Comparison of Implementation of a Bayesian Approach to Nonlinear Mixed Effects Model in SAS® and WinBUGS
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ABSTRACT
Nonlinear mixed-effects models are powerful tools for the analysis of unbalanced longitudinal data. Bayesian method is applied to estimate the parameters by incorporating the prior information for the parameters. The posterior distribution of the parameters and variance components are estimated and compared using SAS® MCMC procedure and WinBUGS. SAS® NLMIXED procedure is also used for implementation of nonlinear mixed effects model and comparison.

The method is illustrated by the estimation of a growth curve model for the simulated growth data set.

The MCMC procedure requires SAS®/STAT 9.2 and later. The author expects intended audience to be familiar with growth curves, mixed effects model and Bayesian method.

INTRODUCTION
Bayesian implementation of nonlinear mixed effects model has gained much attention due to its advantage of incorporating prior knowledge of parameters of interest. Both SAS® PROC MCMC and WinBUGS could be used to implement the Bayesian formulation of nonlinear mixed effects model.

SIMULATED GROWTH DATA
In the simulated dataset, 960 valid observations are generated for 122 subjects. Each of the observations consists of 3 variables: Month, Growth and Subject ID. Since subjects have different numbers of repeated measurements at different time points, the simulated data is referred to as unbalanced longitudinal data.

GROWTH CURVE MODEL
Based on the scatter plot of simulated growth data, we use model \( \mu(t) = \alpha - \beta \cdot \gamma^t \) to describe the pattern of growth with respect to time, with \( \alpha > 0, \beta > 0, 0 < \gamma < 1 \). And the model can be parameterized as a Mitscherlich growth curve model
\[
\mu(t) = \exp(\theta_2) \{1 + \exp(\theta_1 - \theta_2) - 1 \} \cdot \exp(-\theta_3 t) \in \text{the case} \quad \theta_2 > 0 \quad \text{and} \quad \theta_3 > 0.
\]

Figure 1. Profiles of growth data for 122 subjects

NONLINEAR MIXED EFFECTS MODEL FOR GROWTH CURVE
For growth curve model \( \mu(t) = \alpha - \beta \cdot \gamma^t \), we introduce the following nonlinear mixed effects model for unbalanced longitudinal data:
\[
Y_{ij} = (\alpha_i + \alpha) - (\beta_i + \beta) \cdot y^{x_i} + \varepsilon_{ij}, \text{where} \quad \alpha_i \sim N(0, \sigma_\alpha^2), \beta_i \sim N(0, \sigma_\beta^2) \text{and}
\]
\[ \varepsilon_j \sim N(0, \sigma^2) \text{ iid.} \]

**IMPLEMENTATION IN SAS®**

**SAS® PROC MCMC**

PROC MCMC code:

```sas
proc mcmc data=nlm nmc=20000 outpost=postout
   seed=123456 init=random;
ods select Parameters REParameters PostSummaries;

parms alpha 50 beta 14 r 0.8 sigma2 100 sigma2a 100 sigma2b 100;

prior sigma2~igamma(0.01,scale=0.01);
prior alpha~igamma(0.01,scale=0.01);
prior beta~igamma(0.01,scale=0.01);
prior sigma2a~igamma(0.01,scale=0.01);
prior sigma2b~igamma(0.01,scale=0.01);
prior r~beta(0.01,0.01);

random a~normal(0,var=sigma2a) subject=Subject_ID monitor=(a);
random b~normal(0,var=sigma2b) subject=Subject_ID monitor=(b);
part1=alpha+a;
part2=beta+b;
u=part1-part2*r**Month;
model Growth~normal(u,var=sigma2);
run;
```

Procedure MCMC used 48.91 seconds (real time).

**SAS® PROC NLMIXED**

PROC NLMIXED code:

```sas
proc nlmixed data=nlm nmc=20000 outpost=postout
   seed=123456 init=random;
ods select Parameters REParameters PostSummaries;

parms alpha 50 beta 14 r 0.8 sigma2 100 sigma2a 100 sigma2b 100;

prior sigma2~igamma(0.01,scale=0.01);
prior alpha~igamma(0.01,scale=0.01);
prior beta~igamma(0.01,scale=0.01);
prior sigma2a~igamma(0.01,scale=0.01);
prior sigma2b~igamma(0.01,scale=0.01);
prior r~beta(0.01,0.01);

random a~normal(0,var=sigma2a) subject=Subject_ID monitor=(a);
random b~normal(0,var=sigma2b) subject=Subject_ID monitor=(b);
part1=alpha+a;
part2=beta+b;
u=part1-part2*r**Month;
model Growth~normal(u,var=sigma2);
run;
```

Output 1. Output from PROC MCMC statement.
Comparison of Implementation of a Bayesian Approach to Nonlinear Mixed Effects Model in SAS® and WinBUGS

```sas
proc nlmixed data=nlm method=firo;
   parms b1=50 b2=14 b3=0.8 s3u1=100 s3u2=100 c12=0 s3e=100;
   part1=b1+u1;
   part2=b2+u2;
   model Growth ~ normal(part1-part2*b3**Month, s3e);
   random u1 u2 ~ normal([0,0],[s3u1,c12,s3u2]) subject=Subject_ID;
run;
```

