Analytical description of long time scale diffusion MRI of the human lung

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Introduction: Diffusion weighted MRI of the human lung with hyperpolarized noble gas represent a powerful way of probing lung microstructure. Most studies have so far focused on the short diffusion time regime (milliseconds), where the theoretical models of [1,2] can be applied. The long diffusion time regime (seconds) represents an interesting alternative given that long time scale measurements appear to be more sensitive to early changes in emphysema [3,5] and may provide new insights into the role of collateral ventilation [6,9,10]. Here we present an analytical treatment of long time scale DW-MRI of the human lung, based on the symmetric branching geometry of [8]. The theory provides a simple way of understanding how and why the diffusivity may be affected by collateral pathways.

Theory: Long time scale diffusion within the airways of the human lung is modeled as diffusion on a network of connected line segments. We consider exclusively the acinar region given that 90-95% of the gas resides here. Each individual acinus is modeled as a 9 generation binary tree with a spatial configuration given by the symmetric branching geometry [8] i.e. from each line segment (except for the last generation) two new line segments branch off with a fixed branching angle θ in such a way that the parent and its two children lie in the same plane. When the orientation of the line segment representing the transitional bronchiole (first acinar airway) has been specified the position of all subsequent line segments in this acinar model is given by specifying how much each of the above planes have been rotated about the respective parent see Fig. 1. The direction of the i'th line segment is thus given by a unit vector $\mathbf{n}_i$ which depends on these rotation angles. The 3D position $\mathbf{r}$ of a point x (0<x<L) on the i'th line segment is then $\mathbf{r} = L\sum_k \mathbf{n}_k + x\mathbf{n}_i$ where L is the airway length and k runs over all the ancestors of i. The diffusion propagator $P(\mathbf{r}',\mathbf{r};t)$ is found via metric graph theory. $P(\mathbf{r}',\mathbf{r};t)$ is used to derive an analytic expression for the time dependent diffusion coefficient D(t), defined as the mean square displacement in a given direction (here specified by the unit vector $\mathbf{q}$) divided by the double diffusion time. D(t) can be extracted from a Stejskal-Tanner PGSE experiment, which satisfy the narrow pulse and Gaussian phase approximations, in which case D(t) is equal to the time dependent Apparent Diffusion Coefficient ADC. For each acinus we have

$$D(t) = \tfrac{1}{t}\left(\langle(\mathbf{q}\cdot\mathbf{r})^2\rangle - \langle\mathbf{q}\cdot\mathbf{r}\ \mathbf{q}\cdot\mathbf{r}'\rangle\right)$$

where $\langle(\mathbf{q}\cdot\mathbf{r})^2\rangle$ is the radius of gyration in the direction $\mathbf{q}$ i.e. a purely geometric quantity with no time dependence. The time dependent diffusion characteristics enter through the correlation term $\langle\mathbf{q}\cdot\mathbf{r}\ \mathbf{q}\cdot\mathbf{r}'\rangle$. Both $\langle(\mathbf{q}\cdot\mathbf{r})^2\rangle$ and $\langle\mathbf{q}\cdot\mathbf{r}\ \mathbf{q}\cdot\mathbf{r}'\rangle$ are linear combinations of $\mathbf{q}\cdot\mathbf{n}_i\ \mathbf{q}\cdot\mathbf{n}_j$. To get D(t) for the entire lung, we consider an isotropic distribution of acini (i.e. an isotropic distribution of transitional bronchioles) and assume that all spatial configurations within each individual acinus are equally probable, whereby it becomes possible to calculate the ensemble average of $\mathbf{q}\cdot\mathbf{n}_i\ \mathbf{q}\cdot\mathbf{n}_j$ and thus D(t) over all airways of this lung model. The key result is

