Univariate Methods

- The most elementary approach to repeated measurements is to:
  - simplify multivariate data to univariate data
  - reduce a subject's vector of responses to a single measurement
- This avoids the issue of correlation among the repeated measurements for a subject
- For the case of two measurements per subject, well-known methods of this type include the:
  - paired t-test for continuous responses
  - McNemar's test for dichotomous responses
- This approach is most applicable for complete data at common measurement times from:
  - one sample
  - multiple samples (one categorical covariate)

One-Sample Problems

- The data for this special situation can be displayed in an $n \times t$ matrix, as follows:

	Time Point				
Subject	1	$\ldots$	j	$\ldots$	t
1	y_{11}	$\cdots$	y_{1j}	$\cdots$	y_{1t}
$\vdots$	$\vdots$	$\ddots$	$\vdots$	$\ddots$	$\vdots$
i	y_{i1}	$\cdots$	y_{ij}	$\cdots$	y_{it}
$\vdots$	$\vdots$	$\ddots$	$\vdots$	$\ddots$	$\vdots$
n	y_{n1}	$\cdots$	y_{nj}	$\cdots$	y_{nt}

- The corresponding missing value indicators are defined by

$$\delta_{ij} = \begin{cases} 1 & \text{if } y_{ij} \text{ is observed} \\ 0 & \text{otherwise} \end{cases}$$

Univariate Methods: One-Sample Problems

1. Separate comparisons between pairs of time points

Type of Response	Possible Test
normal	paired-t
non-normal	sign rank
categorical	sign

Comments:

- With t time points, $t(t-1)/2$ tests are required
- The test statistics are correlated, due to:
  - dependence between repeated measurements for each subject
  - data from each time point are used in multiple tests
- This method is not recommended

Univariate Methods: One-Sample Problems

2. "Summary statistic" approach

   a. Reduce each subject's data to a single, meaningful measure of association between the response variable and time, e.g.,

      - slope of regression line
      - parametric or nonparametric correlation coefficient

   b. Use parametric (nonparametric) methods to test if the mean (median) of the derived measure differs from zero

Comments:

- Useful for irregularly-spaced measurements
- Results may be misleading if summary measure does not adequately describe each subject's data

Example

- Deal et al. (1979) measured ventilation volumes (l/min) of eight subjects under six different temperatures of inspired dry air

	Temperature (°C)					
Subject	−10	25	37	50	65	80
1	74.5	81.5	83.6	68.6	73.1	79.4
2	75.5	84.6	70.6	87.3	73.0	75.0
3	68.9	71.6	55.9	61.9	60.5	61.8
4	57.0	61.3	54.1	59.2	56.6	58.8
5	78.3	84.9	64.0	62.2	60.1	78.7
6	54.0	62.8	63.0	58.0	56.0	51.5
7	72.5	68.3	67.8	71.5	65.0	67.7
8	80.8	89.9	83.2	83.0	85.7	79.6

- Is ventilation volume affected by temperature?

Reference

Deal, E. C., McFadden, E. R., Ingram, R. H. et al. (1979). Role of respiratory heat exchange in production of exercise-induced asthma. *J Appl Physiol* **46**, 467–475.

Example (Method 1)

Assume that the relationship between temperature and ventilation volume is linear

- For each subject, compute the slope ($\widehat{\beta}$) of the least-squares line

  - Let x_i and y_i denote the temperature and ventilation volume, respectively

  - $\widehat{\beta} = \dfrac{\sum_{i=1}^{6}(x_i - \overline{x})(y_i - \overline{y})}{\sum_{i=1}^{6}(x_i - \overline{x})^2} = \dfrac{\sum_{i=1}^{6}(x_i - \overline{x})y_i}{\sum_{i=1}^{6}(x_i - \overline{x})^2}$

  - Since $\overline{x} = 41.167$ and $\sum_{i=1}^{6}(x_i - \overline{x})^2 = 5050.83$, $\widehat{\beta} = \sum_{i=1}^{6} w_i y_i$, where

$$
\begin{array}{ll}
w_1 = -0.010130 & w_4 = 0.001749 \\
w_2 = -0.003201 & w_5 = 0.004719 \\
w_3 = -0.000825 & w_6 = 0.007688
\end{array}
$$

Example (Method 1, Continued)

- The results for individual subjects are as follows:

Subject	Slope	Signed-Rank
1	−0.00916	−2
2	−0.02009	−4
3	−0.10439	−7
4	0.00443	1
5	−0.12029	−8
6	−0.03838	−5
7	−0.05672	−6
8	−0.01336	−3

- Assuming that the estimated slopes are normally distributed, the one-sample t-test yields

$$t = \frac{\sqrt{8}(-0.044746 - 0)}{0.0458644} = -2.76$$

with two-sided $p = 0.028$ (t_7 distribution)

