A Systematical Approach to Bridge the Two-Stage Parametric Expectation Maximization Algorithm and Full Bayesian Three-Stage Hierarchical Nonlinear Mixed Effect Methods in Complex Population Pharmacokinetic/Pharmacodynamic Analysis: Troxacitabine-induced Neutropenia in Cancer Patients

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INTRODUCTION

The full Bayesian approach has been suggested as a suitable method for population pharmacokinetic/pharmacodynamic (PK/PD) modeling. However, to this day, published examples of its application to real population PK-PD problems are limited due to time/labor intensive, and difficulty in achieving model convergences. Monte-Carlo parametric expectation maximization (MCPEM) is a two-stage hierarchical method that uses Monte-Carlo integration methods for obtaining exact likelihood function and has been used successfully in analyzing complex population PK/PD data.

The S-ADAPT program uses the MCPEM method to provide initial parameters for the three-stage analysis provided in WINBUGS. S-ADAPT also provides a command that systematically packages PK/PD data and the MCPEM results into the BLACKBOX/WINBUGS environment to allow easier Bayesian analysis of PK/PD models.

OBJECTIVES

To develop a systematical approach to bridge the two-stage MCPEM algorithm and full Bayesian three-state hierarchical model in complex population PK/PD analysis

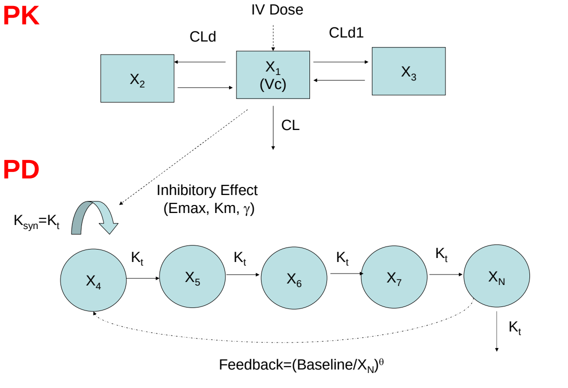
METHODS

DATA

Thirty-one patients with advanced solid malignancies were treated with cisplatin 1-hour intravenous infusion followed by troxacitabine 30-minute intravenous infusion on Day 1 every 28 days at the following cisplatin/troxacitabine (mg/m^2) dose levels: 50/4.8, 75/4.8, 50/6.4, 75/6.4 and 75/8.0. PK samples were obtained during cycle 1 before dosing and at 0, 0.25, 0.5, 1, 2, 4, 8, 24, 48, 72, and 168 hours after the end of the 30 minute intravenous infusion of troxacitabine. The absolute neutrophil count (ANC) was obtained during the documented routine clinical follow-up.

PKPD MODEL

- A three-compartment linear PK model was used to describe the troxacitabine concentration-time profile. The PD model was based on a drug-sensitive progenitor cell compartment, linked to the peripheral blood compartment, through three transition compartments representing the maturation chain in the bone marrow. The model included a feedback mechanism to capture the rebound phenomena. The troxacitabine affected the proliferation of sensitive progenitor cells through an inhibitory sigmoidal Emax model.
- The schematic and differential equations of the PK/PD model for troxacitabine was as follows :



$$\frac{dX_1}{dt}=-\left(\frac{CL+CL_d+CL_{d1}}{V_c}\right)*X_1+\frac{CL_d}{V_2}*X_2+\frac{CL_{d1}}{V_3}*X_3$$

$$\frac{dX_2}{dt}=\frac{CL_d}{V_c}*X_1-\frac{CL_d}{V_2}*X_2$$

$$\frac{dX_3}{dt}=\frac{CL_{d1}}{V_c}*X_1-\frac{CL_{d1}}{V_3}*X_3$$

$$\frac{dX_4}{dt}=k_{syn}*X_4*\left(\frac{Baseline}{X_N}\right)^{\theta}*\left[1-\frac{E_{max}*\left(\frac{X_1}{V_c}\right)^{\gamma}}{km^{\gamma}+\left(\frac{X_1}{V_c}\right)^{\gamma}}\right]-kt*X_4$$

