A novel method of model-based rigid registration for dynamic contrast enhanced MRI studies.

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Introduction Quantitative, model-based, analysis of contrast agent uptake kinetics in dynamic contrast enhanced MRI (DCE-MRI) allows us to estimate the magnitude and spatial distribution of physiological kinetic parameters – such as k^{trans}, v_e and v_p – which provide useful information on the state of microvasculature in tumours and inflammatory conditions[1]. Such analyses usually derive a contrast agent concentration time course and fit a tracer kinetic model within each voxel in a volume of interest (VOI). The parameter estimates can therefore be distorted by patient and physiological motion during the time series acquisition as the voxel-to-tissue mapping varies with time. In particular, failure to correct for the high amplitude motion of abdominal tumours and their surrounding tissues due to breathing can lead to significant modeling errors. However, DCE-MRI data sets pose severe difficulties for conventional registration-based motion correction, for which established methods include registering each image volume in the time series to a "standard" time point or to the time series average[2]. One key problem is the strong signal variation during the time course due to the first pass of contrast agent through tissues and the subsequent contrast agent recirculation and leakage. It has been proved possible to register pre-contrast to "steady-state" post-contrast images using inter-modal registration cost functions, such as mutual information[3], and to incorporate a simplified model of the temporal variations in signal intensity into a registration algortihm[4], but the problem of registering a time-series with a high temporal resolution in abdominal tumours has not been resolved. We propose a novel model-based registration method that addresses these issues.

Data We acquired dynamic 3D spoiled gradient echo (Fast Field Echo) data with a temporal resolution of 4.96 s, voxel size of 2.93 x 2.93 x 4.0 mm^3 and FOV of 375 x 375 x100 mm^3 on a Philips 1.5 T Intera scanner, selecting 7 data sets with independently visually assessed "moderate" or "severe" motion on a 4 point scale. We quantified contrast agent concentration via a T_1 measurement[1], sampled the arterial input function (AIF) by an automated method[5] and manually defined tumour VOIs in 3D on co-localised T_2-weighted and T_1-weighted image volumes.

Registration *Step 1:* Using the locally-written MaDyM package, we fit the modified Kety model[6] (with a measured AIF[5]) to the motion-corrupted DCE time series within the tumour VOI to provide initial estimates of k^{trans}, v_e and v_p[1,7]. *Step 2:* We output 3D maps of the fitted signal intensities for each time point in the series – these are best fit images that display no motion from time point to time point (the motion in the original data leads to blurring and reduced contrast in the best fit images). *Step 3:* We perform a 3 degrees of freedom registration using FLIRT[8], matching each original time point volume to the best fit volume (which serves as the reference volume). We use the normalised correlation cost function, evaluated only within the tumour VOI. We constrain the magnitude of translation to be within the observed magnitude of motion during the time series to minimise the occurrence of unrealistic local minima. *Step 4:* We fit the modified Kety model[6] to the registered time series. We repeat Steps 2 to 4 until a minimum is found in the median sum of the squared error (SSE) on the kinetic model fit within the tumour VOI, at each stage fitting the model to the "last-registered" time series to generate new reference best fit images then registering this time-series to the new best fit images.

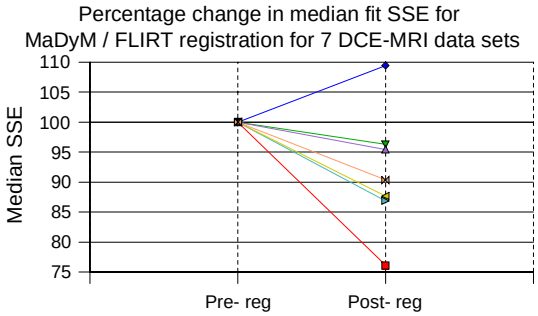

Fig. 1 Median SSE improves in 6 / 7 data sets after registration.

Results In 6 of the 7 data sets the median SSE reduced after at most 6 iterations of the model-based registration (Fig. 1). The SSE increased (and the registration was therefore judged to be a failure) in a single small tumour that had poor contrast to the surrounding normal tissue.

