# Reliability Evaluation of Hyperpolarized 3He Gas Diffusion Models in Lungs in vivo: Wide Range b-value Space

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**Introduction:**

For free diffusion, there is a mono-exponential relationship between the signal attenuation and the b-value for PFG diffusion measurements. In the case of restricted diffusion, such as the diffusion of hyperpolarized $^3$He atoms within the lung, the relationship is no longer mono-exponential, and a variety of models, some purely mathematical and others based on assumptions regarding the underlying geometrical structure of the lung, have been used in the analysis of hyperpolarized $^3$He diffusion data. However, most prior studies have measured the signal attenuation over only a narrow range of b-values. The purpose of this study was to apply the various models to the same set of $^3$He diffusion data from human volunteers to determine the how well each of the models fits actual diffusion actual data over a wide range of b-values.

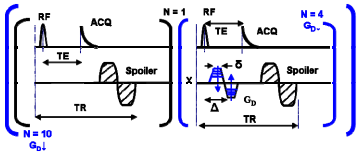


**Figure 1. DWS Sequence**

**Methods and Materials:**

**Diffusion Spectroscopy**: $^3$He diffusion-weighted spectroscopy (DWS) datasets were obtained from 14 healthy volunteers (HY) and three COPD patients on a 1.5T Siemens Sonata MRI system using a $^3$He flexible coil. For each subject, 50 lung spectra were collected (40 diffusion weighted and 10 non-diffusion weighted) using a non-selective 5°, 400 μs Gaussian RF pulse ,TE/TR = 6.2 ms/ 40.5 ms. The diffusion gradient parameters were: bipolar trapezoidal, ramp =0.25 ms, δ=2.35 ms, Δ = 2.75 ms (all fixed), 40 logarithmically sampled b-values : 52 s/cm$^2$ to 0 s/cm$^2$ by varying $G_D$ from 33 mT to 0 mT, direction: A-P during a ~2s s breath hold following the inhalation of 50-80 mL of $^3$He mixed with ~950 mL of nitrogen gas. B-values sampled were (s/cm$^2$): 51.8, 48, 45.7, 42.8, 40.2, 37.7, 35.4, 33.2, 31.3, 31.2, 29.3, 27.5, 25.8, 24.2, 22.7, 22.3, 20,18.8, 15.9, 13.4, 11.4, 9.6, 8.1, 6.9, 5.8, 4.9, 4.1, 3.5, 3, 2.5, 2.1, 1.8, 1.5, 1.1, 0.9, 0.5, 0.2 0.03, 0.01 and 0

**Data Analysis**: Data was processed to obtain signal intensities as described in [2] The models commonly used in analysis of $^3$He ADC imaging *in vivo* were fit to the data: **A**. Two-point model [1]. **B**: Mono-exponential model [2]. **C**. Bi-exponential Model [3] **D** Geometrical model [4] **E**: Kurtosis model [5]. Fitting was done in Matlab (v 7) with '*fmincon*' (B and C) and '*fminsearch*' (D and E), functions To assess the goodness-of-fit for the models B to E, the term **regression residual error** (**RRE**) was defined (Eq 1) where $r_i$ is the fit residual, $y_i$ is the data and N is the number of points. RRE = 0 implies perfect fit, < 1% indicates a good fit while large values implies that the model does not fit the data well.

$$RRE = \sum_{i=1}^{N} \left( \frac{r_i}{y_i} \right)^2 \Big/ N \qquad \textbf{Eq. [1]}$$

**B value Cutoff Experiment**: For model A, ADC was calculated for each of the 39 b-values and b value = 0 s/cm$^2$. For models B to E, since the maximum number of unknowns was 4 (for model C), the minimum number of b-values required would be 4 and consequently, b-value = 0.5 s/cm$^2$ was set as the lower cut-off limit. For each cut-off b-value, models B to E were fit to data {0 to b-value cutoff} and RRE evaluated. For model C, F-statistic and an approximate P value for the significance level (0.05) were calculated with respect to model B. Only those cut-off b-values were accepted for which the F-statistic was significant ($p < 0.05$). For models D, it was observed that the regression function returned error after a minimum cutoff b-value was reached (since the $b_{critical}$ for geometric model is $1/D_{AN}$ [6]) and consequently those cutoff b-values were rejected. For model E, those cut-off b-values were rejected for which the $K_{app} < 0$. For overall analysis, for each model, the minimum cut-off b-value was *set* intersection of the minimum cutoff values, for each volunteer and COPD patient

**Results and Discussion:**

Since the DWS data measurement is global and diffusion in the lung airspaces is restricted, excellent SNR (minimum SNR in HY volunteers = 41±24, and in COPD patients = 15±12) was obtained in human volunteers, even for b values as high as 52 s/cm$^2$. For each model, minimum cutoff b-value obtained after a set intersection: for models: **A** : 0.2 s/cm$^2$, **B** : 1.1 s/cm$^2$, **C** : 6.9 s/cm$^2$, **D** : 8.1 s/cm$^2$, **E:** 4.9 s/cm$^2$ Figures 1 to 10 show the trends seen for models as function of b cutoff.

