Computational Model of NMR Molecular Dynamics for the Analysis of Blood Brain Barrier

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Abstract. In recent years, tremendous attention, and efforts are focused on the development of novel drug delivery systems to improve health care. Substantial improvement of current therapies has necessitated the use of therapeutic modalities that allow for efficient and site-specific transport of drugs to the target tissues. However, there are enormous barriers that a drug molecule must overcome before it reaches its target site within the body. Therefore, discovery of new modalities allowing for effective drug delivery to the brain and central nervous system (CNS) is of great need and importance for treatment of neurodegenerative disorders. In this study, we have solved the time dependent Bloch NMR flow equation analytically for the analysis of glucose content, total protein content and blood cell count in the CNS and brain using MRI experimental data. The associated Laguerre polynomials obtained are applied to evaluate biological flow in the central nervous system. The application of fluid velocity, the NMR relaxation times and the path length for biological flow in the central nervous system are demonstrated.

Keywords: Bloch NMR flow equation, Biological flow, Laguerre polynomials, brain, drug delivery, central nervous system

1 Introduction

The principal reason for the rapid growth of research interest in NMR molecular dynamics for the analysis blood–brain barrier (BBB) is the realization that substantial improvement of current therapies will be crucial for the development of new therapeutic modalities allowing for efficient and site-specific transport of drugs to the target tissues affected by disease [1]. This is because of the enormous barriers that drug molecules need to overcome before it reaches its target site. The BBB has an important feature which proves to be a challenge in effective site – specific drug delivery. This feature is a barrier which impedes the entry of compounds into the brain from the periphery [1] and consequently, many low molecular weight drugs as well as bio-macromolecules, such as DNA and proteins, for treatment of neurological diseases, cannot easily be utilized [1]. The low permeability of the BBB is attributed, in large part, to the brain micro-vessel endothelial cells, which form tight extracellular junctions with low pinocytic activity [1 - 3]. Passive diffusion of substances across the brain microvessel endothelial cells may occur depending on the lipophilicity and molecular weight of these substances. Aside from approaches that cause short-term disruption of the BBB, drug delivery systems need to improve the transcellular routes of drug transport through the micro-vessel endothelial cells [1]. Therefore, discovery of new modalities allowing for effective drug delivery to the central nervous system (CNS) is of great need and importance for treatment of neurodegenerative disorders [1]. Currently, three relatively new approaches for improving drug transport through the BBB have been described [1]:

(i) inhibition of drug efflux transporters in BBB by amphiphilic block copolymers

(ii) using receptor-mediated transport of drugs encapsulated into nanoparticles, and

(iii) artificial hydrophobization of peptides and proteins by fatty acid residues.

The BBB is the separation of circulating blood from the brain extracellular fluid in the central nervous system [4, 5]. It occurs along all capillaries and consists of tight

junctions around the capillaries that do not exist in normal circulation [4]. Endothelial cells restrict the diffusion of microscopic objects (e.g., bacteria) and large hydrophilic molecules into the cerebrospinal fluid (CSF), while allowing the diffusion of small hydrophobic molecules (O_2, CO_2, hormones). Therefore, a molecular analysis of CSF could be very vital in accessing blood brain barrier and every change that occur around them [4].

In this investigation, the Bloch NMR flow equation [6 - 9] has been solved analytically in terms of the associated Laguerre polynomials to obtain the NMR transverse magnetization for the analysis of biological flow in the central nervous system. The motivation for this is that amphiphilic block copolymers and fatty acid polymers both have hydrogen protons which are always available for magnetic resonance [10]. In addition to this, NMR nanoparticles can be easily developed [11] for specific neurological drug discovery. This shows that magnetic resonance may prove to be very important within the framework of current approaches for improving drug transport through the BBB.

Delivering therapeutic agents to specific regions of the brain has proved to be majorly challenging to treatment of most brain disorders [12]. In its neuroprotective role, BBB functions to hinder the delivery of many potentially important diagnostic and therapeutic agents to the brain. Therapeutic solutes and antibodies that might otherwise be effective in diagnosis and therapy are unable to cross the BBB in adequate amounts [12]. Mechanisms for drug targeting in the brain involve going either "through" or "behind" the BBB. Modalities for drug delivery/Dosage form through the BBB entail its disruption by osmotic means; biochemically by the use of vasoactive substances [11]. Other methods used to get through the BBB may entail the use of endogenous transport systems, including carrier-mediated transporters such as glucose and amino acid carriers; receptor-mediated transcytosis for insulin or transferin; and the blocking of active efflux transporters such as p-glycoprotein.

The role of this study in overcoming these challenges rests in the fact that different solutes (including different kinds of designed proteins) have unique hemodynamic and magnetic resonance relaxation parameters. Fortunately, these parameters have being shown by the solutions presented above to determine the value of the transverse

magnetization under several conditions. Secondly, it is worthy of note that T_2 significantly changes [13] when molecular interaction changes. That is, the interaction of drugs with local solutes around the BBB and with receptor sites can easily be captured in a well defined parameter that has direct influence on MRI signal. Furthermore, temporary or permanent disruption to the BBB integrity affects the radius of the space through which the drug or solutes are expected to pass.

