Delta Method Application: Landmark Prediction and Confidence Interval for a Non-Linear Longitudinal Model

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Introduction

Longitudinal model based meta-analysis (MBMA) is performed, using all the relevant in-house and published data, to better understand efficacy and safety characteristics of competitor drugs alongside compounds in development. However, in the Drug Development process new compounds often need to show differentiation from standard of care for a landmark endpoint to meet strategy decisions.

Objectives

To compare four different methods for producing a landmark prediction standard error and confidence interval from a longitudinal model

Longitudinal Model

A non-linear longitudinal model was fitted to summary level, NIH CPSI (National Institute of Health Chronic Prostatitis Symptom Index) Total Score data for the three As of accepted care (A1 Adreno-receptor antagonist, Anti-Inflammatory & NSAID) and placebo. The final model was a 3 parameter E_{max} model over time and was fitted using NONMEM.

$$Total_{ij}(t_j) = base + \eta_{bi} + \eta_{bik} + \frac{(\max_{Placebo} + \eta_{pi} + \max_{Active} + \eta_{ai} + \eta_{aik}) \cdot t_j}{\exp(Et_{50}) + t_j} + \frac{\varepsilon_{ij}}{\sqrt{n_{ij}}}$$

- 3 parameter Emax across time
  - Baseline
  - Maximum Placebo Effect
  - Maximum Active Effect
  - Et50 (time to half maximal effect)
- Random Effects
  - Baseline [*b*]
  - Max Active [*a*] and Max Placebo [*p*] (between)
- Inter-Occasion Variability
  - Baseline [*bk*](4)
  - Max Active [*ak*](3, within)
- Residual Sigma
  - Weighted by sqrt n
- Note [*i*] = Study

Parameter Estimates

Parameter	Estimate	SE
base	24.1	0.615
$max_{Placebo}$	-4.37	1.02
max_{Active}	-9.15	1.2
Et_{50}	0.52	0.131

Parameter Variance/Covariance Matrix

	base	$max_{Placebo}$	max_{Active}	Et_{50}
base	0.378			
$max_{Placebo}$	-0.319	1.05		
max_{Active}	-0.147	-0.1	1.45	
Et_{50}	-0.0539	0.0525	0.0725	0.0171

Methods

Differentiation from standard of care would be required at 6 hours post dose by the product concept for a drug in development.

Four methods were employed and compared to calculate the landmark prediction standard error and confidence interval for the standard of care difference from placebo:

- Simulation in NONMEM, altering the model file to incorporate parameter uncertainty with post processing calculation of the prediction StdErr.
- Simple simulation in R, sampling from the multivariate normal distribution
- Calculating the Delta Method[1] formulae for the model from first principles and implementing in R
- Utilising the Delta Method function in the R msm package[2]

