The impact of different arterial input function models on vascular parameter estimates using DCE-MRI.

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Introduction In order to estimate tissue kinetic parameters from DCE-MRI data it is necessary to estimate, measure or assume a form for the arterial input function (AIF) of the imaged tissues. We have recently developed a methodology that uses a physically motivated functional form for the AIF, the parameters of which are then directly estimated from the tissue data within an ROI [1]. All unknown parameters, including the tissue kinetic parameters and onset times, are determined simultaneously in a Bayesian estimation procedure. A key advantage of this approach is that the AIF is estimated directly from the tissues of interest, and is therefore appropriate for them specifically, but this is of course predicated on the assumption that the functional form used for the AIF is appropriate. Ultimately it will be necessary to directly determine which model most accurately reflects reality, and whether the same model formulation is appropriate for all patients. However, as a precursor it is instructive to investigate the effect different AIF models have on the tissue parameter estimates. If a more complex AIF model produces very similar tissue parameter estimates, then clearly the additional complexity is unnecessary. The models considered here concentrate on evaluating the effect of recirculation/mixing in the AIF on the tissue parameter estimates.

Theory The model for the AIF is split into two parts – the initial bolus and a Body Transfer Function (BTF) that describes the response of the whole body to an idealised impulse bolus. Mathematically this is given by $c_p(t) = c_b(t) + c_b(t) \otimes B_n(t)$, where $c_b(t)$ is the bolus shape, $B_n(t)$ is the body transfer function and $c_p(t)$ is the resulting plasma concentration, i.e. the AIF. The bolus is modelled using a gamma-variate function of the form $c_b(t) = a_b\, \mu_b^2\, t \exp(-\mu_b t)$, where the additional μ_b^2 term implies that a_b is the area of the bolus. This function has been used in DSC-MRI for some time, where only the first-pass response is utilised, and so its use here is a natural extension of this. Depending on its functional form, the BTF has the ability to capture effects such as recirculation, mixing with the plasma and equilibriation with the whole body extracellular-extravascular space (EES). Three BTF models are considered here :

$$B_1(t) = a_e \exp(-\mu_e t), \qquad B_2(t) = a_e \exp(-\mu_e t) + a_m \exp(-\mu_m t), \qquad B_3(t) = a_e \exp(-\mu_e t) + a_r\,(t - \tau_r) \exp(-\mu_r (t - \tau_r)).$$

The first BTF is designed to model equilibriation with the EES only, which is known to follow an exponential function [2]. The second BTF models equilibriation, but includes a second exponential term to describe mixing/recirculation within the plasma. The third model is similar, but here the mixing/recirculation term is a gamma-variate function with an explicit delay term τ_r. This formulation can describe delay and dispersion independently, whereas the equivalent term in model 2 is forced to describe both effects with μ_m, and so has less flexibility.

The acquired data are noisy measurements of the tissue concentration, which are related to the AIF via $c_t(t) = c_p(t) \otimes h(t\text{-}t_0)$, where $c_t(t)$ is the tissue concentration, $h(t)$ is the tissue residue function and t_0 is the bolus arrival time. The residue function used here is from the standard Tofts model [4], $h(t) = K^{trans} \exp(-k_{ep} t)$. With these functional forms all the convolutions can be calculated analytically to give an explicit form for the tissue concentration. The resulting functions for $c_t(t)$ have an overall scaling factor of $a_b K^{trans}$, so it is not possible to determine these parameters independently from the data. Instead we fix $a_b = 0.8$, which matches the bolus area measured in-vivo, as reported in [3]. With this approach the shape of the AIF is entirely determined from the data – only its amplitude scaling is fixed *a priori* via a_b.

Methods Simulations were used to demonstrate that the parameters for the three model variants could in principle be estimated from the tissue data. The three BTF models given above were then used to estimate the AIF and tissue parameters for an example data set from a breast carcinoma containing 442 pixels. The time-series for each pixel consisted of 41 measurements with a sample interval of 7.5 sec, which were converted from MR signal intensity to tracer concentration using standard methods [5]. The estimated AIFs were then compared qualitatively and quantitatively, and the tissue parameters compared quantitatively. The statistic used to compare the estimated tissue parameters was $\Delta_{ij} = (x_i - x_j)/((x_i + x_j)/2) \times 100\%$ where x_i and x_j are the estimates of the given parameter using BTF models i and j respectively.

