Crossover Trial Further Simulation and Plotting

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Function to simulate crossover trial dataset

```
ABBA <- function(n = 10, sdW = 4, sdB = 1, beta = c(8, 1, 0,
    0), alpha = 0.05) {

    # generate data
    Patient <- as.factor(rep(1:(2 * n), rep(2, 2 * n)))
    Treatment <- c(rep(c("Treatment1", "Treatment2"), n), rep(c("Treatment2",
        "Treatment1"), n))
    Order <- rep(c("First", "Second"), 2 * n)
    Data <- data.frame(Patient, Treatment, Order)
    FMat <- model.matrix(~Treatment * Order, data = Data)
    RMat <- model.matrix(~0 + Patient, data = Data)
    Response <- FMat %*% beta + RMat %*% rnorm(2 * n, 0, sdB) +
        rnorm(4 * n, 0, sdW)  # beta here
    Data$Response <- Response

    return(data.frame(Data))
    # analyse Fit <- lme(Response~ Treatment * Order, random=~1 |
    # Patient, data=Data, na.action='na.omit' ) Est <-
    # fixed.effects(Fit)[2] Ste <- sqrt(vcov(Fit)[2,2]) prod(Est
    # + c(-1,1) * qnorm(1-alpha/2) * Ste) > 0
}
```

Generate data and analyse

```
mydata <- ABBA(n = 10, sdW = 2, sdB = 2, beta = c(8, 1, 0, 0),
    alpha = 0.05)

require(nlme)
f <- lme(Response ~ Treatment * Order, random = ~1 | Patient,
    data = mydata, na.action = "na.omit")
anova(f)
```

```
               numDF denDF  F-value p-value
(Intercept)        1    19 421.0340  <.0001
Treatment          1    17   0.5352  0.4744
Order              1    17   0.9612  0.3406
Treatment:Order    1    17   0.4587  0.5073
```

```
summary(f)$tTable
```

```
                                  Value Std.Error DF
(Intercept)                    8.023633 0.7468591 19
TreatmentTreatment2            1.030554 1.0562182 17
OrderSecond                    1.182608 1.0562182 17
TreatmentTreatment2:OrderSecond -1.166955 1.7229741 17
                                  t-value
(Intercept)                    10.7431685
TreatmentTreatment2             0.9757021
OrderSecond                     1.1196628
TreatmentTreatment2:OrderSecond -0.6772910
                                      p-value
(Intercept)                    0.000000001638637
TreatmentTreatment2            0.342892860343766
OrderSecond                    0.278427969007660
TreatmentTreatment2:OrderSecond 0.507334457267561
```

Simulation function for crossover design, preparing to vary an input parameter

```
C.power <- function(a, b, c, d, e, f, g, n.sims = sims) {

    Treatment <- rep(NA, n.sims)
    Order <- rep(NA, n.sims)
    Interaction <- rep(NA, n.sims)

    for (s in 1:n.sims) {

        fake <- ABBA(n = a, sdW = b, sdB = c, beta = c(d, e,
            f, g), alpha = 0.05)

        possibleError <- tryCatch(f1 <- lme(Response ~ Treatment *
            Order, random = ~1 | Patient, data = fake, na.action = "na.omit"),
            error = function(e) e)

        ### http://stackoverflow.com/questions/8093914
        ### /skip-to-next-value-of-loop-upon-error-in-r-trycatch

        if (!inherits(possibleError, "error")) {

            modelint <- possibleError

            z <- as.matrix(summary(modelint)$tTable)
            Treatment[s] <- z[2, 5][[1]]
            Order[s] <- z[3, 5][[1]]
            Interaction[s] <- z[4, 5][[1]]
        }
    }

    trt <- mean(Treatment < 0.05)
    ord <- mean(Order < 0.05)
    int <- mean(Interaction < 0.05)

    c(trt, ord, int)
}

# stand alone, single example that shows power for main
# effect, order effect and interaction effect
C.power(a = 20, b = 1, c = 1, d = 8, e = 1, f = 0, g = 0, n.sims = 100)
```

```
[1] 0.60 0.08 0.10
```

