Improved characterisation of delayed and dispersed residue functions in bolus tracking perfusion MRI

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Introduction: In dynamic susceptibility contrast MRI (DSC-MRI), cerebral blood flow (*CBF*) is calculated by inverting the equation $C(t)=CBF.AIF(t) \otimes R(t)$, where *AIF(t)* is the measured arterial input function, *C(t)* is the measured tissue concentration, and *R(t)* is the unknown tissue residue function. This is an ill-posed problem because of discrete sampling and the presence of noise. We have shown previously that in the presence of bolus delay and/or dispersion, the standard method of inversion, Singular Valued Decomposition (SVD) [1], poorly characterizes *R(t)* and significantly underestimates *CBF* [2,3]. An alternative method is needed in cases where the shape of *R(t)* is of interest, e.g. to assess delay, dispersion, or to calculate flow heterogeneity [4]. Among those proposed, Tikhonov regularization can accurately determine *R(t)* when the bolus is dispersed but has no delay [3]. Circular SVD [5] provides delay insensitive *CBF* measurements, but the shape of *R(t)* is still poor. The iterative method of maximum likelihood-expectation maximisation (ML-EM) can also reconstruct *R(t)* when delays are present [6]. However, the optimum number of iterations depends on the shape of the function being recovered. This work describes a *multistage* approach, introducing a modification of the ML-EM method that uses a *point-wise* stopping criterion for the iterations, enabling the accurate reconstruction of a delayed and/or dispersed *R(t)*, and preventing corruption due to amplification of noise. The methodology was assessed using Monte Carlo simulations.

Methods: The ML-EM method iteratively adjusts an estimate of *R(t)*, to maximise the likelihood of measuring the observed *C(t)*, given *AIF(t)*, *R(t)* and noise [6]. Sampling at TR necessitates the discretisation of the convolution integral with the matrix **A**. Østergaard minimised discretisation errors by using a matrix **A1,** which assumes both the measured *AIF* and recovered *R* vary linearly between time points [1]. The assumption of linearity in *R* can be considered inappropriate for the discontinuity arising from a delayed but undispersed bolus. We therefore also considered the matrix **A2,** which only assumes linearity in *AIF*. Since in real data the presence/absence of delay and dispersion is unknown, a *multistage* approach to the reconstruction was adopted. In the first stage, standard ML-EM reconstructions are performed using both matrices (**A1** and **A2**). The appropriate matrix is selected with automated empirically determined criteria for the final reconstruction, which uses a modified ML-EM method for optimum shape characterisation. The modified algorithm is initiated with a uniform guess for *R*. Low spatial frequencies are recovered in the first few iterations. Further iteration reconstructs the more slowly converging higher frequency components, but inevitably, noise begins to deteriorate *R*. The optimum point to stop is highly dependent on the unknown shape of *R* and also on the SNR: fewer iterations are required to optimally characterise a noisy dispersed function than a delayed but undispersed function. In this work we propose a *point-wise* stopping rule that prevents deterioration due to noise whilst still extracting the high frequency information associated with *R* itself. The stopping criterion is based on the individual convergence of each point in *R*. Points that characterise the low frequency components are recovered first and are then kept at these values until all points in *R* have converged. An automatic convergence condition was empirically determined in terms of the position, *j* and value $r_j^{(n)}$ of the point, the area under $R^{(n)}$, and the convergence of surrounding points.

The methodology was tested on simulated and on patient data. For the simulations, *AIF* was modelled as a gamma-variate function with recirculation [1], and *R(t)* as the dispersed exponential $R(t-t_0)=[\exp(-(t-t_0)/b)-\exp(-(t-t_0)/MTT)]/((b/MTT)-1)$, for delays t_0 and dispersions *b*, where *MTT* is the mean transit time. Tissue curves were simulated for a range of *CBF*, *MTT*, TR, SNR, t_0, *b*, and sampling times. 100 different noisy tissue curves were generated for each parameter combination and the means and standard deviations for the recovered *R* were evaluated. The patient data were acquired on a 1.5T Siemens Symphony scanner using a GE-EPI sequence (TE/TR=47/1500ms) after injecting 0.15mmol/kg of Gd-DPTA. To assess the effect of SNR, denoising was performed using independent component analysis (ICA) [7]. This improves the SNR ($=\sigma_{S0}/S0$) of our data from 50 to 500. For both simulated and real data, the *CBF* and delay were estimated and compared with those obtained using a standard (single stage unconstrained) ML-EM of 200 iterations [8].

