Within Cases ANOVA Part One: Multivariate and Mixed Model Approaches[1]

STA441 Spring 2020

[1]See last slide for copyright information.

Within Cases

Example: A random sample of male and female university students is weighed midway through year 1, 2, 3 and 4. The explanatory variables are gender and year (time). Gender is a between-cases factor and year is a within-cases factor.

- For a within-cases factor, a case contributes a response variable value for more than one value of the explanatory variable — usually all of them.
- It is natural to expect data from the same case to be correlated – *not* independent.
- For example, the same subject appears in several treatment conditions.
- Hearing study: How does pitch affect our ability to hear faint sounds? The same subjects will hear a variety of different pitch and volume levels (in a random order). They press a key when they think they hear something.

Student's Sleep Study (*Biometrika*, 1908)

First Published Example of a t-test

- Patients take two sleeping medicines several days apart.
- Half get A first, half get B first.
- Reported extra hours of sleep are recorded (difference from baseline).
- It's natural to subtract, and test whether the mean *difference* equals zero.
- That's what Gossett did.
- But some might do an independent t-test with $n_1 = n_2$.
- This assumes observations from the same person to be independent.
- It's unrealistic, but is it harmful?

Matched pairs, testing $H_0 : \mu_1 = \mu_2$

Independent *v.s.* Matched t-test

- If population covariance between the two measurements is positive, Type I error probability of both tests is 0.05, but matched t-test has better power.
- If population covariance between measurements is negative, matched t-test has Type I error probability of 0.05, but the independent t-test has Type I error probability greater than 0.05.

Why?

Why the matched t-test is better

- Numerator of both test statistics is $\overline{d} = \overline{y}_1 - \overline{y}_2$.
- Denominator is an estimate of the standard deviation of the difference.
- $Corr(\overline{y}_1, \overline{y}_2) = Corr(y_{i,1}, y_{i,2})$.
- So $Cov(\overline{y}_1, \overline{y}_2)$ has the same sign as $Cov(y_{i,1}, y_{i,2})$.
- $Var(\overline{y}_1 - \overline{y}_2) = Var(\overline{y}_1) + Var(\overline{y}_2) - 2Cov(\overline{y}_1, \overline{y}_2)$.
- If $Cov(\overline{y}_1, \overline{y}_2) > 0$, pretending independence results in overestimation of $Var(\overline{y}_1 - \overline{y}_2)$.
- If $Cov(\overline{y}_1, \overline{y}_2) < 0$, pretending independence results in underestimation of $Var(\overline{y}_1 - \overline{y}_2)$.

Within-cases Terminology

You may hear terms like

- **Longitudinal**: The same variables are measured repeatedly over time. Usually there are lots of variables, including categorical ones, and large samples. If there's an experimental treatment, its usually once at the beginning, like a surgery. Longitudinal studies basically track what happens over time.
- **Repeated measures**: Usually, the same subjects experience two or more experimental treatments. Usually quantitative response variables, and often small samples.

Wine Tasting Example

A single within-cases factor

In a taste test of wine, 6 professional judges judged 4 wines. The numbers they gave do not exactly represent quality. Instead, they are maximum prices in dollars per bottle that the judge thinks the company can charge and still sell most of the wine.

- Cases are judges: $n = 6$
- Each judge tastes and rates all four wines.
- The single factor is Wine: Four categories.

Archery Example: Bow and Arrow

Two within-cases factors

- Cases are archers. There are n archers.
- Test two bows, three arrow types.
- Warmup, then each archer takes 10 shots with each Bow-Arrow combination — 60 shots.
- In a different random order for each archer, of course.
- $Y_{i,1}, \ldots, Y_{i,6}$ are mean distances from arrow tip to centre of target, for $i = 1, \ldots, n$.
- Each $Y_{i,j}$ is based on 10 shots.
- $E(Y_{i,j}) = \mu_j$ for $j = 1, \ldots, 6$.

