AIF and deconvolution

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Introduction

Dynamic susceptibility contrast magnetic resonance imaging (DSC-MRI) is widely used for measuring cerebral perfusion. Both the selection of an arterial input function (AIF) and the following deconvolution of the AIF with the tissue concentration curve are crucial steps in the process converting the measured tissue concentration curves, \( c(t) \), into reliable estimates of CBF, CBV, MTT and Tmax. Several studies have shown that perfusion parameters can be used in acute stroke patients for delineating the ischemic, yet salvageable, tissue (penumbra) [1, 2]. Although surrogate indices such as time to peak and first moment can be readily obtained from \( c(t) \), such parameters are confounded by the underlying vascular architecture, cardiac output and injection rate [3, 4]. Here we will discuss various techniques for estimating perfusion parameters by deconvolution with an AIF.

Measuring the AIF

The AIF, \( c_a(t) \), describes the contrast agent input to the tissue of interest. Ideally the AIF should be measured in a voxel completely contained in the artery feeding the tissue of interest, but due to the spatial resolution typically used in cerebral DSC PWI (around \( 2 \times 2 \times 5 \text{ mm}^3 \)) and the relatively smaller arteries, this is not possible in practice. Instead, the AIF is measured in larger arteries a distance away from the tissue voxel to reduce the contamination of tissue in the voxel used for AIF measurement, the so-called partial volume effects. In practice, one global AIF is usually applied in the perfusion analysis of the entire brain. The measured AIF is therefore not necessarily identical to the contrast agent supply to the tissue voxels because the bolus will be subject to delay (\( t_{\text{delay}} \)) and dispersion traveling from the measuring site to the tissue voxels. This changes the shape of the AIF [5, 6]. In addition to partial volume effects and effects of delay and dispersion, the measured AIF is affected by e.g. signal saturation [7], and by temporal resolution, in-flow and T1 effects [8].

The relation between blood signal and concentration of contrast agent is assumed to be linear in the majority of the published PWI studies. However, it has been shown that the gradient echo relaxation in whole blood, unlike tissue, has a nonlinear dependence on the contrast agent concentration and depends on the hematocrit level [4, 9–12]. Instead of using magnitude-based AIF measurements, it has been suggested by several researchers to use phase-based AIF measurements because the phase is linearly related to the concentration of contrast agent and does not depend on the hematocrit level [13] and moreover is expected to have a
Higher SNR [9, 14–18].

Partial volume effects lead to underestimation of the AIFs depending on the fraction of blood in the voxel. The CBF and CBV scale linearly with the area under the AIF, whereas changes in the shape of the AIF leads to more unpredictable errors in the perfusion estimates. The linearity between CBF and CBV and the area under the AIF has led to different correction schemes such as normalizing the area of the measured $c_a(t)$ to (i) the known injected contrast agent dose [19, 20] or (ii) the area of the venous concentration curve, because the veins has a larger vessel diameter [21, 22]. But not only the fraction of blood in the voxel influences the AIF signal, also the composition of the tissue types within the voxel is important, because the contrast agent filled artery induces field inhomogeneities in the surrounding tissue. Inclusion of this extra contribution to the partial volume effects has been studied theoretically and experimentally by several groups such as [14, 16, 23–27] leading to (i) models trying to quantify the impact of partial volume effects on the perfusion estimates, (ii) suggested optimal locations for the AIF measurement reducing the impact of partial volume effects on the measured AIF and (iii) different correction schemes. The AIF is often measured in voxels adjacent to a large artery instead of in voxels including the artery due to (i) saturation effects in the blood signal caused by the strong dephasing in blood and (ii) a more smooth AIF curve. The signal in such a voxel comes from dephasing of the water protons in the induced field around the contrast agent filled artery in combination with the contribution from the bolus passage in tissue. Therefore a conversion from signal to concentration of contrast agent is not straightforward in these voxels.

Delay and dispersion have been shown to result in underestimation of CBF and overestimation of MTT [6, 28, 29]. In order to reduce this effect, local AIFs have been suggested, but these voxels have severe partial volume of tissue because the blood vessels closer to the tissue are even smaller [30–35].

AIF variation has been proposed to be one of the main reasons for the large variability in the perfusion estimates among patients [21, 36], and therefore several authors have presented algorithms for automatic selection of the AIF in order (i) to reduce operator dependence [37] and (ii) to determine the AIF from the concentration curves looking most ‘arterial-like’, such as early onset, steep rise, large signal drop or large area [37–40].

