Assessment of NONMEM and WinBUGS performances when estimating power and sigmoid Emax models

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Introduction

Non-linear Mixed Effect modelling as implemented in NONMEM is considered one of the key approaches for estimating population PK or PK/PD model parameters. Recently, also Bayesian inference (as implemented in WinBUGS) has gained credibility within the same framework for some of its advantages. A comparison between these two methodologies has already been addressed when considering some PK or PK/PD models[1,2,3,4]. The present work aims at evaluating NONMEM and WinBUGS performances when applied to two of the most frequently used models (power and sigmoid Emax) in drug development under a variety of parameter conditions.

Objectives

- Evaluate the performance of NONMEM and WinBUGS in estimating parameters from two commonly used models under different conditions.
- The effect of different parameter variabilities has been evaluated together with the impact of weakly or more informative experimental designs (expressed in terms of sample size and number of given doses).

Methods

Models

The power model used for simulating the dose-exposure relationship has been implemented as follows:

$$y_{ij} = \left[\vartheta_1 \cdot e^{\eta_{1i}}\right] \cdot d_{ij}^{\left[\vartheta_2 \cdot e^{(\eta_{2i}+\eta_{3i})}\right]} + \varepsilon_{ij}$$

whereas, the sigmoid Emax model used for simulating the dose-response relationship is given by:

$$y_{ij} = \frac{\left[\vartheta_1 \cdot e^{\eta_{1i}}\right] \cdot d_{ij}^{\left(\vartheta_3 \cdot e^{\eta_{3i}}\right)}}{\left[\vartheta_2 \cdot e^{\eta_{2i}}\right]^{\left(\vartheta_3 \cdot e^{\eta_{3i}}\right)} + d_{ij}^{\left(\vartheta_3 \cdot e^{\eta_{3i}}\right)}} + \varepsilon_{ij}$$

For both models:

$$\omega_{1i}^2 = Var\left[\eta_{1i}\right] \quad \omega_{2i}^2 = Var\left[\eta_{2i}\right] \quad \omega_{3i}^2 = Var\left[\eta_{3i}\right]$$

$$\sigma^2 = Var\left[\varepsilon_{ij}\right]$$

Data

Study designs with two cohorts of either 4 or 8 subjects each were considered.

- For the power model, dose levels were 0.5, 1, 2, 4, 6, 10, 15, 20, 30, 40 mg. Three different scenarios were explored by assuming to give doses up to 2 mg, 6 mg or 40 mg, respectively.
- For the Emax model, dose levels were either 1, 5, 10 and 50 mg (thus exploring only part of the sigmoid) or 1, 2, 5, 10, 50 and 100 mg, respectively.

For each of the aforementioned experimental designs and for each of the following sets of fixed and random effects (see Table 1), 50 dose-response and 50 dose-exposure data-sets were simulated using R 2.7.0

Model	ϑ_1	ϑ_2	ϑ_3	ω_1	ω_2	ω_3	σ
Power	20	0.8 1 1.2	-	0.01 0.1 0.2	0.01 0.1 0.2	0 0.02	10 20
Emax	100	10	0.5 1 2	0	0.01 0.2	0 0.01	1 5

Table 1: fixed & random effect parameters

Estimation

The same models used for simulating a variety of data-sets have been implemented in NONMEM VI as well as in WinBUGS 1.4.3. Both tools have been used to estimate fixed and random effect parameters for each simulated data-set. In particular, the FOCE interaction method was chosen for NONMEM. Concerning WinBUGS, non-informative prior distributions were used for the model's hyper-parameters. Statistical computations on each set of 50 simulated data-sets were performed resorting to R 2.7.0 in order to evaluate both accuracy and precision of parameter estimates.

Results

Power model

- Both NONMEM and WinBUGS produce accurate estimates of fixed as well as random effects regardless of the value of the power coefficient (0.8, 1 or 1.2). They both give higher RMSEs when estimating the proportionality coefficient (θ_1) and the additive error SD (σ). Figure 1 shows an example of NONMEM and WinBUGS accuracy when estimating one of the fixed effects (θ_2), while Figure 2 illustrates the differences in precision estimates of random effects (i.e. ω_2) obtained with the two methodologies.

