Journal of Alzheimer's Disease 30 (2012) 1–2
IOS Press

Supplementary Data

Towards a Dynamic Biomarker Model in Alzheimer's Disease

Abderazzak Mouiha[a] and Simon Duchesne[a,b,*], for the Alzheimer's Disease Neuroimaging Initiative[1]
[a]*Institut Universitaire en Santé Mentale de Québec, Québec, Canada*
[b]*Radiology Department, Faculty of Medicine, Université Laval, Québec, Canada*

Accepted 22 January 2012

MODELS DESCRIPTION

Our notation is as follows, whereas $Y = (Biomarker\ Measures)$ is the dependent variable; $X = (ADAS - Cog)$ the independent variable; the sample size; and $\varepsilon_i,\ i = 1, ..., n$ white noise with mean 0 and constant variance.

Linear model

$$Y_i = b_o + b_1 x_i + \varepsilon_i,\ \ i = 1, ..., n; \tag{1}$$

Quadratic model

$$Y_i = \beta_0 + \beta_1 x_i + \beta_2 x_i^2 + \varepsilon_i,\ \ i = 1, ..., n; \tag{2}$$

Penalized B-Spline model

$$Y_i = \beta_0 + \beta_1 x_i + \beta_2 x_i^2 + \sum_{j=1}^{k} \beta_{j+2}(x_i - x_j)_+^2 + \varepsilon_i,\ i = 1, ..., n; \tag{3}$$

where

$$(x - x_j)_+^2 = \begin{cases} (x - x_j)^2, \text{ if } x \succ x_j; \\ 0, \text{ if not;} \end{cases} \tag{4}$$

and $x_1 \leq x_2 \leq ... \leq x_k$ are the abscissas of joint points called knots. The number of knots k is chosen by the user or automatically by the SAS/TRANSREG procedure. Equation (3) is equivalent to a quadratic model in each interval $\left(x_j, x_{j+1}\right]$ [1].

Local regression

$$Y_i = g(x_i) + \varepsilon_i, \tag{5}$$

where $g(.)$ is an unknown locally linear or quadratic function near a chosen reference point $x = x_0$. Each neighborhood is chosen so that it contains a specified percentage of data points, and the parameters of $g(.)$ are estimated in this restricted dataset [2]. The number of reference points is chosen by the user or automatically by the SAS/LOESS procedure, dependent on sample size.

---

[1] Data used in preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (http://adni.loni.ucla.edu). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in analysis or writing of this report. A complete listing of ADNI investigators can be found at: http://adni.loni.ucla.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf

*Correspondence to: Simon Duchesne, Institut Universitaire en Santé Mentale de Québec, 2601 de la Canadiére, Room F-4435, G1J 2G3, Québec, Canada. Tel.: (418) 663 5741; ext. 4777; Fax: (418) 663 5971; E-mail: simon.duchesne@crulrg.ulaval.ca.

ISSN 1387-2877/12/$27.50

Robust quadratic regression

This model is equivalent to the quadratic model above (eq. 2), but using Huber's M-estimation method instead of least square [3]. The resulting model did not remove outliers nor did it assume error normality. Huber's M-estimation used the following weight function

$$W_H(e) = \begin{cases} 1 \quad \text{for } |e| \leq k; \\ {}^{k}/_{|e|} \quad \text{for } |e| \succ k. \end{cases} \tag{6}$$

instead of $W_{LS}(e) = 1$ as in the least square estimation. The tuning constant k depended on the data and number of outliers to be conserved; and

Sigmoid model

$$Y_i = asym/(1 + \exp((xmid - x_i)/scal)) + \varepsilon_i. \tag{7}$$

where *asym* is the asymptote, *xmid* the inflection point and *scal* the slope at point of inflection.

AKAIKE INFORMATION CRITERION

The Akaike Information Criterion (AIC) [4] is based on the log-likelihood, defined as follows:

$$AIC = n.\ln(SSq/n) + 2.p. \tag{8}$$

where *SSq* is the sum of square of the fitted errors, the number of data points and the number of parameters fitted by each model.

To select the best model, we followed this algorithm:

1. *Calculate the AIC for all models;*
2. *Identify the best model with the smallest AIC = AICmin.*

   We could have stopped at this point, and the model thus selected is the model more likely to be correct. But how much more likely? Considering there was not much evidence to choose one model over the other, especially if AIC scores were close, we proceeded as follows:
3. *Calculate the difference in AIC,* $\Delta_i(AIC) = AIC_i - AIC_{\min}$ *for each model i;*
4. *Compute the relative likelihood,* $exp\left(-\frac{1}{2} \cdot \Delta_i(AIC)\right)$ *, for each model i*;
5. *Compute the Akaike weights for each model i, as such:*

$$w_i(AIC) = \frac{exp\left(-\frac{1}{2} \cdot \Delta_i(AIC)\right)}{\sum\limits_{i=1}^{m} exp\left(-\frac{1}{2} \cdot \Delta_i(AIC)\right)}, \tag{9}$$

   where is the number of models. This quantity can be interpreted as the probability that the given model $i, i = 1, \ldots, 6$, is the best model, given the data and the set of candidate models [5]; and
6. *Compute the evidence ratio from the Akaike weights:*

$$evidence\ ratio = \frac{w_i(AIC)}{w_j(AIC)} \tag{10}$$

   and thus get a likelihood ratio for how much support model *i* has over model *j* [6].

REFERENCES

[1] Smith PL (1979) Splines as a useful and convenient statistical tool. *American Statistician* **33**, 57-62.

[2] Cleveland WS (1979) Robust locally weighted regression and smoothing scatter plots. *J Am Stat Assoc* **74**, 829-836.

[3] Huber PJ (1964) Robust estimation of a location parameter. *Ann Math Stat* **33**, 73-101.

[4] Akaike H (1974) A new look at the statistical model identification. *IEEE Trans Automat Contr* **19**, 716-723.

[5] Burnham KP, Anderson DR (2001) Kullback-Leibler information as a basis for strong inference in ecological studies. *Wildlife Res* **28**, 111-119.

[6] Wagenmakers EJ, Farrell S (2004) AIC model selection using Akaike weights. *Psychon Bull Rev* **11**, 192-196.