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A new approach for estimating the uncertainty of covariate effects in full random effects models and comparison with alternative approaches

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BACKGROUND AND OBJECTIVES

BACKGROUND

- The full random effects modeling (FREM) approach^[1] has been developed for covariate model building in nonlinear mixed effects (NLME) models. In a FREM model, the covariates are error-free observations and modeled as parametric distributions with a typical-value and between-subject variability (BSV) term.
- The covariate effect on each parameter is derived from the covariance between the covariate and parameter BSV terms through a full BSV matrix. However, the uncertainty of this full BSV matrix may be time-consuming or difficult to estimate.

OBJECTIVES

- This study aims to propose a new method to estimate the uncertainty of covariates effects in the FREM model and compare it with other alternative approaches.

METHODS

Models to compare

Six previously developed population PK models were employed in the comparison of the methods based on real data.

The IPN approach

Principle

The uncertainty of the covariance between covariates and parameters is approximated by implementing a bootstrap on the samples of the covariate values and Individual Parameters (η_i) vectors simulated from a corrected uncertainty distribution for the empirical Bayesian estimates ($\hat{\eta}_i$) under an assumption of Normally distributed uncertainty.

1. Obtaining the uncertainty of PK parameters in $\hat{\eta}_i$ (denoted $\hat{p}_i$)

The corrected uncertainty in $\hat{p}_i$, denoted $Var_{corr}(\hat{p}_i)$, was derived from the base model and formed as the sum of 2 components: (i) $Var_{est}(\hat{p}_i)$, the estimated uncertainty in $\hat{p}_i$ conditioned on the population parameter estimate of the variance ($\hat{\omega}_p^2$), and (ii) $SE(\hat{\omega}_p^2)$, the uncertainty in the estimate of $\hat{\omega}_p^2$. The former is directly available in the standard NONMEM output (*.phi file), and the latter can be approximated using equation (3) below:

$$\text{Individual Shrinkage: } ISH_i = \frac{Var_{est}(\hat{p}_i)}{\hat{\omega}_p^2} \quad (1)$$

$$\text{Effective number of subjects: } N_p^{eff} = N_{subj} - \sum_{i=1}^{N_{subj}} ISH_i \quad (2)$$

$$SE(\hat{\omega}_p^2) = \hat{\omega}_p^2 \cdot \sqrt{\frac{2}{N_p^{eff}}} \quad (3)$$

$$Var_{corr}(\hat{p}_i) = Var_{est}(\hat{p}_i) + SE(\hat{\omega}_p^2) \quad (4)$$

2. Generation of p_i and cov_i

Fifty parameter-covariate vectors were generated for each subject by sampling from a multivariate normal distribution with a mean vector of the FREM $\hat{p}_i$ estimate and a variance-covariance matrix of $Var_{corr}(\hat{p}_i)$ together with the observed covariate values. Across all individuals this formed the pooled sample (S_{η_i}).

3. Bootstrap

For each bootstrap, N_{subj} parameter vectors were sampled from S_{η_i} and the full BSV matrix computed. The uncertainty of the full BSV matrix could be calculated through repeating the process 2,000 times.

$Var(p_1)$	$Cov(p_1, p_2)$	$Cov(p_1, cov_1)$	$Cov(p_1, cov_2)$
$Cov(p_1, p_2)$	$Var(p_2)$	$Cov(p_2, cov_1)$	$Cov(p_2, cov_2)$
$Cov(p_1, cov_1)$	$Cov(p_2, cov_1)$	$Var(cov_1)$	$Cov(cov_1, cov_2)$
$Cov(p_1, cov_2)$	$Cov(p_2, cov_2)$	$Cov(cov_1, cov_2)$	$Var(cov_2)$

Fig 1: The full BSV matrix of FREM model

The parameters of main interest of the matrix, the parameter-covariate covariances, are red

Alternative uncertainty approaches to compare to:

- Sandwich covariance matrix (COV):** \$COVARIANCE in NONMEM after FOCEI estimation of the FREM model
- Sampling-based covariance matrix (IMP):** \$COVARIANCE after estimating the posterior distribution with importance sampling
- Nonparametric bootstrap (BOOT)**
- Sampling importance resampling (SIR)^[2]:** The SIR method in PsN (SIR_P) or the NONMEM built-in SIR method with T distribution (SIR_T)
- Stochastic simulation and estimation (SSE):** Simulating datasets with FREM model parameter estimates and re-estimating the datasets with the same FREM model

RESULTS

Metric for comparison

- Covariate effects:** quantified by the covariate coefficient which is the parameter-covariate BSV-covariance standardized by the variance of covariate.
- Uncertainty of the covariate coefficient:** represented by the inter-percentile range (IPR) between the 10th and 90th percentile of the distribution of covariates coefficients estimated by different methods. (Fig 2)