$$\frac{dX_5}{dt}=kt*(X_4-X_5);\quad \frac{dX_6}{dt}=kt*(X_5-X_6);\quad \frac{dX_7}{dt}=Kt*(X_6-X_7)$$

$$\frac{dX_N}{dt}=kt*(X_7-X_N)$$

- Interindividual variability was assumed to be log-normally distributed and was fitted by use of an exponential model. Proportional error model was used to describe the intraindividual variability for both PK and PD.
- First, the PKPD model was developed using the MCPEM algorithm implemented in S-ADAPT and fit simultaneously to the PK/PD data. The S-ADAPT program then automatically generated several files (including dose/dosing time, observations, priors, initial parameters, and model template files) needed for the BLACKBOX/WINBUGS program for full Bayesian analysis. The individual and population parameters estimated from MCPEM algorithm served as initial values for the WINBUGS program, and the PKPD data were analyzed simultaneously.
- In S-ADAPT, the differential equations were coded in Fortran. In BLACKBOX/WINBUGS, the differential equations were programmed in component Pascal using the WBDIFF tool as a template environment.

RESULTS AND CONCLUSIONS

FIGURE 1. PKPD MODEL FILE FOR WINBUGS ANALYSIS (Template model file provided by S-ADAPT)

```
model {
    for (k in 1:n.sigma) {
            tau[k] ~ dgamma(tau.a[k], tau.b[k])
            sigma[k] <- 1 / sqrt(tau[k]) }
            omega.inv[1:p, 1:p] ~ dwish(omega.inv.matrix[1:p, 1:p], omega.inv.dof)
            omega[1:p, 1:p] <- inverse(omega.inv[1:p, 1:p])
            mu[1:q] ~ dmnorm(mu.prior.mean[1:q], mu.prior.precision[1:q, 1:q])

            for (i in 1:n.ind) {
# Insert covariate relationships here
            for (j in 1:p) { theta.mean[i, j] <- mu[j]}
# End covariate relationships
            td[i, 1] <- p+qc+1
            theta[i, 1:p] ~ dmnorm(theta.mean[i, 1:p], omega.inv[1:p, 1:p])
# Parameters may be in log form, so need to inverse log so model can use it
            for ( j in 1:p) {td[i,j+1] <- exp(theta[i,j]) }
            for (j in 1:qc) {td[i,p+1+j] <- cmu[j] }
#Load dose information into td here
            td[i, p+qc+2] <- bdim[i];
            td[i, p+qc+3] <- rdim[i];
            for (j in dose_index[i]:dose_index[i+1]-1) {td[i, p+qc+4+j-dose_index[i]]
            <-dose[j]}
            for (j in p+qc+dose_index[i+1]-dose_index[i]+4:tdim) {td[i, j] <- 0.0}
# Here begins the model dependent part
# Load initial conditions from bolus doses and internal steady state conditions
            for (j in 1:bdim[i]) { xmodel[i, 1, j] <- dose[dose_index[j]] }
            for (j in 1:3) { xmodel[i, 1, j] <- 0.0 }
            for (j in 4:8) {xmodel[i, 1, j] <- td[i,8] }
# Now call the ordinary differential equation solver routine.
            xmodel[i, 2:data_time_index[i+1]-data_time_index[i], 1:dim] <-
    ode.Tropkpdn1m(
    xmodel[i, 1, 1:dim],
    data_time[data_time_index[i]+1:data_time_index[i+1]-1],
    td[i,1:tdim],
    dose_time[dose_time_index[i]:dose_time_index[i+1]-1],
    tol)
# Set up volumes of distributions for outputs
            Vc[i,1] <- td[i,3]
            Vc[i,2] <- 1
            for (j in data_index[i]:data_index[i+1]-1) {
            dtyp[j] <- dtype[j]
# Need to convert amount xmodel[ into concentration model
# State variable 1 maps to output 1, but state variable 8 maps to output 2
            model[j] <- xmodel[i,time_index[j],( (cmt[j]-1)*8+(2-cmt[j])*1 )]/Vc[i,cmt[j]]
            smm[j] <- tau[cmt[j]]/(model[j]*model[j])
            data[j] ~ dnorm(model[j], smm[j])
                        }}}
```

