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A finite difference method with periodic boundary conditions for simulations of diffusion-weighted magnetic resonance experiments in tissue

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Abstract

A new finite difference (FD) method for calculating the time evolution of complex transverse magnetization in diffusion-weighted magnetic resonance imaging and spectroscopy experiments is described that incorporates periodic boundary conditions. The new FD method relaxes restrictions on the allowable time step size employed in modeling which can significantly reduce computation time for simulations of large physical extent and allow for more complex, physiologically relevant, geometries to be simulated.

Keywords

finite difference; diffusion; magnetic resonance imaging; modeling

Physics and Astronomy Classification Systems Code:

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Introduction:

Diffusion-weighted MRI (DWMRI) is a noninvasive means of investigating the microscopic random motion of water in biological tissue. On the timescale of the typical DWMRI experiment (several tens of milliseconds), water diffusion is influenced by many cellular and sub-cellular barriers to motion, e.g. cell membranes, intracellular organelles and macromolecules. Because of this, DWMRI has been used to investigate changes in cellular structure of living tissue, and DWMRI-based biomarkers are used in both pre-clinical and clinical studies. For example, the apparent diffusion coefficient (ADC) calculated from DWMRI has been shown to be a sensitive marker in stroke, where the ADC of affected tissue drops significantly after the onset of ischemia (Moseley et al., 1990, Warach et al.,

1992). The ADC has also been shown to be a biomarker of therapeutic response in breast tumors (Galons et al., 1999, Chenevert et al., 2000, Theilmann et al., 2004, Pickles et al., 2006, Lee et al., 2007, Aliu et al., 2009), hepatic cancer (Cui et al., 2008, Schraml et al., 2009, Kamel et al., 2009, Yu et al., 2009), brain tumors (Chenevert et al., 2000, Moffat et al., 2005), and a variety of other cancers (Thoeny and Ross, 2010). The tissue properties impacting measured values of ADC, however, have yet to be fully defined. In typical DWMRI, voxel sizes are on the order of millimeters and contain a variety of intracellular and extracellular compartments with distinct biological properties, separated by semipermeable barriers. The MR signal measured from water in a single voxel arises from all of these distinct compartments and the magnitude and phase of this signal at the echo time, TE, is dependent on the physical space sampled by the water during the diffusion-weighted experiment. Furthermore, the experimental settings used to measure ADCs, e.g. diffusion time, diffusion gradient duration, TE and b-values, can influence the value of ADC measured (Szafer et al., 1995, Harkins et al., 2009).

To better understand the effects of tissue structure on the ADC, a number of analytical, quasi-analytical, and numerical methods have been developed to solve the Bloch-Torrey equations. Analytical solutions require a number of simplifying assumptions be made about geometry, membrane permeability, and experimental procedures. For example, an analytical solution for DWMRI signal decay for the case of free diffusion was presented early after the development of the DWMRI technique (Stejskal and Tanner, 1965). If the short gradient pulse (SGP) approximation is used, which assumes that no molecular diffusion occurs over the duration of the gradient pulses, simple membrane geometries may be accounted for. For example, by incorporating the SPG approximation, solutions have been found for the cases of diffusion between impermeable parallel plates (Tanner and Stejskal, 1968), inside impermeable spheres (Murday and Cotts, 1968), and for the internal and external spaces of a regularly spaced cubic array of cubic cells with permeable membranes (Szafer et al., 1995). While analytical solutions have proven valuable in efforts to understand diffusive processes in biological tissue, the afore-mentioned assumptions are typically not satisfied in actual experiments. This limits the utility of these analytical solutions. Quasi-analytical methods (Stepisnik, 1981, Callaghan, 1997) allow for the simulation of experiments with arbitrary gradient waveforms. However, when using quasi-analytical methods, the geometries that can be modeled are limited to the same ones that can be considered using analytical methods. This, again, limits the utility of such methods when studying diffusion in biological tissue. Numerical methods (Szafer et al., 1995, Hwang et al., 2003, Hagslatt et al., 2003, Xu and et al., 2007, Hall and Alexander, 2009, Panagiotaki et al., 2010) have been developed which solve the Bloch-Torrey equations in order to simulate DWMRI data for predefined tissue structures.