One Between, One Within

- Grapefruit study: Cases are n grocery stores.
- Within stores factor: Three price levels.
- Between-stores factor: Incentive program for produce managers (Yes-No).

Monkey Study

- Train monkeys on discrimination tasks, at 16, 12, 8, 4 and 2 weeks prior to treatment. Different task each time, equally difficult (randomize order).
- Treatment is to block function of the hippocampus (with drug, not surgery), re-tested. Get 5 scores for each monkey.

Train	Train	Train	Train	Train	Inject	Test
-16	-12	-8	-4	-2	0	

- 11 randomly assigned to treatment, 7 to control
- Treatment is between, time elapsed since training is within.

Advantages of Within-cases Designs

If measurement of the response variable does not mess things up too much

- Convenience (sometimes).
- Each case serves as its own control. A huge number of extraneous variables are automatically held constant. The result can be a very sensitive analysis.
- For some models, you can have lots of measurements on just a few subjects — if you are willing to make some assumptions.

Three main approaches for normal response variables

Not in chronological order

- Multivariate
- Classical Mixed model
- Covariance Structure

Multivariate Approach to Repeated Measures

- Multivariate methods allow the analysis of more than one response variable at the same time.
- When a case (subject) provides data under more than one set of conditions, it is natural to think of the measurements as multivariate.
- The humble matched t-test has a multivariate version (Hotelling's T^2).
- Simultaneously test whether the means of several *differences* equal zero.
- Like rating of Wine One minus Wine Two, Wine Two minus Wine Three, and Wine Three minus Wine Four.
- When there are also between-subjects factors (like nationality of judge), use multivariate regression methods.

Pure within-cases: Multiple factors

Archery example

Each archer contributes 6 numbers:

	Arrow type		
Bow type	1	2	3
1	$E(y_{i,1}) = \mu_{11}$	$E(y_{i,2}) = \mu_{12}$	$E(y_{i,3}) = \mu_{13}$
2	$E(y_{i,4}) = \mu_{21}$	$E(y_{i,5}) = \mu_{22}$	$E(y_{i,6}) = \mu_{23}$

- Form (sets of) linear combinations of the response variables.
- Want to test main effect of Bow Type?
  - $H_0 : \mu_{11} + \mu_{12} + \mu_{13} = \mu_{21} + \mu_{22} + \mu_{23}$
  - Calculate $L_i = y_{i,1} + y_{i,2} + y_{i,3} - (y_{i,4} + y_{i,5} + y_{i,6})$.
  - $E(L_i) = \mu_{11} + \mu_{12} + \mu_{13} - (\mu_{21} + \mu_{22} + \mu_{23})$.
  - Test $H_0 : E(L_i) = 0$.
  - Could use an ordinary matched t-test for this one.

Main effect for arrow type
Differences between marginal means

	Arrow type		
Bow type	1	2	3
1	$E(y_{i,1}) = \mu_{11}$	$E(y_{i,2}) = \mu_{12}$	$E(y_{i,3}) = \mu_{13}$
2	$E(y_{i,4}) = \mu_{21}$	$E(y_{i,5}) = \mu_{22}$	$E(y_{i,6}) = \mu_{23}$

- $H_0 : \mu_{11} + \mu_{21} = \mu_{12} + \mu_{22}$ and $\mu_{12} + \mu_{22} = \mu_{13} + \mu_{23}$
- Calculate two linear combinations for each archer:
  - $L_{i,1} = y_{i,1} + y_{i,4} - (y_{i,2} + y_{i,5})$
  - $L_{i,2} = y_{i,2} + y_{i,5} - (y_{i,3} + y_{i,4})$
- Simultaneously test $H_0 : E(L_{i,1}) = 0$ and $E(L_{i,2}) = 0$.
- Use Hotelling's T^2.
- Or something equivalent.

