Population state-space modelling of patient responses in antidepressant studies

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Introduction

A major challenge posed by the analysis of the clinical scores used to assess the disease status in depression trials is the lack of "first principles" from which response models can be derived. The state-space framework, which is based on a set of differential (or difference) equations that describes the evolution of one or more variables characterizing the patient's health state[1], represents an appealing and more mechanistically driven approach to describe these data. In order to develop a comprehensive state-space approach, we address two main questions:

- How to give an adequate description of the clinical response?
- How should flexible dosing schedules be handled within a state-space framework?

Stochastic state-space model of HAMD score

- Continuous- and discrete-time stochastic processes (integrated Wiener processes and integrated random walks[2,3]) were used to describe the time course of the HAMD score, within the framework of population modelling.
- Each individual curve was expressed as the sum of a typical curve and an individual shift, both described as random processes whose statistics were specified through hyperparameters.
- Dose changes were modelled as a step variation of the first derivative of the patient's score.

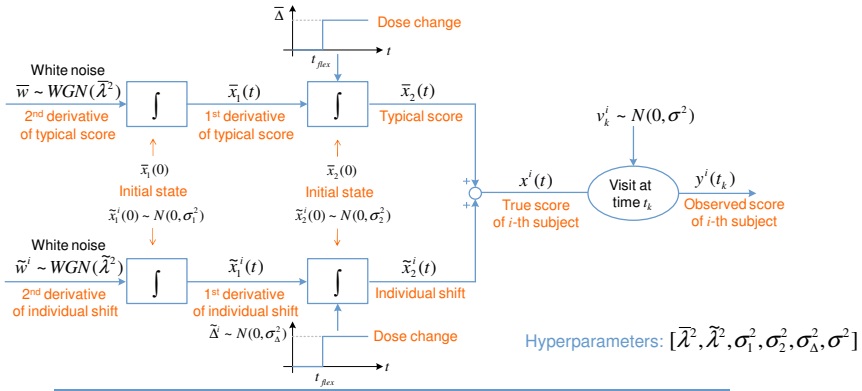

Figure 1: Block-diagram of the stochastic state-space model of HAMD time course

- Within a Bayesian paradigm, the state-space model of *Figure 1* provides a description of the prior probability of the patients' scores. More specifically, the basic assumption is that the second derivative of the HAMD time course is a white noise with finite variance, a classical device to enforce a smoothness prior on the continuous-time score signal.
- $\bar{x}_1(0), \bar{x}_2(0), \bar{w}(t), \tilde{x}_1^i(0), \tilde{x}_2^i(t), \tilde{w}^i(t), \bar{\Delta}, \tilde{\Delta}^i, v_k^i$ are independent of each other.
- A discrete-time stochastic model (integrated random walk, IRW) can be easily obtained by replacing the integrals of the continuous-time one (population smoothing splines, PSS) with discrete sums.
- According to an empirical Bayes paradigm, hyperparameters were estimated through Maximum Likelihood. Estimation and post-processing were carried out with R 2.10.0[4].

Results (1)

- A double-blind, randomized, placebo controlled, flexible dose depression trial was used as a benchmark for alternative state-space approaches.
- Second-order discrete- and continuous-time state-space models were able to fit very satisfactorily the whole range of shapes observed in individual responses (*Figures 2, 3*).
- The continuous-time model appears to be marginally superior to the discrete-time one, in terms of BIC (*Tables 1, 2*).