FIGURE 2. WINBUGS INITIAL FILES (Created by S-ADAPT using final estimates from its MCPEM analysis, and used as initial parameters and informative prior for WINBUGS analysis)

```
list(
# mapping for TAU/SIGMA:
# Tau( 1)=p(14)=slp_pk
# Tau( 2)=p(16)=slp_pd
tau=c(
 44.732, 5.9057),
# mapping for MU:
# mu( 1)=p( 1)=cl
# mu( 2)=p( 2)=v1
# mu( 3)=p( 3)=cld
# mu( 4)=p( 4)=v2
# mu( 5)=p( 5)=cld1
# mu( 6)=p( 6)=v3
# mu( 7)=p( 7)=base
# mu( 8)=p( 8)=emax
# mu( 9)=p( 9)=km
# mu(10)=p(10)=gamc
# mu(11)=p(11)=kn
# mu(12)=p(12)=gamp
mu=c( 2.1521, 2.8090, 1.7539, 5.6511, 2.5841, 3.2085, 8.7571, -0.36156, 1.10992E-02, -0.71696, -3.5760, -1.3076),
#  mapping for OMEGA
omega.inv=structure(
.Data=c(
 128.20, 17.830, -76.996, -51.666, 26.030, 32.644, -6.5793, 45.719, 41.380, 31.414, 164.20, 50.023,
 17.830, 126.77, -109.94, 21.670, 114.73, -82.782, -42.623, 84.813, -29.033, 14.537, -108.61, -74.989,
 -76.996, -109.94, 1004.7, -476.77, -246.43, 70.555, -133.17, -7.5039, 33.706, 85.502, 124.72, 158.16,
 -51.666, 21.670, -476.77, 307.39, 100.45, -59.870, 86.551, -29.149, -49.125, -78.503, -193.70, -123.04,
 26.030, 114.73, -246.43, 100.45, 190.40, -140.86, -9.2131, 144.95, -39.072, -23.698, -187.13, -95.485,
 32.644, -82.782, 70.555, -59.870, -140.86, 154.55, 20.979, -142.44, 52.508, 28.285, 248.83, 92.486,
 -6.5793, -42.623, -133.17, 86.551, -9.2131, 20.979, 53.788, -41.813, 4.1128, -29.747, 8.0396, -0.57548,
 45.719, 84.813, -7.5039, -29.149, 144.95, -142.44, -41.813, 235.66, -20.574, -5.0374, -150.71, -50.520,
 41.380, -29.033, 33.706, -49.125, -39.072, 52.508, 4.1128, -20.574, 31.838, 16.516, 125.03, 54.597,
 31.414, 14.537, 85.502, -78.503, -23.698, 28.285, -29.747, -5.0374, 16.516, 35.253, 83.811, 36.366,
 164.20, -108.61, 124.72, -193.70, -187.13, 248.83, 8.0396, -150.71, 125.03, 83.811, 556.60, 219.70,
 50.023, -74.989, 158.16, -123.04, -95.485, 92.486, -0.57548, -50.520, 54.597, 36.366, 219.70, 135.96),
.Dim=c(12,12)),
# mapping for THETA:
theta=structure(
.Data=c(
 1.5994, 2.5267, 1.0932, 4.4046, 2.1405, 2.6432, 9.2264, -0.32670, -0.71452, -0.46600, -3.4502, -1.4963,
 2.0011, 2.5024, 1.3110, 5.0864, 2.2481, 2.6319, 8.2320, -0.64807, 1.0766, -0.66656, -3.8542, -1.3251,
 1.5935, 2.5493, 1.2816, 4.7174, 2.5627, 3.2497, 8.6382, -0.21972, -1.2304, -1.2593, -3.2884, -1.3246,
 1.5146, 2.4346, 1.5053, 5.2947, 2.6923, 3.0433, 8.4983, -0.23370, 2.53992E-02, -0.70585, -3.2618, -1.6160,
 2.1114, 2.5202, 1.7056, 5.5550, 2.6909, 3.1387, 8.9553, -0.48570, 1.0823, 0.10237, -3.8830, -1.5599,
 2.2911, 2.5819, 1.7788, 5.8201, 2.8015, 3.3538, 7.9757, -0.54541, 1.0289, -0.99543, -3.8261, -1.3328,