Numerical methods such as Monte Carlo (MC) methods and finite difference (FD) methods require fewer assumptions in order to solve complex problems. In terms of computational efficiency, MC methods are comparable to FD methods when used to solve the Bloch-Torrey equations. However, a comprehensive comparison of the two methods is beyond the scope of this note. Using FD methods, a wide variety of biophysical properties can be modeled in complex geometries and under realistic experimental conditions. There are, however, significant challenges to overcome when implementing FD methods. FD methods can

require excessive computing time. To evaluate the effect of a particular biological or experimental parameter requires running simulations multiple times with different values of the parameter. Additionally, the Bloch-Torrey equations do not readily lend themselves to the use of periodic boundary conditions when spatially dependent diffusion gradients are applied, and require much larger physical spaces be simulated in order to avoid errors due to edge effects (Hwang et al., 2003). The work presented here addresses these problems by introducing a new FD method that allows the use of periodic boundary conditions.

Theory:

The Bloch-Torrey equations describe the relationship between the time rate of change of the transverse magnetization, M , including the effects of diffusion, applied magnetic field gradients, and T_2 relaxation in a reference frame rotating at the Larmor precession frequency. In one spatial dimension (x), the Bloch-Torrey equation can be written as

$$\frac{\partial M}{\partial t} = \frac{\partial}{\partial x} \left[D \frac{\partial M}{\partial x} \right] - i\gamma G_x(t)xM - \frac{M}{T_2} \quad 1$$

where D is the diffusion coefficient of the molecule carrying the magnetization, γ is the gyromagnetic ratio, $G_x(t)$ is the magnitude of an applied magnetic field gradient, and x defines the location of the magnetization in the x -direction. This may be implemented using an explicit time-forward center-space finite difference scheme as

$$\frac{M_n^{j+1} - M_n^j}{\Delta t} = \frac{D_{(n,n+1)}}{\Delta x^2} (M_{n+1}^j - M_n^j) + \frac{D_{(n,n-1)}}{\Delta x^2} (M_{n-1}^j - M_n^j) - i\gamma G_x(t) \Delta x M_n^j - \frac{1}{T_2} M_n^j \quad 2$$

where n defines a discrete spatial location, i.e. node, on which magnetization can reside, Δx is the spacing between nodes such that $x = n \Delta x$, Δt is the time increment such that $t = j \Delta t$ ($j = \text{integer} > 0$), and $D_{(n,n+1)}$ is the diffusion coefficient between nodes n and $n+1$. In heterogeneous tissue, diffusion coefficients may vary with spatial location. Equation 2 can be interpreted as follows. The first and second terms in the right hand side represent the evolution of magnetization due to diffusion of water molecules between node $n+1$ and node n and between node $n-1$ and node n . The third term gives the phase change of the magnetization due to diffusion gradients and the final term gives the decay due to T_2 relaxation.

The transverse magnetization, M , can be written in the form

$$M = M_{x'} + iM_{y'} \quad 3$$

where $M_{x'}$ and $M_{y'}$ are the orthogonal components of the transverse magnetization. Equation 3 can be substituted into equation 2 and the resulting equation can be separated into real and imaginary parts. Doing this and solving for the updated magnetizations yield the following finite difference schemes (Fletcher, 1988)

$$M_{x'n}^{j+1} = M_{x'n}^j + \left[\frac{D_{(n,n+1)}}{\Delta x^2} (M_{x'n+1}^j - M_{x'n}^j) + \frac{D_{(n,n-1)}}{\Delta x^2} (M_{x'n-1}^j - M_{x'n}^j) + \gamma G_x \right. \\ \left. (t)xM_{y'n}^j - \frac{1}{T_2} M_{x'n}^j \right] \Delta t \quad 4$$

$$M_{y'n}^{j+1} = M_{y'n}^j + \left[\frac{D_{(n,n+1)}}{\Delta x^2} (M_{y'n+1}^j - M_{y'n}^j) + \frac{D_{(n,n-1)}}{\Delta x^2} (M_{y'n-1}^j - M_{y'n}^j) - \gamma G_x \right. \\ \left. (t)xM_{x'n}^j - \frac{1}{T_2} M_{y'n}^j \right] \Delta t \quad 5$$

