PKPARA And Effect Estimation

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# Introduction

Here the data corresponds to calculation of pharmacokinetic for dataset we read the dataset.

# Data

rm(list = ls(all=TRUE))  
data=read.csv("D:/CHETANA/DATASET/pkparadata.csv",header = F)

# Seperating time point and concetration corresponding to each subject

ti=data[1,5:20]  
ci=data[2:49,5:20]

# Define function pkpara finding pharmacokinetics

* cmax maximum concentration
* time point at which concentration is maximum
* partial area under curve truncated at the population median of t max
* ke rate constant
* elimination half time
* Area under curve zero to infinity

pkpara=function(ti,ci){  
 pkpara=data.frame("tmax"=0,"cmax"=0,"auct"=0,"aucinf"=0,"thalf"=0,"ke"=0)  
 n=length(ti)  
 pkpara$cmax=max(ci)   
 a=which.max(ci)  
 pkpara$tmax=ti[a]   
 pkpara$auct=sum((ci[2:n]+ci[1:(n-1)])\*(ti[2:n]-ti[1:(n-1)]))  
 pkpara$ke=-2.303\*coefficients(lm(log10(ci[(a+1):n])~ti[(a+1):n]))[2]   
 pkpara$thalf=0.693/pkpara$ke   
 pkpara$aucinf=pkpara$auct+ci[n]/pkpara$ke  
 return(pkpara)  
}

# 

out=pkpara(as.numeric(unlist(ti)),as.numeric(unlist(ci[1,])))  
for(i in 2:48){  
 out[i,]=pkpara(as.numeric(unlist(ti)),as.numeric(unlist(ci[i,])))  
}  
out

## tmax cmax auct aucinf thalf ke  
## 1 2.00 10.423 68.87025 69.79368 1.963006 0.3530299  
## 2 1.75 8.016 53.11175 54.42395 2.337678 0.2964480  
## 3 2.00 10.868 58.31750 59.59640 2.032755 0.3409167  
## 4 2.25 8.120 49.31525 50.34711 2.277313 0.3043059  
## 5 2.25 6.925 44.22225 45.84888 2.477481 0.2797196  
## 6 2.25 8.795 58.71875 60.18468 2.330028 0.2974213  
## 7 1.75 10.485 66.56325 67.81949 2.048418 0.3383099  
## 8 2.25 10.279 55.30425 56.48795 2.066254 0.3353895  
## 9 2.00 9.531 55.96900 56.84600 1.986138 0.3489184  
## 10 1.75 8.238 52.37450 53.73041 2.205744 0.3141796  
## 11 2.25 8.026 43.70900 44.45721 2.041364 0.3394789  
## 12 2.00 10.553 58.37725 59.24153 1.907471 0.3633083  
## 13 2.25 6.857 35.74500 36.21033 2.002962 0.3459877  
## 14 2.00 11.547 68.54850 70.09539 2.152599 0.3219364  
## 15 1.75 8.176 47.74925 49.20425 2.291618 0.3024064  
## 16 1.75 6.926 37.95700 38.91297 2.268796 0.3054483  
## 17 2.25 5.987 34.39075 35.10460 2.150872 0.3221949  
## 18 2.00 10.166 68.75125 70.06496 2.142124 0.3235107  
## 19 2.25 6.857 38.26000 38.70740 1.925757 0.3598584  
## 20 2.00 11.547 67.65650 69.06187 2.117222 0.3273157  
## 21 1.50 8.070 48.22425 49.68781 2.305103 0.3006373  
## 22 2.25 7.776 38.72425 39.23220 1.934128 0.3583010  
## 23 2.00 11.184 63.02450 64.36208 1.993420 0.3476438  
## 24 1.75 8.235 47.80800 48.78622 2.145278 0.3230350  
## 25 1.75 6.575 44.77300 45.84041 2.297261 0.3016635  
## 26 2.25 6.119 40.75150 40.98808 1.639511 0.4226871  
## 27 2.25 7.880 46.85025 47.79798 2.071846 0.3344843  
## 28 1.75 9.884 60.75600 62.10063 2.239978 0.3093781  
## 29 1.75 7.295 48.94175 50.12949 2.318604 0.2988868  
## 30 2.00 10.820 67.56400 67.89596 1.620048 0.4277651  
## 31 2.00 9.331 62.06675 63.15632 2.182280 0.3175577  
## 32 1.75 7.236 43.09850 44.32077 2.314295 0.2994432  
## 33 2.25 6.032 38.26250 39.24519 2.182708 0.3174955  
## 34 2.25 7.582 53.88900 54.89175 2.316345 0.2991782  
## 35 1.75 7.333 47.88975 49.44591 2.334245 0.2968840  
## 36 1.75 8.351 52.51025 53.84486 2.212642 0.3132003  
## 37 1.75 8.721 51.31925 52.39210 2.082584 0.3327596  
## 38 2.25 10.018 55.70600 56.91257 2.160595 0.3207450  
## 39 1.75 7.941 46.09625 47.25255 2.207474 0.3139335  
## 40 2.00 7.531 47.00125 48.49960 2.322945 0.2983283  
## 41 1.75 9.543 56.23750 57.23476 2.038639 0.3399327  
## 42 2.00 8.125 38.35100 39.89971 2.401017 0.2886277  
## 43 1.75 7.721 52.05175 53.33779 2.233652 0.3102543  
## 44 1.75 7.741 50.52650 51.64535 2.141886 0.3235467  
## 45 2.25 7.731 41.32875 42.90062 2.464498 0.2811932  
## 46 1.75 8.886 49.60525 50.51734 2.006589 0.3453623  
## 47 2.00 8.479 43.27675 43.74138 1.778940 0.3895578  
## 48 1.50 9.136 56.88475 58.27015 2.143044 0.3233717