Simulate crossover power and vary between person SD

```
## execute the functions numerous times assess changing
## between person SD

sims <- 200

J <- c(2, 2.5, 3, 4)  # here we vary

k <- length(J)

dnam = list(betweenSD = J, Estimate = c("trt effect power", "order power",
    "interaction power"))

pwpr <- array(NA, dim = sapply(dnam, length), dimnames = dnam)


system.time(for (i in 1:k) {
    pwpr[i, ] <- C.power(a = 20, b = 2, c = J[i], d = 8, e = 4,
        f = 0, g = 0, n.sims = sims)
})
```

```
   user  system elapsed
  13.68    0.00   13.71
```

```
print(pwpr, digits = 4)
```

```
         Estimate
betweenSD trt effect power order power interaction power
      2              0.990       0.050             0.055
      2.5            0.975       0.035             0.030
      3              0.920       0.035             0.030
      4              0.785       0.030             0.040
```

Simulate crossover power and vary within person SD

```
sims <- 200

J <- c(2, 2.5, 3, 4)  # here we vary

k <- length(J)

dnam = list(betweenSD = J, Estimate = c("trt effect power", "order power",
    "interaction power"))

pwpr <- array(NA, dim = sapply(dnam, length), dimnames = dnam)


system.time(for (i in 1:k) {
    pwpr[i, ] <- C.power(a = 20, b = J[i], c = 4, d = 8, e = 4,
        f = 1, g = 0, n.sims = sims)
})
```

```
   user  system elapsed
  13.67    0.00   13.67
```

```
print(pwpr, digits = 4)
```

```
         Estimate
betweenSD trt effect power order power interaction power
      2              0.820       0.110             0.035
      2.5            0.795       0.070             0.030
      3              0.615       0.065             0.055
      4              0.515       0.075             0.045
```

Simulate a ABBA data set with known effects that has good power

```
# require(ggpubr)
require(ggplot2)

# state some parameters so we can pick them up later on in
# plot titles
sb <- 2
sw <- 2
beta = c(8, 2, 1, 0)

# check the power, it is not likely the main effect will be
# missed, we even have good power for the order effect.
C.power(a = 100, b = sb, c = sw, d = beta[1], e = beta[2], f = beta[3],
    g = beta[4], n.sims = 1000)
```

```
[1] 1.000 0.704 0.044
```

```
# so lets create the data
mydata <- ABBA(n = 100, sdW = 2, sdB = 2, beta = c(8, 2, 1, 0),
    alpha = 0.05)

# analysis
tryCatch(f1 <- lme(Response ~ Treatment * Order, random = ~1 |
    Patient, data = mydata, na.action = "na.omit"), error = function(e) e)

summary(f1)
```

```
Linear mixed-effects model fit by REML
 Data: mydata
       AIC      BIC    logLik
  1908.478 1932.367 -948.2392

Random effects:
 Formula: ~1 | Patient
        (Intercept) Residual
StdDev:    2.283018 1.813877

Fixed effects: Response ~ Treatment * Order
                                  Value Std.Error  DF
(Intercept)                    7.945616 0.2915874 199
TreatmentTreatment2            1.987840 0.4123668 197
OrderSecond                    1.088590 0.4123668 197
TreatmentTreatment2:OrderSecond 0.123714 0.7406616 197
                                 t-value p-value
(Intercept)                    27.249520  0.0000
TreatmentTreatment2             4.820562  0.0000
OrderSecond                     2.639859  0.0090
TreatmentTreatment2:OrderSecond  0.167031  0.8675
 Correlation:
                               (Intr) TrtmT2 OrdrSc
TreatmentTreatment2            -0.707
OrderSecond                    -0.707  0.807
TreatmentTreatment2:OrderSecond  0.635 -0.898 -0.898
```

```
Standardized Within-Group Residuals:
        Min          Q1         Med          Q3         Max
-2.43567647 -0.53233676  0.03385682  0.54524738  1.89156778

Number of Observations: 400
Number of Groups: 200
```

```
intervals(f1)
```

```
Approximate 95% confidence intervals

 Fixed effects:
                                    lower      est.
(Intercept)                      7.3706182 7.9456158
TreatmentTreatment2              1.1746198 1.9878398
OrderSecond                      0.2753701 1.0885900
TreatmentTreatment2:OrderSecond -1.3369295 0.1237137
                                   upper
(Intercept)                     8.520613
TreatmentTreatment2             2.801060
OrderSecond                     1.901810
TreatmentTreatment2:OrderSecond 1.584357
attr(,"label")
[1] "Fixed effects:"

 Random Effects:
  Level: Patient
                   lower     est.    upper
sd((Intercept)) 1.998192 2.283018 2.608443

 Within-group standard error:
   lower     est.    upper
1.643741 1.813877 2.001623
```

```
# useful concatenation for plotting
mydata$temp <- paste(mydata$Treatment, mydata$Order, sep = ".")
```

