

Second order Markov modelling of HAMD responses in depression trials



University of Pavia

E. Marostica¹, A. Russu¹, S. Zamuner², R. Gomeni^{3*}, G. De Nicolao¹

¹ Department of Industrial and Information Engineering, University of Pavia, Pavia, Italy

² Clinical Pharmacology / Modelling and Simulation, GlaxoSmithKline, Stockley Park, UK

³ Pharmacometrics, GlaxoSmithKline, Upper Merion, PA, USA

* Current address: Pharmacometrics, La Fouillade, France



GlaxoSmithKline

Introduction

- Longitudinal models describing the time course of the clinical scores in psychiatric trials are usually empirical. Moreover, conditional on the individual parameters the response model usually not structurally account for random fluctuations on the disease. The first attempt to include these aspects, presented in¹ resorting to stochastic difference and differential equations, did not give a completely satisfactory description of inter-individual variability.
- We propose an extension of the previous work through a more sophisticated continuous-time dynamic model based on second order Markov processes². The proposed model aims to describe appropriately the clinical response and handle flexible dosing schemes.

Integrated Wiener process and second order Markov model of HAMD score

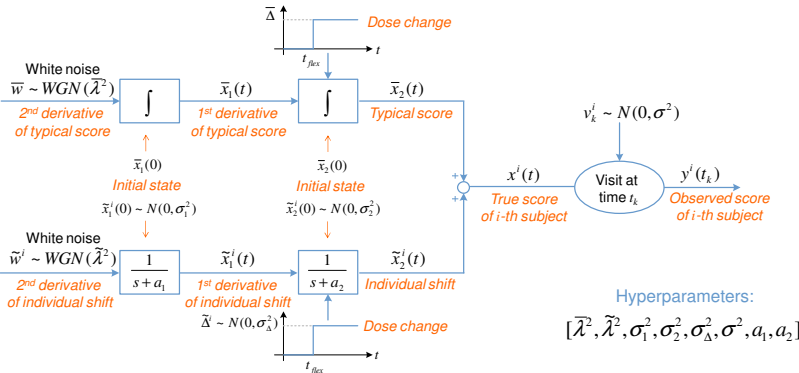
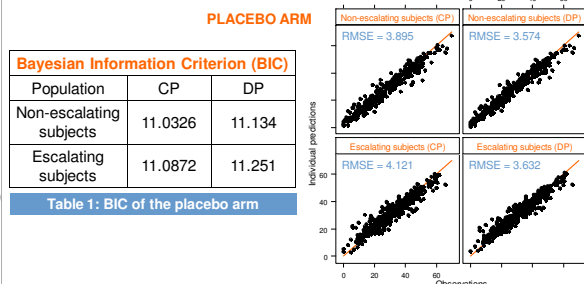


Figure 1: Block-diagram of the integrated Wiener process and second order Markov model of HAMD time course

- The population approach was adopted to model the HAMD clinical scores.
- Integrated Wiener process³ was used to model the typical curve.
- A second order Markov model was adopted to describe the individual shifts with respect to the typical curve.
- Each individual curve was expressed as the sum of a typical curve and an individual shift (Figure 1).
- Two Markov models were analyzed, having in the transfer function
 - ★ two coincident poles (CP, $a_1 = a_2$)
 - ★ two distinct poles (DP)
- Dose changes were accounted for by varying the trend of the response profile (Δ and $\tilde{\Delta}$ in Figure 1).
- Models statistics were specified through hyperparameters (see Figure 1). A unique hyperparameter for the measurement error variance σ^2 was considered in order to simultaneously identify the model on the four subpopulations (placebo and drug: non-escalating and escalating subjects).
- R 2.10.4 was adopted according to the empirical Bayes paradigm.

Results

- A Phase II, double-blind, randomized, placebo-controlled, flexible-dose depression trial was analyzed.
- Both models were able to capture the shapes of individual responses (Figure 2).
- Moreover, good predictive performances in terms of VPCs were obtained. Figure 4 shows VPCs obtained with the second order Markov model with two coincident poles.
- According to the Bayesian Information Criterion (Tables 1, 2), the second order Markov model with two coincident poles in the transfer function should be preferred.
- Individual fittings of a subset of patients (Figure 3) and Visual Predictive Checks of HAMD data (Figure 4) are shown (CP model only).