This method is referred to herein as the standard finite difference (SFD) method. A disadvantage of this method is that M is highly oscillatory if the term $\gamma G_x(t)x$ becomes large. This limits the time step that can be used. To address this limitation, the transverse magnetization can be rewritten as

$$M = m \exp \left[-i\gamma x \int_{t_o}^t G_x(t') dt' \right] \quad 6$$

Where m is the complex amplitude of the transverse magnetization vector, and the integral in the exponent of equation 6 follows the time evolution of the phase of the complex magnetization due to the application of diffusion gradients. Substituting equation 6 into equation 1 results in

$$\frac{\partial m}{\partial t} \exp \left[-i\gamma x \int_{t_o}^t G_x(t') dt' \right] = \frac{\partial}{\partial x} \left[D \frac{\partial}{\partial x} \left(m \exp \left[-i\gamma x \int_{t_o}^t G_x(t') dt' \right] \right) \right] \\ - \frac{1}{T_2} m \exp \left[-i\gamma x \int_{t_o}^t G_x(t') dt' \right]. \quad 7$$

By defining

$$A = \gamma \int_{t_o}^t G_x(t') dt' \quad 8$$

and discretizing equation 7 using an explicit time-forward center-space finite difference scheme yields

$$\begin{aligned} \frac{m_n^{j+1} - m_n^j}{\Delta t} &= \frac{D_{(n,n+1)}}{\Delta x^2} \{ [\exp(-iA^j \Delta x)] m_{n+1}^j - m_n^j \} \\ &+ \frac{D_{(n-1,n)}}{\Delta x^2} \{ [\exp(iA^j \Delta x)] m_{n-1}^j - m_n^j \} - \frac{1}{T_2} m_n^j. \end{aligned} \quad 9$$

The factors $\exp(\pm iA^j x)$ are needed as a result of the spatial dependence of the transformation made in equation 7. Note that in equation 9 the term giving the phase change is absent. If it is assumed that a periodic cubic array of the unit cell considered in the computational domain is representative of the region of tissue under consideration, then m will be periodic as shown by Xu et al. (Xu and et al., 2007). A detailed derivation is included in their work. This method is therefore referred to as the periodic finite difference (PFD) method.

With the substitution

$$m = m_{x''} + im_{y''} \quad 10$$

equation 9 yields

$$\begin{aligned} m_{x''n}^{j+1} &= m_{x''n}^j + \frac{D_{(n,n+1)} \Delta t}{\Delta x^2} [\cos(A^j \Delta x) m_{x''n+1}^j + \sin(A^j \Delta x) m_{y''n+1}^j - m_{x''n}^j] \\ &+ \frac{D_{(n-1,n)} \Delta t}{\Delta x^2} [\cos(A^j \Delta x) m_{x''n+1}^j - \sin(A^j \Delta x) m_{y''n-1}^j - m_{x''n}^j] - \frac{\Delta t}{T_2} m_{x''n}^j \end{aligned} \quad 11$$

$$\begin{aligned} m_{y''n}^{j+1} &= m_{y''n}^j - \frac{D_{(n,n+1)} \Delta t}{\Delta x^2} [\cos(A^j \Delta x) m_{y''n+1}^j - \sin(A^j \Delta x) m_{x''n+1}^j - m_{y''n}^j] \\ &+ \frac{D_{(n-1,n)} \Delta t}{\Delta x^2} [\cos(A^j \Delta x) m_{y''n-1}^j + \sin(A^j \Delta x) m_{x''n-1}^j - m_{y''n}^j] - \frac{\Delta t}{T_2} m_{y''n}^j. \end{aligned} \quad 12$$

The method can be extended to three dimensions.