1. Simulation in NONMEM, altering the model file to incorporate parameter uncertainty.

NONMEM Model

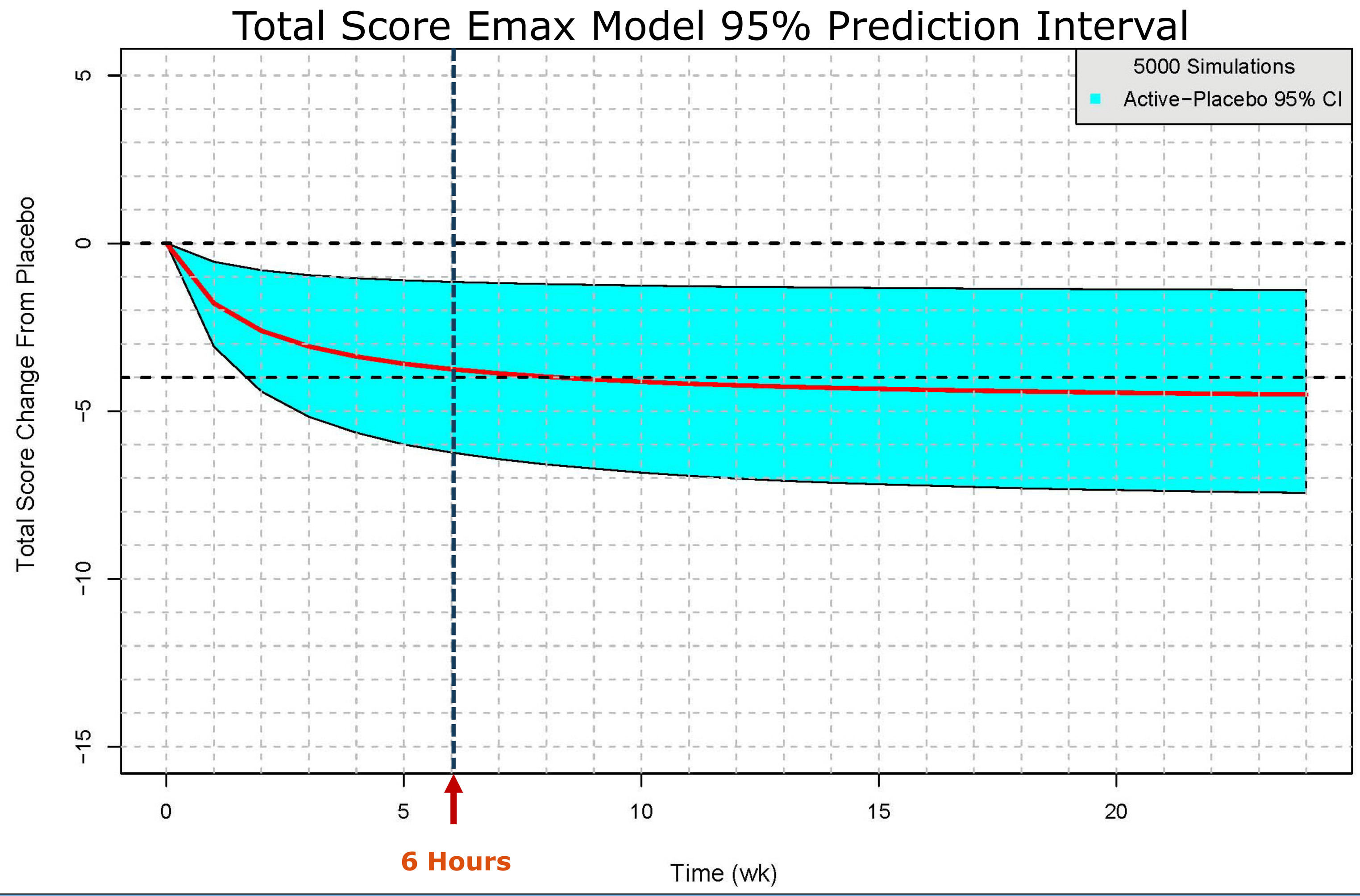
```
$PRED
;------------ EMAX MODEL ----------------
E0=THETA(1)+ ETA(1)
MAXP=THETA(2)+ ETA(2)
MAXA=THETA(3)+ ETA(3)
TE50=EXP(THETA(4)+ ETA(4))
PB = E0 + ((MAXP*TIME)/(TE50+TIME))
ACT= E0 + ((MAXA*TIME)/(TE50+TIME))
RESP=PB*PBO +ACT*ACTV
F=RESP
IPRE=F
Y=F+(ERR(1)* SQRT(1/N))
```

Alter Model: One ETA for each parameter to simulate uncertainty

```
;------------INITIAL ESTIMATES -----------------------
$THETA (24.1)
$THETA (-4.37)
$THETA (-9.15)
$THETA (0.52)
$OMEGA BLOCK (4)
  0.378                          ; E0 parameter uncertainty
 -0.319   1.05                   ; MAXP parameter uncertainty
 -0.147  -0.1    1.45            ; MAXA parameter uncertainty
 -0.0539  0.0525 0.0725  0.0171  ; TE50 parameter uncertainty

$SIGMA 0 FIX
;
$SIMULATE (9999999) SUBPROBLEMS=5000 ONLYSIMULATION
```

