

ANCOVA Comparison Simulations: Skewed, Poisson Data

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Poisson data

As in the other simulations that use Gaussian data, we assume the following linear data-generating process:

$$\tilde{Y}_{ij1} = \beta_0 Y_{ij0} + \beta_j + \gamma_j Z_{ij} + \varepsilon_{ij}$$

for individuals $i = 1, \dots, n_j$, $j = 1, \dots, J$. β_0 is the coefficient for the baseline measurement Y_{i0} , β_j is the mean effect of being at stratum j , Z_{ij} is the treatment level indicator,, γ_j is the effect of treatment at stratum j , and ε_{ij} takes the values 0 or 0.5 with equal probability. We will assume that $\beta_0 = 1$.

Now, instead of Y_{ij0} being normally distributed, we let these baseline measurements come from a truncated Poisson distribution with mean 4, with values greater than 10 censored and set to 10. This is reflective of some survey data where individuals are asked to rate their experience on a scale from 1 to 10. The data are not only discrete but also skewed: more values are in the lower half of the range.

We don't observe \tilde{Y}_{ij1} but Y_{ij1} , which is defined as

$$Y_{ij1} = \begin{cases} 1 & \text{if } \tilde{Y}_{ij1} < 1 \\ 10 & \text{if } \tilde{Y}_{ij1} > 10 \\ \lfloor \tilde{Y}_{ij1} \rfloor & \text{otherwise} \end{cases}$$

Suppose there are three strata with $\beta_1 = 1$, $\beta_2 = 1.5$, and $\beta_3 = 2$. Assume that there are 16 individuals per stratum and treatment assignment is balanced, i.e. 8 people receive each treatment at each stratum.

We use two designs:

- Design 1: $\gamma_1 = \gamma_2 = \gamma_3 = 1$. This is the standard assumption of a constant, additive treatment effect.
- Design 2: $\gamma_1 = \gamma > 0$, $\gamma_2 = \gamma_3 = 0$. This is a constant, additive treatment effect at stratum 1, but no treatment effect at strata 2 and 3. This is a simplistic case of heterogeneous treatment effects.

With these two designs, we vary the distribution of ε . In the first case, we use $\varepsilon \sim N(0, 1)$ to mimic the usual ANCOVA assumptions. In the second case, $\varepsilon \sim t(2)$ so the errors are heavy-tailed. Thus, there are four total simulation designs.

We compare five tests:

- ANCOVA: we fit a linear model of response Y_1 on baseline Y_0 , treatment Z , and a dummy for stratum.
- Stratified permutation: we permute treatment assignment within stratum, then take the difference in means between treated and control outcomes Y_1
- Differenced permutation: we do the same permutation procedure as the stratified permutation test, except we use the difference between outcome and baseline, $Y_1 - Y_0$
- Linear model (LM) permutation: we use the same stratified permutation procedure as above, except use the t -statistic for the coefficient on treatment in the linear regression of Y_1 on Y_0 , Z , and stratum dummies
- Freedman-Lane test: see the other Rmd document for a full description of this procedure

Throughout our simulations, we first fix Y_0 and stratum ID. Treatment Z and the errors ε are randomly drawn according to their respective distributions. Then, Y_1 is constructed using the linear data-generating process above. We regenerate Z , ε , and Y_1 100 times for each design, then compute the empirical power of the five tests.

Data-generation, tests, and plotting functions

```
generate_outcome <- function(baseline, tr_effect, stratum_effect,
  error) {
  Y1 <- baseline + tr_effect + stratum_effect + error
  Y1 <- floor(Y1)
  Y1 <- pmax(pmin(Y1, 10), 1)
  return(Y1)
}

generate_simulated_data <- function(gamma, effect, n = c(16,
  16, 16)) {
  # Input: gamma = the magnitude of the treatment effect effect
  # = 'same effect' or 'single stratum effect' - which strata
  # have a tr effect > 0? n = number of individuals at each
  # stratum Returns: a dataframe containing columns named Y1
  # (response), Y0 (baseline), Z (treatment), gamma_vec
  # (treatment effect per individual), stratumID (stratum),
  # stratum_effect (beta coefficient per individual), and
  # epsilon (errors)

  stratumID <- rep(1:3, times = n)
  N <- sum(n)
  beta <- c(1, 1.5, 2)

  # What is the treatment effect?
  if (effect == "same effect") {
    gamma_vec <- rep(gamma, N)
  } else {
    gamma_vec <- rep(c(gamma, 0, 0), times = n)
  }

  # Generate covariates
  epsilon <- rbinom(N, 1, 0.5) - 0.5
  Y0 <- rpois(N, lambda = 4)
  Y0[Y0 > 10] <- 10
  Z <- rep(0:1, length.out = N)
  stratum_effect <- rep(beta, times = n)
  Y1 <- generate_outcome(Y0, gamma_vec * Z, stratum_effect,
    epsilon)
  return(data.frame(Y1, Y0, Z, gamma_vec, stratumID, stratum_effect,
    epsilon))
}

generate_simulated_pvalues <- function(dataset, reps = 1000) {
  # Inputs: dataset = a dataframe containing columns named Y1
```

```

# (response), Y0 (baseline), Z (treatment), and stratumID
# (stratum) Returns: a vector of p-values first element is
# the p-value from the ANCOVA second element is the p-value
# from the stratified two-sample permutation test third
# element is the p-value from the linear model test,
# permuting treatment fourth element is the p-value from the
# Freedman-Lane linear model test, permuting residuals

# ANCOVA
modelfit <- lm(Y1 ~ Y0 + Z + factor(stratumID), data = dataset)
resanova <- summary(aov(modelfit))
anova_pvalue <- resanova[[1]]["Z", "Pr(>F)"]

# Stratified permutation test of Y1
observed_diff_means <- mean(dataset$Y1[dataset$Z == 1]) -
  mean(dataset$Y1[dataset$Z == 0])
diff_means_distr <- stratified_two_sample(group = dataset$Z,
  response = dataset$Y1, stratum = dataset$stratumID, reps = reps)
perm_pvalue <- t2p(observed_diff_means, diff_means_distr,
  alternative = "two-sided")

# Diffed permutation test of Y1-Y0
dataset$diff <- dataset$Y1 - dataset$Y0
observed_diff_means2 <- mean(dataset$diff[dataset$Z == 1]) -
  mean(dataset$diff[dataset$Z == 0])
diff_means_distr2 <- stratified_two_sample(group = dataset$Z,
  response = dataset$diff, stratum = dataset$stratumID,
  reps = reps)
perm_pvalue2 <- t2p(observed_diff_means2, diff_means_distr2,
  alternative = "two-sided")

# Permutation of treatment in linear model
observed_t1 <- summary(modelfit)[["coefficients"]]["Z", "t value"]
lm1_t_distr <- replicate(reps, {
  dataset$Z_perm <- permute_within_groups(dataset$Z, dataset$stratumID)
  lm1_perm <- lm(Y1 ~ Y0 + Z_perm + factor(stratumID),
    data = dataset)
  summary(lm1_perm)[["coefficients"]]["Z_perm", "t value"]
})
lm_pvalue <- t2p(observed_t1, lm1_t_distr, alternative = "two-sided")

# Freedman-Lane linear model residual permutation
lm2_no_tr <- lm(Y1 ~ Y0 + factor(stratumID), data = dataset)
lm2_resid <- residuals(lm2_no_tr)
lm2_yhat <- fitted(lm2_no_tr)
lm2_t_distr <- replicate(reps, {
  lm2_resid_perm <- permute_within_groups(lm2_resid, dataset$stratumID)
  dataset$response_fl <- lm2_yhat + lm2_resid_perm
  lm2_perm <- lm(response_fl ~ Y0 + Z + factor(stratumID),
    data = dataset)
  summary(lm2_perm)[["coefficients"]]["Z", "t value"]
})
fl_pvalue <- t2p(observed_t1, lm2_t_distr, alternative = "two-sided")

