Water Movements in Biological Tissue and Diffusion-Weighted Imaging (08frg113)

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1 Introduction

This Focussed Research Group (FRG) was organized with two goals. The first goal was to facilitate the interpretation of results from the state-of-the-art diffusion-weighted magnetic resonance imaging (DWI) technique by using a multi-scale mathematical modeling approach to study the transport of ions and water in biological tissue. The second goal was to utilize more realistic models of water transport in tissues, such as the brain-cell micro-environment, to develop methodologies to refine imaging techniques such as DWI. At the FRG, we took initial steps to achieve these goals by focussing on simple models of apparent diffusion coefficient (ADC) and on cell swelling associated with the clinically important problem called cortical spreading depression (CSD). Cell swelling serves as a case study to explore the issues related to co-transport of ions and water as well as those associated with DWI.

The FRG included applied mathematicians involved in modelling, mathematical analysis, and scientific computing of fundamental problems in fluid dynamics and neuroscience (Huang, Lewis, Miura, Wylie) and biomedical and mechanical engineers and a biomechanician involved in applications to mammalian biological tissue (Sotak, Takagi, Yao).

2 Overview of the Field

Diffusion-Weighted Magnetic Resonance Imaging (DWI) is a powerful tool for the non-invasive measurement of the apparent diffusion coefficient (ADC) of tissue water. The ADC is directly related to the Brownian motion of an ensemble of water molecules and reflects the specific characteristics of the tissue micro-architecture that impose restricting barriers to water diffusion. In addition to normal anatomy, DWI is often used to visualize disease states that affect the tissue micro-architecture in ways that change the net displacement of water molecules (and hence the ADC value).

For example, immediately following the onset of acute ischemic stroke, the rapid failure of high-energy metabolism and associated ionic pumps leads to the migration of sodium and calcium into the cell. The subsequent influx of osmotically-obligated water results in cellular swelling (cytotoxic edema) and a decrease in the extracellular volume fraction. The ADC of brain water declines over the first 1-2 h following stroke onset [6] and allows visualization of the ischemic territory as a hyperintense region on the DW image. In addition to acute ischemic stroke, transient ischemic attack (TIA), ischemic depolarizations (IDs), cortical spreading depression (CSD), status epilepitcus, and hypoglycemia also exhibit cellular swelling (cytotoxic

edema) that reduces the net displacement, and hence the ADC of the tissue water molecules as measured by DWI [11]. Water ADC values are also affected by the presence and orientation of barriers to translational water movements (such as cell membranes and myelin fibers) and thus MRI measures of anisotropic diffusion are sensitive to more chronic pathological states where the integrity of these structures are compromised by disease.

The biophysical mechanisms responsible for these ADC changes are still not well understood. However, the water ADCs are temporally well correlated with the relative changes in intra- and extracellular volume fraction and increased extracellular tortuosity, e.g., as measured independently by electrical conductivity and real-time iontophoretic methods [7]. Furthermore, the transient water ADC changes measured during CSD and IDs suggest that MRI diffusion measurements are also sensitive to chemical communication (e.g., via K^+ or glutamate) between cells through the extracellular space (i.e., extrasynaptic or volume transmission, VT).

3 Recent Developments and Open Problems

The exact connection between cellular swelling and decrease in overall water ADC has not been quantified. Various mechanisms have been proposed to explain changes in tissue water ADC [1, 4], and some analytical models have previously been presented to study restricted water self-diffusion [12, 13]. However, earlier attempts to relate MR signals in DWI with morphologic changes have been either qualitative or based on simple non-realistic geometries, such as cylinders and spheres. For better understanding of the factors that affect water diffusion in biological tissues with more complex morphologies, numerical models have been proposed, such as Monte Carlo (MC) [13] and image-based finite difference (FD) methods [3, 15].

In spite of the theoretical models that have been proposed to date, the fundamental biophysical mechanism responsible for the water ADC changes observed during cerebral ischemia, cortical spreading depression, ischemic depolarizations, status epilepticus, and hypoglycemia remains uncertain. However, it is clear that all of these conditions share the common features of acute cell membrane depolarization and subsequent cell volume changes (cytotoxic edema). A more quantitative understanding of how the underlying tissue pathology manifests in the measured water ADC would be important for clarifying the role of these measurements in characterizing the severity of disease as well as the potential outcome in response to treatment. In this regard, improved theoretical modeling of water diffusion in tissue may play an important role in improving the diagnosis and treatment of these diseases using DWI.

