Measurement of Ultra-Short and Long-Range ^{3}He Apparent Diffusion Coefficients in an Elastase-Induced Rat Model of Emphysema

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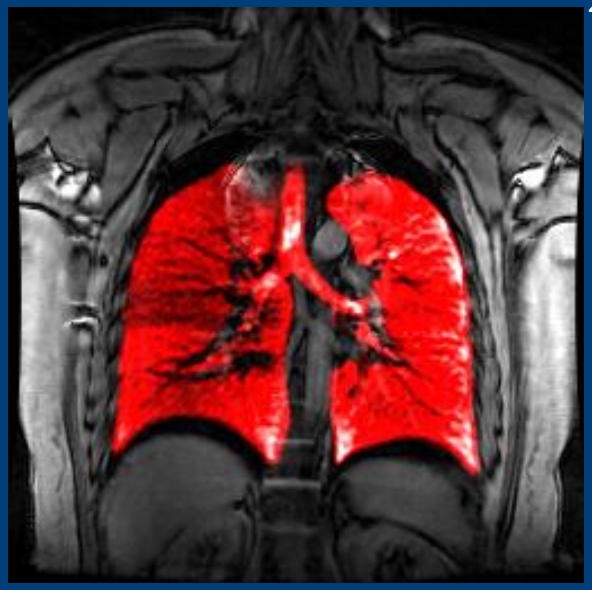
Chronic Obstructive Pulmonary Diseases (COPD)

- COPD is a combination of asthma, chronic bronchitis and emphysema.
- 4th natural cause of death worldwide[1].
- Emphysema is the expansion and destruction of alveolar walls, resulting in breathing difficulties.
- Current clinical method of detecting COPD is spirometry (i.e. FEV_1, D_{LCO}) .

[1]CJ Murray, *Global Burden of Disease Study*, *Lancet* 1997

Hyperpolarized Noble Gas MRI

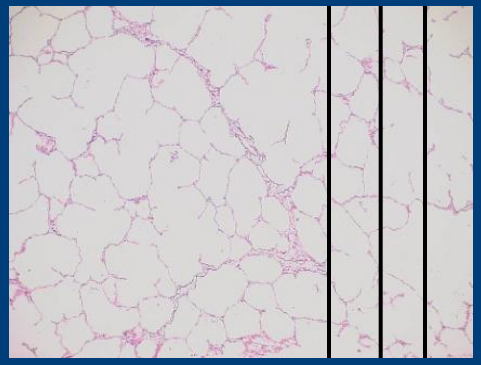
- Inhaled gases (^{3}He, ^{129}Xe) can be used to image the lungs.
- *Hyperpolarization* offsets the insufficient signal due to low density.
- The achieved polarization is 10^{4}-10^{5} times larger than thermal polarization.


[2]

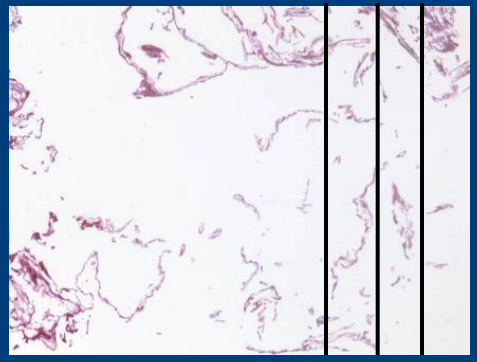
[2]Parraga, Santyr et al, *Investigative Radiology* **42**, 2007

Elastase Disease Model

- Porcine elastase is introduced in the lungs, enlarging and destroying alveolar tissue.



Healthy lung tissue



Elastase-instilled

- Mean linear intercept (L_m) is the average distance separating the alveolar walls.