Matched t-tests with `proc reg`

- Regression with no explanatory variables.
- $y_i = \beta_0 + \epsilon_i \sim N(\beta_0, \sigma^2)$.
- Test $H_0 : \beta_0 = 0$.

Hotelling's T-squared

Multivariate matched t-test

- Official SAS documentation claims that SAS won't calculate Hotelling's T-squared, but ...
- $T^2 = (n-1)\left(\frac{1}{\lambda} - 1\right)$, so just get Wilks' Lambda from the `mtest` statement of `proc reg`. The p-value will be correct.
- In a regression model with *no explanatory variables*, $E(\mathbf{D}_i) = \boldsymbol{\beta}_0$, so test $H_0 : \boldsymbol{\beta}_0 = \mathbf{0}$.

```
proc reg;
     model D1 D2 D3 =  ;
     Wine: mtest intercept=0;
```

- Or just use the test for Wilks' lambda directly.

Designs with both between and within cases factors

- Could have main effects and interactions for between-cases factors,
- Could have main effects and interactions for within-cases factors,
- Could have interactions of between by within.
- Again, observation from the same case are treated as multivariate.
- Again we form linear combinations of response variables and test hypothesis about them.
- **Recipe**: *Use a regression model with effect coding dummy variables for the between-cases factors* (if any). Use these same explanatory variables in every model.
- Response variables (linear combinations) will vary depending on the effect being tested.
- Null hypotheses for all the main effects and interactions are statements about the β values.

Main effects and interactions for the between-cases factors

- These are marginals, averaging μ parameters over the within-cases factors.
- Let $L_i =$ the mean (or sum) of the $y_{i,j}$ values, averaging or adding over j.
- Do a standard between-cases analysis with L_i as the response variable.

Main effects and interactions for the within-cases factors

- Need to average μ parameters over the between-cases factors.
- Effect coding! β_0 is the grand mean.
- Form linear combinations as in the archery example.
- Test $H_0 : \beta_0 = 0$.
- Or test multiple $\beta_{0,j} = 0$ if need be.

Interactions of between by within

- The nature of a within-cases effect *depends* on a between-cases treatment combination.
- Take the linear combinations for the within-cases effect.
- Test the between-cases effect on those.
- For example, factors are Bow Type, Arrow Type and Gender.
- Want to test the Arrow Type by Gender interaction.
- Are the differences between arrow types (averaging over bow types) different for men and women?
- Simultaneously test for gender differences in the two linear combinations representing arrow type one versus two and two versus three.
- It's a standard multivariate test.

You could use proc reg

To test the arrow type by gender interaction

	Arrow type		
Bow type	1	2	3
1	$E(y_{i,1}) = \mu_{11}$	$E(y_{i,2}) = \mu_{12}$	$E(y_{i,3}) = \mu_{13}$
2	$E(y_{i,4}) = \mu_{21}$	$E(y_{i,5}) = \mu_{22}$	$E(y_{i,6}) = \mu_{23}$

```
L1 = y1+y4 - (y2+y5);
L2 = y2+y5 - (y3+y6);

proc reg;
     model L1 L2 = gender;
     arrow_by_sex: mtest gender=0;
```

Or you can let `proc glm` do the dummy variables and linear combinations for you.

If within-cases factors have just two levels
Like before and after, experimental vs. control

- You can always do it with a univariate analysis.
- No fancy software is needed.
- All three approaches to repeated measures yield the same F statistics.
- Make a sum variable and a difference variable.
- Salmon study: Fish are Canadian or Alaskan, Female or Male, Growth is measured in freshwater *and* marine environments.
- Three factors: Species by sex by environment – environment is within cases.
- Response variable is growth.

Salmon example
SAS code not tested

```
sumgrowth = freshgrowth + marinegrowth;
difgrowth = freshgrowth - marinegrowth;
```

Assume effect coding for country and sex.

```
proc reg;
     title2 'Between-cases effects';
     model sumgrowth = country sex cs;
proc reg;
     title2 'Within and between-within';
     model difgrowth = country sex cs;
```

What do the t-tests give you?

