Displays for Statistics 5401/8401

Lecture 14

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Class Web Page

`http://www.stat.umn.edu/~kb/classes/5401`

Single sample profile (repeated measures) analysis

Suppose you have a *random sample* $\mathbf{x}_1, \ldots, \mathbf{x}_n$ from a p-variable multivariate distribution with

- unknown mean vector $\boldsymbol{\mu} = [\mu_1, \mu_2, \ldots, \mu_p]'$
- observations $\mathbf{x} = [x_1, x_2, \ldots, x_p]'$ that are *repeated measures* data. That is, variables $x_1, \ldots, x_p$ are *comparable*.

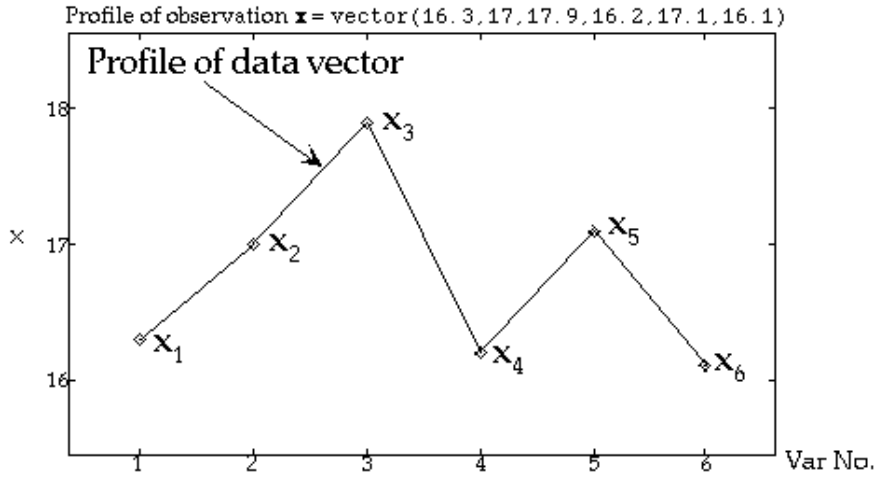
Each x_i represents a measurement on

- the *same quantity* in the same units, for example, blood pressure
- under differing conditions or at differing times.

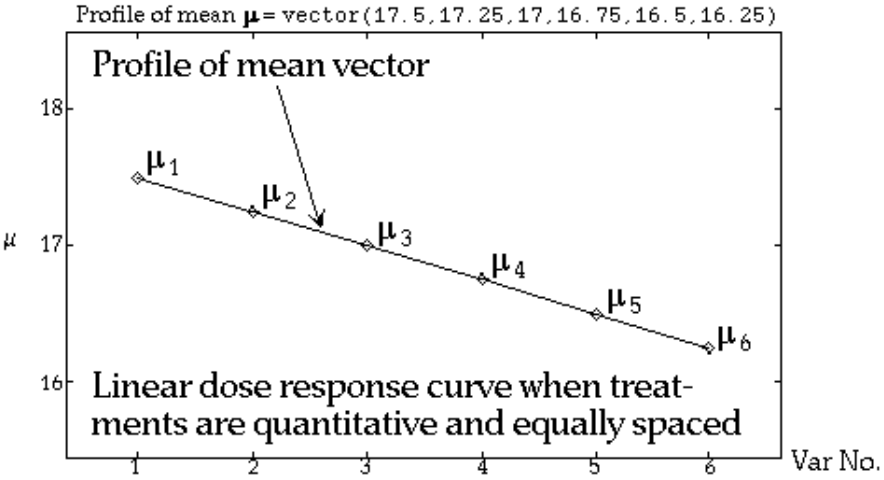
We often call the different times or conditions ***treatments***.

When there are p variables, there are p treatments being compared.