# Five point summary of pharmacokinetic parameter

summary(out)

## tmax cmax auct aucinf   
## Min. :1.500 Min. : 5.987 Min. :34.39 Min. :35.10   
## 1st Qu.:1.750 1st Qu.: 7.569 1st Qu.:44.09 1st Qu.:45.49   
## Median :2.000 Median : 8.150 Median :50.07 Median :51.08   
## Mean :1.964 Mean : 8.533 Mean :51.20 Mean :52.30   
## 3rd Qu.:2.250 3rd Qu.: 9.628 3rd Qu.:57.24 3rd Qu.:58.51   
## Max. :2.250 Max. :11.547 Max. :68.87 Max. :70.10   
## thalf ke   
## Min. :1.620 Min. :0.2797   
## 1st Qu.:2.037 1st Qu.:0.3022   
## Median :2.152 Median :0.3221   
## Mean :2.142 Mean :0.3262   
## 3rd Qu.:2.293 3rd Qu.:0.3402   
## Max. :2.477 Max. :0.4278

# Data of standard 2x2 crossover design

data\_1=read.csv("D:/CHETANA/DATASET/BABEData2.csv")

# Statistical inferences for the fixed effects

* here we calculate carryover, drug formulation effect, period effect
* chat: carryover effect (estimated)
* fhat: linear contrast of the seq by period means
* phat: unbiased estimator of period effect

