# Functional bolus-tracking arterial spin labeling; a new approach to quantitative fMRI

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**Purpose:** BOLD fMRI is the most widely used method for mapping neuronal activity in the brain. The alterations in the BOLD signal when cerebral blood flow (CBF), volume (CBV) and vascular structure change (e.g. due to aging and or neurovascular disease) are relatively unknown. This presents a considerable obstacle when interpreting certain BOLD fMRI studies (1). The purpose of this study is to develop a new quantitative fMRI technique, bolus-tracking arterial spin labeling (ASL) fMRI, which provides a more detailed assessment of the blood perfusion of an activated brain region. To this end, a novel derivation of the Fokker-Planck equation (Eq.1) was utilized that reduces the number of variables required to describe the physiological processes involved in cerebral perfusion. The solution to Eq.1 was fitted to ASL data (Fig.2) and the mean transit time (MTT) and capillary transit time (CTT) were calculated. A rat fMRI study was designed to establish if these parameters change during neuronal activation.

## 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 (2). 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 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

*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 curves of Fig.2). Wistar rats (n=4, age = 3 to 5 months) were first anaesthetized using isoflourane and subsequently switched to sedation with a continuous subcutaneous infusion of medetomidine, which has been shown to provide suitable conditions for fMRI studies in rats (3) and is used for the first time with ASL in this study. Electrical stimulation of the right forepaw (3V, 5Hz, 5ms duration pulses) resulted in neuronal activation in the left primary somatosensory cortex forelimb (S1FL) region, at +0.2mm Bregma. The right S1FL was used as the control ROI.

*Analysis:* Corresponding pairs of labeled and control ASL images were subtracted to provide perfusion-weighted maps for each of the eleven time points. Both the activated (left) S1FL and non-activated (right) S1FL were selected as ROIs. Concentration-time curves for these ROIs (Fig.2) 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 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 (4,5) with the following results: $MTT = V/F$, $CTT = P/F^2$.

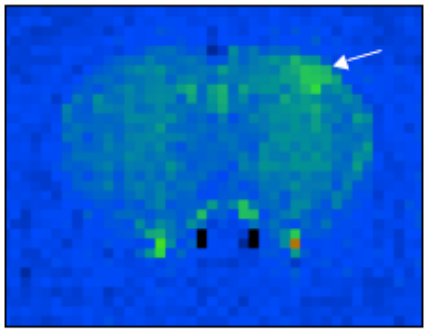

Fig.1: ASL perfusion map - activation in S1FL of the rat somatosensory cortex (white arrow)

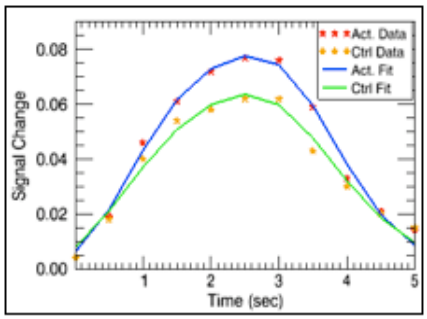


Fig.2: Model (lines) and data (asterisks) for control (ctrl) and activation (act) experiments

**Results:** The ASL perfusion map in Fig.1 demonstrates neuronal activation in the left hemisphere S1FL region. Fig.2 shows the concentration-time curves fitted to the Fokker-Planck model for the control and activated ROIs. The mean MTT (n=4) was 1.87s ± 0.18s (error = σ) and the mean CTT was 1.65s ± 0.06s for the control ROI. For the activation ROI, the mean MTT was reduced to 1.68s + 0.2s and the mean CTT was reduced to 1.37s ± 0.17s. This represents a statistically significant difference ($p<0.01$) between the activated and control ROI, for both transit times.

**Discussion:** We have developed a new fMRI technique, bolus-tracking ASL fMRI, that quantifies the change in MTT and CTT during neuronal activation. The measured decrease in MTT during neuronal activation was expected, as flow to the activated region is known to increase during activation (1). The decrease in CTT can also be attributed to an increase in flow at the activated region (CTT is proportional to $1/F^2$). While the precise mechanism of the reduced CTT is unknown, our approach offers the potential to study its physiological basis repeatedly and non-invasively in the same animal, before and after induction of neurovascular change in animal models of disease.

## References

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