3.1 Some open questions

Model Cell Swelling

1. What is the sensitivity of water ADC changes on parameters such as: intracellular diffusion coefficient (D_{int}), extracellular diffusion coefficient (D_{ext}), cell-membrane permeability, volume fraction, geometry (cell size)? How does the underlying tissue geometry affect the sensitivity analysis of the parameters?

2. Can cell volume changes alone account for all of the percentage-reduction in water ADC observed during CSD or stroke? Can such an analysis be done without making any particular assumptions about the underlying tissue geometry?

3. Given the changes in membrane permeability to ions that accompany CSD, could it be inferred what changes occur in the effective membrane permeability to water that accompanies the osmotic water shifts?

4. From the Goldman-Hodgkin-Katz equation used to model cell membrane potential in CSD, is it possible to get the correct changes in relative volume fraction (due to osmotic swelling) from just the shifts in ions alone (knowing all of the intra- and extracellular ion concentrations both before and after depolarization as well as the channel permeabilities both before and after depolarization)?

5. Based on the volume of the region where reduced ADC is observed by DWI during CSD, it is possible to incorporate this information into a model such that the length scale of the cellular depolarization could be determined? From this length scale, could a "'syncytium size"' be estimated which would correspond to the size of the cell population that is depolarized at any one time during CSD. This would require that both the temporal and spatial aspects of the CSD depolarization be incorporated into the model.

q-Space Analysis

1. Apply the Tanner model to the q-space problem.
2. How should q be chosen, e.g., to estimate higher-order moments?
3. What is the sensitivity of the second-order moment to D_{int}, D_{ext}, permeability, and volume fraction?
4. How can the relationship between the diffusion time and q be exploited to provide additional information about the underlying tissue geometry?
5. What is the effect of noise on the q-space analysis?

4 Diffusion and Displacement Distribution Profile of Water

The data obtained from DWI techniques have typically been interpreted using ideas from diffusion in isotropic homogeneous materials. This effectively means that the techniques are used to estimate a single 'effective' diffusion coefficient that represents an 'effective medium' approximation to the complicated inhomogeneous and anisotropic structure in tissues. This method has been extremely useful in application.

In biological applications, such as the brain, the complex intracellular and extracellular regions that are separated by permeable membranes represent a medium that is far from being either homogeneous or isotropic. Therefore, diffusive processes in the brain differ significantly from those that would be observed in homogeneous and isotropic media. In principle, it is possible to use the data from DWI measurements to determine much more detailed information about the diffusive processes. The natural questions then arise of how much information about the complex structure of the brain can be extracted from the data and how robust is this information to measurement errors. There is also the important question of whether it is possible to extract this information in an acceptable image acquisition time.

4.1 One-, two-, and three-dimensional models

To investigate these questions, we will consider a simple one-dimensional model that contains intra- and extracellular regions that have different sizes and diffusivities and are separated by permeable membranes, and use this as a model for brain tissue. We will determine an exact solution to the diffusion of water in this model environment, and then use this solution to determine the DWI measurements that one would obtain. We will use this data to attempt to reconstruct the parameters that characterize the model system. We will also determine the robustness of this approach when noise is added to the signal. This will allow us to determine what type of information can realistically be obtained from the DWI measurements.

Subsequently, we will extend this model by coupling it to a one-dimensional region of uniform diffusivity containing no boundaries. This region will represent the connected component of the extracellular space, while the original portion of the model will represent the contribution from the diffusive particles that move within and between cells. With this model, it will be possible to separate out the relative importance of the intracellular and extracellular spaces in determining the value of the 'effective diffusion coefficient', and thus, we may use the model to provide insight into the process of cell swelling that occurs in brain ischemia and cortical spreading depression.

