Modeling the effect of cytoplasm sol-gel transitions on magnetization changes during MRI diffusion experiments in brain gray matter

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Abstract. Reversible sol-gel transitions in the cytoplasm have been proposed to influence the Diffusion Weighted Magnetic Resonance Imaging (DW-MRI) of biological tissue [Branco, 2000]. In the present paper, we aim to model the effect of sol-gel cycles on the DW-MRI signal in brain gray matter. This is accomplished by including oscillations of the intracellular apparent diffusion coefficient (ADC) in a two compartment model (corresponding to intracellular and extracellular spaces) of the generation of the DW-MRI signal [Vestergaard-Poulsen et al., 2007]. Simulations yielded oscillations superimposed to the temporal exponential decay obtained with the Vestergaard-Poulsen model. However, this phenomenon may not be reflected in the usual DW-MRI experiments since it heavily depends on the chosen diffusion time. We conclude that the influence of intracellular ADC oscillations on the DW-MRI signal is obscured by the current recording schemes. Therefore, experiments allowing the recording of the magnetization temporal dynamics are necessary for revealing this effect.

Keywords: MRI diffusion, gray matter, biophysical model, sol-gel

1. Introduction
Since the early 1990s, Diffusion Weighted Magnetic Resonance Imaging (DW-MRI) has assumed an important role both in clinical examinations and in neuroscience research. DW-MRI measurement techniques, such as Pulse Gradient Spin Echo (PGSE), permit a detailed study of self-diffusion in fluids confined in biological tissues. In the PGSE pulse sequence, developed by [Stejskal and Tanner, 1965], two diffusion-sensitizing magnetic field gradients of duration $\delta$ and magnitude $g$ are inserted before the acquisition of the DW-MRI signal. The latter is sensitive to diffusion along the gradients direction during the time lag between both pulses, denoted by $\Delta$. The DW-MRI signal, $S(b)$, also depends on the diffusion parameter $b = (\gamma g \delta)^2 (\Delta - \delta/3)$, where $\gamma$ is the gyromagnetic ratio. In free water, its normalized value, $\hat{S}(b) = S(b)/S(0)$, is used to estimate the bulk diffusion coefficient as $D = - \frac{1}{b} \log[\hat{S}(b)]$. By contrast in biological tissues, membranes and organelles constitute barriers that hinder the motion of the diffusing water molecules. In this case, the directional profile of $\hat{S}(b)$ depends on the tissue microstructure and the estimated diffusion coefficient is termed the Apparent Diffusion Coefficient (ADC) [Le Bihan et al., 1998]. The value of the ADC is always lower than the self-diffusion coefficient in free water [Nicholson and Philips, 1981].

Of particular interest for the study of certain pathologies is the understanding of the biophysical mechanisms underlying the generation of the DW-MRI signal in the PGSE experiment. To account for this, several biophysical models have been proposed [Sen et al., 1981, Mitra et al., 1993, Szafer et al.,...
1995, Stanisz et al., 1997, Hansen and Vestergaard-Poulsen, 2006, Vestergaard-Poulsen et al., 2007]. However these models failed explaining the mechanisms causing the changes of the $ADC$ in these pathologies.

One of the theories put forward states that the $DW-MRI$ signal is influenced by the sol-gel transitions in the cytoplasm of the brain gray matter cells [Branco, 2000]. The cytoplasm comprises two phases: sol (solution) and gel (gelatinous). Triggered by changes in calcium ion concentration, the transition between sol and gel phases depends on reversible cytoskeleton actin polymerization [Hameroff, 1996]. Besides, Nuclear Magnetic Resonance Microscopy revealed that the formation of actin assembly leads to a reduction of water mobility [Pauser, 1996], a process that is periodical with a frequency of 40 Hz or more [Woolf and Hameroff, 2001]. Although the importance for the neural and cellular function of sol-gel cycles in the cytoplasm has been pointed out by many authors since the middle of the nineteenth century [Kühne, 1864; Hardy, 1899, 1900; Chambers, 1917; Bayliss, 1920; Just,1924; Seifriz, 1936; Frey-Wyssling, 1948, 1957; De Robertis et al., 1975, Klunowski, 1988; Miyamoto, 1995; Muallem et al., 1995; Hameroff, 1996, Woolf and Hameroff, 2001], this phenomenon has not been incorporated into any biophysical model of the generation of the $DW-MRI$ signal.