2 The General Bloch NMR Flow Equation

When polymers and NMR sensitive nanoparticles are placed within a magnetic field B_0 and RF field is applied to induce spin excitation, the spins move dynamically about the magnetic fields. This spin dynamics is described by the Bloch NMR flow equations [14-16] and can be written as:

$$\frac{\partial M_x}{\partial t} + v\frac{\partial M_x}{\partial x} = -\frac{M_x}{T_2} \tag{1a}$$

$$\frac{\partial M_y}{\partial t} + v\frac{\partial M_y}{\partial x} = \gamma M_z B_1(x) - \frac{M_y}{T_2} \tag{1b}$$

$$\frac{\partial M_z}{\partial t} + v\frac{\partial M_z}{\partial x} = -\gamma M_z B_1(x) + \frac{M_o - M_z}{T_1} \tag{1c}$$

From equation (1b, 1c), we have [12-14]:

$$v^2\frac{\partial M_y}{\partial x^2} + 2v\frac{\partial^2 M_y}{\partial x \partial t} + v\left(\frac{1}{T_1}+\frac{1}{T_2}\right)\frac{\partial M_y}{\partial x} + \left(\frac{1}{T_1}+\frac{1}{T_2}\right)\frac{\partial M_y}{\partial t} +$$
$$\frac{\partial^2 M_y}{\partial t^2} + \left(\frac{1}{T_1 T_2} + \gamma^2 B_1{}^2(x,t)\right)M_y = \frac{\gamma B_1(x,t) M_o}{T_1} \tag{1d}$$

Equation (1d) is a general second order differential equation which can be applied to any NMR fluid flow problem. At any given time t, we can obtain information about the system, provided that appropriate boundary conditions are applied. Starting from equation (1d), we can assume a solution of the form:

$$M_y(x,t) = Ae^{\mu x+\eta t} \tag{1e}$$

subject to the following theoretical conditions(RF limit): $\gamma^2 {B_1}^2(x,t) << \frac{1}{T_1 T_2}$

where μ and η are dependent on the NMR parameters. Taking $\eta^2 = T_g$ and $2\eta = T_o$

Equation (1d) becomes: $v^2 \frac{\partial^2 M_y}{\partial x^2} + T_o \frac{\partial M_y}{\partial t} = F_o \gamma B_1(x,t)$ (1f)

$$\frac{\partial M_y}{\partial t} = D\frac{\partial^2 M_y}{\partial x^2} + \frac{F_o}{T_o}\gamma B_1(x,t) \tag{1g}$$

Provided $D = \left|\frac{v^2}{T_o}\right|$ (1h)

This can be written in generalized coordinate system as:

$$\frac{\partial M_y}{\partial t} = D\nabla^2 M_y + \frac{F_o}{T_o}\gamma B_1(t) \tag{1i}$$

where $F_o = \frac{M_o}{T_1}$, $T_g = \frac{1}{T_1 T_2}$ and $T_0 = \frac{1}{T_1} + \frac{1}{T_2}$

γ is the gyromagnetic ratio, *D* is the diffusion coefficient, v is the fluid velocity, T_1 is the spin lattice relaxation time, T_2 is the spin relaxation time, M_o is the equilibrium magnetization, $B_1(x,t)$ is the applied magnetic field and M_y is the transverse magnetization. Solutions to equation (1) have been discussed by a number of analytical methods [6-9, 14-16], where *D* represents the diffusion coefficient. Equation (1i) is the equation of diffusion of magnetization as the nuclear spins move. The function $\frac{F_o}{T_o}\gamma B_1(x,t)$ is the forcing function, which shows that the application of the RF B_1 field has an influence on the diffusion of magnetization within a voxel. It is interest-

ing to note that the dimensions of Equation (1h) exactly match that of diffusion coefficient. Equation (1i) is only applicable when *D* in non – directional. That is, we have a constant diffusion coefficient (isotropic medium) and hence,

$$\frac{\partial M_y}{\partial t} = \nabla \cdot \left(D \nabla M_y \right) + \frac{F_o}{T_o} \gamma B_1 \left(\vec{r}, t \right) \tag{1j}$$

where $F_o = \frac{M_0}{T_1}$ and $T_o = \frac{1}{T_1} + \frac{1}{T_2}$.

Because these cells will have to queeze their way through the capillaries, we assume that the system which equation (1j) describes has the same radius as the erythrocyte. Therefore, if the MRI signal describing the erythrocytes does not vary appreciably with θ and ϕ:

$$\frac{\partial M_y}{\partial t} = \frac{1}{r^2} \frac{\partial}{\partial r} \left(D(r) r^2 \frac{\partial M_y}{\partial r} \right) + \frac{F_o}{T_o} \gamma B_1 \left(r, t \right) \tag{2}$$

For the purpose of this study, we shall define the RF $B_1(x,t)$ field as

$$\gamma B_1 \left(r, t \right) = f(r) M_y \left(r, t \right) \tag{3}$$

If the diffusion coefficient varies very slowly with the radial distance r, we may write:

$$D(r) \approx D_0 = D \tag{4}$$

Equation (2) then becomes:

$$\frac{\partial M_y}{\partial t} = \frac{D_0}{r^2} \frac{\partial}{\partial r} \left(r^2 \frac{\partial M_y}{\partial r} \right) + \frac{F_o}{T_o} f(r) M_y \tag{5}$$