```

```

    return(c(ANCOVA = anova_pvalue, `Stratified Permutation` = perm_pvalue,
            `Differenced Permutation` = perm_pvalue2, `LM Permutation` = lm_pvalue,
            `Freedman-Lane` = fl_pvalue))
}

compute_power <- function(pvalues) {
  apply((0:99)/100, function(p) mean(pvalues <= p, na.rm = TRUE))
}

plot_power_curves <- function(power_mat, title) {
  melt(power_mat) %>% mutate(pvalue = Var1/100) %>% mutate(Method = Var2) %>%
    ggplot(aes_string(x = "pvalue", y = "value", color = "Method")) +
    geom_line() + geom_abline(intercept = 0, slope = 1, linetype = "dashed") +
    xlab("P-value") + ylab("Power") + ggtitle(title)
}

plot_pvalue_hist <- function(pvalue_mat, title) {
  melt(pvalue_mat) %>% mutate(Method = Var2) %>% ggplot(aes(x = value,
    fill = Method)) + geom_histogram() + facet_wrap(~Method) +
    ggtitle(title)
}

plot_pvalue_scatter <- function(pvalue_mat, title) {
  pvalue_mat %>% as.data.frame() %>% select(ANCOVA, strat = starts_with("Stratified")) %>%
    ggplot(aes(x = ANCOVA, y = strat)) + geom_point() + xlim(0,
    1) + ylim(0, 1) + ylab("Stratified Permutation") + geom_abline(intercept = 0,
    slope = 1, linetype = "dashed") + ggtitle(title)
}

```

Test level: simulation under the null

Before testing for different kinds of effects, we begin checking that the tests have the correct level. We follow the procedure described above, using an effect size of $\gamma = 0$ at all strata and using standard normal errors. To have the correct level means that the test rate of rejection at level α is $\alpha 100\%$. In other words, the p-values are uniformly distributed and the power curve should coincide with the line with slope 1 through the origin. Figure ?? demonstrates that this is the case. If anything, the differenced stratified permutation test has fewer than $\alpha 100\%$ false positives when using level α .

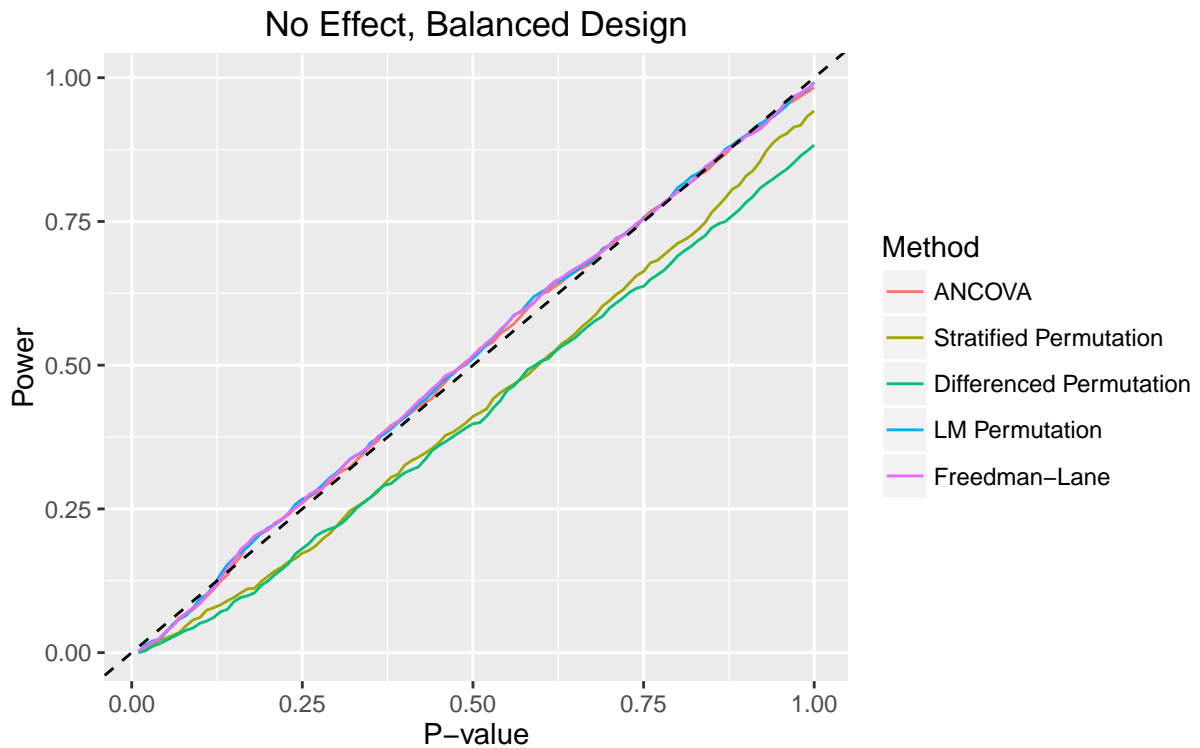
```

set.seed(760682460) # Generated from random.org Timestamp: 2016-11-14 10:21:12 UTC

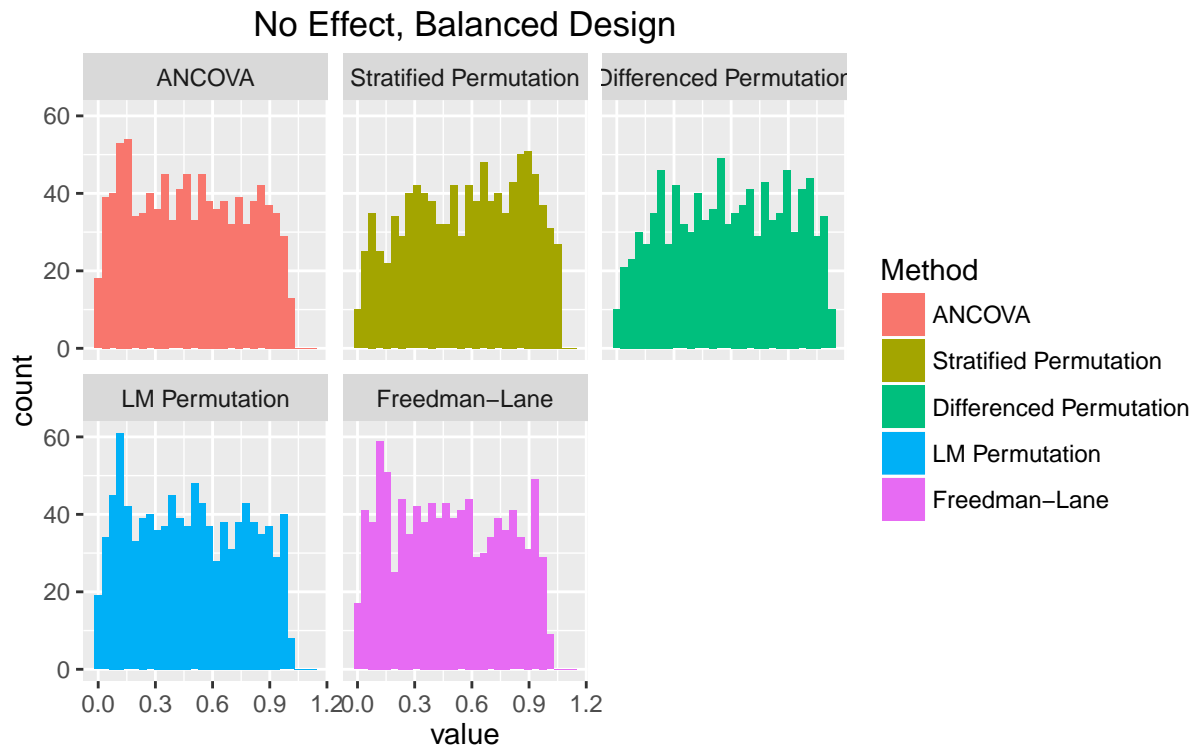
tmp <- generate_simulated_data(gamma = 0, effect = "same effect")
design0_pvalues <- replicate(1000, {
  tmp$epsilon <- rnorm(nrow(tmp))
  tmp$Z <- permute_within_groups(tmp$Z, tmp$stratumID)
  tmp$Y1 <- generate_outcome(tmp$Y0, rep(0, nrow(tmp)), tmp$stratum_effect,
    tmp$epsilon)
  generate_simulated_pvalues(tmp)
})
design0_pvalues <- t(design0_pvalues)
colnames(design0_pvalues) <- c("ANCOVA", "Stratified Permutation",
  "Differenced Permutation", "LM Permutation", "Freedman-Lane")
design0_power <- apply(design0_pvalues, 2, compute_power)

```

```
plot_power_curves(design0_power, "No Effect, Balanced Design")
```



```
plot_pvalue_hist(design0_pvalues, "No Effect, Balanced Design")
```



