THE UTILITY OF MIXED-EFFECT MODELS IN THE EVALUATION OF COMPLEX GENOMIC TRAITS IN-VITRO

Supplementary Data: Diagnostic Plots (with Code)

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Data Availability:

R Scripts and data necessary to reproduce our analysis are available and can be cloned using the following public repository. (http://nathanalade.github.io/In-Vitro-NLME/)

Final Model Residual Plots (UM/EM)

Rich Study Designs (0-20% CV)

```
par(mfrow = c(1, 2))
plot(rich_covar.nlme, main = "UM/EM Rich (0% CV)")
plot(rich_CV5_covar.nlme, main = "UM/EM Rich (5% CV)")
plot(rich_CV10_covar.nlme, main = "UM/EM Rich (10% CV)")
plot(rich_CV20_covar.nlme, main = "UM/EM Rich (20% CV)")
                       UM/EM Rich (0% CV)
                                                                                        UM/EM Rich (5% CV)
 Standardized residuals
                                                                   Standardized residuals
                                                 1500
                                                                                                                     1500
                             Fitted values
                                                                                               Fitted values
                      UM/EM Rich (10% CV)
                                                                                       UM/EM Rich (20% CV)
                                                                                                              0
                                            0
 Standardized residuals
                                                                   Standardized residuals
                                    0
                         500
                                        1000
                                                        1500
                                                                                          500
                                                                                                          1000
                                                                                                                         1500
                             Fitted values
                                                                                               Fitted values
```

Sparse Study Designs (3pt, 0-20% CV)

```
par(mfrow = c(1, 2))
plot(sparse3pt_covar.nlme, main = "UM/EM Sparse (3pt, 0% CV)")
plot(sparse3pt_CV5_covar.nlme, main = "UM/EM Sparse (3pt, 5% CV)")
plot(sparse3pt_CV10_covar.nlme, main = "UM/EM Sparse (3pt, 10% CV)")
plot(sparse3pt_CV20_covar.nlme, main = "UM/EM Sparse (3pt, 20% CV)")
                   UM/EM Sparse (3pt, 0% CV)
                                                                                   UM/EM Sparse (3pt, 5% CV)
                                                                 Standardized residuals
 Standardized residuals
                                                                                                                      o
          8
                                   1000
                                                1500
                                                                                                        1000
                      500
                                                                                        500
                                                                                                                        1500
                            Fitted values
                                                                                            Fitted values
                  UM/EM Sparse (3pt, 10% CV)
                                                                                  UM/EM Sparse (3pt, 20% CV)
                                                0
 Standardized residuals
                                                                 Standardized residuals
                                                0
                                                       0
                                                                                                   0
                                                     8
                                                                                                                      0
                                                0
                                        1000
                                                        1500
                                                                                                       1000
                                                                                                                       1500
          0
                         500
                                                                                        500
                                                                         0
                            Fitted values
                                                                                            Fitted values
```

Sparse Study Designs (4pt, 0-20% CV)

```
par(mfrow = c(1, 2))
plot(sparse4pt_covar.nlme, main = "UM/EM Sparse (4pt, 0% CV)")
plot(sparse4pt_CV5_covar.nlme, main = "UM/EM Sparse (4pt, 5% CV)")
plot(sparse4pt_CV10_covar.nlme, main = "UM/EM Sparse (4pt, 10% CV)")
plot(sparse4pt_CV20_covar.nlme, main = "UM/EM Sparse (4pt, 20% CV)")
                   UM/EM Sparse (4pt, 0% CV)
                                                                                  UM/EM Sparse (4pt, 5% CV)
 Standardized residuals
                                                                 Standardized residuals
                                                                                                                     8
                                   1000
                                                1500
                                                                                        500
                                                                                                        1000
                                                                                                                       1500
                            Fitted values
                                                                                            Fitted values
                  UM/EM Sparse (4pt, 10% CV)
                                                                                  UM/EM Sparse (4pt, 20% CV)
                                                     °8
 Standardized residuals
                                                                 Standardized residuals
                                                0
                                                                                                   0
                                                                                                                    0 80
                                                                                                   8
                                                    08
                                                                                                                      8
                                   0
                                                0
                                                      0
          Ó
                         500
                                        1000
                                                        1500
                                                                                        500
                                                                                                       1000
                                                                                                                       1500
                                                                         0
                            Fitted values
                                                                                            Fitted values
```

