Alternative parameterisations of saturable (E_{max}) models allowing for nesting of non-saturable models

Andreas V Groth, Biomodelling, Novo Nordisk A/S, Copenhagen, Denmark, ✉ avg@novonordisk.com

Background

The saturable E_{max} model parameterised with E_{max}, EC_{50} and possibly a Hill coefficient γ is widely used within the PKPD area, frequently using EC_{50} values to express relative potencies of different drugs. Being non-saturable, a linear effect model must be formulated with different model parameters. Thus, the conditions for comparing such models with a likelihood ratio test are not met[1,2].

It may often be the case that only levels of effect far below E_{max} are achievable in vivo and thus therapeutically relevant[3]. In such cases, both of the E_{max} and EC_{50} parameters may be estimated only with substantial uncertainty. Thus in such cases, comparisons of potency based on estimated EC_{50} values may be highly uncertain.

Aims:

- Reparameterising the commonly used simple and Hill E_{max} models to allow nesting of non-saturable models within saturable models
- Investigating estimation properties of the new population parameters under conditions of a limited data range

Nomenclature

The E^*-α parameterisation:

(C^*, E^*) is a (concentration, effect)-pair on the model-predicted population curve, one being chosen appropriately and the other being an estimated model parameter[4] (Fig. 1). Preferably, these are within the therapeutically relevant range so that one can be used as the potency estimate for the drug.

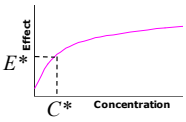

Figure 1

Other model parameters:

$\alpha := EC_{50}^{-1}$ (allows nesting) , γ: Hill coefficient (unchanged) , δ: Richards asymmetry parameter (unchanged)

References

[1] Rao CR, *Linear Statistical Inference and Its Applications, 8À Math. 67-177 Wiley, New York*, (1965)

[2] Van der Graaf PH, Schoemaker RC, *Journal of Pharmacology and Toxicology*, Vol. 41 (1999)

[3] Schoemaker RC et al., *Journal of Pharmacokinetics and Biopharmaceutics*, Vol. 26, No. 5, 1 (1998)

[4] Bachman WJ, Gillespie WR. *Clin. Pharmacol. Ther.* 63:199 (1998).

[5] Lindbom L et al., *Comput Methods Programs Biomed.* 2004 Aug;75(2):85-94.

Model nesting allowing for comparisons by likelihood-ratio tests

Constraints

$$\alpha \geq 0,\ \gamma \geq 0,\ \delta > 0$$

$$E = E^* \frac{C^\gamma}{C^{*\gamma}} \frac{1+(\alpha C^*)^\gamma}{\sqrt[\delta]{(\alpha C)^{\gamma(\delta-1)} + (\alpha C)^{\gamma\delta}}}$$

Richards asymmetrical model

$\Rightarrow \delta = 1$

$$E = E^* \frac{C^\gamma}{C^{*\gamma}} \frac{1+(\alpha C^*)^\gamma}{1+(\alpha C)^\gamma}$$

Hill E_{max} model

$\Rightarrow \gamma = 1$

$$E = E^* \frac{C}{C^*} \frac{1+\alpha C^*}{1+\alpha C} = E^* \frac{\frac{C}{C^*} + \alpha C}{1+\alpha C}$$

Simple E_{max} model

$\Rightarrow \alpha = 0$

$$E = \frac{E^*}{C^*} C$$

Linear model

$\Rightarrow \alpha = 0$

$$E = E^* \frac{C^\gamma}{C^{*\gamma}} = \frac{E^*}{C^{*\gamma}} C^\gamma$$

Power function model

$\Rightarrow \gamma = 1$

Robustness of potency estimation

Methods

100 simulated data sets, each with 33 subjects and 3 PD observations per subject, were generated from a one-compartment PK model with log-normal IIV on $T_{½}$ (CV= 70%) combined with a E_{max}-EC_{50} parameterised PD model (E_{max}=100, EC_{50}=100) with log-normal IIV on E_{max} (CV=30%). Data sets were truncated at C_{max}=50. For the alternative E^*-α parameterised model, C^* = 12.5 was chosen so that E^* was to be used as the potency estimate and IIV was estimated on E^* only. Using Perl-speaks-NONMEM (PsN)[5], both parameterisations were estimated from each data set, and the relative errors of the θ's of the respective "potency parameters" (E^* and EC_{50}, respectively) were compared between the parameters estimated from each data set.

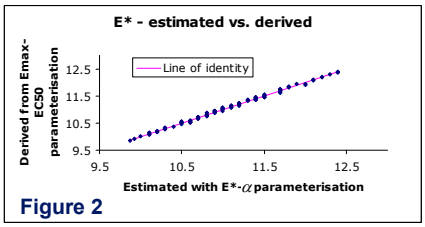

Figure 2

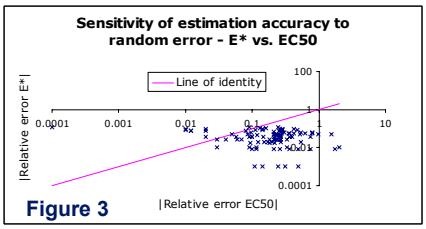

Figure 3

Results & Discussion

When deriving E^* from estimated population parameters E_{max} and EC_{50} of that parameterisation, values were very similar to those obtained by estimating population E^* directly (Fig. 2).

In 90% of the 100 simulations, population E^* was estimated with less relative error than population EC_{50} from the same data set, shown by 90 of the 100 points lying below the line Y=X on Fig. 3.

Thus, very similar values of population E^* and hence potency estimates may eventually be obtained in both ways, but with the E^*-α parameterisation this information is contained in a single estimated parameter with direct information on the standard error of this potency estimate. In contrast, with the E_{max}-EC_{50} parameterisation this potency estimate must be derived from both of the two correlated estimation parameters.

Conclusions

- Replacing E_{max} and EC_{50} by parameters taking finite values also for non-saturable models enables nesting of non-saturable and saturable models – linear, Hill E_{max} and Richards asymmetrical models - within the same parameter structure, allowing for comparisons by likelihood ratio tests.
- In situations when the therapeutically relevant concentration is small compared to EC_{50} , a therapeutically relevant E^* may be chosen as a potency parameter with apparently more robust estimation properties than EC_{50}.
- It seems worth investigating reparameterisations for optimising properties of the widely used E_{max} model.

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