Design 1: Constant additive effect

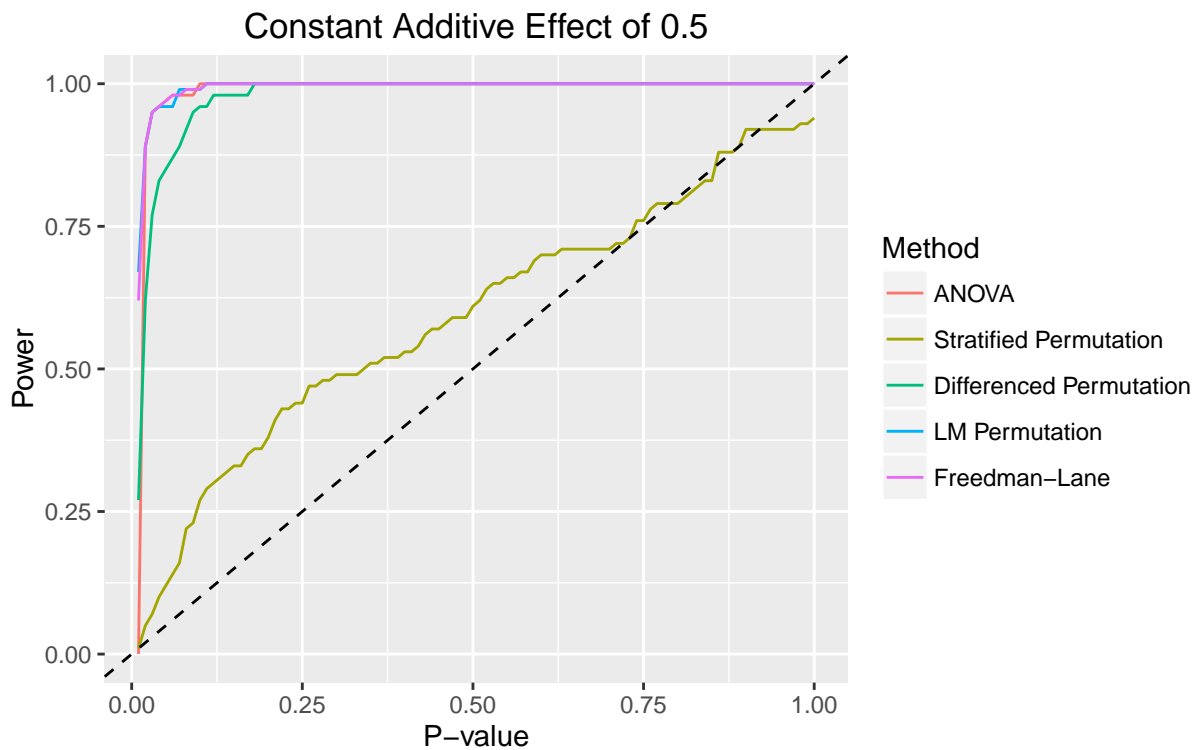
There is no discernable difference in power between the ANCOVA, the differenced stratified permutation test, the LM permutations, or the Freedman-Lane test. However, the simple stratified permutation test of Y_1 has substantially less power than the other four. Without controlling for the baseline values, the variance in Y_1 masks the treatment effect.

```
set.seed(760682460) # Generated from random.org Timestamp: 2016-11-14 10:21:12 UTC

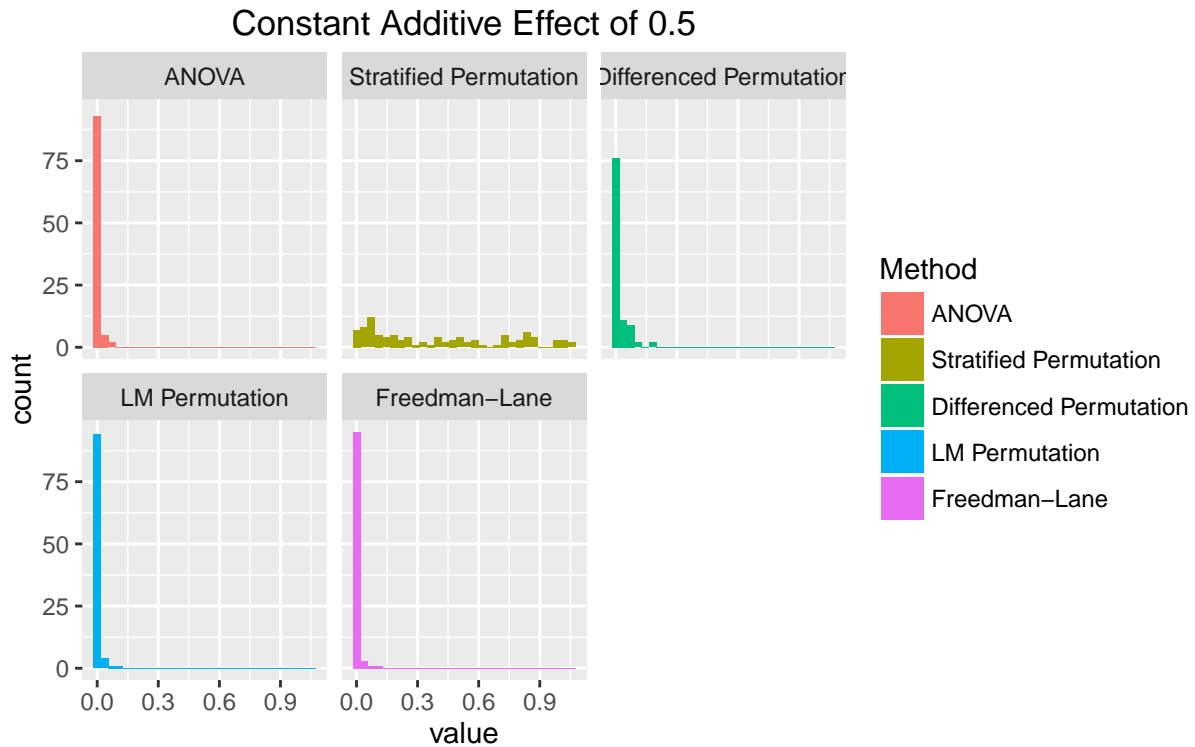
tmp <- generate_simulated_data(gamma = 0.5, effect = "same effect")
design1_pvalues <- replicate(1000, {
  tmp$Z <- permute_within_groups(tmp$Z, tmp$stratumID)
  tmp$epsilon <- rbinom(nrow(tmp), 1, 0.5) - 0.5
  tmp$Y1 <- generate_outcome(tmp$Y0, tmp$Z * tmp$gamma_vec,
    tmp$stratum_effect, tmp$epsilon)
  generate_simulated_pvalues(tmp)
})

design1_pvalues <- t(design1_pvalues)
colnames(design1_pvalues) <- c("ANCOVA", "Stratified Permutation",
  "Differenced Permutation", "LM Permutation", "Freedman-Lane")
design1_power <- apply(design1_pvalues, 2, compute_power)

p1 <- plot_power_curves(design1_power, "Constant Additive Effect of 0.5")
p1
```



```
plot_pvalue_hist(design1_pvalues, "Constant Additive Effect of 0.5")
```