Micrographs courtesy of Jim Hogg, iCAPTURE

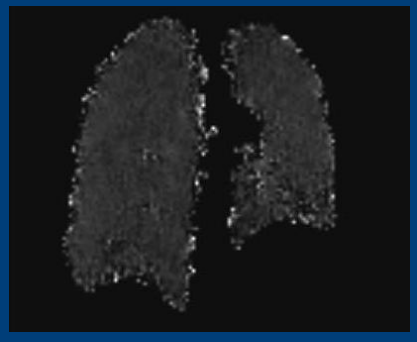
Apparent Diffusion Coefficient (ADC)

- Einstein's theory of Brownian motion led to the following relationship for 1D free-diffusion:

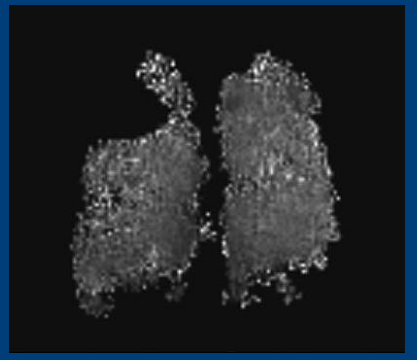
$$l_0 = \sqrt{2D_0\Delta}$$

- In restricted environments, the observed diffusion coefficient is called an **ADC**.

- In the context of NMR, ADCs depend on the **geometry of the environment**, and the **diffusion time**.



[2]Healthy



Severe COPD

[2]Parraga, Santyr et al, *Investigative Radiology* **42**, 2007

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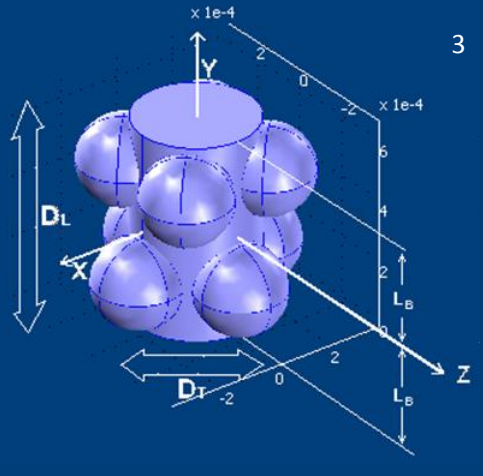
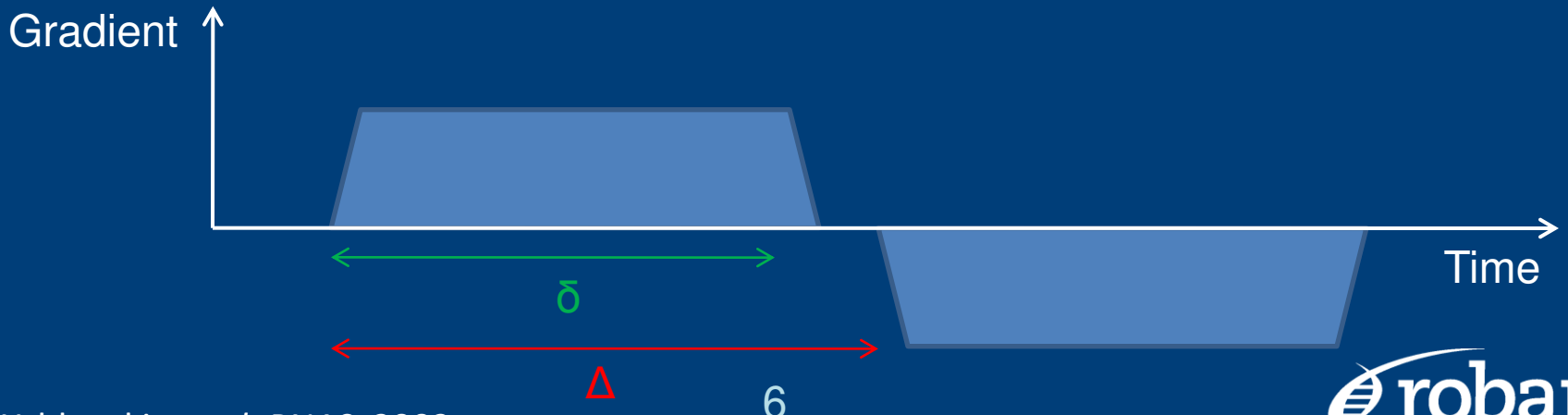
ADC measured with MRI

- For ultra-short diffusion times (< 1ms), the diffusion behaves anisotropically, and can be decomposed into two components: D_L and D_T.