Classical Mixed Model Approach to Repeated Measures

First we need some background.

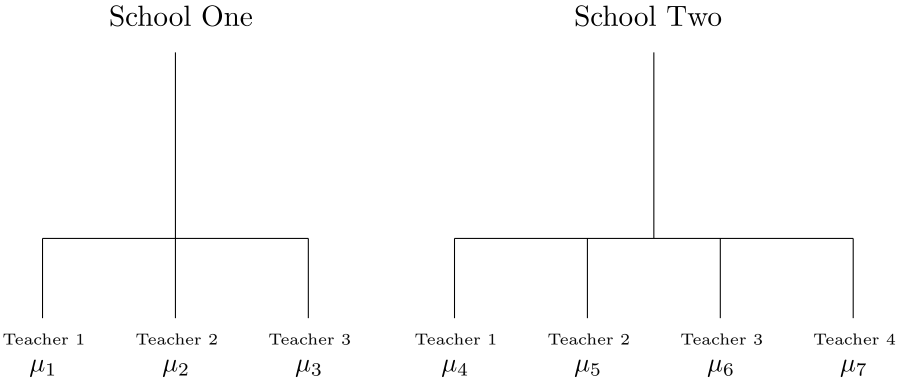
- Nested designs
- Fixed and random effects.

Nested Designs
Example

A chain of commercial business colleges is teaching a software certification course. After 6 weeks of instruction, students take a certification exam and receive a score ranging from zero to 100.

- The owners want to see whether performance is related to which school students attend, or which instructor they have – or both.
- They compare two schools; one of the schools has three instructors teaching the course, and the other school has 4 instructors teaching the course.
- A teacher only works in one school.
- There are two categorical explanatory variables, school and teacher.
- But it's not a factorial design, because "Teacher 1" does not mean the same thing in School 1 and School 2.
- It's a different person.

Teacher is nested within school



Schools $H_0 : \frac{1}{3}(\mu_1 + \mu_2 + \mu_3) = \frac{1}{4}(\mu_4 + \mu_5 + \mu_6 + \mu_7)$

Teachers within Schools $H_0 : \mu_1 = \mu_2 = \mu_3$ and $\mu_4 = \mu_5 = \mu_6 = \mu_7$

Tests of nested effects are tests of contrasts

$H_0 : \frac{1}{3}(\mu_1 + \mu_2 + \mu_3) = \frac{1}{4}(\mu_4 + \mu_5 + \mu_6 + \mu_7)$
$H_0 : \mu_1 = \mu_2 = \mu_3$ and $\mu_4 = \mu_5 = \mu_6 = \mu_7$

You can specify the contrasts yourself, or you can take advantage of `proc glm`'s syntax for nested models.

```
proc glm;
     class school teacher;
     model score = school teacher(school);
```

The notation `teacher(school)` should be read "teacher within school."

Easy to extend the ideas

- Can have more than one level of nesting. You could have climate zones, lakes within climate zones, fishing boats within lakes, ...
- There is no problem with combining nested and factorial structures. You just have to keep track of what's nested within what.
- Factors that are not nested are sometimes called "crossed."
- The combination of nesting and *random effects* is very powerful.

Random Effects

As opposed to *fixed effects*

A random factor is one in which the *values of the factor are a random sample* from a populations of values.

- Randomly select 10 schools, test students at each school. School is a random factor with 10 values.
- Randomly select 15 naturopathic medicines for arthritis (there are quite a few), and then randomly assign arthritis patients to try them. Drug is a random factor.
- Randomly select 15 lakes. In each lake, measure how clear the water is at 20 randomly chosen points. Lake is a random factor.
- Randomly select 20 fast food outlets, survey customers in each about quality of the fries. Outlet is a random factor with 20 values. Amount of salt would be a fixed factor, which could be crossed with outlet.

