Advanced Population Analysis Features in the S-ADAPT/MCPEM Program

Robert J. Bauer
XOMA (US) LLC

PAGE meeting June 13-15, 2007
Copenhagen, Denmark

S-ADAPT Features

- S-ADAPT is a Fortran 95 open-source, free program distributed by U. of Southern California, Biomedical Simulations Resource department (USC, BMSR),
- S-ADAPT provides an environment for performing population analysis of data, with or without covariates, using complex PK/PD models with extensive simulation tools, based on ADAPT II modeling algorithms.

Population Analysis Methods

- Importance Sampling Monte Carlo Parametric Expectation Maximization (MCPEM)
  - Accurate, exact likelihood method, best for sparse data
- Importance Sampling MCPEM facilitated by Maximum a Posterior (MAP) estimation
  - Accurate, exact likelihood, best for rich data and complex PK/PD models
- Direct Sampling
  - Accurate but inefficient, suitable for very sparse data, simple models
- Iterative Two Stage (ITS)
  - Good for exploration of model and data
- Two Stage

Standard Error/ Parameter Uncertainty Assessment

- **MCPEM facilitated second order information matrix**
  - standard error, very fast and accurate
- **Finite difference second order information matrix**
  - standard error, slower, most appropriate for ITS
- **Full boot strap method**
  - provides quantile ranges as well as standard error
- **Bayesian Analysis**
  - similar to WinBUGS
  - provides quantile ranges as well as standard error

S-ADAPT Environment

- **Several interface types**
  - Command line
  - Forms for parameter settings
  - Menus or sessions for guiding analysis
  - Script file system
- **Template model files for basic PK models based on the various Advan/Trans algorithms in NONMEM**
- **Uses data in NONMEM format**

S-ADAPT Help System

- On-line Help within S-ADAPT:
  - Search by topic, or search string
- HTML Web Browser readable
- Printable Version

Algebraic Interpreter at S-ADAPT Command Window

- Set tstop=70*7
- Set xmax=tstop+7
- Set k10=log(2)/termHL
- Setg r=randmt(4.0) (returns random number that is t-distributed with 3 degrees of freedom)
- Piterate npopiter=200 pmethod=8
- Poperr
- Tabtofil my_stuff_varc my_stuff_varc.txt

S-ADAPT Script System at Run-Time

- All commands can be written into a text file, then executed:
  - **`Include my_commands.cmd root 34`**
- Navigation Commands for Script file:
  - **`if(i.gt.nrow) backup label1`**
  - **`If(error.eq.1) close`**
- A script file may execute a script file, up to 20 levels

Tables

- Tables are S-ADAPT command window accessible spreadsheets with row and column layout.
- Cells of tables may contain real numbers, complex numbers, or text
- **`Edit my_table`**

Population Analysis Example

- Write model code
- Compile code
- Execute program
- Perform main analysis
- Perform standard error assessment

Differential Equations Routine

```
      Subroutine DIFFEQ(T,X,XP)
…
       XP(1) = -K10*X(1) -
      & VM*X(1)*X(2)/(X(1)+KM) + r(1)
       XP(2) =  -VM*X(1)*X(2)/(X(1)+KM)
      & - K20*X(2) + K02
       Return
       End
```

Output Routine

```
      Subroutine OUTPUT(Y,T,X)
C Initialize state variables at time 0
            if(t.le.0.0d+00) x(2)=k02/k20
C Relate model states to outputs
     (PK=1, PD=2,
C for example)
            y(1)=x(1)/vc
            y(2)=x(2)/vc
            Return
            End
```

Intra-Subject Variance Routine

```
Subroutine VARMOD(V,T,X,Y,J)
        V(1) = SD1*SD1*Y(1)**2
        V(2) = SD2*SD2*Y(2)
        Return
        End
```

Transform Population Parameters

```
      subroutine poptrn(pz)
C transform parameters
C In this example, parameters are
  log
C transformed, but they may be
C transformed using any function
          do i=1,6
          pz(i)=dlog(pz(i))
          enddo
          return
          end
```

Inverse Transform Must be Supplied

```
subroutine popitrn(pz)

      do i=1,6
      pz(i)=dexp(pz(i))
      enddo
      return
      end
```

Constraints on Population Parameters

```
 subroutine popfinal
C  Example:  Constrain Inter-subject
C variance matrix pcov(*,*) to diagonal
C matrix
      d0 i=1,nsparam
       do j=1,nsparam
       if(i.ne.j) pcov(i,j)=0.0d+00
       enddo
       enddo
       return
       end
```

Covariate Model

```
      subroutine popmod(kj,ipat,pz,pz_prev,wx,ir)
   …
C Enter covariate relationships here
      gender=getcelli(nfcov,kj,0)
      age=getcelld(nfcov,kj,1)
      pz(1)=   ! Model for Vc
     & (1.0d+00-gender)*pz(5)*age**pz(7) +
     & gender*pz(6)*age**pz(8)
      pz(2)=   !  Model for CL
     & (1.0d+00-gender)*pz(9)*age**pz(11) +
     & gender*pz(10)*age**pz(12)
      return
      end
```

Compile, Link, and Execute Program

- sadapt my_prog
- my_prog
- session

Population Analysis Session

PROCESS	INFORMATION
DEFINE ROOT AND VERSION	Root=SAMP5, Version=1
GETDATA	Get data and dose information from SAMP
EDIT DATA TABLE	**Edit SAMP5_dat**
Get Covariates Table	Get covariates from SAMP5.cov
EDIT COV Table	Edit SAMP5_cov
Modify Pmean, Pcov	Modify Population Parameters from Pmean
Parameter Boundaries	Set parameter boundaries
Model Switches	Modify variance parameters
POP ANALYSIS PARAMETERS	Modify Population Analysis Parameters
PITERATE	Start population analysis
View MEAN	View population mean parameters
View Iter	View iterations table
View PAR	View individual mean parameters
View IPRED	View Individual predicted, residuals
Error Analysis	Perform error analysis
Bootstrap sort	Sort results from Bootstrap error analy
View VARC	View standard errors
POSTHOC ANALYSIS	Perform Posthoc Analysis
VIEW POSTHOC FITS	View the posthoc fits