Summary stats

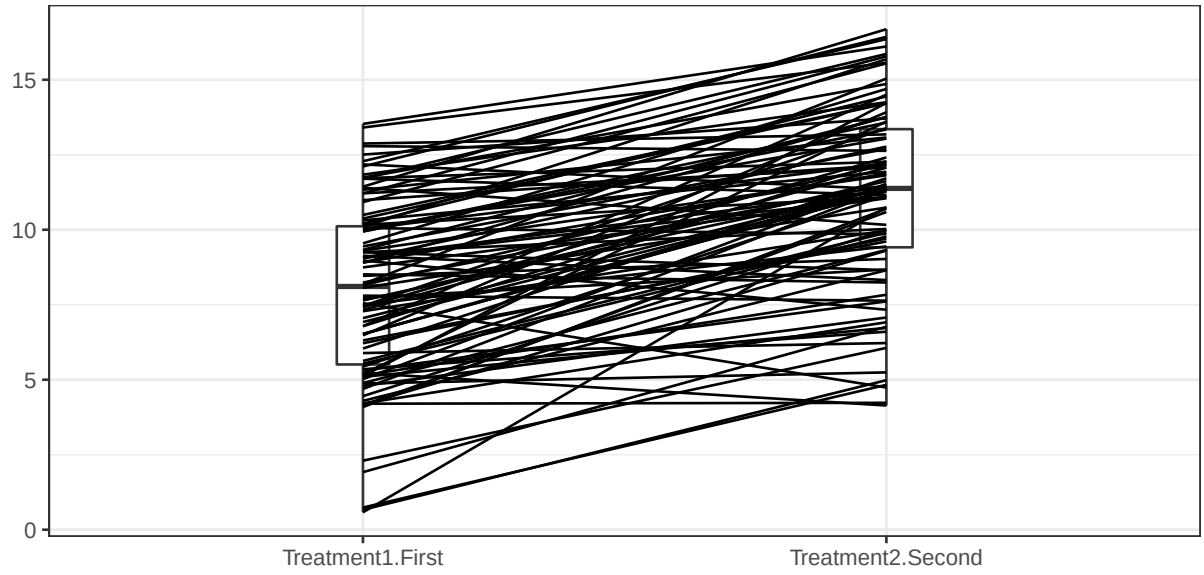
```
library("tidyverse")
group_by(mydata, temp) %>% summarise(count = n(), median = median(Response,
    na.rm = TRUE), IQR = IQR(Response, na.rm = TRUE))
```

```
# A tibble: 4 x 4
  temp              count median   IQR
  <chr>             <int>  <dbl> <dbl>
1 Treatment1.First    100   8.11  4.61
2 Treatment1.Second   100   9.04  3.65
3 Treatment2.First    100   9.92  4.26
4 Treatment2.Second   100  11.4   3.94
```

```
# I tried this package, it was only ok

# B <- mydata[mydata$temp %in% 'Treatment1.First' |
# mydata$temp %in% 'Treatment2.Second',] B1 <-
# ggpubr::ggpaired(B, x='Treatment', y = 'Response', color =
# 'Treatment', line.color = 'gray', line.size = 0.4, palette
# = 'npg', , title='First period comparison') +
# stat_compare_means(paired = TRUE) C <- mydata[mydata$temp
# %in% 'Treatment2.First' | mydata$temp %in%
# 'Treatment1.Second',] C1 <- ggpubr::ggpaired(C,
# x='Treatment', y = 'Response', color = 'Treatment',
# line.color = 'gray', line.size = 0.4, palette = 'npg' ,
# title='Second period comparison')+
# stat_compare_means(paired = TRUE)

# print(B1);print(C1)
```

