# Bolus-tracking arterial spin labeling; A new marker for age and age related neurological diseases

**M. E. Kelly[1], C. W. Blau[1], R. Bechara[1], M. A. Lynch[1], and C. M. Kerskens[1]**
[1]Trinity College Institute of Neuroscience, Trinity College Dublin, Dublin, Ireland

**Purpose:** Arterial spin labeling (ASL) can be used to provide a quantitative assessment of cerebral perfusion. Despite the development of a number of theoretical models to facilitate quantitative ASL, some key challenges remain. The purpose of this study is to develop a quantitative ASL method based on a macroscopic model that reduces the number of variables required to describe the physiological processes involved. To this end, a novel Fokker-Planck equation (Eq.1) consisting of stochastically varying macroscopic variables was derived. By fitting the solution to Eq.1 to CASL data (Fig.1), the mean transit time (MTT) and capillary transit time (CTT) can be calculated. It is expected that these parameters will vary under varying physiological and pathophysiological conditions. In order to test this hypothesis, a study was carried out in groups of rats of different ages. The initial findings from this ongoing study are presented (Fig.2).

## Methods

*Theory:* The Fokker-Planck equation of motion that describes the distribution of labeled spins in the brain, Eq.1, was derived from a general Langevin equation (1). The equation incorporates three factors that affect the concentration of labeled spins, $c$, at the region of interest (ROI): transport due to bulk flow, $F$, pseudo-diffusion within the microvasculature (perfusion coefficient, $P$) and $T_1$ relaxation of the labeled magnetization. V in this case represents the average volume from the ASL labeling plane to the ROI. Eq.1 was solved for the following boundary conditions that describe a labeled bolus of a defined duration flowing into the ROI: $c(V,t)=c_0(t)$ for $V=0$ and $c(V,t)=0$ for $t=0,V>0$.

$$\frac{\partial c}{\partial t} = -F\frac{\partial c}{\partial V} + P\frac{\partial^2 c}{\partial V^2} - \frac{c}{T_1}$$

Eq.1: Fokker-Planck equation of motion

*Experiment:* The ASL sequence consisted of a 5s preparation interval, containing an inversion pulse of 3s duration and two variable delays, followed by snapshot FLASH image acquisition (7T Bruker Biospin MRI scanner, $TH_S$=2mm, TR=8.56ms, TE=3.04ms, Flip angle=$30^0$, FOV=3.0x3.0cm, NSA=8). The position of the inversion pulse within the preparation interval was varied using the variable delays to simulate a bolus flowing into the imaging plane (thereby providing the eleven time points in the concentration-time curve of Fig.1). Male Wistar rats of varying age (young: 3 to 5 months, middle aged: 12 to 14 months, aged: 22 to 24 months) were used in the study. The animals were anaesthetized using isoflourane.

*Analysis:* Corresponding pairs of labeled and control ASL images were subtracted to provide perfusion-weighted maps for each of the eleven time points. ROIs in the cerebral cortex, hippocampus and whole brain were selected and concentration-time curves (Fig.1,whole brain ROI) were formed by calculating the mean signal intensity within the ROIs and plotting the change in signal versus time. The solution to Eq.1 for a 3 sec bolus was fitted to the experimental concentration–time curves (Fig.1) using the curve-fitting routine in IDL (Research Systems, Boulder, CO, U.S.A.). The MTT and CTT were calculated from the first and second moments of the curve respectively (2,3) with the following results: $MTT = V/F$, $CTT = P/F^2$.

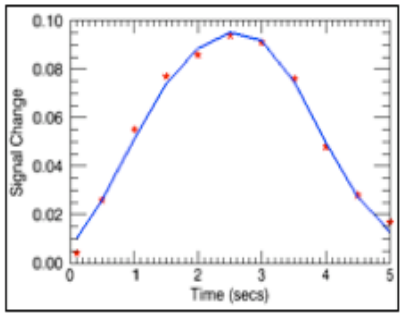


Fig.1: Model (blue) fitted to data (red) for 3.0s bolus

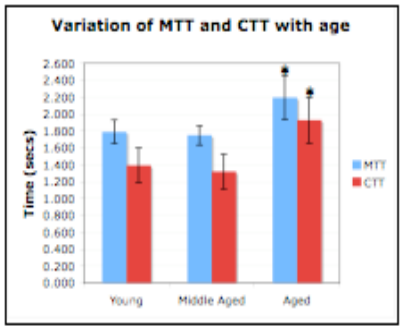


Fig.2: Significant difference (*one-way ANOVA p<0.01) between aged group and young and middle-aged groups

## Results

The theoretical model was found to be in excellent agreement with the experimental data for all datasets (chi-square ≈ 0.0001 for 20 iterations). The mean MTT value for the young, middle-aged and aged groups were 1.79s ± 0.14s, 1.75 ± 0.12s and 2.2s ± 0.26s respectively (error = $2\sigma$). The mean CTT value for these groups was 1.39s ± 0.2s, 1.32 ± 0.21s and 1.93s ± 0.27s respectively. No significant difference was found between young and middle-aged groups but a significant difference in both the MTT and CTT between these two groups and the aged group was identified (one-way ANOVA, p<0.01), as shown in Fig.2.

## Discussion

We have developed a new ASL protocol that is capable of consistently measuring both the MTT and CTT. It has been proposed that while the MTT describes the time taken for a bolus to reach a ROI, the CTT describes the dispersion of that bolus at the ROI (4). The unique of ability of this technique to provide a consistent measure of both transit times holds much promise for future experiments. The technique is applied here to an aging study and a marked difference in both transit times for varying age has been demonstrated. Alterations in vascular dynamics due to aging, such as increased vessel tortuosity, atherosclerosis and reduced vascular reactivity are known to affect cerebral blood flow (CBF) (5). Consequently, a comparison between healthy aged subjects and subjects with various neurological diseases that affect resting CBF using this technique would be of particular interest.

## References

[1] Zwanzig R 2001 *Nonequilibrium Statistical Mechanics*: Oxford University Press
[2] Meier P and Zierler KL 1954 *Journal of Applied Physiology* **6** 731-44
[3] Kim T and Kim SG 2006 *Magnetic Resonance in Medicine* **55** 1047-57
[4] Weisskoff et al 1993 *Magnetic Resonance in Medicine* **29** 553-8
[5] D'Esposito et al 2003 *Nature Neuroscience* **4** 863-872