

Title: Automated Population Power Analysis Using The S-ADAPT MC-PEM Scripting Program: Application to Oncology Biotherapeutics

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Objectives: The combination of Population fitting and simulation procedures is necessary to estimate the probability of obtaining successful outcomes in future trials (Power). Thousands of series of data sets must go through the same cycle of simulation/fitting which ultimately allows one to design the optimal trial with the required power.

The S-ADAPT program offers easy ways to automate all these steps with minimum of scripting language. At the same time, the optimization techniques necessary to estimate the model parameters from each simulated data set combine both advanced deterministic and stochastic algorithms that make the program robust, stable, efficient and unbiased for even very complicated models. These optimization methods include: direct sampling, iterative two-stage, importance sampling expectation-maximization (EM), importance sampling EM facilitated by deterministic techniques to increase convergence efficiency, Markov chain Monte-Carlo stochastic approximation EM, and three hierarchical stage Bayesian analysis. The main objective of this work was to provide the optimal trial design for future oncology experiments by running one series of simple scripts which would generate automatically output files from which the optimal power can be easily computed.

Methods: The EM optimization algorithms consists of two main steps, the expectation step (E Step) where Monte-Carlo sampled model parameters contribute to assessing the conditional means and variances for each subject, at the current values of the population parameters and inter-subject variances. The E-Step is then followed by the maximization step which updates the population parameter characteristics. The S-ADAPT simulation kit uses Monte Carlo methods to generate new data sets. In this exemplary study we characterized the dose (PK) response (Tumor Volume) relationship with minimum in vivo experimentation. A multiple dose in vivo study was performed on both benchmark (BM) and our proprietary candidate antibody. The biological processes (tumor growth, binding of drug to target and Pharmacokinetics of the drug) were translated into a mathematical framework using the data from the study.

Results: The first script that was written allowed estimating the PK/PD model parameters. All these estimated model parameters were then used in the subsequent scripts except for the in vivo potency of our antibody (K_{md} , one of the PD model parameters) that was allowed to vary. The next “simulating scripts” automatically generated a series of data sets with different ratios between the in vivo potency of BM and our antibody. An “automated “fitting script” followed, which for each ratio, estimated the probability to detect superiority in favor of our drug (statistically significant superiority of in vivo potency in favor of our drug). All these automated processes helped to design the next study with increased chance to detect superiority of our drug.

Conclusions: A large number of Population fitting and simulation procedures were performed automatically using the S-ADAPT scripting program and helped designing future studies. The automated system was run for two days without any additional man power intervention. Both the EM algorithms and optimized scripting facility makes the S-ADAPT program most suitable for large scale fitting procedure often required for the design of new studies.

References:

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