In the present paper we extend the two-compartment model in [Vestergaard-Poulsen et al., 2007], for the generation of the $DW-MRI$ signal in brain gray matter, by including the effect of sol-gel transitions in the cytoplasm of the cells. In our model, intracellular $ADC$ ($ADC_i$) is considered as a dynamic property of the tissue which oscillates with the same frequency of the sol-gel cycle. The dependence of the observation signal (the $DW-MRI$ signal in the PGSE experiment) and the model state variables (the magnetization changes in each compartment) on the frequency of the oscillation, is investigated.

2. Material and Methods

In this section, the Vestergaard – Poulsen (VP) model [Vestergaard-Poulsen et al., 2007] is briefly described. Then, we propose a model of $ADC_i$ oscillations due to sol-gel cycles and include it in the VP model.

2.1 Vestergaard – Poulsen Model

Modeling gray matter

In the VP model each gray matter voxel comprises several basic units. Each unit consists of two compartments: the extracellular space and an intracellular compartment representing neurons and astrocytes. Taking into account that around 80% of the intracellular volume in the gray matter lays within dendrites and axons [Kandel, 2000] the intracellular compartment is represented as a prolate ellipsoid, which is randomly oriented (Fig. 1). In Fig 1C, subscripts $I$ and $E$ denote the parameters corresponding to the intra- and extracellular compartment, respectively. $V_{I,E}$ are the intra and extracellular compartments volumes, which are assumed to be normalized: $V_I + V_E = 1$. The intracellular compartment has a long axis denoted by $a(\parallel)$ and a short axis denoted by $a(\perp)$. The diffusion coefficients $D_I$ and $D_E$ are the free-diffusion coefficients of the intra- and extracellular volume fractions. The compartments have individual $T_2$ relaxation rates, $T_2I$ and $T_2E$. Exchange rates between the compartments are given by $k_I$ and $k_E$, and are interpreted as the inverse of the lifetime of a spin in the corresponding compartment.
Figure 1. Modeling a gray matter voxel. (A) Brain gray matter (B) A gray matter voxel (orange square) consist of several basic units randomly oriented (C) The basic unit comprises intracellular and extracellular volume fractions \( \left(V_{i}, V_{e}\right) \), transverse relaxation times \( \left(T_{1i}, T_{1e}\right) \), free diffusion coefficients \( \left(D_{i}, D_{e}\right) \), exchange rate \( \left(k_{i}, k_{e}\right) \), and geometric parameters \( \left(a(\perp), a(||)\right) \).

**Intracellular diffusion**

The intracellular \( ADC \) \( \left(ADC_{i}\right) \) is calculated using an expression for echo attenuation developed by Tanner [Tanner, 1978] for a PGSE experiment, which consider restricted diffusion between infinite long parallel non permeable membranes with separation distance \( \ell \):

\[
ADC_{i} = \frac{1}{b} \ln \left[ 2 \frac{1 - \cos(\gamma g \delta \ell)}{(\gamma g \delta \ell)^2} + 4(\gamma g \delta \ell)^2 \sum_{n=1}^{\infty} \exp \left(-n^2 \pi^2 D_i \frac{\Delta}{\ell^2}\right) \left(1 - \frac{n}{n^2 \pi^2 - \left(\gamma g \delta \ell\right)^2}\right) \right]
\]  

This is clearly an approximation because the \( VP \) model uses ellipsoids and not parallel membranes, but has been found to be correct within 2% for very prolate ellipsoids [Stanisz et al., 1997; Hansen and Vestergaard- Poulsen, 2006; Vestergaard- Poulsen et al, 2007]. In Eq. 1, \( a(\perp) \) and \( a(||)/2 \) are restriction lengths used for parallel and orthogonal gradient direction (respect to long axis of ellipsoid). The sum in Eq. 1 converges after few terms (only the first five terms are used in the simulations shown in this paper).