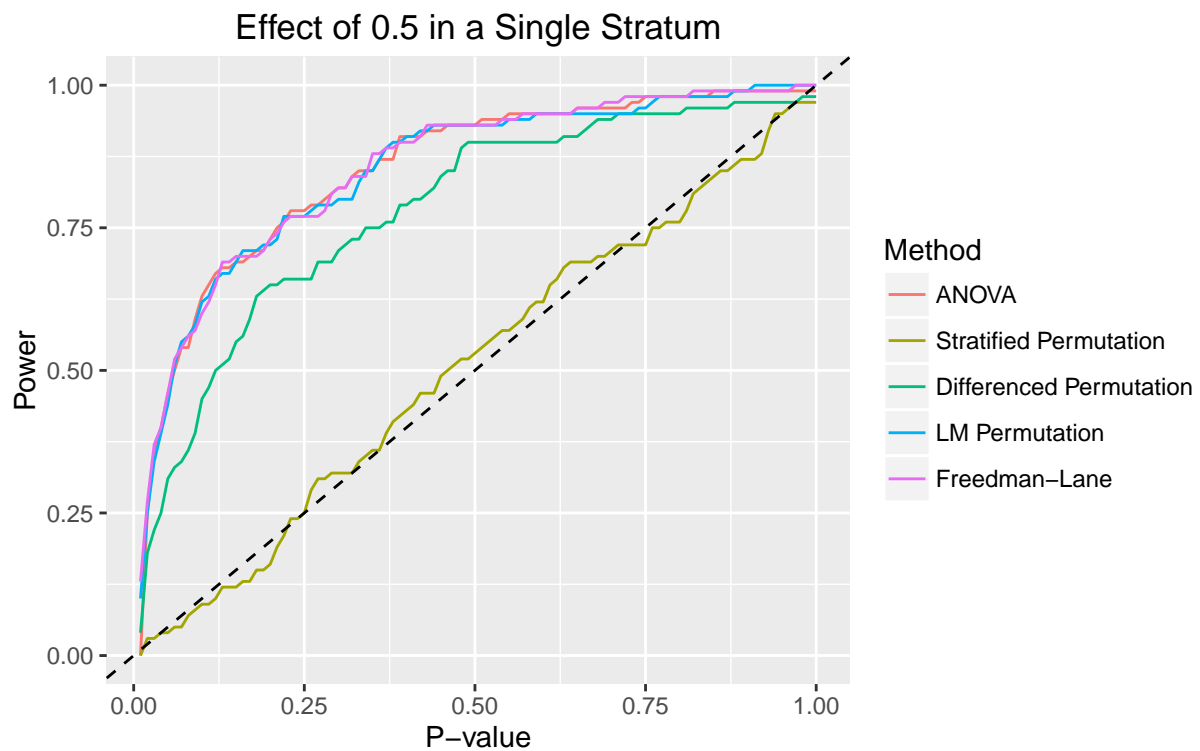
Design 2: Single stratum effect

A similar pattern emerges: the simple stratified permutation test has low power, while the other four power curves roughly coincide. The Freedman-Lane test may have the highest power for small p-values, but this could also just be noise. All five power curves are closer to the line passing through the origin: since the effect is only present at one stratum, it is more difficult to detect.

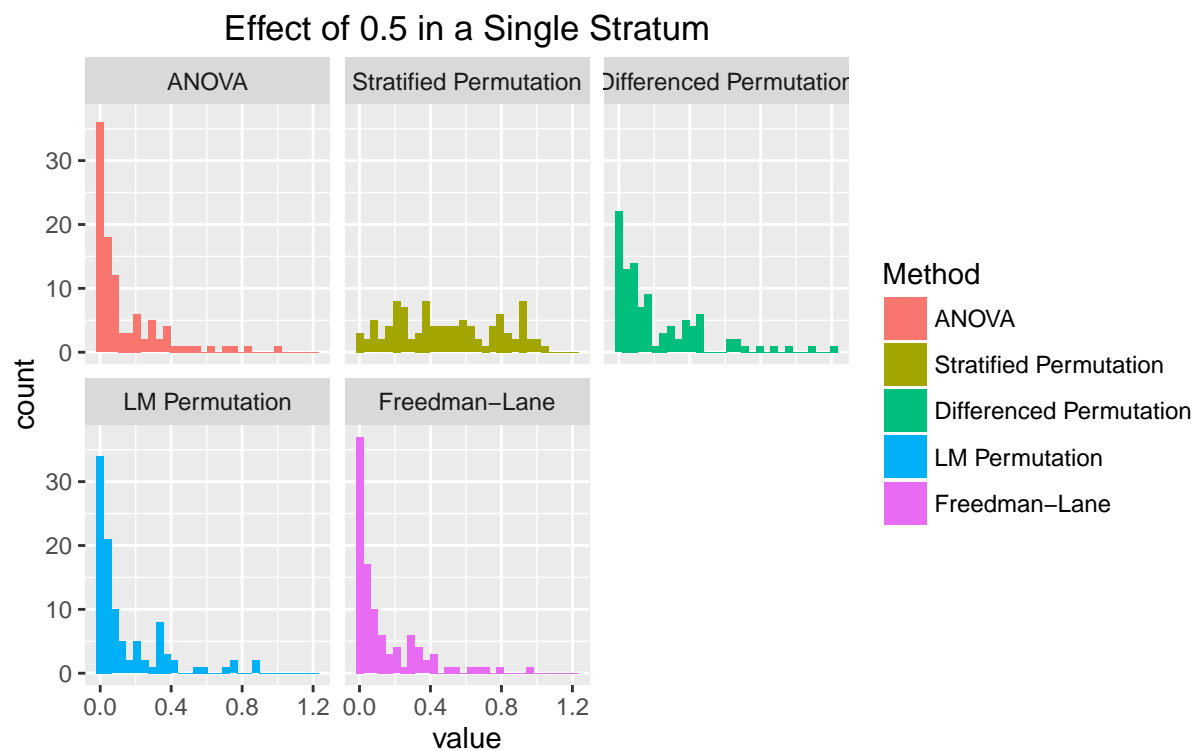
```
set.seed(760682460) # Generated from random.org Timestamp: 2016-11-14 10:21:12 UTC

tmp <- generate_simulated_data(gamma = 0.5, effect = "single stratum effect")
design2_pvalues <- replicate(1000, {
  tmp$Z <- permute_within_groups(tmp$Z, tmp$stratumID)
  tmp$epsilon <- rbinom(nrow(tmp), 1, 0.5) - 0.5
  tmp$Y1 <- generate_outcome(tmp$Y0, tmp$Z * tmp$gamma_vec,
    tmp$stratum_effect, tmp$epsilon)
  generate_simulated_pvalues(tmp)
})
design2_pvalues <- t(design2_pvalues)
colnames(design2_pvalues) <- c("ANCOVA", "Stratified Permutation",
  "Differenced Permutation", "LM Permutation", "Freedman-Lane")
design2_power <- apply(design2_pvalues, 2, compute_power)

p2 <- plot_power_curves(design2_power, "Effect of 0.5 in a Single Stratum")
p2
```



```
plot_pvalue_hist(design2_pvalues, "Effect of 0.5 in a Single Stratum")
```



Design 3: Unpredictive baseline

Suppose that the baseline measure is not strongly predictive of the outcome. Then, we'd expect that controlling for baseline will not improve the power of the test, and may even make it worse. Suppose that in the linear data-generating process above, we have $\beta_0 = 0.25$, meaning that Y_1 and Y_0 have a correlation of 0.25.

