effect estimation

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#Import the dataset

data=read.csv("C:/Users/DELL/Downloads/clinical.csv",header = F)

#Let find the PK Parameters. #Tmax: Time at which maximum concentration appears. #Cmax: Maximum concentration. #AUC:Area Under curve (Time Vs Concetration) #AUCinf=portion of remaining area from tk to infinity #ke=elimination rate constant #thalf=time require for concentration to half.

data1=data[,5:20]  
t=unlist(data1[1,])  
conc=unlist(data1[2,])  
cmax=max(conc)  
a=which.max(conc)  
tmax=t[a]  
k=length(conc)-1  
auc=sum((conc[2:(k+1)]+conc[1:k])\*(t[2:(k+1)]-t[1:k])/2)  
ke=-2.303\*coefficients(lm(log10(conc[a+1:k+1])~t[a+1:k+1]))[2]  
AUCinf=auc+conc[k+1]/ke  
thalph=0.693/ke  
df=data.frame('c\_max'=cmax,'tmax'=tmax,'auct'=auc,'ke'=ke,'aucinf'=AUCinf,'thalf'=thalph)

#create a fuction for finding pkparameter for 24 subject name as “pkpara”

pkpara=function(t,conc){  
 cmax=max(conc);cmax  
 a=which.max(conc)  
 tmax=t[a];tmax  
 k=length(conc)-1;k  
 auc=sum((conc[2:(k+1)]+conc[1:k])\*(t[2:(k+1)]-t[1:k])/2)  
 ke=-2.303\*coefficients(lm(log10(conc[a+1:k+1])~t[a+1:k+1]))[2]  
 AUCinf=auc+conc[k+1]/ke  
 thalph=0.693/ke  
 df=data.frame('c\_max'=cmax,'tmax'=tmax,'auct'=auc,'ke'=ke,'aucinf'=AUCinf,'thalf'=thalph)  
return(df)  
}  
  
t=unlist(data1[1,])  
conc=unlist(data1[2,])  
pkpara(t,conc)

## c\_max tmax auct ke aucinf thalf  
## V11 10.423 2 34.43512 0.3493368 35.36832 1.983759

#for entire data

for (i in 2:49){   
 df=rbind(df,pkpara(t,unlist(data1[i,])))  
}  
df1=df[2:49,]  
df1

## c\_max tmax auct ke aucinf thalf  
## V111 10.423 2.00 34.43512 0.3493368 35.36832 1.983759  
## V10 8.016 1.75 26.55588 0.2914392 27.89063 2.377854  
## V112 10.868 2.00 29.15875 0.3286040 30.48558 2.108921  
## V12 8.120 2.25 24.65762 0.2930892 25.72897 2.364468  
## V121 6.925 2.25 22.11113 0.2766613 23.75574 2.504868  
## V122 8.795 2.25 29.35938 0.2927376 30.84876 2.367308  
## V101 10.485 1.75 33.28162 0.3352967 34.54916 2.066826  
## V123 10.279 2.25 27.65212 0.3142887 28.91529 2.204979  
## V113 9.531 2.00 27.98450 0.3403519 28.88357 2.036128  
## V102 8.238 1.75 26.18725 0.3113974 27.55528 2.225452  
## V124 8.026 2.25 21.85450 0.3176994 22.65400 2.181308  
## V114 10.553 2.00 29.18863 0.3513875 30.08223 1.972182  
## V125 6.857 2.25 17.87250 0.3235249 18.37014 2.142030  
## V115 11.547 2.00 34.27425 0.3101936 35.87970 2.234089  
## V103 8.176 1.75 23.87463 0.2929674 25.37650 2.365451  
## V104 6.926 1.75 18.97850 0.2960414 19.96485 2.340889  
## V126 5.987 2.25 17.19537 0.3050577 17.94933 2.271701  
## V116 10.166 2.00 34.37562 0.3181914 35.71130 2.177934  
## V127 6.857 2.25 19.13000 0.3418689 19.60094 2.027093  
## V117 11.547 2.00 33.82825 0.3187396 35.27143 2.174189  
## V9 8.070 1.50 24.11212 0.2928691 25.61450 2.366245  
## V128 7.776 2.25 19.36212 0.3346070 19.90605 2.071086  
## V118 11.184 2.00 31.51225 0.3355397 32.89808 2.065329  
## V105 8.235 1.75 23.90400 0.3164424 24.90260 2.189972  
## V106 6.575 1.75 22.38650 0.2982042 23.46630 2.323911  
## V129 6.119 2.25 20.37575 0.4205734 20.61352 1.647750  
## V1210 7.880 2.25 23.42512 0.3262801 24.39668 2.123942  
## V107 9.884 1.75 30.37800 0.3056030 31.73924 2.267648  
## V108 7.295 1.75 24.47087 0.2946168 25.67583 2.352208  
## V119 10.820 2.00 33.78200 0.4238376 34.11703 1.635060  
## V1110 9.331 2.00 31.03337 0.3118096 32.14303 2.222510  
## V109 7.236 1.75 21.54925 0.2910951 22.80657 2.380665  
## V1211 6.032 2.25 19.13125 0.3054279 20.15277 2.268948  
## V1212 7.582 2.25 26.94450 0.2950128 27.96141 2.349051  
## V1010 7.333 1.75 23.94487 0.2923141 25.52537 2.370737  
## V1011 8.351 1.75 26.25512 0.3082893 27.61099 2.247889  
## V1012 8.721 1.75 25.65962 0.3270436 26.75122 2.118984  
## V1213 10.018 2.25 27.85300 0.3052911 29.12064 2.269965  
## V1013 7.941 1.75 23.04812 0.3061497 24.23382 2.263599  
## V1111 7.531 2.00 23.50062 0.2884570 25.05025 2.402438  
## V1014 9.543 1.75 28.11875 0.3348138 29.13125 2.069807  
## V1112 8.125 2.00 19.17550 0.2694366 20.83452 2.572034  
## V1015 7.721 1.75 26.02587 0.3062851 27.32858 2.262598  
## V1016 7.741 1.75 25.26325 0.3192821 26.39704 2.170495  
## V1214 7.731 2.25 20.66437 0.2650366 22.33207 2.614733  
## V1017 8.886 1.75 24.80262 0.3385626 25.73303 2.046889  
## V1113 8.479 2.00 21.63837 0.3755358 22.12035 1.845363  
## V91 9.136 1.50 28.44237 0.3206090 29.83972 2.161511

