

Tests for Mixed Paired and Two-Sample Designs

(<https://github.com/sjricht2/REU-2021>)

Mixed Paired and Two-Sample Designs

Coyotes.

- ▶ It was desired to compare two methods (QIAGEN DNeasy Kit, traditional chloroform isoamyl alcohol method) for extracting DNA from coyote blood samples.
- ▶ The response variable (Y) was mean concentration of DNA.
- ▶ A total of 30 coyotes were available for the study.
- ▶ Ideally, both methods would be used on each coyote
 - ▶ Reduced variability, as differences between treatments would be on the same subject
 - ▶ Fewer subject (coyotes) required

Mixed Paired and Two-Sample Designs-Coyotes

Due to constraints, however, both methods were used on only 6 coyotes (randomly selected). The kit was randomly assigned to be used for 8 of the remaining coyotes and the traditional method for the remaining 16 coyotes.

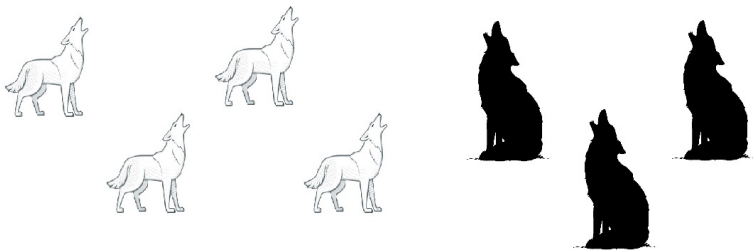


Figure 1. alt text

Mixed Paired and Two-Sample Designs-Laser Eye Surgery

Clinical trial to compare two methods of laser eye surgery.

- ▶ Patients with both eyes eligible have one eye randomly assigned to each treatment (dependent samples)
- ▶ Patients with only one eye eligible will each have one eye randomly assigned to one treatment (independent samples)

Analysis of Paired Data: Paired t -test

Under the assumptions

- ▶ The treatment response differences for the 6 coyotes receiving both treatments are independent
- ▶ The response differences for the population of all coyotes are normally distributed

The statistic

$$t_{paired} = \frac{\bar{d}}{s/\sqrt{n}} \sim t(n-1)$$

where

- ▶ $n = 6$ is the number of paired data points
- ▶ $\bar{d} = \bar{x} - \bar{y}$ is the mean of the paired differences
- ▶ s is the standard deviation of the paired differences
- ▶ $t(n-1)$ is the Student's t -distribution with $n-1$ degrees of freedom

Analysis of Unpaired Data: Pooled t -test

Under the assumptions

- ▶ The responses for the 24 “unpaired” coyotes are independent
- ▶ The populations of responses are both normally distributed
- ▶ The populations of treated and untreated responses have the same variance

The statistic

$$t_{unpaired} = \frac{(\bar{X} - \bar{Y}) - (\mu_1 - \mu_2)}{\sqrt{\frac{s_p^2}{n_1} + \frac{s_p^2}{n_2}}} \sim t(n_1 + n_2 - 2)$$

where

- ▶ $n_1 = 8, n_2 = 16$ are the sizes of the unpaired samples
- ▶ $\bar{X} - \bar{Y}$ is the treatment mean difference for the unpaired data
- ▶ s_1, s_2 are the standard deviations of the unpaired samples
- ▶ $s_p^2 = \frac{(n_1-1)s_1^2 + (n_2-1)s_2^2}{n_1 + n_2 - 2}$ is the pooled variance
- ▶ $t(n_1 + n_2 - 2)$ is the **Student's t -distribution** with $n_1 + n_2 - 2$ degrees of freedom

Can the separate paired and unpaired tests be combined in order to use all of the resulting data for a single test?

Consider the statistic

$$t_{combined} = \lambda t_{paired} + (1 - \lambda) t_{unpaired}$$

Note that $t_{combined} = t_{paired}$ when $\lambda = 1$ and $t_{combined} = t_{unpaired}$ when $\lambda = 0$.

- ▶ Much of the previous research has been focused on trying to approximate the distribution of $t_{combined}$.
- ▶ (More on this in the next presentation.)