NONMEM Data Set Editable Within S-ADAPT

```
Page           6    @AD6TR1_DAT
0:SET   1:ID    2:JID   3:TIME  4:CONC  5:DOSE  6:RATE  7:EVID  8:MDV   9:CMT

87:30   2       2       20      0.60834 0       0       0       0       2
88:30   2       2       22      1.2502  0       0       0       0       2
89:30   2       2       26      1.8803  0       0       0       0       2
90:30   2       2       28      1.5223  0       0       0       0       2
91:30   3       3       0       0       100     0       1       1       1
92:30   3       3       0       0       1       0       1       1       2
93:30   3       3       0       0.66999 0       0       0       0       2
94:30   3       3       0.05    0.91229 0       0       0       0       1
95:30   3       3       0.05    0.55575 0       0       0       0       2
96:30   3       3       0.25    0.51269 0       0       0       0       1
97:30   3       3       0.25    0.46786 0       0       0       0       2
98:30   3       3       0.5     0.45948 0       0       0       0       1
99:30   3       3       0.5     0.35078 0       0       0       0       2
100:30  3       3       0.75    0.23894 0       0       0       0       1
101:30  3       3       0.75    0.30443 0       0       0       0       2
102:30  3       3       1       0.13069 0       0       0       0       1
/EX=exit /RED to redisplay /HELP for more commands
91:0:
```

Population Analysis Session

PROCESS	INFORMATION
DEFINE ROOT AND VERSION	Root=SAMP5, Version=1
GETDATA	Get data and dose information from SAMP
EDIT DATA TABLE	Edit SAMP5_dat
Get Covariates Table	Get covariates from SAMP5.cov
EDIT COV Table	Edit SAMP5_cov
Modify Pmean, Pcov	**Modify Population Parameters from Pmean**
Parameter Boundaries	Set parameter boundaries
Model Switches	Modify variance parameters
POP ANALYSIS PARAMETERS	Modify Population Analysis Parameters
PITERATE	Start population analysis
View MEAN	View population mean parameters
View Iter	View iterations table
View PAR	View individual mean parameters
View IPRED	View Individual predicted, residuals
Error Analysis	Perform error analysis
Bootstrap sort	Sort results from Bootstrap error analy
View VARC	View standard errors
POSTHOC ANALYSIS	Perform Posthoc Analysis
VIEW POSTHOC FITS	View the posthoc fits

Population Parameter Entry

```
0:NAME       1:MEAN       2:TYPE       3:PXT
-------------------------------------------
1:CL         5            P            1
2:V1         2            P            1
3:Q          2            P            1
4:V2         2            P            1
5:SDin       0            N            1
6:SDsl       0.1          V            1
7:
8:
```

Population Variance Entry

0:NAME	5:CL	6:V1	7:Q	8:V2
1:CL	0.3			
2:V1	0	0.3		
3:Q	0	0	0.3	
4:V2	0	0	0	0.3
5:SDin	0	0	0	0
6:SDsl	0	0	0	0
7:				
8:				

Population Analysis Session

PROCESS	INFORMATION
DEFINE ROOT AND VERSION	Root=SAMP5, Version=1
GETDATA	Get data and dose information from SAMP
EDIT DATA TABLE	Edit SAMP5_dat
Get Covariates Table	Get covariates from SAMP5.cov
EDIT COV Table	Edit SAMP5_cov
Modify Pmean, Pcov	Modify Population Parameters from Pmean
Parameter Boundaries	Set parameter boundaries
Model Switches	Modify variance parameters
POP ANALYSIS PARAMETERS	**Modify Population Analysis Parameters**
PITERATE	Start population analysis
View MEAN	View population mean parameters
View Iter	View iterations table
View PAR	View individual mean parameters
View IPRED	View Individual predicted, residuals
Error Analysis	Perform error analysis
Bootstrap sort	Sort results from Bootstrap error analy
View VARC	View standard errors
POSTHOC ANALYSIS	Perform Posthoc Analysis
VIEW POSTHOC FITS	View the posthoc fits

Set Population Analysis Settings

```
Page           1    Population Analysis Parameters
Pmethod 4             Npopiter 15           Npopc   1000          Npop    100
Poptmethod 1          Preqmin 1.0000E-02    Vreqmin 1.0000E-04    Vapprox -4
Geffici 1.000         Gamma_min 0.3000      Gamma_max 3.000       Dfran   0
Popconv_test 0        Popconv_rows 5        Popconv_alpha 0.05000
Popgauss 0            Covgauss 1            Poprepeat  10.00      Npopce  0
Gnstart 1.000         Gnstop  1.000         Gnstep  2.000         Gnsize  1.000
Patlist 0             Npoplast 0            Iptransform 0         Npenv      2
Ediag      0          Ndelpar    0
Iminran    0          Ipfitonce  0          Iasymcov   1          Isumcov    1
Iranpar    2          Iptailcalc 1          Ipcovtype1 2          Ipcovtype2 2
Poperr_type  8              Npopeiter    1              Poperr_intra 1
Popreq       1.0000E-04     ESK          0              Poperr_resume 0
/EX=exit /DCL=shell /RED=redisplay !command /HELP for more commands
```


