

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

Serge Guzy* (1), (1), Serge Guzy (2), Robert Bauer (2)

XOMA US (LLC), Berkeley, CA

ABSTRACT

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.

Results and Conclusions: 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 (Kmd, 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.

References:

- [1] Bauer RJ, Guzy S, Ng C. A Survey of Population Analysis Methods and Software for Complex Pharmacokinetic and Pharmacodynamic Models with Examples. *AAPS Journal*. 2007; 9(5): Article 7. DOI: [10.1208/aapsj0901007](https://doi.org/10.1208/aapsj0901007).
- [2] Robert J. Bauer and Serge Guzy. Monte Carlo Parametric Expectation Maximization (MCPEM) Method for Analyzing Population Pharmacokinetic/ Pharmacodynamic (PK/PD) Data. In: D.Z. D'Argenio, ed. *Advanced Methods of Pharmacokinetic and Pharmacodynamics Systems Analysis*, Vol.3. Boston: Kluwer Academic Publishers (2004),pp 135-163.

MODEL DEVELOPMENT

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.

$$\frac{dx(1)}{dt} = -k01.x(1)$$

$$\frac{dx(2)}{dt} = k01.x(1) - k10.x(2) - k12.x(2) + k21.x(3) - vmpk.x(2)/(x(2) + kmpk.V)$$

$$\frac{dx(3)}{dt} = k12.x(2) - k21.x(3)$$

$$\frac{dx(4)}{dt} = k \exp.x(4) - vmpd.x(4).x(2)/(x(2) + kmpd.V)$$

$$t = 0, x(4) = tv0$$

where:

$x(1), x(2), x(3)$ are amount of drug in the extravascular compartment, plasma compartment and peripheral compartment, respectively.

$x(4)$ is the tumor volume

$k01$: Absorption rate

$k10$: First order elimination rate

$k12$: Transfer rate from the plasma to peripheral compartment

$k21$: Transfer rate from the peripheral to the plasma compartment

$vmpk$: Maximum rate of target mediated clearance

$kmpk$: Affinity of the antibody to the target

$k \exp$: Exponential growth rate

kin : Production rate of tumor volume

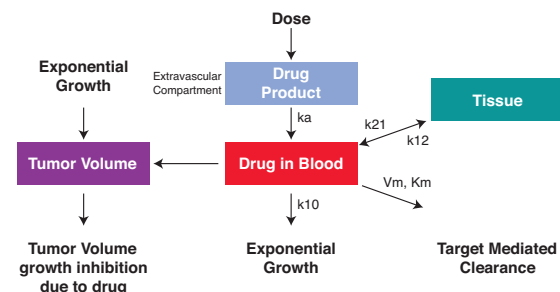
$kout$: Elimination rate of tumor volume

$vmpd$: Maximum rate of tumor volume inhibition

$kmpd$: Potency

$tv0$: Initial tumor volume

MODEL DIAGRAM



RESULTS

Results of the fitting procedure to the observed data

- No significant difference between potencies of the two drugs
 - Assuming affinity maturation would improve our affinity by 20 fold, a simulation was performed with the 20 fold better potency for our drug
 - 200 data sets, 7 groups per data set, 3 patients per group
 - 0,0.1,0.5 and 5 mg/kg groups for Drug A
 - 0,0.1,0.5 and 5 mg/kg groups for Drug B
 - 1 Placebo group

Simulation script

- Popsets_simulate;npoppats=21;npopsets=200
 - Description
 - Simulate 200 data sets with 21 patients each
 - Use the population mean, variance covariance, dosage and observation time information stored in memory

Simulation script: Stored Population mean and variance-covariance

Name	Mean	Type	k exp	tv0	v	k10	k01	k12	k21	vmpk	kmpk	vmpd	kmpd
k exp	0.099536	P	0.070675										
tv0	152.9644	P	0.0109	0.003206									
v	50	N	0	0	0								
k10	0.144953	N	0	0	0	0							
k01	5	N	0	0	0	0	0						
k12	0.14	N	0	0	0	0	0	0					
k21	0.096	N	0	0	0	0	0	0	0				
vmpk	148.9048	N	0	0	0	0	0	0	0	0			
kmpk	6.561854	N	0	0	0	0	0	0	0	0	0		
vmpd	0.066495	P	0.079882	0.013232	0	0	0	0	0	0	0	0.226591	
kmpd	1.704089	PC	0.265495	0.039876	0	0	0	0	0	0	0	0.234688	1.443258
Sdpk	0.19156	V	0	0	0	0	0	0	0	0	0	0	0
Sdpd	0.05	V	0	0	0	0	0	0	0	0	0	0	0
kmd_ab	0.1	C	0	0	0	0	0	0	0	0	0	0	0
kmd_avast	2	C	0	0	0	0	0	0	0	0	0	0	0
vmpdd_ab	0.001586	N	0	0	0	0	0	0	0	0	0	0	0
vmpdd_avast	4.37E-07	N	0	0	0	0	0	0	0	0	0	0	0