$$\begin{aligned}
m_{x''n,m,l}^{j+1} = & m_{x''n,m,l}^j + \frac{D_{(n,n+1,m,l)}\Delta t}{\Delta x^2} \left[\cos(A_x^j \Delta x) m_{x''n+1,m,l}^j \right. \\
& + \sin(A_x^j \Delta x) m_{y''n+1,m,l}^j - m_{x''n,m,l}^j \left. \right] \\
& + \frac{D_{(n-1,n,m,l)}\Delta t}{\Delta x^2} \left[\cos(A_x^j \Delta x) m_{x''n-1,m,l}^j - \sin(A_x^j \Delta x) m_{y''n-1,m,l}^j - m_{x''n,m,l}^j \right] \\
& + \frac{D_{(n,m,m+1,l)}\Delta t}{\Delta y^2} \left[\cos(A_y^j \Delta y) m_{x''n,m+1,l}^j + \sin(A_y^j \Delta y) m_{y''n,m+1,l}^j - m_{x''n,m,l}^j \right] \\
& + \frac{D_{(n,m-1,m,l)}\Delta t}{\Delta y^2} \left[\cos(A_y^j \Delta y) m_{x''n,m-1,l}^j - \sin(A_y^j \Delta y) m_{y''n,m-1,l}^j - m_{x''n,m,l}^j \right] \\
& + \frac{D_{(n,m,l,l+1)}\Delta t}{\Delta z^2} \left[\cos(A_z^j \Delta z) m_{x''n,m,l+1}^j + \sin(A_z^j \Delta z) m_{y''n,m,l+1}^j - m_{x''n,m,l}^j \right] \\
& + \frac{D_{(n,m,l-1,l)}\Delta t}{\Delta z^2} \left[\cos(A_z^j \Delta z) m_{x''n,m,l-1}^j - \sin(A_z^j \Delta z) m_{y''n,m,l-1}^j - m_{x''n,m,l}^j \right] \\
& - \frac{\Delta t}{T_2} m_{x''n,m,l}^j
\end{aligned} \tag{13}$$

$$\begin{aligned}
m_{y''n,m,l}^{j+1} = & m_{y''n,m,l}^j + \frac{D_{(n,n+1,m,l)}\Delta t}{\Delta x^2} \left[\cos(A_x^j \Delta x) m_{y''n+1,m,l}^j \right. \\
& - \sin(A_x^j \Delta x) m_{x''n+1,m,l}^j - m_{y''n,m,l}^j \left. \right] \\
& + \frac{D_{(n-1,n,m,l)}\Delta t}{\Delta x^2} \left[\cos(A_x^j \Delta x) m_{y''n-1,m,l}^j + \sin(A_x^j \Delta x) m_{x''n-1,m,l}^j - m_{y''n,m,l}^j \right] \\
& + \frac{D_{(n,m,m+1,l)}\Delta t}{\Delta y^2} \left[\cos(A_y^j \Delta y) m_{y''n,m+1,l}^j - \sin(A_y^j \Delta y) m_{x''n,m+1,l}^j - m_{y''n,m,l}^j \right] \\
& + \frac{D_{(n,m-1,m,l)}\Delta t}{\Delta y^2} \left[\cos(A_y^j \Delta y) m_{y''n,m-1,l}^j + \sin(A_y^j \Delta y) m_{x''n,m-1,l}^j - m_{y''n,m,l}^j \right] \\
& + \frac{D_{(n,m,l,l+1)}\Delta t}{\Delta z^2} \left[\cos(A_z^j \Delta z) m_{y''n,m,l+1}^j - \sin(A_z^j \Delta z) m_{x''n,m,l+1}^j - m_{y''n,m,l}^j \right] \\
& + \frac{D_{(n,m,l-1,l)}\Delta t}{\Delta z^2} \left[\cos(A_z^j \Delta z) m_{y''n,m,l-1}^j + \sin(A_z^j \Delta z) m_{x''n,m,l-1}^j - m_{y''n,m,l}^j \right] \\
& - \frac{\Delta t}{T_2} m_{y''n,m,l}^j
\end{aligned} \tag{14}$$

Methods:

To assess the relative computational performance of the SFD and PFD methods, relative computational time was estimated by calculating the parameter t_{max} for each model for several node spacings. We define t_{max} to be the maximum time step allowed by the model within which stability and accuracy (to specified precision) is achieved. The advantages of the PFD method are the greatest when relatively large gradient strengths are used, like those implemented in oscillating gradient diffusion experiments (Schachter et al., 2000). The following comparisons of t_{max} allowed by the SFD and PFD methods are given for a

sinusoidal oscillating gradient diffusion simulation. A sinusoidal wave form with 25 periods of 1 ms each was used. The diffusion coefficient was set to $3 \mu\text{m}^2/\text{ms}$ and a b-value of $0.3 \text{ ms}/\mu\text{m}^2$ was used. The right hand sides of equations 4, 5, 11 and 12, contain terms proportional to t . Each of these terms represents the effect on the magnetization of a particular process, e.g. exponential decay due to T_2 , phase accumulation due to applied gradients, and the effects of diffusion. Each imposes limits on the time step used in simulations for stability and accuracy, as discussed in the following.