Total Score Emax Model 95% Prediction Interval



2. A simple simulation in R using parameter uncertainty.

R Code

```
library(mvtnorm)
x <- rmvnorm(n=10000, mean=mean,
sigma=cova)
colMeans(x)
var(x)
xsave<-data.frame(x)

names(xsave)<-c("x1","x2","x3")
attach(xsave)
```

```
y<-(x1*6/(exp(x3)+6))-(x2*6/(exp(x3)+6))
m.y<-mean(y)
sd.y<-sd(y)

#95%
m.y-(1.96*sd.y)
m.y+(1.96*sd.y)
```

3. Calculating the Delta Method formulae for the model and implementing using matrix multiplication in R.

The Delta Method: A general method for finding the variance of a non-linear function of one or more variables (frequently the estimator(s) of parameter(s) of interest)

Calculating the std error of a prediction based on an example E_{max} model:

Prediction at time t_j : $\hat{y} = \hat{E}_0 + \frac{\hat{E}_{max} t_j}{e^{\hat{\theta}} + t_j}$ Where $\hat{E}T_{50} = e^{\hat{\theta}}$

Variance of prediction: $Var(\hat{E}_0) + Var\left(\frac{\hat{E}_{max} t_j}{e^{\hat{\theta}} + t_j}\right) + 2Cov\left(\hat{E}_0, \frac{\hat{E}_{max} t_j}{e^{\hat{\theta}} + t_j}\right)$

The standard error is the square root of this variance.

To evaluate the second and third terms we use the delta method for calculating the variance of a function of random variable.

2nd Term: $Var\left(\frac{\hat{E}_{max} t_j}{e^{\hat{\theta}} + t_j}\right)$ Let $f = f(E_{max}, \theta) = \frac{E_{max} t_j}{e^{\theta} + t_j}$, $\frac{\partial f}{\theta} = \frac{-E_{max} t_j e^{\theta}}{(e^{\theta} + t_j)^2}$, $\frac{\partial f}{E_{max}} = \frac{t_j}{e^{\theta} + t_j}$

Taylor series:

$$Var\left(\frac{\hat{E}_{max} t_j}{e^{\hat{\theta}} + t_j}\right) = \left(\frac{\partial f}{E_{max}}\right)^2 Var(\hat{E}_{max}) + \left(\frac{\partial f}{\theta}\right)^2 Var(\hat{\theta}) + 2\left(\frac{\partial f}{E_{max}}\right)\left(\frac{\partial f}{\theta}\right) Cov(\hat{E}_{max}, \hat{\theta})$$

$$= \frac{E^2_{max} t^2_j}{(e^{\theta} + t_j)^2}\left[\frac{Var(\hat{E}_{max})}{E^2_{max}} + \frac{e^{2\theta} Var(\hat{\theta})}{(e^{\theta} + t_j)^2} - 2\frac{e^{\theta} Cov(\hat{E}_{max}, \hat{\theta})}{E_{max}(e^{\theta} + t_j)}\right]$$

3rd Term:

$$Cov\left(\hat{E}_0, \frac{\hat{E}_{max} t_j}{e^{\hat{\theta}} + t_j}\right) = \left(\frac{\partial E_0}{E_0}\right)\left(\frac{\partial\left[\frac{E_{max} t_j}{e^{\theta} + t_j}\right]}{E_{max}}\right) Cov(\hat{E}_0, \hat{E}_{max}) + \left(\frac{\partial E_0}{E_0}\right)\left(\frac{\partial\left[\frac{E_{max} t_j}{e^{\theta} + t_j}\right]}{\theta}\right) Cov(\hat{E}_0, \theta)$$

$$= (1)\frac{t_j}{e^{\theta} + t_j} Cov(\hat{E}_0, \hat{E}_{max}) + (1)\frac{-E_{max} t_j e^{\theta}}{(e^{\theta} + t_j)^2} Cov(\hat{E}_0, \hat{\theta})$$