We will also consider the diffusion of water in fully two- and three-dimensional cellular media. We will use closed regions within the domain to model the intracellular space. A permeable boundary will separate these regions from a continuously connected region that represents the extracellular space. In this case, it will not be possible to derive an exact solution, and thus numerical approximations will be made. With this model,

we can consider further the questions discussed above. In particular, we will consider how the variation of the anisotropy, in addition to the inhomogeneities, affects the value of the 'effective diffusion coefficient'. Furthermore, we can extend the discussion to include Diffusion Tensor Imaging (DTI), which is an extension of the effective medium assumption that drops the assumption of isotropy while maintaining the assumption of homogeneity.

4.2 Displacement distribution profile

By Fourier transformation of the decay of the DWI signal for water, it is possible to extract the displacement distribution profile. Some models have been set up to simulate water diffusion in tissues, but it is difficult to solve the inverse problem for these models. Since the displacement distribution profile is determined by the movement of intracellular or extracellular molecules, we set up a compartmental (lumped parameter) model based on molecular thermodynamics theory. This model allows us to simulate the displacement distribution profile and to solve the inverse problem.

Suppose the tissue consists of two compartments: the intracellular and extracellular spaces, and water molecules can move between these two compartments. Then the velocity distribution of the water in the tissue can be simplified to give

$$\alpha f(\alpha, v) + (1-\alpha) g(\alpha, v) + \beta h(v) = P(v) \tag{1}$$

where α is the intracellular volume fraction and β is the fraction of water molecules exchanged between the intracellular and extracellular spaces. $f(\alpha, v)$ is the velocity distribution of the intracellular water molecules, and $g(\alpha, v)$ is the velocity distribution of the extracellular water molecules. $h(v)$ is the tissue water molecules without considering cell boundaries. $P(v)$ is the velocity distribution profile that can be inferred from the distribution profile of the DWI, i.e., by dividing the displacement by time t. If we know these velocity distributions, then we can get the optimum values of α and β.

4.3 Theoretical velocity distribution

If these two compartments are homogeneous, then from our knowledge of statistical mechanics, the velocity distribution can be defined by a Maxwell-Boltzmann distribution

$$\phi(v) = C \exp((-Kv^2)/2) \tag{2}$$

where C and K are constants. Obviously, C and K are affected by the volume (or boundary) of the compartment and the tortuosity within the compartment. Therefore, $f(\alpha, v), g(\alpha, v)$, and $h(v)$ can be defined as

$$f(\alpha, v) = C_I(\alpha) \exp((-K_I(\alpha)v^2)/2), \tag{3}$$

$$g(\alpha, v) = C_E(\alpha) \exp((-K_E(\alpha)v^2)/2), \tag{4}$$

$$h(v) = C_W \exp((-K_W v^2)/2). \tag{5}$$

If we can determine expressions for the parameters, $C_I(\alpha), C_E(\alpha), C_W, K_I(\alpha), K_E(\alpha)$, and K_W, and obtain the velocity distribution profile over a short enough time, then we should be able to solve the inverse problem for this model.

5 Comparison of the Predicted Apparent Diffusion Coefficient Using Three Different Models

Although the apparent diffusion coefficient (ADC) is often used to characterize water movement in brain-tissue, the actual phenomenon is not dominated only by the diffusion process. The permeability of water molecules through cell membranes also is an important factor. Since the spatial scale of MRI measurements is much larger than the cell size, the measured ADC is just an indicator to show how far water molecules can spread. There exist several simple models for evaluating macroscopic water movement that take into

Table 1: Parameter values from Latour et al. [4]. a: radius of sphere (cell), ϕ: volume fraction of the extracellular region, c_{int}: water concentration in intracellular region, D_{int}: diffusion coefficient of the intracellular region, D_{ext}: diffusion coefficient of the extracellular region.

Sample	a μm	ϕ	c_{int}	D_{int} $\times 10^{-5}$ cm^2/s	D_{ext} $\times 10^{-5}$ cm^2/s	Permeability $\times 10^{-3}$ cm/s
A	2.1	0.19	0.71	1.56	2.12	6.3±1.4
B	2.1	0.19	0.71	1.56	2.12	3.7±1.4
C	2.3	0.00	0.78	1.64	2.12	1.1

Table 2: Effective diffusion coefficient (D_{eff}) based on three models using permeability coefficient [10^6 cm^2/s] estimated by Latour et al. [4].

