

Model fitting of spatially smoothed DCE-CT and DCE-MRI data in bladder tumours

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Introduction Anti-angiogenic and vascular targeting agents tend to reduce blood flow, blood volume and/or capillary permeability. The ability to measure these physiological parameters is important to provide specific information on mechanisms of action and potentially in helping to identify tumour characteristics that may act as biomarkers of response or prognosis. Dynamic contrast enhanced (DCE) imaging techniques provide us with the possibility of extracting information related to each of the above parameters with the use of tracer kinetic models. The use of models able to provide unique flow, permeability and blood volume information (e.g. the adiabatic approximation to the tissue homogeneity (AATH) model [1]) is confounded by their requirements for high temporal resolution data acquisition and the instability of the model fitting process. However, whole tumour ROI analysis using the AATH model suggests that the mean transit time in the bladder tumours is sufficiently long compared with the temporal resolution of the DCE-CT data to allow separation of flow and permeability. The aims of this study were: 1) to assess the statistical justification for fitting complex time series models over simpler kinetic models (e.g. the extended Kety model [2]) to DCE-MRI and DCE-CT data; and 2) to determine if spatial smoothing of DCE-MRI and DCE-CT data improves the robustness of AATH model fitting.

Methods DCE-CT and DCE-MRI data was acquired for 10 male subjects with bladder cancer – average age 69 years. Mean time between scans was 4.1 +/-2.2 days. DCE-CT: field of view ranged from 340x340x20 mm³ to 380x380x20 mm³ (subject dependent). Data were acquired continuously at a 1 s temporal resolution for a 60 s period followed by a single 1 s scan every 30 s for a further 4 min (5 min total scan time). Four contiguous 5 mm slices were reconstructed to a 512x512 matrix with square in-plane voxel dimension of 0.66–0.74 mm. DCE-MRI: field-of-view 375x375x100 mm³ for all subjects, variable flip angle T₁ measurement (2, 10 and 20 deg) [3], followed by 180 dynamics using 3D axial RF spoiled gradient echo scans with flip angle of 20 deg. TR/TE = 4 ms/0.8 ms, single signal average, temporal resolution 4.9 s, total scan time 6 minutes. Twenty-five contiguous 4 mm slices were reconstructed to a 128x128 matrix with square in-plane voxel dimension of 2.93 mm. For DCE-CT, iohexol (Omnipaque 300, GE Healthcare) was administered as a standard bolus (100 ml) at a rate of 5 ml/s prior to the start of the dynamic imaging, ie bolus duration = 20 s. For DCE-MRI, gadodiamide (Omniscan, GE Healthcare) was administered intravenously after the 6th dynamic scan at a standard dose of 0.1 mmol/kg body weight using a power injector at a rate of 3 ml/s, followed by a saline flush of equal volume (for 70kg person: 14ml contrast agent injected, bolus duration = ~4.5 s). The arterial input functions (AIF) for both MRI and CT were manually defined in the iliac arteries using a small ROI. In CT, the contrast agent concentration is directly proportion to the change in signal intensity. Signal intensity in the dynamic series was converted to contrast agent concentration using the baseline T₁ maps and by assuming a contrast agent relaxivity of 4.5 s⁻¹mM⁻¹. For more details see [4].

CT concentration maps were smoothed using mean filters applied over square kernels in the slice plane as follows: 4x4 (leading to an effective voxel size of 2.7 to 3 mm), 8x8 (5.3 to 5.9 mm) and 16x16 (10.6 to 11.8 mm). MRI concentration maps were analysed at full resolution (2.9 mm, similar effective voxel size to 4x4 smoothed CT data) and smoothed as follows: 2x2 (5.9 mm) and 4x4 (11.7 mm). The extended Kety and AATH models were used to analyse the data in ROIs that excluded regions which were contaminated by non-tumour tissue during the dynamic time series, for example as a result of bladder filling. The model (extended Kety or AATH) that best describes the data was determined using the Akaike

information criterion (AIC) [5], which provides a probability that a more complex model (in this case the AATH model) is a more appropriate fit to the data than a simpler model (extended Kety), taking into account fit residuals and degrees of freedom.

