COMPUTATIONAL MODEL OF RESTRICTED DIFFUSION FOR NMR STUDIES OF SICKLE CELL DISEASE

Michael Oluwaseun Dada[1], Bamidele Omotayo Awojoyogbe[1], Simona Baroni[2], and Samarendra Mohanty[3]

[1]Department of Physics, Federal University of Technology, Minna, Niger State, Nigeria, [2]Invento Laboratory, Molecular Biotechnology Center (MBC), Torino, Turin, Italy, [3]Department of Physics, Biophysics and Physiology group, University of Texas, Arlington, Texas, United States

INTRODUCTION

Sickle cell disease (SCD) is an inherited disorder of hemoglobin structure that has no established cure in adult patients. The most important pathophysiologic event in sickle cell anemia, which explains most of its clinical manifestations, is vascular occlusion; this may involve both the micro- and macrovasculature[1]. The primary process that leads to vascular occlusion is the polymerization of sickle hemoglobin (Hb) on deoxygenation, which in turn results in distortion of the shape of red blood cells (RBC), cellular dehydration, and decreased deformability and stickiness of RBC, which promotes their adhesion to and activation of the vascular endothelium[1]. SCD has been regarded as a molecular disease without any established cure. Finding a realiable cure for this disease may be dependent on much we know about the molecular processes that lead to it and how we could possibly represent them in terms of images for classical observation. This study presents a contribution to the understanding of SCD using the Bloch – Torrey equation so that we can easily represent the associated chemical processes in MRI images. Vascular occlusion is used to describe any form of blockage to blood vessels.

THEORETICAL FORMULATION

For this study, we shall consider vascular occlusion to be showing restricted flow within the blood vessel, which we can call restricted geometry. To describe the diffusion of the erythrocytes within the blood vessel, we shall use the Bloch – Torrey equation. A variant of this equation is given as follows[2]:

$$\frac{\partial M_y}{\partial t} = \nabla \cdot \left(D \nabla M_y\right) + \frac{F_o}{T_o}\gamma B_1(\vec{r},t) \quad \text{; where } F_o = \frac{M_o}{T_1} \text{ (} M_o \text{ is equilibrium magnetization), } T_g = \frac{1}{T_1 T_2} \text{ and } T_o = \frac{1}{T_1} + \frac{1}{T_2} \tag{1}$$

If we consider a cylindrical blood vessel in which the transverse magnetization changes very slowly with z and □, we write[2]: $\frac{\partial M_y}{\partial t} = \frac{D}{r}\frac{\partial}{\partial r}\left(r\frac{\partial M_y}{\partial r}\right) + \frac{F_o}{T_o}\gamma B_1(r,t)$ (2)

If we apply the oscillating magnetic field for restricted diffusion such that: (3)

$$\frac{F_o}{T_o}\gamma B_1(r,t) = f(r) M_y(r,t) = -M_y(r,t)\frac{vD}{T_g V(r)}\gamma G r$$

where v is the fluid velocity, D is the effective diffusion coefficient and V(r) is the volume of the voxel being imaged. For this investigation, we shall use a voxel in which the length h = 2r, so that V = $2\pi r^3$. Hence, we write: (4)

$$\frac{\partial M_y}{D\partial t} = \frac{1}{r}\frac{\partial}{\partial r}\left(r\frac{\partial M_y}{\partial r}\right) - \frac{\gamma G v}{2\pi r^2 T_g} M_y$$

Using separation of variables[2] and noting that the radial part can be written as Malmsten's differential equation, we have the solution: $M_y(r,t) = A_0 I_n(\alpha r) e^{\alpha^2 D t}$; $A_0 = A c_1$ (5)

where $n = \sqrt{\frac{2\gamma G v}{\pi T_g}}$, $\alpha = \frac{\gamma G T_0}{T_g}$, and $I_n(x)$ is a modified Bessel function of the first kind. Since we require that M_y has a finite value at all radial distances, we set $c_2 = 0$.

DISCUSSIONS AND CONCLUSION

Using experimental data in ealier studies [3,4] and eqn (5), we have mapped values of correlation time to diffusion coefficent in the table below.