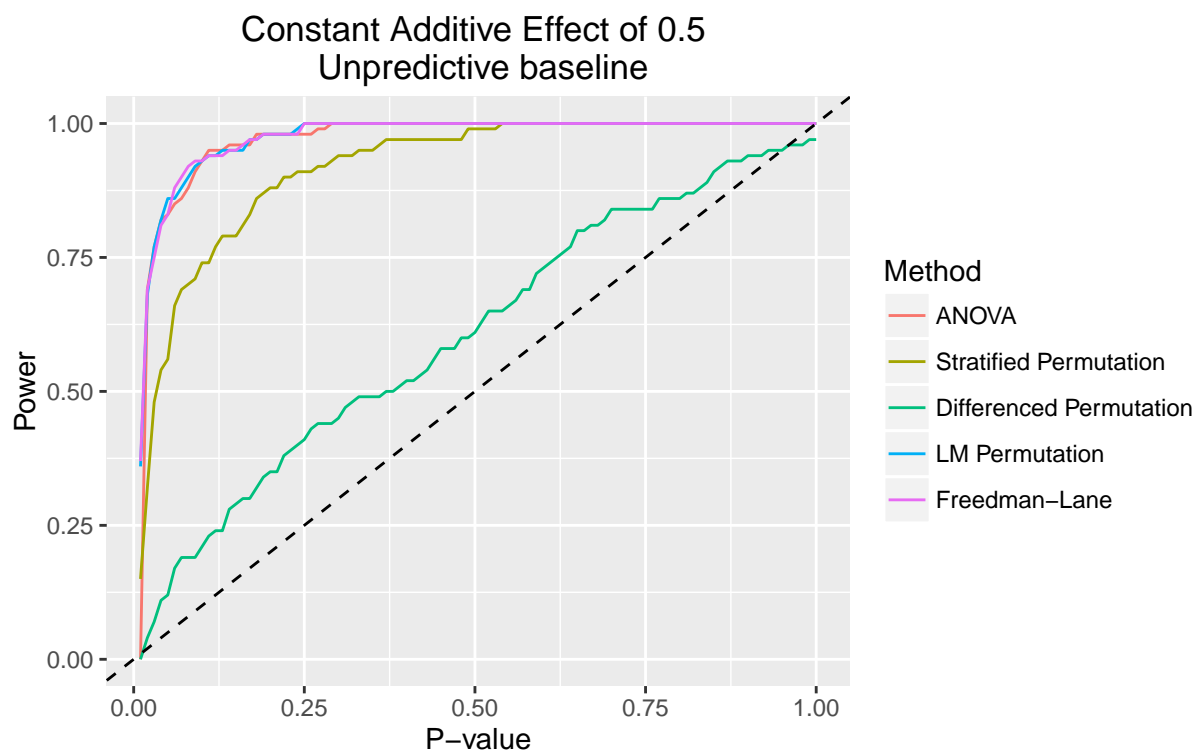
The power curves for this design look similar to those from Design 1 with one important difference: the stratified permutation test has power very close to ANCOVA and the two linear model tests, while the differenced permutation test has lower power. This suggests that one should be careful when incorporating control variables; naively taking the difference $Y_1 - Y_0$ does not capture the correct relationship between baseline and outcome.

```
set.seed(760682460) # Generated from random.org Timestamp: 2016-11-14 10:21:12 UTC

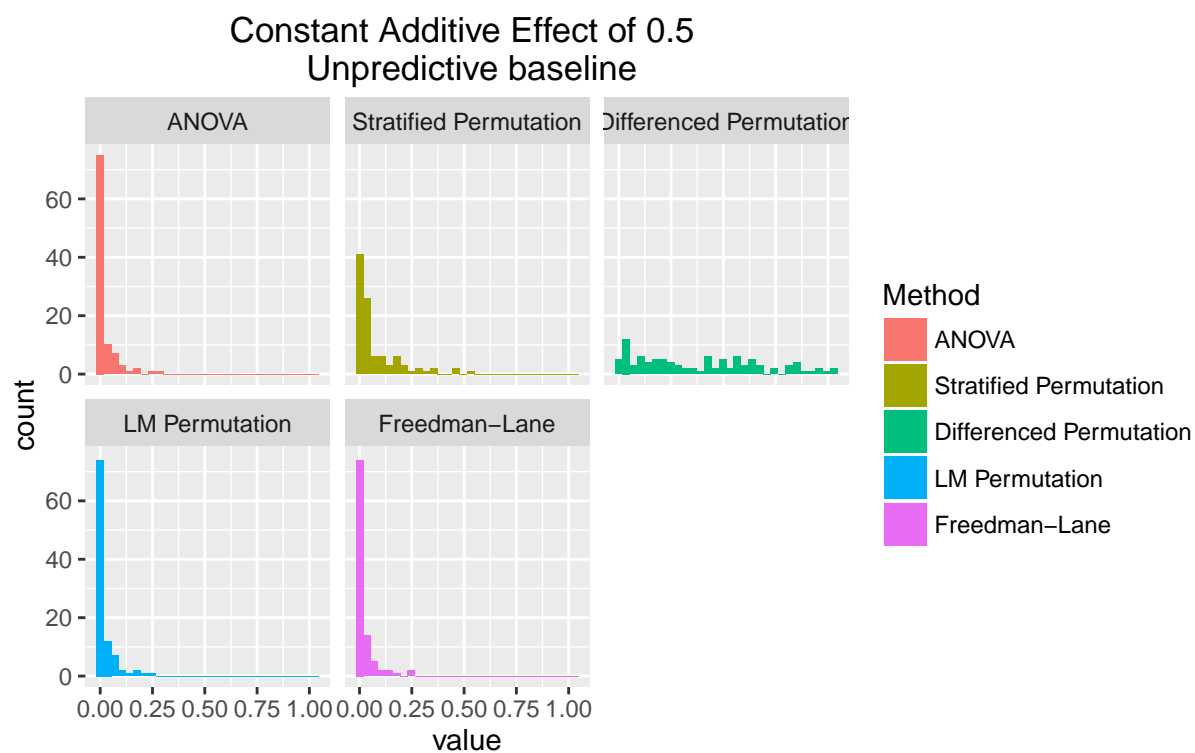
tmp <- generate_simulated_data(gamma = 0.5, effect = "same effect")
design3_pvalues <- replicate(100, {
  tmp$Z <- permute_within_groups(tmp$Z, tmp$stratumID)
  tmp$epsilon <- rbinom(nrow(tmp), 1, 0.5) - 0.5
  tmp$Y1 <- generate_outcome(0.1 * tmp$Y0, tmp$Z * tmp$gamma_vec,
    tmp$stratum_effect, tmp$epsilon)
  generate_simulated_pvalues(tmp)
})

design3_pvalues <- t(design3_pvalues)
colnames(design3_pvalues) <- c("ANCOVA", "Stratified Permutation",
  "Differenced Permutation", "LM Permutation", "Freedman-Lane")
design3_power <- apply(design3_pvalues, 2, compute_power)

p3 <- plot_power_curves(design3_power, "Constant Additive Effect of 0.5 \n Unpredictive baseline")
p3
```



```
plot_pvalue_hist(design3_pvalues, "Constant Additive Effect of 0.5 \n Unpredictive baseline")
```



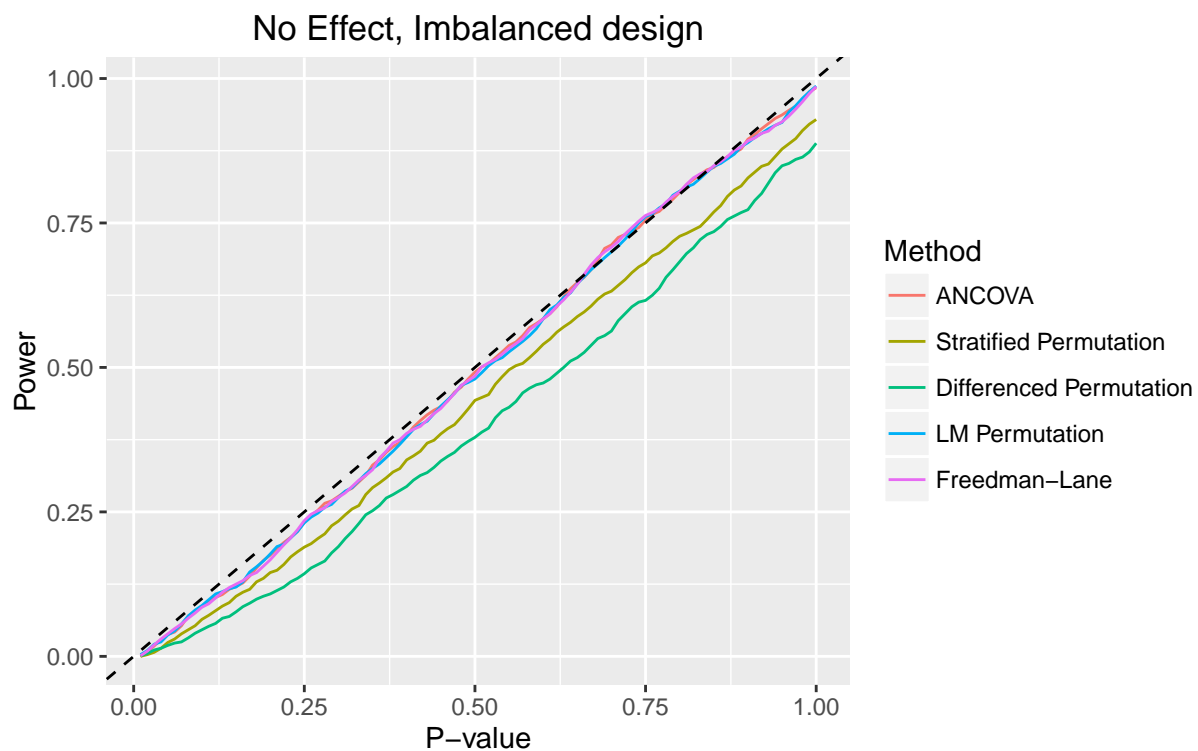
Test level: imbalanced design

Suppose that instead of having 16 individuals per stratum, we distribute them unequally across strata: stratum 1 has 8 patients, stratum 2 has 16 patients, and stratum 3 has 24 patients. This imbalance does not violate any assumptions of the ANCOVA. However, it may reduce power if the effect is concentrated in strata with fewer patients.