Using the method of separation of variables, we write

$$M_y(r,t) = R(r) G(t) \tag{6}$$

$$R\frac{dG}{dt}=\frac{D_0G}{r^2}\frac{d}{dr}\left(r^2\frac{dR}{dr}\right)+\frac{F_o}{T_o}f(r)RG \tag{7}$$

$$\frac{1}{G}\frac{dG}{dt}=\frac{D_0}{r^2R}\frac{d}{dr}\left(r^2\frac{dR}{dr}\right)+\frac{F_o}{T_o}f(r) \tag{8}$$

Both sides of equation (7) must be equal to a constant $-\xi^2$. Therefore, we have the following equations:

$$\frac{dG}{dt}=-\xi^2G \tag{9}$$

$$\frac{D_0}{r^2}\frac{d}{dr}\left(r^2\frac{dR}{dr}\right)+\left(\xi^2+\frac{F_o}{T_o}f(r)\right)R=0 \tag{10i}$$

The solution to equation (9) is: $G(t)=Ae^{-\xi^2t}$ (10ii)

where A is a constant. Re – arranging equation (10i) gives:

$$\frac{D_0}{r^2}\frac{d}{dr}\left(r^2\frac{dR}{dr}\right)+\frac{F_o}{T_o}f(r)R=-\xi^2R \tag{11}$$

We shall define the function f(r) as follows:

$$f(r)=-\frac{F_vr}{\hbar M_0}-\frac{D_0}{M_0r^2} \tag{12}$$

$$f(r)=-\frac{D_0}{M_0r^2}-\frac{6\pi\eta vr^2}{\hbar M_0} \tag{13}$$

where $F_v=6\pi\eta vr$ represent the viscous drag, r is the hydrodynamic radius of the cell, v is the velocity of micro fluidic flow, η is the viscosity of the medium, M_0 is the

equilibrium magnetization, $\hbar$ is the reduced Planck constant and n is a dimensionless parameter. Equation (11) then becomes:

$$\frac{D_0}{r^2}\frac{d}{dr}\left(r^2\frac{dR}{dr}\right)-\frac{F_o}{T_o}\left(\frac{D_0}{M_0 r^2}+\frac{6\pi\eta v r^2}{\hbar M_0}\right)R=-\xi^2 R \tag{14}$$

$$-\frac{D_0}{r^2}\frac{d}{dr}\left(r^2\frac{dR}{dr}\right)+\left(\frac{1}{T_o T_1}\frac{D_0}{r^2}+\frac{6\pi\eta v r^2}{\hbar T_o T_1}\right)R=\xi^2 R \tag{15}$$

$$-\frac{D_0}{r^2}\frac{d}{dr}\left(r^2\frac{dR}{dr}\right)+\left(\frac{1}{T_o T_1}\frac{D_0}{r^2}+\frac{6\pi\eta v r^2}{\hbar T_o T_1}-\xi^2\right)R=0 \tag{16}$$

$$-D_0\frac{1}{r^2}\frac{d}{dr}r^2\frac{dR}{dr}+\left(\frac{1}{T_o T_1}\frac{D_0}{r^2}+\frac{6\pi\eta v r^2}{\hbar T_o T_1}-\xi^2\right)R=0$$

We shall introduce a dimensionless variable as follows: $\alpha=\sqrt{k}r^2$ (17)

where $k=\dfrac{6\pi\eta v}{\hbar D_0 T_o T_1}$ (18)

$$\frac{d}{dr}=\frac{d\alpha}{dr}\frac{d}{d\alpha}=2k^{\frac{1}{4}}\alpha^{\frac{1}{2}}\frac{d}{d\alpha} \tag{19}$$

we have: $-D_0\dfrac{\sqrt{k}}{\alpha}\dfrac{d}{dr}\dfrac{\alpha}{\sqrt{k}}\dfrac{dR}{dr}+\left(\left(\dfrac{D_0}{T_o T_1}\dfrac{\sqrt{k}}{\alpha}\right)+\left(\dfrac{6\pi\eta v}{\hbar T_o T_1}\dfrac{\alpha}{\sqrt{k}}\right)-\xi^2\right)R=0$ (20)

$$-D_0\left(\frac{\sqrt{k}}{\alpha}2k^{\frac{1}{4}}\alpha^{\frac{1}{2}}\frac{d}{d\alpha}\right)\left(\frac{\alpha}{\sqrt{k}}2k^{\frac{1}{4}}\alpha^{\frac{1}{2}}\frac{dR}{d\alpha}\right)+\left(\left(\frac{D_0}{T_o T_1}\frac{\sqrt{k}}{\alpha}\right)+\left(kD_0\frac{\alpha}{\sqrt{k}}\right)-\xi^2\right)R=0$$