One random factor

A nice simple example

- Randomly select 5 farms.
- Randomly select 10 cows from each farm, milk them, and record the amount of milk from each one.
- The one random factor is Farm.
- Total $n = 50$.
- The idea is that "Farm" is a kind of random shock that pushes all the amounts of milk from the cows in the farm up or down by the same amount.
- You could also think of cow (the cases are cows) as a random factor nested within farm.

$$y_{ij} = \mu + \tau_i + \epsilon_{ij}$$

- $i = 1, \ldots, 5$ and $j = 1, \ldots, 10$.

Analysis of variance

$$y_{ij} = \mu + \tau_i + \epsilon_{ij}$$

$$\begin{aligned} Var(y_{ij}) &= Var(\mu + \tau_i + \epsilon_{ij}) \\ &= Var(\tau_i) + Var(\epsilon_{ij}) \\ &= \sigma^2_\tau + \sigma^2 \end{aligned}$$

- Split the variance up into two parts: The part that comes from farms, and the part that comes from cows (within farms).
- *Analysis* of variance.
- Test $H_0 : \sigma^2_\tau = 0$
- Estimate $\frac{\sigma^2_\tau}{\sigma^2_\tau + \sigma^2}$

Distribution of $y_{ij} = \mu_. + \tau_i + \epsilon_{ij}$

- $y_{ij} \sim N(\mu_., \sigma^2_\tau + \sigma^2)$
- Observations are not all independent.
- Covariance matrix of the vector of response variables is block diagonal: Matrix of matrices.
  - Off-diagonal matrices are all zeros.
  - Matrices on the diagonal ($k \times k$) have the *compound symmetry* structure

$$\begin{pmatrix} \sigma^2 + \sigma^2_\tau & \sigma^2_\tau & \sigma^2_\tau \\ \sigma^2_\tau & \sigma^2 + \sigma^2_\tau & \sigma^2_\tau \\ \sigma^2_\tau & \sigma^2_\tau & \sigma^2 + \sigma^2_\tau \end{pmatrix}$$

(Except it's 10×10.)

Mixed models

The classical approach

- There can be both fixed and random factors in the same experiment. This makes it a *mixed* model.
- Factors can be nested or crossed, in various patterns.
- Random factors can be nested within fixed.
- Fixed effects cannot be nested within random.
- The interaction of any random factor with another factor (whether fixed or random) is random.
- F-tests are often possible, but they don't always use Mean Squared Error in the denominator of the F statistic.
- Often, it's the Mean Square for some interaction term.
- The choice of what error term to use is relatively mechanical for balanced models — based on expected mean squares.
- Mechanical means SAS can do it for you.

One more example

And some sample questions

Independent random samples of 10 Canadian and 10 U.S. large companies were selected. In each company, 25 female and 25 male managers were randomly selected, and their formal education in years was recorded.

1. Is this an observational study, or experimental? Observational.
2. What are the factors? Nation, Company and Sex.
3. Designate the factors as fixed or random. Nation and Sex are fixed. Company is random.
4. Describe the nesting, if any. Company is nested within Nation.

Classical Mixed Model Approach to Repeated Measures

- The effect for case (person, subject) is a random shock that pushes all the observations from that case up or down by the same amount – like farm.
- Case is one of the factors.
- It's a *random effects* factor that is *nested* within combinations of the between-cases factors, and *crosses* the within-cases factors.
- There are no interactions between case and the other factors.
- Uses a mixed model ANOVA.
- The F-tests depend on balanced experimental designs.

