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# Predicting Shrinkage of Individual Parameters in More Complex NLME Models Using Bayesian Fisher Information Matrix


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## PURPOSE

When data are sparse, parameters derived from a non-linear mixed effects model analysis can shrink to the mean and can be misleading. The objective of this project was to predict the shrinkage on parameters using Bayesian methodology and test whether the results of a published 1 compartment model example by Combes et al., are applicable to more complex models.

## METHOD

- Shrinkage values were predicted using the Bayesian FIM of PFIM (BPFIM) and compared to values obtained from NONMEM.
- Step 1: Initially, the work completed by Combes et al. involving a 1 compartment IV model was replicated.
- Step 2: Utilized the methods to predict and determine shrinkage on individual parameters in more complex models; 1 and 2 compartment oral and IV models.
- Various scenarios ranging from high (53.29%CV) to low (2.5%CV) variance and utilizing combined and additive error models were examined.
- Each scenario was evaluated with a range of sampling times at optimized time points which were obtained using PFIM with 2-8 points per profile.
- Observed shrinkages were calculated using conditional estimation with interaction and MAXEVAL=0, using NONMEM 7.4.
- The predicted and observed shrinkage values were then compared.

## RESULTS

- Observed and predicted shrinkage values obtained from all the scenarios were plotted on x and y axis respectively.
- Predicted shrinkage values for combined error models were greater than predicted shrinkage for additive error models.
- There was a larger degree of deviation between BPFIM predicted and NONMEM estimated shrinkage for additive error models with larger variances compared to smaller variances.
- Combined error models had more accurate shrinkage predictions compared to NONMEM estimated values.
- Shrinkage is dependent on number of samples collected per subject and is inversely proportional to parameter variance (omega) and directly proportional to residual variability (sigma).
- The largest difference in predicted and observed shrinkages was seen in the KA and Q parameters of the two compartment oral absorption model.

**Table 1: NONMEM versus BPFIM reported shrinkage values for various models and parameters**

| Model<br>Parameters | 1 _CMT_IV<br>NONMEM/ BPFIM % | 1_CMT_PO<br>NONMEM/ BPFIM % | 2_CMT_IV<br>NONMEM/ BPFIM % | 2_CMT_PO<br>NONMEM/ BPFIM % |
|---|---|---|---|---|
| Clearance | 0-57.628 /0.001-57.852 | 0-56.979 /0.0008-57.699 | 4.185-92.896 /0.719-93.06 | 12-91.8 / 1.54-92.56 |
| Central Volume | 0-74.432 /0.00015-73.850 | 0-74.432 /0.00015-73.850 | 0-83.323/ 0.0005-81.613 | 2.47-82.6 / 0.141-82.80 |
| Ka | ___ | 0-88.040 /0.004-87.131 | ___ | 7.73-85.94 / 0.181-86.065 |
| Peripheral Volume | ___ | ___ | 2.444-79.599 /0.231-79.977 | 1.79-77.18/ 0.426-79.113 |
| Inter-Compartmental Clearance | ___ | ___ | 0-86.554 / 0.012-85.92 | 0-79.1/ 0.0208-79.5972 |

**Table 2: Median difference (Observed minus Predicted) Shrinkage value in different models**

| Parameters | Value | 1_CMT_IV | 1_CMT_PO | 2_CMT_IV | 2_CMT_PO |
|---|---|---|---|---|---|
| Clearance | 0.6 | 2.864 | 1.812 | -0.16 | -0.451 |
| Central Volume | 8 | -0.001 | 0.484 | 2.481 | 1.303 |
| Ka | 1.5 | ___ | 1.205 | ___ | 4.927 |
| Peripheral Volume | 40 | ___ | ___ | 2.603 | 1.872 |
| Inter-Compartmental Clearance | 3.5 | ___ | ___ | 6.19 | 4.953 |

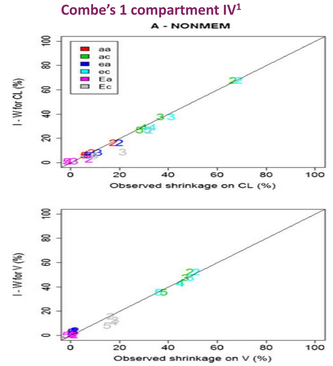
**Table 3: Random effects list – for simulations**

| Omega List | 0.1 (O1) | 0.025 (O2) | 0.05 (O3) | 0.25 (O4) | 0.5 (O5) |
|---|---|---|---|---|---|

