CTLDA: A Combined Test for Longitudinal Data Analysis in Randomized Clinical Trials

Contents

Overview

CTLDA package implements MMRM (last-visit), pAUC (partial AUC), PMRM (delay-based), PMRM (decline-based), NCS, and CTLDA methods for the treatment effect estimates and signal detection in longitudinal data analysis with repeated measures.

System Requirements

The package development version is tested on the following systems:

Mac OSX (R version 4.3.1)

Windows 10 (R version 4.3.1)

The CRAN package should be compatible with Windows and Mac operating systems.

Installing Guide

CTLDA package requires R with version 4.3.1 or higher

Package Installation

```
library(devtools)

devtools::install_github("yaowuliu/ACAT") # Need to install ACAT first
devtools::install_github("zhaiso1/CTLDA")
```

Demo

Part 1: Simulate longitudinal data

```r
## time-to-response function in placebo arm

f <- function(x) 1/(1 + exp(-3*x/4+5))
```

```r
M <- seq(0, 12, 3)

# mean response for placebo arm
mean_pbo <- round(f(M), 3)

# mean response for active arm
mean_act<- round(simulate_TE(f, M, pattern = 5), 3) # pattern = 5: proportional decline

# variance-covariance matrix
cov_cor <- simulate_corr(pattern = "AR1", M)
cov_adni <- cov_cor$cov
cor_adni <- cov_cor$cor

# sd
sd = 0.15

# simulated data
set.seed(11)
dat <- simulate_trial(n_arm = 200,
                      M = M,
                      mean_pbo = mean_pbo,
                      mean_act = mean_act,
                      cov = cov_adni,
                      sd = sd)
```

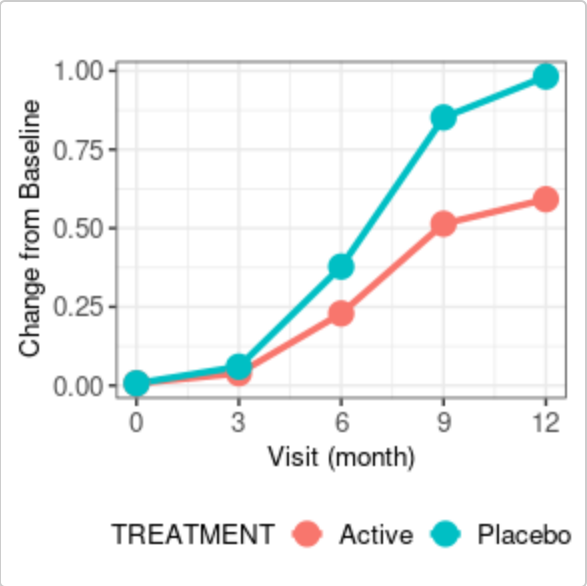
```r
# Check simulated data

df <- dat %>% group_by(trt, M) %>% summarise(Y=round(mean(y), 3))

df <- df %>% mutate(trt = as.character(trt), trt = ifelse(trt == "act", "Active", "Placebo")) %>%
  rename(TREATMENT = trt)

p <- ggplot(df, aes(x=M, y=Y, group=TREATMENT, color=TREATMENT)) +
  geom_line(size=1.2) +
  geom_point(size=4) +
  labs(x = "Visit (month)", y = "Change from Baseline", title = "") +
  scale_x_continuous(breaks = seq(0,12,3), labels = c(0,3,6,9,12)) +
  theme_bw() +
  theme(legend.position = "bottom",
        axis.text = element_text(size = 10),
        axis.title = element_text(size = 10),
        plot.title = element_text(size = 10),
        legend.text = element_text(size = 10),
        legend.title = element_text(size = 10),
        legend.key.size = unit(0.5, 'cm'))
```

```
p
```



Part 2: Main analysis

MMRM (last-visit)

```
fit1 <- MMRM(dat, duration = 12)

p1 <- fit1$contrast$Pvalue; theta1 <- fit1$contrast$Contrast

print(paste0("The treatment effect is measured as the decline (i.e., the vertical difference) at the
         last visit, which equals to ", round(theta1, 2), "; p-value = ", round(p1, 3)))
```

```
## [1] "The treatment effect is measured as the decline (i.e., the vertical difference) at the last
visit, which equals to 0.39; p-value = 0.023"
```

pAUC (partial AUC)

```
fit2 <- pAUC(dat, start = 2, nboot = 1000)

p2 = fit2$p; theta2 = fit2$obs

print(paste0("The treatment effect is measured as the area between the active and placebo curves over
         the post-baseline visits, which equals to ", round(theta2, 2), "; p-value = ", round(p2,
         3)))
```

```
## [1] "The treatment effect is measured as the area between the active and placebo curves over the
post-baseline visits, which equals to 2.08; p-value = 0.04"
```

PMRM (proportional decline)

```
fit3 <- prop.decline.m12(dat)

p3 = fit3$p; theta3 = fit3$mod$coefficients[6]*100

print(paste0("The treatment effect is measured as the average proportion of decline across the post-
         baseline visits, which equals to ", round(theta3, 2), "%; p-value = ", round(p3, 6)))
```

```
## [1] "The treatment effect is measured as the average proportion of decline across the post-
baseline visits, which equals to 39.99%; p-value = 3.8e-05"
```

PMRM (constant decline)

```
fit4 <- const.decline.m12(dat)

p4 = fit4$p; theta4 = fit4$mod$coefficients[6]

print(paste0("The treatment effect is measured as the average decline across the post-baseline
         visits, which equals to ", round(theta4, 2), "; p-value = ", round(p4, 3)))
```

```
## [1] "The treatment effect is measured as the average decline across the post-baseline visits,
which equals to 0.1; p-value = 0.164"
```

PMRM (unstructured decline)

```
fit5 <- unstruct.decline.m12(dat)

p5 = fit5$p; theta5 = fit5$mod$coefficients[6:9]

print(paste0("The treatment effect is measured as declines across the post-baseline visits, which
         equal to ", paste0(round(theta5, 2), collapse = ", "), ", respectively; p-value = ",
         round(p5, 3)))
```

```
## [1] "The treatment effect is measured as declines across the post-baseline visits, which equal to
0.02, 0.15, 0.34, 0.39, respectively; p-value = 0.003"
```

PMRM (delay-based)

PMRM (delay-based) methods generally have inflation in Type I error.

NCS

```
fit6 <- ncs_ranslp_df2(dat, intercept = FALSE)

p6 = fit6$wald.test$p_val; theta6 = summary(fit6$mod)$coefficients[3:4,1]
```

```
print(paste0("The treatment effect is measured as treatment-by-time (i.e., basis functions of time)
         interaction coefficients, which equal to ", paste0(round(theta6, 2), collapse = ", "), ",
         respectively; p-value = ", round(p6, 3)))
```

```
## [1] "The treatment effect is measured as treatment-by-time (i.e., basis functions of time)
interaction coefficients, which equal to -0.44, -0.36, respectively; p-value = 0.005"
```

CTLDA

```
p7 = CTLDA(pvec = c(p2, p3, p5))

print(paste0("Cauchy Combination Test p-value = ", round(p7, 4), "; treatment effect measurement is
         not available for CTLDA method"))
```

```
## [1] "Cauchy Combination Test p-value = 1e-04; treatment effect measurement is not available for
CTLDA method"
```