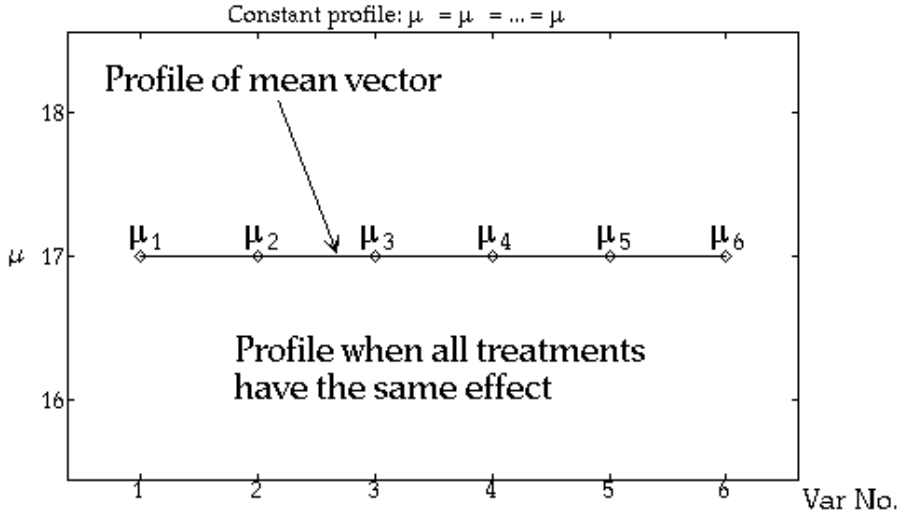
A data vector **x** can be depicted by a "profile" -- a plot of x_i against j.



And you can plot μ_j vs j to obtain a *population mean* profile plot of $\boldsymbol{\mu}$.



When $\mu_1 = \mu_2 = \ldots = \mu_p$, the profile is <u>flat</u>.



This <u>simple pattern</u> in the profile <u>graphically represents</u> the *null hypothesis*

$$H_0: \mu_1 = \mu_2 = \ldots = \mu_p$$

of <u>no treatment differences</u>.

When treatments are *quantitative*, the population profile may be viewed as a <u>dosage response curve</u>.

When the profile is a straight line, the response is linear in the dose.

Usually one goal in repeated measures analysis is to *compare* the treatment means μ_i.

This investigates the *shape of the profile* of $\boldsymbol{\mu}$, that is, the pattern of differences $\mu_i - \mu_j$. The shape isn't changed by adding a constant to each mean.

You can label a data matrix like this.

	Trt 1	Trt 2	Trt 3	. . .	Trt p
Case 1	x_{11}	x_{12}	x_{13}	. . . .	x_{1p}
Case 2	x_{21}	x_{22}	x_{23}	. . . .	x_{2p}
Case 3	x_{31}	x_{32}	x_{33}	. . . .	x_{3p}
Case 4	x_{41}	x_{42}	x_{43}	. . . .	x_{4p}
. . . . .	. . . .	. . . .	. . . .	. . . .	. . . .
Case n	x_{n1}	x_{n2}	x_{n3}	. . . .	x_{np}

This is reminiscent of a table of data from a randomized block experiment.

Analogy with RCBD

The single sample profile analysis situation appears to be quite similar to a univariate *randomized complete block* (RCB) situation with n blocks, but when p > 2, the analysis is different.

- Each repeated measures individual or case corresponds to a RCB "block".
- Each response variable for a case corresponds to a "plot" in a block "treated" with the distinguishing feature of that measurement.

In a randomized block situation with n replicates of p treatments, you have n×p experimental units (EUs).

- EUs are grouped in n homogeneous blocks (replicates), each with p "plots"
- Treatments assigned randomly to the p EUs in each block

After randomizing, a field experiment with p = 4 and n = 6 might look like

Block 1	Treatment 4	Treatment 2	Treatment 1	Treatment 3
Block 2	Treatment 4	Treatment 2	Treatment 3	Treatment 1
Block 3	Treatment 1	Treatment 2	Treatment 4	Treatment 3
Block 4	Treatment 2	Treatment 1	Treatment 3	Treatment 4
Block 5	Treatment 4	Treatment 1	Treatment 2	Treatment 3
Block 6	Treatment 4	Treatment 1	Treatment 3	Treatment 2

Every block (row of table) contains a complete set of p treatments, *in random order*.

Examples of blocks

- Time periods (day, week), with the treatments in random order within the time period
- Batches of flour split into smaller quantities used to make a loaf of bread with varying amounts of an ingredient. The amounts are randomly assigned to the loaves (plots) from the same batch of flour (block).
- Compact regions of a field or greenhouse bench with treatments assigned randomly to different positions (plots) in the field or on the bench.
- Subjects getting various treatments *in random order* (plot = time of treatment)

How does repeated measures differ from a RCB?

In repeated measures analysis, the "treatment" levels are not randomized.

From the multivariate point of view, in a RCB you can view the data as *repeated measurements* on a block, with each block a "case".