$$-D_0\left(\frac{1}{\alpha}4k^{\frac{1}{2}}\alpha^{\frac{1}{2}}\frac{d}{d\alpha}\right)\left(\alpha^{\frac{3}{2}}\frac{dR}{d\alpha}\right)+\left(\left(\frac{D_0}{T_oT_1}\frac{\sqrt{k}}{\alpha}\right)+\left(kD_0\frac{\alpha}{\sqrt{k}}\right)-\xi^2\right)R=0$$

$$-\sqrt{k}D_0\left[\frac{4}{\alpha}\alpha^{\frac{1}{2}}\frac{d}{d\alpha}\left(\alpha^{\frac{3}{2}}\frac{dR}{d\alpha}\right)+\left(-\left(\frac{D_0}{T_oT_1}\frac{1}{\alpha}\right)-\alpha+\frac{\xi^2}{\sqrt{k}D_0}\right)R\right]=0 \tag{21}$$

If we write $$\frac{1}{T_oT_1}=n(n+1) \tag{22}$$

$$-\sqrt{k}D_0\left[\frac{4}{\alpha}\alpha^{\frac{1}{2}}\frac{d}{d\alpha}\left(\alpha^{\frac{3}{2}}\frac{dR}{d\alpha}\right)+\left(-\frac{n(n+1)}{\alpha}-\alpha+\frac{\xi^2}{\sqrt{k}D_0}\right)R\right]=0 \tag{23}$$

$$-\sqrt{k}D_0\left[4\alpha\frac{d^2R}{d\alpha^2}+6\frac{dR}{d\alpha}+\left(-\frac{n(n+1)}{\alpha}-\alpha+\frac{\xi^2}{\sqrt{k}D_0}\right)R\right]=0 \tag{24}$$

The solution to equation (23) can be found by assuming a solution of the following form:

$$R(\alpha)=\alpha^{\frac{n}{2}}\exp\left(-\frac{\alpha}{2}\right)L(\alpha) \tag{25}$$

$$\frac{dR(\alpha)}{d\alpha}=\frac{n}{2}\alpha^{\frac{n}{2}-1}\exp\left(-\frac{\alpha}{2}\right)L(\alpha)-\frac{1}{2}\alpha^{\frac{n}{2}}\exp\left(-\frac{\alpha}{2}\right)L(\alpha)+\alpha^{\frac{n}{2}}\exp\left(-\frac{\alpha}{2}\right)\frac{dL(\alpha)}{d\alpha}$$

$$\frac{dR(\alpha)}{d\alpha}=\alpha^{\frac{n}{2}}\exp\left(-\frac{\alpha}{2}\right)\left[\frac{n}{2\alpha}L(\alpha)-\frac{1}{2}L(\alpha)+\frac{dL(\alpha)}{d\alpha}\right] \tag{26}$$

$$\frac{d^2R(\alpha)}{d\alpha^2}=\frac{n}{2}\left(\frac{n}{2}-1\right)\alpha^{\frac{n}{2}-2}\exp\left(-\frac{\alpha}{2}\right)L(\alpha)-\frac{n}{4}\alpha^{\frac{n}{2}-1}\exp\left(-\frac{\alpha}{2}\right)L(\alpha)+\frac{n}{2}\alpha^{\frac{n}{2}-1}\exp\left(-\frac{\alpha}{2}\right)\frac{dL(\alpha)}{d\alpha}$$
$$-\frac{n}{4}\alpha^{\frac{n}{2}-1}\exp\left(-\frac{\alpha}{2}\right)L(\alpha)+\frac{1}{4}\alpha^{\frac{n}{2}}\exp\left(-\frac{\alpha}{2}\right)L(\alpha)-\frac{1}{2}\alpha^{\frac{n}{2}}\exp\left(-\frac{\alpha}{2}\right)\frac{dL(\alpha)}{d\alpha}+\frac{n}{2}\alpha^{\frac{n}{2}-1}\exp\left(-\frac{\alpha}{2}\right)\frac{dL(\alpha)}{d\alpha} \quad (27)$$
$$-\frac{1}{2}\alpha^{\frac{n}{2}}\exp\left(-\frac{\alpha}{2}\right)\frac{dL(\alpha)}{d\alpha}+\alpha^{\frac{n}{2}}\exp\left(-\frac{\alpha}{2}\right)\frac{d^2L(\alpha)}{d\alpha^2}$$

$$4\alpha\frac{d^2R(\alpha)}{d\alpha^2}=\frac{n}{2}\left(\frac{n}{2}-1\right)\alpha^{\frac{n}{2}-1}\exp\left(-\frac{\alpha}{2}\right)L(\alpha)-\frac{n}{4}\alpha^{\frac{n}{2}}\exp\left(-\frac{\alpha}{2}\right)L(\alpha)+\frac{n}{2}\alpha^{\frac{n}{2}}\exp\left(-\frac{\alpha}{2}\right)\frac{dL(\alpha)}{d\alpha}$$
$$-\frac{n}{4}\alpha^{\frac{n}{2}}\exp\left(-\frac{\alpha}{2}\right)L(\alpha)+\frac{1}{4}\alpha^{\frac{n}{2}+1}\exp\left(-\frac{\alpha}{2}\right)L(\alpha)-\frac{1}{2}\alpha^{\frac{n}{2}+1}\exp\left(-\frac{\alpha}{2}\right)\frac{dL(\alpha)}{d\alpha}+\frac{n}{2}\alpha^{\frac{n}{2}}\exp\left(-\frac{\alpha}{2}\right)\frac{dL(\alpha)}{d\alpha} \quad (28)$$
$$-\frac{1}{2}\alpha^{\frac{n}{2}+1}\exp\left(-\frac{\alpha}{2}\right)\frac{dL(\alpha)}{d\alpha}+\alpha^{\frac{n}{2}+1}\exp\left(-\frac{\alpha}{2}\right)\frac{d^2L(\alpha)}{d\alpha^2}$$