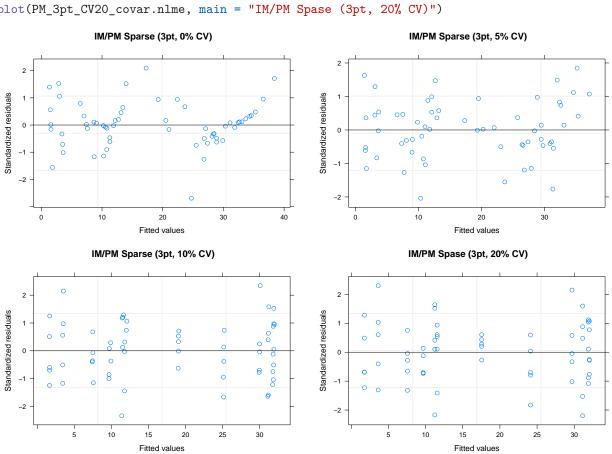
Final Model Residual Plots (IM/PM)

Rich Study Designs (IM/PM, 0-20% CV)

```
par(mfrow = c(1, 2))
plot(PM_covar.nlme, main = "IM/PM Rich (0% CV)")
plot(PM_CV5_covar.nlme, main = "IM/PM Rich (5% CV)")
plot(PM_CV10_covar.nlme, main = "IM/PM Rich (10% CV)")
plot(PM_CV20_covar.nlme, main = "IM/PM Rich (20% CV)")
                       IM/PM Rich (0% CV)
                                                                                        IM/PM Rich (5% CV)
 Standardized residuals
                                                                   Standardized residuals
                             Fitted values
                                                                                               Fitted values
                      IM/PM Rich (10% CV)
                                                                                        IM/PM Rich (20% CV)
 Standardized residuals
                                                                   Standardized residuals
                                   20
                                                                                         10
                                                                                                                     30
                             Fitted values
                                                                                               Fitted values
```

Sparse Study Designs (IM/PM, 3pt, 0-20% CV)

```
par(mfrow = c(1, 2))
plot(PM_3pt_covar.nlme, main = "IM/PM Sparse (3pt, 0% CV)")
plot(PM_3pt_CV5_covar.nlme, main = "IM/PM Sparse (3pt, 5% CV)")
plot(PM_3pt_CV10_covar.nlme, main = "IM/PM Sparse (3pt, 10% CV)")
plot(PM_3pt_CV20_covar.nlme, main = "IM/PM Spase (3pt, 20% CV)")
```



Sparse Study Designs (IM/PM, 4pt, 0-20% CV)

Fitted values

```
par(mfrow = c(1, 2))
plot(PM_4pt_covar.nlme, main = "IM/PM Sparse (4pt, 0% CV)")
plot(PM_4pt_CV5_covar.nlme, main = "IM/PM Sparse (4pt, 5% CV)")
plot(PM_4pt_CV10_covar.nlme, main = "IM/PM Sparse (4pt, 10% CV)")
plot(PM_4pt_CV20_covar.nlme, main = "IM/PM Sparse (4pt, 20% CV)")
                   IM/PM Sparse (4pt, 0% CV)
                                                                                   IM/PM Sparse (4pt, 5% CV)
                                                                                                                      0
 Standardized residuals
                                                                 Standardized residuals
                           0
                                                     88
89
80
                                                                                                                    00
                                                                                                                    000
                                                     0 &
                          0
                                                     0 %
                        10
                                      20
                                                    30
                                                                                       10
                                                                                                     20
                                                                                                                    30
                            Fitted values
                                                                                            Fitted values
                   IM/PM Sparse (4pt, 10% CV)
                                                                                  IM/PM Sparse (4pt, 20% CV)
                                                     0
 Standardized residuals
                                                      \infty
                                                                 Standardized residuals
                                                                                                                     0
                                                                                          8
                                                    0
                                                                                                                    . 8
                                              0
                                                                                                                     0
                                                     30
                        10
                                      20
                                                                         Ó
                                                                                       10
                                                                                                      20
                                                                                                                     30
```

Fitted values

Predicted vs Observed Plots by CYP2D6 Genotype (UM/EM)