Results: The proposed method enables the reconstruction of many different residue function shapes by minimising the risk of over/under iteration of different parts of the function. The standard deviation of the individual recovered points of *R* is reduced compared with standard ML-EM, especially at lower SNR, and individual residue functions are smoother. Figure 1 shows the simulated and a typical recovered *R(t)* for *CBF*=60 ml/100g/min, *MTT*=4s, t_0=2s and *b*=0s with tissue SNR=50. Between 100 and 200 iterations are required to characterise the sharp rise to maximum of a delayed exponential function, whereas fewer than 50 iterations are needed for the convergence of the tail points. The method is robust across the tested *CBF* range. Even for short *MTT*, a TR of less than 1.5s avoids the *CBF* underestimation usually observed with other algorithms [1], although in these cases, for a delayed and non dispersed bolus, it is difficult to reconstruct the true maximum of *R(t)* (because of the very high frequencies involved). In general, however, the function-dependent convergence criteria enable robust and accurate shape characterisation for SNRs greater than around 50 and sampling time greater than around 50 seconds.

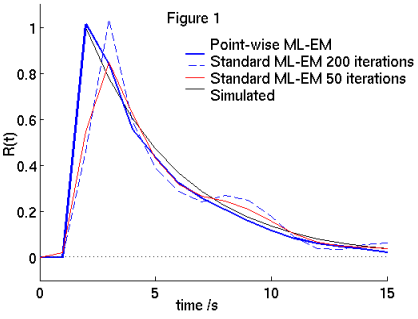
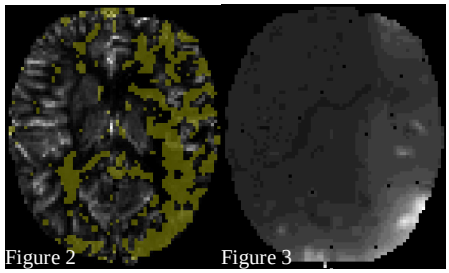


Figure 2 illustrates the results found for in vivo data from a patient with middle cerebral artery (MCA) stenosis. The *CBF* map was created using ICA denoised data with an *AIF* measured in the contra-lateral MCA. Pixels are classified as dispersed (highlighted yellow) or undispersed (no colouring) according to the choice of matrix **A** made in the first stage of the reconstruction. For comparison, figure 3 shows a map of the time-to-peak for the *local AIF* [7] (an alternative method for estimating bolus dispersion). Pixels classified as dispersed measure low *CBF*, and broadly correspond to those pixels with late time-to-peaks.



Discussion: A new deconvolution method, based on a modified ML-EM approach is described. The appropriate choice of convolution matrix and point-wise stopping criteria for the ML-EM reconstruction improves the characterisation of the residue function. Iteration of the tail points in *R(t)* is stopped before the points defining the maxima and rise to maxima. As a result sharper residues are reconstructed with more iterations, and noise fitting is minimised. This was demonstrated with both simulated and patient data. In addition to accurate residue function characterisation, maps indicating the presence of delay and/or dispersion can be created from the patient data. Since the presence of delay and dispersion introduce bias in *CBF*, these maps could be used to indicate the reliability of the *CBF* estimates and could help improve tissue classification models.

References: [1] Østergaard L *et al.* (1996) *MRM* 36:715. [2] Calamante F *et al.* (2000) *MRM* 44:466. [3] Calamante F *et al.* (2003) *MRM* 50:1237. [4] Simonsen CZ *et al.* (2002) *Radiology* 225:269. [5] Wu O *et al.* (2003) *MRM* 50:856. [6] Vonken EPA *et al.* (1999) *MRM* 41:343. [7] Calamante F *et al.* (2004) *MRM* 52:789. [8] van Osch MJP *et al.* (2003) *MRM* 50:614.