$$4\alpha\frac{d^2R(\alpha)}{d\alpha^2}=\alpha^{\frac{n}{2}}\exp\left(-\frac{\alpha}{2}\right)\left[\begin{array}{l}\frac{4n}{2}\left(\frac{n}{2}-1\right)\frac{1}{\alpha}L(\alpha)-nL(\alpha)+2n\frac{dL(\alpha)}{d\alpha}-nL(\alpha)+\alpha L(\alpha)-2\alpha\frac{dL(\alpha)}{d\alpha}\\+2n\frac{dL(\alpha)}{d\alpha}-2\alpha\frac{dL(\alpha)}{d\alpha}+4\alpha\frac{d^2L(\alpha)}{d\alpha^2}\end{array}\right]$$

$$4\alpha\frac{d^2R(\alpha)}{d\alpha^2}=\alpha^{\frac{n}{2}}\exp\left(-\frac{\alpha}{2}\right)\left[4\alpha\frac{d^2L(\alpha)}{d\alpha^2}+4(n-\alpha)\frac{dL(\alpha)}{d\alpha}+\left\{\frac{n(n-2)}{\alpha}+\alpha-2n+\right\}L(\alpha)\right] \quad (29)$$

$$6\frac{dR(\alpha)}{d\alpha}=\alpha^{\frac{n}{2}}\exp\left(-\frac{\alpha}{2}\right)\left[6\frac{dL(\alpha)}{d\alpha}-3L(\alpha)+\frac{3n}{\alpha}L(\alpha)\right] \quad (30)$$

If we substitute for equation (29) and (30) in equation (24), we have:

$$-\sqrt{k}D_0\alpha^{\frac{n}{2}}\exp\left(-\frac{\alpha}{2}\right)\left\{\begin{array}{l}\left[4\alpha\frac{d^2L(\alpha)}{d\alpha^2}+4(n-\alpha)\frac{dL(\alpha)}{d\alpha}+\left\{\frac{n(n-2)}{\alpha}+\alpha-2n+\right\}L(\alpha)\right]\\+6\frac{dL(\alpha)}{d\alpha}-3L(\alpha)+\frac{3n}{\alpha}L(\alpha)+\left(-\frac{n(n+1)}{\alpha}-\alpha+\frac{\xi^2}{\sqrt{k}D_0}\right)L(\alpha)\end{array}\right\}=0 \quad (31)$$

$$-\sqrt{k}D_0\alpha^{\frac{n}{2}}\exp\left(-\frac{\alpha}{2}\right)\left\{4\alpha\frac{d^2L(\alpha)}{d\alpha^2}+(4n+6-4\alpha)\frac{dL(\alpha)}{d\alpha}+\left(\frac{n(n-2)}{\alpha}-2n-\frac{n(n+1)}{\alpha}+\frac{\xi^2}{\sqrt{k}D_0}-3+\frac{3n}{\alpha}\right)L(\alpha)\right\}=0$$

$$-\sqrt{k}D_0\alpha^{\frac{n}{2}}\exp\left(-\frac{\alpha}{2}\right)\left\{4\alpha\frac{d^2L(\alpha)}{d\alpha^2}+(4n+6-4\alpha)\frac{dL(\alpha)}{d\alpha}+\left(\frac{-3n}{\alpha}-2n+\frac{\xi^2}{\sqrt{k}D_0}-3+\frac{3n}{\alpha}\right)L(\alpha)\right\}=0$$

$$-\sqrt{k}D_0\alpha^{\frac{n}{2}}\exp\left(-\frac{\alpha}{2}\right)\left\{4\alpha\frac{d^2L(\alpha)}{d\alpha^2}+(4n+6-4\alpha)\frac{dL(\alpha)}{d\alpha}+\left(\frac{\xi^2}{\sqrt{k}D_0}-(2n+3)\right)L(\alpha)\right\}=0$$

$$-4\sqrt{k}D_0\alpha^{\frac{n}{2}}\exp\left(-\frac{\alpha}{2}\right)\left\{\alpha\frac{d^2L(\alpha)}{d\alpha^2}+\left(n+\frac{3}{2}-\alpha\right)\frac{dL(\alpha)}{d\alpha}+\left(\frac{\xi^2}{4\sqrt{k}D_0}-\frac{1}{4}(2n+3)\right)L(\alpha)\right\}=0 \quad (32)$$

