A Comparison of Estimation Methods in Nonlinear Mixed-effect Modeling for Population Pharmacokinetic-pharmacodynamic Analysis

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INTRODUCTION

NONMEM is the current reference software for population pharmacokinetic/ pharmacodynamic (PK/PD) analysis. In the last ten years, a series of new tools for population PK/PD modeling have become available. These include methods based on exact likelihood functions and three-stage Bayesian method. Here we compare population analysis results for several of these programs with results from NONMEM.

OBJECTIVES

To provide a brief overview of the statistical basis of the selected estimation methods and assess the utility of these methods in various population PK/PD modeling problems.

THEORY

A. Two-Stage Nonlinear Mixed Effects Model

Objective function (twice negative logarithm of the joint marginal density) for m subjects:

$$L = -2\sum_{i=1}^{m}\log\left(\int_{-\infty}^{+\infty} l(y_i|\theta,\sigma)h(\theta|\mu,\Omega)d\theta\right)$$

$l(y_i|\theta,\sigma)$ = probability density of observed data (intra-individual variability)

$h(\theta|\mu,\Omega)$ = probability density of parameters among individual (inter- individual variability

GOAL

To find the set of mean population parameters **μ**, population variance **Ω**, and residual error coefficients **σ** that best fit the data from m subjects by maximizing the above marginal density of **y** with respect to **μ**, **Ω**, and **σ** by (or minimizing the objective function *L*)

Classification of the Parametric Two-Stage Nonlinear Mixed Effects Models

Methods based on analytical approximation of the objective function

1. **FO Method**: linearization of data deviation at the inter- and intra-individual error level. (NONMEM FO)
2. **FOCE Method**: linearization of data deviation at the intra-individual error level. (NONMEM FOCE)
3. **EM Methods**
   - **Iterative 2-stage EM (ITS)** linearization of data deviation at the intra-individual data level.

Methods based on exact objective function

1. **Gaussian Quadrature (SAS PROC NLMIXED)**
2. **EM Methods:**
   - **Monte-Carlo Parametric Expectation Maximization (MCPEM)**
     - SADAPT-MCPEM, PDx-MCPEM
   - **Stochastic approximation of EM (SAEM)**
     - MONOLIX

B. Three-Stage Nonlinear Mixed Effects Model/Bayesian Method (WinBUGS)

GOAL

Bayesian three-stage nonlinear mixed effects model does not minimize the objective function. Rather, a series of possible **μ**'s, **Ω**'s, and **σ**'s are collected with a frequency that is based on their likelihood of explaining the data using the following probability:

$$p(\mu,\Omega,\sigma|y,q,H,W,\tau) = \frac{\left\{\prod_{i=1}^{m}\int_{-\infty}^{+\infty} l(y_i|\theta,\sigma)h(\theta|\mu,\Omega)d\theta\right\}\pi(\mu,\Omega,\sigma|q,H,W,\tau)}{\int_{-\infty}^{+\infty}\left\{\prod_{i=1}^{m}\int_{-\infty}^{+\infty} l(y_i|\theta,\sigma)h(\theta|\mu,\Omega)d\theta\right\}\pi(\mu,\Omega,\sigma|q,H,W,\tau)d\mu d\Omega d\sigma}$$

The probability $\pi(.)$ is the distribution of **μ**, **Ω**, and **σ** based on prior knowledge. Typically, the distribution of **μ** is modeled as a normal distribution with a prior mean **q** and variance **H**. The **Ω** inter-individual variance is modeled as a Wishart distribution with prior parameters **W**, and the residual variance **σ** is modeled as a gamma distribution with prior parameter **τ**.

METHODS

Analyses were performed on a Dell Pentium 4 3.20 Ghz computer, with 1 gigabyte non-ECC 400 MHz DDR2 memory, and 80 GB SATA 7200 rpm hard drive with Data Burst Cache. The operating system was Windows XP, and the NONMEM VI, S-ADAPT, and PDx-MCPEM software packages were compiled using Intel Fortran 9.1. The BlackBox/Component Pascal system was used to compile WinBUGS models.

RESULTS AND CONCLUSIONS

DATA SET 1

2-compartment PK model with 2 data points per subjects, 1000 subjects. Dose = 100 units IV bolus dose. Data were simulated at 2 PK sampling times from a discrete set of times: 0.1, 0.2, 0.4, 0.7, 1, 2, 4, 7, 10, 10, 20 40, and 70 times units. All possible pairs of times were equally represented among the subjects.