But randomization and constant σ^2 (not affected by the treatments) imply that $\boldsymbol{\Sigma}$ for the p observations in a block has a *very special* structure, namely

$$\boldsymbol{\Sigma} = \begin{bmatrix} \sigma^2 & \rho\sigma^2 & \rho\sigma^2 & \dots & \rho\sigma^2 \\ \rho\sigma^2 & \sigma^2 & \rho\sigma^2 & \dots & \rho\sigma^2 \\ \rho\sigma^2 & \rho\sigma^2 & \sigma^2 & \dots & \rho\sigma^2 \\ \dots & \dots & \dots & \dots & \dots \\ \rho\sigma^2 & \rho\sigma^2 & \rho\sigma^2 & \dots & \sigma^2 \end{bmatrix}, \quad \rho > -1/(p-1)$$

- All variances $\sigma_{ii} = \sigma^2$ are the same
- All covariances $\sigma_{ij} = \rho\sigma^2$, $i \neq j$, are the same
- This means that all correlations $\rho_{ij} = \rho$, $i \neq j$, are the same, too.

In multivariate repeated measures, you don't have the randomization and $\boldsymbol{\Sigma}$ does not usually have this simple structure.

A $\boldsymbol{\Sigma}$ of this form (equal diagonal values and equal off-diagonals) is said to have **intraclass** structure.

Even without randomization, when $\boldsymbol{\Sigma}$ has intraclass structure, a two-way univariate ANOVA is a correct way to analyze the data.

When $\boldsymbol{\Sigma}$ does have this special structure, univariate ANOVA will be better than a multivariate analysis because

- tests will have greater power
- confidence intervals will be shorter.
- It works when $n \leq p$

When $\boldsymbol{\Sigma}$ does not have this structure, univariate ANOVA is *not* appropriate.

However, adjustments to degrees of freedom due to Greenhouse and Geisser can sometimes be made to make ANOVA "work".

$\boldsymbol{\Sigma}$ can have other special forms besides intraclass structure.

For example, when $x_1, x_2, \ldots, x_p$ are observations at times $t_1 < t_2 < \ldots < t_p$, correlations might be $\rho_{jk} = \rho^{|t_j - t_k|}$. For <u>equally spaced times</u> $t_j = j$, $\boldsymbol{\Sigma}$ would look like

$$\boldsymbol{\Sigma} = \sigma^2 \begin{bmatrix} 1 & \rho & \rho^2 & \rho^3 & \ldots & \rho^{p-1} \\ \rho & 1 & \rho & \rho^2 & \ldots & \rho^{p-2} \\ \rho^2 & \rho & 1 & \rho & \ldots & \rho^{p-3} \\ \ldots & \ldots & \ldots & \ldots & \ldots & \ldots \\ \rho^{p-1} & \rho^{p-2} & \rho^{p-3} & \rho^{p-4} & \ldots & 1 \end{bmatrix}$$

This is a <u>first order autoregression</u> (AR(1)) structure.

Analysis that takes this structure into account will be better than one that does not.

This is a type of analysis you can use SAS **Proc Mixed** for.

Profile analysis questions of interest

These are much the same as for randomized block analysis.

- Test the null hypothesis of *no treatment effects*

$$H_0: \mu_1 = \mu_2 = \ldots = \mu_p.$$

- **Multiple comparisons**: test all hypotheses of the form $H_{0jk}: \mu_j = \mu_k$, $j \neq k$
- Find **simultaneous confidence limits** for all $\mu_j - \mu_k$, $j \neq k$

The model in the RCB situation is often written as

$$x_{ij} = \mu + \alpha_i + B_j + \varepsilon_{ij}$$

That is

$$x_{ij} = \mu_i + B_j + \varepsilon_{ij}, \text{ with } \mu_i = \mu + \alpha_i$$

- $\mu_i = \mu + \alpha_i$, $i = 1, .., p$
- The $\{\alpha_i\}$ are fixed <u>treatment effects</u>, usually with $\sum_{1 \le i \le p} \alpha_i = 0$. This implies $\mu = \overline{\mu}_. = (1/p)\sum_{1 \le i \le p} \mu_i$ so that $\alpha_i = \mu_i - \mu$.
- The $\{B_j\}$ are <u>fixed</u> block effects with $\sum_{1 \le j \le n} B_j = 0$ or <u>random</u> block effects with $E(B_j) = 0$
- The $\{\varepsilon_{ij}\}$ are <u>independent</u> $N(0,\sigma^2)$ (constant variance)

The repeated measures model is

$$x_{ij} = \mu + \alpha_i + \varepsilon_{ij}$$

$$V[\boldsymbol{\varepsilon}_i] = \boldsymbol{\Sigma}, \ \boldsymbol{\varepsilon}_i = [\varepsilon_{1j}, \varepsilon_{2j}, \ldots, \varepsilon_{pj}]'$$

If $\sum_i c_i \mu_i$ is a <u>contrast</u> among the <u>means</u> μ_i ($\sum c_i = 0$), then

$$\sum_i c_i \mu_i = \sum_i c_i \alpha_i$$

the same contrast among the <u>effects</u>.