y11=data\_1[data\_1$Per==1&data\_1$Seq==1,1];n1=length(y11)  
y12=data\_1[data\_1$Per==1&data\_1$Seq==2,1]  
y21=data\_1[data\_1$Per==2&data\_1$Seq==1,1]  
y22=data\_1[data\_1$Per==2&data\_1$Seq==2,1];n2=length(y22)  
U1=y11+y21 # subject total w.r.t. sequence 1  
U2=y12+y22 # subject total w.r.t. sequence 2  
D1=(y21-y11)/2 # period differences for each subject within each sequence 1  
D2=(y22-y12)/2 # period differences for each subject within each sequence 2  
O1=D1  
O2=D2  
sd2u=((n1-1)\*var(U1)+(n2-1)\*var(U2))/(n1+n2-2) # pooled estimate of U  
sd2d=((n1-1)\*var(D1)+(n2-1)\*var(D2))/(n1+n2-2) # pooled estimate of D  
chat=mean(U2)-mean(U1)   
fhat=mean(D1)-mean(D2)   
phat=mean(O1)-mean(O2)   
vchat=sd2u\*(1/n1+1/n2) # pooled sample variance of carryover effect  
vfhat=sd2d\*(1/n1+1/n2) # pooled sample variance of drug formulation effect  
effect=c("carry","drug","perid")  
mvue=c(chat,fhat,phat)  
vhat=c(vchat,vfhat,vfhat)  
test\_stat=mvue/sqrt(vhat)  
pv=2\*(1-pt(abs(test\_stat),n1+n2-2))  
df=data.frame(effect,round(mvue,2),ss=round(vhat,2),f\_ratio=round(test\_stat,3),pv=round(pv,4))  
df

## effect round.mvue..2. ss f\_ratio pv  
## 1 carry -9.59 245.63 -0.612 0.5468  
## 2 drug -2.29 13.94 -0.613 0.5463  
## 3 perid -2.29 13.94 -0.613 0.5463

* carryover effect vs H\_11:P1-P2 not equal to 0 here from p\_value we fail to reject at 5% level of significance
* Drug formulation effect vs H\_12:F1-F2 not equal to 0 here from p\_value we fail to reject at 5% level of significance
* Period effect vs H\_13:P1-P2not equal to 0 here from p\_value we fail to reject at 5% level of significance

# Data of standard 2x2 crossover design

data\_1=read.csv("D:/CHETANA/DATASET/BABEData2.csv")

# Anova for standard 2x2 crossover design

n=length(data\_1$Y)  
y11=data\_1[data\_1$Per==1&data\_1$Seq==1,1];n1=length(y11)  
y12=data\_1[data\_1$Per==1&data\_1$Seq==2,1]  
y21=data\_1[data\_1$Per==2&data\_1$Seq==1,1]  
y22=data\_1[data\_1$Per==2&data\_1$Seq==2,1];n2=length(y22)  
ss\_total=((n-1)/n)\*var(data\_1[,1])  
df=data.frame(c(y11,y12),c(y21,y22))  
ss\_within=sum(apply(df,1,var))  
n1=length(y11)  
n2=length(y22)  
ss\_between=2\*sum((apply(df,1,mean)-mean(data\_1$Y))^2)  
sstotal=(n-1)\*var(data\_1$Y)  
chat=(mean(y12)+mean(y22))-(mean(y11)+mean(y21))  
sscarry=2\*n1\*n2/(n1+n2)\*chat^2/4  
ssinter=ss\_between-sscarry  
fhat=(((mean(y21)-mean(y11))-(mean(y22)-mean(y12)))/2)^2  
ssdrug=2\*n1\*n2/(n1+n2)\*fhat  
  
phat=(((mean(y21)-mean(y11))-(mean(y12)-mean(y22)))/2)^2  
ssperiod=2\*n1\*n2/(n1+n2)\*phat  
  
ssintra=ss\_within-ssdrug-ssperiod  
source1=c("carry","inter","drug","period","intra","total")  
df=c(1,(n1+n2-2),1,1,(n1+n2-2),2\*(n1+n2)-1)  
ss=c(sscarry,ssinter,ssdrug,ssperiod,ssintra,sstotal)  
msq=ss/df  
fcal=rep(0,6)  
fcal[1]=msq[1]/msq[2]  
fcal[2:4]=msq[2:4]/msq[5]  
pv=1-pt(msq,1,n1+n2-2)  
data.frame("source"=source1,"df"=df,"sumofsq"=ss,mss=round(msq,3),"fcal"=round(fcal,4),"p\_val"=pv)

