Tests for Mixed Paired and Two-Sample Designs

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.

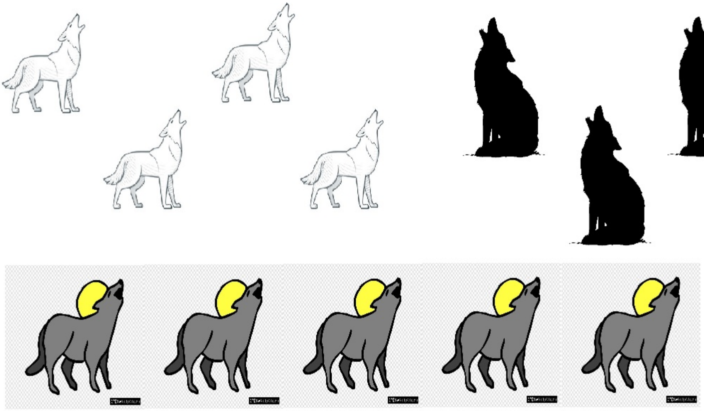

Figure 1: alt text

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

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

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 treatment responses are both normally distributed
- The populations of treated and untreated responses have the same variance

The statistic

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

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 $\lambda = 1$.

- 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:	$\bar{X}_{new_1}$
Trad	X_1	Y_2	X_3	Y_4	Y_5	Y_6:	$\bar{Y}_{new_1}$

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	$\ldots$	X_7	X_8:	$\bar{X}_{obs}$
Trad	Y_1	Y_2	Y_3	$\ldots$	Y_{15}	Y_{16}:	$\bar{Y}_{obs}$

One possible rerandomization:

Kit	Y_1	X_2	Y_2	$\ldots$	X_7	X_8:	$\bar{X}_{new_1}$
Trad	X_1	Y_3	X_3	$\ldots$	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

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- Einsporn, R.L., Habtzghi, D. (2013). Combining paired and two-sample data using a permutation test. *Journal of Data Science*, 11:767-779.
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