XOMA

Population Analysis Session

PROCESS	INFORMATION
DEFINE ROOT AND VERSION	Root=SAMP5, Version=1
GETDATA	Get data and dose information from SAMP
EDIT DATA TABLE	Edit SAMP5_dat
Get Covariates Table	Get covariates from SAMP5.cov
EDIT COV Table	Edit SAMP5_cov
Modify Pmean, Pcov	Modify Population Parameters from Pmean
Parameter Boundaries	Set parameter boundaries
Model Switches	Modify variance parameters
POP ANALYSIS PARAMETERS	Modify Population Analysis Parameters
PITERATE	**Start population analysis**
View MEAN	View population mean parameters
View Iter	View iterations table
View PAR	View individual mean parameters
View IPRED	View Individual predicted, residuals
Error Analysis	Perform error analysis
Bootstrap sort	Sort results from Bootstrap error analy
View VARC	View standard errors
POSTHOC ANALYSIS	Perform Posthoc Analysis
VIEW POSTHOC FITS	View the posthoc fits

Follow Objective Function Improvement During Analysis

```
ad3tr4> piteraten
 iteration           1
 Average Neffective=       1155. Average Nsample=       1000. Fitness=  0.95405E+00
 OBJFIT=   125.230569463061        OBJDER=  0.000000000000000E+000
 iteration           2
 Average Neffective=       4151. Average Nsample=       1000. Fitness=  0.80239E+00
 OBJFIT=  -496.153033902559        OBJDER=  0.000000000000000E+000
 iteration           3
 Average Neffective=        517. Average Nsample=       1000. Fitness=  0.90276E+00
 OBJFIT=  -530.633511320540        OBJDER=  0.000000000000000E+000
 iteration           4
 Average Neffective=        614. Average Nsample=       1000. Fitness=  0.92619E+00
 OBJFIT=  -550.538847021806        OBJDER=  0.000000000000000E+000
 iteration           5
 Average Neffective=        846. Average Nsample=       1000. Fitness=  0.93415E+00
 OBJFIT=  -558.904355062808        OBJDER=  0.000000000000000E+000
 iteration           6
 Average Neffective=        969. Average Nsample=       1000. Fitness=  0.93355E+00
 OBJFIT=  -562.376671488572        OBJDER=  0.000000000000000E+000
 iteration           7
 Average Neffective=       1038. Average Nsample=       1000. Fitness=  0.93465E+00
 OBJFIT=  -567.956681665702        OBJDER=  0.000000000000000E+000
 iteration           8
 Average Neffective=       1010. Average Nsample=       1000. Fitness=  0.93372E+00
 OBJFIT=  -570.145921882317        OBJDER=  0.000000000000000E+000
 iteration           9
 ^K
 Average Neffective=       1009. Average Nsample=       1000. Fitness=  0.93334E+00
 OBJFIT=  -569.048779750710        OBJDER=  0.000000000000000E+000

 CPU time      (DDD:HH:MM:SS.dd) 000:00:00:29.48
 Elapsed time  (DDD:HH:MM:SS.dd) 000:00:00:30.00
```

Population Analysis Session

PROCESS	INFORMATION
DEFINE ROOT AND VERSION	Root=SAMP5, Version=1
GETDATA	Get data and dose information from SAMP
EDIT DATA TABLE	Edit SAMP5_dat
Get Covariates Table	Get covariates from SAMP5.cov
EDIT COV Table	Edit SAMP5_cov
Modify Pmean, Pcov	Modify Population Parameters from Pmean
Parameter Boundaries	Set parameter boundaries
Model Switches	Modify variance parameters
POP ANALYSIS PARAMETERS	Modify Population Analysis Parameters
PITERATE	Start population analysis
View MEAN	View population mean parameters
View Iter	**View iterations table**
View PAR	View individual mean parameters
View IPRED	View Individual predicted, residuals
Error Analysis	Perform error analysis
Bootstrap sort	Sort results from Bootstrap error analy
View VARC	View standard errors
POSTHOC ANALYSIS	Perform Posthoc Analysis
VIEW POSTHOC FITS	View the posthoc fits

Iteration Tables Maintains Permanent Record of Parameter Advancement

CL	V1	Q	V2	CL~CL	V1~V1	Q~Q	V2~V2	OBJFUN	SFIT
2	2	2	2	0.4	0.4	0.4	0.4	125.2	0.9540
4.649	3.585	1.687	8.640	0.1536	0.5697	0.3297	0.3027	-496.2	0.8024
4.847	3.837	1.850	9.416	0.1522	0.4767	0.2770	0.2662	-530.6	0.9028
4.932	3.998	1.939	9.845	0.1544	0.3808	0.2664	0.2344	-550.5	0.9262
4.983	4.160	1.976	10.09	0.1562	0.3153	0.2626	0.2152	-558.9	0.9342
5.019	4.298	1.992	10.21	0.1582	0.2632	0.2588	0.2003	-562.4	0.9335
5.055	4.399	2.011	10.25	0.1605	0.2236	0.2568	0.1919	-568.0	0.9346
5.075	4.504	2.034	10.30	0.1615	0.1946	0.2509	0.1855	-570.1	0.9337
5.090	4.565	2.044	10.36	0.1634	0.1781	0.2506	0.1819	-569.0	0.9333
5.102	4.588	2.054	10.34	0.1634	0.1686	0.2406	0.1774	-571.5	0.9364
5.106	4.642	2.062	10.38	0.1632	0.1614	0.2371	0.1744	-572.0	0.9343
5.109	4.664	2.084	10.37	0.1656	0.1591	0.2305	0.1715	-571.2	0.9355
5.121	4.693	2.087	10.39	0.1655	0.1554	0.2249	0.1691	-572.5	0.9362
5.120	4.714	2.086	10.39	0.1667	0.1529	0.2207	0.1700	-571.8	0.9328
5.127	4.701	2.097	10.42	0.1668	0.1542	0.2182	0.1662	-571.4	0.9339
5.132	4.715	2.093	10.40	0.1669	0.1513	0.2203	0.1657	-571.1	0.9361
5.133	4.720	2.095	10.40	0.1664	0.1473	0.2195	0.1643	-572.1	0.9374
5.129	4.725	2.101	10.42	0.1676	0.1481	0.2156	0.1642	-571.4	0.9356
5.138	4.725	2.103	10.44	0.1668	0.1462	0.2103	0.1622		