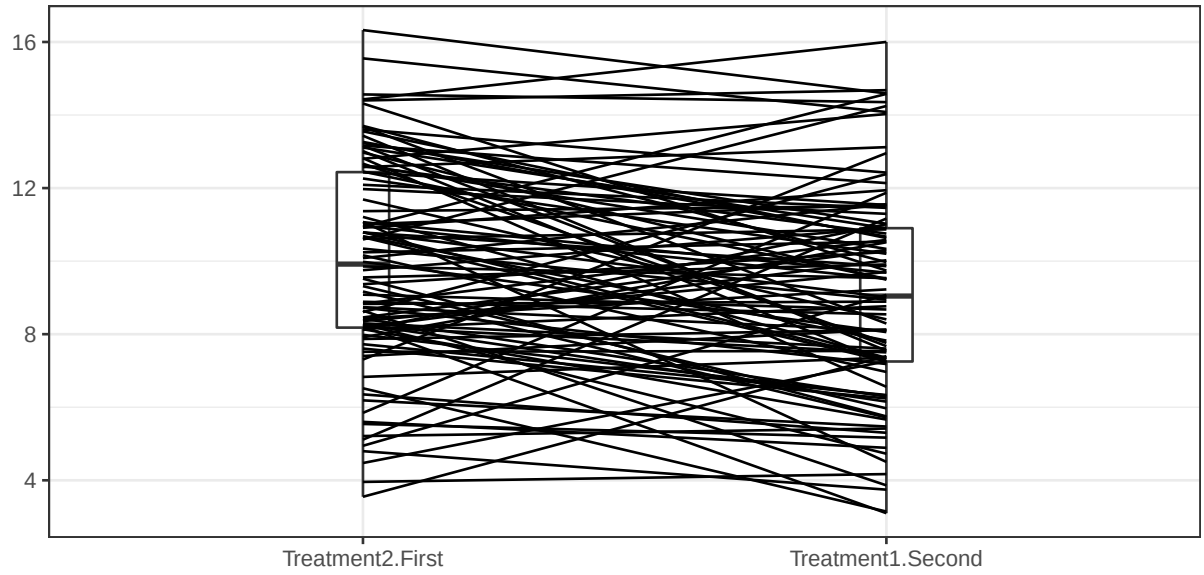
Use a package to plot AB sequence then BA sequence, should be mirror image ideally

```
require("PairedData")
Treatment1.First <- subset(mydata, temp == "Treatment1.First",
    Response, drop = TRUE)
Treatment2.Second <- subset(mydata, temp == "Treatment2.Second",
    Response, drop = TRUE)

pd <- paired(Treatment1.First, Treatment2.Second)
plot(pd, type = "profile") + theme_bw()
```




```
cat("\n\n\\pagebreak\n")
```

```
Treatment2.First <- subset(mydata, temp == "Treatment2.First",
    Response, drop = TRUE)
Treatment1.Second <- subset(mydata, temp == "Treatment1.Second",
    Response, drop = TRUE)

pd <- paired(Treatment2.First, Treatment1.Second)
plot(pd, type = "profile") + theme_bw()
```