Table 1: Comparison of Final Parameter Estimates from Different Estimation Methods

Parameter	References	Initial Values	NONMEM FO	NONMEM FOCE	SADAPT ITS	SADAPT MCPEM	MONOLIX	WinBUGS
CL	4.96	2	4.50 (0.0786)	5.30 (0.0873)	4.94 (0.0849)	4.90 (0.078)	4.89 (0.0766)	4.90 (0.0853)
V1	5.06	2	5.52 (0.123)	5.53 (0.116)	5.04 (0.116)	5.16 (0.120)	5.14 (0.0957)	5.16 (0.123)
Q	1.99	2	2.20 (0.0911)	2.03 (0.0761)	1.58 (0.0822)	1.97 (0.0857)	1.96 (0.0478)	1.97 (0.0922)
V2	9.83	2	14.7 (0.422)	10.1 (0.300)	8.36 (0.343)	9.50 (0.321)	9.42 (0.183)	9.50 (0.336)
Var(CL)	0.163	0.8	0.208 (0.0160)	0.190 (0.011)	0.181 (0.0126)	0.184 (0.0128)	0.183 (0.0102)	0.185 (0.0127)
Var(V1)	0.154	0.8	0.155 (0.0251)	0.175 (0.0188)	0.225 (0.0214)	0.138 (0.0129)	0.137 (0.0112)	0.141 (0.0197)
Var(Q)	0.154	0.8	0.242 (0.0682)	0.230 (0.0368)	0.373 (0.0726)	0.173 (0.0481)	0.179 (0.0156)	0.167 (0.0497)
Var(V2)	0.147	0.8	0.153 (0.0561)	0.124 (0.0179)	0.240 (0.0523)	0.146 (0.0269)	0.128 (0.0109)	0.139 (0.0325)
Sigma	0.25	0.25	0.273 (0.0190)	0.205 (0.00937)	0.173 (0.00277)	0.243 (0.0120)	0.244 (0.00691)	0.246 (0.0129)
-2LL			-300.347	-2630.7	-2530.6	-2729.5	-2716.97	-
Computation Time			1 min	3 min	2 h	14 min	11 min	41 min (80000 samples)

Numbers in red – Estimated value more than 3 SE from reference.
Numbers in green – Estimated value more than 2 SE from reference.
Values in () are standard errors of the reported means.

DATA SET 2

One-compartment PK model with first-order elimination and saturable elimination, plus an indirect response PD model, requiring numerical integration of a set of differential equations:

$$\frac{dX_1}{dt} = -k_{10} * X_1 - \frac{V_m * X_1 * X_2}{(K_m + X_1)}$$

$$\frac{dX_2}{dt} = K_{syn} - K_{deg} * X_2 - \frac{V_m * X_1 * X_2}{(K_m + X_1)}$$

Each of 25 simulated subjects received an IV bolus of 100 units followed by an IV infusion of 1000 units over 1 time unit at time 7. PKPD samples were collected at 0.05, 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 5, 7, 7.125, 7.25, 8, 10, 12, 14, 16, 18, 20, 22, 26, and 28 units. The PKPD data were analyzed simultaneously.

Table 2: Comparison of Final Parameter Estimates from Different Estimation Methods

