A Pharmacokinetic Model enabling Modelling of DCE-MRI data of normal and cancerous Liver

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Introduction Following a bolus injection of a low molecular weight contrast agent, liver tissue displays a bi-phasic contrast enhancement due to the arrival of contrast from the hepatic artery, followed after a short delay by contrast from the hepatic portal vein. Quantitative modelling of DCE-MRI liver data therefore requires plasma concentration curves for these two inputs, and an additional parameter is needed in the tissue model to enable the localised flow contribution from these vessels to be quantified. The permeability of normal liver tissue is very high, so unlike many tissues, the vascular and extra-vascular contrast concentrations are very similar throughout a dynamic acquisition. Although the total distribution volume can be evaluated, further division into the vascular and extra-vascular volume fractions is therefore typically not possible in liver tissue. On the other hand, metastatic liver tumours tend to develop with only an arterial blood supply, and the vessel permeability is such that evaluation of the vascular and extra-vascular volume fractions is possible. In this abstract we present a model that can describe both these tissue types in the same system, resulting in a compact but comprehensive methodology for voxel-wise fitting over entire liver volumes. By modelling the whole organ a more detailed understanding of liver tumours may be obtained, in particular the complexities surrounding growth and infiltration at tumour boundaries that are particular to metastatic liver disease.

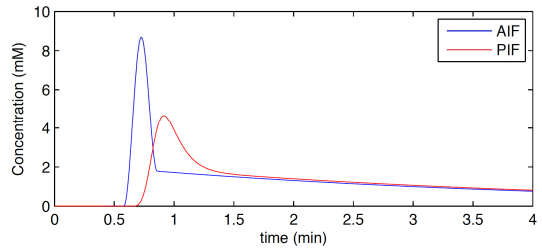

Figure 1: Plasma curves for arterial and portal-venous inputs.

Methods A dual-input single-compartment model is used for liver tissue [1], of the form $C_t(t) = [\gamma C_a(t) + (1-\gamma)C_v(t)] \otimes F\exp[-F/V_D.(t-\tau_0)]$, where C_a and C_v are the arterial and venous input concentrations, F is the inflow rate, V_D is the distribution volume, γ is the fractional inflow from the arterial input and τ_0 is the contrast arrival time. A single-input dual-compartment model is used for tumour tissue, of the form $C_t(t) = v_p C_a(t) + C_a(t) \otimes K^{trans} \exp[-K^{trans}/v_e.(t-\tau_0)]$, where v_p and v_e are the fractional volumes of the plasma and extra-cellular extra-vascular spaces, and K^{trans} is a mixed flow-permeability parameter. To combine these models we introduce three auxiliary parameters, x, y and z that will be manipulated by the curve fitting algorithm (along with τ_0) to best fit the data. Let γ and v_p be defined with the following functions of z: $\gamma(z) = \{z$ for $0 < z < 1$; 1 for $1 < z < 2\}$, and $v_p(z) = \{0$ for $0 < z < 1$; $z - 1$ for $1 < z < 2\}$, then the fitted curve is given by $C_t(t) = [\gamma(z)C_a(t) + (1-\gamma(z))C_v(t)] \otimes x \exp[-x/y.(t-\tau_0)] + v_p(z)C_a(t)$. Thus z is constrained to be between 0 and 2, and x and y have interpretations that depend on z: for $z < 1$, $x = F$ and $y = V_D$, for $z > 1$, $x = K^{trans}$ and $y = v_e$. The limits $x > 0$ and $0 < y < 1$ should also be used in the fitting routine, and these are appropriate under both interpretations of the model. The fact that this combined model can be successfully used to fit noisy data is a result of both component models having the same number of unknown parameters, together with continuous changes in the auxiliary parameters x, y, and in particular z leading to continuous changes in the fitted curve. This means that a well defined minimum exists in a least-squares cost function that can be found using standard library routines.

DCE-MRI data were acquired coronally on a 1.5T Siemens Avanto from a patient with neuro-endocrine liver metastases, using a 3D FFE sequence under sequential breath-hold at expiration [1]. Two image volumes were acquired in 6 sec followed by a 6 sec breathing gap, and 40 images were acquired during the study. The imaging parameters were TR/TE = 3.28/1.10 ms, FA = 18°, 12×5mm thick slices, NSA = 1, IPAT = 2, FOV = 350mm, 128×128 interpolated to 256×256 matrix. The dynamic scan was preceded by a calibration scan with the same parameters except FA = 2° to enable the dynamic sequence to be converted to contrast agent concentration.

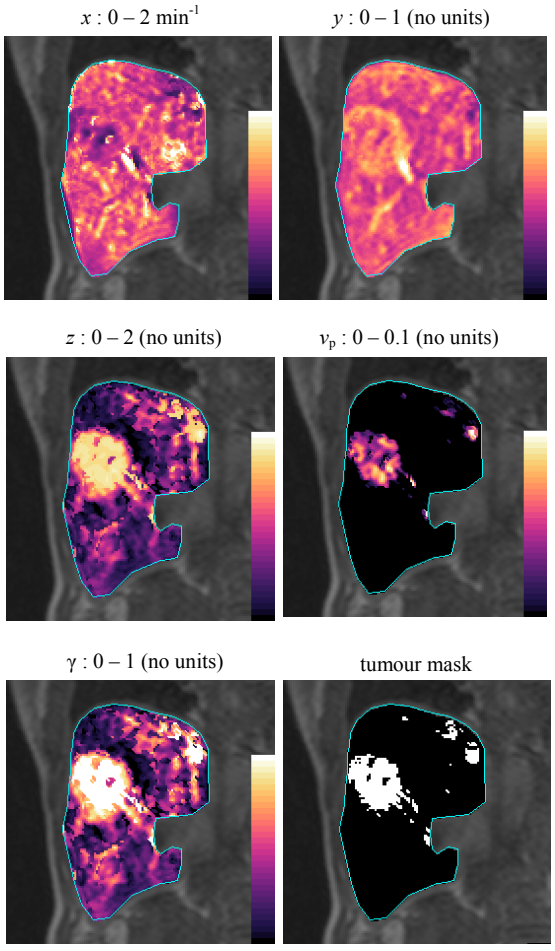

Figure 2: Example maps for various parameters derived from the combined liver-tumour tissue model.

Results Figure 1 shows the plasma concentration time curves for the arterial input (derived from a population averaged curve [2]) and portal-venous input (derived using methods outlined in [3]) used to derive the parameter maps shown in figure 2. The tumour mask image is a binary image showing the regions $z < 1$ (black = liver) and $z > 1$ (white = tumour).

Discussion and Conclusions This model provides a single framework for modelling DCE-MRI data taken from liver and liver tumour tissues. As can be seen from the parameter maps, the tumours are clearly identified in this example, in particular in the v_p and tumour mask images. The extents of the largest tumour are different on the various maps associated with z (i.e. z, v_p and γ), but also between y (i.e. v_e or V_D) and v_p. Further work is needed to understand the significance of such regions identified by this model around the periphery of tumours.

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[2] Parker GJ, et. al., *Magn Reson Med*. 2006; **56**(5):993-1000.
[3] Orton MR, et. al., *Proc. Intl. Soc. Mag. Reson. Med.* 15 (2009), 3615.