- Alternatively, the Wilcoxon signed-rank statistic is $R_1 = 1$ (two-sided $p < 0.05$)

Example (Method 2)

Assume only that the relationship between temperature and ventilation volume is monotonic

- The ranks and Spearman's rank correlation coefficient r_s for each subject are given below:

	Temperature (°C)						
Subject	-10	25	37	50	65	80	r_s
1	3	5	6	1	2	4	$-.257$
2	4	5	1	6	2	3	$-.257$
3	5	6	1	4	2	3	$-.543$
4	3	6	1	5	2	4	$-.086$
5	4	6	3	2	1	5	$-.314$
6	2	5	6	4	3	1	$-.371$
7	6	4	3	5	1	2	$-.771$
8	2	6	4	3	5	1	$-.257$

- The Wilcoxon signed-rank statistic is $R_1 = 0$ (two-sided $p < 0.02$)

- The two-sided exact sign test p-value is 0.0078

Multi-Sample Problems

- The data can be displayed as follows:

		Time Point				
Group	Subject	1	$\ldots$	j	$\ldots$	t
1	1	y_{111}	$\cdots$	y_{11j}	$\cdots$	y_{11t}
	$\vdots$	$\vdots$	$\ddots$	$\vdots$	$\ddots$	$\vdots$
	i	y_{1i1}	$\cdots$	y_{1ij}	$\cdots$	y_{1it}
	$\vdots$	$\vdots$	$\ddots$	$\vdots$	$\ddots$	$\vdots$
	n_1	y_{1n_11}	$\cdots$	y_{1n_1j}	$\cdots$	y_{1n_1t}
$\cdots$	$\cdots$	$\cdots$	$\cdots$	$\cdots$	$\cdots$	$\cdots$
h	1	y_{h11}	$\cdots$	y_{h1j}	$\cdots$	y_{h1t}
	$\vdots$	$\vdots$	$\ddots$	$\vdots$	$\ddots$	$\vdots$
	i	y_{hi1}	$\cdots$	y_{hij}	$\cdots$	y_{hit}
	$\vdots$	$\vdots$	$\ddots$	$\vdots$	$\ddots$	$\vdots$
	n_h	y_{hn_h1}	$\cdots$	y_{hn_hj}	$\cdots$	y_{hn_ht}
$\cdots$	$\cdots$	$\cdots$	$\cdots$	$\cdots$	$\cdots$	$\cdots$
s	1	y_{s11}	$\cdots$	y_{s1j}	$\cdots$	y_{s1t}
	$\vdots$	$\vdots$	$\ddots$	$\vdots$	$\ddots$	$\vdots$
	i	y_{si1}	$\cdots$	y_{sij}	$\cdots$	y_{sit}
	$\vdots$	$\vdots$	$\ddots$	$\vdots$	$\ddots$	$\vdots$
	n_s	y_{sn_s1}	$\cdots$	y_{sn_sj}	$\cdots$	y_{sn_st}

Univariate Methods: Multi-Sample Problems

1. Separate comparisons among groups at individual time points

Type of Response	Possible Test
normal	one-way ANOVA
non-normal	Kruskal-Wallis test
categorical	Pearson's chi-square test

2. Separate comparisons between pairs of time points for individual groups

Type of Response	Possible Test
normal	paired-t
non-normal	sign rank
categorical	sign

In both cases:

- Multiple tests are required
- The test statistics are correlated

Univariate Methods: Multi-Sample Problems

3. "Summary statistic" approach

   a. Reduce each subject's data to a single, meaningful measure of association between the response variable and time, e.g.,

      - slope of regression line
      - parametric or nonparametric correlation coefficient

   b. Use parametric (nonparametric) methods to test for differences among groups

Comments:

- Useful for irregularly-spaced measurements
- Results may be misleading if summary measure does not adequately describe each subject's data

Example

- In a nutrition study, three groups of rats were put on different diets

- After a settling-in period, their body weights (in grams) were recorded weekly over a nine-week period

- During the sixth week of recording, an additional treatment was given to each animal

  (This will be ignored for the time being)

- Do the growth profiles of the three groups differ?

Reference

Crowder, M. J. and Hand, D. J. (1990). *Analysis of Repeated Measures*. London: Chapman and Hall, p. 19.