**Extracellular diffusion**

The water extracellular motion can be described by a tortuosity coefficient \( \lambda \) [Nicholson and Philips, 1981]. If the free path of water molecules \( \left(D_{e} \Delta \right)^{1/2} \) is longer than the dimension of the cell, the diffusion around the cell can be described by an extracellular \( ADC \) \( \left(ADC_{e}\right) \) given by:

\[
ADC_{e} = D_{e} \left(1 - V_{i}\right)^{1/2} \]  

Since only ellipsoids obstruct the diffusional motion of extracellular water molecules, the \( ADC_{e} \) is calculated as:

\[
ADC_{e} = D_{e} \left(1 - V_{i}\right)^{1/2} \]  

where \( L \) depends on the diffusion gradient orientation with respect to ellipsoids long axis (parallel \( (||) \) and orthogonal \( (\perp) \)):

\[
L_{||} = \ln \left( \frac{2a(||)}{a(\perp)} - 1 \right) \left(\frac{a(\perp)}{a(||)}\right)^2
\]  

\[
L_{\perp} = \frac{1}{2} \left(1 - L_{||}\right)
\]
Exchange between compartments and behavior of the magnetization

In the work of [Kärger et al., 1998] the Chapman-Kolmogorov equations are adapted to describe the behavior of the magnetization due to magnetic resonance echo attenuation in the PGSE experiment and the exchange between compartments. Kärger’s equations were modified by [Hansen and Vestergaard-Poulsen, 2006] and [Vestergaard-Poulsen et al., 2007] to allow for individual $T_2$ relaxation rates $2_I$ and $2_E$, and exchange rates $k_{iE}$ between the compartments.

The system of deterministic differential equations describing the magnetization changes in each compartment is:

$$\frac{d\tilde{M}_I}{dt} = - (\gamma g \delta)^2 ADC_i \tilde{M}_I - k_i \tilde{M}_I + k_E \tilde{M}_E - \left( \frac{1}{T_{2I}} \right) \tilde{M}_I$$

$$\frac{d\tilde{M}_E}{dt} = - (\gamma g \delta)^2 ADC_e \tilde{M}_E - k_E \tilde{M}_E + k_i \tilde{M}_I - \left( \frac{1}{T_{2E}} \right) \tilde{M}_E$$

(5)

Where $\tilde{M}_I$ and $\tilde{M}_E$ denote the transversal magnetization of the intra- and extracellular compartments respectively. If $V_i$ denotes de volume of the compartment $i = (I, E)$ and equal proton densities are assumed in all compartments then $\tilde{M}_i \propto V_i$. At initial time ($t = 0$) when no signal change due to diffusion or relaxation has yet occurred the initial conditions for the magnetizations are then:

$$\tilde{M}_I (t = 0) = V_i$$

$$\tilde{M}_E (t = 0) = V_E$$

(6)

and using the normalization of the volume ($V_i + V_E = 1$) then yields:

$$\tilde{M}_I (0) + \tilde{M}_E (0) = 1$$

(7)

In the steady state, an equal number of spins leave and enter the cells, and the volume of each compartment stays constant. This imposes the following relationship between the exchanges rates:

$$k_i \tilde{M}_I (t = 0) = k_E \tilde{M}_E (t = 0)$$

(8)