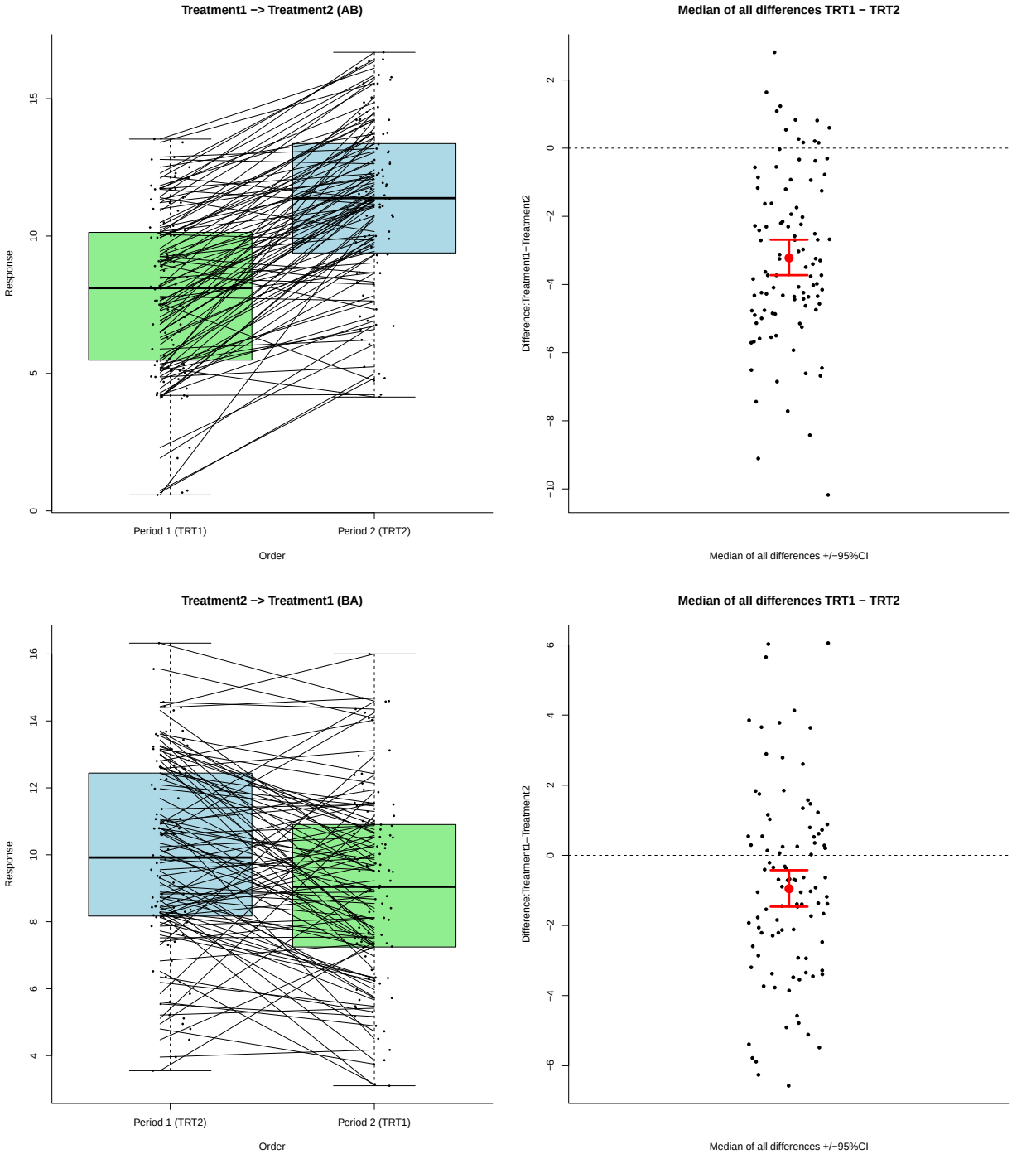
My code to plot treatment comparisons

```
# http://www.surefoss.org/visualisation/visualizing-small-scale-paired-data-combining-boxplots-stripcha

# main effect 4 and an order effect of 1, no interaction so
# second period gets a boost of +1


co.plot <- function(mydata) {

    par(mfrow = c(2, 2))

    # creat a concatenated variable
    mydata$temp <- paste(mydata$Treatment, mydata$Order, sep = ".")

    # pull out AB data
    post <- as.vector(mydata[grepl("Treatment1.First", mydata$temp),
        4])
    pre <- as.vector(mydata[grepl("Treatment2.Second", mydata$temp),
        4])
    s <- seq(length(pre))
    par(bty = "l")

    # boxplot AB
    boxplot(post, pre, main = "Treatment1 -> Treatment2 (AB)",
        xlab = "Order", ylab = "Response", names = c("Period 1 (TRT1)",
            "Period 2 (TRT2)"), col = c("lightgreen", "lightblue"))

    # Add raw data with jitter
    stripchart(list(post, pre), vertical = T, pch = 16, method = "jitter",
        cex = 0.5, add = T)
    # join lines, this would be better if jittered points were
    # joined
    segments(rep(0.95, length(pre))[s], post[s], rep(2, length(pre))[s],
        pre[s], col = 1, lwd = 0.5)

    # Wilcoxon signed rank test
    res <- wilcox.test(post, pre, paired = T, conf.int = T)
    stripchart(post - pre, vertical = T, pch = 16, method = "jitter",
        main = "Median of all differences TRT1 - TRT2", ylab = "Difference:Treatment1-Treatment2",