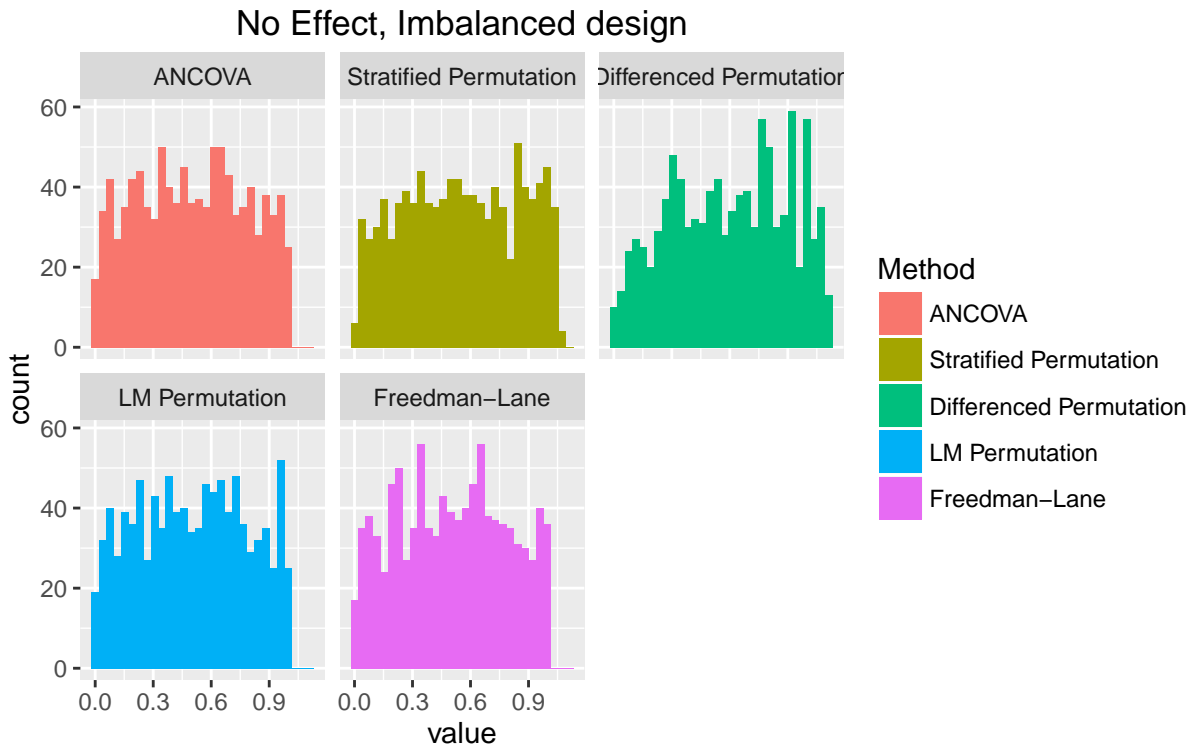
```
set.seed(760682460) # Generated from random.org Timestamp: 2016-11-14 10:21:12 UTC
```

```
tmp <- generate_simulated_data(gamma = 0, effect = "same effect",  
  n = c(8, 16, 24))  
design00_pvalues <- replicate(1000, {  
  tmp$epsilon <- rnorm(nrow(tmp))  
  tmp$Z <- permute_within_groups(tmp$Z, tmp$stratumID)  
  tmp$Y1 <- generate_outcome(tmp$Y0, rep(0, nrow(tmp)), tmp$stratum_effect,  
    tmp$epsilon)  
  generate_simulated_pvalues(tmp)  
})  
design00_pvalues <- t(design00_pvalues)  
colnames(design00_pvalues) <- c("ANCOVA", "Stratified Permutation",  
  "Differenced Permutation", "LM Permutation", "Freedman-Lane")  
design00_power <- apply(design00_pvalues, 2, compute_power)
```

```
plot_power_curves(design00_power, "No Effect, Imbalanced design")
```



```
plot_pvalue_hist(design00_pvalues, "No Effect, Imbalanced design")
```



Design 4: Constant additive effect, imbalanced design

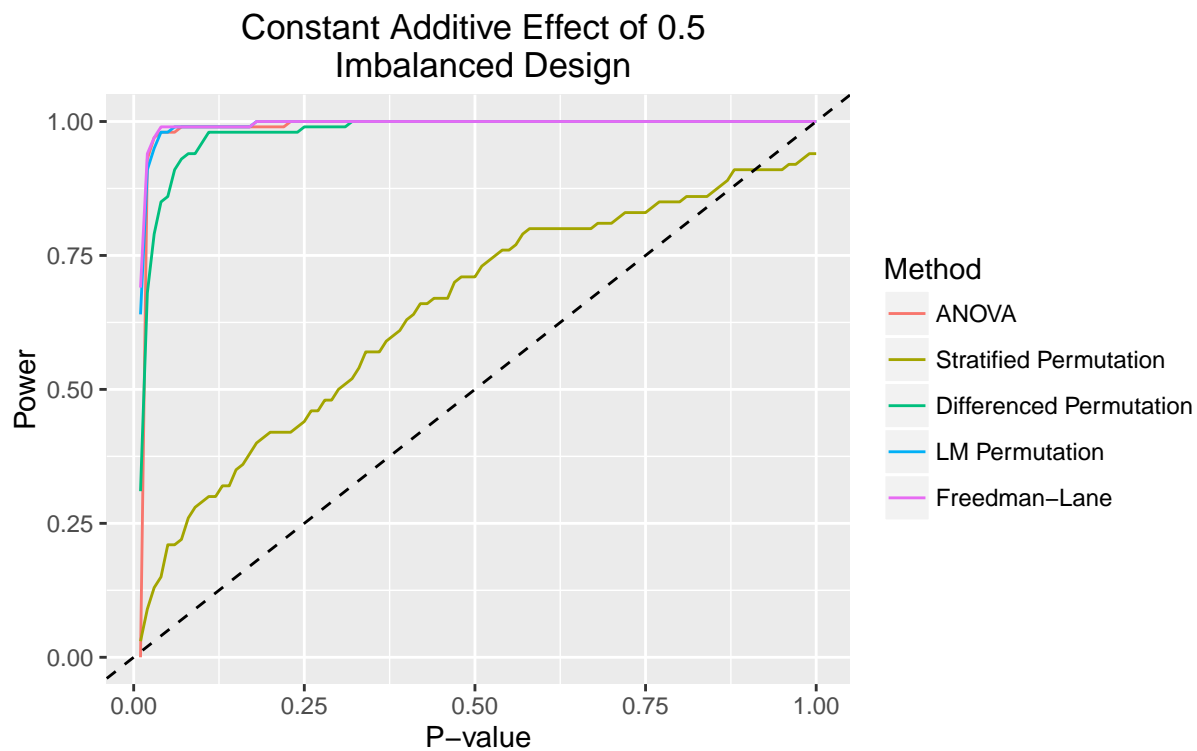
The power curves here are very similar to those in Design 1. This result is expected, since the effect is still present among all patients who received treatment.

```
set.seed(760682460) # Generated from random.org Timestamp: 2016-11-14 10:21:12 UTC

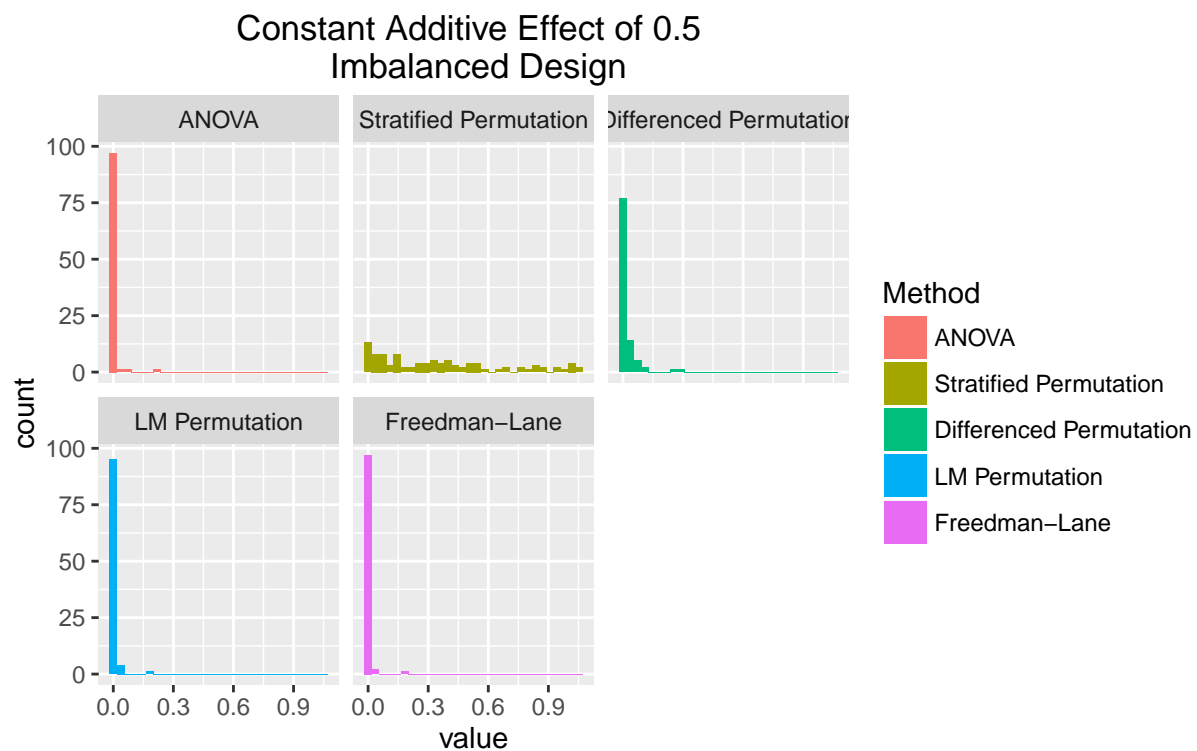
tmp <- generate_simulated_data(gamma = 0.5, effect = "same effect",
  n = c(8, 16, 24))
design4_pvalues <- replicate(1000, {
  tmp$Z <- permute_within_groups(tmp$Z, tmp$stratumID)
  tmp$epsilon <- rbinom(nrow(tmp), 1, 0.5) - 0.5
  tmp$Y1 <- generate_outcome(tmp$Y0, tmp$Z * tmp$gamma_vec,
    tmp$stratum_effect, tmp$epsilon)
  generate_simulated_pvalues(tmp)
})

design4_pvalues <- t(design4_pvalues)
colnames(design4_pvalues) <- c("ANCOVA", "Stratified Permutation",
  "Differenced Permutation", "LM Permutation", "Freedman-Lane")
design4_power <- apply(design4_pvalues, 2, compute_power)

p4 <- plot_power_curves(design4_power, "Constant Additive Effect of 0.5 \n Imbalanced Design")
p4
```



```
plot_pvalue_hist(design4_pvalues, "Constant Additive Effect of 0.5 \n Imbalanced Design")
```



