Crossover Designs

BIOE 498/598

Crossover Designs

Crossover Designs (CODs) are used when individual experimental units are rare or expensive.

For example, you're doing a Phase I clinical trial to determine the PD/PK of a drug.

These trials should be small, but small samples are difficult to randomize.

If you used a standard control/experiment split, it would be difficult to find two similar groups of people.

Instead, we give all experimental units both treatments.

Planning CODs

In CODs every subject will receive every treatment. The number of treatment levels must be small.

The number of subjects is also (relatively) small, so drop-outs are a concern if the number of treatment is large.

Treatments are sequential, so the effects can persist into the next treatment. This is called *carryover*.

Two methods to deal with carryover:

- Allow a washout period between treatments (easy but costly)
- Include carryover effects in the model (more difficult)

Sample COD: AB, BA for two treatments

We have two treatments (A & B) and two groups of subjects (I & II).

- Group I receives treatment A followed by treatment B.
- Group II receives treatment B followed by treatment A.

Group	Period 1	Washout	Period 2
I	A	—	B
II	B	—	A

How do we model CODs?

The response of every subject in each period involves multiple factors:

$$\underbrace{y}_{\text{response}} = \underbrace{\mu}_{\text{mean}} + \underbrace{\tau}_{\text{treatment}} + \underbrace{\pi}_{\text{period}} + \underbrace{s}_{\text{subject}}$$

- The mean effect (μ) is the overall response of all subjects to either treatment in either period.
- The treatment effects (τ) are what we're trying to measure.
- The period effects (π) block for changes between the first and second periods, assuming all subjects were run simultaneously.
- The subject effects (s) block for differences between each experimental unit.

Normally we can't include blocking factors for every experimental unit (since there is usually one unit per run). Since CODs make multiple independent measurements on the same unit (period 1 vs. 2), we have enough data to fit a parameter for each individual.

Modeling the AB, BA experiment

Group	Period 1	Washout	Period 2
I	A	—	B
II	B	—	A

Group	Period 1	Period 2
I	$y = \mu + \tau_A + \pi_1 + s_i$	$y = \mu + \tau_B + \pi_2 + s_i$
II	$y = \mu + \tau_B + \pi_1 + s_i$	$y = \mu + \tau_A + \pi_2 + s_i$

$$\#\text{ parameters} = 1 + \#\text{ treatments} + \#\text{ periods} + \#\text{ subjects}$$

$$\#\text{ observations} = (\#\text{ groups})(\#\text{ periods})(\#\text{ subjects})$$

Example: Plasma concentrations of antifungal agent

```
head(antifungal, n=20)
```

```
##    Group Subject Period Treat   pl
## 1      1       2      1     A 12.8
## 2      1       3      1     A 16.5
## 3      1       6      1     A 18.7
## 4      1       8      1     A 11.6
## 5      1      11      1     A 13.6
## 6      1      12      1     A  9.8
## 7      1      15      1     A 12.8
## 8      1      17      1     A 12.1
## 9      2       1      1     B 10.9
## 10     2       4      1     B 13.5
## 11     2       5      1     B 13.7
## 12     2       7      1     B 12.2
## 13     2       9      1     B 12.6
## 14     2      10      1     B 13.0
## 15     2      13      1     B 10.7
## 16     2      14      1     B 14.2
## 17     2      16      1     B 12.2
## 18     1       2      2     B  8.2
## 19     1       3      2     B 13.1
## 20     1       6      2     B 15.9
```

Building the linear model

```
##
## Call:
## lm(formula = pl ~ Treat + Period + Subject, data = antifungal,
##     contrasts = list(Subject = contr.sum, Period = contr.sum,
##         Treat = contr.sum))
##
## Residuals:
##    Min     1Q Median     3Q    Max
## -2.900 -1.321  0.000  1.321  2.900
##
## Coefficients:
##             Estimate Std. Error t value Pr(>|t|)
## (Intercept) 13.15882    0.36634  35.920 5.78e-16 ***
## Treat1       0.29722    0.36698   0.810   0.4306
## Period1     -0.14722    0.36698  -0.401   0.6939
## Subject1    -1.55882    1.46536  -1.064   0.3043
## Subject2    -2.65882    1.46536  -1.814   0.0897 .
## Subject3     1.64118    1.46536   1.120   0.2803
## Subject4    -0.65882    1.46536  -0.450   0.6594
## Subject5     1.69118    1.46536   1.154   0.2665
## Subject6     4.14118    1.46536   2.826   0.0128 *
## Subject7     0.34118    1.46536   0.233   0.8190
## Subject8    -0.25882    1.46536  -0.177   0.8622
## Subject9     1.24118    1.46536   0.847   0.4103
## Subject10    2.09118    1.46536   1.427   0.1740
## Subject11    0.04118    1.46536   0.028   0.9780
## Subject12   -0.60882    1.46536  -0.415   0.6837
## Subject13   -4.05882    1.46536  -2.770   0.0143 *
## Subject14    0.14118    1.46536   0.096   0.9245
## Subject15    0.24118    1.46536   0.165   0.8715
## Subject16   -0.65882    1.46536  -0.450   0.6594
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
## Residual standard error: 2.136 on 15 degrees of freedom
## Multiple R-squared:  0.634,  Adjusted R-squared:  0.1948
```

Anova (Type III since we have unequal group sizes)

```
Anova(modl, type = "III")
```

```
## Anova Table (Type III tests)
##
## Response: pl
##              Sum Sq Df   F value   Pr(>F)
## (Intercept) 5887.3  1 1290.2269 5.78e-16 ***
## Treat          3.0  1    0.6560   0.4306
## Period         0.7  1    0.1609   0.6939
## Subject      114.6 16    1.5703   0.1942
## Residuals     68.4 15
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1
```

Comparing Treatment Effects

```
lsmeans(modl, pairwise ~ Treat)
```

```
## $lsmeans
##  Treat lsmean    SE df lower.CL upper.CL
##  A       13.5 0.519 15     12.4     14.6
##  B       12.9 0.519 15     11.8     14.0
##
## Results are averaged over the levels of: Period, Subject
## Confidence level used: 0.95
##
## $contrasts
##  contrast estimate    SE df t.ratio p.value
##  A - B       0.594 0.734 15 0.810   0.4306
##
## Results are averaged over the levels of: Period, Subject
```

```
lsmeans(modl, pairwise ~ Period)
```

```
## $lsmeans
##  Period lsmean    SE df lower.CL upper.CL
##  1        13.0 0.519 15     11.9     14.1
##  2        13.3 0.519 15     12.2     14.4
##
## Results are averaged over the levels of: Treat, Subject
## Confidence level used: 0.95
##
## $contrasts
##  contrast estimate    SE df t.ratio p.value
##  1 - 2      -0.294 0.734 15 -0.401  0.6939
##
## Results are averaged over the levels of: Treat, Subject
```