Alternative: Randomization/Permutation test

Idea: Compute p -value based on the results of all hypothetical experiments

- ▶ **Assume there is no treatment effect**
- ▶ “Rerandomize (permute)” the observed data and compute the resulting test statistic
- ▶ Repeat for all possible rerandomizations
- ▶ Compare the test statistic of the actual randomization to the set all possible results
 - ▶ If the result looks “unusual”, it is likely because the initial assumption is wrong, and there is a treatment effect

Analysis of Paired Data: Randomization/Permutation test

- ▶ Compute the test statistic, t_{paired} , for all possible randomizations
- ▶ Example of a rerandomization (*paired responses must stay paired*)

Observed data:

Coyote	1	2	3	4	5	6	
Kit	X_1	X_2	X_3	X_4	X_5	X_6 :	\bar{X}_{obs}
Trad	Y_1	Y_2	Y_3	Y_4	Y_5	Y_6 :	\bar{Y}_{obs}

One possible rerandomization:

Coyote	1	2	3	4	5	6	
Kit	Y_1	X_2	Y_3	X_4	X_5	X_6 :	\bar{X}_{new1}
Trad	X_1	Y_2	X_3	Y_4	Y_5	Y_6 :	\bar{Y}_{new1}

Analysis of unpaired Data: Randomization/Permutation test

- ▶ Compute the test statistic, $t_{unpaired}$, for all possible randomizations
- ▶ Example of a rerandomization

Observed data:

Kit	X_1	X_2	X_3	\dots	X_7	$X_8:$	\bar{X}_{obs}
Trad	Y_1	Y_2	Y_3	\dots	Y_{15}	$Y_{16}:$	\bar{Y}_{obs}

One possible rerandomization:

Kit	Y_1	X_2	Y_2	\dots	X_7	$X_8:$	\bar{X}_{new_1}
Trad	X_1	Y_3	X_3	\dots	Y_{15}	$Y_{16}:$	\bar{Y}_{new_1}

Advantages of Randomization/Permutation tests

- ▶ Valid under any distribution of responses
- ▶ Yield exact p -values

Randomization/Permutation test for combined statistic

- ▶ Rerandomize paired and unpaired responses separately
- ▶ Compute $t_{combined} = \lambda t_{paired} + (1 - \lambda)t_{unpaired}$
- ▶ Repeat for all possible rerandomizations
- ▶ Compute p -value using randomization distribution

Randomization/Permutation test using ranks

- ▶ Tests based on $t_{combined}$ not resistant to “heavy-tailed” distributions or if outliers are present
- ▶ Rank-based methods are resistant to outliers

Rank-based analogues to t_{paired} and $t_{unpaired}$ tests:

- ▶ Wilcoxon signed-ranks test (W_{paired})
- ▶ Wilcoxon rank-sum/Mann-Whitney test ($W_{unpaired}$)

Randomization/Permutation tests can also be used on ranks

Randomization/Permutation test for combined statistic

Consider

$$W_{combined} = \lambda W_{paired} + (1 - \lambda) W_{unpaired}$$

- ▶ The randomization/permutation test can be carried out exactly as before

Previous Research

Methods based on normal distributions:

- ▶ Bhoj (1978). Showed $t_{combined}$ can be approximated by a Student's t -distribution. However, the degrees of freedom must be odd, which limited its usefulness.
- ▶ Bhoj (1989). Used transformations of t_{paired} and $t_{unpaired}$ to achieve an improved approximate normal distribution for $t_{combined}$
- ▶ None of the statistics was shown to be superior under all conditions
- ▶ It was not clear how they are affected by nonnormality or outliers

Previous Research

Nonparametric approaches:

- ▶ Dubnicka, et. al. (2002). Proposed combined test based on Wilcoxon statistics.
- ▶ Magel & Fu (2014). Proposed slight modification of Dubnicka statistic that performed better in some cases.
- ▶ Einsporn & Habtzghi (2013). Investigated permutation version of Bhoj (1978) test.
- ▶ Johnson (2018). Proposed permutation versions of Dubnicka and Magel & Fu tests; performed extensive simulation study to compare various tests.
- ▶ Wang (2020(REU)). Investigated confidence intervals based on combined statistics.

References

- ▶ Bhoj, D.S. (1978). Testing equality of means of correlated variates with missing data on both responses. *Biometrika*, 65:225-228.
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References

- ▶ Magel, R.C., Fu, R. (2014). Proposed nonparametric test for the mixed two-sample design. *Journal of Statistical Theory and Practice*, 8:221-237.
- ▶ Wang, R. (under review). Comparing Confidence Intervals for Mixed Paired-Unpaired Data.