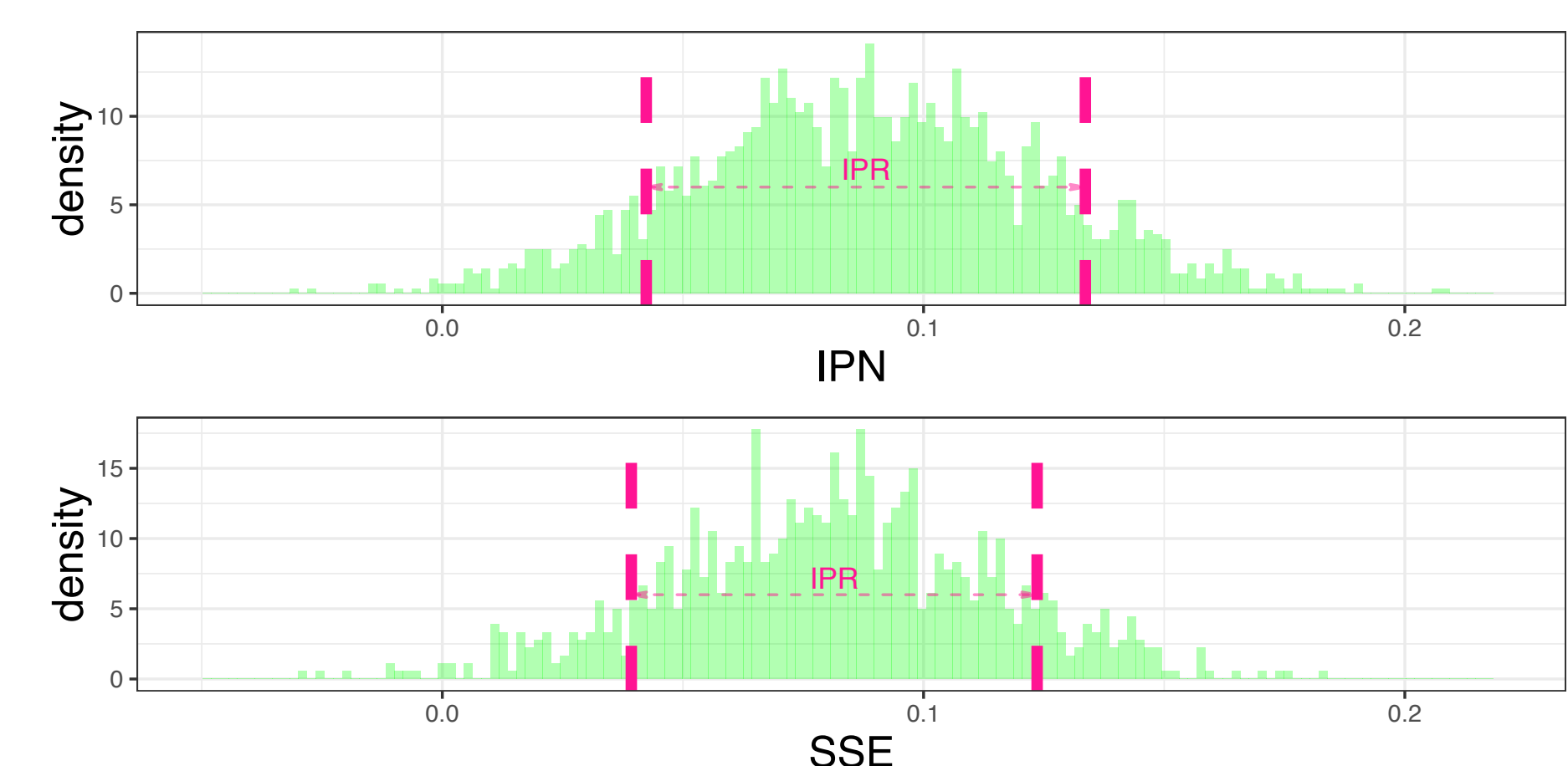


Fig 2: Demonstration of IPR

Demonstration of IPR for two of the methods in comparison; the green area is the distribution of one of the covariate coefficients calculated by the method; the vertical red dashed lines indicate the 10th and 90th percentile of the distribution and the range between the percentiles are utilized, as IPR, to measure the uncertainty of the covariate coefficient.

