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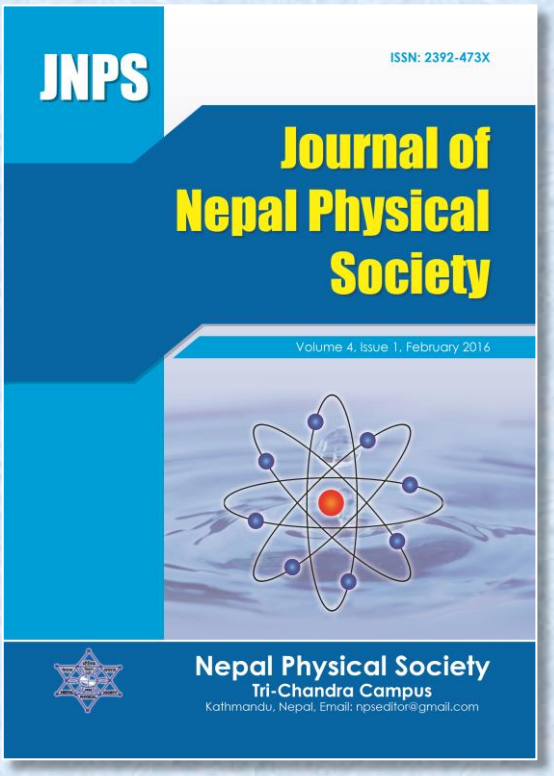

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Research Article

Oxygen Detection in Biological Aqueous Solutions using Positive Muon for Cancer Research

Amba Datt Pant
Institute of Materials Structure Science, Muon Science Laboratory
High Energy Accelerator Research Organization (KEK),
203-1 Shirakata, Tokai-mura, Naka-gun, Ibaraki 319-1106 Japan
Corresponding Email: pant@post.kek.jp

ABSTRACT

Spin relaxation of muonium (Mu) observed in molecular oxygen (O_2) dissolved in water shows characteristic behaviour which enables us to detect O_2 in aqueous solution of albumin, serum and haemoglobin (Hb). These results suggest development of a new method using positive muon to measure oxygen level in biological systems which can be applied for diagnosis and treatment of cancer.

Keywords: Hypoxia, Muonium, Asymmetry, Aqueous solutions, Biological molecule.

INTRODUCTION

Low oxygenation called hypoxia is known as an important factor in tumor biology and the response of tumors to treatment by radiation. Its measurement in specific region (tissue) of cancer patients may have an important predictive value in the management of treatment and outcome of the disease (Mancini *et al.*, 1994; James *et al.*, 1996; Kavanagh *et al.*, 1999). The National Cancer Workshop (Tatum *et al.*, 2006) on hypoxia imaging techniques pointed out the need of improved O_2 detection methods for cancer treatment. Here, a new method using polarized positive muon (μ^+) produced at the accelerator facility is proposed to probe existence of the paramagnetic O_2 in the cancer of eventually human body.

There are some existing techniques for this purpose with limitations (Tatum *et al.*, 2006). For example; (a) **PET** 18F-labelled fluoro-misonidazole (18F-FMISO) tracer is widely used in PET for hypoxia. It does not directly measure molecular O_2 in the tumor, but the tracer retention affected primarily by O_2. After radiation therapy, it images hypoxic cells and re-oxygenation. So it is like off-line technique. (b) **MRI** Blood oxygen level-dependent (BOLD) MRI does not directly measure O_2 molecule in blood but rather detects deoxy-Hb. During measurement we need to have special attention for use of the high magnetic fields for in-situ MRI. (c) **EPR** is another method which is not non-invasive.

Brown J. M. *et al.*, (2004) mentioned that the concentration of oxygen in tumorous part in human body is heterogeneous (less than 5 mmHg). From muon spin measurements, the muon spin can probe oxygen in water (Jean *et al.*, 1979; Nagamine and Nishiyama 1982; Roduner *et al.*, 1995) between 0.3 to 300 mmHg which perfectly matches to the range of hypoxia.

The proposed Mu relaxation method is able to detect and measure molecular O_2 concentration in tissues directly. It can be used non-invasively in a small area of human body at any temperature and without any strong magnetic fields. So it will act as non-invasive sensitive needle with high spatial resolution.

Here, muon spin rotation and relaxation (μSR) measurement on pure water, aqueous biological solutions of serum, albumin and hemoglobin under controlled O_2 concentration is presented.

EXPERIMENT

In μSR method, based on characteristic properties of positive muon-asymmetric decay and parity violation in weak interaction, decayed positrons from muons are collected by spectrometer around sample. Relation of asymmetry at any time can be written as difference between forward and backward counts as

$$\text{Asymmetry} = \frac{\text{FW} - \text{BW}}{\text{FW} + \text{BW}} \times 100\ \%$$

Where FW is counts collected by forward counters and BW is that by backward counters. The time evolution of polarization (that is asymmetry) of an

ensemble of muons implanted in a sample provides physical information about the interaction of the muon with its local environment. Muonium (bound state of μ^+ with electron) is like an light isotopes of hydrogen.