Simulation script: Snapshot of the Dosage and observation times

Patient	PT	Time	Conc	Omit	Dose	Rate	Evid	MDV	CMT
1	1	0	0		0	0	0	0	2
1	1	3	0		0	0	0	0	2
1	1	7	0		0	0	0	0	2
1	1	10	0		0	0	0	0	2
1	1	14	0		0	0	0	0	2
1	1	16	0		0	0	0	0	2
2	21	0	0		5000	0	1	1	1
2	21	0	0		0	0	0	0	2
2	21	3	0		5000	0	1	1	1
2	21	3	0		0	0	0	0	2
2	21	7	0		5000	0	1	1	1
2	21	7	0		0	0	0	0	2
2	21	10	0		5000	0	1	1	1
2	21	10	0		0	0	0	0	2
2	21	14	0		5000	0	1	1	1
2	21	14	0		0	0	0	0	2
2	21	16	0		5000	0	1	1	1
2	21	16	0		0	0	0	0	2

Fitting procedure

- The PK/PD model was fit to the 200 data sets with (potency allowed to be different between the two drugs) and without covariate assumption (same potency assumed in the model)
- The goal was to estimate the probability to detect superiority in favor of our drug (statistically significant superiority of in vivo potency in favor of our drug)
 - This was done by calculating for each data set the difference between the 2.log-likelihood with and without covariate (S) and compare the result to the 5% quantile of a chi-square distribution with one degree of freedom (3.84)
 - The proportion of data sets showing $S > 3.84$ is an estimate of the power

Main fitting script

- popsets_fit sets=1-200 file=fit_sp001_cov.cmd
- popsets_summary
- tabtofil <nfile>_summary <nfile>_cov_summary.csv
- del <nfile>_summary
- tabtofil <nfile>_found <nfile>_cov.csv
- del <nfile>_found
- popsets_fit sets=1-200 file=fit_sp001_no_cov.cmd
- popsets_summary
- tabtofil <nfile>_summary <nfile>_no_cov_summary.csv
- del <nfile>_summary
- tabtofil <nfile>_found <nfile>_no_cov.csv
- del <nfile>_found

Covariate analysis script (fit_sp001_cov.cmd)

- setg nfileo=nfile
- set nfile=sp001_pk_pd_cov_sim
- popget
- set nfile=<nfileo>
- del <nfile>_par
- table_safe=0
- cswitch=1
- cswitch_vm=0
- covsource=1
- table_safe=0
- piteraten pmethod=8 vapprox=3 poperr_type=3 npopiter=19 npopc=3000 npop=100
- piterate pmethod=8 vapprox=-4 poperr_type=8 npopiter=1 npopc=3000 npop=100
- table_safe=1
- close_tables

No Covariate analysis script (fit_sp001_no_cov.cmd)

- setg nfileo=nfile
- set nfile=sp001_pk_pd_cov_sim
- popget
- set nfile=<nfileo>
- del <nfile>_par
- table_safe=0
- cswitch=1
- cswitch_vm=0
- covsource=1
- table_safe=0
- piteraten pmethod=8 vapprox=3 poperr_type=3 npopiter=19 npopc=3000 npop=100
- piterate pmethod=8 vapprox=-4 poperr_type=8 npopiter=1 npopc=3000 npop=100
- table_safe=1
- close_tables

CONCLUSION

A large number of Population fitting and simulation procedures were performed automatically using the S-ADAPT scripting program and helped designing future

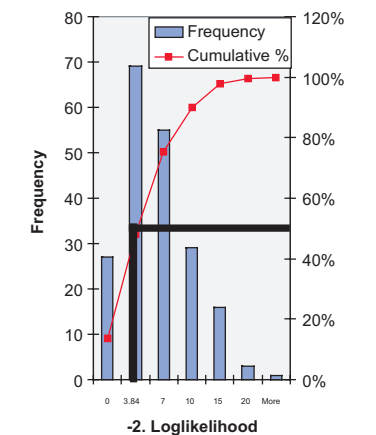
studies. The automated system was run for two days without any additional man power intervention. Both the EM algorithms and optimized scripting facility makes the

S-ADAPT program most suitable for large scale fitting procedure often required for the design of new studies.

Result of Power Analysis

The results of this automated process allowed one estimating the probability of detecting a better potency in favor of our drug. Figure 1 graphs the distribution of the statistic -2. Loglikelihood based on 200 data sets, each including 21 patients equally distributed around the 7 dosage groups (N=3 per group). The Power is estimating to be about 50%

Figure 1:-2x Loglikelihood Distribution: 200 data sets and N=3 per group



Power to detect our antibody with better affinity ~50%

Power vs. Sample Size

The same set of scripts was then used when changing subsequently the sample size per group from 3 to 5, 10 and 20; respectively. Figure 2 shows the results which suggest about 17 animals per group to insure a power of 80% to detect our drug with better potency.

Figure 2: Power vs. Sample size

