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Approximate prediction percentiles for non-linear mixed effects models with continuous responses

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Introduction

Non-linear mixed effects models are used in pharmacokinetics (PK) studies to describe the evolution of drug concentrations in a target population as a function of time and the dosage regimen. Prediction percentiles derived from such models allow to build PK reference ranges used e.g. for the interpretation of drug concentration monitoring results. These percentiles are commonly calculated using a large number of Monte Carlo (MC) simulations. In some applications (e.g. implementation on miniaturized systems, repeated calculations to build confidance intervals), the computation time is critical and approximation methods are desirable.

Objectives

- **Consider the distribution of a second order Taylor approximation of a non-linear mixed effects model and derive analytically its first four moments.**
- **Match these with corresponding moments of a flexible family of distributions that can accomodate different degrees of skewness and kurtosis.**
- **Compare accuracy & computational time of the proposed method against MC simulations when calculating reference ranges for a population PK model of an anti-fungal agent (Voriconazole).**

Methods

Let $Y = f(X)$ be the outcome (at time t) of a non-linear function $f : \mathbb{R}^p \to \mathbb{R}$ of a set of p random variables (r.v.) $\boldsymbol{X} = X_1, ..., X_p$ with $\boldsymbol{X} \sim \mathcal{N}_p(\mu, \boldsymbol{\Sigma})$. In the context of non-linear mixed effects models with fixed effects θ, one realization of Y is modelled as:

$$y_i \equiv y_i(t) = f_\theta(\eta_i, \epsilon_i(t))$$
$$\eta_i \sim \mathcal{N}_q(0, \boldsymbol{\Omega}) \quad : \text{random effects}$$
$$\epsilon_i(t) \sim \mathcal{N}(0, \sigma^2) \quad : \text{residual error}$$

and thus $\boldsymbol{X} = \{\eta, \epsilon\}, \boldsymbol{\mu} = E[\boldsymbol{X}] = 0$ and $\boldsymbol{\Sigma} = \begin{pmatrix} \boldsymbol{\Omega} & 0 \\ 0 & \sigma^2 \end{pmatrix}$ with $p = q + 1$.

Considering $\boldsymbol{\Sigma} = \boldsymbol{B}\boldsymbol{B}'$, it is easier to work on transformed data $\boldsymbol{Z} = (\boldsymbol{X} - \mu)\,\boldsymbol{B}^{-1}$ such that $\boldsymbol{Z} \sim \mathcal{N}_p(0, \boldsymbol{I})$.

Second order Taylor expansion of f around μ

$$y_i = f(x_i) = g(z_i)$$
$$\approx f(\mu) + \nabla f'_\mu \boldsymbol{B}' z_i + \frac{1}{2} z_i' \boldsymbol{B} \boldsymbol{\nabla^2 f}_\mu \boldsymbol{B}' z_i$$
$$\approx \alpha + \beta' z_i + z_i' \boldsymbol{\Psi} z_i$$

$\alpha + \beta' z_i$: Linear term (l_i)

$z_i' \boldsymbol{\Psi} z_i$: Quadratic form ($q_i$)

$L \sim \mathcal{N}(\alpha, \beta'\beta)$

Q is a linear combination of p independent $\chi^2_{(1)}$ distributions (moments given in [1])

The distribution of $T = L + Q$ is difficult to characterize but moments $m_k(T)$ for k in 1,...,4 can be expressed as functions of $m_k(L), m_k(Q)$ and the following terms:

$$\mathrm{cov}(L^2, Q) = 2\beta'\boldsymbol{\Psi}\beta$$
$$\mathrm{cov}(L^3, Q) = 6\alpha\beta'\boldsymbol{\Psi}\beta$$
$$\mathrm{cov}(L^2, Q^2) = 4\,\mathrm{Tr}\,(\boldsymbol{\Psi})\beta'\boldsymbol{\Psi}\beta + 8\beta'\boldsymbol{\Psi}\boldsymbol{\Psi}\beta$$

The sinh-arcsinh (SHASH) distributions [2]

A r.v V_λ following a SHASH distribution with parameter vector $\lambda = \{\gamma, \tau, \xi, \kappa\}$ is obtained by applying transformation h to $U \sim \mathcal{N}(0, 1)$:

$$V_\lambda = h(U, \lambda) = \gamma + \tau \sinh\left(\frac{\sinh^{-1}(U) + \xi}{\kappa}\right)$$

γ: location
τ: scale
ξ: shape (related to skewness)
κ: shape (related to kurtosis)

The SHASH distribution can accommodate different degrees of skewness and kurtosis while containing the gaussian as a particular case. Its first four moments are functions of the parameter vector λ (see [2]).

