



Simultaneous vs. Sequential Fitting of a Physiological Flow Model to Multivariate Pharmacokinetic Data



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BACKGROUND

In multivariate response data fitting, a multicompartmental model can be fit to all the response components simultaneously (SIM), or each response component(s) can be fit separately, conditioning on the non-modeled components (SEQ). A previous study found that SEQ is faster, numerically simpler, and produces as precise parameter estimates as SIM for a causally strictly sequential PK/PD model.

Focusing on a special case of multi-response model corresponding to a physiological flow model (PFM, Figure 1), this study aims to (i) provide an algorithm for applying SEQ to multivariate response data from a PFM; (ii) examine the performance of SEQ vs. SIM W/O model misspecification; (iii) make recommendations regarding the use of SEQ for multivariate response data.

The basic PFM (variants of which are used for simulation) has 4 homogenous compartments. All are sampled: arterial blood (A), non-eliminating tissue (N), eliminating tissue (E), and venous blood (V), the dosing compartment. Parameters are blood flow rates to E and N (Q_E, Q_N), volumes of distribution of A, E, N, V (V_V, V_A, V_E, V_N), elimination rate constant (k) from E, and observation error variances.

METHODS

Three models are used to simulate data (DSM) from a generic individual using NONMEM: DSM1: V, A, E and N are homogenous and elimination from E is a first order process; DSM2: Elimination from E is a Michaelis-Menten process, otherwise same as DSM1; DSM3: N has a deep compartment (D), otherwise same as DSM1. Using a data-analytic model (DAM) identical to DSM1, SIM fits the PFM to all response observations simultaneously; SEQ first estimates the identifiable parameter combinations for each response type by linearly interpolating the observation from the donor tissue(s), and then solves the simultaneous equations linking these, to the primary model parameters of interest. The simulation and analysis steps are repeated 1000 times. Performances are compared with respect to parameter estimation error (when DAM and DSM are identical), and interpolated prediction error (when DAM and DSM are/are not identical). The ability of SIM and SEQ to identify the correct model is also examined by comparing their failure rates in rejecting the wrong DAM. Two kinds of weighted residuals for SEQ are studied: RESA are obtained from the tissue-specific fits; RESB are obtained from predictions made with the final SEQ parameters.

RESULTS

The parameter estimation errors with SEQ are generally 25% larger than those with SIM (Figure 2) when the DAM is identical to the DSM. The prediction error of SEQ is 10 times larger than that of SIM when the DAM is identical to the DSM (Figure 3), and is about 3 times larger when the two are different (results not shown). However, SIM fails to identify the correct model twice as often as SEQ (results not shown). The ratio of root mean squared RESB vs. RESA (RMSR) of SEQ analysis is positively correlated with SEQ's prediction error ($R^2 = .71$, Figure 4, left panel). A receiver operating characteristic (ROC) curve shows that the easily estimated RMSR can be used as a diagnostic tool for the ability of the final parameter estimates obtained by SEQ analysis to predict new data (Figure 4, right panel).

CONCLUSIONS

Despite its greater convenience and speed, and its clear advantages for model selection, SEQ's final parameter estimates cannot be trusted when the multivariate system being modeled involves feedback. The size of the ratio of the two root mean squared SEQ residuals can, however, be used to indicate when SEQ's final estimates may be trustworthy.

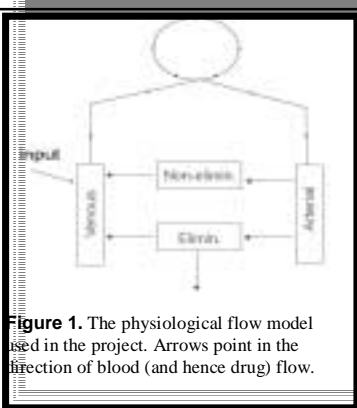


Figure 1. The physiological flow model used in the project. Arrows point in the direction of blood (and hence drug) flow.

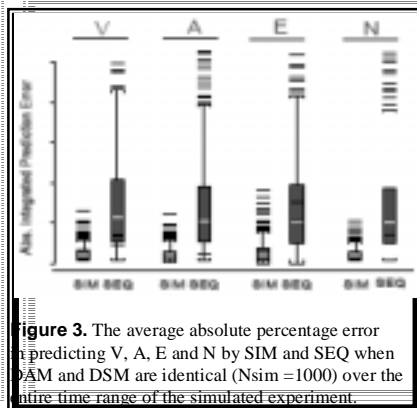


Figure 3. The average absolute percentage error in predicting V, A, E and N by SIM and SEQ when DAM and DSM are identical ($N_{sim} = 1000$) over the entire time range of the simulated experiment.

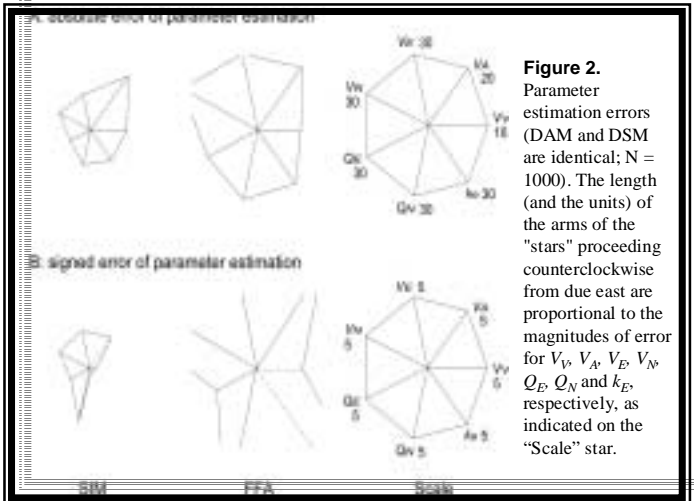


Figure 2. Parameter estimation errors (DAM and DSM are identical; $N = 1000$). The length (and the units) of the arms of the "stars" proceeding counterclockwise from due east are proportional to the magnitudes of error for $V_V, V_A, V_E, V_N, Q_E, Q_N$ and k_E , respectively, as indicated on the "Scale" star.

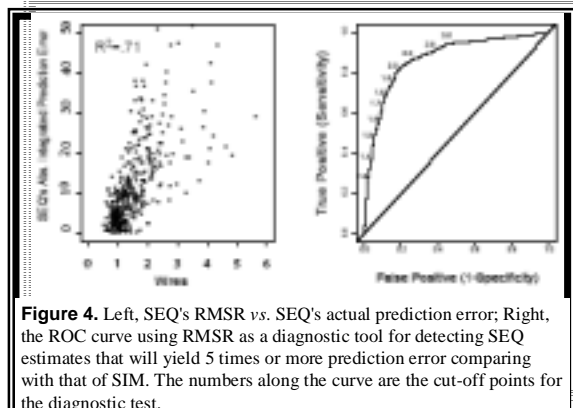


Figure 4. Left, SEQ's RMSR vs. SEQ's actual prediction error; Right, the ROC curve using RMSR as a diagnostic tool for detecting SEQ estimates that will yield 5 times or more prediction error comparing with that of SIM. The numbers along the curve are the cut-off points for the diagnostic test.