Bayesian Mixed-Effect Model for Breast Cancer Treatment Studies

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INTRODUCTION

Dynamic contrast-enhanced MRI (DCE-MRI) is frequently used to gauge the success of cancer treatment based on its sensitivity to depict vascularity changes. Generally, pixel-by-pixel values of pharmacokinetic model parameters are derived as summary metrics of the time-enhancement data – usually K^{trans} and/or IAUC values [1]. However, contrast agent concentration time curves (CTC) are available in each imaging voxel; this information is lost through statistical summaries after model fitting. We propose a comprehensive Bayesian mixed-effect model to analyse all CTC from all scans, across all patients in a study simultaneously.

METHODS

A hierarchical Bayesian formulation [2] is used to model the CTC of all voxels. The dynamic series in each voxel is assumed to follow a standard compartment model [3] $C_t(t) = v_p\, C_p(t) + C_p(t) \otimes K^{\text{trans}} \exp(-k_{ep}\, t)$ plus white noise. *A priori*, the transfer rates from plasma to EES, K^{trans} are assumed to follow a mixed-effect model; *i.e.*, K^{trans} in a voxel i of scan s of patient n follows the equation $\log\left(K^{\text{trans}}_{nsi}\right) = \alpha + \beta x_s + \gamma_n + \delta_n x_s + \varepsilon_{nsi}$. Here α is a baseline value, β is the (fixed) treatment effect with $x_s = 1$ for post treatment scans and $x_s = 0$ else, γ_n is the random effect of patient n, δ_n the random interaction effect of patient n and treatment and ε_{nis} is a random effect of voxel nsi. An analogous formulation is used for the rate parameter k_{ep} for transport from EES to plasma, and an independent uninformative prior is used for the vascular volume space v_p.

The first nine patients from a previously reported [4,5] breast cancer study were included in the analysis. Each patient underwent a DCE-MRI study before and after six weeks of chemotherapy (5-fluorouracil, epirubicin and cyclophosphamide). Regions of interest were drawn manually by an expert radiologist to define tumor voxels.

RESULTS

All parameter estimates are derived from the posterior distribution, for example, error estimates can be derived directly from the posterior. Fig.1 shows the posterior distribution of the baseline α and treatment effect β. The result shows statistically significant reduction of K^{trans}. Fig.2 depicts the patient effects for all nine patiens with 95% credibility intervals, and Fig.3 shows the interaction effect plus treatment. The patient effect has a range of +/- 0.5 on the log-scale; *i.e.* patients show different properties pre treatment, but are relatively similar. The interaction effect is higher for patients 7 to 9; these patients actually were identified as non-responders in a pathological response [4]. Thus, our approach can help to identify potential non-responders in such a study. Fig.4 shows boxplots of the voxel effects for each scan indicating the heterogeneity within the tumor in each scan. At this point in time the voxel effect is mainly for quality control and provides information on how well the compartmental model performs.

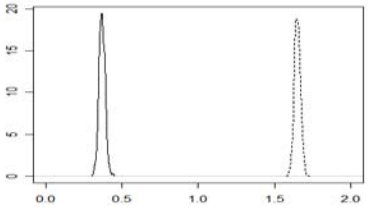

Figure 1: Posterior distributions of baseline effect α (dotted line) and of baseline+treatment effect α+β for K^{trans}

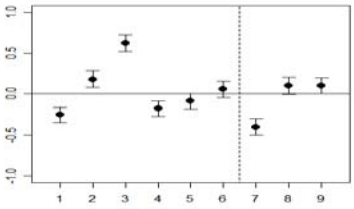

Figure 2: Patient effect of K^{trans} (log scale) with 95% credibility intervals for all patients.

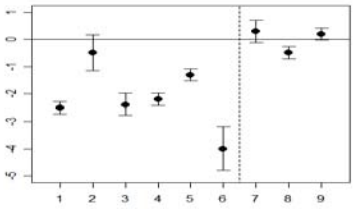

Figure 3: Effect of interaction + treatment (log scale) of K^{trans} with 95% credibility intervals for all patients.

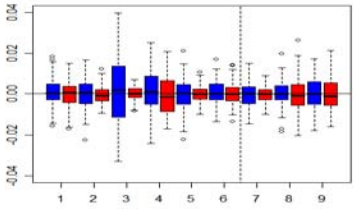

Figure 4: Boxplots of mean voxel effects (log scale) for all scans. Blue: Pre treatment scans, red: post treatment.

DISCUSSION AND CONCLUSIONS

DCE-MRI scans are rather cost-intensive. Our approach uses all available information to evaluate the treatment effect and provide error estimates. In addition, patient-specific information can be assessed, possibly identifying non-responding patients, and information about tumor heterogeneity for each patient is available.

REFERENCES

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