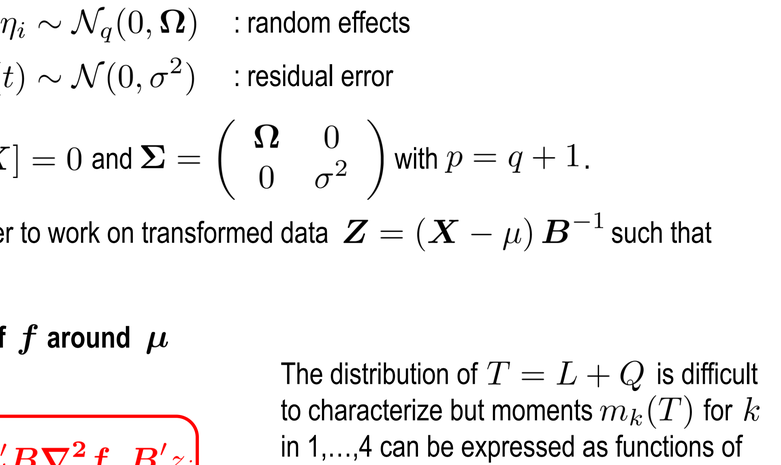

Figure 1: Example of SHASH densities for γ and τ fixed to 0 and 1, respectively.

Method of moments and percentile calculations

General idea: $Y \approx T = L + Q \approx V_\lambda$

Find $\hat{\lambda}$ such that $m_k(T) = m_k(V_{\hat{\lambda}})$ for k in 1,...,4 (Newton algorithm). Then:

- the α-quantile of Y is approximated by $h(u_\alpha)$ where u_α is the corresponding quantile of U
- the quantile associated with observation y_i is approximated by $\Phi\left(h^{-1}(y_i, \hat{\lambda})\right)$

Results

Pascual et al [3] developped a population PK model describing Voriconazole plasma concentrations in 55 adults with invasive fungal infection. Inter-individual variability was placed on bioavailability coefficient F and clearance CL, the latter depending on Rifampicin co-administration (RIF) and presence of severe hepatic cholestasis (CHOL). Using parameter estimates in [3], prediction percentiles at steady-state for a sub-population of patients with RIF=CHOL=0 receiving a dose D of 400 mg twice daily were derived according to 4 approximate methods, and compared with the reference (100,000 MC simulations).

Inter-individual variability:

$$\begin{cases} \mathrm{F}_i = \mathrm{logit}^{-1}\left[\mathrm{logit}(\theta_\mathrm{F}) + \eta_{i1}\right] \\ \mathrm{CL}_i = \theta_\mathrm{CL}(1 + \theta_\mathrm{RIF}\mathrm{RIF}_i)(1 + \theta_\mathrm{CHOL}\mathrm{CHOL}_i) \cdot e^{\eta_{i2}} \\ \eta_i \sim \mathcal{N}_2\left(0, \begin{bmatrix} \omega_1^2 & 0 \\ 0 & \omega_2^2 \end{bmatrix}\right) \end{cases}$$

Concentration-time profile: (steady-state model)

$$\mathrm{C}_i(t) = \frac{\mathrm{F}_i \mathrm{D} \theta_{\mathrm{K_a}}}{\theta_\mathrm{V}\theta_{\mathrm{K_a}} - \mathrm{CL}_i} \left[\frac{e^{-\frac{\mathrm{CL}_i}{\theta_\mathrm{V}} t}}{1 - e^{-\frac{\mathrm{CL}_i}{\theta_\mathrm{V}}\Gamma}} - \frac{e^{-\theta_{\mathrm{K_a}} t}}{1 - e^{-\theta_{\mathrm{K_a}}\Gamma}}\right] e^{\epsilon_i(t)}$$

Percentile	MC-10,000 med. [95%CI]	Taylor 1 (normal)	Taylor 2 (normal)	Taylor 2 (SHASH)
1%	5.0 [2.0-10.8]	47.8	24.7	5.4
5%	2.3 [0.9- 5.3]	25.9	7.3	3.1
10%	1.8 [0.7- 4.1]	19.2	2.2	2.3
25%	1.3 [0.5- 3.3]	12.2	3.4	0.4
50%	1.0 [0.4- 2.6]	9.7	4.2	0.4
75%	1.1 [0.4- 2.6]	10.0	3.0	2.5
90%	1.4 [0.5- 3.1]	12.7	0.9	3.8
95%	1.6 [0.5- 4.0]	15.3	3.1	3.8
99%	2.8 [0.9- 7.2]	22.3	10.5	1.7
Time (s)	3.44 [3.40-3.58]	0.41	1.08	1.37

Table 1: Maximum absolute value of the relative difference (% of concentration values) between approximate and reference percentiles for the 4 approximate methods: 10,000 MC simulations (repeated 1000 times to assess simulation error), first order Taylor expansion of the model for log-concentrations (Taylor 1, normal), and second order Taylor expansion (Taylor 2) of the model for log-concentration using either a normal approximation (normal) or the SHASH distribution. Reference percentiles were computed using 100,000 MC simulations. Indicative computational times (desktop computer) are also reported.

