A Joint Bayesian Method for Robust Estimation of PK and AIF Parameters for DCE-MR Imaging

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Introduction

When applying pharmacokinetic (PK) models to DCE-MRI time-series data it is necessary to estimate the arterial input function (AIF) for the tissues of interest. This is commonly done by fitting a function to the time-series for a nearby blood vessel, organ or suitable tissue [1,2], or by using a generalised AIF [3,4]. The assumption is that this AIF is a good approximation to the AIF in the tissue of interest, but this is often not the case due to differential dispersion and other factors. In this case the PK parameter estimates will be inaccurate and unreliable. A better approach would be to infer the AIF directly from the tissues of interest, which has the advantage of producing a patient/region-specific model. The difficulty is how to differentiate between the AIF and the transport process between the plasma and ESS. Our approach is to use a Bayesian methodology that allows for the incorporation of *a priori* information. More importantly in this case, it produces estimates of the PK parameters that include all the uncertainty of the AIF estimate, leading to more precise and robust estimates.

Method

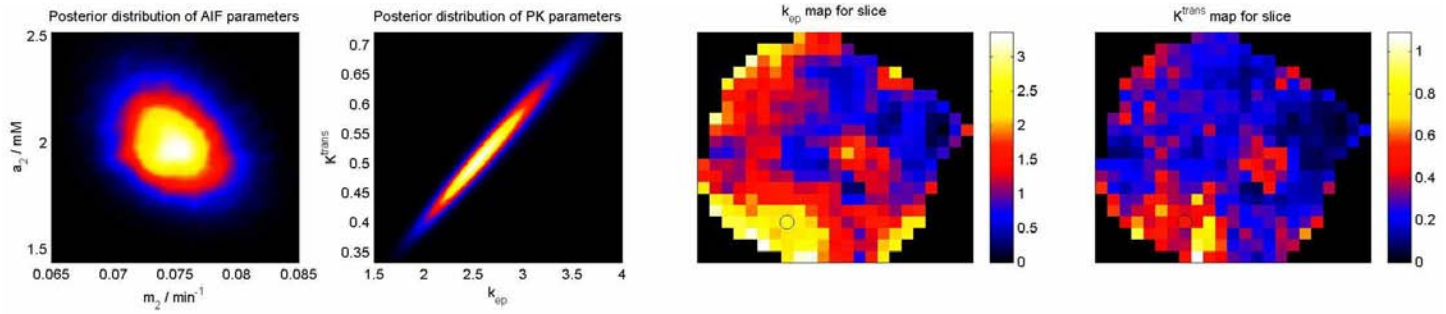
A standard compartmental PK model [5] is used with $h(t) = K^{trans}e^{-k_{ep}(t-t_0)}$, and the local diffusion parameters, denoted $\boldsymbol{\kappa}_i = \{K^{trans}, k_{ep}, t_0\}$ for pixel i, are taken to be independent for each pixel. It is further assumed that there is one AIF for the whole ROI with parameters $\boldsymbol{\theta}$. If the concentration time-series for pixel i is $\mathbf{y}_i$, and is observed through noise, then the likelihood of observing such data is $p(\mathbf{y}_i \mid \boldsymbol{\kappa}_i, \boldsymbol{\theta})$, the form of which will depend on the noise statistics. By applying a suitable prior to $\boldsymbol{\kappa}_i$, it is possible to account for the diffusion parameters for each pixel by calculating $p(\mathbf{y}_i \mid \boldsymbol{\theta}) = \int p(\mathbf{y}_i \mid \boldsymbol{\kappa}_i, \boldsymbol{\theta})\, p(\boldsymbol{\kappa}_i)\, \mathrm{d}\boldsymbol{\kappa}_i$. Due to the assumed independence of the diffusion parameters between pixels, the joint likelihood of observing all the data is given by the product $p(\mathbf{y}_{1:N} \mid \boldsymbol{\theta}) = \prod_{i=1}^{N} p(\mathbf{y}_i \mid \boldsymbol{\theta})$, where $\mathbf{y}_{1:N} = \{\mathbf{y}_1, \mathbf{y}_2, \ldots, \mathbf{y}_N\}$. Combining this with a suitable prior for $\boldsymbol{\theta}$ using Bayes theorem leads to the posterior distribution $p(\boldsymbol{\theta} \mid \mathbf{y}_{1:N})$, which can be used to find estimates of the AIF parameters if desired. The PK parameters are of most interest, and they can be estimated from $p(\boldsymbol{\kappa}_i \mid \mathbf{y}_{1:N}) = \int p(\boldsymbol{\kappa}_i \mid \boldsymbol{\theta}, \mathbf{y}_i)\, p(\boldsymbol{\theta} \mid \mathbf{y}_{1:N})\, \mathrm{d}\boldsymbol{\theta}$, where $p(\boldsymbol{\kappa}_i \mid \boldsymbol{\theta}, \mathbf{y}_i) = p(\mathbf{y}_i \mid \boldsymbol{\kappa}_i, \boldsymbol{\theta})\, p(\boldsymbol{\kappa}_i) / p(\mathbf{y}_i \mid \boldsymbol{\theta})$. For the results presented below a method using a Gaussian approximation [6] was used to calculate the integrals, though it is anticipated that Markov Chain Monte Carlo methods [7] will be able to produce more accurate results whilst incorporating important prior information.