Population Analysis Session

PROCESS	INFORMATION
DEFINE ROOT AND VERSION	Root=SAMP5, Version=1
GETDATA	Get data and dose information from SAMP
EDIT DATA TABLE	Edit SAMP5_dat
Get Covariates Table	Get covariates from SAMP5.cov
EDIT COV Table	Edit SAMP5_cov
Modify Pmean, Pcov	Modify Population Parameters from Pmean
Parameter Boundaries	Set parameter boundaries
Model Switches	Modify variance parameters
POP ANALYSIS PARAMETERS	Modify Population Analysis Parameters
PITERATE	Start population analysis
View MEAN	View population mean parameters
View Iter	View iterations table
View PAR	View individual mean parameters
View IPRED	View Individual predicted, residuals
Error Analysis	Perform error analysis
Bootstrap sort	Sort results from Bootstrap error analy
View VARC	**View standard errors**
POSTHOC ANALYSIS	Perform Posthoc Analysis
VIEW POSTHOC FITS	View the posthoc fits

View Population Means, Variances, and their Standard Error Results

@SAMP5_VARC	27R x 31C			03-MAY-2007
0:AVERAGE	1:MEAN	2:SE	3:%CV	4:OBJMIN
1:CL	5.128	0.2367	4.617	-571.4
2:V1	4.730	0.2358	4.984	
3:Q	2.117	0.1466	6.926	
4:V2	10.51	0.5807	5.523	
5:SDin	0	0		
6:SDsl	0.2363	8.8831E-03	3.759	
7:CL~CL	0.1669	2.7121E-02	16.25	
8:V1~CL	-8.6334E-03	2.2337E-02	258.7	
9:V1~V1	0.1294	3.2299E-02	24.96	
10:Q~CL	1.2909E-02	2.7423E-02	212.4	
11:Q~V1	-1.7085E-02	4.1007E-02	240.0	
12:Q~Q	0.1829	5.1274E-02	28.03	
13:V2~CL	-1.5710E-02	2.2831E-02	145.3	
14:V2~V1	9.7759E-03	2.8989E-02	296.5	
15:V2~Q	2.7379E-02	3.8150E-02	139.3	
16:V2~V2	0.1592	3.6046E-02	22.64	