[3]

$$S = S_0 exp(-b\bar{D}) f(b, D_{AN}) \quad b := (\gamma, G, G_0, \Delta, \delta)$$
$$\bar{D}, D_{AN} := (D_L, D_T)$$



[3]D. A. Yablonskiy *et al*, *PNAS,* 2002.

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Purpose

- Computational analysis[4] using the budded cylinder alveolar model predicted optimal sensitivity to disease for D_T at Δ = 360 µs (^{3}He).

- ^{3}He anisotropic ADCs were investigated at 3.0 T using an elastase induced emphysema rodent model at two diffusion times (360 µs and 800 µs).

[4]X. Xu *et al*, *ISMRM*, 2010

Methods
i) Animal model

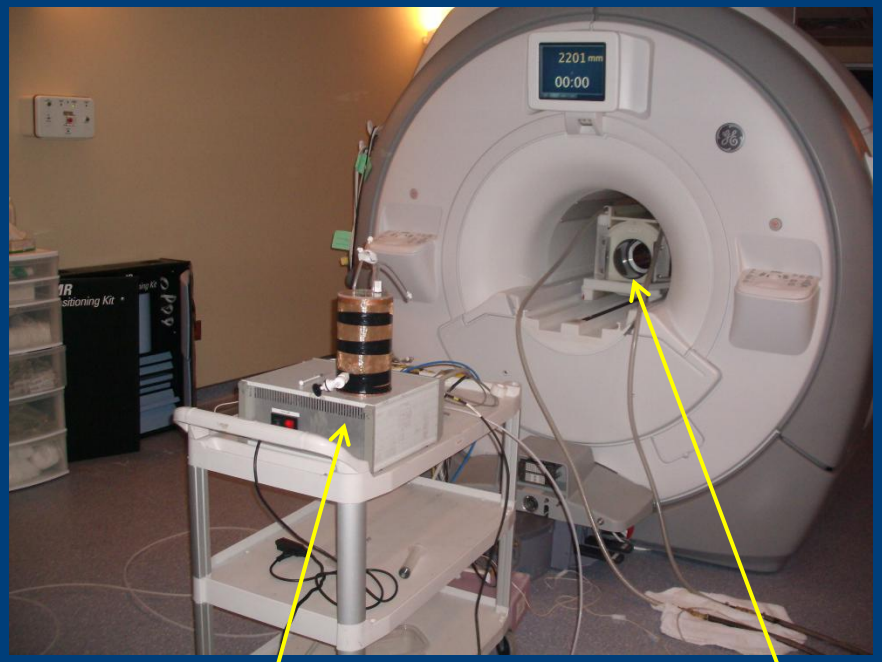
- *All experiments were performed following a University of Western Ontario Council on Animal Care approved protocol.*

- Seven Wistar rats were sham-instilled with saline (3) or instilled with elastase (4) 6-8 weeks prior to imaging.

- An endotracheal tube was inserted in and tied tightly around the trachea for secure breath holds.

Methods
ii) Hardware

3.0 T GE MR750 system



Malmö Ventilator

Insert Gradient (Rutt)

Helispin ^{3}He Polarizer (GEHC)