## source df sumofsq mss fcal p\_val  
## 1 carry 1 276.00021 276.000 0.3745 0.06353175  
## 2 inter 22 16211.48870 736.886 4.4060 0.02381758  
## 3 drug 1 62.79188 62.792 0.3754 0.27390098  
## 4 period 1 35.96672 35.967 0.2151 0.45909187  
## 5 intra 22 3679.42953 167.247 0.0000 0.10465168  
## 6 total 47 20265.67703 431.185 0.0000 0.04069208

# Conclusion

* carryover effect vs H\_11:P1-P2 not equal to 0 here from p\_value we fail to reject at 5% level of significance
* from p\_value we can conclude that inter subject variability is not present
* Drug effect vs H\_13:P1-P2not equal to 0 here from p\_value we fail to reject at 5% level of significance
* period effect vs H\_14:F1-F2 not equal to 0 here from p\_value reject at 5% level of significance
* from p\_value we can conclude that intra subject variability is present

# Here we combine dataframe of BABEData2 and six pk parameter dataframe

df=data.frame(data\_1,out)

crosanova=function(Y,Seq,Sub,Per){  
 df=data.frame(Y,Seq,Sub,Per)  
 Y=df[,1]  
 n=length(Y)  
 sst=((n-1)/n)\*var(Y)  
 y11=df[df$Per==1&df$Seq==1,1];n1=length(y11)  
 y12=df[df$Per==1&df$Seq==2,1]  
 y21=df[df$Per==2&df$Seq==1,1]  
 y22=df[df$Per==2&df$Seq==2,1];n2=length(y22)  
 df1=data.frame(y11,y21)  
 df2=data.frame(y12,y22)  
 v1=apply(df1,1,var)  
 v2=apply(df2,1,var)  
 sswit=sum(v1)+sum(v2)  
 m1=sum((apply(df1,1,mean)-mean(Y))^2)  
 m2=sum((apply(df2,1,mean)-mean(Y))^2)  
 ssbet=2\*(m1+m2)  
 u1=y11+y21;u2=y12+y22  
 d1=(y21-y11)/2;d2=(y22-y12)/2  
 o1=d1;o2=d2  
   
 chat=mean(u2)-mean(u1)  
 fhat=mean(d1)-mean(d2)  
 phat=mean(o1)-mean(o2)  
 sscarry=2\*n1\*n2/(n1+n2)\*chat^2/4  
 ssdrug=2\*n1\*n2/(n1+n2)\*fhat^2  
 ssperiod=2\*n1\*n2/(n1+n2)\*phat^2  
 ssintra=sswit-ssdrug-ssperiod  
 ssinter=ssbet-sscarry  
   
 source1=c("carry","inter","drug","period","intra","Total") #source of var  
 dof=c(1,n1+n2-2,1,1,n1+n2-2,n-1)  
 ss=c(sscarry,ssinter,ssdrug,ssperiod,ssintra,sst)  
 msq=ss/dof  
 fcal=rep(0,6)  
 fcal[1]=msq[1]/msq[2]  
 fcal[2:4]=msq[2:4]/msq[5]  
 pval=rep(0,6)  
 pval[1]=1-pf(fcal[1],dof[1],dof[2])  
 pval[2:4]=1-pf(fcal[2:4],dof[2:4],dof[5])  
 return(data.frame("s\_var"=source1,"DF"=dof,"sof\_squ"=round(ss,4),"Fcal"=round(fcal,4),"p\_value"=round(pval,4)))  
}