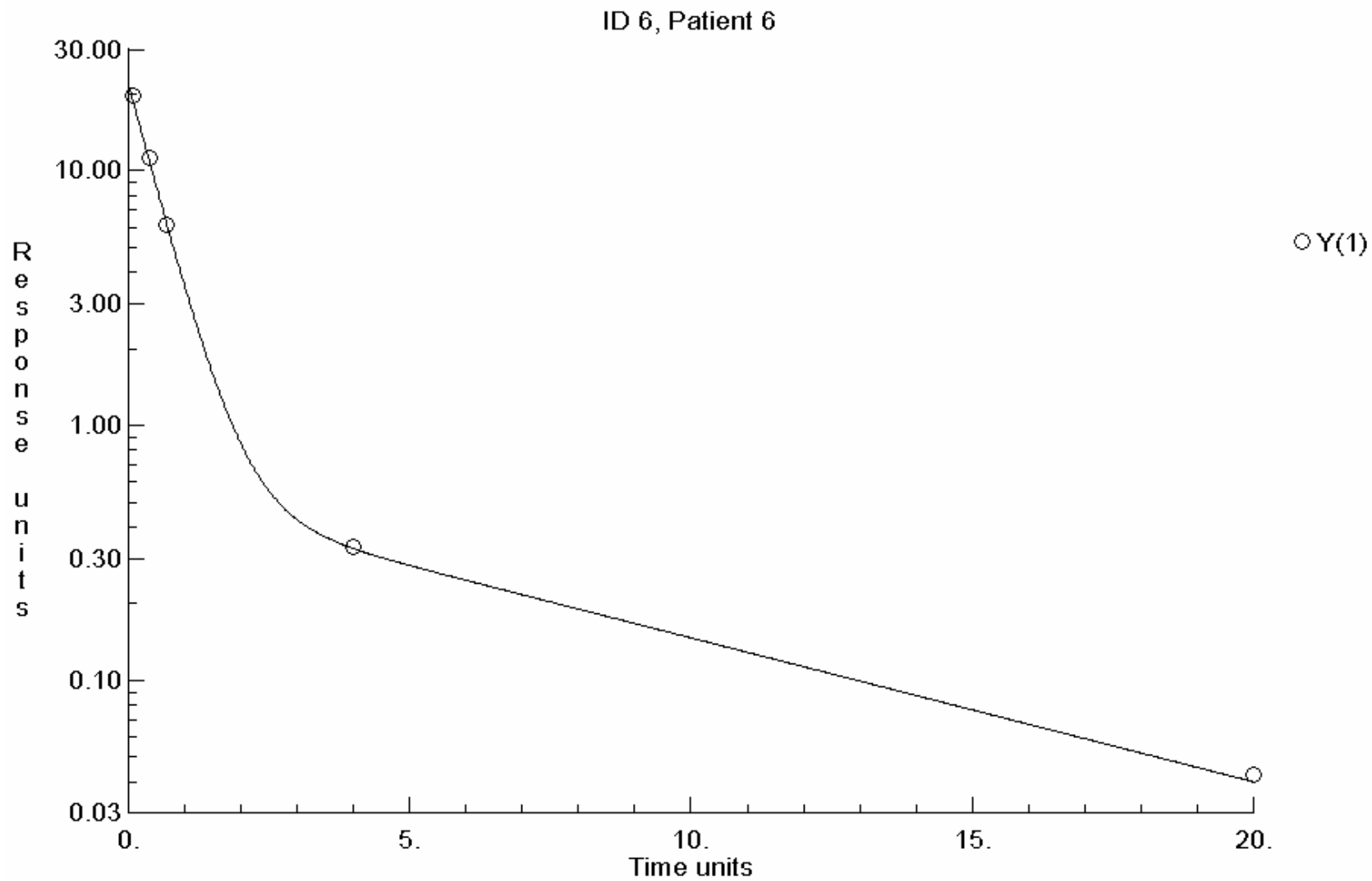
XOMA

Population Analysis Session

PROCESS	INFORMATION
DEFINE ROOT AND VERSION	Root=SAMP5, Version=1
GETDATA	Get data and dose information from SAMP
EDIT DATA TABLE	Edit SAMP5_dat
Get Covariates Table	Get covariates from SAMP5.cov
EDIT COV Table	Edit SAMP5_cov
Modify Pmean, Pcov	Modify Population Parameters from Pmean
Parameter Boundaries	Set parameter boundaries
Model Switches	Modify variance parameters
POP ANALYSIS PARAMETERS	Modify Population Analysis Parameters
PITERATE	Start population analysis
View MEAN	View population mean parameters
View Iter	View iterations table
View PAR	View individual mean parameters
View IPRED	View Individual predicted, residuals
Error Analysis	Perform error analysis
Bootstrap sort	Sort results from Bootstrap error analy
View VARC	View standard errors
POSTHOC ANALYSIS	Perform Posthoc Analysis
VIEW POSTHOC FITS	**View the posthoc fits**

