

Statistical Primer: Performing repeated measures analysis

2 **Short title:** Performing repeated measures analysis

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32 **SUMMARY**

34 **Purpose:** Longitudinal data arises when repeated measurements are taken on the same
individuals over time. Inference about between group differences of within-subject change
36 is usually of interest. This statistical primer for cardiothoracic and vascular surgeons aims to
provide a short and practical introduction of biostatistical methods on how to analyse
38 repeated measures data.

40 **Methods:** Several methodological approaches for analysing repeated measures will be
introduced, ranging from simple approaches to advanced regression modelling. Design
42 considerations of studies involving repeated measures are discussed and the methods
illustrated with a dataset measuring coronary sinus potassium in dogs after occlusion.

44

Conclusion: Cardiothoracic and vascular surgeons should be aware of the myriad of
46 approaches available to them for analysing repeated measures data, including the relative
merits and disadvantages of each. It is important to present effective graphical displays of
48 the data, and to avoid arbitrary cross-sectional statistical comparisons.

50 **Key words:** statistics; repeated measurements; serial measurements; longitudinal data

52

INTRODUCTION

54 Repeated measures data—also known as longitudinal data and serial measures
data—are routinely analysed in many studies [1]. The data can be collected both
56 prospectively and retrospectively, allowing for changes over time and its variability within
individuals to be distinguished; for example, echocardiographic measurements recorded at
58 different follow-up times after allograft implantation, or Interleukin-6 measured in rats at
pre-specified times following cardiopulmonary bypass. The guidelines for reporting
60 mortality and morbidity after cardiac valve interventions also propose the use of
longitudinal data analysis for repeated measurement data in patient undergoing
62 cardiovascular surgery [2].

The focus of this Statistical Primer will be on measurements repeatedly recorded
64 over time, although repeated measures can occur in other circumstances, for example when
the conditions are changed (e.g. treatment) and the same patients are measured under
66 each experimental condition. Unlike measurements taken on different patients, repeated
measures data, however, are not independent. In other words, repeated observations on
68 the same individual will be more similar to each other than to observations on other
individuals. This necessitates statistical methodology that can account for this dependency.

70

DESIGN CONSIDERATIONS

72 **Balanced versus unbalanced data**

When subjects are measured at a fixed number of time points that are common to
74 all subjects, then the data are said to be balanced. For example, rats might be tested at
times 0, 2-hours, 6-hours, 12-hours, and 24-hours. In some designed studies, these
76 measurements may be *mistimed*, e.g. in human studies where patients are delayed
returning to clinic for scheduled follow-up appointments. In some observational studies, i.e.
78 naturalistic cohort studies, measurement times will often vary between subjects and can
vary substantially in the number of measurements recorded. Moreover, the patients may
80 have different durations of follow-up observation for various reasons, and may be censored
due to terminal events. This would be classed as unbalanced data, and precludes the use of
82 certain statistical methodologies. For balanced and unbalanced measurements, the datasets
are often stored in so-called 'wide format' (**Table S1a**) and 'long format' (**Table S1b**),
84 respectively.

Missing data

86 Missing data are not uncommon in longitudinal outcome studies. For example, if a
patient fails to attend a scheduled appointment, then measurements cannot be taken, and
88 the observation is deemed missing or incomplete. Approaches to handling missing data
include complete-case analysis, i.e. deleting patients with one or more missing
90 measurement values; last observation carried forward (LOCF) or interpolation methods; and
other imputation techniques. Assumptions about the mechanism leading to missing data
92 dictates the appropriateness of different techniques; however, in general it is widely
accepted that simple techniques such as complete-case analysis and LCOF lead to serious
94 bias, and therefore should be avoided. Alternative methods are discussed elsewhere [3].

96 **METHODOLOGY**

Two-stage methods

98 For balanced data, the comparison of treatments might be done by performing
separate statistical tests at each time point (**Figure 2A**). However, this approach is
100 inappropriate as it often fails to address relevant research questions and is subject to
statistical deficiencies such as ignoring that observations on a given subject are likely to be
102 correlated, and multiple testing [4]. Additionally, the accompanying presentation is
frequently inadequate [5], as illustrated in the example shown in **Figure 2A**. One alternative
104 approach is to *reduce* the data for each subject to a *single* meaningful statistic, which are
then analysed using standard methods for independent groups, e.g. the independent
106 samples *t*-test [4]. The choice of statistic will depend on the data and the study question, in
particular whether the data display a growth-like pattern or a peaked-like pattern; see **Table**
108 **S2** for examples. Even when not used for the primary analysis, such reduced data summary
statistics can be useful, yet it must still be recognised that there might be some information
110 loss with this approach.