        xlab = "Median of all differences +/-95%CI")
    points(1, res$estimate, col = "red", pch = 16, cex = 2)
    arrows(1, res$conf.int[1], 1, res$conf.int[2], col = "red",
        code = 3, lwd = 3, angle = 90)
    abline(h = 0, lty = 2)  #Zero-effect line









    # repeat for BA sequence
```

```
    pre <- as.vector(mydata[grepl("Treatment2.First", mydata$temp),
        4])
    post <- as.vector(mydata[grepl("Treatment1.Second", mydata$temp),
        4])
    s <- seq(length(pre))
    par(bty = "l")

    boxplot(pre, post, main = "Treatment2 -> Treatment1 (BA)",
        xlab = "Order", ylab = "Response", names = c("Period 1 (TRT2)",
            "Period 2 (TRT1)"), col = c("lightblue", "lightgreen"))
    stripchart(list(pre, post), vertical = T, pch = 16, method = "jitter",
        cex = 0.5, add = T)
    segments(rep(0.95, length(pre))[s], pre[s], rep(2, length(pre))[s],
        post[s], col = 1, lwd = 0.5)

    res <- wilcox.test(post, pre, paired = T, conf.int = T)
    stripchart(post - pre, vertical = T, pch = 16, method = "jitter",
        main = "Median of all differences TRT1 - TRT2", ylab = "Difference:Treatment1-Treatment2",
        xlab = "Median of all differences +/-95%CI")
    points(1, res$estimate, col = "red", pch = 16, cex = 2)
    arrows(1, res$conf.int[1], 1, res$conf.int[2], col = "red",
        code = 3, lwd = 3, angle = 90)
    abline(h = 0, lty = 2)  # Zero-effect line
    par(mfrow = c(1, 1))

}
```