- Q-Q plot of the IPRs for all the covariate coefficients

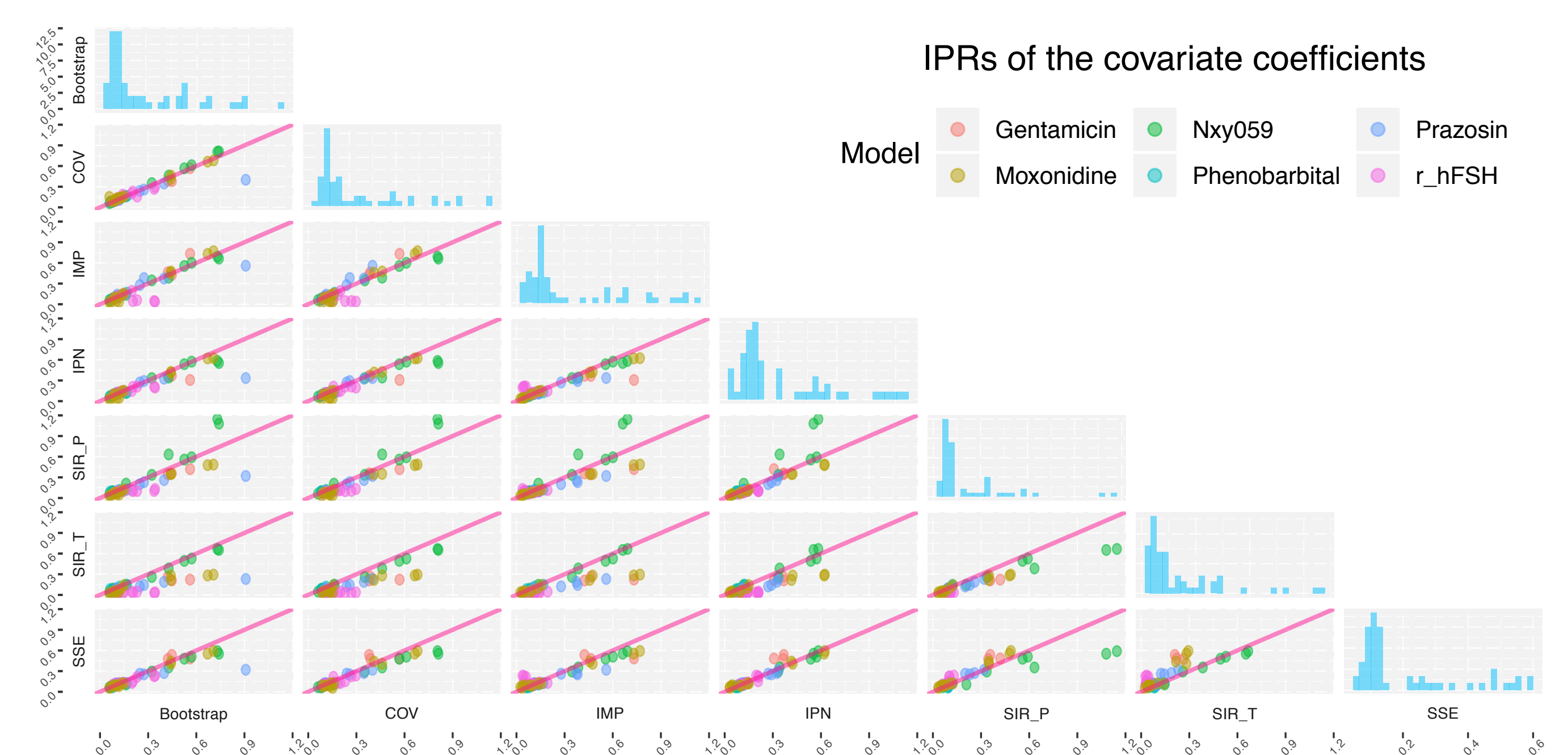


Fig 3: The Q-Q plot of the IPRs for all the covariate coefficients

- The geometric means of covariate coefficient IPRs relative to SSE

Model	Bootstrap	COV	IMP	IPN	SIR_P	SIR_T
Gentamicin ^[3]	102%	99%	106%	86%	86%	43%
Moxonidine ^[4]	111%	128%	86%	85%	76%	59%
Nxy059 ^[5]	112%	119%	110%	103%	137%	102%
Phenobarbital ^[6]	110%	116%	108%	108%	118%	116%
Prazosin ^[7]	108%	102%	112%	104%	85%	65%
r_hFSH ^[8]	112%	113%	60%	102%	67%	24%
Overall	109%	113%	92%	98%	88%	56%

CONCLUSION

Compared to generally accepted methods for uncertainty estimation, the IPN method can achieve a satisfactory estimation of the uncertainty of FREM covariate coefficients in a significantly shorter runtime and without reliance on computations that may fail.

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