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Population methods for dose escalation studies: an MCMC approach

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INTRODUCTION

In dose escalation studies, cohorts of patients receive increasing dose levels of a candidate drug. Depending on exposure measurements (AUC or Cmax), decisions are taken on the next doses to be given. In recent years there has been a growing interest in Bayesian methods for the sequential estimation of either the safety probability [1] or the dose-exposure relationship [2, 3].

OBJECTIVES

The aims of our study were to:

- Enhance the model proposed in [2], by means of less subjective priors and allowing for inter-individual variability of all parameters
- Abandon the closed-form formulas of [2] in favour of a more general MCMC approach
- Provide the clinician with a tool for dose escalation studies, featuring plots of the risk of exceeding the safety margin
- Statistical choice of model complexity

METHODS

Data The clinical study considered was a single-blind, randomised, placebo-controlled design in 2 cohorts of healthy male subjects to assess PK, safety and tolerability of a new candidate drug.

Model assumptions The approach proposed by Whitehead et al. [2] was extended to take into account inter-individual variability on the population parameters describing the intercept and the slope of the model. Fixed relationships among hyper-parameters were dropped and priors were introduced based on ML estimates. The final model adopted was:

$$y_{ij} = (\theta_1 + s_i) + (\theta_2 + t_i) l_{ij} + \varepsilon_{ij}$$

y_{ij} log-exposure of i-th subject to j-th administered dose

$\boldsymbol{\theta} = [\theta_1 \quad \theta_2]'$ population parameters

s_i random effect of i-th subject on θ_1

t_i random effect of i-th subject on θ_2

l_{ij} log-dose administered to i-th subject

ε_{ij} measurement error

Hyper-parameters included variances ξ_s and ξ_t of random effects s_i and t_i as well as the measurement error variance v.

MCMC Methodology The statistical model was implemented in WinBUGS. The quantities to be sampled are represented by nodes as in Fig.1.

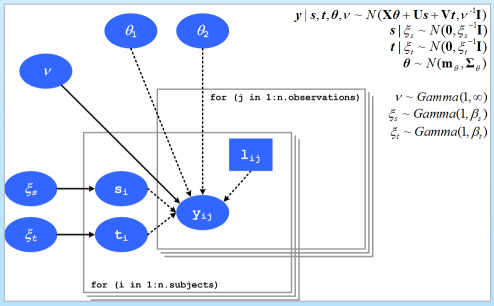

Fig. 1: graphical representation of the model in WinBugs

RESULTS

The proposed method was successfully validated on simulated datasets featuring different individual slopes (data not shown). In order to compare the proposed model with the MCMC implementation of Whitehead's model, AIC and Schwarz (BIC) criteria were used (Table 1). Although more complex with respect to Whitehead's, the more general model presented herein yields lower values of both AIC and BIC.

Figs. 2-7 show the simplified model of [2] (left column) and our model (right column) applied to the clinical study dataset: confidence intervals for a new subject with predictive distributions for an untested dose (Figs. 2-3), dose-exposure curves of two subjects together with confidence intervals (Figs. 4-5) and corresponding risk curves (Figs. 6-7) are shown.

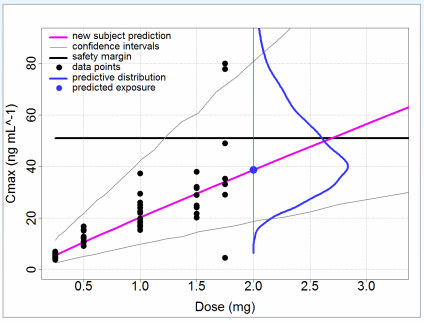

Fig. 2: new subject dose-exposure curve (Whitehead's model)

