

Title: Three-Stage Hierarchical Bayesian Analysis for Population Analysis of Complex PK/PD Models in S-ADAPT

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Objectives: Three-stage hierarchical Bayesian analysis has been recently implemented within the S-ADAPT program, which provides a convenient interface for complex PK/PD population analysis. While Winbugs offers a general environment for Bayesian analysis, its interface does not allow one to easily perform complex PK/PD model analysis on population data. Here we compare the results of a Bayesian analysis performed in S-ADAPT 1.55 with those of Winbugs/Blackbox version 1.4 for data simulated using a receptor-mediated clearance and indirect response model typically used in antibody therapeutics.

Methods: As a first step, a maximum likelihood estimate of the population model parameters is obtained using the standard MCPDM algorithm in S-ADAPT [1]. The S-ADAPT program automatically formats the MCPDM output as input for a subsequent Bayesian analysis. The maximum likelihood estimates from the first step serve as estimates of the mode of the Bayesian distributions we want to generate. For this example, uninformative prior information was supplied for the three-stage hierarchical Bayesian analysis. S-ADAPT uses a Gibbs sampler [2] or Metropolis-Hastings algorithm [3] to carry out the Markov chain Monte Carlo (MCMC) procedure to generate a large sample of the desired distributions.

Results: A data set was simulated using a typical PK/PD model often used in antibody therapeutics (antibody-receptor dynamics). The data set consisted of 50 patients each with a rich sampling of 17 PK and 18 PD observations per individual, sampled over a period of 50 days after receiving a bolus dose of therapeutic followed by a short infusion dose one week later. The model was programmed as 3 differential equations, consisting of a 2 compartment (V_c , k_{12} , k_{21}) PK model with both non-specific linear (k_{10}) and receptor-mediated saturable clearance (V_{max} , K_{mc}) components for the therapeutic concentration, and an indirect response PD model for the receptor level. Receptors are generated through a zero order process (k_{03}) and are either removed through an endogenous first order rate of internalization (k_{30} , non drug related) or through accelerated internalization via formation of the drug-receptor complex (V_{max} , K_{mc}). Therefore, the total number of population parameters is 46 (8 population parameters, 8 inter-subject variances, 28 inter-subject covariances, and two intra-individual error coefficients). S-ADAPT used 1000 iterations as burn-in period followed by 30,000 iterations. The Winbugs setting was similar to S-ADAPT (4000 burn in and 30,000 subsequent iterations) and both programs generated 46 different cumulative distributions that were subject to comparison. For all parameters, extensive random mixing occurred in S-ADAPT and Winbugs sampling history. The mean difference between sorted samples generated from S-ADAPT and Winbugs was less than 0.5% of the sample means. The root mean square differences between sorted samples from S-ADAPT were typically 2-5% of the standard errors of the estimates.

Conclusions: The S-ADAPT program has been expanded to allow full three-stage hierarchical Bayesian analyses. The results from S-ADAPT are almost identical to the ones generated with Winbugs, allowing the user to easily perform population Bayesian analysis on complex PK/PD models using NONMEM style data sets.

References:

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