After substituting Eq. 8 in Eq. 5 and normalizing the magnetization the following system is obtained:

$$\frac{dM_I (b,t)}{dt} = \left[ - (\gamma g \delta)^2 ADC_i (b) - k_i - \frac{1}{T_{2I}} \right] M_I (b,t) + k_E M_E (b,t)$$

$$\frac{dM_E (b,t)}{dt} = k_i \left( \frac{V_i}{V_E} \right) M_I (b,t) + \left[ - (\gamma g \delta)^2 ADC_e - k_i \left( \frac{V_i}{V_E} \right) - \frac{1}{T_{2E}} \right] M_E (b,t)$$

(9)

Where $M = \frac{\tilde{M}_I}{\tilde{M}_I (t = 0)}$. System given by Eq. 9 has the following analytic solution:

$$M (b,t) = M (b,0) \exp (F(b) t) = \exp (F(b) t)$$

(10)

Where $M (b,t) = \begin{bmatrix} M_I(t) \\ M_E(t) \end{bmatrix}$, the initial condition are $M (b,0) = \begin{bmatrix} 1 \\ 1 \end{bmatrix}$, and:

$$F(b) = \begin{bmatrix} -(\gamma g \delta)^2 ADC_i (b) - k_i - \frac{1}{T_{2I}} \\ k_i \left( \frac{V_i}{V_E} \right) - (\gamma g \delta)^2 ADC_e - k_i \left( \frac{V_i}{V_E} \right) - \frac{1}{T_{2E}} \end{bmatrix}$$

(11)

Signal generation

To obtain the signal observed in a gray matter voxel (where diffusion is mostly isotropic), the approximation proposed by [Szafer et al., 1995] to characterize diffusion in a non-isotropic system by its overall diffusion properties is employed, ignoring the information related to anisotropy.
Approximating the integration over all ellipsoid orientations (Fig 1B) with regard to gradient direction [Hansen and Vestergaard-Poulsen, 2006] yields:

\[ S(b) = \frac{2}{3} S_\perp(b) + \frac{1}{3} S_\parallel(b) \]  

(12)

where:

\[ S_\perp = M_\perp(b, \perp) + M_\parallel(b, \perp) \]
\[ S_\parallel = M_\perp(b, \parallel) + M_\parallel(b, \parallel) \]  

(13)

and for obtaining \( M_{1,E}(b, \perp) \) and \( M_{1,E}(b, \parallel) \) Eq. 10 is evaluated for perpendicular and parallel gradients direction, at time \( t = \Delta \) for each \( b \).

2.2 Influence of sol-gel transitions in the intracellular ADC

In this section we extend the VP model described above to include the effect of sol-gel phase transitions within the cytoplasm of the cells constituting the brain gray matter. For this, we propose the introduction of oscillations in the \( ADC_j \):

\[ ADC_j' = wADC_j \left(1 + \cos(\pi ft)\right) \]  

(14)

Where \( ADC_j' \) is given by equation Eq. 1, \( f \) is the oscillation frequency, and \( w \) is a weight introduced in order to modulate the amplitude of the oscillation. Fig. 2 depicts the typical behavior of Eq. 14 for an arbitrary set of parameters, and represents how the \( ADC_j \) oscillates depending on the state of the sol-gel phase transitions. In the sol phase state (turquoise color zone), the mobility of water molecules is higher than in the gel phase state (tan color zone). Thus, the \( ADC_j \) in the sol state has higher values than in the gel state.

Then, the system of differential equations describing the magnetization changes in each compartment is:

\[
\frac{dM_\perp(b,t)}{dt} = \left(-\frac{\gamma g \delta}{2} ADC_j(b,t) - k_l - \frac{1}{T_{2E}}\right) M_\perp(b,t) + k_l M_\parallel(b,t)
\]

\[
\frac{dM_\parallel(b,t)}{dt} = k_l \left(\frac{V_T}{V_E}\right) M_\perp(b,t) + \left(-\frac{\gamma g \delta}{2} ADC_j - k_l \left(\frac{V_T}{V_E}\right) - \frac{1}{T_{2E}}\right) M_\parallel(b,t)
\]  