Results The figure shows the three estimated AIF curves for the duration of data acquisition. The washout phase for $t > 2$ min is very similar for all three curves, the area under each being 2.041, 2.079 and 2.040 for models B_1 - B_3 respectively. Since a_b is fixed to 0.8, the different bolus heights and durations are accounted for by the bolus rate constants μ_b, which are 14.1, 20.0 and 18.0 for the three models. The major difference between the curves is the period between t = 0.8 – 2.0 min which represents the mixing/recirculation phase. Model B_1 has no explicit term for this phase, so it appears to compensate by widening the bolus term, as evidenced by the blue curve and smaller μ_b. Model B_2 does model the mixing phase, and this is evidenced by the red curve being higher than the blue for t = 0.8-2.0 min. Model B_3 is the most detailed, and the curve demonstrates that the estimated parameters describe a specific recirculation peak.

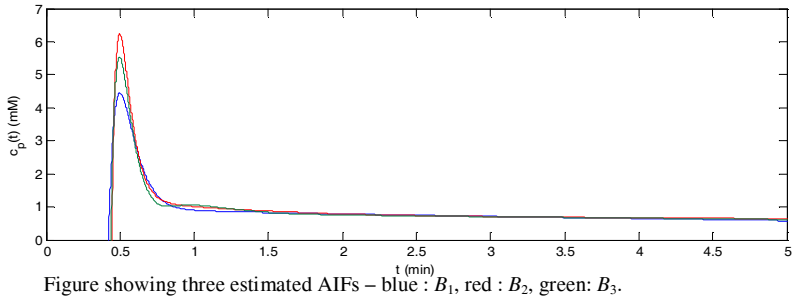

Figure showing three estimated AIFs – blue : B_1, red : B_2, green: B_3.

All tissue parameter estimates were within their normal ranges. The table shows the median, 5- and 95-percentiles of the similarity statistic over the 442 pixels, for the three tissue parameters, including $v_e = K^{trans}/k_{ep}$. The first column compares models 1 and 2, and the results indicate that there is about a 10% reduction in the estimates of K^{trans} and k_{ep}, though the change in v_e is much less significant. The second column compares models 2 and 3, where an increase in the estimates is seen, but once again the change in v_e is small. The final column compares models 1 and 3, and here the changes are of the order of 5%, but the percentile figures indicate that the range of changes is roughly symmetric about 0.

	Δ_{12}	Δ_{23}	Δ_{13}
K^{trans}	-12.6 (-14.8, -6.12)	9.02 (-2.66, 18.5)	-4.12 (-12.6, 9.30)
k_{ep}	-10.9 (-18.2, -6.97)	6.83 (-0.157, 24.2)	-3.96 (-12.3, 9.67)
v_e	-1.99 (-3.49, 6.61)	1.50 (-8.02, 5.32)	0.00934 (-6.12, 5.35)

Table showing test statistic comparing the 3 BTF models for each tissue parameter. Large numbers are median values over all pixels, bracketed numbers are 5- and 95-percentiles.

Conclusions Given the limitations of each model, all the estimated AIF curves are plausible, and a tentative interpretation of the parameters in each case has been given. Model B_3 is the most realistic, and for the data set used here the estimated parameters give an AIF that conforms to prior expectations. The results for the tissue parameter differences are mixed. The table shows that overall the changes were relatively small – around 10-20% or less – so a more extensive study is required to determine these changes more confidently. The more surprising result is that models B_1 and B_3 have the most similar tissue parameter estimates. If further work can confirm this conclusion, then the implication is that although the tissue data does contain enough information to estimate quite complicated AIF models, this additional complexity is unnecessary as it has little impact on the tissue parameter estimates.

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