Early time point perfusion imaging: Estimating tissue transit time directly from the data time course

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Introduction
In MR perfusion analysis, the tissue mean transit time τ is normally estimated indirectly by using the ratio of regional cerebral blood volume (rCBV) and regional cerebral blood flow (rCBF). We propose two different methods to estimate τ directly using signals from the tissue contrast agent bolus concentration time course.

Early time points perfusion imaging
In susceptibility contrast-enhanced MRI of Gd-DTPA bolus injection, rCBF can be measured by the Early Time Points Perfusion imaging method (ET) (Kwong et al., 2010). The concept of ET, an idea close to the microsphere perfusion model, proposes to calculate rCBF by measuring the amount of Gd-DTPA arriving within a time window before any contrast agent has a chance to leave the tissue. That time window is in the order of the tissue mean transit time τ, a quantity known to be a few seconds for gray matter in humans. Given that basic assumption of *before the contrast agent having a chance to clear from the tissue*, the quantity of Gd-DTPA present in the tissue will be proportional to local CBF.

$$\text{For ET, } R(t)=1;\ C(t) \approx f\big(AIF \otimes R(t)\big);\ \frac{dC(t)}{dt} \approx f\frac{d}{dt}\big(AIF \otimes R(t)\big);\ rCBF = ratio\ of\ C(t) = ratio\ of\ \frac{dC(t)}{dt} = ratio\ of\ f$$

where $C(t)$ is the contrast agent bolus concentration time curve, f is the perfusion term, AIF is arterial input function, $\otimes$ is the convolution symbol and $R(t)=1$ is the residue function that meets ET's basic assumption. It shows that flow ratio can be obtained from the bolus time course as well as from its derivatives of all orders.

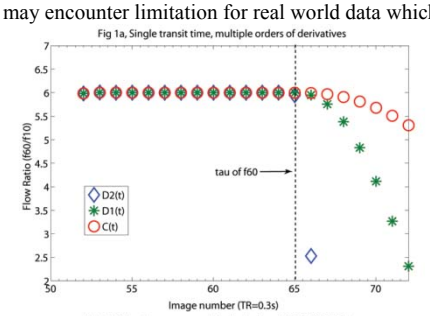
Approach 1 - using the flow ratio time course to locate τ
Based on this basic assumption of ET, a flow ratio calculated from the ratio of gray matter voxel time course and a reference white matter voxel time course would remain constant until τ is reached. Once τ is exceeded, there would be a growing discrepancy between the calculated flow ratio and the "true" flow ratio. The point of departure of the discrepancy provides an estimation of τ. Fig. 1 demonstrates this approach to detect τ with simulation data. It shows a time course of flow ratio of flow level f60 (60ml/100g/min) and the reference flow level f10 (10ml/100g/min). The flow ratio of 6 is evaluated three times using 1) the bolus signal intensity $C(t)$, 2) the first derivative $D1(t)$,and 3) the second derivative $D2(t)$. Fig 1a shows that the flow ratio made from $D2(t)$ is better for τ visualization than that made from $C(t)$. Approach 1 works well for simulation flow data of a single transit time. However, real world data frequently includes the partial volume mixing of several flow levels/transit times in a single voxel. Fortunately, Fig 1b shows that Approach 1 does not reduce its sensitivity to τ detection even with mixed flow levels of two different transit times, f50 (50ml/100mg/min) and f70 (70ml/100mg/min). f50 and f70 with different τ's were equally mixed to give a mean flow value of f60.

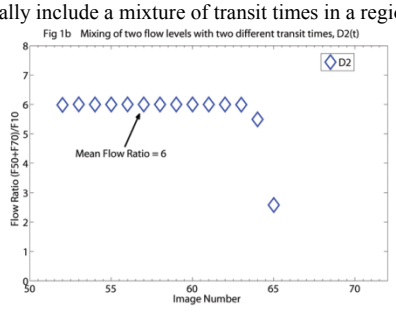
Approach 2 - using the bolus time course itself to locate τ
A flow ratio time course is not required to estimate τ. τ is in principle directly observable from an abrupt change in the shape of a bolus time course without the need of comparing it with a reference flow level. Given $R(t)=1$, the discontinuity of $R(t)$at τ can change the shape of the bolus time course. Fig 2a demonstrates how Approach 2 can be used to detect τ of f(60). While no obvious change is observable at $C(t)$ *or* $D1(t)$, $D2(t)$ again allows the visualization of τ. Unlike Approach 1, the Approach 2's example of Fig 2b shows that partial volume mixing of transit times of f50 and f70 reduces the visibility of any abrupt change in $D2(t)$ of f60.

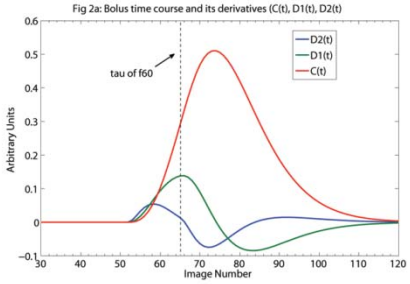
Methods
Noiseless simulation data: Bolus signal curves were simulated at TR=300ms with an AIF modeled by a gamma variate. We generated tissue signal curves $C(t)$as well as their first derivatives $D1(t)$ and second derivatives $D2(t)$. Flow ratio is 6 (f60/f10) . Experimental monkey brain imaging data: Bolus Gd-DTPA injection. TR=300ms, TE=31ms. Gradient Echo-EPI, spatial resolution 3mmx3mmx3mm. Flow ratio was taken from gray and white matter regions of interest (ROI).

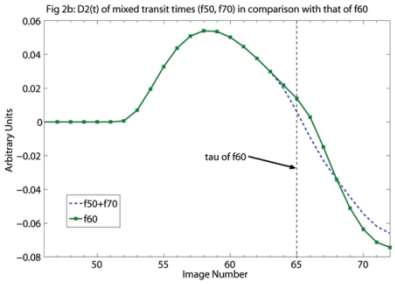
Experimental Results
Monkey's gray/white matter flow ratio (~3.2) time courses at **Fig 3** show similarity with simulation time courses of Fig 1, suggesting the possibility of using flow ratio to search for τ. If flow ratio is not used, monkey's D2(t) alone did not show any obvious abrupt change in the time course (data not shown), suggesting that the inevitable mixed transit times of experimental voxels may reduce significantly the sensitivity of Approach 2 for τ detection.

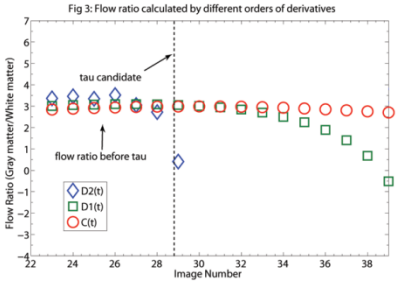
Discussion and conclusion
The flow ratio approach is more sensitive and practical for the estimation of τ because the deviation from the true flow ratio (Fig 1), a marker for τ detection, is enhanced by using a reference time course which does not exceed τ. Mixed transit times also does not affect the ability of Approach 1 to detect τ. Without the advantage of a reference time course, Approach 2 is hurdled by the limited visibility in the change of shape of $D2(t)$ at τ and is handicapped by the mixed transit times. Approach 2 may encounter limitation for real world data which normally include a mixture of transit times in a region of interest and even in a single voxel.











Reference
Kwong, K.K., Reese, T.G., Nelissen, K., Wu, O., Chan, S.T., Benner, T., Mandeville, J.B., Foley, M., Vanduffel, W., Chesler, D.A., 2010. Early time points perfusion imaging. Neuroimage.