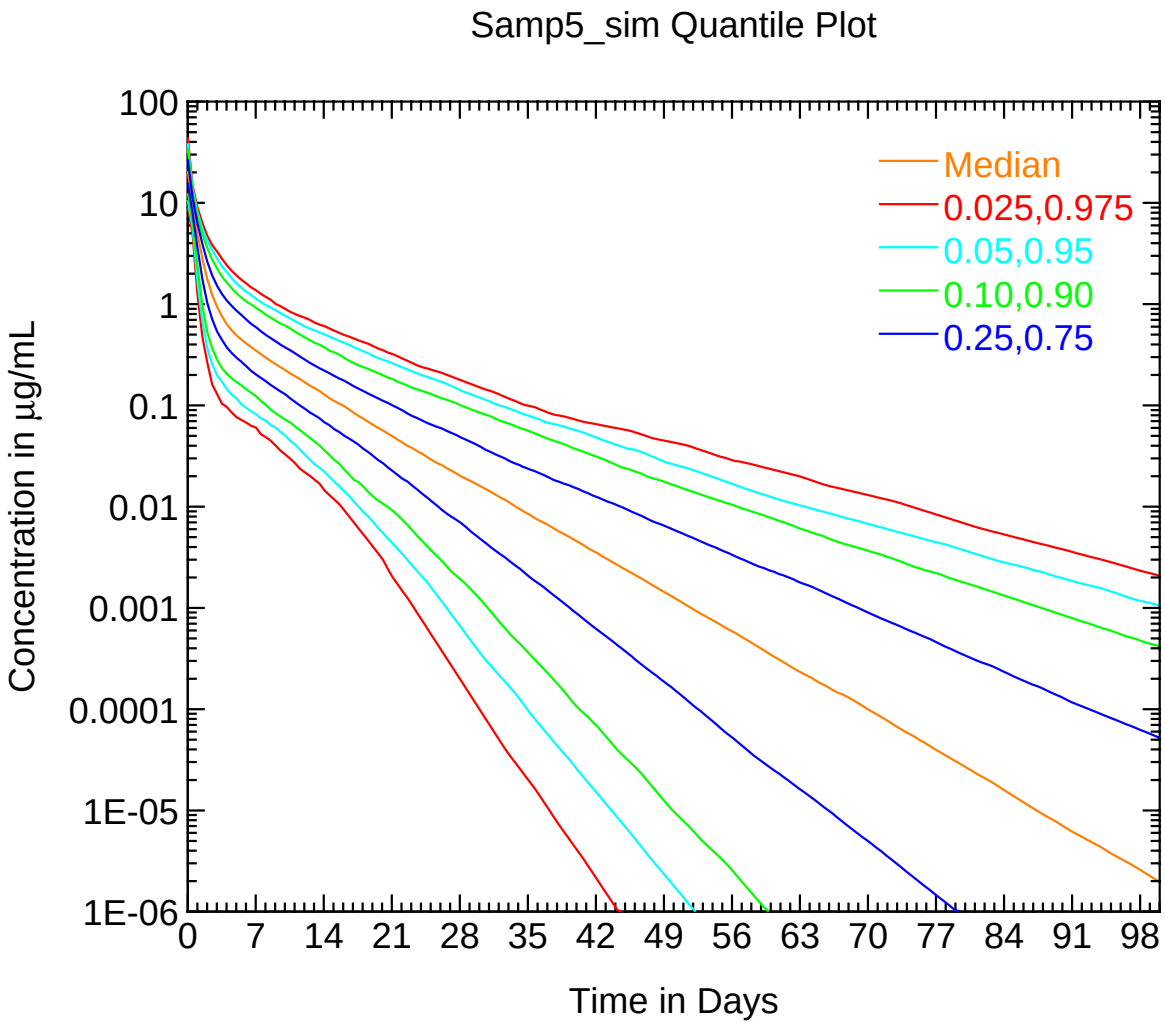
XOMA

View Post-Hoc Fits

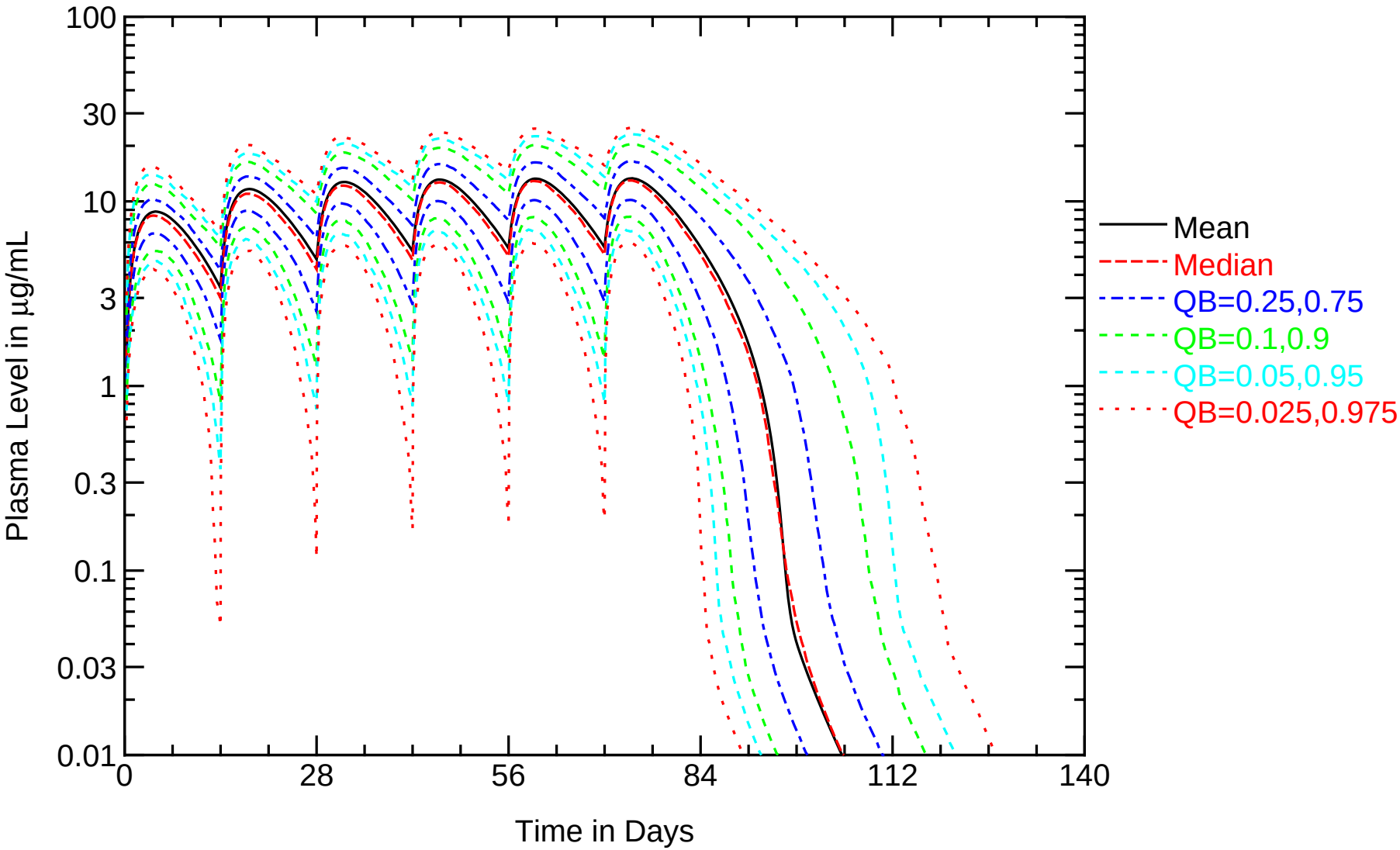


XOMA

Example Quantile Plot



Example Quantile Plot



XOMA

Simulation/Validation

- Test a particular trial design
- Test a particular population analysis method
- Are precision and bias in parameters acceptable?
- Perform posterior predictive check after Analysis

Strategy to Simulation/Validation

- Simulate a number of data sets based on trial design, sampling pattern, a PK/PD model, and statistical model
- Analyze in batch the data sets using a particular population analysis method
- Obtain summary statistics of simulated analysis

Set Up Simulation Templates

- Set up a template data table ad3tr4a_tdat, containing dose information and placeholder data for 1 or more subject types
- Set up a template population means and variances table ad3tr4a_tmean

The Template ad3tr4a_TDAT

PATIENT	PT	TIME	CONC	OMIT	DOSE	RATE	EVID	MDV	CMT
1	1	0			100	0	1	1	1
1	1	0.25	1				0	0	1
1	1	1	1				0	0	1
1	1	4	1				0	0	1
1	1	24			100	20	1	1	1
1	1	24	1				0	0	1
1	1	29	1				0	0	1
1	1	36	1				0	0	1
1	1	48	1				0	0	1
1	1	72	1				0	0	1
2	2	0			100	50	1	1	1
2	2	2	1				0	0	1
2	2	3	1				0	0	1
2	2	4	1				0	0	1
2	2	8	1				0	0	1
2	2	24			100	20	1	1	1
2	2	24	1				0	0	1
2	2	29	1				0	0	1
2	2	36	1				0	0	1
2	2	72	1				0	0	1

The Template ad3tr4a_TMEAN

NAME	MEAN	TYPE	OBJFUN		CL	V1	Q	V2
CL	6	P	0	CL	0.3			
V1	60	P		V1	0.1	0.8		
Q	30	P		Q	-0.2	0.2	0.5	
V2	100	P		V2	0.2	0.1	-0.2	0.5
SDin	0	N		SDin	0	0	0	0
SDsl	0.1	V		SDsl	0	0	0	0