Pictures of crossing and nesting

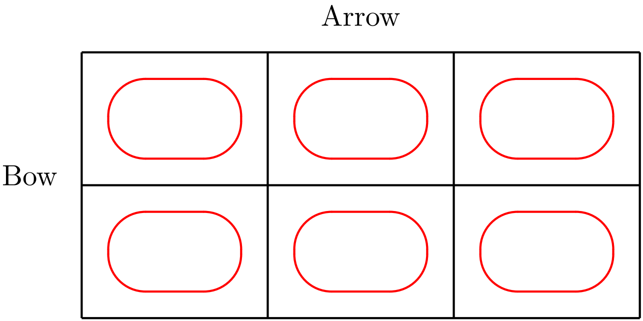
Cases (subjects) is a random effects factor nested within combinations of the between-cases factors and crossing the within-cases factors.

- Recall the archery example – two bow types, three arrow types.
- Suppose each archer only used one type of bow and one type of arrow.
- Make a diagram showing the nesting/crossing of cases.

Both Factors between

Make a diagram showing the nesting/crossing of cases.

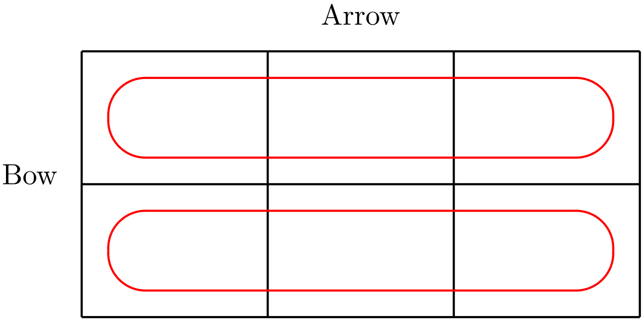
- Each archer only uses one type of bow and one type of arrow.
- Both factors are between cases.
- Cases are nested within both bow and arrow.



One factor between and one within

Make a diagram showing the nesting/crossing of cases.

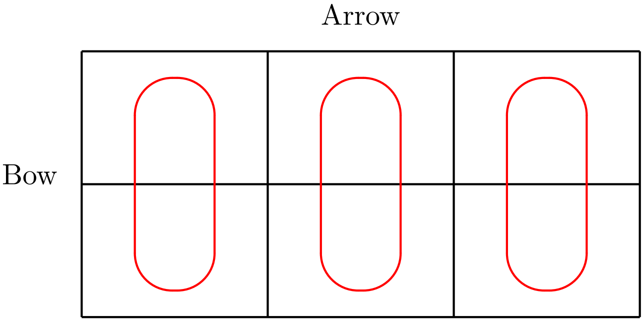
- Suppose each archer only uses one type of bow, but all 3 types of arrow.
- Bow is between cases, arrow is within (repeated measures on arrow).
- Cases are nested within bow, but cross arrow.



Another one factor between and one within

Make a diagram showing the nesting/crossing of cases.

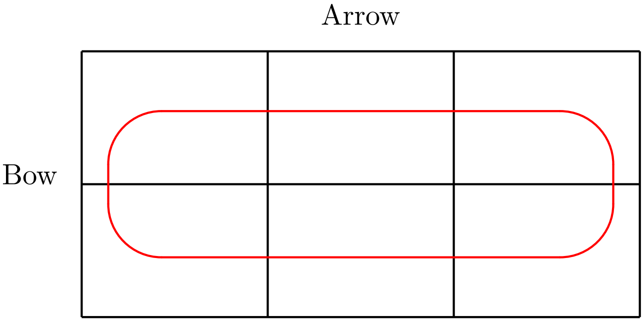
- Suppose each archer uses both types of bow, but only one type of arrow.
- Bow is within cases, Arrow is between (repeated measures on Bow).
- Cases are nested within Arrow, but cross Bow.



Both factors within

As in the original example

- Each archer uses both types of bow and all three types of arrow.
- Both factors are within cases (repeated measures on both Bow and Arrow).
- Cases cross both Bow and Arrow.



One More Example
Without a picture

- Experienced archers and beginners try both bows and all three arrow types.
- Experience is between cases, Bow and Arrow are within.
- Cases are nested within experience.

You draw the picture.

Copyright Information