Can we use simple linear model for the relaxometry to represent the concentration of metal ions?

Chih-Ching Lai[1] and Fu-Nien Wang[1]

[1]*Department of Biomedical Engineering and Environmental Sciences, National Tsing Hua University, Hsinchu, Taiwan*

Introduction: Iron (Fe) and copper (Cu) are essential element for metabolism and biochemical functions in the brain. They are cofactors in particular proteins and catalyzing electron transfer reactions. [1] Divalent Fe and Cu ions (Fe^{2+} and Cu^{2+}), and trivalent Fe ion (Fe^{3+}), are highly effective paramagnetic relaxation metal in capable of accelerating both T_1 and T_2 relaxation. Previous studies have shown the susceptibility weighting imaging (SWI) could be employed to quantify iron accumulation in human brain [2]. Other studies combining MRI and laser ablation inductively coupled plasma mass spectrometry (LA-ICP-MS) also demonstrated that the distribution of metal elements could be depicted in SWI [3]. However, there are various metal ions in biological tissue including Fe^{2+}, Fe^{3+} and other metal ions such as copper and manganese, and all of them may contribute to relaxation of magnetization if the concentration is high enough. Besides, the Fe^{2+} and Fe^{3+} can not be differentiated from the measurement of mass spectrometer. It would be interesting to ask a question: Can we quantify the metal concentration under this complicated environment? Therefore, in this study, we designed a simplified phantom experiment to measure the relaxometry of Fe^{2+}, Fe^{3+}, and Cu^{2+} solutions and investigate whether the relaxation rates of Fe and Cu solutions could be modeled as a linear combining relationship. If the linear relationship is confirmed, then it is possible to compute the concentrations of iron and copper independently from relaxation rate via fitting the linear model.

Methods: In phantom study, we utilized iron (II)sulfate, iron(III) sulfate and Copper(II) sulfate to produce the different groups of phantom in a range of concentrations according to the in vivo environment. They are 0.1mM, 0.2mM, 0.3mM, 0.4mM and 0.5mM and two groups were mixed with Cu^{2+} by using Fe^{2+} and Fe^{3+} in the same concentration respectively. The samples were used to fill in the 1c.c. syringe and five different concentration of samples were fixed to the 50ml centrifugal tube than it was full of deionized water. MRI experiments were performed on a 4.7T Bruker Biospin with a volume coil. The images were acquired with IR-EPI and MSME sequences by using the following parameter: TR=12000ms, with TE=54ms and ten inversion times(TI) were used, varying from 50 to 5450 ms in T_1 measurement with IR-EPI and TR=2000ms, TE=50 to 1000ms with 50 interval of 50ms for T_2 measurement with MSME. The T_1 and T_2 were calculated by linear least-squares curve fitting, and linear addition of R_1 and R_2 was calculated by the following equation: $R_{1,2}([Fe],[Cu]) = R_{1,2}(0) + r_{1,2,Cu}[Cu] + r_{1,2,Fe}[Fe]$, where $R_{1,2}(0)$ and $r_{1,2}$ represent the pure water relaxation rate and relaxivity of metal ions, respectively. All data were processed by self-written MATLAB scripts.

Result: Fig.1 shows the R_1 and R_2 of Fe^{2+}, Fe^{3+}, Cu^{2+}, and their mixture solutions under various concentrations. Both R_1 and R_2 of Fe^{2+} and Cu^{2+} increased linearly with ion concentration, while Fe^{3+} and its mixtures presented a nonlinear trend similar to exponential growth. The R_1 and R_2 in Fe^{2+} and Fe^{3+} solutions increased with the presence of Cu^{2+}, since Cu^{2+} is capable to shorten both T_1 and T_2. Comparison on R_1 and R_2 of phantom results and linear model prediction was shown in Fig. 2. In Fe^{2+} mixture, linear calculation gave a similar curve to phantom experiment both in R_1 and R_2. In Fe^{3+} part, R_1 and R_2 were both overestimated by linear assumption. The linear calculated R_1 curve separated more from the measured R_1 curve as ion concentration arises, while the R_2 curves from actual value and linear calculation kept parallel among our concentration settings.

Discussion: The phantom study was designed to examine whether the relaxation rate reflect iron and copper storage linearly. In this study, we found that the R_2 of Fe^{2+} and Cu^{2+} mixture could be predicted successfully by R_2 from pure Fe^{2+} and Cu^{2+} solutions independently. This characteristic, however, didn't hold in Fe^{3+} experiments. It is speculated that under a low pH value around 3, other species of ferric ions may form including dinuclear and more highly condensed species, with some alterations in the relaxivity, as described in literature. [4] As a result, the linearity of Fe^{3+} relaxation rate diminishes along with decreasing pH value. Overall, this study suggests that the concentrations of Fe^{2+}/Cu^{2+} are possible to be quantified simply by measuring relaxation rate, but it may not be so straightforward in mixture solution with Fe^{3+} in low pH level. The quantification of iron concentration may be utilized to investigate issues related to abnormal iron accumulation in human brain. Further studies should be conducted to examine this feasibility since the interactions of ferric, ferrous and copper ions are believed to be more complicated *in vivo*.

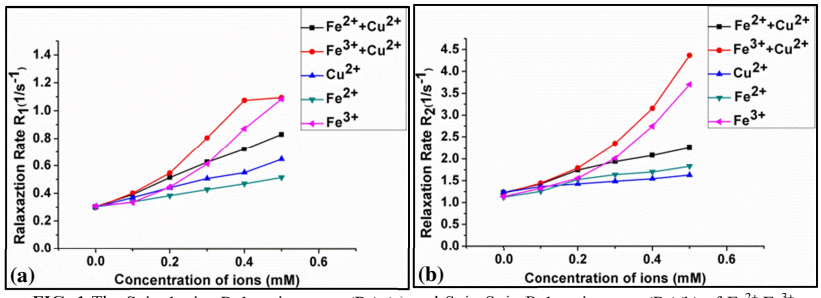

FIG. 1 The Spin–lattice Relaxation rates (R_1) (a) and Spin-Spin Relaxation rates(R_2)(b) of Fe^{2+},Fe^{3+} and Cu^{2+} solutions.

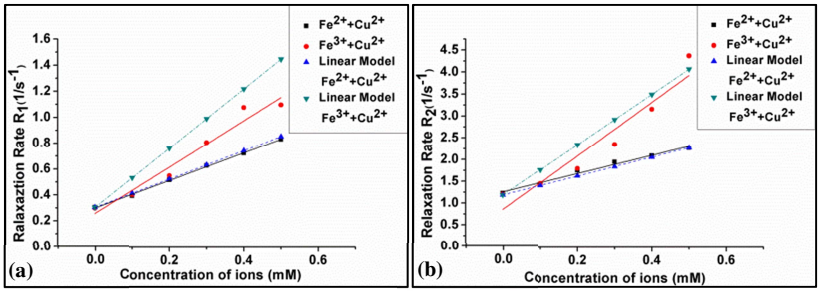

FIG. 2 The Spin–lattice Relaxation rates (R_1) measurement compare with linear model (a) and Spin-Spin Relaxation rate(R_2) measurement compare with linear (b)

References: [1].Madsen,E, et al. Annu. Rev. Neurosci.(2007). [2].Bing Yao, et al. NeuroImage.(2009) [3] A-M. Oros-Peusquens, et al. Proc. Of ISMRM. (2011) [4].J C Gore, et al. Phys. Med. Biol.(1984)