Plot AB sequence then BA sequence, should be mirror image ideally

```
co.plot(mydata)
```

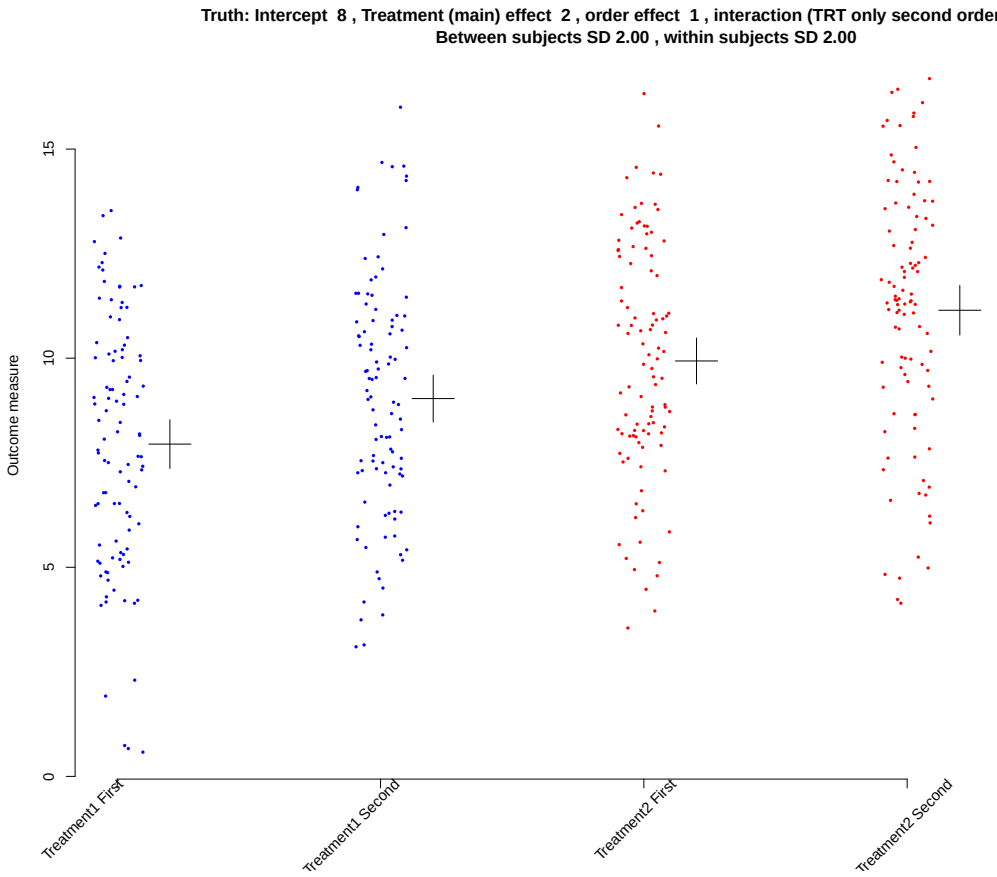


My code to plot all data in a useful way

```
d1 <- mydata
require(reshape)
d1$grp <- paste(d1$Treatment, d1$Order, sep=" ")
d1 <- rename(d1, c(Response="count"))
d1 <- rename(d1, c(grp="spray"))
d1 <- d1[order(d1$spray),]

attach(d1)
sprayTypes <- unique(spray)

y <- as.numeric(as.character(d1[,4]))

plot(y, as.factor(d1[,5]) ,  ylim=c(min(y),max(y)) , xlim=c(1, 5) , xaxt="n",
     main=paste("\nTruth: Intercept ",beta[1],", Treatment (main) effect ",beta[2],", order effec
                ", \n Between subjects SD",p2(sb),", within subjects SD", p2(sw) ),
     xlab="", ylab="Outcome measure", frame.plot  =F , col="white")
##if not white I get a nasty boxplot

axis(1,  at=1:4, labels=F )

text(x=1:length(sprayTypes)*1.05, par("usr")[3]-0.08 , labels = sprayTypes,
     srt = 45, pos = 2, xpd = TRUE,
     cex.axis=.5 )

##make colours
chk <- as.character(d1$spray)
x <- as.data.frame(table(chk))
freq <- x[,2]
value <- max(dput(1:dim(x)[1]))
```