When energetic polarized positive muons are injected and stopped in water, these μ^+ take electronic states of diamagnetic μ^+ such as μ^+OH with a fraction of 60%, paramagnetic Mu with a fraction of 20% and a missing fraction of 20% (Jean *et al.*, 1979; Nagamine and Nishiyama, 1982; Roduner *et al.*, 1995). In the Mu fraction a half becomes ortho state with spin 1, providing a spin rotation signal with 100 times faster precession pattern with respect to the diamagnetic μ^+. Spin rotation and its relaxation were detected under 2.1 G transverse fields. All the measurements were performed at room temperature.

The concentration of O_2 is controlled in the sample and continuously circulated the sample to expose to muon beam. The experimental set up and the details about sample preparation can be found in (Pant, 2015; Pant *et al.*, 2014; Nagamine *et al.*, 2014). Measurements have been performed in aqueous biological samples of albumin, serum and hemoglobin. The O_2 concentration in liquid is measured by commercially available NeoFox oxygen monitor which is calibrated as O_2 concentration in gas phase being from 0 % with N_2 gas and 20.7 % in air. Experiments were conducted at Port 2 of the RIKEN RAL muon facility in UK, using 60 MeV/c decay-in-flight polarized positive muons.

RESULTS AND DISCUSSION

The time spectra of asymmetry of μSR data observed in pure water with O_2 concentration at less than 1 % and 7.5 % are presented in figure 1 (a) and (b), respectively. The Mu spin rotation signal (100 times larger frequency than that of μ^+) superimposes with spin rotation of diamagnetic μ^+. The spin precession of the Mu took faster relaxation against the increase of O_2 concentration. These time spectra are fitted with function;

$$F(t) = A_\mu \cos(\omega_\mu t + \phi_\mu) + A_{Mu} \exp(-\lambda t)\cos(\omega_{Mu} t + \phi_{Mu}) + B \quad \text{.....(1)}$$

where B is the time-independent background and τ_μ is the muon lifetime (2.20 μs). The terms A_μ and A_{Mu} are the amplitudes of the spin precession corresponding to the polarization asymmetry for the μ^+ in diamagnetic states and in Mu, respectively. The parameter λ is the muonium relaxation rate while the relaxation rate of μ^+ in diamagnetic species is assumed to be negligible, the ω_μ and the ω_{Mu} are the muon and Mu precession frequencies, ϕ_μ and ϕ_{Mu} are the respective initial phases of their precessions.

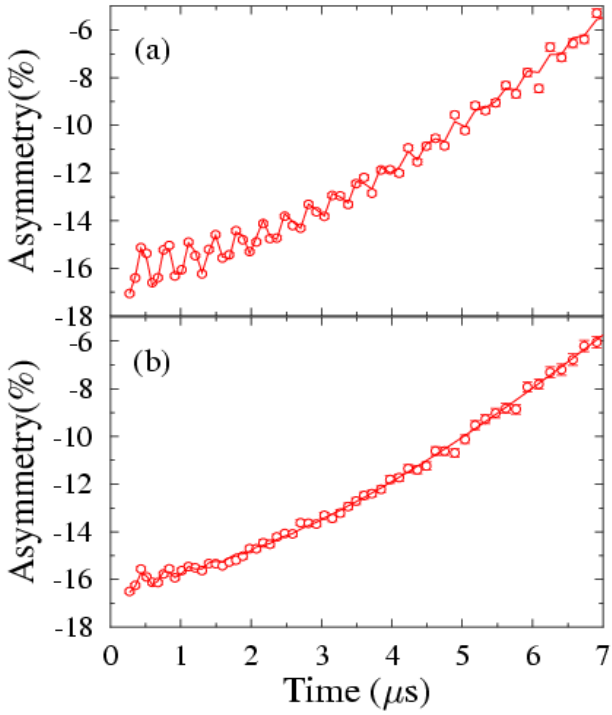

Fig. 1. Muon spin rotation time spectrum in water with O_2 concentration (a) below 1% and (b) 7.5%, at room temperature under 2.1 G transverse field. Similar O_2 dependence nature was observed in other biological aqueous solutions.

The relaxation rate of Mu with O_2 concentration in pure water shows consistency with previous data (Roduner *et al.*, 1995). Then the measurement was carried out in biological molecules. It is found that Mu exhibits similar relaxation change against the increase of O_2 contents in albumin and serum aqueous solution as shown in figure 2. In albumin solution, the Mu takes stronger response to the increase of the O_2 concentration. It suggests, in the presence of albumin, interaction between Mu and O_2 becomes more active in higher concentration.

The O_2 dependence Mu behavior in 0.5 g L^{-1} Hb is presented in figure 2. Here, because of strong O_2 absorption by deoxy-Hb (magnetic) to change it into oxy-Hb (nonmagnetic), it was expected the Mu relaxation takes a slower response against O_2 increase in comparison with pure water and other biological aqueous solutions. The weakened response of Mu with increasing O_2 concentration

may be due to an influence of decreasing deoxy-Hb concentration with increasing dissolved molecular O_2 concentration.