(15)

The solution of Eq. 15 is:

\[ M(b,t) = \exp \left(A(b,t) - A(b,0)\right) \]  

(16)

Where:

\[ A(b,t) = \int_0^t F(b,\xi) d\xi \quad \text{(17)} \]

\[
F(b,\xi) = \begin{bmatrix}
-\left(\frac{\gamma g \delta}{2} ADC_j(b,\xi) - k_l - \frac{1}{T_{2E}}\right) & k_l \\
k_l \left(\frac{V_T}{V_E}\right) & -\left(\frac{\gamma g \delta}{2} ADC_j - k_l \left(\frac{V_T}{V_E}\right) - \frac{1}{T_{2E}}\right)
\end{bmatrix}
\]  

(18)

In this case, for obtaining the signal, Eq. 17 is integrated for both gradients directions, in the time interval \( t = [0, \Delta] \) for each \( b \) value.
3. Results

In this section, numerical solutions of the proposed model (from this point onward referred as Model 1) are compared with the VP model. Predictions are derived from the results obtained.

3.1. Simulations

In the simulations presented here, parameters shared by both models have the same values: $V_i = 0.85$, $T_{ii} = 0.02 \text{s}$, $T_{Ei} = 0.1 \text{s}$, $k_i = 0.5 \text{s}^{-1}$, $D_i = 7 \cdot 10^{-4} \text{mm}^2/\text{s}$, $D_k = 3.2 \cdot 10^{-3} \text{mm}^2/\text{s}$, $a(\perp) = 8 \cdot 10^{-3} \text{mm}$, $a(\parallel) = 15 \cdot 10^{-3}$. Diffusion times were: $\Delta/\delta = 0.0355 \text{s}/0.0224 \text{s}$. Due to the introduction of the oscillatory $ADC_i$, in the case of Model 1 there are two additional parameters: $w$, $f$. In this section we will explore the Model 1 for several frequency values and fixed weight: $w = 5$.

Fig. 3 shows the behaviour of the magnetization in the intracellular compartment for the two gradient directions, when varying $b$, for both models. In the case of Model 1 two frequency values, 40 and 40 Hz, were explored. In both models, the magnetization decays in a multi-exponential way, but this decrease is more pronounced in Model 1 for both gradient directions. As seen in the figure, with the increase of $b$ the difference between the two models is accentuated. According to the results, no appreciable differences in the magnetization of the extracellular compartment for each model were obtained, so these variables are not plotted.

As the diffusive process occurs in time (for each $b$ value), for the complete analysis of the mechanisms behind the generation of the signal we need to study the temporal behaviour of the magnetization. Fig. 4 shows the temporal dynamics of the magnetization in the intracellular compartment for $b = 100, 1000, 4000 \text{s/mm}^2$ and both gradients direction. The influence of the oscillatory term on the magnetization is expressed as oscillations superimposed to the multi-exponential decay. These oscillations appear at the frequency of the sol-gel cycles (parameter $f$).

Given the magnetizations shown in Fig. 4, the corresponding diffusion signals (mapped as function of $b$) that would be observed in a PGSE experiment are simulated (see Fig. 5). As seen in figure Fig. 5 the oscillatory effect is not obtained in these signals.
Figure 3. Behaviour of the magnetization in the intracellular compartment for a b value range of 0 – 6000 s/mm² for longitudinal (left) and transversal gradients (right). In the simulation corresponding to Model 1 we use two frequency values: $f = 40, 80$ Hz.

Figure 4. Temporal behaviour of the magnetization in the intracellular compartment for VP and model 1. three different b values: $b = 100, 1000, 4000$ s/mm² and both gradients directions studied for VP model and two frequencies values in the Model 1 ($f = 40, 80$ Hz).
Figure 5. Diffusion signals for Model 1 for two values of \( f \) parameter (\( f = 40, 80 \) Hz) (red and green curve respectively) and VP model (blue curve).

