A Bayesian hierarchical framework for pharmacokinetic modelling in dynamic contrast-enhanced magnetic resonance cancer imaging

Volker Schmid 1, Brandon Whitcher 2, Guang-Zhong Yang 1

1 Institute of Biomedical Engineering, Imperial College, London UK
2 Translational Medicine and Genetics, GlaxoSmithKline, Greenford UK

Abstract: Dynamic contrast enhanced magnetic resonance imaging (DCE-MRI) is a novel approach to the identification and assessment of tumors in living bodies. After a contrast agent has been injected, continued MR scans are made over a period of 10 minutes. Pharmacokinetic (PK) models of the time series in each voxel describe the blood flow and therefore the spread of a tumor. From a statistical point of view, PK models are non-linear regression models. We use a fully Bayesian approach in order to overcome convergence problems of fitting PK parameters and to assess estimation errors. In a refined approach, we include contextual information via a Gaussian Markov random field (GMRF). As tissue is very heterogeneous, an adaptive approach is necessary. This framework allows smoothing in homogeneous parts of the tissue, but retains sharp features. Due to the use of spatial information, outliers are suppressed and parameter estimation error is reduced. As application to our framework, data on a breast cancer study are presented.

Keywords: Gaussian Markov random fields, Bayesian Inference, Oncology, Magnetic resonance imaging, pharmacokinetic models

1 Introduction

In recent years, magnetic resonance imaging (MRI) became a standard medical tool for many different purposes. For cancer imaging, dynamic contrast-enhanced MRI (DCE-MRI), plays an important role. In DCE-MRI, during a number of scans, a contrast, usually Gadolinium (Gd), is injected into the patient; as Gd is toxic, a complex like Gadolinium diethylyltrimetapentaacetic acid (Gd-DTPA) is used. DCE-MRI scans show the flow of the contrast agent, and therefore the blood flow, between vascular space and the so-called extracellular extravascular space (EES); the contrast agent is to large to enter the cells. Growth of tumor depends on its ability to initiate formation of new blood vessels, that can grow into the tumor; a process which is called angiogenesis. So tumors are regions of
high blood flow and of high fraction of vascular space, and therefore can be detected via DCE-MRI.

Often spatial information is not used in imaging. That is, each voxel in analyzed independently. One common approach is to smooth parameter maps in a post-processing step. However, one can easily assume, that parameters in some voxels are correlated depending on the spatial structure. Recent papers in fMRI imaging make use of spatial information in the model.

Cancer tissue often is heterogeneous. Though, smoothing techniques for DCE-MRI cancer imaging need to have edge-preserving qualities. Also, smoothing has to be different in normal tissue and cancer tissue and, as coil effects and other sources of errors differ over the field of view. Adaptive smoothing approaches are recently under investigation for fMRI.

We use the widely used standard pharmacokinetic models for DCE-MRI as basis for our data model in a Bayesian hierarchical framework. After describing the standard procedure in DE-MRI, we develop the estimation of pharmacokinetic parameters using Bayesian inference. We then include the spatial information via an adaptive Gaussian Markov random field, that is, we use the data to estimate smoothing weights in the model. The local smoothing weights can also be used to depict the borders of the tumor and of heterogeneous regions in tumor tissue, as we show on a study on breast cancer. The results can be used to specify a mask of the tumor and give further information about tumor type.

2 Principles of DCE-MRI

Quantitative analysis of DCE-MRI is achieved by applying pharmacokinetic (PK) models to the contrast agent concentration after contrast injection. A distinct advantage over the semi-parametric approach is, that each PK parameter has a direct relationship with key biological processes of interest, like $K_{\text{trans}}$, the transfer rate from blood plasma to EES or volume fractions of the tissue.