Fig. 2 shows subtraction images in a liver tumour comparing the reference (best-fit) signal intensity to the corresponding measured signal intensity before and after registration. After registration the values in the difference images are closer to zero and more uniform within the VOI, implying that the registration is reducing the motion effects. Maps of the SSE show similar patterns to the subtraction images of Fig. 2, and are also more uniform after registration (data not shown).

Median k^{trans}, v_e and v_p over the tumour VOI were all within 10% of their pre-registration values; however, the parameter maps output by the modeling software change significantly, indicating better localisation of microvascular functional features (Fig. 3).

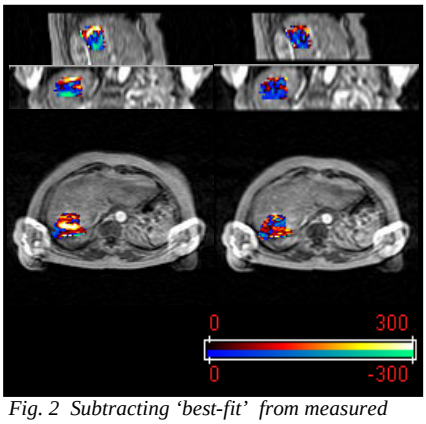

Fig. 2 Subtracting 'best-fit' from measured signal intensities shows increased homogeneity in the tumour VOI after registration. Pre-reg to left, post-reg to right; top – sagittal view, middle – coronal view, bottom – axial view. Scale is signal intensity units.

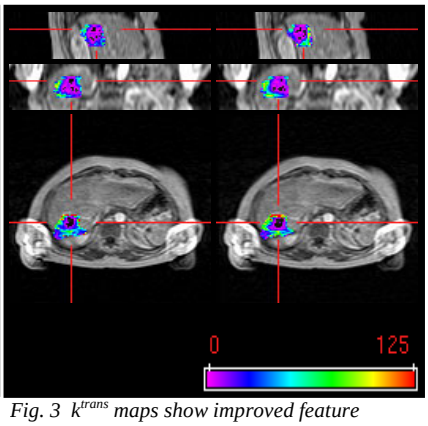

Fig. 3 k^{trans} maps show improved feature localisation after registration. Pre-reg to left, post-reg to right; top – sagittal view, middle – coronal view, bottom – axial view. Scale is 100 × k^{trans} min^{-1}.

Discussion Model-based registration improves the fitting of physiological kinetic models to DCE-MRI time series data, as demonstrated by a reduction in SSE of the model fit and better localisation of microvascular functional features. Our method performed significantly better than conventional time series registration applied to the same data (data not shown). To achieve this result, it was essential for the registration process to incorporate a model that accurately predicted the expected changes in signal intensity within the tissues of interest. For highly vascular lesions studied at high temporal resolution, as in our study, the first passage of contrast agent is often observed in the tumour tissue, requiring a model that accounts for the vascular space (v_p). With such data it is critical to use an accurate arterial input function in the modeling process or we run the risk that the DCE-MRI volumes acquired during bolus passage will be significantly mis-registered.

Our proposed method has the potential to significantly improve the accuracy and reproducibility of quantitative DCE-MRI analyses and may therefore make it possible to reveal trends (for example as a result of drug action) that are obscured by movement in organs subject to severe motion, such as the liver.

References 1. G.J.M. Parker & A.R. Padhani *in* P.S. Tofts (ed.) *"Quantitative MRI of the brain"*, Wiley, 2003. 2. M. Jenkinson *et al. NeuroImage*, **17**, 825-841, 2002. 3. D. Rueckert *et al. IEEE Trans. Med. Imag.*, **18**, 712-721, 1999. 4. P. Hayton *et al*., *Med. Image Anal*, **1**, 207-224, 1997. 5. G.J.M. Parker *et al. Proc. Int. Soc. Magn. Reson. Med.*, 1264, 2003. 6. P.S. Tofts *et al*., . *J. Magn. Reson. Imag.* **10**, 223-232, 1999. 7. J.U. Harrer *et al. J. Magn. Reson. Imag.*, **20**, 748-757, 2004. 8. M. Jenkinson & S. Smith. *Medical Image Analysis.* **5**, 143-156, 2001.