Results and Discussion Figure 1 shows that no degree of simple spatial smoothing applied to the CT data leads to the AATH being selected as a more appropriate analysis for the vast majority of data sets, ie to obtain an AIC probability >0.5. It is only when averaging over the entire tumour volume (data not shown) that any preference for the AATH model becomes apparent, and this is not for all data. It is possible that data acquisitions with better contrast-to-noise ratio and, perhaps, higher temporal resolution during the bolus passage phase of the time series would increase the likelihood of the AATH approach describing the data better.

Both the full resolution (green diamonds) and smoothed DCE-MRI data suggest that the AATH model is a more robust fit than for DCE-CT. One reason for this could be the difference in the injection rates of the contrast agent across the modalities. This leads to a broader AIF for the DCE-CT data and possibly less sensitivity to the variation in broadening of the first pass peak that is caused by a finite capillary mean transit time, to which the AATH model is responsive (figure 2). It is therefore possible that the AATH model, first commonly applied to DCE-CT data, is better suited to the analysis of data acquired from DCE-MRI, as the ratio of the mean transit time to the bolus duration is higher for DCE-MRI. However, it could be argued that the better temporal resolution of the DCE-CT data is similarly advantageous. This dependence on AIF first pass shape could potentially be reduced by altering the contrast agent administration scheme. Reducing the volume of the bolus is unlikely to be beneficial, as this would reduce the dose and therefore the contrast enhancement in the tumour. However, a dual bolus approach, as suggested in [6] would maintain tissue contrast characteristics and allow AIFs with finer peaks.

Conclusion Simple smoothing is not sufficient to allow the AATH model to be fitted to the DCE-CT reliably. Smoothing of DCE-MRI data leads to a higher probability that the AATH model is effective in describing the data, when compared with the extended Kety, for a similar effective voxel size.

References 1. St. Lawrence KS, Lee T-Y. *J Cereb Blood Flow Metab* 18:1365–1377, 1998; 2. PS Tofts, *J Magn Reson Imag* 7:91–101, 1997; 3. Fram et al. *Magn Reson Imag* 5(3):201–208, 1987; 4. Bains LJ et al. *Magn Reson Med* 64:595:603, 2010; 5. Akaike H. *IEEE T Automat Contr* 19:716–723, 1974; 6. Kim SM et al, *Med Phys* 35(12):5921–5933, 2008. **Acknowledgements** This study was funded by AstraZeneca.

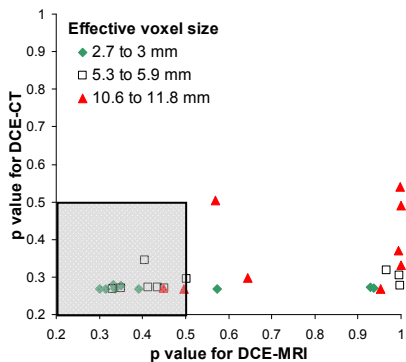


Fig 1. Probability, according to the AIC [5], that that AATH model [1] better describes DCE-MRI and DCE-CT data than the extended Kety [2] for varying effective voxel size/degree of smoothing. p <0.5 - extended Kety, p >0.5 - AATH.

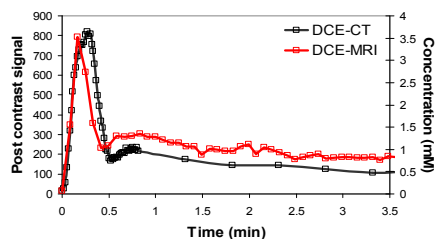


Fig 2. Example AIFs for DCE-CT and DCE-MRI