The standard model for quantitative analysis of Dynamic contrast-enhanced magnet resonance imaging is the compartmental model described by Kety (1960). The flow of the contrast agent from blood plasma to extravascular extracellular space (EES) is expressed with differential equations. Recently, more complex models where suggested, like the extended Tofts-Kermode model:

$$C_{\text{t}}(t) = v_p C_p(t) + C_p(t) \otimes K_{\text{trans}} \exp(-k_{\text{ep}} t).$$  \hspace{1cm} (1)

Here, $C_{\text{t}}(t)$ denotes the concentration of the contrast agent at time $t$, $C_p(t)$ denotes the arterial input function and $K_{\text{trans}}$ represents the volume transfer constant between blood plasma and EES, whereas $k_{\text{ep}}$ represents the rate constant between EES and blood plasma. The third parameter $v_p$ represents the fraction of tissue occupied by blood.
The arterial input function describes the input of the contrast agent to the tissue. A standard AIF was proposed by Tofts (1991):

\[ C_p(t) = D \sum_{i=1}^{2} a_i \exp(-m_i t) \] (2)

with given values for \( a \) and \( m \). By carrying out the convolution in (1) the following model can be derived

\[ C_t(t) = v_p C_p(t) + D K^{\text{trans}} \sum_{i=1}^{2} \frac{a_i \{ \exp(-m_i t) - \exp[-k_{ep} t] \}}{k_{ep} - m_i} \] (3)

Now, the quantitative pharmacokinetic (PK) parameters \( K^{\text{trans}}, k_{ep} \) and \( v_p \) are estimated by fitting the nonlinear regression model to the observations independently in each voxel. Inference is performed by minimizing the sum of squared errors \( \min \sum \epsilon^2 \). We use the parameterization \( \exp(\theta_1) \) instead of \( K^{\text{trans}} \), and \( \exp(\theta_2) \) instead of \( k_{ep} \), to ensure positive values for \( K^{\text{trans}} \) and \( k_{ep} \). In the likelihood framework, parameter estimates are known to be asymptotically normal. Hence, asymptotic confidence intervals and asymptotic probabilities of exceeding a particular threshold value were easily constructed.

### 3 A Bayesian hierarchical model for including spatial information

Be \( C^{(i)}_t(t) \) the true, unknown contrast concentration in the tissues in voxel \( i \) at time \( t \). Then the observed concentration is

\[ y_i(t) = C^{(i)}_t(t) + \epsilon_{it}, \quad i = 1, \ldots, n; t = 0, \ldots, T. \] (4)

For the observation error \( \epsilon \) we assume independent Gaussian distributions with unknown variance

\[ \epsilon_{it} \sim N(0, \tau^{-1}_{\epsilon}). \] (5)

We define \( C_t \) according to (3)

\[ C_{t;i}(t) = v_{p;i} C_p(t) + D K^{\text{trans}} \sum_{i=1}^{2} \frac{a_i \{ \exp(-m_i t) - \exp[-k_{ep;i} t] \}}{k_{ep;i} - m_i} \] (6)

that is, we follow the usual physio-biological assumptions on the contrast agent concentration time series.

As mentioned above, we assume neighboring voxels to have similar properties in terms of the rate parameters. We use a Gaussian Markov random field as prior for the logarithms of these parameters. \( W = (w_{ij}) \) and
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\( \mathbf{V} = (\mathbf{v}_{ij}) \) as precision matrices, respectively:

\[
p(\log(K_{\text{trans}})) \propto |\mathbf{W}|^{-1/2} \exp \left( -0.5 (\log(K_{\text{trans}}) \mathbf{W} \log(K_{\text{trans}})) \right) \quad (7) \\
p(\log(k_{\text{ep}})) \propto |\mathbf{V}|^{-1/2} \exp \left( -0.05 (\log(k_{\text{ep}}) \mathbf{V} \log(k_{\text{ep}})) \right) \quad (8)
\]

with \( |\mathbf{W}| \) the product of non-zero eigen values of \( \mathbf{W} \).

The weights specify the local smoothness of the parameter map. We use independent flat Gamma priors for the weights:

\[
w_{i,j} \sim \text{Ga}(1, 10^{-4}), \quad v_{i,j} \sim \text{Ga}(1, 10^{-4}); \quad (9)
\]

that is, we give enough flexibility to estimate the smoothness rather from the data as from the prior.

For the vascular fraction \( v_p \) we use the same prior distribution as in the voxel-per-voxel model, \( v_p \sim \text{U}[0, 1] \). The model is completed with the prior for the the error precision. As above, this is also a Gamma distribution \( \tau \sim \text{Ga}(1, 10^{-4}) \).

Acknowledgments: Financial support for Dr. Schmid was provided by GlaxoSmithKline. We thank Dr. Anwar Padhani and Dr. N. Jane Taylor, Paul Strickland Scanner Centre, Mount Vernon Hospital, for data and support.

References


