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

Amba Datt Pant

Journal of Nepal Physical Society
Volume 4, Issue 1, February 2017
ISSN: 2392-473X

Editors:
Dr. Gopi Chandra Kaphle
Dr. Devendra Adhikari
Mr. Deependra Parajuli

JNPS, 4 (1), 7-10 (2017)

Published by:
Nepal Physical Society
P.O. Box : 2934
Tri-Chandra Campus
Kathmandu, Nepal
Email: npseditor@gmail.com
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 (O₂) dissolved in water shows characteristic behaviour which enables us to detect O₂ 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 O₂ 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 O₂ 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 O₂ in the tumor, but the tracer retention affected primarily by O₂. 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 O₂ 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 O₂ 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 O₂ 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 $\mu^+$ with electron) is like an light isotopes of hydrogen.

When energetic polarized positive muons are injected and stopped in water, these $\mu^+$ take electronic states of diamagnetic $\mu^+$ such as $\mu^+\text{OH}$ 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 $\mu^+$. 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 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 $\mu^+$) superimposes with spin rotation of diamagnetic $\mu^+$. The spin precession of the Mu took faster relaxation against the increase of $O_2$ concentration. These time spectra are fitted with function:

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

where $B$ is the time-independent background and $\tau_\mu$ is the muon lifetime (2.20 $\mu$s). The terms $A_{\mu}$ and $A_{Mu}$ are the amplitudes of the spin precession corresponding to the polarization asymmetry for the $\mu^+$ in diamagnetic states and in Mu, respectively. The parameter $\lambda$ is the muon relaxation rate.

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 weakened response of Mu with increasing $O_2$ concentration

\begin{figure}[h]
\centering
\includegraphics[width=0.5\textwidth]{fig1.png}
\caption{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.}
\end{figure}
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

$$\lambda_{Mu} = R_1(Mu) + R_2(Mu)$$ ...

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 $\lambda$ 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.

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.

ACKNOWLEDGEMENTS

I would like to thank Professors E. Torikai of University of Yamanashi; K. Nagamine of KEK, RIKEN, UCR Riverside; J. S. Schultz from University of California; K. Shimomura of KEK, W. Higemoto of JAEA and F. Pratt of ISIS, RAL for their fruitful discussion and every support. This work was supported by Grant-in-Aid for Scientific

REFERENCES


