MI210

Phase I Simulation

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Tim Bergsma

1 Purpose

This script simulates subjects for a phase1 study. It creates a NONMEM data set for simulation. After simulation, it harvests the simulated DV. It creates 3 data sets for assembly illustration.

2 Model

Phase 1 subjects are male and female, ages 18-55, mean age about 35. We plan 4 subjects each at doses 1, 5, 10, 50, and 100 ng, to be coded in ug for DV in ug/L (ng/mL). Mean weight is 85(74) kg male(female). Mean height is 176(162) cm male(female). Height variance is 42; log of weight variance is 0.021, covariance of height and log(weight) is .458 per background material. We sample at 14 timepoints: 0, 15min, 30 min, and 1, 2, 3, 4, 6, 8, 12, 18, 24, 48, 72hr. 20 subjects (4 per dose) is repeated for fed and fasted arms: total 40 subjects. These are healthy non-smokers. We assume their BSA-normalized CRCN is random uniform on [80,150].

3 Data Specification

Model input requires a data set with this header:

C ID TIME EVID AMT DV FED WT SMK DS AGE CRCN

4 Subjects

Listing 1:

```
> library(MIfuns)
```

```
MIfuns 3.7.0 loaded
Installing SIGCHLD signal handler...Done.
```

Listing 2:

```
> library(mvtnorm)
> set.seed(1968)
> sigma <- diag(c(.021,42))
> sigma[2,1] <- 0.458
> sigma[1,2] <- 0.458
> sigma
```

```
      [,1]   [,2]
[1,] 0.021  0.458
[2,] 0.458 42.000
```

Listing 3:

```
> males <- as.data.frame(rmvnorm(n=20, mean= c(log(86), 176), sigma = sigma))
> females <- as.data.frame(rmvnorm(n=20, mean= c(log(74), 162), sigma = sigma))
> males$FED <- rep(0:1,each=nrow(males)/2)
> females$FED <- rep(0:1,each=nrow(females)/2)
> males$SEX <- 1
> females$SEX <- 0
> subject <- rbind(males,females)
> names(subject) <- c('lnwt','HEIGHT','SEX','FED')
> subject$WEIGHT <- exp(subject$lnwt)
> subject$AGE <- exp(runif(40,log(18),log(55)))
> mean(subject$AGE)
```

```
[1] 34.46838
```

Listing 4:

```
> subject[] <- lapply(subject,signif,3)
> subject$lnwt <- NULL
> subject$SUBJ <- 1:nrow(subject)
> subject$DOSE <- c(1,5,10,50,100)*1000
> subject
```

```
   HEIGHT SEX FED WEIGHT  AGE SUBJ  DOSE
1     174   0   1   74.2 29.1    1 1e+03
2     177   0   1   80.3 36.8    2 5e+03
3     180   0   1   94.2 46.4    3 1e+04
4     177   0   1   85.2 30.3    4 5e+04
5     166   0   1   82.8 32.5    5 1e+05
6     164   0   1   63.9 18.8    6 1e+03
7     175   0   1   91.6 37.5    7 5e+03
8     168   0   1   89.8 31.8    8 1e+04
9     190   0   1  117.0 47.7    9 5e+04
10    182   0   1   96.8 37.1   10 1e+05
11    180   1   1  114.0 50.6   11 1e+03
12    168   1   1   79.0 27.5   12 5e+03
13    177   1   1  104.0 27.8   13 1e+04
14    169   1   1   76.7 50.7   14 5e+04
15    159   1   1   66.0 24.5   15 1e+05
16    178   1   1   91.5 42.7   16 1e+03
17    178   1   1   98.9 21.0   17 5e+03
18    173   1   1   76.8 49.4   18 1e+04
19    170   1   1   74.7 44.5   19 5e+04
20    181   1   1  103.0 47.9   20 1e+05
21    162   0   0   70.7 21.1   21 1e+03
22    148   0   0   63.2 54.5   22 5e+03
23    167   0   0   89.0 28.4   23 1e+04
24    171   0   0   85.8 28.9   24 5e+04
25    160   0   0   67.9 21.7   25 1e+05
26    166   0   0   86.2 35.9   26 1e+03
27    155   0   0   90.0 35.0   27 5e+03
```

```
28    152   0   0   61.9 39.6   28 1e+04
29    162   0   0   77.2 22.0   29 5e+04
30    159   0   0   61.0 35.4   30 1e+05
31    165   1   0   78.4 20.2   31 1e+03
32    162   1   0   86.6 48.9   32 5e+03
33    175   1   0   86.7 26.2   33 1e+04
34    164   1   0   72.1 39.5   34 5e+04
35    164   1   0   63.1 34.2   35 1e+05
36    165   1   0   81.7 45.6   36 1e+03
37    165   1   0   88.2 22.4   37 5e+03
38    163   1   0   77.5 39.7   38 1e+04
39    164   1   0   74.0 21.7   39 5e+04
40    170   1   0   77.3 22.9   40 1e+05
```