The terms $-t_{\max}M/T_2$ in the SFD method and $-t_{\max}m/T_2$ in the PFD method approximate exponential MR signal attenuation due to the dephasing of transverse magnetization (T_2 relaxation). The constraint imposed on $t_{\max}$ in the SFD and PFD methods by the T_2 relaxation term requires that $t_{\max} \ll T_2$. Because we are only interested in species of protons with T_2 s on the order of tens of millisecond this constraint does not significantly limit the time step and is not considered further.

The impact of the value of $t_{\max}$ on the accuracy of the estimates for phase accumulation processes was assessed. To do so, the time evolution of the magnetization due to the application of diffusion gradients in the absence of diffusion was calculated using the analytical expression

$$m_A = m_0 \exp \left[-i\gamma L_x \int_{t_0}^t G_x(t') dt' \right], \quad 15$$

where m_0 is the complex magnetization at t_0 and L_x is the distance to the edge of the simulation boundary from the center of the grid (i.e. where the gradient in the diffusion direction is zero). The time evolution of the magnetization is then estimated using the SFD method. The magnetization after the j^{th} time step due to repeated application of the explicit time stepping procedure is

$$m_E^J = m_0 \prod_{j=0}^{J-1} (1 - i\gamma G_x^j L_x \Delta t) \quad 16$$

where G_x^j is the diffusion gradient strength at the j^{th} point in time and the total time of the experiment $t = J \Delta t$. The error in the estimated magnetization phase is calculated using

$$\varepsilon = |m_A - m_E^J| / |m_A|. \quad 17$$

$t_{\max}$ was determined for a given nodespacing, Δx , and physical simulation length, L_x , by varying Δt until $\varepsilon < 0.0500$ for the oscillating gradient diffusion experiment described above.

Terms $(D \Delta t / \Delta x^2)$ which estimate changes in the magnetization due to diffusive processes are found in both the SFD method, and the PFD method. In order to ensure the stability of these calculations, $t_{\max}$ must be chosen such that the Courant-Friedrichs-Lewy condition is satisfied, i.e.,

$$\Delta t_{\max} \leq \frac{\Delta x^2}{CD}$$

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where $C = 2$ for a one-dimensional simulation, 4 for two dimensions, and 6 for three dimensions. It is important to note that increasing the dimensionality when using a FD method to simulate a diffusion experiment decreases $t_{\max}$. In the SFD method, for a given node spacing, it will be shown that there is a model size for which the oscillatory term adds a more stringent restriction on the value of $t_{\max}$ than the restriction which is required by the diffusive term. In contrast, in the PFD method, the diffusive terms always impose the most stringent restriction on $t_{\max}$.

Results and Discussion:

Comparisons of the $t_{\max}$ allowed by the constraints imposed by the phase and diffusive terms are shown in Figure 1. The constraints on $t_{\max}$ are clearly dependent on both the size of the physical space being simulated (L_x) and the node spacing used in the simulation. At a node spacing of 0.1 μm (Fig. 1A), the diffusive term sets the limit on the allowable $t_{\max}$ up to a simulation size of 9.5 μm , and neither the PFD nor the SFD offer any advantage. Above that size, however, the SFD requires a smaller $t_{\max}$. At node spacings of 0.2 μm (Fig. 1B) and 0.5 μm , the simulation size where the PFD has an advantage over the SFD is reduced to 4.5 μm and 1.5 μm , respectively. Figure 1D shows the ratio of the PFD method $t_{\max}$ and the SFD method $t_{\max}$ for 0.1, 0.2, and 0.5 μm node spacing as a function of the physical size of the space being simulated. Using the PFD method, for simulations of physically realistic experiments, the diffusive term always limits the maximum size of the usable time step. However, when using the SFD method, there is a maximum physical extent for the simulation at which the term that approximates the phase of the magnetization drives down the maximum size of the time step that can be used while keeping that approximation valid.