out=summary(df1)  
out

## c\_max tmax auct ke   
## Min. : 5.987 Min. :1.500 Min. :17.20 Min. :0.2650   
## 1st Qu.: 7.569 1st Qu.:1.750 1st Qu.:22.05 1st Qu.:0.2949   
## Median : 8.150 Median :2.000 Median :25.03 Median :0.3116   
## Mean : 8.533 Mean :1.964 Mean :25.60 Mean :0.3170   
## 3rd Qu.: 9.628 3rd Qu.:2.250 3rd Qu.:28.62 3rd Qu.:0.3301   
## Max. :11.547 Max. :2.250 Max. :34.44 Max. :0.4238   
## aucinf thalf   
## Min. :17.95 Min. :1.635   
## 1st Qu.:23.30 1st Qu.:2.099   
## Median :26.07 Median :2.224   
## Mean :26.73 Mean :2.204   
## 3rd Qu.:29.90 3rd Qu.:2.350   
## Max. :35.88 Max. :2.615

#join the seq and period columns to pkpara data

dff=cbind(data[2:49,1:4],df1)  
colnames(dff)=c(data[1,1:4],colnames(df1))  
View(dff)

#create fuction for calculating anova

crossanova=function(Y,Seq,Per,Sub){  
  
 df=data.frame(Y,Seq,Per,Sub)  
y=df[,1]  
n=length(y)  
SST=var(y)\*(n-1)  
Y11=df[df$Per==1&df$Seq==1,1];n1=length(Y11);   
Y12=df[df$Per==1&df$Seq==2,1];n2=length(Y12);   
Y21=df[df$Per==2&df$Seq==1,1];  
Y22=df[df$Per==2&df$Seq==2,1];  
  
df1=data.frame(Y11,Y21)  
df2=data.frame(Y12,Y22)  
  
m=apply(df1,1,var);m  
m1=apply(df2,1,var);m1  
sswithin=sum(m)+sum(m1)  
me=sum((apply(df1,1,mean)-mean(y))^2);me  
me1=sum((apply(df2,1,mean)-mean(y))^2);me1  
ssbetween=2\*(me+me1)  
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;  
Chat=mean(U2)-mean(U1);Chat  
Fhat=mean(D1)-mean(D2);Fhat  
Phat=mean(O1)-mean(O2);Phat  
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=sswithin-ssdrug-ssperiod  
ssinter=ssbetween-sscarry  
source1=c("carry","inter","drug","period","intra","Total")  
df22=c(1,n1+n2-2,1,1,n1+n2-2,2\*(n1+n2)-1)  
ss=c(sscarry,ssinter,ssdrug,ssperiod,ssintra,SST)  
Msq=ss/df22  
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],df22[1],df22[2])  
Pval[2:4]=1-pf(Fcal[2:4],df22[2:4],df22[5])  
return(data.frame("source"=source1,"DF"=df22,"sumofsq"=ss,Fcal,Pval))  
}