<table>
<thead>
<tr>
<th>Fit Statistics</th>
</tr>
</thead>
<tbody>
<tr>
<td>-2 Log Likelihood</td>
</tr>
<tr>
<td>AIC (smaller is better)</td>
</tr>
<tr>
<td>AICC (smaller is better)</td>
</tr>
<tr>
<td>BIC (smaller is better)</td>
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</table>

<table>
<thead>
<tr>
<th>Parameter Estimates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parameter</td>
</tr>
<tr>
<td>b1</td>
</tr>
<tr>
<td>b2</td>
</tr>
<tr>
<td>b3</td>
</tr>
<tr>
<td>s3u1</td>
</tr>
<tr>
<td>s3u2</td>
</tr>
<tr>
<td>c12</td>
</tr>
<tr>
<td>s3e</td>
</tr>
</tbody>
</table>

Output 2. Output from PROC NLMIXED statement.

**IMPLEMENTATION IN WINBUGS**

Use WinBUGS to do iteration 20000 times with the first 10000 times as burn-in runs. WinBUGS code:

```winbugs
model{
  for( j in 1 : N) {
    y[j] ~ dnorm(mu[j], tau)
    mu[j] <- (a+ran.a[Subject[j]])-(b+ran.b[Subject[j]])*pow(r,x[j])
  }
  a~dgamma(0.001,0.001)
  b~dgamma(0.001,0.001)
  r~dbeta(0.001,0.001)
  tau~dgamma(0.001, 0.001)
  sigmavu.square <- 1/tau
  for(i in 1:NumSubj) {
    ran.a[i] ~ dnorm(0.0, tau.a)
  }
  tau.a~dgamma(0.001, 0.001)
  sigmavu.square<-1/tau.a
  for(i in 1:NumSubj) {
    ran.b[i] ~ dnorm(0.0, tau.b)
  }
  tau.b~dgamma(0.001, 0.001)
  sigmabu.square<-1/tau.b
}
```
Comparison of Implementation of a Bayesian Approach to Nonlinear Mixed Effects Model in SAS® and WinBUGS

<table>
<thead>
<tr>
<th>Node statistics</th>
<th>node</th>
<th>mean</th>
<th>sd</th>
<th>MC error</th>
<th>2.5%</th>
<th>median</th>
<th>97.5%</th>
<th>start</th>
<th>sample</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>50.05</td>
<td>0.1326</td>
<td>0.008292</td>
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<td>50.05</td>
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<tr>
<td>b</td>
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<td>0.1634</td>
<td>0.008068</td>
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<td>14.72</td>
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<tr>
<td>deviance</td>
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<td>27.2</td>
<td>0.4944</td>
<td>2242.0</td>
<td>2292.0</td>
<td>2347.0</td>
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<td>10000</td>
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<tr>
<td>r</td>
<td>0.8641</td>
<td>0.002068</td>
<td>6.31E-5</td>
<td>0.8599</td>
<td>0.8642</td>
<td>0.8681</td>
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<td>10000</td>
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</tr>
<tr>
<td>sigmau.squared</td>
<td>1.812</td>
<td>0.2591</td>
<td>0.003383</td>
<td>1.37</td>
<td>1.792</td>
<td>2.384</td>
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<td>10000</td>
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</tr>
<tr>
<td>sigmabu.squared</td>
<td>2.743</td>
<td>0.4614</td>
<td>0.008551</td>
<td>1.946</td>
<td>2.708</td>
<td>3.765</td>
<td>10001</td>
<td>10000</td>
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</tr>
<tr>
<td>sigmau.squared</td>
<td>0.639</td>
<td>0.03484</td>
<td>5.233E-4</td>
<td>0.5744</td>
<td>0.6379</td>
<td>0.711</td>
<td>10001</td>
<td>10000</td>
<td></td>
</tr>
</tbody>
</table>

DIC

\[
D_{\text{bar}} = \text{post.mean of } -2\log L; \quad D_{\text{hat}} = -2\log L \text{ at post.mean of stochastic nodes}
\]

<table>
<thead>
<tr>
<th></th>
<th>Dbar</th>
<th>Dhat</th>
<th>pD</th>
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</thead>
<tbody>
<tr>
<td>y</td>
<td>2292.620</td>
<td>2086.840</td>
<td>205.779</td>
<td>2498.390</td>
</tr>
<tr>
<td>total</td>
<td>2292.620</td>
<td>2086.840</td>
<td>205.779</td>
<td>2498.390</td>
</tr>
</tbody>
</table>

Output 3. Output from WinBUGS.

WinBUGS takes 63 seconds to run 20000 times to obtain the posterior statistics of the parameters.

CONCLUSION

To implement Bayesian nonlinear mixed effects model, SAS® PROC MCMC and WinBUGS are two good choices. They produce very close results but SAS® PROC MCMC is faster in the implementation, and we expect the speed difference would be even larger when the data size grows. When the priors for the parameters are non-informative, the results produced by SAS® PROC NLMIXED are also very close to those generated by SAS® PROC MCMC and WinBUGS for implementation of Bayesian nonlinear mixed effects model.

REFERENCES


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CONTACT INFORMATION

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