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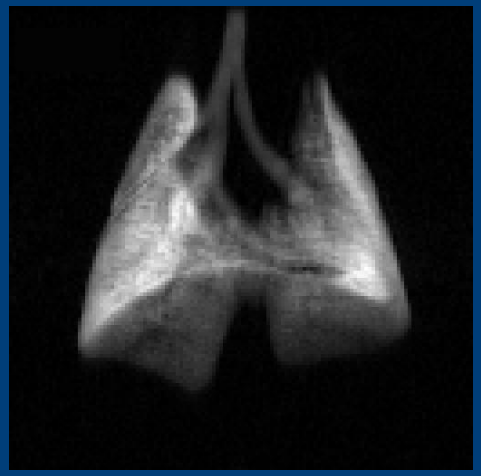
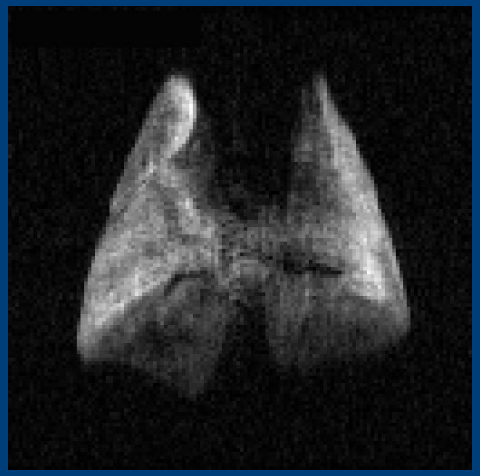
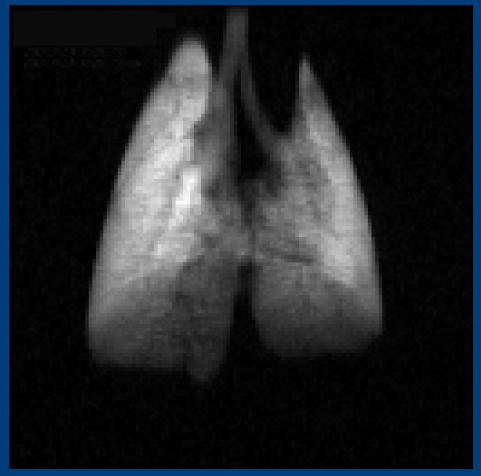
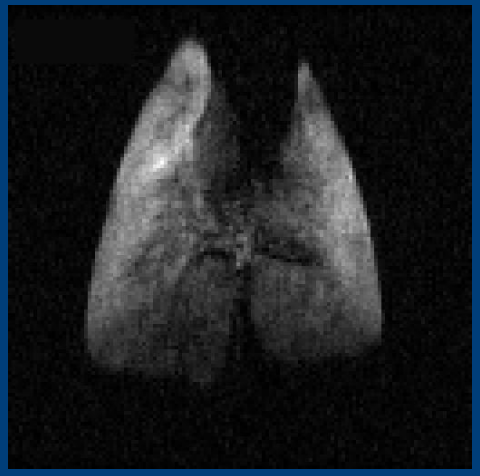
Methods

iii) Pulse Sequences and Analysis

- A 2D fast-gradient recalled echo (FGRE) pulse sequence was used.
  - 128 x 128 matrix, 5 cm x 5 cm FOV, BW = 31.25 kHz, TE = minimum and TR = 3 ms.
  - b-values ranged between 1 to 100 s/cm^2.
- A non-linear least squares Matlab algorithm (The Mathworks, Natick MA) was used to fit data to the Yablonskiy model of anisotropic ADC, on a pixel-by-pixel basis.
- Mean linear intercept (L_m) was measured from histology and correlated with results.