An intuitive understanding of the proposed method can be found by first considering the pixel-wise AIF likelihoods, $p(\mathbf{y}_i \mid \boldsymbol{\theta})$ as functions of $\boldsymbol{\theta}$. These functions will be very diffuse, indicating that there is very little information about the AIF parameters from individual pixels. When multiplied together this combines the information from all pixels, and only the values of $\boldsymbol{\theta}$ that have enough evidence from all the pixels will have a large value, and this region should be reasonably compact. The distributions of clinical interest are $p(\boldsymbol{\kappa}_i \mid \mathbf{y}_{1:N})$, where it is explicit that all the data are used to estimate the PK parameters.

To demonstrate the potential of this method it was applied to some data from a 323 pixel ROI containing a liver metastasis, using an AIF of the form $c_a(t) = a_1 e^{-m_1 t} + a_2 e^{-m_2 t}$. In order to simplify the analysis, the parameters describing the rapid distribution phase following the bolus injection were assumed known, ($a_1 = 3.6$ and $m_1 = 4.9$), and these were derived from the data using an alternative analysis method [3,8] (it is ultimately intended to include a_1 and m_1 in the analysis). The noise was assumed to be i.i.d. Gaussian, and the onset time was very easy to identify so did not need estimating, though the method will be extended to be able to estimate this in the future. Consequently there were two global AIF parameters to estimate, a_2 and m_2, and two local PK parameters, k_{ep} and K^{trans}.

Results

In order to evaluate the effectiveness of a Bayesian analysis it is important to establish that the posterior distributions are well localised, so that estimates (such as maximum a posteriori -- MAP, and minimum mean squared error -- MMSE) calculated from them can be trusted. In the figure below we show the posterior for the AIF parameters $p(a_2, m_2 \mid \mathbf{y}_{1:323})$, which has a peak and 2σ uncertainty at $m_2 = 0.074 \pm 0.003$ and $a_2 = 1.94 \pm 0.3$. Also shown is the posterior $p(K^{trans}, k_{ep} \mid \mathbf{y}_{1:323})$ for a pixel (circled in the RH figures) with strong enhancement, and images of MAP estimates of k_{ep} and K^{trans} for the ROI containing a metastasis.



Discussion and Conclusions

By using a Bayesian methodology it is possible to combine the information from all the pixels in an ROI to produce a tailored AIF, which leads to more robust and reliable estimates of the PK parameters. By suitable selection of prior distributions any relevant information can in principle be rigourously included in the analysis, for example it is known that $K^{trans} < k_{ep}$. The probabilistic framework given above is independent of the particular AIF and PK models, so in principle any such model will fit into the same analysis structure, including additional vascular-plasma terms and/or exchange parameters.

References

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