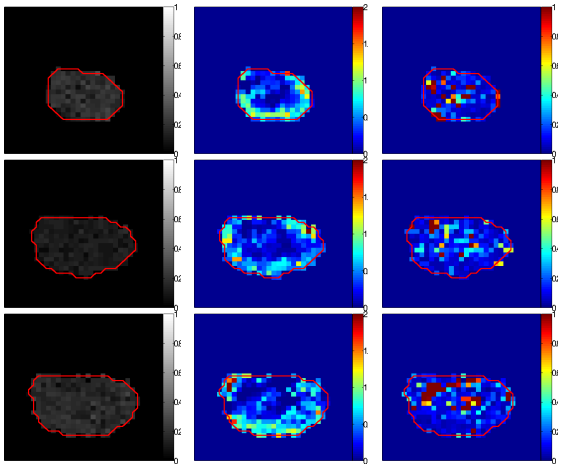
PHARMACOKINETIC MODELLING OF LONGITUDINAL DCEMRI SCANS FOR ASSESSMENT OF TUMOUR GROWTH

Monica Enescu[1], Amalia Cifor[1], Veerle Kersemans[2], Danny Allen[2], Stuart Gilchrist[2], John Beech[2], Sean Smart[2], Michael A Chappell[1], and Julia A Schnabel[1]
[1]*Institute of Biomedical Engineering, University of Oxford, Oxford, United Kingdom,* [2]*Preclinical Imaging Group, University of Oxford, Oxford, United Kingdom*

Background: Dynamic contrast enhanced MRI (dceMRI) is increasingly used for cancer imaging, as it provides information about tumour microvasculature changes that occur during growth or treatment. These changes are typically quantified using pharmacokinetic (PK) modelling. The model, which is fitted to the contrast enhancement-time curves at each voxel, describes the flow of contrast agent (CA) from the extravascular extracellular space (EES) in terms of PK parameters. In this work, the CA uptake is described using the Tofts[1] model, which is governed by three parameters: K_{ep}, V_e and K^{trans}. The latter is considered the most meaningful from a physiological viewpoint, as it indicates a combination between tissue perfusion and vessel permeability.

Purpose: 1) Measuring tumour growth from longitudinal imaging data using a new registration approach. We have adapted a previously developed multichannel non-rigid registration algorithm[4] to align subsequent time points over the tumour growth cycle to the first time point (Tp). The novelty of this approach resides in using the PK parameter maps K_{ep} and V_e, alongside the image intensity as channels in the registration (Fig.1). The Jacobian of these transformations is used as an indicator of tumour volume change. 2) Investigating whether K^{trans} at the first Tp has predictive value for tumour growth in subsequent images.

Materials and methods: Three mice were injected with MC38 (colon carcinoma) tumour cells to develop subcutaneous tumours and imaged with dceMRI at three time points over the tumour growth cycle (days 21, 23 and 24 post injection). This enables direct investigation of tumour growth and heterogeneity. The animals were immobilised for imaging using gaseous anaesthesia. dceMRI was performed at 4.7T (Agilent VNMRS) using a respiratory-gated 3D gradient echo sequence (TE 0.6ms, TR 1.1ms and a nominal flip angle of 5°). 128×64×64 voxels covered a field of view of 54×27×27mm encompassing the entire volume of the birdcage coil. 50-100 repeats of this scan, each lasting ca. 8-12s were acquired with Gadolinium contrast agent (Omniscan, 30 ul in 5s). To quantify the T_1 change, $T_{1(0)}$ mapping was performed using an array of flip angles, and correction of the B_1 inhomogeneities was performed using a respiration gated modification of the actual flip angle method[2].



(a)Image intensity (b)Kep (c)Ve

Fig.1 Pharmacokinetic parameter maps together with corresponding dceMRI images. Each row corresponds to a longitudinal time point: Row 1 (day 21), Row 2 (day 23), Row 3 (day 24)

Pharmacokinetic modelling of each time-point was performed using the Tofts model[1] and the Weinmann bi-exponential arterial input function with population averaged parameters as derived by Heilmann et al.[3]. To enable a spatial comparison of the PK parameter maps, the differences in mouse positioning were eliminated using rigid registration. We assume the remaining differences are due to tumour growth. To capture these differences, we use the Hybrid Feature-based Diffeomorphic[4] (HFD) registration method. In this multichannel approach we use both image intensity and the PK parameter maps to drive the registration. HFD consists of the estimation of two types of forces for each input channel: (1) Demons-like forces estimated locally, and (2) forces computed with the block-matching strategy, which encode spatial correspondences. This amounts to the computation of a family of n=6 forces F_n. These are then smoothed with Gaussian kernels $K\sigma_n$, σ_n={2,2,2,4,4,4}mm within a diffeomorphic framework. The final diffeomorphic deformation encodes the contribution of each smooth update field given by an individual force. We refer the reader to Cifor et al.[4] for more details.