To test the accuracy of the PFD Model, simulations were carried out and compared to those of a previously published FD method (Harkins et al., 2009). 3D PFD simulations were implemented in C and CUDA (Nvidia). In these simulations, tissue was modeled as $10\mu\text{m} \times 10\mu\text{m} \times 10\mu\text{m}$ cubic cells, in a cubic lattice with a cell spacing of 10.8 μm . A node spacing of 0.2 μm was used. T_2 relaxation times were set to 150 ms and diffusion coefficients were set to 3.0 $\mu\text{m}^2/\text{ms}$ at all locations. Membrane permeabilities of 0.1 and 0.01 $\mu\text{m}/\text{ms}$ were simulated as well as infinitely permeable (free diffusion) and completely impermeable membranes. Both FD and PFD methods simulated diffusion experiments with TE = 80 ms and diffusion time = 50 ms. The FD method used by Harkins et al. necessarily assumes the SGP approximation. To allow comparison of the two methods, diffusion gradient durations of 0.0005 ms were used in the PFD method. Analytical solutions are only applicable in the case of free diffusion, and completely impermeable membranes. Representative results of these simulations are shown in Figure 2, where MR signal as a function of b -value is plotted. Where analytical solutions are found, the methods are in good agreement with each other and with the analytic solution.

Where there is no analytical solution, i.e. when finite permeability is incorporated, the methods are in very good agreement with each other. Table 1 lists the values of the ADC calculated from the decay of signal for each condition simulated. ADCs were determined by fitting simulated data to a single exponential decay between b -values of 0 and $1 \mu\text{m}^2/\text{m}$. The ADCs calculated from the methods are very similar, differing at most by 0.5%, as in the case of impermeable membranes.

A major limitation of the FD method used by Harkins et al. is its reliance on the SGP approximation. As mentioned previously, the SGP approximation is almost never valid in clinical DWMRI experiments. Figure 3 shows a representation of the gradient waveforms of three different MR pulse sequences. In the first experiment, the diffusion gradients are short ($\delta = 0.00001 \text{ ms}$) compared to their separation ($\tau = 50 \text{ ms}$). In this case the SGP approximation is valid. In the second experiment, the diffusion gradient waveform has $\delta = 5 \text{ ms}$ and $\tau = 50 \text{ ms}$. In this case $\delta/\tau = 0.1$ and the validity of the SGP approximation would be questionable. In the third experiment, the diffusion gradient waveform has $\delta = 20 \text{ ms}$ and $\tau = 50 \text{ ms}$. In this case $\delta/\tau = 0.4$ and the SGP approximation is clearly violated. Because the PFD method does not require the SGP assumption, the effects of finite diffusion gradients can be assessed. Simulations of one-dimensional water diffusion between impermeable barriers were carried out using the PFD method under the three experimental conditions described above. The results of those simulations are plotted in Figure 4 and compared to the analytical solution for signal attenuation due to diffusion between two completely impermeable parallel plates. Table 2 lists the ADCs determined from these simulations by fitting signal attenuation between $b = 0$ and $1 \mu\text{m}^2/\text{m}$. The simulations demonstrate that, in a restricted geometry, the use of longer diffusion gradient durations results in a lower measured ADC.

This effect has been known for some time and has been dealt with in many ways (Coy and Callaghan, 1994; Linse and Sodeerman, 1995; Mitra and Halperin, 1995; Cohen and Assaf, 2002; Bar-Shir, 2008; Aslund and Topgaard, 2009). The PFD method was also compared to a FD method reported by Xu et al. (Xu et al., 2007) which implements revised periodic boundary conditions, herein referred to as the revised periodic boundary condition (RPFD) method. The RPFD method estimates the effects of diffusion, applied gradients, and T_2 dephasing by breaking the calculation into two distinct parts. First, for each time step, the effects of diffusion on the magnetization are estimated. Then, the magnetization at each node is multiplied by the appropriate analytical expression in order to take into account the effects of diffusion gradients and T_2 dephasing over the time step. This is in contrast to the PFD method where all effects over a time step are estimated by a single expression. In the RPFD method, periodic boundary conditions are applied by matching the magnetization phase at one end of the domain with that at the other end with a phase shift. Results of comparison 1D simulations, implemented in MATLAB, between the PFD and RPFD method are shown in Figure 5. The length of the space being simulated was $10 \mu\text{m}$, a diffusion coefficient of $3 \mu\text{m}^2/\text{ms}$ was used, rectangular diffusion pulses were implemented with a diffusion gradient duration of 20 ms , a diffusion time of 50 ms was used, nodes were spaced at $0.2 \mu\text{m}$, and a single impermeable membrane was simulated in the center of the space. Table 3 Lists the ADCs calculated from the simulated signal decay between $b = 0$ and $1 \mu\text{m}^2/\text{m}$. The two methods are in excellent agreement.