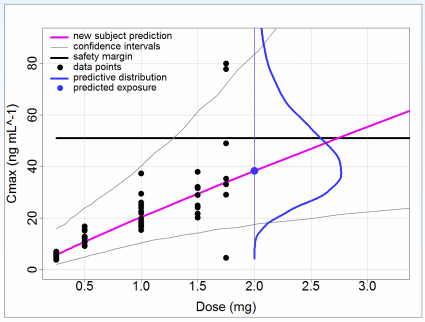

Fig. 3: new subject dose-exposure curve (new model)

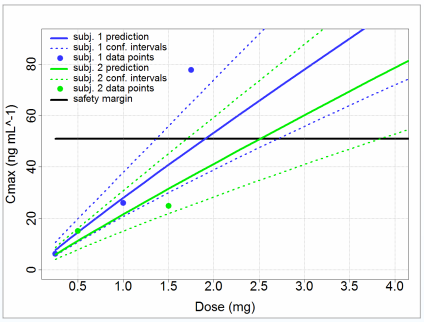

Fig. 4: real subjects dose-exposure curve (Whitehead's model)

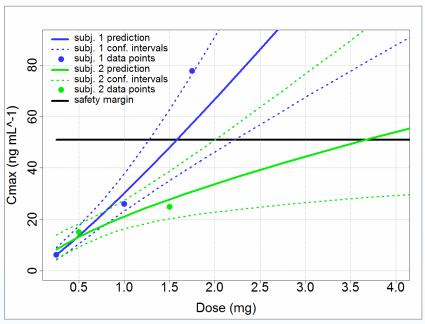

Fig. 5: real subjects dose-exposure curve (new model)

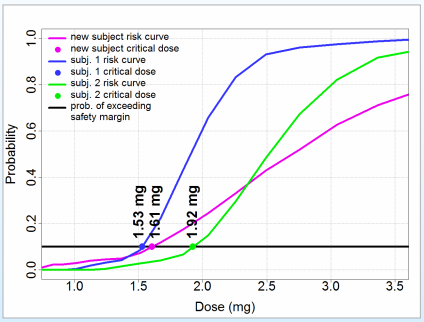

Fig. 6: new and real subjects risk curves (Whitehead's model)

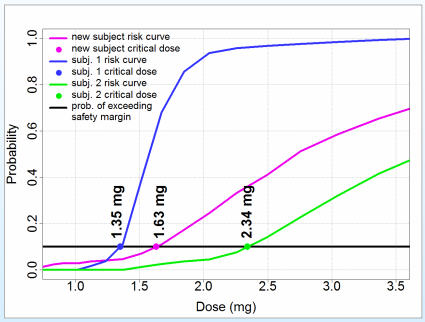

Fig. 7: new and real subjects risk curves (new model)

Model	SSR (N = 57)	Degrees of freedom	AIC	BIC
Whitehead	3.705	21.435	2.062	-2.241
New	0.854	38.003	1.176	-4.305

Table 1: model comparison results

CONCLUSIONS

The new method improves over existing approaches in that it allows a greater flexibility in modelling of individual dose-exposure curves. Depending on the specific dataset, one can select the most appropriate model according to statistical criteria such as AIC and BIC. Confidence intervals for new and existing subjects as well as risk curves are produced, giving valuable support to the decision making within dose-escalation studies.

[1] O'Quigley, J., Pepe, M. and Fisher, L. (1990). Continual reassessment method: a parctical design for phase I clinical trials in cancer. *Biometrics* 46, 33-48.
[2] Whitehead, J., Zhou, Y., Patterson, S., Webber, D., Francis, S. (2001). Easy-to-implement Bayesian methods for dose escalation studies in healthy volunteers. *Biostatistics* 2, 47-61.
[3] Berry, D.A., Müller, P., Grieve, A.P., Smith, M., Parke, T., Blazek, R., Mitchard, N., Krams, M. (2001). *Adaptive Bayesian designs for dose-ranging drug trials*. in Gatsonis C., Kass R.E., Carlin B., Carriquiry A., Gelman A., Verdinelli I., West M. (eds.), Case Studies in Bayesian Statistics V. New York: Springer-Verlag, 99–181.