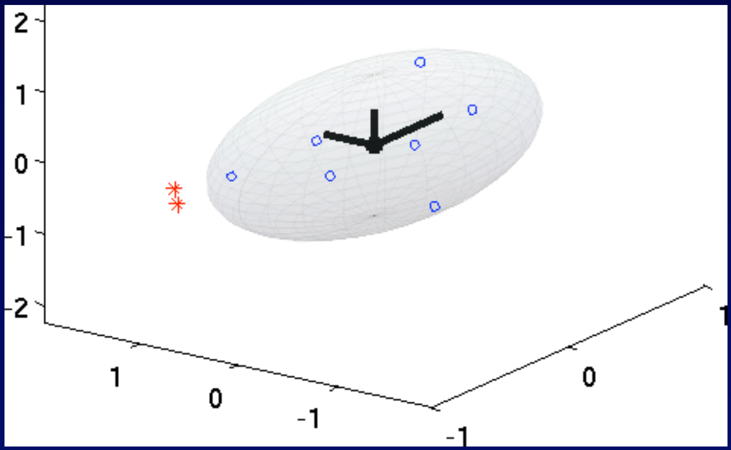




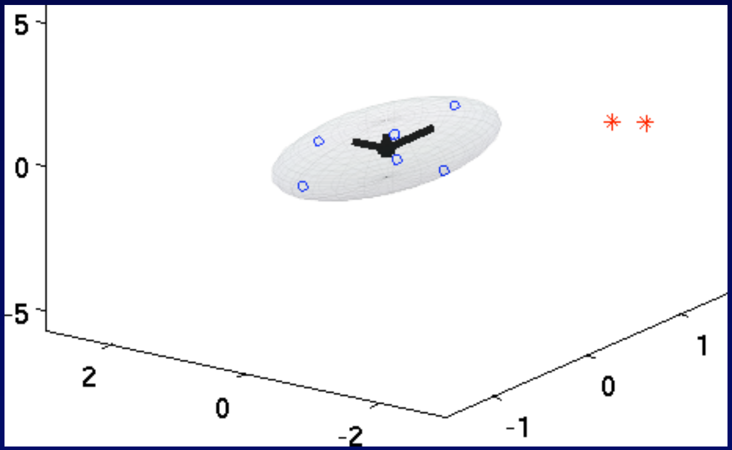
Detection of Hypertrophic Hearts

Collaborators: K. Padya, O. Smithes

α_H



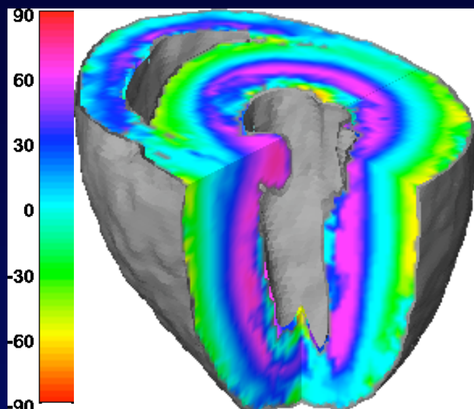
Anisotropy



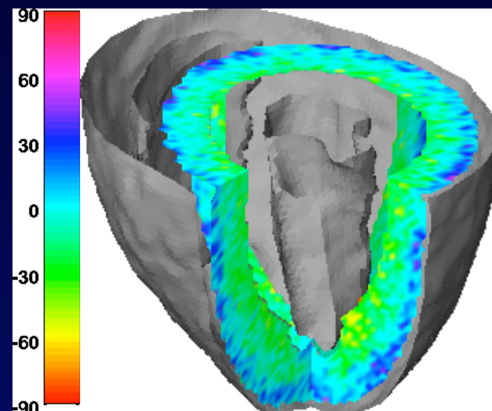
Ellipses include 95% of data with ± 2SD in each dimension in 3D PCA space

Pixel-wise Comparison

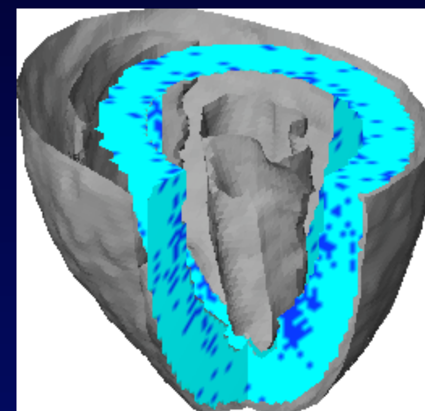
Fiber Orientation Helix Angle



Group Mean



Difference



Significance

Whole-heart comparison can be advantageous

Conclusions

- Alternative to histology found
- Inter-species differences significant
- Intra-species variability tractable

Works in Progress

- Even more efficient DTI acquisitions
- Better in vivo cardiac DTI
- Vector or tensor-based statistics
- 4D and longitudinal atlases

Acknowledgments

Contributors

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