# Anova corresponds to concentration

# Anova corresponds to concentration  
crosanova(df$cmax,df$Seq,df$Sub,df$Per)

## s\_var DF sof\_squ Fcal p\_value  
## 1 carry 1 0.0009 0.0004 0.9845  
## 2 inter 22 49.2591 1.0421 0.4619  
## 3 drug 1 4.1219 1.9184 0.1799  
## 4 period 1 4.1219 1.9184 0.1799  
## 5 intra 22 47.2709 0.0000 0.0000  
## 6 Total 47 2.1828 0.0000 0.0000

# Conclusion

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* Drug effect vs H\_13:P1-P2not equal to 0 here from p\_value we fail to reject at 5% level of significance
* period effect vs H\_14:F1-F2 not equal to 0 here from p\_value fail to reject at 5% level of significance
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# Anova corresponds to time point

crosanova(df$tmax,df$Seq,df$Sub,df$Per)

## s\_var DF sof\_squ Fcal p\_value  
## 1 carry 1 0.0638 2.3744 0.1376  
## 2 inter 22 0.5911 0.3211 0.9949  
## 3 drug 1 0.0013 0.0156 0.9019  
## 4 period 1 0.0013 0.0156 0.9019  
## 5 intra 22 1.8411 0.0000 0.0000  
## 6 Total 47 0.0521 0.0000 0.0000

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* from p\_value we can conclude that intra subject variability is not present

# Anova corresponds to partial auc truncated at the population median of t max

crosanova(df$auct,df$Seq,df$Sub,df$Per)

## s\_var DF sof\_squ Fcal p\_value  
## 1 carry 1 157.6223 1.9211 0.1796  
## 2 inter 22 1805.0995 0.8116 0.6857  
## 3 drug 1 50.1138 0.4957 0.4888  
## 4 period 1 50.1138 0.4957 0.4888  
## 5 intra 22 2224.1200 0.0000 0.0000  
## 6 Total 47 89.3139 0.0000 0.0000

# Conclusion

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# Anova corresponds to rate constant

crosanova(df$ke,df$Seq,df$Sub,df$Per)

## s\_var DF sof\_squ Fcal p\_value  
## 1 carry 1 0.0000 0.0432 0.8372  
## 2 inter 22 0.0207 0.8416 0.6553  
## 3 drug 1 0.0002 0.1787 0.6766  
## 4 period 1 0.0002 0.1787 0.6766  
## 5 intra 22 0.0246 0.0000 0.0000  
## 6 Total 47 0.0010 0.0000 0.0000

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* from p\_value we can conclude that intra subject variability is not present

# Anova corresponds to area under curve zero to infinity

crosanova(df$aucinf,df$Seq,df$Sub,df$Per)

## s\_var DF sof\_squ Fcal p\_value  
## 1 carry 1 155.5224 1.8624 0.1861  
## 2 inter 22 1837.1598 0.8069 0.6904  
## 3 drug 1 56.9716 0.5505 0.4660  
## 4 period 1 56.9716 0.5505 0.4660  
## 5 intra 22 2276.7308 0.0000 0.0000  
## 6 Total 47 91.3199 0.0000 0.0000

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# Anova corresponds to elimination half time

crosanova(df$thalf,df$Seq,df$Sub,df$Per)

## s\_var DF sof\_squ Fcal p\_value  
## 1 carry 1 0.0000 0.0000 0.9950  
## 2 inter 22 0.7806 0.9248 0.5719  
## 3 drug 1 0.0051 0.1335 0.7183  
## 4 period 1 0.0051 0.1335 0.7183  
## 5 intra 22 0.8441 0.0000 0.0000  
## 6 Total 47 0.0341 0.0000 0.0000

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* from p\_value we can conclude that intra subject variability is not present

time=unlist(ti)  
y1=apply(data[data$V3==1,5:20],2,mean)  
x1=plot(time,y1,type="l",col='blue',xlab = "time",ylab="concentration")  
par(new=TRUE)  
y2=apply(data[data$V3==2,5:20],2,mean)  
x2=plot(time,y2,type="l",col='red',xlab = "time",ylab="concentration")

