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Background
- Improvements in statistical softwares for estimation in NLMEM
- Algorithms tested with PD data for categorical and count models
- Communications1, 2 done for continuous models

Objectives
To compare estimation performance of FOCE in NONMEM and R, LAPLACE in NONMEM and SAS, adaptive Gaussian quadrature in SAS, and SAEM in NONMEM and MONOLIX for a set of continuous population PD models

Methods
- Stochastic Simulations and Estimations study
- 6 models (m): All derived from a sigmoid Emax model
  - 2 residual error e models (Additive, Proportional) & 3 Hill factor γ values (1, 2, 3)
  - Yij = E0ij + eij or Yij = E0ij (1 + eij)
  - E0ij = EO0ij + EEd50ij + Dose
  - \( \theta = \theta_0 \cdot e^{\gamma} \)

- 2 designs: 100 patients included in this hypothetical study
- 4 dose levels: 0, 100, 300 and 1000mg

- 2 initial conditions:
  - Initial estimates set to values used during simulation (True)
  - Or to a set of values chosen far away from the truth (False)

- FOCE_R: simulated random effects as initial conditions

- Settings of the 9 algorithms (ε):

<table>
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<tr>
<th>Algorithm</th>
<th>Software</th>
<th>Method</th>
<th>Settings</th>
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<tr>
<td>FOCE_NM</td>
<td>NONMEM7</td>
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<td>AGQ_SAS</td>
<td>SAS 9.2</td>
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References

Results
- Runtimes (mean s.GHz):
  - Min, mean and max between models. Corrected with computer frequencies. Relative to the fastest for each model.

- Completion rates (mean %):
  - Min, mean and max between models. Runs reaching convergence criteria.

- Accuracy and Precision of the algorithms:
  - Relative Estimation Error (RER) for each dataset - Example of ED50

\[ RER_{ED50}(\%) = \left( \frac{\hat{\theta}_{model,\text{ED50}} - \theta_{true,\text{ED50}}}{\theta_{true,\text{ED50}}} \right) \times 100 \]

- RMSE for each model (A = Add, P = Prop & 1, 2, 3 = Hill factor values)

\[ \text{RMSE}_{\text{A,P}} = \text{Mean}(\text{RMSE}_{\text{A,P,1,2,3}}) \]

- RMRSE for each model.

Discussion
- True initial conditions: Small bias and similar RMSER between algorithms among parameters except for FOCE_R (biased)
- False initial conditions: Similar RMSE for AGQ_SAS, LAP_SAS, FOCE_NM, and SAEM_MLX run for Rich and even Sparse designs. Problems with SAEM_MLX, SAEM_NM vs. FOCE_R and SAEM_NM