Example: $c_1 = 1$, $c_2 = -1$, $c_3 = \ldots = c_p = 0$, $\sum_i c_i \mu_i = \mu_1 - \mu_2 = (\mu+\alpha_1) - (\mu+\alpha_2) = \alpha_1 - \alpha_2$

I will usually state hypotheses about comparisons of treatments in terms of $\{\mu_i\}$, but they can also be stated in terms of $\{\alpha_i\}$. For example, with the convention that $\sum_i \alpha_i = 0$,

$$H_0: \mu_1 = \mu_2 = \ldots = \mu_p$$

is equivalent to the hypothesis of no treatment effects, that is, to

$$H_0: \alpha_1 = \alpha_2 = \ldots = \alpha_p = 0$$

There are lots of ways to state the hypothesis of no treatment effects:

$$H_0: \text{ all } \mu_i\text{'s equal}$$

A. All *pairs of successive means* are the same, that is

$$H_{0a}: \mu_2-\mu_1 = 0,\ \mu_3-\mu_2 = 0,\ \ldots,\ \mu_p-\mu_{p-1} = 0$$

This has p-1 "components", none of which may be omitted. The first $\mu_i-\mu_{i-1} \neq 0$ marks a *change point*.

B. *All means are the same as* μ_1, that is

$$H_{0b}: \mu_2-\mu_1 = 0,\ \mu_3-\mu_1 = 0,\ \ldots,\ \mu_p-\mu_1 = 0$$

These are p-1 essential components and, when p > 2, they differ from those defining H_{0a}.

You might be interested in these when treatment 1 is a "control" or a base-line level, and you are comparing all other treatments with it.

C. μ_k = *average* of $\mu_1, \mu_2, \ldots, \mu_{k-1}$ for k = 2, 3, ..., p

$$\begin{aligned} H_{0c}:\ & \mu_2 - \mu_1 = 0, \\ & \mu_3 - (\mu_1 + \mu_2)/2 = 0, \\ & \mu_4 - (\mu_1 + \mu_2 + \mu_3)/3 = 0, \ldots, \\ & \mu_p - (\mu_1 + \mu_2 + \ldots + \mu_{p-1})/(p-1) = 0 \end{aligned}$$

Multiplying by -1, -2, -3, ..., H_{0c} is

$$\begin{aligned} H_{0c}:\ & \mu_1 - \mu_2 = 0, \\ & \mu_1 + \mu_2 - 2\mu_3 = 0, \\ & \mu_1 + \mu_2 + \mu_3 - 3\mu_4 = 0, \\ & \ldots\ldots\ldots\ldots\ldots\ldots, \\ & \mu_1 + \mu_2 + \ldots + \mu_{p-1} - (p-1)\mu_p = 0 \end{aligned}$$

These are contrast with integer weights.

H_{0c}, too, has p-1 essential components.

These, too, might be of interest when looking for a change point.

D. *Every* pair of μ's are equal

$$H_{0d}: \mu_i = \mu_j, \text{ all } i \neq j$$

Unlike H_{0a}, H_{0b}, and H_{0c}, H_{0d} is symmetric in the μ_j's.

H_{0d} has $p(p-1)/2$ distinct components, most of which are *redundant*.

For example, for $p \geq 3$, $\mu_2 = \mu_1$ and $\mu_3 = \mu_2$ together imply $\mu_3 = \mu_1$.

However, you need at least $p-1$ of them to fully specify the null hypothesis that all treatment means are the same.

Note: All these hypotheses are statements about the true means, not conclusions from statistical analysis.

When $\mu_1 = \mu_2$ and $\mu_2 = \mu_3$, then $\mu_1 = \mu_3$ must be true by mathematics.

