Biostatistics III

Lecture 16

2 x 2 crossover design:

\[ D_{ij} = Y_{ij2} - Y_{ij1} \]

\[ P2 - P1 \]

\[ B - A \]

\[ E(D_{ij}) = \pi + \gamma + \sigma + \delta \]

\[ A - B \]

\[ E(D_{ij}) = \pi - \gamma \]

\[ \text{var}(D_{ij}) = 2\sigma_e^2 \]

Similarly,

Group 2

\[ D_{21}, D_{22}, \ldots, D_{2n_2} \] (P2 - P1)

\[ \text{iid } \mathcal{N}(\pi - \gamma, 2\sigma_e^2). \]

[Observe that the 2 groups are independent.]

\[ \text{Totals: } (P1 + P2) \]

Group 1

\[ T_1, T_{12}, \ldots, T_{1n}, \]

\[ \text{iid } \mathcal{N}(2\mu + \gamma + \pi + \sigma + \delta, 2\sigma_e^2 + 4\sigma_g^2). \]

check.
Again, to get the variance, observe that

\[ T_{ij} = Y_{ij1} + Y_{ij2} \]

\[ = (\eta_{ij1} + \eta_{ij2}) + e_{ij1} + e_{ij2} + 2\sigma_{ij} \]

constant

So,

\[ \text{var} (T_{ij}) = 2\sigma_e^2 + 4\sigma_s^2 \]

Similarly,

\text{Group 2} \quad T_{21}, T_{22}, \ldots, T_{2n2} \text{ size } n_2 \]

\[ \text{iid } N(2\mu + \gamma + \pi, 2\sigma_e^2 + 4\sigma_s^2) \]

Consider the totals:

\text{Gp 1: } T_{11}, \ldots, T_{1n1}, \quad 2\mu + \gamma + \pi + \eta

\text{Gp 2: } T_{21}, \ldots, T_{2n2}, \quad 2\mu + \gamma + \pi

Thus, subtracting the totals \((\text{Gp 1} - \text{Gp 2})\) gives \((\gamma + \pi)\).

This suggests basing a test for no interaction/carry-over on \(\overline{T}_1 - \overline{T}_2\).

\(H_0: \gamma + \pi = 0\).

\(\text{i.e. order of B, A doesn't matter.}\)
The t-statistic is:

\[ t = \frac{\overline{T}_1 - \overline{T}_2}{s_p \sqrt{\frac{1}{n_1} + \frac{1}{n_2}}} \text{ on } n_1 + n_2 - 2 \text{ d.f.} \]

where \( s_p \) is the pooled estimate of st. dev.

\[ s_p^2 = \frac{1}{n_1 + n_2 - 2} \left\{ \sum_{j=1}^{n_1} (T_{1j} - \overline{T}_1)^2 + \sum_{j=1}^{n_2} (T_{2j} - \overline{T}_2)^2 \right\} \]

This estimates

\[ 4\sigma_s^2 + 2\sigma_e^2 \]

If we retain hypothesis of no interaction/equal carryover, we use the differences to test for treatment and period effects.

1. Period effect: apply the 2-sample t-test to

\[ D_{11}, D_{12}, \ldots, D_{1n_1} \text{ and } D_{21}, D_{22}, \ldots, D_{2n_2} \]

6 group 1

6 group 2
because, if no period effect
\( (\Pi = 0 \text{, and } \gamma + \pi = 0) \) then

\[
E(\overline{D}_1.) = -E(\overline{D}_2.) \quad \text{← check}
\]

because treatments given in opposite order.

Thus

\[
t = \frac{\overline{D}_1. + \overline{D}_2.}{s_0 \sqrt{\frac{1}{n_1} + \frac{1}{n_2}}} \quad \text{on } n_1 + n_2 - 2 \text{ d.f.}
\]

gives a test of

\[
H_0 : 2\Pi = 0.
\]

\( s_0^2 \) is the pooled within-group estimate of \( \text{var}(D_{ij}) \)

\[
= \frac{1}{(n_1 + n_2 - 2)} \left\{ \sum_{j=1}^{n_1} (D_{1ij} - \overline{D}_1.)^2 + \sum_{j=1}^{n_2} (D_{2ij} - \overline{D}_2.)^2 \right\}
\]
(2) Treatment effects: use the 2-sample t-test

\[ t = \frac{\bar{D}_1 - \bar{D}_2}{s_0 \sqrt{\frac{1}{n_1} + \frac{1}{n_2}}} \text{ on } n_1 + n_2 - 2 \text{ d.f.} \]

If \((\gamma + \rho = 0)\) this gives a test of \(H_0: \tau = 0\).

\[ E(\bar{D}_1 - \bar{D}_2) = E(\bar{D}_1) - E(\bar{D}_2) = (\pi + \tau + \gamma + \rho) - (\pi - \tau) \]
\[ = 2\tau \text{ if } \gamma + \rho = 0. \]

A sequential approach:

Step 1: test for interaction/carry-over. \((H_0)\)

Step 2a: insufficient evidence to reject \(H_0\)

\[ \rightarrow \text{test for period effect} \]
\[ \rightarrow \text{test for treatment effect} \]
Step 2b: If reject H₀, interpretation more difficult.

- usually need external information on possible causes:
  1. True carry-over effects of treatment. (different)
  2. Psychological carry-over effects.
  3. True interaction. period x treatment.

If true interaction:
- transform data e.g. \( \log y \) or may decide to discard P₂ data, analyse P₁ data only.

Why? period effects, treatment effects are marginal to interaction.

Is it justified? Yes, because of randomization.
but is considerably less powerful.

Original sample size calculations based on crossover design

- $\sigma_e^2$ now enters treatment comparison.

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Problem with sequential approach:
t-test for no interaction lacks power too: because it's based on the $T_{ij}$ with

$$\text{VAR}(T_{ij}) = 2\sigma_e^2 + 4\sigma_s^2.$$  

Using baseline measurements $Z_{ij}$ can help.

E.g. For each subject, calculate

$$T'_{ij} = T_{ij} - 2Z_{ij},$$

then test

$$T_{ij}' - T_{ij}.$$  

Similarly for PI data only procedure:

calculate

$$Y_{ij}' = Y_{ij} - Z_{ij},$$

and compare $\overline{Y}_{ij}'$ with $\overline{Y}_{aji}'.$
Useful plots:
Do these first.

1) **Subject-profile plots**:
Simplest. For each group, plot change in subjects responses.

IE. \( y_{ij1} \) vs \( P_1 \)
\( y_{ij2} \) vs \( P_2 \)
and join by a line.

E.g. Group 1 (AB)

**Response**

\[ y \]

**Period**

A

B

Idea: compare treatments within groups.

Look for: trends, outliers, anything unusual.
2) **Groups x periods plot**

Plot the 4 group x period means, and join treatments by lines.

- **Group 1**
  - \( \bar{y}_{1.1} \) (IA)
  - \( \bar{y}_{1.2} \) (IB)

- **Group 2**
  - \( \bar{y}_{2.1} \) (2B)
  - \( \bar{y}_{2.2} \) (2A)

3) **Subject differences vs totals plot**

- Most helpful.
- Gives overall view of data and effects.
- Can see variation within and between groups.

For each subject, plot \( d_{ij} \) vs \( t_{ij} \)

Use different plotting symbol for each group, and draw convex hull.
Horizontal separation of groups suggests interaction/carryover.

Vertical separation suggests treatment difference.