Diffusion model	Sample A	Sample B	Sample C
Latour et al.	4.2	3.50	2.70
ADC_{ps}	3.95 (3.71-4.17)	3.50 (3.26-3.73)	2.25
ADC_{sp}	4.10 (3.87-4.32)	3.66 (3.42-3.88)	2.25

consideration the water permeability through membrane. Here, we discuss and evaluate the ADCs obtained using different phenomenological models.

Latour et al. [4] obtained time dependent ADCs based on experiments using red blood cells. They evaluated the permeability of water through cell membranes from the long time asymptotic behavior of ADC. They used Effective Medium Theory and called this long time ADC an effective diffusion coefficient (D_{eff}). The parameters they used and the estimated permeabilities are shown in Table 1.

5.1 Estimation of D_{eff}

Using these values, we evaluated the ADCs using two other models, given in Szafer et al. [13], which are called the Parallel-Series Approximation and the Series-Parallel Approximation. In these models, the ADCs are computed as follows. Let the volume fraction of the intracellular region be $f = 1 - \phi$, and the length of the periodic volume is given by

$$L = \frac{2a}{g} \tag{1}$$

where $g = f^{1/3}$. Define

$$D_{\text{c}} = \left(\frac{2}{PL} + \frac{1}{D_I c_{\text{int}}} \right)^{-1}. \tag{2}$$

The ADC using the Parallel-Series Approximation ADC$_{\text{ps}}$) is given by

$$ADC_{\text{ps}} = g^2 \left(\frac{g}{D_C} + \frac{1-g}{D_E} \right)^{-1} + (1-g^2) D_E \tag{3}$$

and that using the Series-Parallel Approximation (ADC$_{\text{sp}}$) is given by

$$ADC_{\text{sp}} = \left(\frac{g}{g^2 D_C + (1-g^2) D_E} + \frac{1-g}{D_E} \right)^{-1}. \tag{4}$$

It is noted that these formulas, (3) and (4), are slightly different from the original ones, since they have the effect of water concentration in the cell (c_{int}) in D_c given by Eq.(2). This c_{int} is not taken into account in the original formula given in [13]. The comparisons of the effective diffusion coefficients (D_{eff}), i.e., ADCs at large time, are shown in Table 2.

It can be seen that the differences in D_{eff} is less than 5% in Sample A and B, and 20% in Sample C. Since the differences between the models is primarily in the geometric shapes of the cells, these values indicate that the D_{eff} is insensitive to the geometric shape of the cells, provided the same physical parameters are used.

Table 3: Permeability (10^{-3} cm/s) estimation based on three different models using the same effective diffusion coefficient obtained by Latour et al. [4]

Diffusion model	Sample A	Sample B	Sample C
Latour et al.	6.3±1.4	3.7±1.4	11
ADC_{ps}	7.90	3.70	13.9
ADC_{sp}	6.94	2.81	13.9

5.2 Estimation of Permeability Coefficients

We also did another type of analysis; namely, we used D_{eff} obtained from Latour et al. [4] to estimate the permeability coefficients using the models given by Eqs. (3) and (4). The results are shown in Table 3. Interestingly, the estimation of permeability coefficients has a larger error than that in the effective diffusion coefficients. There is more than a 20% difference in some cases.

5.3 Discussion

From the results given above, it is concluded that the estimation of D_{eff} using the same permeability coefficients is less sensitive to the models than is the permeability coefficients when using the same D_{eff}. This characteristic suggests that obtaining the permeability by different experimental means and using them to evaluate apparent diffusion coefficient is a more robust way to probe into scales smaller than the MRI resolution allows.