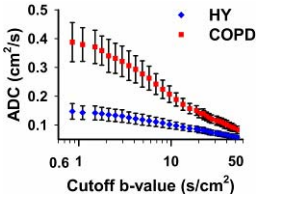


**Figure 1. Model A**

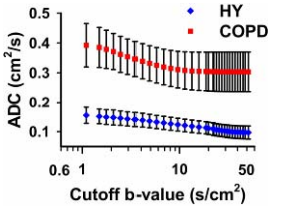


**Figure 2 Model B**

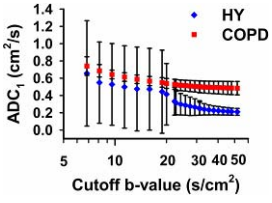


**Figure 3. Model C [ADC1]**

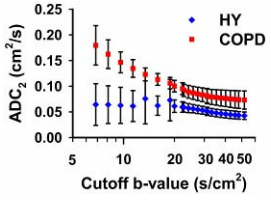


**Figure 4. Model C [ADC2]**

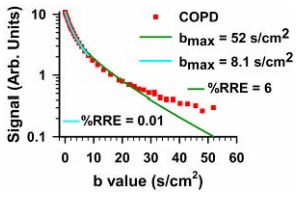


**Figure 5 Model D:COPD**

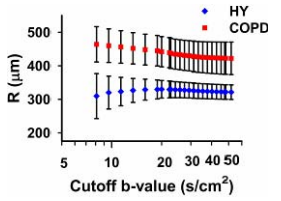


**Figure 6. Model D: [R]**

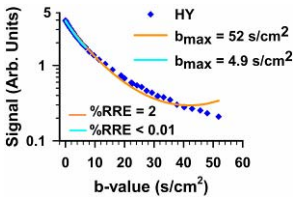


**Fig 7: Model E : Fails at ↑ b**

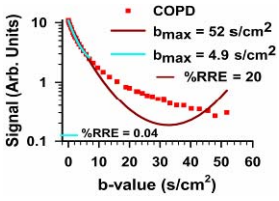


**Fig 8: Model E : Fails at ↑ b**

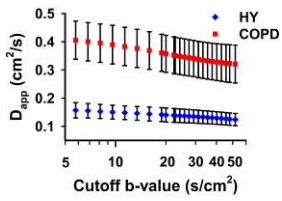


**Fig 9: Model E : [$D_{app}$]**

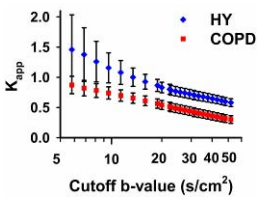


**Fig 10: Model E : [$K_{app}$]**

Overall, with most models, two distinct operating regions are observed, with $b_{cutoff}$ = 20 s/cm$^2$ serving as the critical hinge-point (Fig 11). On the left side of this critical b-value region, the sensitivity for detecting ADC changes in pathology is higher, but with increased intra-group variability. On the right side of this hinge point, the intra-group variability was lower, albeit with lower differences between HY and COPD. For all models, statistically significant differences ($p<0.05$) between HY and COPD were seen for each $b_{cutoff}$. For model B, %RRE increases from < 2% at $b_{cutoff}$ = 20 s/cm$^2$ to > 50% for $b_{cutoff}$ = 52 s/cm$^2$. This suggests that effects of non-Gaussian behavior become apparent at b > 20 s/cm$^2$, and is effectively captured by the bi-exponential model (Fig 3 and 4. For model D, an asymptotic value (~330 μm) was reached for the external radius R for $b_{cutoff}$ = 25 s/cm$^2$ to 52 s/cm$^2$ with a median $b_{cutoff}$ for failure = 5.8 s/cm$^2$. This suggests that for model D, measurements must be done with b-value > 6 s/cm$^2$. For model E, large deviations from data were seen for higher b values (RRE > 2%), which increased in severity for COPD patients (RRE = 19%). Both $D_{app}$ and $K_{app}$ decreased at higher $b_{cutoff}$ along with reduced intra-group CV (from 52% to 10% as $b_{cutoff}$ decreased for $K_{app}$) The failure of models D and E in case of COPD is expected as these models are sensitive to diffusion anisotropy and in case of COPD; anisotropy is progressively lost due to alveolar destruction[4,6]. The decrease in $K_{app}$ with increasing range of $b_{cutoff}$ is consistent with results obtained in kurtosis model from rat lung [6].

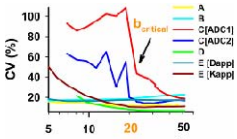


**Fig 11**.

**Conclusion:** A low b-value measurement provides increased sensitivity for detecting COPD, though the measurements with higher b-values improve chances of detecting changes with COPD with greater confidence (narrower 95% confidence intervals). For both geometric and kurtosis models, a critical b-value of ~ 6 cm$^2$/s has to sampled to perform reliable evaluation of lung microstructure.

**References:** [1] Radiology 2002; **222**:252-260. [2]. MRM 1999; **42**:721-728. [3] Proc. of the 13th Annual Meeting of ISMRM, Miami Beach,FL, USA, 2005. **p.51**. [4]. Proc Natl Acad Sci U.S.A, 2002; **99**:3111-3116,.[5]. MRM 2005; **53**:1432-1440 [6]. [6] JMR 2007; **188**:357-366.