As shown in the simulations, the inclusion of \( ADC_i \) oscillations affects the temporal dynamics of the intracellular magnetization. For studying this phenomenon further we run the same simulation as in Fig. 4 for Model 1 but using three frequency values: \( f = 40, 60, 80 \) Hz, while the other parameters remained fixed. As shown in Fig. 6 the signals don’t follow a clear regularity. That is, after the signal obtained for \( f = 40 \) Hz, instead of the signal for \( f = 60 \) Hz, appears the signal calculated for \( f = 80 \) Hz.

We also analyze the temporal behaviour of the magnetization for a fixed \( b \) (\( b = 2000 \text{s/mm}^2 \)) when varying the frequency. As shown in Fig. 7 the magnetization presents oscillations superimposed in the multi-exponential decay. This effect explains the apparently contradictory result depicted in Fig. 6. From Fig. 7 it is evident that the relationship between the magnetization curves depends on the diffusion time (for the simulations presented in this paper we used \( \Delta = 0.035 \text{s} \) ) at which the magnetization value is registered for a fixed \( b \) value. According to Fig. 7 it is possible to chose a diffusion time in which all the magnetization curves meet (\( \Delta = t \approx 0.021 \text{s} \) ), so it would be impossible to distinguish between the diffusion signals. For \( \Delta = t \approx 0.0145 \text{s} \) only two diffusion signals would overlap (those obtained for \( f = 60 \text{Hz} \) and \( f = 80 \text{Hz} \)).
Figure 6. Signal generated using Model 1 for different frequency values: $f = 40, 60, 80\, \text{Hz}$.

Figure 7. Temporal behaviour of the magnetization in the intracellular compartment for $b = 2000\, \text{s/mm}^2$ and three different frequencies $f = 40, 60, 80\, \text{Hz}$. 
4. Discussion and Conclusions

In this paper we extended a previous biophysical model of magnetization changes in brain gray matter [Vestergaard-Poulsen et al., 2007], by including the phenomenon of sol-gel cycles in the cytoplasm of the cells. We assumed that sol-gel transitions are traduced in $ADC_I$ oscillations. Simulations were carried out for comparing the proposed model (Model 1) with the VP model.

In all performed simulations, we found no significant differences in the magnetization behavior of the extracellular compartment for both models. In the case of the intracellular compartment, for a same $b$ value, Model 1 had a lower magnetization than the VP model. By increasing the $b$ value, the gap increases.

When studying the relationship between the oscillation frequency and the obtained diffusion signal, we found that there was not a clear rule. The explanation for this was found in the temporal dynamics of the magnetization, where oscillations were presented superimposed to the multi-exponential decay. From the results is evident that this phenomenon is highly dependent on the chosen diffusion time. According to this, for certain diffusion times the intracellular magnetizations calculated with different frequencies in Model 1 have the same value. This result in an overlap in the diffusion signals mapped as a function of $b$. In all simulations, the other parameter introduced to model the $ADC_I$ oscillations, the weight $w$ remained fixed. The value of the weight was set to $w = 5$ so that the effect of $ADC_I$ oscillations on the magnetization dynamics could be easily observed. For the sake of simplicity in this work we didn’t introduce a parameter for modelling the phase ($\phi$) of the sol-gel cycles oscillations. In future works, it would be interesting to extend Eq. 14 to consider this parameter:

$$ADC_I = wADC_I (1 + \cos(\pi ft + \phi))$$

The main conclusion derived from this work is that the influence of $ADC_I$ oscillations, evident in the temporal dynamics of magnetization, is obscured by the characteristics of the diffusion signal acquisition scheme. Thus, experiments allowing the recording of the magnetization temporal dynamics are necessary for revealing this phenomenon.

In this paper we included oscillations only in the $ADC_I$. However, variations in volume fractions are also of interest. This will be the subject of a separate publication.

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