Based on behavior of oxygen in hemoglobin and Mu in pure water with increasing O_2 concentration, a theoretical predication of the behavior of Mu has also done as below. For the qualitative understandings, it is assumed that the experimental data of Mu relaxation rate in aqueous solution of various Hb concentration and O_2 concentration can be approximated in the simplest way as

$$\lambda_{M\mu} = R_1(Mu)+R_2(Mu) \quad \text{.....(2)}$$

The $R_1(Mu)$ is relaxation rate of Mu due to deoxy-Hb in solution, which is estimated using Hills equation, and the $R_2(Mu)$ is relaxation rate of Mu due to O_2 in solution. In order to calculated $R_2(Mu)$, both measurement in pure water and conversion of deoxy oxy-Hb taken into account. The result of theoretical estimation is presented in figure 3 (solid line is plot of equation 2 and marks are λ of from equation 1). Theoretically it is easy to understand the minimum in the estimated curve which may be at the state of saturation. This behavior will be checked experimentally between 2-5% O_2 concentrations. Furthermore, at less than 1 % O_2, relaxation rate of Mu shows linear relation with the Hb concentration up to 2 g L^{-1} Hb concentration.

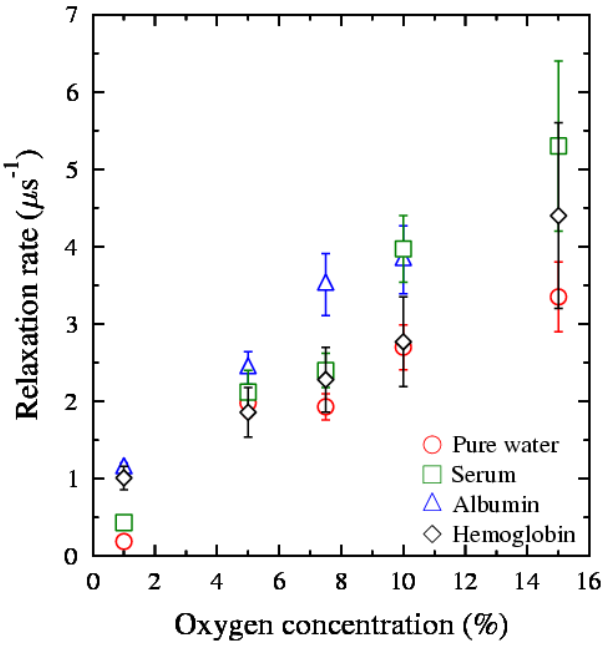

Fig. 2. Variation of relaxation rate of Mu with oxygen concentration in different biological aqueous solutions.

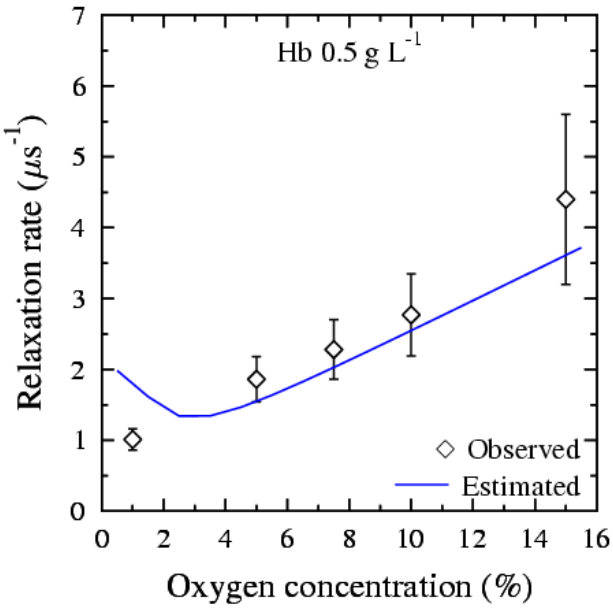

Fig. 3. Observed and estimated data of O_2 concentration dependence of the Mu relaxation rate in 0.5 g L^{-1} Hb aqueous solution.

CONCLUSION AND FUTURE DIRECTIONS

Concentration of molecular oxygen has successfully detected from the direct observation of muonium spin rotation signal in aqueous solution of albumin, serum and Hb. The result is encouraging to apply the present method to a wide variety of the biological systems and at higher Hb concentration. Although measurements should be extended to more cases before clinical application, the most important case of the Hb aqueous solution was successfully studied which can be used for monitor of oxygen in human body (O_2 concentration in lung is 15%). Before clinical application, since the biological system is complex, systematic studies using high spatial resolution muon micro beam of ultra slow muon (now under developing) in J-PARC (Yashuhiro *et al.*, 2014; Nagamine, 2014) will provide further idea about behavior of other magnetic molecules in human body and magnetism of blood.

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