$$\overline{\mathbf{q}\cdot\mathbf{n}_i\ \mathbf{q}\cdot\mathbf{n}_j} = \begin{cases} \frac{1}{3}\cos(\theta)^m & \text{if } i=j \text{ or } i \text{ is an ancestor of } j \text{ or vice versa} \\ \frac{1}{3}\cos(2\theta)\cos(\theta)^m & \text{otherwise} \end{cases} \qquad (1)$$

where the bar denotes ensemble average and m is the number of airways in the shortest path between the start of airways i and j in the canonical airway tree. The resulting expression for D(t) is independent of direction and has only three free parameters, namely the airway length L, the branching angle θ and the effective line segment diffusion coefficient D_0. Since the ensemble averaged $\langle(\mathbf{q}\cdot\mathbf{r})^2\rangle$ only depend on where the line segments are in space but not how they are connected, this term should not change much if line segments in close spatial proximity are connected via a collateral path. If however the collateral path is such that many gas atoms "find it easier" to move between airways related through a distant ancestor (large m in Eq. 1) these atoms will contribute less to the averaged correlation term $\langle\mathbf{q}\cdot\mathbf{r}\ \mathbf{q}\cdot\mathbf{r}'\rangle$ due to the smaller geometric weight (Eq. 1) and as a result D(t) will increase. Many conceivable collateral pathways do however not satisfy this condition and can thus not be expected to yield a significant effect.

Results: In Fig. 2-3 we compare D(t) with ^{3}He ADC data from a healthy subject found in [4]. The stimulated echo method used in this study is bound to satisfy the narrow pulse approximation, while it is not clear whether the Gaussian phase approximation is fully satisfied for the used 15mm tag wavelength, it does however seem reasonable to assume that the measured ADC is not very far from the empirical D(t). The used airway length of 1.35mm is the best fit by eye. The commonly cited average value is 0.73mm [7]. The value of 20° for the branching angle is likewise the best fit.

Conclusion: We have presented an analytical treatment of long time scale DW-MRI of the human lung, in terms of the time dependent diffusion coefficient, whereby e.g. the role of collateral ventilation may be assessed. Depending on the value of D_0 full agreement between theory and experimental data may require the presence of collateral pathways, this effect is however unlikely to be very dramatic as shown in Fig. 3. In order to make any final conclusions about collateral ventilation more data which satisfy the Gaussian phase approximation is needed. We are currently working on establishing how high D(t) can go as a result of adding collateral pathways. This may allow us to estimate the diffusion time at which there is the greatest sensitivity to collateral pathways and thus potentially to early emphysema.

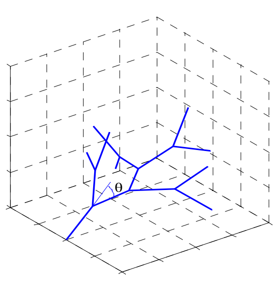

Fig. 1. A realization of the first few airways in the acinar model. The "stem" of the tree is the transitional bronchiole.

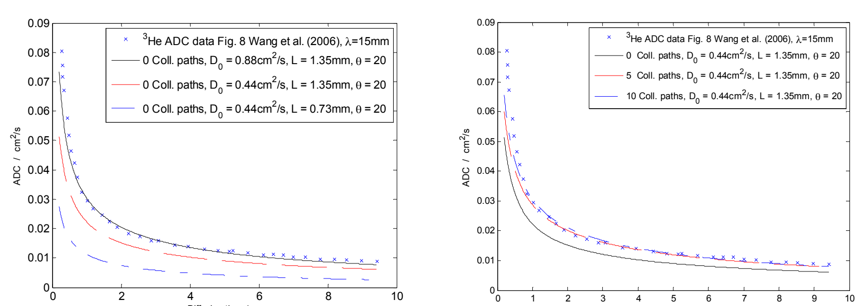

Fig. 2-3. ^{3}He D(t) calculated via the above theory for different parameter values and number of collateral pathways. The main increase in D(t) seen in Fig. 3. is due to a strategic collateral pathway in the third generation. The shown data from [4] has the longest tag wavelength we could find.

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