Rich Study Designs

```
par(mfrow = c(1, 2))
plot(rich_covar.nlme,log(V)~log(fitted(.))|Diplotype,
     abline = c(0,1), main = "Rich (0% CV)",
     xlab = "log(Fitted values)")
plot(rich_CV5_covar.nlme, log(V)~log(fitted(.))|Diplotype,
     abline = c(0,1), main = "Rich (5% CV)",
     xlab = "log(Fitted values)")
plot(rich_CV10_covar.nlme, log(V)~log(fitted(.))|Diplotype,
     abline = c(0,1), main = "Rich (10% CV)",
     xlab = "log(Fitted values)")
plot(rich_CV20_covar.nlme, log(V)~log(fitted(.))|Diplotype,
     abline = c(0,1), main = "Rich (20% CV)",
     xlab = "log(Fitted values)")
                    Rich (0% CV)
                                                                        Rich (5% CV)
                 2 3 4 5 6 7
                                                                       4 5 6 7
                                                    log(V)
                              1/2x2
                     log(Fitted values)
                                                                         log(Fitted values)
                    Rich (10% CV)
                                                                        Rich (20% CV)
                 2 3 4 5 6 7
                                                                    2 3 4 5 6 7
                                                          2 3 4 5 6 7
                     log(Fitted values)
                                                                         log(Fitted values)
```

Sparse Study Designs (3pt)

```
par(mfrow = c(1, 2))
plot(sparse3pt_covar.nlme, log(V)~log(fitted(.))|Diplotype,
     abline = c(0,1), main = "Sparse (3pt, 0% CV)",
     xlab = "log(Fitted values)")
plot(sparse3pt_CV5_covar.nlme, log(V)~log(fitted(.))|Diplotype,
     abline = c(0,1), main = "Sparse (3pt, 5% CV)",
     xlab = "log(Fitted values)")
plot(sparse3pt_CV10_covar.nlme, log(V)~log(fitted(.))|Diplotype,
     abline = c(0,1), main = "Sparse (3pt, 10% CV)",
     xlab = "log(Fitted values)")
plot(sparse3pt_CV20_covar.nlme, log(V)~log(fitted(.))|Diplotype,
     abline = c(0,1), main = "Sparse (3pt, 20% CV)",
     xlab = "log(Fitted values)")
                  Sparse (3pt, 0% CV)
                                                                       Sparse (3pt, 5% CV)
                                                     log(V)
                           2 3 4 5 6 7
      2 3 4 5 6 7
                                                           2 3 4 5 6 7
                                                                                2 3 4 5 6 7
                     log(Fitted values)
                                                                          log(Fitted values)
                  Sparse (3pt, 10% CV)
                                                                      Sparse (3pt, 20% CV)
                 2 3 4 5 6 7
                                                                      2 3 4 5 6 7
                                                     log(V)
                            2 3 4 5 6 7
                                                           2 3 4 5 6 7
                                                                                2 3 4 5 6 7
                     log(Fitted values)
                                                                          log(Fitted values)
```

Sparse Study Designs (4pt)

```
par(mfrow = c(1, 2))
plot(sparse4pt_covar.nlme, log(V)~log(fitted(.))|Diplotype,
     abline = c(0,1), main = "Sparse (4pt, 0% CV)",
     xlab = "log(Fitted values)")
plot(sparse4pt_CV5_covar.nlme, log(V)~log(fitted(.))|Diplotype,
     abline = c(0,1), main = "Sparse (4pt, 5% CV)",
     xlab = "log(Fitted values)")
plot(sparse4pt_CV10_covar.nlme, log(V)~log(fitted(.))|Diplotype,
     abline = c(0,1), main = "Sparse (4pt, 10% CV)",
     xlab = "log(Fitted values)")
plot(sparse4pt_CV20_covar.nlme, log(V)~log(fitted(.))|Diplotype,
     abline = c(0,1), main = "Sparse (4pt, 20% CV)",
     xlab = "log(Fitted values)")
                  Sparse (4pt, 0% CV)
                                                                       Sparse (4pt, 5% CV)
                                                     log(V)
                           2 3 4 5 6 7
      2 3 4 5 6 7
                                                           2 3 4 5 6 7
                                                                                2 3 4 5 6 7
                     log(Fitted values)
                                                                          log(Fitted values)
                  Sparse (4pt, 10% CV)
                                                                      Sparse (4pt, 20% CV)
                 2 3 4 5 6 7
                                                                     2 3 4 5 6 7
                                                     log(V)
                            2 3 4 5 6 7
                                                           2 3 4 5 6 7
                                                                                2 3 4 5 6 7
                     log(Fitted values)
                                                                          log(Fitted values)
```