6 Cell Swelling in CSD

Under pathological conditions such as stroke, the depletion of oxygen due to reduced blood supply leads to failure of ion pumps and a resulting depolarization of the cell membrane potential. Consequently, the intracellular ion concentration increases and water moves into cells due to osmotic pressure and the cells swell. This has been observed by diffusion weighted MRI measurements since cell swelling reduces extracellular space and restricts water diffusion [10]. Understanding the relationship between these pathological conditions and restricted diffusion due to cell swelling could help us to identify regions in the brain at risk and limit further damage. However, since complex biological and biochemical processes typically occur during dramatic pathological conditions, such as stroke, it is difficult to identify cell swelling as the single most important factor to affect the MRI signals. On the other hand, less severe physiological phenomena, which do not involve energy failure, also could lead to cell swelling and alter the characteristics of water movement in the brain-cell microenvironment. Studying these phenomena could provide useful clues for us to understand the underlying biological and biochemical processes involved in cell swelling. Cortical spreading depression is one such phenomenon and is relatively easy to study using diffusion-weighted-imaging (DWI) techniques such as MRI [11].

6.1 Cortical spreading depression

Cortical spreading depression (CSD) is a slowly propagating chemical wave phenomenon observed in the cortex of various brain structures in a diverse set of experimental animals. CSD is characterized by depression of cellular electrical activity and pathological shifts in ion concentrations, e.g., extracellular potassium concentration can reach values as high as 50 mM during CSD. The primary clinical interest in CSD is due to its presence in the visual cortex of humans during migraine with aura (aka classic migraine). Although CSD was discovered in 1944 by the Brazilian neurophysiologist, A.A.P. Leão [5], the mechanisms producing CSD and their quantitative explanations remain elusive.

Some of the mechanisms that are believed to be of importance in CSD instigation and propagation are ion diffusion, cell (neuronal and glial) membrane electrical activities (ionic channels and metabolic pumps), release of neurotransmitter (due to increased extracellular potassium), spatial buffering (effects of electrotonic spread of depolarization along glial cell syncytia), and cell swelling due to osmotic effects. While several

of these effects have been considered in different models, all of them have not been incorporated into a comprehensive model, see [9, 14]. The need for parameter values in quantitative modeling motivates the use of DWI in helping to establish upper and lower bounds on these parameter values.

6.2 Spatially independent model of CSD

During the FRG, it was decided that a first step in a more comprehensive study of CSD would be to construct a spatially independent compartmental model of Hodgkin-Huxley (HH) type. This model would include water movement in the direction of osmotic pressure differences between the intra- and extracellular compartments. The basic model takes the following form

$$\frac{dC_j^E}{dt} = I_j + P_j; \quad \frac{dC_j^I}{dt} = -(I_j + P_j), \tag{5}$$

where C_j^E and C_j^I are the extra- and intracellular ion concentrations, respectively, with j=Na, K, Cl, and Ca for sodium, potassium, choride, and calcium ions, respectively. The ion channel fluxes for Na and K are given by,

$$I_K = g_K(V - V_K), \quad I_{Na} = g_{Na}(V - V_{Na}) \tag{6}$$

where

$$V_j = \frac{RT}{Fz_j} \ln \frac{C_j^E}{C_j^I} \tag{7}$$

is the Nernst potential and R, T, F, and z_j are the universal gas constant, the temperature, Faraday constant, and the valence for ion j, respectively. The cell membrane potential can be computed using either the Goldman-Hodgkin-Katz (GHK) formula

$$V = \frac{RT}{F} \ln \frac{g_{Na}C_{Na}^E + g_K C_K^E + g_{Ca}C_{Ca}^E + g_{Cl}C_{Cl}^I}{g_{Na}C_{Na}^I + g_K C_K^I + g_{Ca}C_{Ca}^I + g_{Cl}C_{Cl}^E} \tag{8}$$

or the Hodgkin-Huxley (HH) equation

$$\begin{aligned} V &= \frac{RT}{F(g_{Na} + g_K + g_{Ca} + g_{Cl})} \\ &\quad \times \left(g_{Na} \ln \frac{C_{Na}^E}{C_{Na}^I} + g_K \ln \frac{C_K^E}{C_K^I} + g_{Ca} \ln \frac{C_{Ca}^E}{C_{Ca}^I} + g_{Cl} \ln \frac{C_{Cl}^I}{C_{Cl}^E} \right). \end{aligned} \tag{9}$$

For the conductance, we use the Hodgkin-Huxley formulas for g_{Na} and g_K given by

$$g_{Na} = \bar{g}_{Na} m^3 h, \quad g_K = \bar{g}_K n^4 \tag{10}$$

where m, h, and n are given by equations in the form

$$\frac{du}{dt} = \frac{u_\infty - u}{\tau_u} \tag{11}$$

with coefficients

$$\tau_u = \frac{1}{\alpha_u + \beta_u}, \quad u_\infty = \tau_u \alpha_u \tag{12}$$

for $u = m$, h, and n, respectively. As a simplification, we assume that the conductance for Cl is a constant, $g_{Cl} = 0.5\bar{g}_K n_\infty^4$ and the calcium conductance is zero, i.e., $g_{Ca} = 0$.