Listing 5:

```
> subject <- subject[,c('SUBJ','HEIGHT','WEIGHT','SEX','AGE','DOSE','FED')]
> subject$SMK <- 0
> subject$DS <- 0
> subject$CRCN <- signif(runif(1:nrow(subject),min=80,max=150),3)
> hr <- c(0,0.25,0.5,1,2,3,4,6,8,12,18,24,48,72)
> pk <- expand.grid(SUBJ=subject$SUBJ,HOUR=hr,DV=NA)
> dose <- data.frame(stringsAsFactors=FALSE, SUBJ=subject$SUBJ,AMT=subject$DOSE,
    HOUR=0)
> pk <- sort(as.keyed(pk,c('SUBJ','HOUR')))
> dose <- as.keyed(dose,c('SUBJ','HOUR'))
> subject <- as.keyed(subject,'SUBJ')
> tran <- as.nm(
+       aug(dose,EVID=1,SEQ=1) +
+       aug(pk,  EVID=0,SEQ=0) |
+       subject
+ )
```

```
outer join of 40 rows and 560 rows on SUBJ, HOUR, EVID, SEQ
left join of 600 rows and 40 rows on SUBJ
```

Listing 6:

```
> names(tran)
```

```
 [1] "C"      "SUBJ"   "TIME"   "SEQ"    "HOUR"   "EVID"   "AMT"    "DV"
 [9] "HEIGHT" "WEIGHT" "SEX"    "AGE"    "DOSE"   "FED"    "SMK"    "DS"
[17] "CRCN"   "ID"     "TAFD"   "TAD"    "LDOS"   "MDV"
```

Listing 7:

```
> spec <- c('C','ID','TIME','EVID','AMT','DV','FED','WEIGHT','SMK','DS','AGE','
    CRCN')
> spec <- c(spec,setdiff(names(tran),spec))
> spec
```

```
 [1] "C"      "ID"     "TIME"   "EVID"   "AMT"    "DV"     "FED"    "WEIGHT"
 [9] "SMK"    "DS"     "AGE"    "CRCN"   "SUBJ"   "SEQ"    "HOUR"   "HEIGHT"
[17] "SEX"    "DOSE"   "TAFD"   "TAD"    "LDOS"   "MDV"
```

Listing 8:

```
> setdiff(spec,names(tran))

character(0)
```

Listing 9:

```
> tran <- tran[,spec]
> write.nm(tran,'../data/ph1/derived/ph1sim.csv')
> write.csv(dose,'../data/ph1/source/dose.csv',row.names=FALSE,quote=FALSE)
> write.csv(subject,'../data/ph1/source/dem.csv',row.names=FALSE,quote=FALSE)
```

5 NONMEM

6 Integrate

After simulation, recover DV.

Listing 10:

```
> sim <- read.table('../nonmem/ph1sim/ph1sim.tab',skip=1,header=TRUE)
> sim <- sim[sim$EVID==0,c('ID','TIME','DV')]
> sim$DV[sim$DV < 0] <- 0
> pk$DV <- NULL
> names(sim) <- c('SUBJ','HOUR','DV')
> pk <- stableMerge(pk,sim)
> pk$DV <- signif(pk$DV,3)
> write.csv(pk,'../data/ph1/source/pk.csv',row.names=FALSE,quote=FALSE,na='.')
```