Equation (32) may hold only if

$$\alpha\frac{d^2L(\alpha)}{d\alpha^2}+\left(n+\frac{3}{2}-\alpha\right)\frac{dL(\alpha)}{d\alpha}+\left(\frac{\xi^2}{4\sqrt{k}D_0}-\frac{1}{4}(2n+3)\right)L(\alpha)=0 \quad (33a)$$

Equation (33) is the generalized (or associated) Laguerre equation which has a solution $L_\beta^a(\alpha)$ known as the associated Laguerre polynomial where

$$a=n+\frac{3}{2}-1 \quad (33b)$$

and

$$\beta=\frac{\xi^2}{4\sqrt{k}D_0}-\frac{1}{4}(2n+3) \quad (33c)$$

From equations (17, 18, 25), we have:

$$R(r)=\left(\sqrt{k}r^2\right)^{\frac{n}{2}}\exp\left(-\frac{\sqrt{k}r^2}{2}\right)L_\beta^a\left(\sqrt{k}r^2\right) \quad (34)$$

Finally, using equation (6, 10ii, 34), we may write:

$$M_y(r,t)=A\left(\sqrt{k}r^2\right)^{\frac{n}{2}}\exp\left(-\xi^2t-\frac{\sqrt{k}}{2}r^2\right)L_\beta^a\left(\sqrt{k}r^2\right) \quad (35)$$

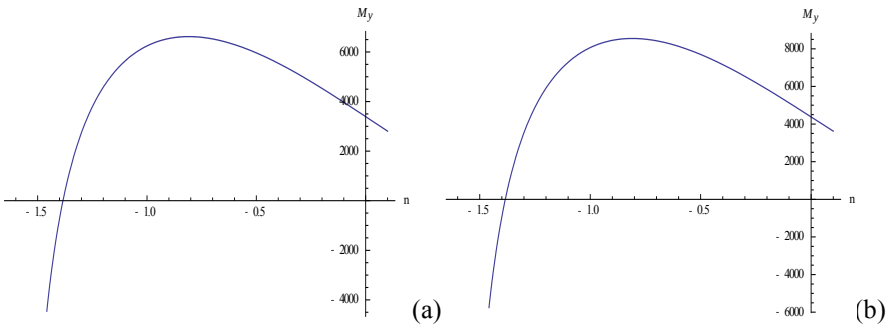
Setting $\xi^2=\omega_0$ (where ω_0 is the Larmor frequency), the transverse NMR magnetization becomes

$$M_y(r,t) = A\left(\sqrt{k}r^2\right)^{\frac{n}{2}} \exp\left(-\omega_0 t - \frac{\sqrt{k}}{2}r^2\right) L_\beta^a\left(\sqrt{k}r^2\right) \tag{36}$$

where $a = n + \frac{1}{2}$, $\beta = \frac{\omega_0}{4\sqrt{k}D_0} - \frac{n}{2} - \frac{3}{4}$ (37)

3 Analysis of Results

Cerebrospinal fluid (CSF) flows throughout the inner ventricular system in the brain and is absorbed back into the bloodstream, rinsing the metabolic waste from the central nervous system through the BBB. This allows for homeostatic regulation of the distribution of neuroendocrine factors, to which slight changes can cause problems or damage to the nervous system. Hence, due to the access that CSF has in and around the BBB, we shall analyse the above results with physical and relaxation parameters of CSF at 1.5T: T_1 = 2.65s, T_2 = 0.28s, η = 0.0007Nsm^{-2}, $D_0 = 2.34 \times 10^{-9}$m^{2}s^{-1} [11, 14-16] and v = 1.75×10^{-7}ms^{-1} [5]. Using the relaxation times as end-to-end boundaries, we shall show the changes in the NMR transverse magnetization as a function of the hydrodynamic radius r and changes in relaxation parameters (as expressed by the term n equation (22)). This may prove to be very invaluable in real – time imaging of processes around the BBB in the presence of solutes (used as drugs). From the above data, we have the following plots:



(a) (b)

Fig. 1. Plots of M_y against the relaxation parameter n for r = 5.0nm, ω_0 = 64MHz, A = 8000 and (a) t = 4.0ps (b) t = 4.0ns

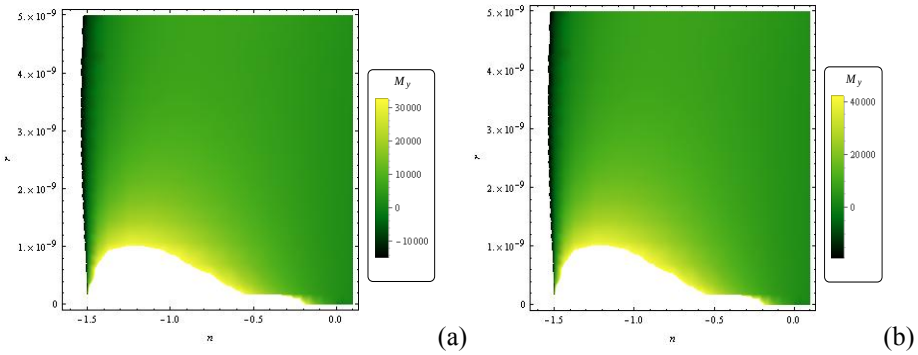


Fig. 2. 3D maps of M_y as it varies with relaxation parameter n and r for (a) t = 4.0ns (b) t = 4.0ps. ω_0 = 64MHz, A = 8000.