Results

Images at 3.0 T

	Not diffusion weighted	Diffusion weighted
Sham-instilled		
Elastase-instilled		

FOV
5 cm x 5 cm

Results

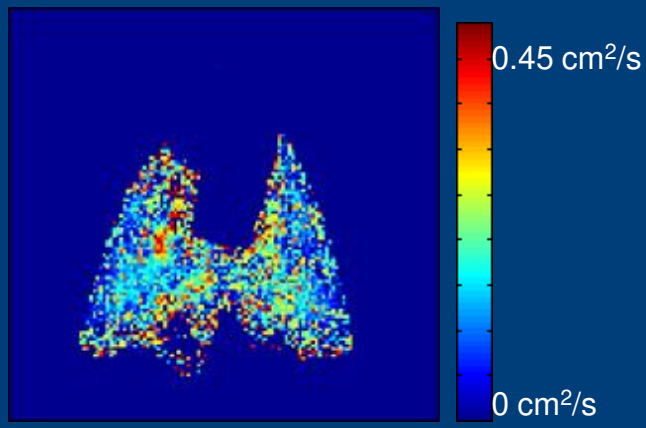
Ultra-short range ADC

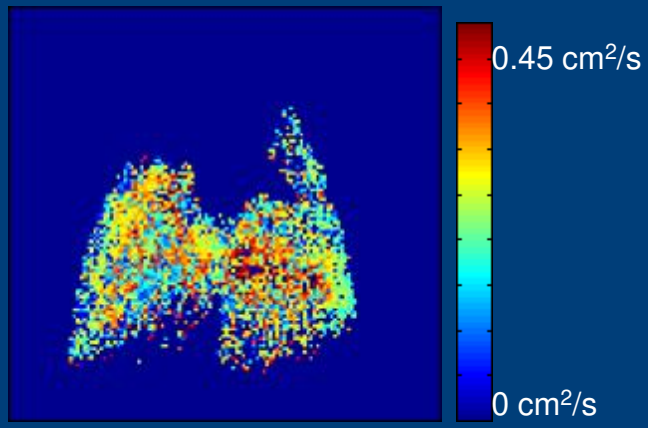
Sham-Instilled

Elastase-Instilled

D_T maps

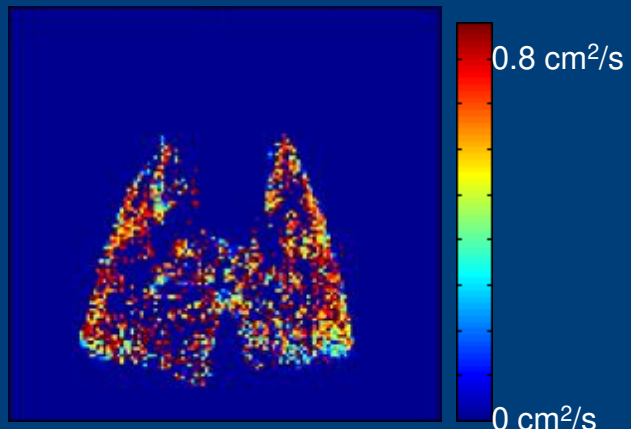
(δ = 360 μs)

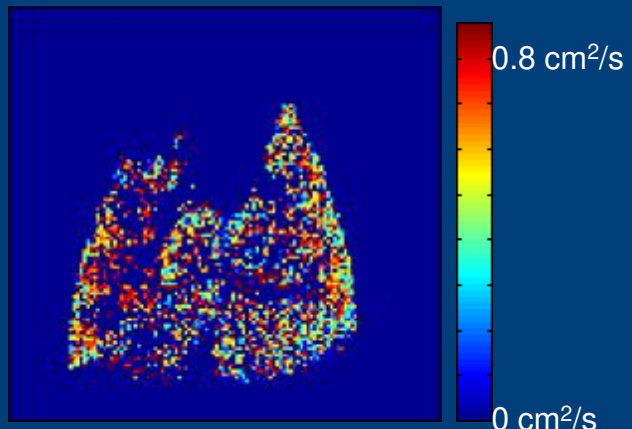




D_L maps

(δ = 800 μs)





FOV
5 cm x 5 cm

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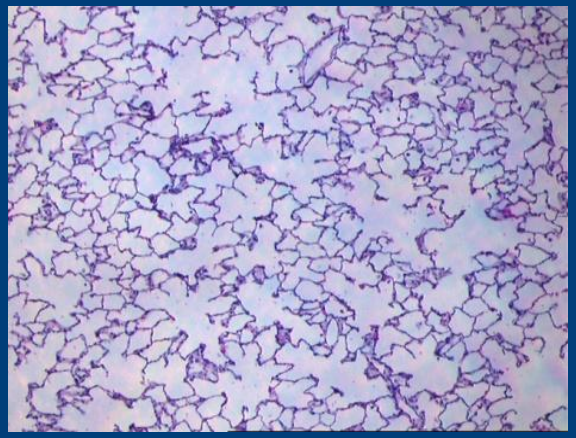
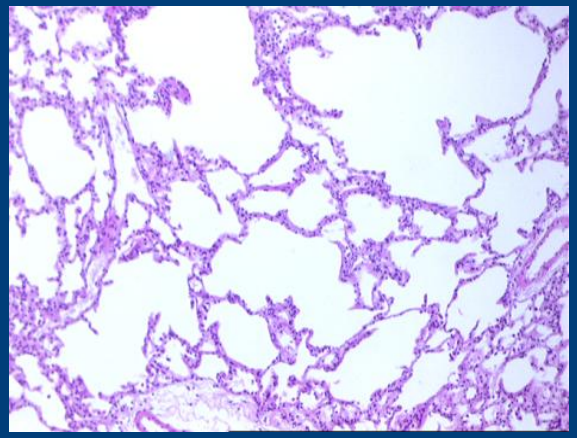
Results

