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A control point interpolation method for the non-parametric quantification of cerebral haemodynamics from dynamic susceptibility contrast MRI

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ABSTRACT

DSC-MRI analysis is based on tracer kinetic theory and typically involves the deconvolution of the MRI signal in tissue with an arterial input function (AIF), which is an ill-posed inverse problem. The current standard singular value decomposition (SVD) method typically underestimates perfusion and introduces non-physiological oscillations in the resulting residue function. An alternative vascular model (VM) based approach permits only a restricted family of shapes for the residue function, which might not be appropriate in pathologies like stroke. In this work a novel deconvolution algorithm is presented that can estimate both perfusion and residue function shape accurately without requiring the latter to belong to a specific class of functional shapes. A control point interpolation (CPI) method is proposed that represents the residue function by a number of control points (CPs), each having two degrees of freedom (in amplitude and time). A complete residue function shape is then generated from the CPs using a cubic spline interpolation. The CPI method is shown in simulation to be able to estimate cerebral blood flow (CBF) with greater accuracy giving a regression coefficient between true and estimated CBF of 0.96 compared to 0.83 for VM and 0.71 for the circular SVD (oSVD) method. The CPI method was able to accurately estimate the residue function over a wide range of simulated conditions. The CPI method has also been demonstrated on clinical data where a marked difference was observed between the residue function of normally appearing brain parenchyma and infarcted tissue. The CPI method could serve as a viable means to examine the residue function shape under pathological variations.

Introduction

Dynamic susceptibility contrast magnetic resonance imaging (DSC-MRI) is frequently used in the measurement of cerebral perfusion in stroke and other pathological conditions. It has been shown that perfusion parameters like cerebral blood flow (CBF), cerebral blood volume (CBV) and mean transit time (MTT) can be used in acute stroke patients for quantification of cerebral ischaemia (Kane et al., 2007; Østergaard, 2005; Østergaard et al., 1996a, 1996b). The measurement of these perfusion parameters is based on tracer kinetic theory (Gobbel and Fike, 1994; Østergaard et al., 1996a, 1996b; Zierler, 1962) that considers the tissue concentration time curve as the convolution of the arterial input function (AIF) with a CBF-scaled tissue residue function. The residue function describes the fraction of tracer remaining in the tissue vasculature at a time after its arrival. One major concern in inferring the crucial perfusion parameters from DSC-MRI is reliable and accurate deconvolution of the observed concentration time curve (CTC) with respect to the measured AIF.

Initially an analytical model-dependent deconvolution technique was proposed (Jacquez, 1972) but it has been superseded by more flexible nonparametric approaches like frequency domain deconvolution (Fourier transform) (Gobbel and Fike, 1994; Rempp et al., 1994) and later by algebraic singular value decomposition (SVD) method (Østergaard et al., 1996a, 1996b). Variants of the SVD approach such as tSVD (truncated SVD) (Østergaard et al., 1996a, 1996b) and the time insensitive oSVD (circular-SVD) (Wu et al., 2003) are widely used to estimate the tissue response function (TRF; defined as residue function multiplied with CBF), its maximum value being used to estimate CBF. The key issues with SVD-based methods are the underestimation of CBF and also the introduction of non-physiological oscillations in the resulting residue function, making the residue function difficult to interpret. There have been attempts with various regularization approaches to reduce the oscillation in the residue function. Some of the widely used regularization methods involve: truncated SVD (threshold using Psvd (Østergaard et al., 1996a, 1996b)), oSVD using oscillation index (OI) (Wu et al., 2003) or adding of a penalty term in the optimization, for example

Abbreviations: AIF, Arterial input function; CBF, Cerebral blood flow; CBV, Cerebral blood volume; CP, Control point; CPI, Control point interpolation; DSC-MRI, Dynamic susceptibility contrast magnetic resonance imaging; GRE, Gradient echo; MTT, Mean transit time; oSVD, Circular SVD; SNR, Signal to noise ratio; SVD, Singular value decomposition; tSVD, Truncated SVD; VM, Vascular model.

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the Tikhonov regularization of Calamante et al. (2003). Despite all these efforts the estimation of realistically smooth residue functions has not yet been achieved with SVD methods.

More recently Mouridsen et al. (2006) have proposed a vascular model (VM) implemented within a Bayesian framework as an alternative to SVD methods. The model is based on a vascular architecture where a gamma probability distribution function is assumed to model the underlying tracer transit times. The VM perfusion values are believed to produce more accurate estimates compared to the SVD method, but, being a model-based solution, it lacks the flexibility of SVD methods. In particular, the underlying gamma distribution in the VM is controlled by two parameters that permit only a restricted family of shapes for the tissue response function which might not be appropriate in modelling altered vasculature in pathologies like stroke.

The shape of residue function is also of interest because it contains information about tissue vascular integrity (Østergaard et al., 1999). For *in vivo* analysis the actual residue function shape is not known *a priori* and, particularly in pathology, might not be drawn from the set of functions currently assumed for typical residue functions. Hence an analysis approach that is both model-free and non-parametric would be desirable. The goal of this work was therefore to develop a deconvolution algorithm that produces accurate perfusion values by improved estimation of the residue function over a wide range of physiological conditions. We propose a Bayesian control point interpolation (CP-interpolation, CPI) deconvolution method that can estimate cerebral perfusion along with a physiologically plausible residue function without requiring it to belong to a specific class of functional shapes. The resulting residue function shapes can be used to assess the residue function variability among different brain regions and changes in the residue function in pathology.