But it can happen that $\overline{x}_2 - \overline{x}_1$ and $\overline{x}_3 - \overline{x}_2$ are not significantly different from 0, but $\overline{x}_3 - \overline{x}_1$ is.

You can express all these various reformulations of H_0, each of which specifies M contrasts, as

$$H_0: \mathbf{C}\mu = \mathbf{0}$$

for a matrix M by p $\mathbf{C}$, satisfying $\mathbf{C1}_p = \mathbf{0}$, that is, each row sums to 0.

$$\mathbf{C} = \begin{bmatrix} c_{11} & c_{12} \ldots & c_{1p} \\ \ldots & \ldots \ldots & \ldots \\ c_{M1} & c_{M2} \ldots & c_{Mp} \end{bmatrix} \quad \begin{matrix} \sum_i c_i \\ 0 \\ \ldots \\ 0 \end{matrix}$$

Each row of $\mathbf{C}$ defines a linear contrast in $\mu_1, \ldots, \mu_p$ which defines one "component" of the hypothesis.

For H_{0a}, H_{0b} and H_{0c}, $M = p-1$.

For H_{0d}, $M = p(p-1)/2$.

For H_{0a}, $\mathbf{C} = \mathbf{C}_a$ is p-1 × p:

$$\mathbf{C}_a = \begin{bmatrix} -1 & 1 & 0 & 0 & . & . & . & 0 \\ 0 & -1 & 1 & 0 & . & . & . & 0 \\ 0 & 0 & -1 & 1 & . & . & . & 0 \\ . & . & . & . & . & . & . & . \\ 0 & 0 & 0 & 0 & . & . & -1 & 1 \end{bmatrix}$$

For H_{0b}, $\mathbf{C} = \mathbf{C}_b$ is p-1 × p:

$$\mathbf{C}_b = \begin{bmatrix} -1 & 1 & 0 & 0 & . & . & . & 0 \\ -1 & 0 & 1 & 0 & . & . & . & 0 \\ -1 & 0 & 0 & 1 & . & . & . & 0 \\ . & . & . & . & . & . & . & . \\ -1 & 0 & 0 & 0 & . & . & 0 & 1 \end{bmatrix}$$

For H_{0c}, $\mathbf{C} = \mathbf{C}_c$ is p-1 × p:

$$\mathbf{C}_c = \begin{bmatrix} 1 & -1 & 0 & 0 & . & . & . & 0 \\ 1 & 1 & -2 & 0 & . & . & . & 0 \\ 1 & 1 & 1 & -3 & . & . & . & 0 \\ . & . & . & . & . & . & . & . \\ 1 & 1 & 1 & 1 & . & . & 1 & -(p-1) \end{bmatrix}$$

Each $\mathbf{C}$ satisfies $\mathbf{C1}_p = \mathbf{0}$, that is the sum of each row of $\mathbf{C}$ is 0. That is, each row of $\mathbf{C}$ defines a *contrast*.

$\mathbf{C}_a$, $\mathbf{C}_b$ and $\mathbf{C}_c$

- have p-1 rows
- are of *full rank*, that is of rank p-1.

This is another way of saying all components are essential.

For H_{0d}, $\mathbf{C} = \mathbf{C}_d$ is p(p-1)/2 by p:

$$\mathbf{C}_d = \begin{bmatrix} -1 & 1 & 0 & 0 & . & . & 0 & 0 \\ -1 & 0 & 1 & 0 & . & . & 0 & 0 \\ -1 & 0 & 0 & 1 & . & . & 0 & 0 \\ . & . & . & . & . & . & . & . \\ -1 & 0 & 0 & 0 & . & . & 0 & 1 \\ 0 & -1 & 1 & 0 & . & . & 0 & 0 \\ 0 & -1 & 0 & 1 & . & . & 0 & 0 \\ . & . & . & . & . & . & . & . \\ 0 & 0 & 0 & 0 & . & . & -1 & 1 \end{bmatrix}$$

$\mathbf{C}_d$ is *not* of full rank (unless p = 2) but has rank p-1 < p(p-1)/2.

Suppose now that $\mathbf{C}$ is a full rank $p-1 \times p$ matrix with $\mathbf{C}1_p = \mathbf{0}$ so that $\mathbf{C}\mu = \mathbf{0}$ if and only if $\mu_1 = \mu_2 = \ldots = \mu_p$.