Therefore prediction at time t_j : $Var(\hat{y}) = Var(\hat{E}_0)$

$$+ \frac{E^2_{max} t^2_j}{(e^{\theta} + t_j)^2}\left[\frac{Var(\hat{E}_{max})}{E^2_{max}} + \frac{e^{2\theta} Var(\hat{\theta})}{(e^{\theta} + t_j)^2} - 2\frac{e^{\theta} Cov(\hat{E}_{max}, \hat{\theta})}{E_{max}(e^{\theta} + t_j)}\right] + 2\left(\frac{t_j}{e^{\theta} + t_j} Cov(\hat{E}_0, \hat{E}_{max}) + \frac{-E_{max} t_j e^{\theta}}{(e^{\theta} + t_j)^2} Cov(\hat{E}_0, \hat{\theta})\right)$$

R Code

```
# Calculate difference at 6 weeks ACT
#(MAXA*6)/(TE50+6))-((MAXP*6)/(TE50+6))
Pchg<-(A*t/(T+t))-(P*t/(T+t))

# Delta Method Matrix Multiplication
# Two functions
#f1 = (A*t)/(exp(theta)+t)
#f2 = (P*t)/(exp(theta)+t)

# differentiate with respect to each parameter
df1.A <- t/(T+t)
df1.P <- 0
df1.theta <- -(A*t*T)/((T+t)**2)
df1 <- c(df1.A,df1.P,df1.theta)
```

[0.7810438 0 1.5647816]

```
df2.A <- 0
df2.P <- t/(T+t)
df2.theta <- -(P*t*T)/((T+t)**2)
df2 <- c(df2.A,df2.P,df2.theta)
```

[0 0.7810438 0.7473329]

Delta Method Function 1

$$\left(\frac{\partial f_1}{E_{maxA}}\right)^2 Var(\hat{E}_{maxA}) + \left(\frac{\partial f_1}{\theta}\right)^2 Var(\hat{\theta}) + 2\left(\frac{\partial f}{E_{maxA}}\right)\left(\frac{\partial f}{\theta}\right) Cov(\hat{E}_{maxA}, \hat{\theta})$$

```
# Matrix multiplication
```

Delta Method Function 2

```
Pchg.SE <-sqrt((t(df1)%*%COV.mat%*%df1)+(t(df2)%*%COV.mat%*%df2)
        -(2*(t(df1)%*%COV.mat%*%df2)))))
```

Delta Method Function 1, Function 2

```
#95%
Pchg-(1.96*Pchg.SE)
Pchg+(1.96*Pchg.SE)
```

4. Utilising the delta method function in the R msm package

R Code

```
library(msm)

# Calculate difference from placebo at 6 weeks

#Parameters
#E0 24.1
#MaxP -4.37          :x2
#MaxA -9.15          :x1
#TE50=EXP(0.52)     :x3

# ACT - PB at 6 weeks
#(MAXA*6)/(TE50+6))-((MAXP*6)/(TE50+6))
Pchg<-(-9.15*6/(exp(0.52)+6))-(-4.37*6/(exp(0.52)+6))
```

```
# Delta Method
mean<-c(-9.15,-4.37,0.52)
cova<-matrix(c(1.45,-0.1,0.0725,-
0.1,1.05,0.0525,0.0725,0.0525,0.0171),nrow=3)
Pchg.SE<-deltamethod(~(x1*6/(exp(x3)+6))-(x2*6/(exp(x3)+6)),mean,cova)

#95%
Pchg-(1.96*Pchg.SE)
Pchg+(1.96*Pchg.SE)
```

Results

All four methods produced similar results.

	Difference	StdErr	95% Lower	95% Upper
NONMEM Simulation	-3.736108	1.281891	-6.23505	-1.15085
Simple Simulation	-3.72785	1.303936	-6.283564	-1.172136
Delta Matrix Multiplication	-3.733389	1.297707	-6.276896	-1.189883
Delta Function	-3.733389	1.297707	-6.276896	-1.189883

Conclusions

The Delta Method is a quick method to produce prediction standard errors.

The Delta Method function in R gives the same result and removes the need for differentiation and computer intensive simulation.

References

[1] Oehlert, G. W. A note on the delta method. American Statistician 46(1), 1992

[2] Christopher H. Jackson (2011). Multi-State Models for Panel Data: The msm Package for R. Journal of Statistical Software, 38(8), 1-29

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