#anova corresponding to concentration.

crossanova(dff$c\_max,dff$seq,dff$Per,dff$Sub)

## source DF sumofsq Fcal Pval  
## 1 carry 1 6.435745 3.5146472796 0.07416735  
## 2 inter 22 40.284668 0.7469596193 0.75025498  
## 3 drug 1 0.000867 0.0003536707 0.98516528  
## 4 period 1 4.121924 1.6814347152 0.20817029  
## 5 intra 22 53.931520 0.0000000000 0.00000000  
## 6 Total 47 104.774724 0.0000000000 0.00000000

#anova corresponding to timepoint.

crossanova(dff$tmax,dff$seq,dff$Per,dff$Sub)

## source DF sumofsq Fcal Pval  
## 1 carry 1 0.105468750 1.7855711 0.1951245  
## 2 inter 22 1.299479167 1.2632911 0.2941422  
## 3 drug 1 0.063802083 1.3645570 0.2552530  
## 4 period 1 0.001302083 0.0278481 0.8689908  
## 5 intra 22 1.028645833 0.0000000 0.0000000  
## 6 Total 47 2.498697917 0.0000000 0.0000000

#anova corresponding to area under curve to max time.

crossanova(dff$auct,dff$seq,dff$Per,dff$Sub)

## source DF sumofsq Fcal Pval  
## 1 carry 1 22.65589 1.1909814 0.2869400  
## 2 inter 22 418.50318 0.7232103 0.7733056  
## 3 drug 1 39.40556 1.4981182 0.2339081  
## 4 period 1 12.52844 0.4763055 0.4973173  
## 5 intra 22 578.67425 0.0000000 0.0000000  
## 6 Total 47 1071.76732 0.0000000 0.0000000

#anova corresponding to elimination rate constant.;

crossanova(dff$ke,dff$seq,dff$Per,dff$Sub)

## source DF sumofsq Fcal Pval  
## 1 carry 1 3.542169e-05 0.05009629 0.8249612  
## 2 inter 22 1.555559e-02 0.53000698 0.9278721  
## 3 drug 1 3.674560e-04 0.27543758 0.6049562  
## 4 period 1 2.096456e-04 0.15714612 0.6956166  
## 5 intra 22 2.934978e-02 0.00000000 0.0000000  
## 6 Total 47 4.551789e-02 0.00000000 0.0000000

#anova corresponding to Area Under Curve Infinity.

crossanova(dff$aucinf,dff$seq,dff$Per,dff$Sub)

## source DF sumofsq Fcal Pval  
## 1 carry 1 22.79998 1.1357448 0.2981100  
## 2 inter 22 441.64821 0.7331796 0.7636917  
## 3 drug 1 37.82230 1.3813525 0.2524346  
## 4 period 1 16.25859 0.5937988 0.4491507  
## 5 intra 22 602.37385 0.0000000 0.0000000  
## 6 Total 47 1120.90293 0.0000000 0.0000000

#anova corresponding to t\_half.

crossanova(dff$thalf,dff$seq,dff$Per,dff$Sub)

## source DF sumofsq Fcal Pval  
## 1 carry 1 0.0005927271 0.02160898 0.8844709  
## 2 inter 22 0.6034525870 0.51748737 0.9350093  
## 3 drug 1 0.0085347146 0.16101572 0.6920940  
## 4 period 1 0.0069153586 0.13046499 0.7213960  
## 5 intra 22 1.1661204079 0.00000000 0.0000000  
## 6 Total 47 1.7856157952 0.00000000 0.0000000

data2=read.csv("C:/Users/DELL/Downloads/clinical.csv",header = T)

par(mfrow=c(1,2))  
plot(t,apply(data2[data2$treat==2,5:20],2,mean),type='l',xlab="time",ylab="Average Concentration corresponding Test Drug")  
plot(t,apply(data2[data2$treat==1,5:20],2,mean),type='l',xlab="time",ylab="Average Concentration corresponding Reference Drug")

