Computation of 3He Apparent Diffusion Coefficient in a Simple Model Acinus

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Synopsis: Using a Monte Carlo simulation, the apparent diffusion coefficient (ADC) for ^{3}He has been computed in two very different models of an acinus with a variety of parameters. This work represents an early step toward a quantitative understanding of the physical meaning of ADC measurements. The present simulation results show that ADC is a strong function of the size of the constraining spaces (the alveoli). At the same time, the trends in common between two very different models suggest that ADC can be interpreted even without knowledge of the exact details of the lung structure.

Introduction: The apparent diffusion coefficient (ADC) of hyperpolarized noble gases has been measured in the lungs of patients with emphysema and other lung diseases. Diseased lungs have been shown to exhibit higher ADC compared to healthy lungs. Measured ADC is smaller than the free diffusivity because the gas is confined by the walls of pulmonary airways and alveoli, and because histological studies have already shown larger alveoli in diseased lungs relative to healthy lungs, the lower ADC in healthy lungs is well in line with expectations. Some researchers have hypothesized that ADC is sensitive to early stages of lung disease, before the disease becomes clinically apparent. In order to better understand how physical changes in the lung structure might be manifested in ADC measurements, this work presents initial simulations of ADC in two models which are motivated by the known structure of acini and alveoli. The work is intended to shed light on, 1) the extent to which the details of the acinar model are critical, 2) the extent to which the constrained ADC varies with changes in the free diffusion characteristics (e.g., with changing gas composition during inhalation of a ^{3}He breath), 3) the scaling of ADC with changes in alveolus/airway size during disease progression or inhalation/exhalation, and 4) the surprisingly small change in measured ADC between large and small animals, even as the alveolar volumes change by a factor of ~70.

Diffusion is the result of random interactions between gas molecules. The root-mean-square displacement ℓ of a gas molecule in along a given axis in time τ is given by $\ell = \sqrt{2D\tau}$, where D is the diffusion coefficient or diffusivity. The diffusivity depends on the speed of the diffusing molecule (in this study, the ^{3}He atom) and on the size of the other molecules (nitrogen and oxygen, for example). Larger molecules present a bigger obstacle to a ^{3}He atom crossing the gas sample; thus the diffusivity for ^{3}He in a pure ^{3}He environment has been measured to be 2.05 cm^2/s, but it falls below 0.9 cm^2/s for ^{3}He mixed with nitrogen and oxygen. Diffusion in MRI is measured by application of a bipolar gradient before the readout pulse [1]; the first half of the gradient introduces a position-dependence in the phase of the spins, and the inverse gradient does not perfectly rephase those atoms which have moved during the pulse.

Methods: The simulation tracks atoms from collision to collision for the duration of the bipolar gradient. The velocity of the atom and the time until the next collision are chosen from appropriate random distributions. Each collision is assumed to randomize the velocities of the colliding particles, and collisions are separated by a mean free evolution time of

$$\bar{\tau} = \left(\frac{8}{3\pi}\right)^2 \frac{\sqrt{2}mD}{kT}$$

The phase of the nuclear spin is incremented based on the local magnetic field, *i.e.* based on the position of the nucleus and the time elapsed since the start of the bipolar gradient. A mean diffusivity is computed by computing the phase offset for many particle tracks.

The first model was designed as much for programming simplicity as for realistically modeling the physical structure of the lung. The alveolar ducts are approximated as rectangular solids, with cubic "alveoli" branching off from each face of the duct. Each alveolar duct contains 20 alveoli, and then branches at right angles to the next generation. Each generation was the same size. Three generations were simulated. The length scale is defined by the size of the cubic alveoli. Several length scales were simulated; when the size of an alveolus is changed, the entire "acinus" scales with that change.

The second model is that of Denny and Schroter [2]. The alveoli are approximated as truncated regular octahedrons in a volume-filling arrangement comprised of 2552 unit blocks. Faces of the polyhedrons are removed to give each polyhedron a single path to an exit from the "acinus". Then a simulated annealing algorithm is applied to optimize the path distances from each polyhedron to the exit and the gas-exchange surface area. The details of the optimization are such that several relevant features of histological studies are reproduced. Again the length relevant length scale is the size of an alveolus. Both models were simulated with a length scale of 76 μm, the length scale used by Denny and Schroter. A number of other length scales and a number of diffusivities were simulated.

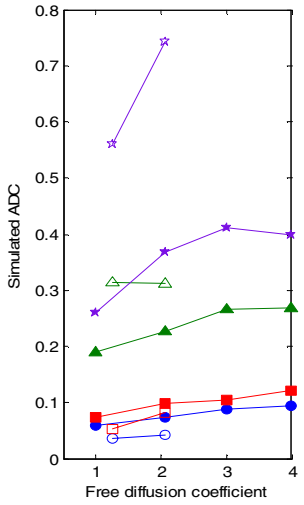

Figure 1. Simulated variation of ADC with free diffusion coefficient in cubic model (open markers) and that of [1] (filled markers) at physiological length scale (blue circles), 30% larger (red squares), 250% larger (green triangles) and 500% larger (purple stars)

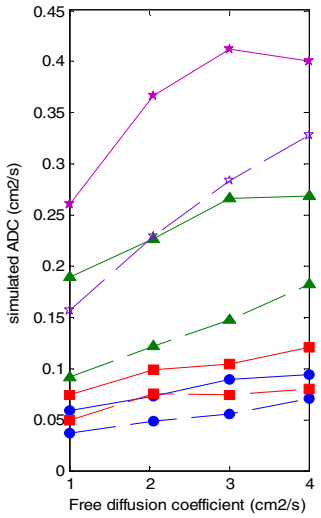

Figure 2. Simulated variation of ADC with free diffusion coefficient with diffusion-sensitizing gradients of 0.5 ms (solid lines) and 1.5 ms (dotted lines) in the acinar model of [1]. This result highlights the experimentally noted decrease of ADC as the tortuous small airways are sampled.

Results and Discussion: The smallest length scale simulated in both models was 76 μm, which was chosen to approximate the measured size of the alveolus in a rat lung, and yet the computed ADC in both models was much smaller than ADC measured in rats. This suggests that either the hyperpolarized gas diffusion MRI does not sample the acinar spaces as expected, or that there is more gas transport between neighboring alveoli than has been previously assumed. A similar result has already been shown in simulations of diffusion in lungs on time scales greater than one second [2]. For highly restricted diffusion, the dependence of ADC on D becomes very weak, justifying the interpretations which ignore changing gas concentrations during inhalation. No significant dependence was found on the orientation of the diffusion-sensing gradients.

Conclusion: Except at very large length scales, general trends in ADC are independent of the details of the model, suggesting that at least for simply connected models, interpretation of ADC results does not require a detailed understanding of lung structure. Measured ADC is significantly larger than ADC computed from either model when the length scale is set to the estimated size of a physical alveolus. The models are consistent with each other but inconsistent with data, and this suggests the assumptions upon which ADC measurement is motivated may have issues which are more fundamental than the exact details of the physical lung structure.

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References:

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