 2.1389, 2.8878, 1.8935, 5.5625, 2.7437, 3.1484, 9.7172, -0.35006, -0.29843, -0.17315, -3.4096, -1.6687,
 1.9913, 2.3438, 1.4404, 5.0341, 3.0473, 4.3979, 8.4401, -0.14970, -0.88231, -0.74565, -3.9298, -1.1621,
 2.4409, 3.7186, 2.2556, 6.3387, 2.6750, 3.2628, 8.9524, -0.28322, -1.7963, -2.1964, -2.9131, -0.72147,
 2.5607, 3.1199, 2.3523, 6.5946, 3.0789, 3.6701, 9.2534, -0.37879, 0.38560, -0.16834, -3.7537, -1.0935,
 2.1902, 3.4046, 1.7724, 5.7686, 2.1875, 3.4550, 8.2455, -0.19470, 6.44494E-02, -2.0294, -3.5450, -1.0765,
 2.3730, 3.2715, 2.0836, 6.1135, 2.7276, 3.6302, 8.9629, -0.37338, 0.99279, -0.95147, -3.8588, -1.2079,
 2.4913, 3.7953, 1.8008, 5.6675, 1.9142, 2.6889, 8.6911, -0.65594, 0.84611, -2.1493, -3.6692, -0.96176,
 2.2001, 2.4908, 1.4222, 5.1875, 2.1573, 2.6710, 8.1442, -0.51940, 1.33633E-02, -1.1608, -3.5160, -1.5202,
 1.6585, 2.6712, 1.7220, 5.5608, 2.8692, 3.0597, 8.9702, -0.40071, 0.86381, -0.12610, -3.5159, -1.5549,
 2.0383, 2.6081, 1.7604, 5.6435, 2.6105, 3.0198, 9.3417, -0.41993, 1.1671, 0.47850, -3.8666, -1.5712,
 2.3448, 2.7460, 2.2345, 6.6081, 3.0618, 3.3632, 8.6057, -0.43683, 1.1941, -4.99334E-02, -3.6726, -1.4072,
 2.2122, 2.9987, 2.2029, 6.2788, 3.2796, 3.8336, 8.8994, -0.33694, 0.35155, -0.65671, -3.5700, -1.2867,
 2.5537, 3.0572, 1.7997, 5.6254, 2.3774, 3.1829, 8.7642, -0.48555, -0.20350, -1.3100, -3.6764, -1.1702,
 2.2817, 3.1109, 2.0827, 6.0390, 3.0173, 3.6461, 9.1807, -0.38726, 8.13161E-02, -0.58787, -3.6598, -1.1168,
 2.0028, 2.2394, 1.7737, 5.8498, 2.6841, 2.8712, 8.6334, -0.28760, -5.57120E-02, 0.14738, -3.3122, -1.7577,
 2.2076, 2.1438, 1.1204, 4.6786, 1.8904, 2.4217, 8.4429, -0.54430, -9.07299E-02, -0.50668, -3.7348, -1.6135,
 1.7184, 2.4988, 1.9370, 6.3754, 2.6871, 2.7464, 8.7367, -0.20470, 1.0715, 0.73115, -3.3621, -1.5645,
 2.1579, 3.2085, 2.0175, 6.0406, 2.8866, 3.8947, 9.0854, -7.23615E-02, -1.1148, -0.81402, -3.4507, -0.87456,
 2.4817, 2.6725, 1.6081, 5.5391, 2.1518, 2.4088, 7.9700, -0.67035, -6.92179E-02, -1.5683, -3.4181, -1.2918,
 2.3449, 2.6871, 1.7376, 5.7029, 2.5808, 3.3059, 8.4836, -0.40116, -8.95108E-05, -0.75093, -3.6902, -1.2870,
 2.2674, 2.8540, 1.6952, 5.6728, 2.2958, 3.1971, 8.3782, -0.25087, -0.70643, -1.1858, -3.4336, -1.2273,
 2.5243, 2.8303, 1.8453, 5.7779, 2.5580, 3.3755, 8.9648, -0.38657, -0.39024, -0.50501, -3.7435, -1.1500,
 2.3372, 3.1069, 1.9990, 5.8329, 2.6504, 3.2561, 9.8688, -0.21479, -1.3736, -0.17718, -3.3603, -1.1522,
 2.1085, 2.9977, 1.4237, 5.2216, 2.0596, 3.2885, 8.3575, -0.21113, -0.51294, -1.5863, -3.6457, -1.0160,
 1.9764, 2.5006, 1.7145, 5.5909, 2.7781, 3.6062, 8.8537, -0.13287, -0.46150, -0.19265, -3.5857, -1.4271),
.Dim=c(31,12)))
```