Deconvolution

The tissue concentration curves $c_t(t)$ and the AIF, $c_a(t)$, are related by the following relation

$$c_t(t) = \text{CBF} \cdot \int_{-\infty}^{t} c_a(\tau) R(t - \tau) d\tau,$$

(1)

where $R(t)$ is the residue function, which equals the fraction of contrast agent that remains within the volume of interest at time $t$ after entering it. CBF is estimated from Eq. [1] by deconvolving the measured concentration curves and thereby obtaining the perfusion weighted residue function $R_{pw}(t) = \text{CBF} \cdot R(t)$. It follows theoretically, that CBF = $R_{pw}(t = 0)$ from
the definition of the residue function \( R(t = 0) = 1 \) in the case of no delay between \( c_a(t) \) and \( c_t(t) \). In case of delay, the flow is best approximated by the maximum of \( R_{pw}(t) \). The cerebral blood volume (CBV) is usually obtained from

\[
\text{CBV} = \frac{\int_0^\infty c_t(t)dt}{\int_0^\infty c_a(t)dt}.
\]

MTT is calculated using the central volume theorem \([41, 42]\).

Different deconvolution methods have been suggested over the years and the most popular methods are singular value decomposition (SVD) and Fourier transform (FT) \([43–45]\). Standard SVD (sSVD) displays an unwanted dependence on \( t_{\text{delay}} \) \([6]\), whereas FT is inherently delay insensitive due to its periodic nature. The periodicity of FT, however, leads to underestimation of the initial point of \( R_{pw}(t) \) due to FT interpolation at the discontinuity in the function at \( t = t_0 \) where \( R_{pw}(t) \) increases from zero to CBF instantaneously. Thus, CBF estimated as the maximum of \( R_{pw}(t) \), is typically found at the second sample of \( R_{pw}(t) \), leading to underestimation of CBF. The underestimation depends on TR (defines the timing between the first and second sample of \( R_{pw}(t) \)) and MTT (defining the width of \( R_{pw}(t) \)) and the overall shape of the true \( R_{pw}(t) \) \([43]\).

In 2003, Wu et al. \([45]\) introduced the block circulant SVD (cSVD) which is mathematically equivalent to FT, \([46, 47]\), in order to correct for the delay sensitivity. The reproduced CBFs still display a strong dependence on the underlying residue function as was the case with the sSVD results in \([43]\). The year after, Smith et al. \([48]\) introduced a delay insensitive version of sSVD.

The above mentioned methods are model-independent methods, but also model-dependent approaches have been suggested covering different fitting methods. Fitting methods are in general more computational demanding compared to the methods presented above. The fitting methods, however, have the advantage of being able to estimate the high CBF values more accurately and produce more smooth versions of \( R_{pw}(t) \) as prescribed by the models \([49–51]\).

Regularization is necessary in order to produce robust estimates of \( R_{pw}(t) \). The low-pass filter originally employed by Østergaard and colleague was a window function (truncation) reducing the eigenspace of the AIF by excluding the small eigenvalues which usually represents the high frequency components, which again are considered to represent noise \([43]\). This filter was adopted by Wu and coworkers \([45]\) in both cSVD and oSVD. The latter method uses an oscillatory index (OI) to penalize unphysiological oscillations in the estimated \( R_{pw}(t) \) in combination with the truncation filter. It is an adaptive regularization method that introduces different regularization levels in the individual voxels, whereas the other methods use a global regularization level. In contrast to the truncation filter, different smooth filters have been investigated such as the Hann filter \([44]\), Tikhonov filter \([52, 53]\) and Wiener filter \([43, 54, 55]\) in combination with both SVD and FT.

Ideally, regularization only removes noise components and not components of the underlying function, but for low SNRs this is impossible. The strength of the regularization is determined by the regularization level which must be optimized for its specific use in order to produce
the optimal result. The regularization levels of the sSVD, cSVD and oSVD were optimized to best reproduce CBF over a large range of CBF’s, MTT’s, CBV’s averaging over three different residue models (1) exponential (a well mixed compartment), (2) boxcar and (3) triangular shaped in order to catch the expected physiological variability in residue functions [43] for different SNRs [45, 56]. Using the optimal regularization level Wu et al. showed that the high CBFs are systematically underestimated due to the corresponding short MTT for exponential residue functions whereas for boxcar residue function the high CBFs are systematically overestimated.

Concluding remarks

As outlined above, there are still research to be performed in this field and solving some of the methodological challenges, will lead PWI to be a powerful tool in the study and management of neurological diseases, in particular acute stroke. Robust perfusion estimates are crucial, since tissue mean transit time (MTT), normalized cerebral blood flow (CBF) values, or time to maximum of the residue function (Tmax), are compared across subjects to establish a perfusion threshold that may guide the selection of patients for thrombolytic treatment [57–59].

References