The ion pumps play a crucial role in maintaining homeostatic ion concentrations and cell membrane potential. The basic ion pump is the sodium-potassium exchange pump, which is modeled as

$$P_{Na} = 3\hat{P}, \quad P_K = -2\hat{P} \tag{13}$$

where

$$\hat{P} = 2.01 \times 10^{-3} \left(\frac{C_K^E}{C_K^E + 176.5} \right)^2 \left(\frac{C_{Na}^I}{C_{Na}^I + 0.6} \right)^3 \frac{0.052 \sinh(\gamma)}{0.026 \exp(\gamma) + 22.5 \exp(-\gamma)} \tag{14}$$

with

$$\gamma = \frac{F(V + 176.5)}{RT}.$$

Finally, the volume fraction of the extracellular space, α_E, can be computed using

$$\frac{d\alpha_E}{dt} = g_w \alpha_E^{\frac{2}{3}} \left(\sum_j c_j^E - \sum_j c_j^I - \frac{A_i}{1 - \alpha_E} \right) \tag{15}$$

where g_w is the conductance and A_i is the number of immobile anions inside the cell.

In summary, the above system of ordinary differential equations can be used to compute the evolution of the ion concentrations and membrane potential from a given set of initial data.

6.3 Numerical tests

We use the parameter values, $R = 8.31$, $T = 310$, and $F = 95$, specify the initial conditions as $c_{Na}^E = 145$, $c_{Na}^I = 10$, $c_K^E = 2$, $c_K^I = 140$, $c_{Ca}^E = 1.8$, $c_{Ca}^I = 2 \times 10^{-4}$, $c_{Cl}^E = 110$, $c_{Cl}^I = 5$, $\alpha_E = 0.2$, and set $A_i = (1 - \alpha_E) \sum_j \left(c_j^E - c_j^I \right)$, $g_{Na} = 0.01 g_K$, $g_{Cl} = 0.5 g_K$. Since the effect of calcium on the osmotic pressure is small, we have neglected the effects of Ca by setting $g_{Ca} = 0$, and the conductance for Cl is assumed to be fixed. Finally, we set $\bar{g}_{Na} = 120$ and $\bar{g}_K = 3.6$. The water conductance is set at $g_w = 0.1$.

The numerical results show that using the GHK formula, the membrane will automatically depolarize from about -95 mV to a much higher value and the cell swells. The behavior of the system changes little when KCl is injected except that the cell shrinks initially before swelling. The HH formula for membrane potential, on the other hand, maintains the resting membrane potential (computed based on the initial ion concentrations). Furthermore, when we inject KCl, the membrane depolarizes as expected. However, the cell shrinks instead of swells. Note that there is no recovery in these results because spatial diffusion is not included.

6.4 Discussion

The preliminary studies conducted during the FRG suggest that further modeling is needed. As shown in [8], the GHK and HH formulas for membrane potential are two asymptotic limiting equilibrium cases. Therefore, a dynamic approach which yields more consistent equations for membrane potential and ionic currents is desirable, as indicated by [2].

7 Scientific Progress and Outcome of the Meeting

Comparison of the continuous medium theory of Latour et al. [4] with that of Szafer et al. [13] showed a good correspondence using the permeability data from the Latour et al. paper to predict the water ADC values from the Szafer et al. model. The results of this comparison will be considered for a conference abstract.

The FRG has proved to be a very effective way to bring our group of researchers to a common level of understanding and competence to work together on several different projects related to Water Movements in Biological Tissue and Diffusion-Weighted Imaging. We have identified several interesting problems that will continue to be studied. The group worked together very well and had a very productive week.

List of Participants

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