Results: Fig. 1 shows the resulting PK parameter maps for Mouse 2, for all the three Tps. These images were rigidly registered to ensure spatial correspondence. On a visual evaluation, the PK maps do not radically change over time, the tumour maintaining a necrotic core and an enhancing rim.

Non-rigid multichannel image registration was then performed between Tp2 (day 23) – Tp1 (day 21) and Tp3 (day 24) –Tp1 for all the mice. The success of HFD multichannel is reported in Table 1 in terms of Dice overlap (%). To illustrate the importance of including the PK maps as channels, the method was compared with HFD based only on image intensity, and is shown to outperform it. 'Rigid' represents the results after rigid registration only.

The Jacobian matrices of the deformation were calculated to evaluate tumour growth. These results are shown in Fig. 2. The Jacobian maps (in grey) generally indicate volume expansion (bright gray) in the tumour core and volume preservation (Jac=100) at the enhancing rim. We also computed the expected volume change by integrating over the Jacobian. This yielded an average volume increase (over all the mice) of 55.7±10% for TP2 and 116.7±27% for TP3. This is an overestimation compared to the volume calculation from ground truth tumour delineations (36.8±13% for TP2 and 84.3±19% for TP3).

To investigate whether PK parameters at the first Tp can be a predictor of volume change, we have investigated the relationship between K^{trans} maps at Tp1 and the Jacobians, which indicate volume change between Tp1-Tp2 and Tp1-Tp3. The scatter plots of Volume change–K^{trans} for two mice, Tp1-Tp2 are shown in Fig. 2. The measures appear to be correlated for more homogeneous tumours (row 1). In the case of more complex, heterogeneous tumours (row 2), the Jacobian appears to be a too simplistic model for tumour growth.

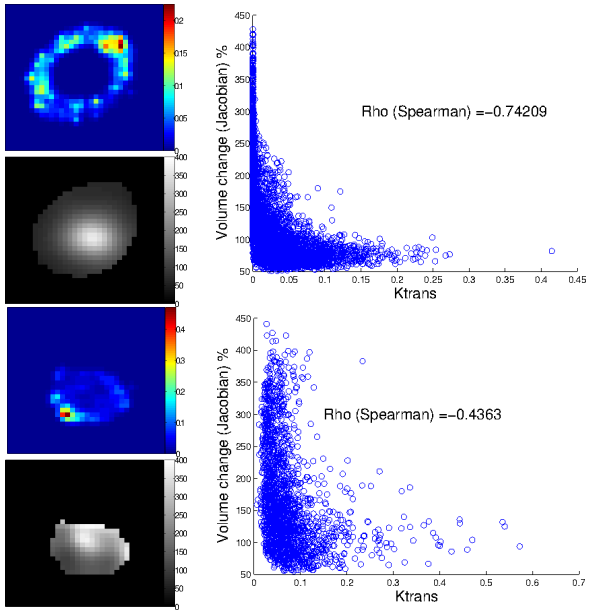


Fig. 2 The correlation between the Ktrans map (TP1) (in color) and the Volume change indicated by the Jacobian (in gray). Jacobian=100 indicates volume preservation. The top plot represents the volume change between TP1-TP2 for Mouse 1 (more homogeneous PK maps). The bottom plot represents the volume change between TP1-TP2 for Mouse 3 (more heterogeneous PK maps).

	Table 1 DICE overlap (%) for the tumour area					
DICE(%)	Mouse1		Mouse2		Mouse 3	
	Tp1-Tp2	Tp1-Tp3	Tp1-Tp2	Tp1-Tp3	Tp1-Tp2	Tp1-Tp3
Rigid	78.56	84.42	81.2	63.65	75.07	64.57
HFD intensity	79.57	79.41	66.83	72.23	61.94	79.24
HFD multichannel	**80.47**	**90.55**	**84.19**	**86.96**	**87.22**	**87.69**

Discussion and Conclusion: We have proposed a new, model based approach to quantify tumour growth from longitudinal dceMRI images. Subsequent Tps were registered to the first Tp using a multichannel registration method based on PK parameter maps. This method was shown to successfully recover tumour growth, on data where the tumour change is small and gradual. However, the registration is based on non-linear deformation, which is not able to account for the deposition of new tumour cells. In future work, a more complex tumour model will be included. We have also investigated whether K^{trans} at the first time point can act as a predictor of localized tumour growth. For more homogeneous tumours presenting a well defined necrotic core and an enhancing rim, there appears to be a relationship between K^{trans} and tumour growth as indicated by the Jacobian. A more complex model will be required for modelling more heterogeneous tumour growth.

References: [1] P.S. Tofts Magn Res in Med 1991. [2] V.L. Yarnykh Magn Res in Med 2007. [3] M. Heilmann Magn Res Mat in Physics Biology and Med 2007. [4] A. Cifor IEEE Trans on Medical Imaging 2013.