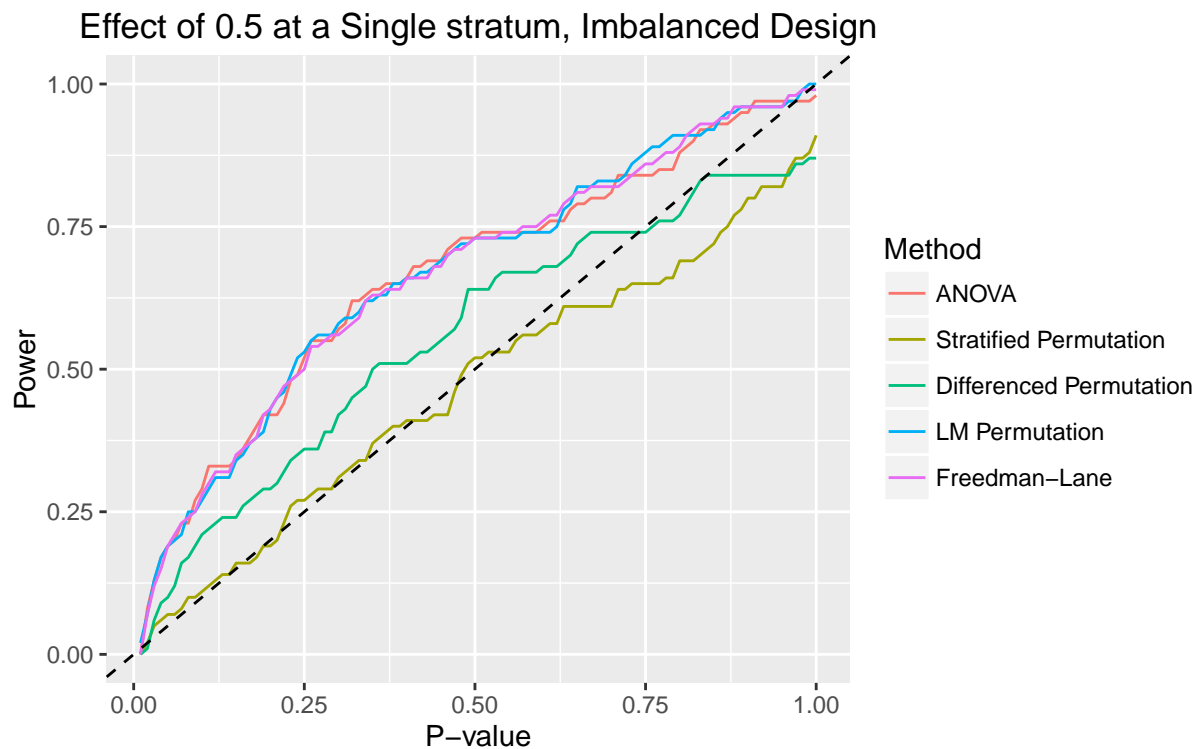
Design 5: Single stratum effect, imbalanced design

There is very low power to detect the effect here, since in the simulated data, the stratum with only 8 patients was the only stratum with a nonzero effect of treatment. The treatment effect is on the same order of magnitude as the error variance.

```
set.seed(760682460) # Generated from random.org Timestamp: 2016-11-14 10:21:12 UTC

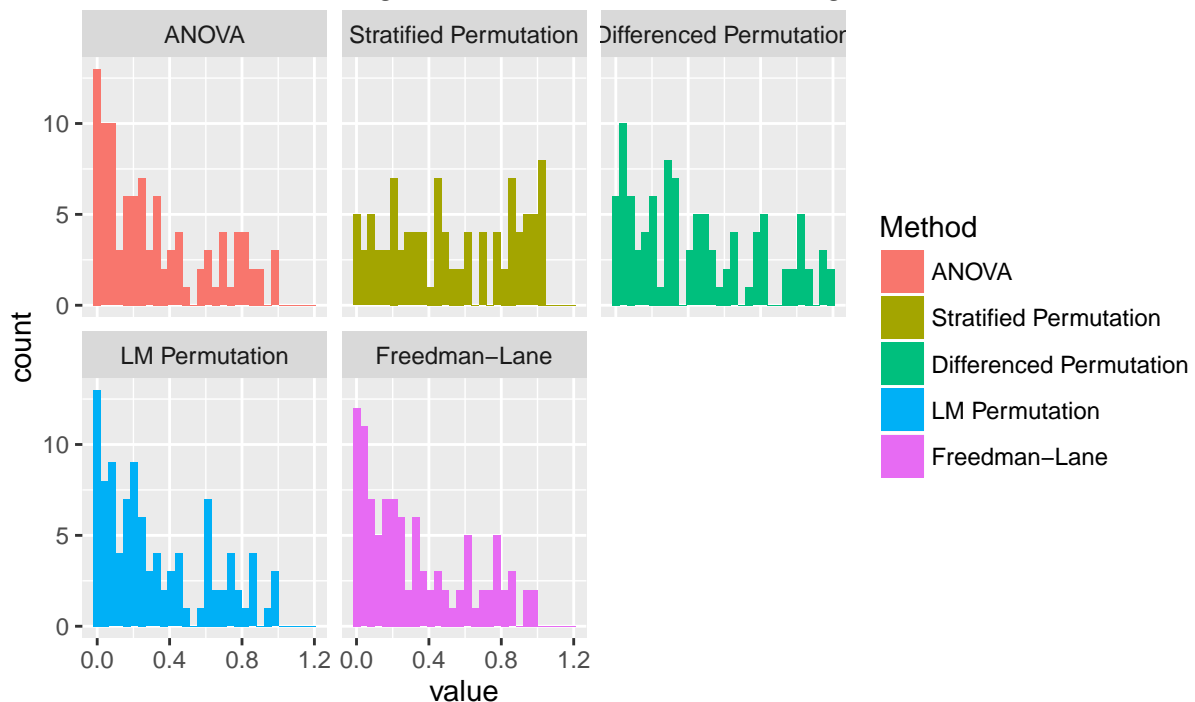
tmp <- generate_simulated_data(gamma = 0.5, effect = "single stratum effect",
  n = c(8, 16, 24))
design5_pvalues <- replicate(100, {
  tmp$Z <- permute_within_groups(tmp$Z, tmp$stratumID)
  tmp$epsilon <- rbinom(nrow(tmp), 1, 0.5) - 0.5
  tmp$Y1 <- generate_outcome(tmp$Y0, tmp$Z * tmp$gamma_vec,
    tmp$stratum_effect, tmp$epsilon)
  generate_simulated_pvalues(tmp)
})
design5_pvalues <- t(design5_pvalues)
colnames(design5_pvalues) <- c("ANCOVA", "Stratified Permutation",
  "Differenced Permutation", "LM Permutation", "Freedman-Lane")
design5_power <- apply(design5_pvalues, 2, compute_power)

p5 <- plot_power_curves(design5_power, "Effect of 0.5 at a Single stratum, Imbalanced Design")
p5
```



```
plot_pvalue_hist(design5_pvalues, "Effect of 0.5 at a Single stratum, Imbalanced Design")
```