A comprehensive comparison of these two methods is beyond the scope of this note and the relative advantages of each method could depend on a number of parameters, including the specific type of hardware employed in the computations.

Conclusion:

The PFD method described in this paper employs truly periodic boundaries and enables simulation of realistic DWMRI experiments. The use of periodic boundary conditions and the relaxed constraints on maximum allowable time step size allow for more rapid simulations compared to a more direct SFD method. Advantages of the PFD will be maximized in simulations of structures with large spatial extent, e.g. >10 microns. With continued advances in computational power, the use of the PFD method may allow for more accurate simulations of diffusion in tissue where larger physical extent can be modeled with a greater numbers of experimental and biological parameters.

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Figure 1.

Comparison of $t_{\max}$ for the phase estimation term found in the SFD method, $t_{\max}$ for the phase term found in the PFD method, and $t_{\max}$ for the estimation of diffusive effects found in both methods. Comparisons were done for a node spacing of A) $0.1 \mu\text{m}$, B) $0.2 \mu\text{m}$, and C) $0.5 \mu\text{m}$. Figure 1 D) shows the ratio of $t_{\max}$ for the PFD method to $t_{\max}$ for the SFD for the three node spacings. Note that as node spacing increases this ratio becomes greater than 1 at lower values of L_x and $t_{\max}/L_x$ is larger.

Figure 2.

Comparison of the PFD method and the FD method used by Harkins et al for a 3D cubic lattice of cubic cells. The FD method used by Harkens et al assumed the SGP approximation. A δ/ϵ of 0.00001 was in simulations run using the PFD method so that the SGP approximation was satisfied. The solid line represents the theoretical signal decay as a function of b-value for free diffusion. The methods are in very good agreement.

Figure 3. Graphical representations of three pulse sequences simulated using the PFD method. Pulse sequences with a δ/τ of 0.00001 (top), a δ/τ of 0.1 (middle), and a δ/τ of 0.4 (bottom) were simulated.

Figure 4. Signal attenuation as a function of b-value for rectangular gradients using a δ/Δ of 0.00001, 0.1, and 0.4. The solid line represents the theoretical signal decay as a function of b-value for diffusion between impermeable parallel membranes under the SGP approximation. The decrease in signal attenuation with increasing δ/Δ suggests that using methods that assume the SGP approximation to analyze data leads to an underestimation of the calculated ADC.

Figure 5.

Comparison of the RPF method and the PFD method for a 1D model of diffusion. Simulations were run for diffusion between impermeable parallel membranes, parallel membranes with a permeability of 0.1 $\mu\text{m}/\text{ms}$, and free diffusion. A δ/λ of 0.4 was used. The solid line represents the theoretical signal decay as a function of b-value for free diffusion. The methods are in excellent agreement. Only one set of symbols for each gradient duration can be seen because differences between the results obtained using the RPF method and those obtained using the PFD method were negligible.

Table 1.

Calculated ADCs from the FD and PFD methods at different values of membrane permeability

Method	Permeability ($\mu\text{m}/\text{ms}$)			
	Free Diffusion	0.1	0.01	0.0*
ADC ($\mu\text{m}^2/\text{ms}$)				
PFD	3.0	0.982	0.485	0.390
FD	3.0	0.966	0.472	0.378

*
impermeable membranes

Table 2.

Calculated ADCs from the PFD method at different diffusion gradient durations

δ	ADC ($\mu\text{m}^2/\text{ms}$)
0.0 [*]	0.170
0.00001	0.170
0.1	0.111
0.4	0.0535

^{*}The SGP approximation assumes infinitesimal diffusion gradient duration

Table 3.

Calculated ADCs from the PFD and RPFD methods at different values of membrane permeability

Method	Permeability ($\mu\text{m}/\text{ms}$)		
	Free Diffusion	0.1	0.0
ADC ($\mu\text{m}^2/\text{ms}$)			
PFD	3.00	0.716	0.0535
RPFD	3.00	0.716	0.0535