Simulate Data Set

- **Set nfile=ad3tr4a**
- **Set npopsets=30 <*30 data sets*>**
- **Set npoppats=100 <*100 subjects per data set*>**
- **popsets_simulate**

Sample Data Set File Created: ad3tr4a.tdt

SET	ID	PT	TIME	CONC	DOSE	RATE	E	M	CMT
1	1	1	0.00000E+00	0.00000E+00	0.10000E+03	0.00000E+00	1	1	1
1	1	1	0.25000E+00	0.89936E+00	0.00000E+00	0.00000E+00	0	0	1
1	1	1	0.10000E+01	0.70885E+00	0.00000E+00	0.00000E+00	0	0	1
1	1	1	0.40000E+01	0.34108E+00	0.00000E+00	0.00000E+00	0	0	1
1	1	1	0.24000E+02	0.00000E+00	0.10000E+03	0.20000E+02	1	1	1
1	1	1	0.24000E+02	0.26216E+00	0.00000E+00	0.00000E+00	0	0	1
1	1	1	0.29000E+02	0.87142E+00	0.00000E+00	0.00000E+00	0	0	1
1	1	1	0.36000E+02	0.60785E+00	0.00000E+00	0.00000E+00	0	0	1
1	1	1	0.48000E+02	0.51771E+00	0.00000E+00	0.00000E+00	0	0	1
1	1	1	0.72000E+02	0.34804E+00	0.00000E+00	0.00000E+00	0	0	1
1	2	2	0.00000E+00	0.00000E+00	0.10000E+03	0.50000E+02	1	1	1
1	2	2	0.20000E+01	0.15049E+01	0.00000E+00	0.00000E+00	0	0	1
1	2	2	0.30000E+01	0.11793E+01	0.00000E+00	0.00000E+00	0	0	1

Set Up a Population Analysis Script: ad3tr4a_workshop

```
set pcov(*,*)=0
set pcov(*)=0.5
set pmean(*)=2
set sdsl~=0.3 sdin~=0
del <nfile>_par
del <nfile>_pare
piteraten npopiter=20 vapprox=-4 pmethod=4
```

Analyse All Data Sets

- `Popsets_fit sets=1-30 file=ad3tr4a.`
- `Popsets_summary`

Summary Table

0:Statistic	1:CL	2:V1	3:Q
1:Template Values	6.0	60.0	30.0
2:Mean Reference	6.051	59.67	29.30
3:Mean Estimate	6.053	59.73	29.11
4:			
5:Variability of Reference (%)	4.800	10.06	7.061
6:Variability of Estimate (%)	4.589	10.00	9.292
7:Average Standard Error (%)	5.506	8.997	9.097
8:STD of %Standard Error	0.4791	1.275	1.373
9:			
10:Bias (%)	2.5405E-02	0.1060	-0.4658
11:STD of %Bias	0.7533	2.902	5.759
12:ImPrecision (%)	0.5529	2.361	4.384
13:			
14:Relative Bias Index	0	0	-0.1
15:Confidence Index, 2SE (%)	100	100	100
16:Confidence Index, 3SE (%)	100	100	100

Bayesian Analysis

- Perform EM Analysis
- Perform MCMC Bayesian analysis, Winbugs-like, but within S-ADAPT, to obtain 2.5%, 50%, and 97.5% quantile ranges for estimates.

Bayesian Analysis Results

Parameter	EM Estimate	SE	Bayesian Estimate	SE	q=0.025	q=0.5	q=0.975
CL	4.904	0.083	4.920	0.081	4.760	4.923	5.080
V1	5.156	0.120	5.200	0.115	4.983	5.201	5.432
Q	1.972	0.086	2.023	0.106	1.809	2.023	2.210
V2	9.501	0.321	9.632	0.309	9.006	9.657	10.203
SDsl	0.243	0.012	0.251	0.012	0.226	0.250	0.276
CL~CL	0.184	0.013	0.184	0.012	0.160	0.184	0.209
V1~CL	0.003	0.012	0.002	0.011	-0.018	0.002	0.023
V1~V1	0.138	0.019	0.127	0.016	0.100	0.127	0.159
Q~CL	0.013	0.018	0.012	0.017	-0.017	0.012	0.046
Q~V1	0.043	0.026	0.077	0.024	0.033	0.077	0.131
Q~Q	0.173	0.048	0.173	0.043	0.102	0.171	0.265
V2~CL	0.026	0.015	0.026	0.015	-0.005	0.026	0.058
V2~V1	-0.014	0.021	-0.001	0.019	-0.039	0.000	0.032
V2~Q	0.000	0.024	0.003	0.024	-0.032	-0.005	0.055
V2~V2	0.146	0.027	0.158	0.028	0.115	0.154	0.226

Distributed Computing System

- A means to divide up the labor of the expectation step of each iteration among several computers.
- Manager computer needs network access to local drives of worker computers

Beotable

```
0:ON=1/OFF= 1:Node Name   2:Directory   3:Command
-------------------------------------------------------------
1:1         PK03 (Local)
2:1         PK06 (W)      w:\beo2\      psexec \\pk06 -d -w c:\beo2
                                        c:\beo2\<progname>.exe
3:1         PK05 (V)      v:\beo2\      psexec \\pk05 -d -w c:\beo2
                                        c:\beo2\<progname>.exe
4:1         PK04 (U)      u:\beo2\      psexec \\pk04 -d -w c:\beo2
                                        c:\beo2\<progname>.exe
5:1         PK02 (T)      t:\beo2\      psexec \\pk02  -d -w c:\beo2
                                        c:\beo2\<progname>.exe
6:1         PK01 (S)      s:\beo2\      psexec \\pk01 -d -w c:\beo2
                                        c:\beo2\<progname>.exe
```