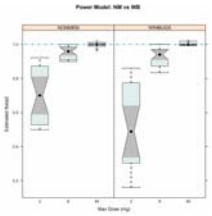

Fig 1: Power coefficient estimates as a function of max dose (θ_2=1)

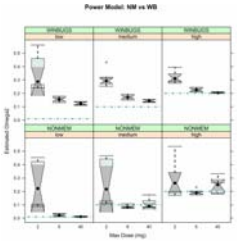

Fig 2: Estimate of ω_2 as a function of max dose (θ_2=1)

- The number of administered doses rather than the number of dosed subjects has a major impact on the accuracy (for both tools) and precision (mainly for WinBUGS) of all parameter estimates. This is particularly true for the random effects: as an example, Table 2 summarizes median and 95th percentile RMSEs obtained when estimating ω_2 as a function of maximum given dose and number of subjects.

Model	Max Dose (mg)	Number of Subjs	Median RMSE	95% CI on RMSE
NM	2	4	0.49	(0.115 -1.085)
WB	2	4	0.28	(0.128 – 1.561)
NM	2	8	0.30	(0.115 – 0.908)
WB	2	8	0.21	(0.105 – 1.005)
NM	6	4	0.07	(0.017 – 0.163)
WB	6	4	0.09	(0.039 – 0.205)
NM	6	8	0.05	(0.013 – 0.126)
WB	6	8	0.07	(0.037 – 0.173)
NM	40	4	0.04	(0.005 – 1.472)
WB	40	4	0.06	(0.037 – 0.131)
NM	40	8	0.03	(0.004 – 1.352)
WB	40	8	0.04	(0.028 – 0.107)

Table 2: Median and 95th percentile RMSEs on ω_2

Sigmoid Emax model

- NONMEM produces accurate estimates of all random effects as well as of the Hill coefficient (θ_3) regardless of the conditions tested for θ_3 (0.5, 1, 2). WinBUGS seems to have more difficulties in producing accurate estimates of the random effects when they have very small (or null) values (this problem may be due to the choice of the non-informative hyper-priors or their initial conditions). Figure 3 illustrates such behaviour.

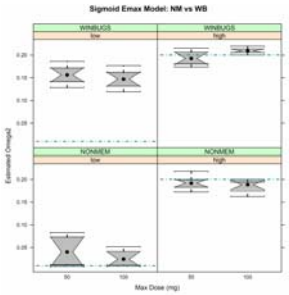

Fig 3: Estimate of ω_2 as a function of max dose (θ_3=2)

- Whenever the experimental design is less informative (i.e. explored doses do not allow to obtain a good estimate of Emax (θ_1) and ED_{50} (θ_2) for values of the Hill coefficient lower than one), both NONMEM and WinBUGS appear to be less accurate and precise (though WinBuGS is often more precise than NONMEM). An example is given in Table 3.

Model	Hill coeff (θ_3)	Median RMSE	95% CI on RMSE
NM	0.5	7.17	(1.002 – 897.59)
WB	0.5	18.67	(1.034 – 154.66)
NM	1	1.19	(0.232 – 5.895)
WB	1	1.65	(0.251 – 8.071)
NM	2	0.71	(0.096 – 9.931)
WB	2	0.92	(0.164 – 32.61)

Table 3: Median and 95th percentile RMSEs on ED_{50} (θ_2)

Conclusions

- In the range of explored experimental designs, both NONMEM and WinBUGS showed a generally comparable accuracy in estimating fixed effect parameters with either highly or less informative data-sets. However, WinBUGS showed some difficulties in accurately estimating the random effects when they were assigned very small (or null) values.
- In general, WinBUGS provided more precise estimates of model parameters than NONMEM did. This is particularly true for the random effects of both models.
- This work is not an exhaustive analysis of the performances that can be obtained with these two different methodologies. As such, different experimental designs or more critical conditions may be further evaluated in the future.

References

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