Biostats VHM 802 Course
Winter 2019, Atlantic Veterinary College, PEI
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Exercises for Session 9: Cross-over designs

Exercise 9.1

Cross-over trial

In a study of treatments against asthma in children, the investigators allocated 14 children to one of two treatment sequences (FS or SF). The two inhalation treatments were formoterol (F; dose 12 μg) and salbutamol (S; dose 200μg). Eight hours after treatment the children's peak expiratory flow (PEF) was measured. Child no. 8 failed to complete both periods of treatment, and is excluded from the present data. (Data from Graff-Lonnevig, V. & Browaldh, L. (1990), Twelve hours bronchodilating effect of inhaled formoterol in children with asthma: a double-blind cross-over study versus salbutamol, *Clinical and Experimental Allergy* **20**, 429–432.)

		PEF reading	
Sequence	Patient	Period 1	Period 2
FS	1	310	270
	4	310	260
	6	370	300
	7	410	390
	10	250	210
	11	380	350
	14	330	365
SF	2	370	385
	3	310	400
	5	380	410
	9	290	320
	12	260	340
	13	90	220

(a) Initially, we assume that no carry-over effects are present. Formulate a statistical model that incorporates assess both period and treatment effects, as well as subject effects, and carry out the corresponding analysis. Try also to assess the treatment effects by analysing suitable differences within each subject, and convince yourself that results are the same as in the combined model. If you are interested, do the same thing for the period effect.

(b) In order to enable an assessment of carry-over effects one must take the subject effect as a random effect. First, compare the analysis of *(a)* with an analysis with subject random effects. Second, expand the model by including a period by treatment interaction. Explain why the interaction would be expected to include any carry-over effects. Draw conclusions about the existence of carry-over effects, as well as overall conclusions from the study. (*Note:* A random effects model with treatment by period interaction cannot be fit by the ANOVA-based method in Minitab in the `General Linear Model` menu, but it can be fit with likelihood-based methods available in other software as well as in the new `Mixed Effect Models` menu in Minitab 18.)

Exercise 9.2

Combination of Latin squares

This exercise extends Example 13.12 in the textbook (GO). Milk production (pounds per 6 weeks) were 18 obtained for 18 cows each fed three diets (A: roughage; B: limited grain; C:full grain). The design and data are displayed below (in a slightly different format than GO Table 13.4).

	Cow			Cow			Cow		
Period	1	2	3	7	8	9	13	14	15
1	A 1376	B 2088	C 2238	A 1655	B 1938	C 1855	A 1342	B 1344	C 1627
2	B 1246	C 1864	A 1724	B 1517	C 1804	A 1298	B 1294	C 1312	A 1186
3	C 1151	A 1392	B 1272	C 1366	A 969	B 1233	C 1371	A 903	B 1066
	Cow			Cow			Cow		
Period	4	5	6	10	11	12	16	17	18
1	A 1863	B 1748	C 2012	A 1384	B 1640	C 1677	A 1180	B 1287	C 1547
2	C 1755	A 1353	B 1626	C 1535	A 1284	B 1497	C 1245	A 1000	B 1297
3	B 1462	C 1339	A 1010	B 1289	C 1370	A 1059	B 1082	C 1078	A 887

Following the discussion in GO, analyze the log-transformed yields. Fit and interpret the results of the following models, including appropriate comparisons between models:

1) an additive model in treatments, periods and cows,

2) a model with a period by square interaction,

3) a model with a period by square type interaction, where Latin square types are denoted 1 and 2 (corresponding to upper and lower parts of the table),

4) a model with treatment effects split into direct effects and carry-over effects, as explained in the text (GO).

Summarize your analysis by writing up a small description of the treatment effects, including both the direct and carry-over effects.