Beowulf Setup and Execute

- **Beosetup**
  - Sets up working directory and support files to worker computers
- **Piterate npopiter=100 npopc=3000**
  - With beowulf set to 1, the piterate command automatically parses the job among the workers

Additional S-ADAPT Features

- 2 Stage and 3 Stage Heirarchical Non-Linear Mixed Effects Population Analysis
  - priors on population means and variances may be incorporated
- Inter-occasion variability, population mixtures, and below quantification limit (BQL) data may also be modeled in S-ADAPT.
- Import/Export Facilities, Including for Excel, WinBUGS

S-ADAPT is a Full Package
Exploratory and Population Analysis Program

- Study model, vary parameters and plot curve to see effect
- Plot individual data, and individual curve fits
- Perform population analysis
- Perform Bayesian analysis
- Model Validation Process
- S-ADAPT May be batch controlled by other programs
- S-ADAPT may control other programs
- Batch controlled import and export of data, parameters, etc.

S-ADAPT is Integratable into Your General Analysis Environment

- S-ADAPT does not have extended Plot Diagnostic Features, but….
- General Analysis programs (S-PLUS, RS/1, MATLAB, etc) can control S-ADAPT and obtain results for Additional Analysis

S-ADAPT is Integratable into Your General Analysis Environment

- S-ADAPT is User Versatile
- S-ADAPT is Completely Open-Source
- S-ADAPT is Fully Interactive
- S-ADAPT is Fully Automatable
- S-ADAPT is fully Controllable

Publications: MCPEM Methodology

- Bauer RJ, Guzy S. Monte Carlo parametric expectation maximization (MC-PEM) method for analyzing population pharmacokinetic/pharmacodynamic data. In: D'Argenio DZ, ed. *Advanced Methods of Pharmacokinetic and Pharmacodynamic Systems Analysis.* Vol 3. Boston: Kluwer Academic Publishers; 2004:135-163.
- Bauer RJ, Guzy S, Ng CM. A survey of population analysis methods and software for complex pharmacokinetic and pharmacodynamic models with examples. AAPS Journal 2007;9(1):E60-83
- Ng CM, Bauer RJ. Comparing the scalability of the model converging time for the FO, FOCE, and Laplacian Method in NONMEM and Monte-carlo expectation maximization algorithm in population data analysis. *Poster presentation, American Association of Pharmaceutical Scientist Annual Meeting, San Antonio, TX 2006*
- Ng CM, Bauer RL. The use of beowulf cluster to accelerate the performance of monte-carlo parametric expectation maximization (MCPEM) algorithm in analyzing complex population pharmacokinetic/pharmacodynamic/efficacy data. *Clin Pharmacol Ther 2006;79(2):P54*
- Ng CM, Guzy S, Bauer RL. Validation of Monte-Carlo parametric expectation algorithm in analyzing population pharmacokinetic/pharmacodynamic data. *Clin Pharmacol Ther 2006;79(2):P28*

Publications: Applications in S-ADAPT

- Hong Y, Mager DE, Blum RA, Jusko WJ. Population pharmacokinetic/pharmacodynamic modeling of systemic corticosteroid inhibition of whole blood lymphocytes: modeling interoccasion pharmacodynamic variability. Pharm Res 2007;24(6):1088-97
- Ng CM, Stefanich E, Banmeet SA, Fielder PJ, Vaickus L. Pharmacokinetic/pharmacodynamic of non-depleting anti-CD4 antibody (TRX1) in healthy human volunteer. *Pharm Res 2006;23(1):95-103*
- Ng CM, Joshi A, Dedrick RL, Garovoy MR, Bauer RJ. Pharmacokinetic-pharmacodynamic-efficacy analysis of efalizumab in patients with moderate to severe psoriasis. *Pharm Res 2005;22(7):1088-1100*
- Ricart AD,Tolcher AW, Liu G, Schwartz G, Weiss G, Yazji S, Ng CM, Wilding G. Volociximab (M200, EOS 200-4), a chimeric monoclonal antibody that specifically binds α5β1 integrin: A phase I pharmacokinetic, and biologic correlative study *(Submitted)*
- Ng CM, Bai S, Takimoto CH, Tolcher AW, Yazji S. Mechanism-based receptor-binding model to describe the population pharmacokinetic and pharmacodynamic of an anti-α5β1 integrin monoclonal antibody (voloxicimab) in cancer patients *(in preparation)*
- Ng CM, Takimoto CH, Graham M, Lockwood G. Mechanism-based population pharmacokinetic modeling of unbound and total plasma platinum concentrations of oxaliplatin in cancer patients *(in preparation)*
- Ng CM*, Beeram M, Takimoto CH, Lin C, Patnaik A. A semi-physiological population pharmacodynamic model that can simultaneously describe the chemotherapy-induced thrombocytopenia and neutropenia in cancer patients *(in preparation)*

Presentations on MCPEM at PAGE 2007 (PDX-MCPEM and S-ADAPT)

- **Posters Wednesday Morning (group I)**
- ***P1-15 Robert Bies*** An MCPEM approach to understanding inter-animal and inter-treatment changes with in vivo striatal dopamine clearance in rats
- **P1-25 Serge Guzy** Combining interoccasion variability and mixture within a MCPEM framework
  P1-30 Chee Meng Ng A Comparison of Estimation Methods in Nonlinear Mixed-effect Model for Population Pharmacokinetic-pharmacodynamic Analysis
- **P1-31 Chee Meng Ng** 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
- **Posters Wednesday Afternoon (group II)**
- **P2-20 Douglas Eleveld** Is the expected performance of a target-controlled-infusion system influenced by the population analysis method
- **Posters Thursday Morning (group III)**
- **P3-20 Serge Guzy** Comparison between NONMEM and the Monte-Carlo Expectation Maximization (MC-PEM) Method Using a Physiologically-Based Glucose-Insulin Model