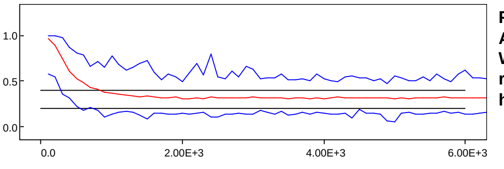


FIGURE 3. Metropolis Acceptance Rate of the WINBUGS Run (Total run times is about 18 hrs)

TABLE 1. Summary of Posterior Distribution for Population Parameters in the PKPD Model[a]

Parameter	Mean	SD	Median	2.5%	97.5%
PK					
CL (L/hr)	2.14	0.0661	2.14	2.01	2.27
V_c (L)	2.80	0.108	2.80	2.59	3.01
CL_d (L/hr)	1.76	0.0829	1.75	1.60	1.92
V_2 (L)	5.66	0.139	5.66	5.38	5.94
CL_{d1} (L/hr)	2.63	0.124	2.63	2.38	2.87
V_3 (L)	3.22	0.124	3.22	2.97	3.46
PD					
Baseline	8.71	0.121	8.71	8.48	8.96
E_{max}	-0.872	0.175	-0..869	-1.22	-0.562
K_m (ng/mL)	-0.934	0.532	-0.852	-2.20	-0.111
γ	2.09	0.875	2.07	0.412	3.66
Kt (hr^{-1})	-3.59	0.0787	-3.59	-3.74	-3.43
θ	-1.69	0.128	-1.70	-1.91	-1.41

[a] PKPD parameters were expressed as log-transformed values

FIGURE 4. Posterior Distribution for OMEGA in the PKPD Model

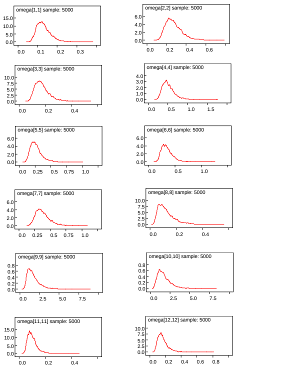
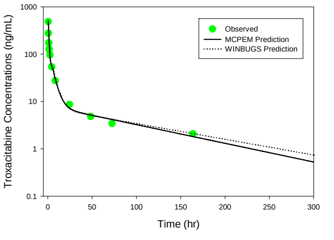
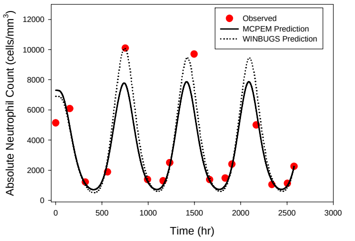


FIGURE 5. Representative Plot of Individual Observation and Model Prediction for Troxacitabine Concentration-time (LEFT) and Absolute Neutrophil Count-time Profile (RIGHT). Solid line – MCPEM Prediction; Dotted line – WINBUGS Prediction





CONCLUSIONS:

1. Using prior information provided by the final parameters estimated from the MCPEM algorithm, the full Bayesian model developed using WINBUGS program was stable and able to generate reasonable model predictions.
2. The proposed systematic bridging approach offers a practical solution for using full Bayesian three-stage hierarchical nonlinear mixed effect method in complex population PKPD analysis.

REFERENCES:

1. Jonsson F, et al. *J Biopharm Stat* 2007;17(1):65-92; 2. Kathman SJ, et al. *Clin Pharmacol Ther* 2007;81(1):88-94; 3. Ng CM, et al. *Pharm Res* 2005;22(7):1088-1100; 4. Friberg L, et al. *Invest. New Drugs* 2003;183-94