Histology

Sham-instilled



Elastase-instilled

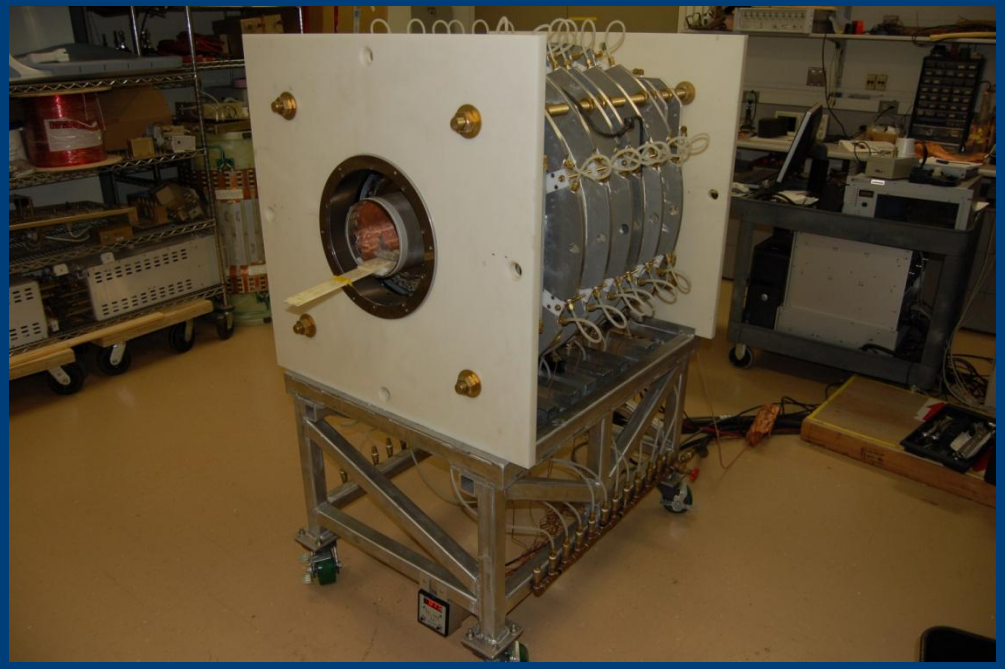


	L_m (μm)	D_T (δ =360μs)	D_L (δ=360μs)	D_T (δ=800μs)	D_L (δ=800μs)
Sham-instilled (n=3)	**86 ± 7**	**0.06 ± 0.06**	0.28± 0.04	0.03 ± 0.03	0.54 ± 0.08
Elastase-instilled(n=4)	**140 ± 46**	**0.14 ± 0.09**	0.25± 0.12	0.03 ± 0.02	0.70 ± 0.10
p-value	**0.0015***	**0.00195***	0.4674	0.5739	0.00933*
Pearson linear regression (P)	**0.0072**				

Conclusion

^{3}He D_T measured at Δ = 360 μs is sensitive to elastase damage in an emphysema rat model, and correlates well with L_m measured from histology.