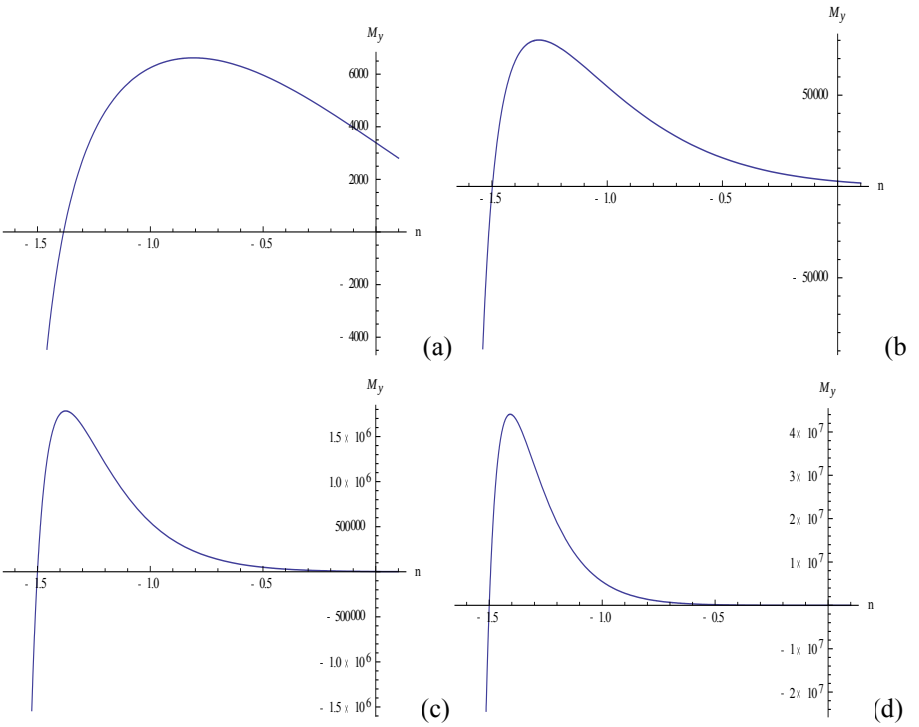


Fig. 3. Plots of M_y against the relaxation parameter n for 4.0ps, ω_0 = 64MHz, A = 8000 and (a) r = 5.0nm (b) r = 0.5nm (b) r = 50pm (d) r = 5.0pm.

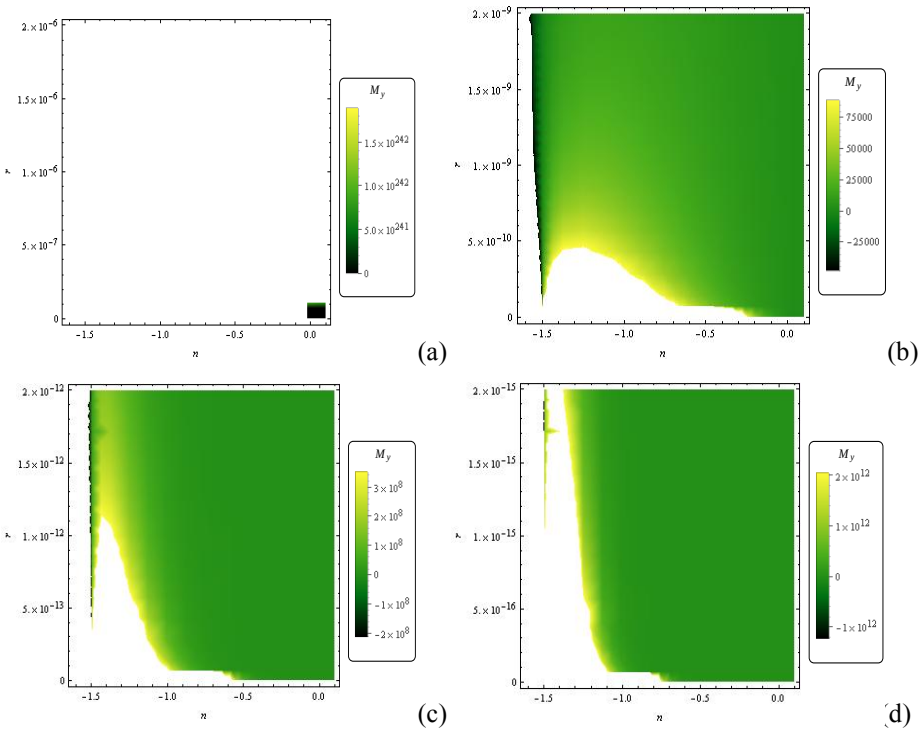


Fig. 4. 3D maps of M_y as it varies with relaxation parameter n and r for t = 4.0ns and r within (a) micrometer range (b) nanometer range (c) picometer range (d) femtometer range. ω_0 = 64MHz, A = 8000.