First, theoretical concepts of tracer kinetic theory, SVD deconvolution and VM method are described followed by the framework for the CP-interpolation method and its estimation procedure. Subsequently, the simulation protocol that was used to evaluate the method will be elaborated. Finally, examples are given where the CP-interpolation method was applied to analyze data from a healthy participant and a cerebrovascular diseases patient and the results compared with SVD and VM methods.

Theory

For a given tissue voxel it is assumed that the intravascular tracer delivery to the capillaries can be represented by an arterial input function (AIF), denoted by $Ca(t)$. According to the indicator-dilution theory (Gobbel and Fike, 1994; Østergaard et al., 1996a, 1996b; Zierler, 1962), the concentration of the tracer in the capillaries at time t can be expressed as the convolution of $Ca(t)$ with the tissue residue function $R(t)$, scaled by the cerebral blood flow (CBF):

$$C(t) = \alpha \cdot \mathrm{CBF} \cdot (Ca\,(\mathrm{t}) \otimes R(t)) = \alpha \cdot \mathrm{CBF} \int_0^{\tau} Ca\,(\tau) \cdot R\,(t-\tau) d\tau \qquad (1)$$

Where $C(t)$ is the measured concentration time curve, $\otimes$ represents convolution as defined on the right-hand side of the equation and the proportionality constant α is a measure of brain tissue density and difference in haematocrit between capillaries and large vessels (compensating for the fact that only plasma volume is accessible to contrast agent) (Calamante et al., 1999). Since the parameter α is generally indeterminable, it is usually replaced by a fixed value (Calamante et al., 1999; Knutsson et al., 2010). The residue function is a monotonically decaying function with an initial value of one, $R\,(0) = 1$. The analysis of Eq. (1) typically involves deconvolution of the chosen AIF from the measured CTC. The resulting tissue response function contains the information about both CBF and the residue function shape. The estimated residue function shape itself contains information on microvascular flow heterogeneity (Jespersen and Østergaard, 2012; Østergaard et al., 1999). Another important perfusion parameter calculated from the CTC is the mean transit time (MTT). This signifies the average time for a contrast molecule to pass through the tissue vasculature following an ideal bolus injection and can either be calculated using the central volume theorem (Zierler, 1962, 1965)

$$MTT = \frac{CBV}{CBF} \qquad (2)$$

where,

$$CBV = \frac{\int C(t)\,dt}{\int Ca(t)\,dt} \qquad (3)$$

or, estimated as the area under the deconvolved residue function (Knutsson et al., 2007, 2010; Wirestam et al., 2007):

$$MTT = \int R(t)\,dt \qquad (4)$$

The most frequently used methods for the deconvolution process are truncated singular value decomposition (tSVD) (Østergaard et al., 1996a, 1996b) and its time insensitive variant circular-SVD (oSVD) (Wu et al., 2003). These use a discrete matrix representation of Eq. (1) and perform SVD to calculate the pseudo-inverse of the AIF matrix. The resultant TRF (tissue response function) from a simple SVD methodology (linear deconvolution process) usually has a highly oscillatory solution hence the tSVD method uses a threshold (Psvd) for singular values in the SVD methodology (typically 20% of the largest singular values). The introduction of Psvd enables it to regularize the resulting residue function. The oSVD variant instead uses a circular deconvolution matrix as well a local regularization parameter, oscillation index (OI), to derive an optimal threshold that balances CBF underestimation and noise-induced instability of the computed solution. The circular deconvolution was proposed as a means to make the deconvolution insensitive to bolus arrival delay, where bolus arrival delay (δ) signifies the temporal delay in the arrival of the tracer to the tissue with respect to the measured AIF. The maximum of the resultant TRF is the value of CBF. The oSVD method has been demonstrated to provide a substantial improvement over tSVD, hence is widely used in practice. However, in spite of employing a better regularization technique, the method is still unable to provide a smooth characterization of the residue function shape and results in significant underestimation of CBF particularly for high flow and short MTT values. The same is true for any regularization approach as oscillations in resulting solution is an inherent property of model-free-deconvolution regularized methods (*e.g.* SVD methods); regularization dampens the oscillations at the cost of losing accuracy in perfusion estimates.

The more recently proposed vascular model (VM) based approach was introduced to estimate a smooth monotonically decreasing residue function shape along with more accurate estimates of perfusion values (Mouridsen et al., 2006). The VM assumed a parallel distribution of capillaries in the tissue volume that is being supplied. This was characterized by a continuous distribution of transit time for which a gamma distribution was chosen:

$$h\,(t;\alpha,\beta) = \frac{1}{\beta^{\alpha} \cdot \Gamma\,(\alpha)} \cdot t^{\alpha-1} \cdot \exp^{-t/\beta} \;;\alpha,\beta > 0 \qquad (5)$$

where, $h\,(t)$ was the density function of the transit times, α was the shape and β was the scale parameters respectively.

From this an analytic form for the residue function could be written:

$$R\,(t) = \int_t^{\infty} h(\tau;\alpha,\beta) d\tau \qquad (6)$$