τ_c (s)	T_1 (s)	T_2 (s)	D (m^2s^{-1})	r_s (Å)	t (s)	α	n	M_y	$\|M_\perp\|^2$
5.00E-08	0.001051	0.000736	2.43E-11	30.77335	0.10000	15215.09	3.44445388	918.1079196	842922.152
1.00E-07	0.001132	0.000499	2.37E-11	42.97944	0.09364	13886.86	2.94342921	60314.01238	3637780089
1.50E-07	0.001386	0.000414	2.31E-11	51.96826	0.08727	15325.78	2.96661983	73470.51925	5397917199
2.00E-07	0.00169	0.000357	2.24E-11	59.09158	0.08091	17428.81	3.04198851	1380.121823	1904736.25
2.50E-07	0.002018	0.000313	2.18E-11	65.17557	0.07455	19846.88	3.11252508	2038.406505	4155101.08
3.00E-07	0.002357	0.000276	2.12E-11	70.40688	0.06818	22418.2	3.15874409	2938.513949	8634864.23
3.50E-07	0.002705	0.000246	2.06E-11	74.96425	0.06182	25125.76	3.19470895	4138.127003	17124095.1
4.00E-07	0.003057	0.000221	2.00E-11	78.96444	0.05545	27909.94	3.21902215	5673.476133	32188331.4
4.50E-07	0.003412	0.000201	1.94E-11	82.48855	0.04909	30762.24	3.24326660	7598.992569	57744688.1
5.00E-07	0.003770	0.000183	1.87E-11	85.36746	0.04273	33657.11	3.25294207	9955.447738	99110939.7
5.50E-07	0.004130	0.000168	1.81E-11	88.08606	0.03636	36594.55	3.26219394	12799.97764	163839428
6.00E-07	0.004491	0.000156	1.75E-11	90.46513	0.03000	39566.05	3.27803764	16182.87492	261885441

It is very interesting to note that from table 1, the values of M_y for normal hemoglobin increases and then reduces sharply at τ_c = 200ns. M_y starts steady increase afters this for sickled hemoglobin (cycled in Fig.1 (a) and (b)). Sickled hemoglobin molecules have been known to be functionally impaired and amino acid residues have been replaced. Fig. 1 (b) shows that the functional impairment is a progressive molecular process with small signal changes as a function of T_0.Fig. 1 (c) shows the possibility of using the results obtained in this work to study the structure of normal and abnormal hemoglobin. It is noteworthy that we have an additional advantage of being able to specify the relaxation rate as the structure changes. This may prove to be very important in the search for new treatment directions for SCD.

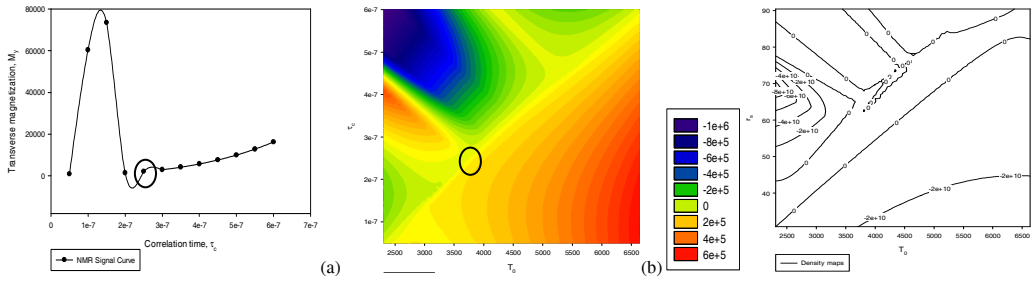

Table 1: Relaxation and hydrodynamic parameters of normal and sickled haemoglobin molecules at B_0 = 0.23T [3,4] together with the corresponding M_y and spin density; r = 5μm, G = 0.2Tm^{-1}, $A_0 = 1\times10^8$.

Fig. 1: (a) Plot of M_y vs τc (b) Contour image of M_y vs and T_0 (c) Contour map of the spin density as it varies with T_0 and r_s. We have used selected parameters in the above table to make these images.

In conclusion, we have been able to show the usefulness of the modified Bloch – Torrey equation in the NMR studies of normal and abnormal hemoglobin. The results has afforded us the opportunity of doing 2D molecular studies of these molecules and perform 3D imaging concurrently. 3D images can help experimental scientists see how these diseases evolve. Investigation of changes in structural integrity of hemoglobin has been shown as well. It worthy of note that the results in this study can be extended to other molecular diseases such as Hemophilia, Thalassemia, Alzheimer's Disease and Muscular Dystrophy.

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