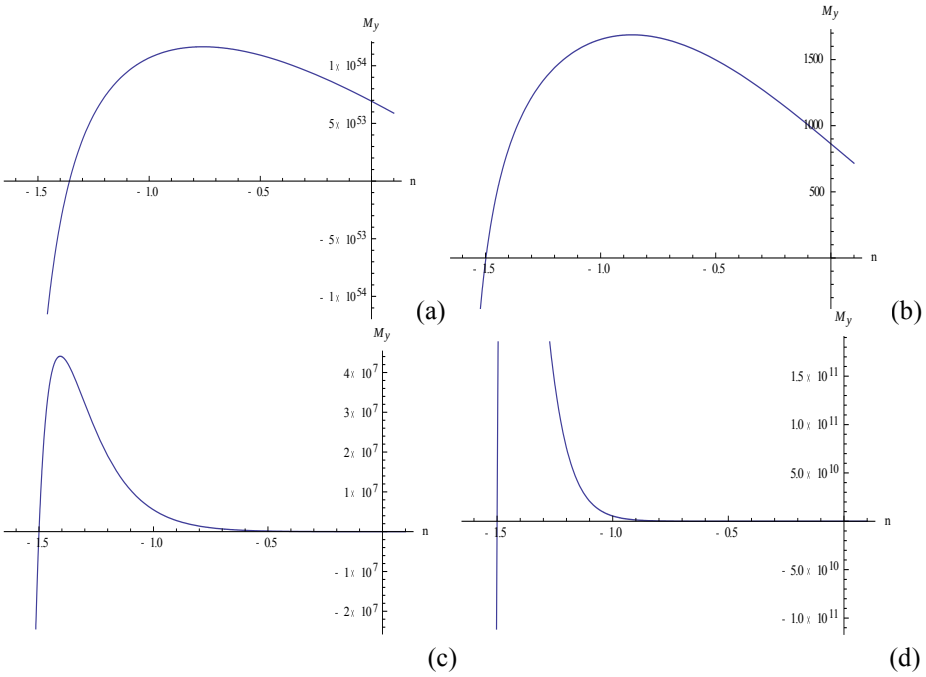


Fig. 5. Plots of M_y against the relaxation parameter n for 4.0ps, ω_0 = 64MHz, A = 8000 and (a) r = 50nm (b) r = 0.5nm (b) r = 50fm (d) r = 5.0fm.

3.1 Molecular Dynamics of Drugs Targeting The Brain

We have earlier noted that the interaction of drugs with local solutes around the BBB and receptor sites can be captured in a well defined parameter. Fortunately, the parameter n has the dynamic information from different interactions. This is because it incorporates both MR relaxation and hemodynamic properties of molecular structures. In cases of temporary or permanent disruption to the BBB, cellular integrity abnormalities have direct influence the radius of the space through which the drug or solutes would pass and the viscosity.

Therefore, this study may prove to be very useful in the molecular spectroscopic studies of drug interaction within the brain and real – time imaging of these processes. It is quite interesting to note that Figures 1 and 2 show that processes within picose-

conds range can be easily observed on MR scans. In fact, it is observed that meaningful image contrast does not exist at higher time range. This confirms that this study is particularly suited to molecular imaging.

Figures 3 and 5 show that different radial openings of the BBB show unique contrast with magnificent NMR signal magnitude. This shows the possibility of using this study to investigate progressive disruption to BBB especially as it concerns inflammation processes. With these methods, we may be able to observe and design better treatment plans for meningitis [17], brain abscess [17], epilepsy, multiple sclerosis, neuromyelitis optica [18], progressive multifocal leukoencephalopathy, Alzheimer's Disease, etc. Figure 2 and 4 show that 3D reconstruction of the molecular processes around the BBB can easily be done. Figure 4(a) is particularly strange because it shows that at microscopic r, the NMR signal is incredibly high but only captures a very small section of the region we have considered in the simulation of results.

4 Conclusion

We have solved the time dependent Bloch NMR flow equation analytically for the analysis of biological flow at the molecular level. The associated Laguerre polynomials obtained as solutions to the Bloch NMR flow equation can be applied to evaluate biological flow around the BBB in the brain and central nervous system. Using appropriate MRI experimental data, the dynamics of fluid velocity, the NMR relaxation times and the path length for biological flow in the blood brain barrier are demonstrated. Figures (2, 4) show the density images and the corresponding 3D plots of NMR transverse magnetisation based on experimental data [11, 14-16]. Since the diffusion coefficient varies very slowly with the radial distance r, it is interesting to note that parameter f(r) in equations (3, 13) can be appropriately defined to solve specific biological and medical problems in the brain. It is very interesting to note that f(r) is related to the viscous drag involving brain hemodynamics. This means that we can define this function for different brain diseases. Specifically, equations (1h, 18, 22, 37) can be very vital for molecular analysis of CSF in accessing blood brain barri-

er and every change that occur around them. Based on these equations, the viscous drag, the hydrodynamic radius r, the velocity v of micro fluidic flow, the viscosity η and the diffusion coefficient for specific biological and medical problems in the brain and nervous system can be simultaneously determined by computational MRI as demonstrated in this study.

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