1:4

```
IR <- value+1
clr <- rainbow(IR)
clr <- c("blue","red")
wR <- (2*IR-1:IR)/(2*IR)
##colour made
for (i in 1 : length(sprayTypes)){
  y <- count[spray == sprayTypes[i]]
  n <- sum(spray == sprayTypes[i])
  points(jitter(rep(i, n), amount = .1), y, pch = 16, cex = .5,
         col=ifelse(i<3,clr[1],clr[2])

  )

  col=ifelse(Treatment=="Treatment1",clr[1],clr[2])

  lines(i + c(.12, .28), rep(mean(y), 2), lwd = 1, col="black")
  lines(rep(i + .2, 2),
         mean(y) + c(-1.96, 1.96) * sd(y) / sqrt(n),  lwd = 1, col="black"

  )
}
```



This is a useful plot to look at all the data together. Perhaps lines joining the pairs might be an improvement to show between and within person variation. The crosses are the arithmetic means and 95% CIs. The first left cross is an estimate of the intercept. We can see the treatment effect, the red data is greater than blue. The order effect is apparent too, second period is higher than first. We are expecting this (we know the truth). We did power this study, so there is a high probability the main effect should manifest and to a lesser probability also the order. We know in truth there is no interaction.

Computing Environment

```
sessionInfo()
```

```
R version 3.6.1 (2019-07-05)
Platform: x86_64-w64-mingw32/x64 (64-bit)
Running under: Windows 10 x64 (build 17134)

Matrix products: default

locale:
[1] LC_COLLATE=English_United Kingdom.1252
[2] LC_CTYPE=English_United Kingdom.1252
[3] LC_MONETARY=English_United Kingdom.1252
[4] LC_NUMERIC=C
[5] LC_TIME=English_United Kingdom.1252

attached base packages:
[1] stats     graphics  grDevices utils     datasets
[6] methods   base

other attached packages:
 [1] reshape_0.8.8    PairedData_1.1.1 lattice_0.20-38
 [4] mvtnorm_1.0-11   gld_2.5          MASS_7.3-51.4
 [7] forcats_0.4.0    stringr_1.4.0    dplyr_0.8.3
[10] purrr_0.3.2      readr_1.3.1      tidyr_0.8.3
[13] tibble_2.1.3     tidyverse_1.2.1  ggplot2_3.2.0
[16] nlme_3.1-140     knitr_1.23

loaded via a namespace (and not attached):
 [1] tidyselect_0.2.5 xfun_0.8         haven_2.1.1
 [4] colorspace_1.4-1 generics_0.0.2   vctrs_0.2.0
 [7] htmltools_0.3.6  yaml_2.2.0       utf8_1.1.4
[10] rlang_0.4.0      e1071_1.7-2      pillar_1.4.2
[13] glue_1.3.1       withr_2.1.2      modelr_0.1.4
[16] readxl_1.3.1     plyr_1.8.4       munsell_0.5.0
[19] gtable_0.3.0     cellranger_1.1.0 rvest_0.3.4
[22] evaluate_0.14    labeling_0.3     lmom_2.8
[25] class_7.3-15     fansi_0.4.0      broom_0.5.2
[28] Rcpp_1.0.1       backports_1.1.4  scales_1.0.0
[31] formatR_1.7      jsonlite_1.6     hms_0.5.0
[34] digest_0.6.20    stringi_1.4.3    grid_3.6.1
[37] cli_1.1.0        tools_3.6.1      magrittr_1.5
[40] lazyeval_0.2.2   crayon_1.3.4     pkgconfig_2.0.2
[43] zeallot_0.1.0    xml2_1.2.0       lubridate_1.7.4
[46] assertthat_0.2.1 rmarkdown_1.14   httr_1.4.0
[49] rstudioapi_0.10  R6_2.4.0         compiler_3.6.1
```

This took 78.44 seconds to execute.