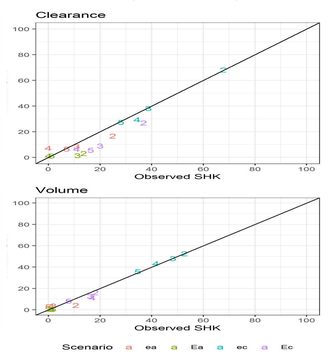
**Table 4: Residual errors list (additive, proportional) – for simulations**

| Sigma (inter, slope) | 0.15, 0.15 (R1) | 0.30, 0.15 (R2) | 0.30, 0.30 (R3) | 0.15, 0 (R4) | 0.3, 0 (R5) | 0.5, 0 (R6) |
|---|---|---|---|---|---|---|

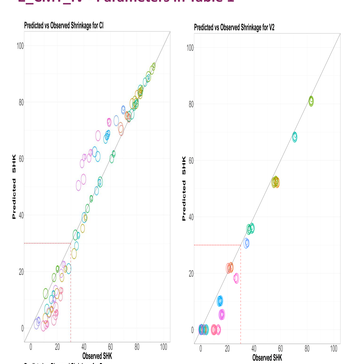
Combe's 1 compartment IV[1]



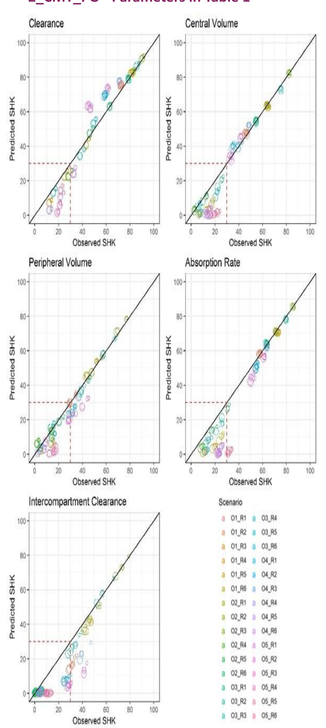

Combe's 1 compartment IV - replication



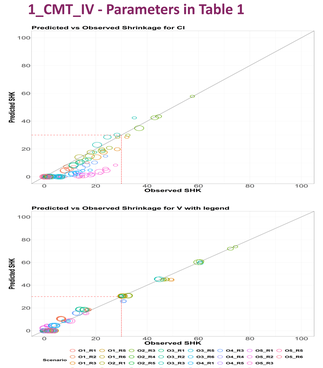

2_CMT_IV - Parameters in Table 1



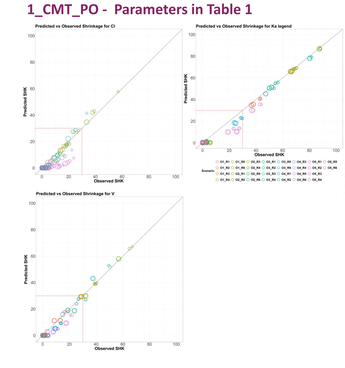

2_CMT_PO - Parameters in Table 1




1_CMT_IV - Parameters in Table 1




1_CMT_PO - Parameters in Table 1




## CONCLUSIONS

- Results demonstrate that there is a correlation between BPFIM predicted and NONMEM estimated shrinkage values even for more complex models.
- The observed and predicted shrinkage values are roughly centered on the line of identity for most models, though not as well as the IV 1 compartment model presented by Combes et al.
- BFIM as implemented in PFIM is a useful method to predict shrinkage, especially for combined error models.

## REFERENCES


- [1]Combes, F.P., Retout, S., Frey, N. et al. Pharm Res (2013) 30: 2355. https://doi.org/10.1007/s11095-013-1079-3
- [2]Nguyen, T.H.T., Nguyen, T.T. & Mentré, F. Pharm Res (2017) 34: 2119. https://doi.org/10.1007/s11095-017-2217-0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