Effect of 0.5 at a Single stratum, Imbalanced Design

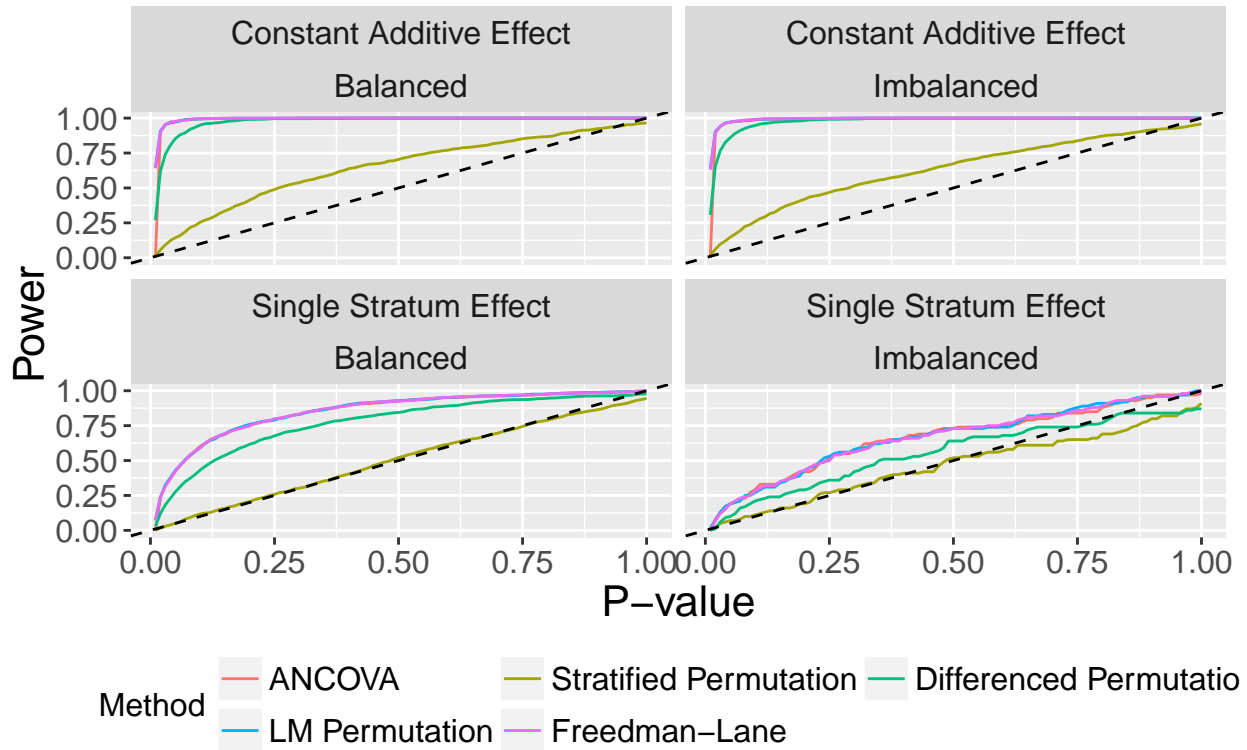


```
# plots4 <- lapply(list(p1, p2, p4, p5), function(pl) pl +
# theme(legend.position = 'none') + ggtitle(''))
# do.call(grid.arrange, plots4)
```

```
powers <- list(design1_power %>% as.data.frame() %>% mutate(Treatment = rep("Constant Additive Effect",
nrow(design1_power)), Design = rep("Balanced", nrow(design1_power))),
design2_power %>% as.data.frame() %>% mutate(Treatment = rep("Single Stratum Effect",
nrow(design2_power)), Design = rep("Balanced", nrow(design2_power))),
design4_power %>% as.data.frame() %>% mutate(Treatment = rep("Constant Additive Effect",
nrow(design4_power)), Design = rep("Imbalanced", nrow(design4_power))),
design5_power %>% as.data.frame() %>% mutate(Treatment = rep("Single Stratum Effect",
nrow(design5_power)), Design = rep("Imbalanced", nrow(design5_power))),
design0_power %>% as.data.frame() %>% mutate(Treatment = rep("No Effect",
nrow(design0_power)), Design = rep("Balanced", nrow(design0_power))),
design00_power %>% as.data.frame() %>% mutate(Treatment = rep("No Effect",
nrow(design00_power)), Design = rep("Imbalanced", nrow(design00_power))))
```

```
all_power_curves <- do.call(rbind, powers)
twobytwo <- all_power_curves %>% filter(Treatment != "No Effect") %>%
melt(id.vars = c("Treatment", "Design")) %>% mutate(pvalue = rep((1:100)/100,
5 * 4)) %>% mutate(Method = variable) %>% ggplot(aes_string(x = "pvalue",
y = "value", color = "Method")) + geom_line() + geom_abline(intercept = 0,
slope = 1, linetype = "dashed") + xlab("P-value") + ylab("Power") +
facet_wrap(Treatment ~ Design) + ggtitle("Discrete, Skewed Data") +
theme(axis.text.x = element_text(size = 12), axis.text.y = element_text(size = 12),
axis.title = element_text(size = 16), title = element_text(size = 16),
legend.title = element_text(size = 12), legend.text = element_text(size = 12),
strip.text.x = element_text(size = 12), legend.position = "bottom") +
guides(color = guide_legend(nrow = 2, byrow = TRUE))
```

Discrete, Skewed Data



```
pdf(file = "../ms/fig/skewed_simulation_power.pdf", width = 8)
twobytwo
dev.off()
```

```
## pdf
## 2
```

```
summary05 <- t(sapply(powers, function(x) x[5, c(6, 7, 1:5)]))
summary05 <- summary05[c(5, 1, 2, 6, 3, 4), ]
summarytab <- xtable(summary05, digits = 3, align = "rp{1.25in}|p{0.7in}|p{0.6in}|p{0.8in}|p{0.8in}|p{0.8in}",
  caption = "Empirical power at level $0.05$ for discrete, skewed simulated data",
  label = "tab:skewed_power")
print(summarytab, hline.after = c(-1, 0, 3, nrow(summarytab)),
  type = "latex", file = "../ms/fig/skewed_simulation_power_summary.tex")
summarytab
```


Treatment	Design	ANCOVA	Stratified Permutation	Differenced Permutation	LM Permuta- tion	Freedman- Lane
No Effect	Balanced	0.036	0.025	0.021	0.035	0.037
Constant Additive	Balanced	0.974	0.143	0.853	0.972	0.977
Effect						
Single Stratum Ef- fect	Balanced	0.422	0.050	0.275	0.429	0.424
No Effect	Imbalanced	0.038	0.024	0.019	0.037	0.039
Constant Additive	Imbalanced	0.971	0.147	0.860	0.970	0.972
Effect						
Single Stratum Ef- fect	Imbalanced	0.190	0.070	0.100	0.190	0.190

Table 1: Empirical power at level 0.05 for discrete, skewed simulated data