Then $\mathbf{y} = \mathbf{C}\mathbf{x}$ is a vector of $q = p-1$ **contrasts** in $x_1, \ldots, x_p$. That is

- (a) $y_1 = x_2 - x_1$, $y_2 = x_3 - x_2$, ..., $y_{p-1} = x_p - x_{p-1}$.
- (b) $y_1 = x_2 - x_1$, $y_2 = x_3 - x_1$, ..., $y_{p-1} = x_p - x_1$
- (c) $y_1 = x_1 - x_2$, $y_2 = x_1 + x_2 - 2x_3$, ..., $y_{p-1} = x_1 + x_2 + \ldots + x_{p-1} - (p-1)x_p$

Then

- $\mu_y = E[\mathbf{y}] = \mathbf{C}\mu_x$ (M by 1)
- $\Sigma_y = \mathbf{C}\Sigma_x\mathbf{C}'$ (M by M).
- H_0: $\mathbf{C}\mu_x = \mathbf{0}$ can be restated as H_0: $\mu_y = \mathbf{0}$, which you can test with Hotelling's T^2

  $T_c^2 = \overline{\mathbf{y}}'(\hat{V}[\overline{\mathbf{y}}])^{-1}\overline{\mathbf{y}} = (\mathbf{C}\overline{\mathbf{x}})'(n^{-1}\mathbf{C}\mathbf{S}_x\mathbf{C}')^{-1}(\mathbf{C}\overline{\mathbf{x}})$.

Under H_0 and assuming normality, since $f_e = n - 1$ and the dimension $q = p-1$,

$T_c^2 = \{(f_e q)/(f_e - q + 1)\}F_{q,f_e-q+1} = \{(n-1)(p-1)/(n-p+1)\}F_{p-1,n-p+1}$

($T_c^2 = \chi_q^2$ in large samples)

Note: If you analyze the data using two-way ANOVA *as if* it were a RCB, the F test has degrees of freedom

f_h = hypothesis DF = $DF_{trt} = p - 1$

$\tilde{f}_e$ = error DF = $DF_{error} = (n-1)(p-1) \neq f_e$.

In repeated measures analysis, you use an F critical value with

- the *same* numerator degrees of freedom $q = p - 1$
- *different* denominator degrees of freedom $f_e - q + 1$, where $f_e = n - 1$
- $\{(n-p+1)/((n-1)(p-1))\}T^2 \neq$ ANOVA-F.

Conclusion: the test based on T^2 is different from the test based on ANOVA F.

Q. How do you choose $\mathbf{C}$?

A. For T^2 it doesn't matter.

Fact

For any two <u>full rank</u> p-1 × p contrast matrices $\mathbf{C}_1$ and $\mathbf{C}_2$, defining

$$\mathbf{y}_1 = \mathbf{C}_1\mathbf{x} \text{ and } \mathbf{y}_2 = \mathbf{C}_2\mathbf{x}$$

Then, always $T_{c_1}^2 = T_{c_2}^2$

where

$$T_{c_1}^2 = \overline{\mathbf{y}}_1'(\hat{V}[\overline{\mathbf{y}}_1])^{-1}\overline{\mathbf{y}}_1$$

and

$$T_{c_2}^2 = \overline{\mathbf{y}}_2'(\hat{V}[\overline{\mathbf{y}}_2])^{-1}\overline{\mathbf{y}}_2$$

- Therefore T_c^2 does *not* depend on $\mathbf{C}$
- The various T_c^2 tests of $H_0: \mu_1 = \mu_2 = \ldots = \mu_p$ based on contrasts $\mathbf{y} = \mathbf{C}\mathbf{x}$ are *identical*.

You can also *Bonferronize* each of the q = p-1 t-tests of the components of $\boldsymbol{\mu}_y$.

This *does* depend on the choice of $\mathbf{C}$, since different $\mathbf{C}$'s define different sets of contrasts.

For H_{0d}, $\mathbf{C}_d$ is not full rank and you can't compute T^2 the same way.

However, it makes good sense to Bonferronize t-tests

$$t_{ij} = \overline{y}_{ij}/\sqrt{\{\hat{V}[\overline{y}_{ij}]\}} = (\overline{x}_i - \overline{x}_j)/\sqrt{(\{s_{ii} - 2s_{ij} + s_{jj})/n\}}$$

for the M = p(p-1)/2 contrasts specified by the rows of $\mathbf{C}_d$. Divide the significance level α by M or multiply the P-value by M.

Each t_{ij} is is effectively a paired t based on differences $d_{ij} = x_i - x_j$.