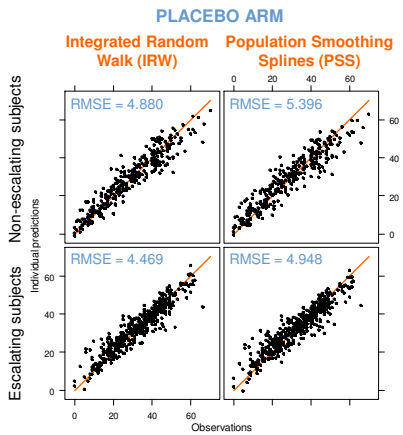

Figure 2: Goodness-of-fit plots to HAMD data of the placebo arm

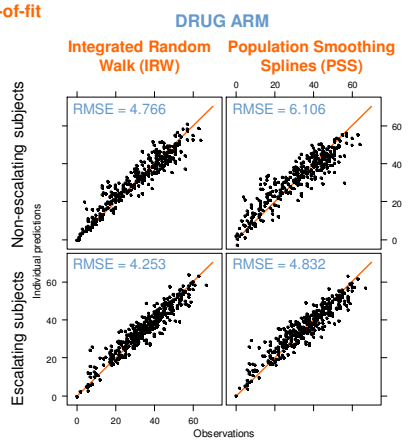

Figure 3: Goodness-of-fit plots to HAMD data of the drug arm

Root Mean Square Error (RMSE)		
	IRW	PSS
Non-escalating subjects	4.880	5.396
Escalating subjects	4.469	4.948
Bayesian Information Criterion (BIC)		
	IRW	PSS
Non-escalating subjects	11.009	10.678
Escalating subjects	11.224	10.851

Table 1: RMSE and BIC of the placebo arm

Root Mean Square Error (RMSE)		
	IRW	PSS
Non-escalating subjects	4.766	6.106
Escalating subjects	4.253	4.832
Bayesian Information Criterion (BIC)		
	IRW	PSS
Non-escalating subjects	11.422	10.921
Escalating subjects	11.085	10.799

Table 2: RMSE and BIC of the drug arm

Results (2)

The continuous-time model (PSS) provided good individual fittings (*Figure 4*) and satisfactory Visual Predictive Checks (*Figure 5*) for both treatment arms.

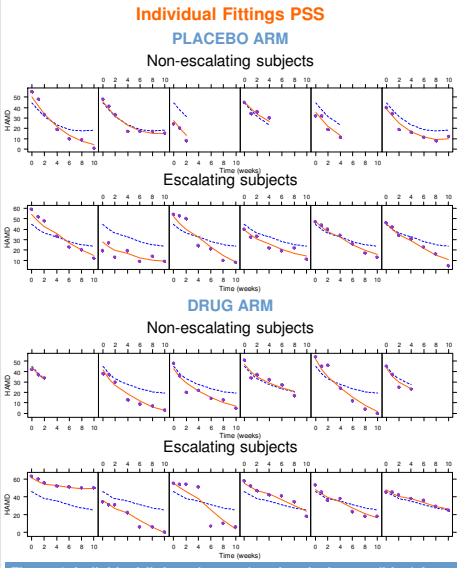

Figure 4: Individual fittings (orange) and typical curve (blue) for a subset of subjects using the continuous-time model (PSS)

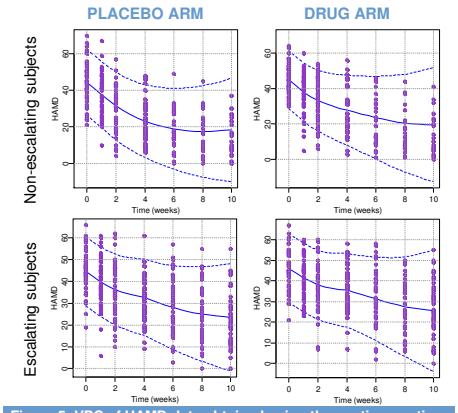

Figure 5: VPC of HAMD data obtained using the continuous-time model (PSS). Median, 5th and 95th percentiles are shown

Conclusions

- The results demonstrate that state-space approaches not only provide adequate description of population responses but are also easily adapted to account for possible dose changes during the trial.
- Among the advantages, there is the possibility to model the presence of random perturbations that affect the patient's health state.
- Alternative state-space models whose output converges to a stationary process, e.g. auto-regressive moving average (ARMA) models[5], may be considered.
- A further step will be the development of an integrated response and dropout model within the state-space framework.

References

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