Parameter	References	Initial Values	NONMEM FO[a,b]	NONMEM FOCE[b]	SADAPT ITS	SADAPT MCPEM	PDx-MCPEM	WinBUGS
Vc	47.7	2	110	7.8	47.4 (3.41)	47.9 (2.99)	47.7 (1.3)	47.8 (3.44)
K_{10}	0.0943	2	0.0468	0.0955	0.0959 (0.00583)	0.0943 (0.00543)	0.997 (0.006)	0.0960 (0.00666)
Vm	9.40	2	6.91	9.30	9.28 (0.699)	9.33 (0.689)	9.2 (0.88)	9.21 (0.757)
Km	1.12	2	1.16	1.10	1.09 (0.0698)	1.11 (0.0647)	1.10 (0.10)	1.09 (0.0765)
Ksyn	37.9	2	57.8	37.8	37.7 (2.81)	38.1 (2.67)	37.5 (3.1)	37.6 (2.80)
Kdeg	0.507	2	0.504	0.510	0.507 (0.0341)	0.513 (0.0311)	0.505 (1.2)	0.506 (0.0335)
Var(Vc)	0.101	2	0.667	0.0924	0.0970 (0.126)	0.0963 (0.0271)	0.096	0.127 (0.0393)
Var(K_{10})	0.0795	2	4.49	0.0758	0.0798 (0.286)	0.0774 (0.0227)	0.071	0.118 (0.0393)
Var(Vm)	0.133	2	0.0748	0.122	0.129 (0.325)	0.131 (0.0380)	0.122	0.166 (0.0526)
Var(Km)	0.0725	2	0.841	0.0710	0.0756 (0.0973)	0.0721 (0.0231)	0.070	0.112 (0.0371)
Var(Ksyn)	0.130	2	0.414	0.109	0.116 (0.466)	0.118 (0.0339)	0.103	0.137 (0.0426)
Var(Kdeg)	0.0932	2	0.119	0.0808	0.0829 (0.366)	0.0845 (0.0251)	0.080	0.107 (0.0334)
Sigma_PK	0.1	0.3	0.817	0.0957	0.0940 (0.00356)	0.0956 (0.0363)	0.096	0.0964 (0.00359)
Sigma_PD	0.15	0.3	0.314	0.147	0.0148 (0.00490)	0.0147 (0.00449)	0.0147	0.147 (0.00452)
-2LL			-96.732	-4028.374	-4027.4	-4027.1	-4013	
Computation Time			3 min, 1 restart	8 hr, 1 restart	5.5 min	12 min	30 min	9.8 h (70000 samples)

[a] Best final estimates were obtained by fitting the model to log-transformed data.
[b] Standard error could not obtained for NONMEM FO and FOCE methods, so those of WinBUGs were used for assessing the relative deviation from references. Numbers in red – Estimated value more than 3 SE from reference. Values in () are standard errors of the reported means.
MONOLIX 1.1 version did not support differential equation solver and was not tested in DATA SET 2

Table 3: Quantiles from Bayesian Analysis in S-ADAPT and WinBUGS (Percentile of the Model Parameters)

Parameter	S-ADAPT 0.025	WinBUGS 0.025	S-ADAPT 0.5	WinBUGS 0.5	S-ADAPT 0.975	WinBUGS 0.975
Vc	42.4	41.6	48.4	47.7	54.5	55.3
K10	0.0830	0.0840	0.0943	0.0960	0.1065	0.1103
VM	7.74	7.81	9.28	9.23	11.0	10.8
Kmc	0.966	0.944	1.13	1.09	1.34	1.25
K02	33.0	32.5	38.0	37.6	43.5	43.6
K20	0.455	0.444	0.510	0.506	0.585	0.576
SD1	0.0881	0.0897	0.0961	0.0963	0.103	0.104
SD2	0.137	0.139	0.147	0.147	0.157	0.157
Var(Vc)	0.0692	0.0720	0.121	0.120	0.246	0.223
Var(K10)	0.0580	0.0657	0.0947	0.111	0.185	0.210
Var(Vm)	0.0869	0.0919	0.161	0.157	0.326	0.298
Var(Kmc)	0.0455	0.0594	0.0994	0.105	0.210	0.202
Var(K02)	0.0727	0.0774	0.138	0.129	0.264	0.242
Var(K20)	0.0649	0.0602	0.106	0.100	0.171	0.189

WinBUGS took 80 minutes to complete 10000 random samples, S-ADAPT took 50 minutes.

CONCLUSIONS:

1. Monte Carlo EM algorithms (S-ADAPT, MONOLIX, PDx-MCPEM) can provide accurate results with sparse or rich data
2. MCPEM methods perform more slowly than NONMEM FOCE for simple models, but perform more quickly and requires fewer interventions than NONMEM FOCE for complex models.
3. WinBUGs provides accurate assessments of the population parameters and standard error for both simple and complex models.
4. WinBUGS and S-ADAPT provided additional Bayesian analysis, allowing assessment of quantile ranges on the uncertainties of the parameters. The two programs provided similar results.

REFERENCE:

1. Bauer RJ, Guzy S, Ng C. A survey of population analysis methods and software for complex pharmacokinetic and pharmacodynamic models with examples. *The AAPS Journal* 2007;9(1):E60-83