Optimal Parameter Choice in Predicting Final Outcome in Acute Stroke

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Introduction

PWI and DWI are important tools in detecting haemodynamic and microstructural changes in acute stroke and may to some extent support prediction of lesion progression [1], supporting clinical decision making. Due to the increasing number of MRI tissue markers hypothesized to signal infarct risk, there is a growing need for tools that may identify key parameters with high predictive power, thereby optimising diagnostic setup and increasing our understanding of acute stroke pathophysiology. Especially, we hypothesize that (i) due to MTTs inverse relation to perfusion pressure, using the *extent* of MTT prolongation (i.e. the lesion-contralateral MTT *difference* rather than the *ratio*) improves predictive performance and (ii) the novel marker Flow Heterogeneity (FH) [2] may improve predictions. In this study we examined the relative importance of MRI tissue markers using a modern regression strategy known as Multivariate Adaptive Regression Splines (MARS) [3].

Theory

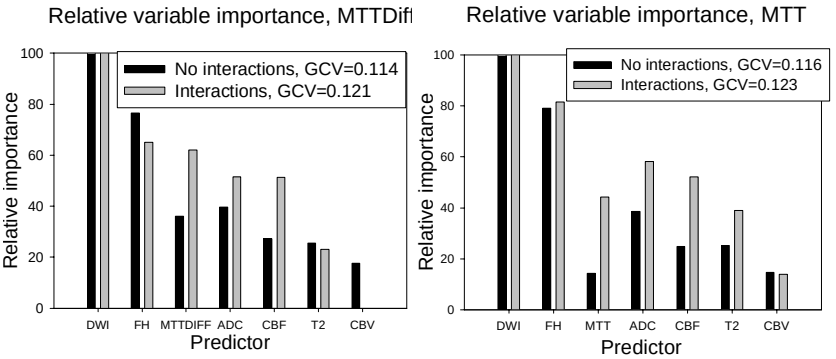
Standard regression techniques such as the generalized linear models (GLM) and the generalized additive models (GAM) which are commonly applied to model a binary outcome require *a priori* knowledge about the true, often non-linear, functional relationship between predictors and response which may bias the results. In addition these techniques are often out-performed in terms of predictive performance by computer intensive "black-box" methods such as k-nearest neighbor and neural networks. These methodologies on the other hand render inference on predictive parameters virtually impossible.

In order to gain data-guided insight into the relative importance and functional form of predictive parameters while retaining high predictive power we applied the MARS algorithm. MARS uses expansions in piecewise linear basis functions of the form $(x-a)_+$ and $(a-x)_+$ where x is a predictor and a is a so-called knot; the "+" means positive part so $(x-a)_+ = x-a$ if $x>a$ and 0 otherwise. A model is built by iteratively adding and multiplying basis functions in order to minimize a lack of fit criterion which reflects prediction error. This is estimated by the generalized cross-validation criterion (GCV) [4], $\mathrm{GCV} = \sum_{i=1}^{N}(y_i-\hat{y}_i)^2 \Big/ \left(1-\frac{C(M)}{N}\right)^2$, which is essentially the mean squared error between the observed y_i and the predicted $\hat{y}_i$. The term $C(M)$ is a penalty for the variance of a model with M basis functions. Associated with $C(M)$ is a smoothing parameter d which reflects the cost of adding a new basis function. The GCV criterion can conveniently be used to estimate relative variable importance in the final model by estimating the relative increase in GCV when all terms involving a certain parameter are dropped. The final model can be written as a sum of main effects plus sums of higher order interactions which facilitate traditional regression interpretations. In addition interactions beyond a specified order can be prohibited before MARS is run to protect against spurious interactions.

Materials and methods

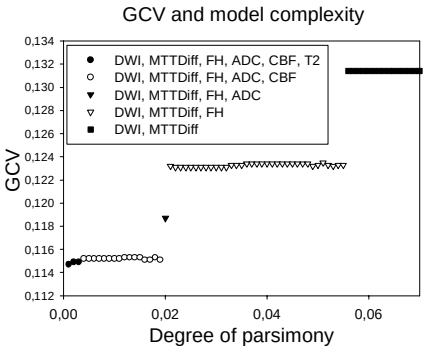
We used data from a previous study [1] in which diffusion- and perfusion-weighted images of 14 patients with acute (onset time <12h) cerebral ischemia were obtained and isotropic DWI, ADC, T2, CBF, CBV and MTT maps were calculated and co-registered. We further included a novel perfusion parameter, flow heterogeneity (FH), which maps the distribution of flow rates relative to the mean flow in a given voxel [2]. In the analysis relative images (rADC, rCBF etc) obtained by normalization with normal appearing contralateral gray matter were used. The prescript r is dropped.

To test whether *subtracting* lesion values (MTTdiff) from the contralateral, normal values, rather than using, as is common, relative values (MTT), we applied MARS twice using all perfusion and diffusion parameters, changing only the representation of mean transit time. We then compared the GCV value and examined estimates of relative variable importance in the final models. In each case the smoothing parameter d was determined by 10-fold cross-validation. To assess how many, and which, variables are necessary to produce well performing predictive models we forced variable parsimony by introducing penalty on the lack of fit criterion (GCV) - resulting in a cost for introducing a predictor not already present in the model at a given stage.



Results

GCV results for the respective parameters are shown in the graphs. MTTdiff (left graph) showed lower GCV than MTT (right graph) in interaction models as well as main effect models (GCV=0.114 vs. 0.116 and GCV=0.121 vs. GCV=0.122, respectively). It is clear from the relative importance plots that MTT in both cases is a weaker predictor than MTTDiff. DWI has clearly the highest predictive power, just as the models rely (in order of importance) on FH, MTTDiff, ADC and CBF. The area under the ROC curve, as calculated in [1], for the MTTDiff-interaction model is AUC=0.821. The figure below shows GCV for optimal models, forcing predictor parsimony. T2 and CBV are considered uninformative as expected from the variable importance plots. Also ADC and CBF can be excluded from the model without severely increasing GCV. Of note, a two-parameter model based on DWI and MTTDiff performs well, AUC=0.806.



Conclusion and discussion

We have shown that in choosing diffusion and perfusion indices to allow prediction of infarct progression, key parameters (in order of importance) are DWI, FH, MTT, ADC and CBF. MTT should be parameterized by its difference relative to the unaffected tissue. The analysis confirms the hypothesized importance of FH, a parameter believed to be associated with oxygen transport efficacy in the tissue, in tissue viability. Interestingly, despite being coupled to the DWI and MTT values, respectively, ADC and CBF seemingly contributes independently to outcome prediction. We speculate that MARS represents a convenient framework for studying the relations and functional dependence among such physiological parameters.

Reference List

1. Wu O *et.al.* Stroke 32: 933-42, 2001. 2.Ostergaard L, *et.al.* Stroke 31: 1097-103, 2000.
3. Friedman, J. Annals of Statistics 19: 1-141, 1991. 4. Craven P, Wahba G. Numer Math 31: 317-403, 1979.