Goodness-of-fit

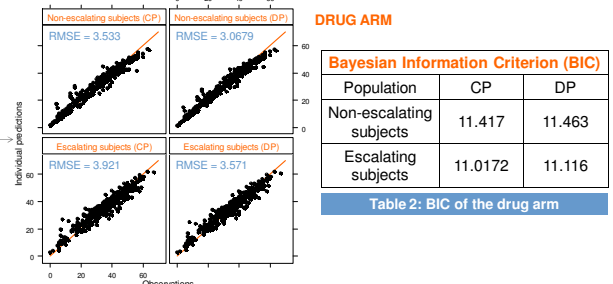


Figure 2: Goodness-of-fit plots to HAMD data of the placebo (left panel) and drug (right panel) arms

Individual fittings

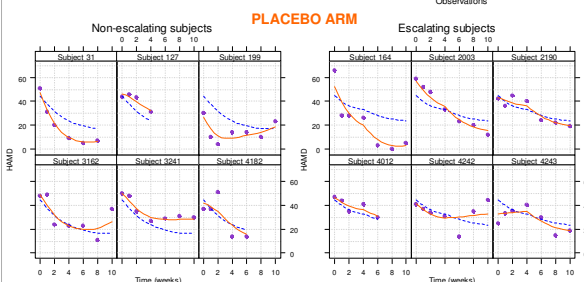
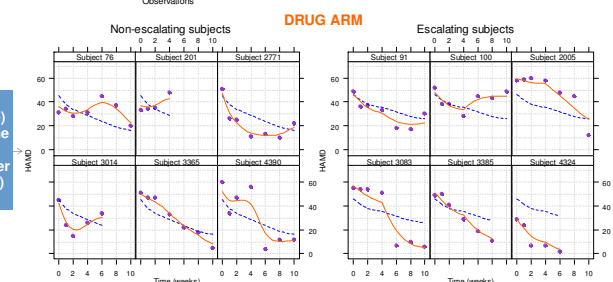


Figure 3: Individual fittings (orange) and typical curve (blue) for a subset of subjects using the integrated Wiener process (typical curve) + the second order Markov model (individual shifts) with two coincident poles (CP)



Visual Predictive Checks

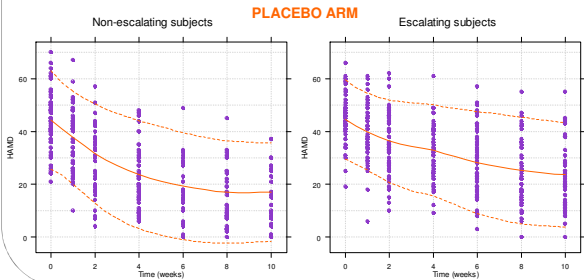
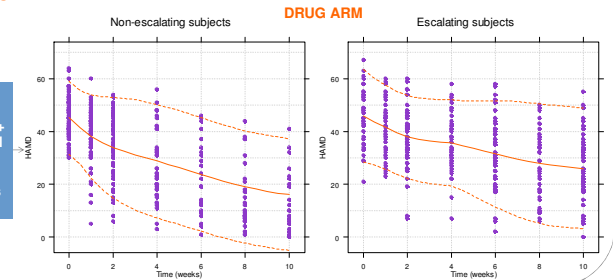


Figure 4: VPC of HAMD data obtained using the integrated Wiener process (typical curve) + the second order Markov model (individual shifts) with two coincident poles (CP). Median, 5th and 95th percentiles are shown



Conclusions

- The results demonstrate the feasibility and effectiveness of second order Markov processes as an innovative modelling approach for longitudinal data, when mechanistic knowledge is poor or absent.
- The proposed models yield good individual fittings as well as a good estimate of the population response and an appropriate representation of the inter-individual variability.
- Interestingly, both models are able to easily handle dose changes and account for random perturbations with greater flexibility than previous approaches¹.

References

- Marostica E, Russu A, De Nicolao G, Gomeni R (2011). Population state-space modelling of patient responses in antidepressant studies, Population Approach Group Europe (PAGE) 20th Meeting, Abstract 2133.
- Mortensen SB (2010). Markov and mixed models with applications, PhD Thesis, Technical University of Denmark (DTU), Kgs. Lyngby.
- Neve M, De Nicolao G, Marchesi L (2007). Nonparametric identification of population models via Gaussian processes, Automatica 43, pp. 1134–1144.
- R Development Core Team. R: A Language and Environment for Statistical Computing. R Foundation for Statistical Computing, Vienna, Austria (2010). <<http://www.R-project.org>>.