

HIERARCHICAL VERSUS VOXEL-WISE MODELS FOR DCE-MRI IN A HEAD AND NECK STUDY WITH LAPATINIB

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Introduction

Quantitative analysis of the DCE-MRI study provides biologically-relevant parameters that summarize tissue perfusion and allows one to compare results across studies -- extremely useful in a clinical development plan for anti-angiogenic agents. When estimating the kinetic parameters from the (extended) Kety model [1] on a voxel-by-voxel basis, one must summarize the multiple parameter estimates within the tumor ROI in order to test for differences at the group level. An alternative to summary statistics, such as the mean or median, is to acknowledge that there are different sources of variability in the DCE-MRI data and explicitly model them using a Bayesian hierarchical model (BHM) [2]. We compare the results from a quantitative analysis of DCE-MRI data using summary statistics from a non-linear regression analysis, using both optimization and Bayesian methods, and the output from a Bayesian hierarchical model in a phase II study of lapatinib in patients with locally advanced squamous cell carcinoma of the head and neck.

Methods

Acquisition. A total of 11 subjects were scanned using from two sites: 3 subjects from the Royal Marsden Hospital, London (Philips Intera 1.5T) and 8 subjects from Vall d'Hebron University Hospital, Barcelona (GE Signa Excite 1.5T). Two subjects were excluded due to data quality. The intrinsic tissue relaxation rate was estimated using a 3D FFE sequence at 2,8,12,18,24° flip angles, FOV = 256mm, TR = 4ms, TE = 1ms, and total imaging time per volume was approximately 4.5s. The dynamic sequence involved 96 acquisitions at 24° using identical parameters, with a bolus injection of contrast agent at the sixth acquisition. Signal intensity was converted to gadolinium concentration using the estimated relaxation rate.

Modelling. The gadolinium concentration time curve in each voxel is assumed to follow a standard compartment model $C_t(t) = v_p C_p(t) + C_p(t) * [K^{trans} \exp(-k_{ep} t)]$ plus white noise. Parameter estimation for the voxel-based methods was performed using the Levenburg-Marquardt algorithm and Markov Chain Monte Carlo (MCMC). For the BHM, K^{trans} and k_{ep} are assumed to follow a generalized additive model; i.e., K^{trans} in a voxel i of scan s of patient n follows the equation $\log(K^{trans})_{isn} = \alpha + \alpha_i x_i + \beta_t x_s x_t + \beta_p x_s x_p + \gamma_n + \delta_n x_s + \epsilon_{isn}$, with $x_s = 1$ for post-treatment scans, $x_t = 1$ for subjects in treatment group, $x_p = 1$ for subjects in placebo group, $x_i = 1$ for scans at site 2, and $x_n = 0$ otherwise. The parameter α is the baseline level of K^{trans} , α_i is the (fixed) effect of the site i , β_t is the (fixed) effect of treatment, β_p is the (fixed) effect of placebo, γ_n is the random effect for patient n , δ_n the random interaction effect of patient n and the treatment, and ϵ_{isn} is a random effect of the voxel.

Results

Although a slight reduction was observed post-treatment, there was no significant difference in post-treatment K^{trans} between the placebo and lapatinib groups (Figure 1). Using the posterior distribution from the BHM, we note that $K^{trans} < 1 \text{ min}^{-1}$ for the post-treatment lapatinib group, whereas the posterior distribution of K^{trans} for the placebo group has substantial mass between 1 and 2 min^{-1} . Estimates of K^{trans} were compared between nonlinear regression and Bayesian estimation for all scans in the study (a single tumor ROI is shown in Figure 2). For the majority of voxels there is excellent agreement in K^{trans} between the two methods, but the Bayesian technique (a) does not produce as many extreme parameter estimates and (b) does not produce as many parameter estimates at zero. This is due to the dependence of non-linear optimization procedures on convergence criteria and good-quality starting values. The ROI associated with Figure 2 contains 284 estimates of $K^{trans} > 10 \text{ min}^{-1}$ using nonlinear regression and only 19 estimates of $K^{trans} > 10 \text{ min}^{-1}$ for Bayesian estimation via MCMC.

Discussion and Conclusions

A Bayesian analysis of the kinetic parameters from a standard compartmental model produced good-quality parameter estimates that do not suffer from convergence problems associated with optimization procedures in non-linear regression. The BHM allows one to directly test for a treatment effect while accounting for several sources of error. In addition, the BHM produces estimates that reflect within-tumor heterogeneity and between-subject variability.

References [1] Parker, GJM, Buckley, DL (2005). In *Dynamic Contrast-Enhanced Magnetic Resonance Imaging in Oncology*, pp. 81-92. [2] Schmid, V, Whitcher, B, Padhani, AR, Taylor, JN, Yang, GZ (2008). *Mag. Res. Med.*, in press.

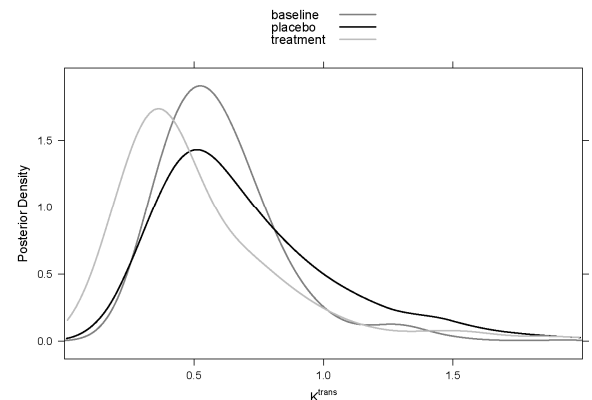


Figure 1: Posterior distributions of K^{trans} over all subjects and scans in the study.

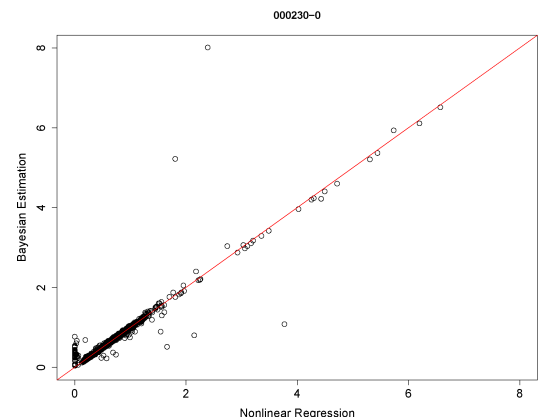


Figure 2: Scatterplot of voxel-wise estimates of K^{trans} over a single ROI for subject 230.