Preliminary results at 74 mT



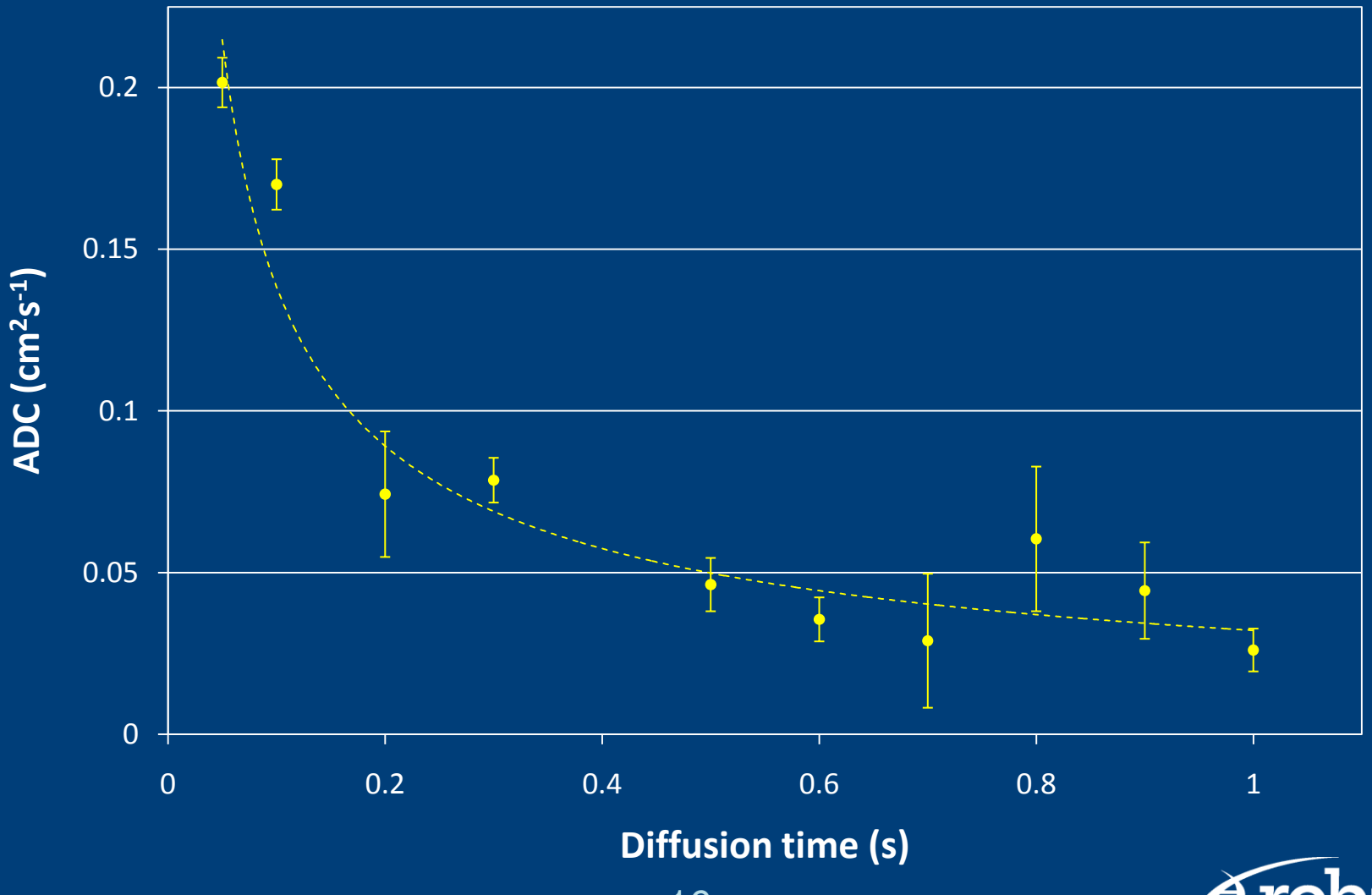
[5]

Long range (Δ = 50 ms – 1 s) whole lung ADCs were measured in 5 healthy Sprague-Dawley rats.

[5]Dominguez-Viqueira *et al*, *Conc. in Magn. Res. Part B*, 2008

Preliminary results

Long range ADC at 74 mT



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Discussion

- Preliminary whole-lung long range ^{3}He ADC data has not shown sensitivity to our disease model.
- Pulmonary ADC mapping must be attempted to provide further conclusions.
- Anisotropic ^{129}Xe ADC sensitivity to an elastase disease model at short diffusion times will be verified using a low field MR system.

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