Predicted vs Observed Plots by CYP2D6 Genotype (IM/PM)

Rich Study Designs

```
par(mfrow = c(1, 2))
plot(PM_covar.nlme, log(V)~log(fitted(.))|Diplotype,
     abline = c(0,1), xlab = "log(Fitted values)",
     main = "PM Rich (0% CV)")
plot(PM_CV5_covar.nlme, log(V)~log(fitted(.))|Diplotype,
     abline = c(0,1), xlab = "log(Fitted values)",
     main = "PM Rich (5% CV)")
plot(PM_CV10_covar.nlme, log(V)~log(fitted(.))|Diplotype,
     abline = c(0,1), xlab = "log(Fitted values)",
     main = "PM Rich (10% CV)")
plot(PM_CV20_covar.nlme, log(V)~log(fitted(.))|Diplotype,
     abline = c(0,1), xlab = "log(Fitted values)",
     main = "PM Rich (20% CV)")
                   PM Rich (0% CV)
                                                                      PM Rich (5% CV)
log(V)
                                                    log(V)
                     log(Fitted values)
                                                                         log(Fitted values)
                   PM Rich (10% CV)
                                                                      PM Rich (20% CV)
                                                       2
log(V)
                     log(Fitted values)
                                                                         log(Fitted values)
```

Sparse Study Designs (3pt)

```
par(mfrow = c(1, 2))
plot(PM_3pt_covar.nlme, log(V)~log(fitted(.))|Diplotype,
      abline = c(0,1), xlab = "log(Fitted values)",
      main = "PM Sparse (3pt, 0% CV)")
plot(PM_3pt_CV5_covar.nlme, log(V)~log(fitted(.))|Diplotype,
      abline = c(0,1), xlab = "log(Fitted values)",
      main = "PM Sparse (3pt, 5% CV)")
plot(PM_3pt_CV10_covar.nlme, log(V)~log(fitted(.))|Diplotype,
      abline = c(0,1), xlab = "log(Fitted values)",
      main = "PM Sparse (3pt 10% CV)")
plot(PM_3pt_CV20_covar.nlme, log(V)~log(fitted(.))|Diplotype,
      abline = c(0,1), xlab = "log(Fitted values)",
      main = "PM Sparse (3pt, 20% CV)")
                 PM Sparse (3pt, 0% CV)
                                                                       PM Sparse (3pt, 5% CV)
 (x) gol 2
                                                      (\)bol 2
                      log(Fitted values)
                                                                           log(Fitted values)
                 PM Sparse (3pt 10% CV)
                                                                      PM Sparse (3pt, 20% CV)
                            0.5 1.0 1.5 2.0 2.5 3.0 3.5
                                                                                 0.5 1.0 1.5 2.0 2.5 3.0 3.5
 log(V)
                                                      (×)gol 5
      0.5 1.0 1.5 2.0 2.5 3.0 3.5
                                                          0.5 1.0 1.5 2.0 2.5 3.0 3.5
                      log(Fitted values)
                                                                           log(Fitted values)
```

Sparse Study Designs (4pt)

```
par(mfrow = c(1, 2))
plot(PM_4pt_covar.nlme, log(V)~log(fitted(.))|Diplotype,
     abline = c(0,1), xlab = "log(Fitted values)",
     main = "PM Sparse (4pt, 0% CV)")
plot(PM_4pt_CV5_covar.nlme, log(V)~log(fitted(.))|Diplotype,
     abline = c(0,1), xlab = "log(Fitted values)",
     main = "PM Sparse (4pt, 5% CV)")
plot(PM_4pt_CV10_covar.nlme, log(V)~log(fitted(.))|Diplotype,
     abline = c(0,1), xlab = "log(Fitted values)",
     main = "PM Sparse (4pt, 10% CV)")
plot(PM_4pt_CV20_covar.nlme, log(V)~log(fitted(.))|Diplotype,
     abline = c(0,1), xlab = "log(Fitted values)",
     main = "PM Sparse (4pt, 20% CV)")
                PM Sparse (4pt, 0% CV)
                                                                    PM Sparse (4pt, 5% CV)
    2
 log(V)
                                                    log(V)
                     log(Fitted values)
                                                                         log(Fitted values)
                PM Sparse (4pt, 10% CV)
                                                                    PM Sparse (4pt, 20% CV)
 log(V)
                                                       0
                      log(Fitted values)
                                                                         log(Fitted values)
```