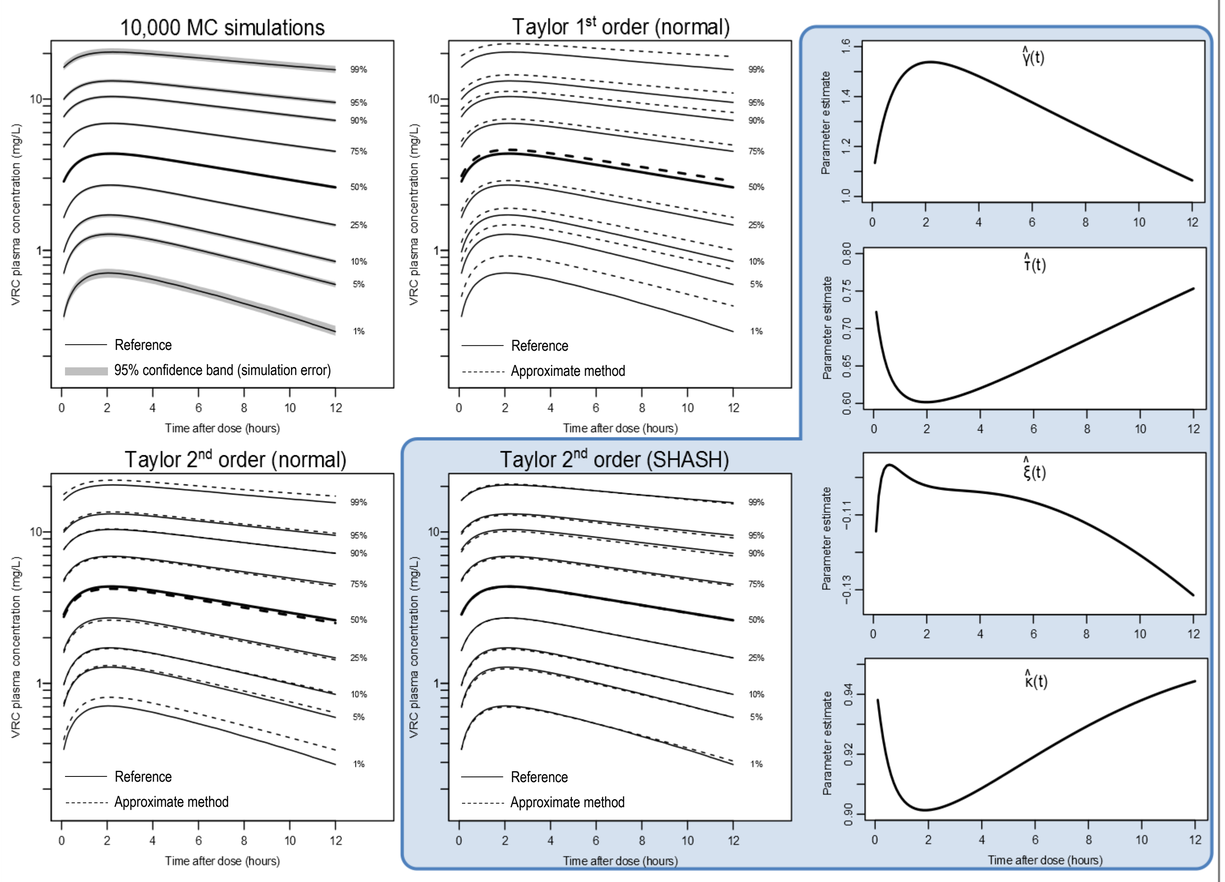

Figure 2: Percentile curves for 4 approximate methods against the reference (100,000 MC simulations). The percentiles were recalculated 1000 times with 10,000 MC simulations (panel 1) to evaluate the simulation error. Estimates of the SHASH parameters as a function of time are plotted on the right panels.

Conclusions

- **First results suggest that the proposed approach can be used as an alternative to MC simulations to describe the predictive distribution of the outcome at one time point.**
- **Opens new perspectives for meta-analysis of PK reference ranges since the whole predictive distribution can be explicitely summarized by 4 parameters.**
- **Accuracy limited by the 2nd order approximation (acceptable in many applications)**
- **Currently restricted to unimodal outcomes that are functions of gaussian stochastic elements.**
- **Validation using different parameter sets and models is still warranted.**

References

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[3] Pascual A. et al. (2012) Clinical Infectious Diseases 55 (3) 381-390