Rat Body Weights

	Day										
ID	1	8	15	22	29	36	43	44	50	57	64
Group 1:											
1	240	250	255	260	262	258	266	266	265	272	278
2	225	230	230	232	240	240	243	244	238	247	245
3	245	250	250	255	262	265	267	267	264	268	269
4	260	255	255	265	265	268	270	272	274	273	275
5	255	260	255	270	270	273	274	273	276	278	280
6	260	265	270	275	275	277	278	278	284	279	281
7	275	275	260	270	273	274	276	271	282	281	284
8	245	255	260	268	270	265	265	267	273	274	278
Group 2:											
9	410	415	425	428	438	443	442	446	456	468	478
10	405	420	430	440	448	460	458	464	475	484	496
11	445	445	450	452	455	455	451	450	462	466	472
12	555	560	565	580	590	597	595	595	612	618	628
Group 3:											
13	470	465	475	485	487	493	493	504	507	518	525
14	535	525	530	533	535	540	525	530	543	544	559
15	520	525	530	540	543	546	538	544	553	555	548
16	510	510	520	515	530	538	535	542	550	553	569

Univariate Analysis

- For each subject, compute the slope ($\widehat{\beta}$) of the least-squares line (assuming a linear relationship)

  - Let x_i and y_i denote time (in days) and weight (in grams), respectively

  - $\widehat{\beta} = \dfrac{\sum_{i=1}^{11}(x_i - \overline{x})(y_i - \overline{y})}{\sum_{i=1}^{11}(x_i - \overline{x})^2} = \dfrac{\sum_{i=1}^{11}(x_i - \overline{x})y_i}{\sum_{i=1}^{11}(x_i - \overline{x})^2}$

  - Since $\overline{x} = 33.545$ and $\sum_{i=1}^{11}(x_i - \overline{x})^2 = 4162.73$, $\widehat{\beta} = \sum_{i=1}^{11} w_i y_i$, where

$$
\begin{array}{ll}
w_1 = -.007818301 & w_7 = .002271238 \\
w_2 = -.006136711 & w_8 = .002511465 \\
w_3 = -.004455121 & w_9 = .003952828 \\
w_4 = -.002773531 & w_{10} = .005634418 \\
w_5 = -.001091941 & w_{11} = .007316008 \\
w_6 = .000589648 &
\end{array}
$$

Univariate Analysis

- The results for individual subjects are as follows:

Group	ID	Slope	Group	ID	Slope
1	1	0.484	2	9	1.011
	2	0.330		10	1.341
	3	0.398		11	0.363
	4	0.330		12	1.148
	5	0.406	3	13	0.919
	6	0.318		14	0.315
	7	0.202		15	0.493
	8	0.409		16	0.905

- The mean & s.d. of the slopes in each group are:

Group	Mean	S.D.
1	.3596	.0845
2	.9655	.4242
3	.6580	.3022

- One-way ANOVA: $F_{2,13} = 7.57$, $p = .007$

  Kruskal-Wallis: $\chi^2_2 = 5.80$, $p = .055$

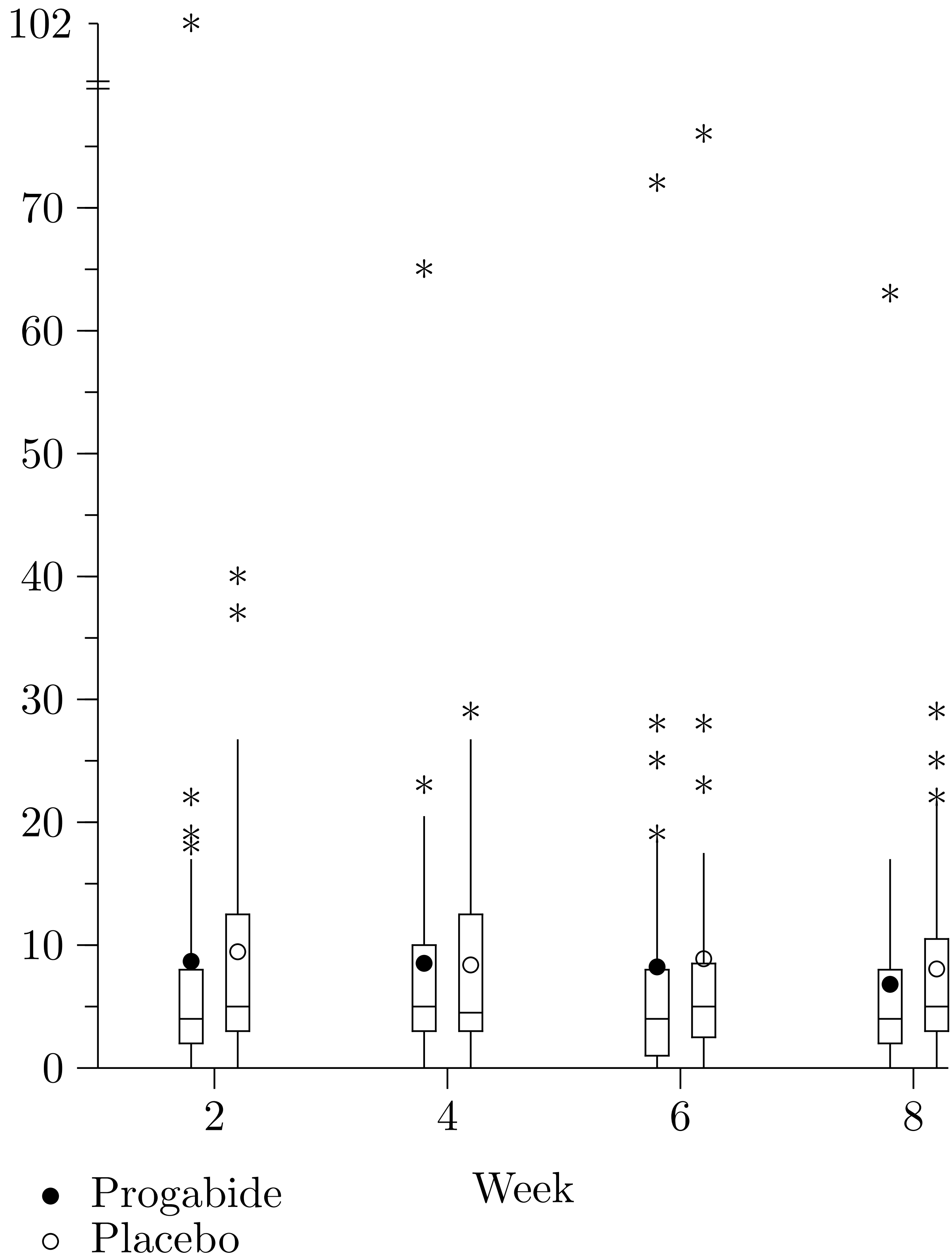
Example

- Leppik et al. (1987) conducted a clinical trial in 59 epileptic patients
- Patients suffering from simple or complex partial seizures were randomized to receive either the antiepileptic drug progabide (31 patients) or a placebo (28 patients)
- At each of four successive postrandomization visits, the number of seizures occurring during the previous two weeks was reported
- The medical question of interest is whether or not progabide reduces the frequency of epileptic seizures

Reference

Leppik IE, Dreifuss FE, Porter R et al. (1987). A controlled study of progabide in partial seizures: methodology and results. *Neurology* **37**, 963–968.

Modified Box Plots of Seizure Counts



Example (continued)

- The distributions of the total seizure counts are extremely non-normal in both treatment groups at all time points

  (p-values from the Shapiro-Wilk (1965) test of normality are all less than 0.001)

- One possible approach is to reduce the vector of four observations from each subject (weeks 2, 4, 6, and 8) to a single measurement

  - The total seizure count is one potential summary statistic

  - The median of the four measurements from each subject is another choice

    (this summary statistic will be less affected by extreme observations)

Data for Summary Statistic Approach

Progabide Group

ID	Total	Median	ID	Total	Median
101	42	10.0	143	39	7.0
102	28	7.5	147	7	1.5
103	7	1.5	203	32	8.0
108	13	3.0	204	3	0.5
110	19	5.0	207	302	68.5
111	11	3.0	208	13	3.5
112	74	18.0	209	26	6.5
113	20	4.5	211	10	2.0
117	10	3.0	214	70	15.5
121	24	7.0	218	13	3.5
122	29	4.5	221	15	3.5
124	4	1.0	225	51	13.5
128	6	1.0	228	6	1.5
129	12	3.5	232	0	0.0
137	65	14.5	236	10	2.5
139	26	6.5			

Placebo Group

ID	Total	Median	ID	Total	Median
104	14	3.0	205	59	13.0
106	14	3.0	206	16	2.5
107	11	3.0	210	6	1.5
114	13	4.0	213	123	29.0
116	55	13.5	215	15	4.0
118	22	6.0	217	16	4.5
123	12	3.0	219	14	3.5
126	95	21.5	220	14	3.5
130	22	5.5	222	13	3.0
135	33	9.5	226	30	8.0
141	66	17.0	227	143	24.5
145	30	7.0	230	6	1.5
201	16	4.0	234	10	2.5
202	42	10.5	238	53	13.0

Summary Statistic Approach

- The median total seizure counts in the progabide and placebo groups are 15 and 16, respectively

- Using the Mann-Whitney-Wilcoxon test, there is insufficient evidence to conclude that progabide reduces the total seizure count
  - The two-sided p-value is 0.19

- The median of the median seizure counts in the progabide and placebo groups are 3.5 and 4, respectively

- Using the Mann-Whitney-Wilcoxon test, there is insufficient evidence to conclude that progabide reduces the median seizure count
  - The two-sided p-value is 0.27