Repeated measures analysis of variance (RM-ANOVA)

112 RM-ANOVA can only be applied for balanced data [6]. When there is also a between
group variable (e.g. treatment) the standard RM-ANOVA decomposes the total variation
114 into (i) between subject variation due to treatment effect; (ii) time effect; (iii) time-and-
treatment effect; and (iv) the residual error variation. This can be leveraged to test different
116 hypotheses, respectively: (a) an overall treatment effect; (b) differences in outcomes over

time; (c) a different effect of treatment over time. The latter derives from the interaction
 118 between time and treatment, which if zero would imply effects are parallel through all time
 points. In addition to the usual assumption imposed on ANOVA, RM-ANOVA depends on the
 120 assumption of sphericity. Effectively, this can be considered as being equivalent to equal
 variability of measurements at each time (i.e. homogeneity) and equal correlations between
 122 any pair of time points (e.g. $\text{corr}(y_{\text{time}_1}, y_{\text{time}_2}) \approx \dots \approx \text{corr}(y_{\text{time}_1}, y_{\text{time}_3})$) for
 measurements y recorded at times 1, 2, 3, ...). This assumption is restrictive for longitudinal
 124 data, since measurements taken closely together are often more correlated than those
 taken at larger time intervals [7]. Violation of this assumption typically results in an inflated
 126 type I error rate and can bias the interaction effect [7]. If used, it is essential that this
 assumption is checked and reported. Typically, this is achieved through Mauchly's epsilon
 128 test; however, this test is known to have low power. When sphericity is violated, there are
 several corrections to the degrees of freedom of the F -test that can be used [8], including
 130 Greenhouse-Geisser and Huynh-Feldt methods.

Linear mixed models (LMMs)

132 Linear mixed models are extensions of more conventional linear models. Let Y_{ij}
 denote the observed outcome measured on subject i ($i = 1, \dots, n$) at time t_{ij} ($j = 1, \dots, n_i$),
 134 where n_i is the number of measurements for subject i . By pooling the data, one can fit a
 linear regression model

$$136 \quad Y_{ij} = \beta_0 + \beta_1 t_{ij} + \varepsilon_{ij},$$

where ε_{ij} is a measurement error term (or residual), which allows for the outcome to
 138 randomly vary above or below the mean value for each time point. Here, β_1 represents the
 population slope (**Figure 1A**, black line): the constant effect on the outcome corresponding
 140 to a one-unit increase in time. LMMs can also be fitted to unbalanced datasets with
 irregularly spaced time points (**Figure 1B**), hence each measurement time (t_{ij}) being
 142 allowed to be different between subjects in model above. Linear mixed models are
 predicated on the idea that each subject has their own mean response profile which
 144 deviates randomly from the average (overall) trajectory [9]. That is, for each subject i , we
 extend the model above by including a random intercept b_{0i} and a random slope b_{1i} :

$$146 \quad Y_{ij} = (\beta_0 + b_{0i}) + (\beta_1 + b_{1i})t_{ij} + \varepsilon_{ij},$$

where (b_{0i}, b_{1i}) are called subject-specific random effects, and assumed to follow a zero-
148 mean multivariate normal distribution and be correlated. An intuitive graphical
representation of this is shown in **Figure 1A**. Here, β_0 and β_1 , averaged across all subjects,
150 have the same interpretation, i.e. fixed population-level intercept and slope effects, as for
the simple linear regression model. The combination of fixed and random effects is why we
152 refer to this model as a *mixed effects* model, which are also sometimes referred to as multi-
level models, random-effects models, random growth-curve models, etc. As well as allowing
154 for subject-specific trajectories, the random effects also ensures that observations within-
subjects are more correlated than observations between-subjects, with the case presented
156 here allowing for heterogeneity over time. In the above we assumed time was measured
continuously and linearly; however, we might relax this assumption by treating time as
158 measured categorically (providing the data are balanced) or through spline functions, which
allow for smooth regression curves that capture nonlinearity [10]. In such cases, we can
160 include additional higher-order random effects; the linear model was presented here for
purposes of demonstration. LMMs can also include other adjustment covariates, including
162 time-varying covariates. In particular, one might want to adjust for the baseline
measurement of Y rather than treat it as an outcome at the baseline time point, i.e. before
164 treatment intervention [11].

166 **EXAMPLE**

As an example, we consider data from Grizzle and Allen [12], who describe a
168 laboratory experiment that collected serial measurements of coronary sinus potassium
(CSP) (mEq/L) from four groups of dogs. The groups were:

- 170 • Control group: $N=9$ untreated dogs with coronary occlusion.
- ECD (3-weeks) group: $N=10$ dogs given extrinsic cardiac denervation (ECD) 3-weeks
172 prior to coronary occlusion
- ECD (0-weeks) group: $N=8$ dogs treated similarly to above, but given ECD
174 immediately prior to coronary occlusion.
- Sympathectomy group: $N=9$ dogs treated with bilateral thoracic sympathectomy and
176 stellectomy three weeks prior to coronary occlusion.

The response variable was recorded at times 1, 3, 5, 7, 9, 11, and 13 minutes. Before we
178 analyse the data, we inspect the data graphically (**Figure 2B**), where we observe a growth-
like trend and substantial between-subject heterogeneity.

180 If the primary scientific objective was to describe changes in CSP over the 12-minute
follow-up period and determine whether the pattern of change differed between groups,
182 then we could fit a linear mixed model including treatment effect and time as a continuous
covariate with an interaction term to capture non-parallel growth trends. Despite **Figure 2B**
184 indicating some non-linearity towards the end of the study follow-up, we note that we've
made a strong assumption of linearity in this example. Fitting this model (**Table 2**) indicates
186 that there is a significant increase in CSP during follow-up in the control group (i.e. a
significant effect for time; 0.08 [95% CI: 0.05 to 0.12]), and no discernible difference from
188 this trend in group ECD (0-weeks) (i.e. non-significant interaction term with time; -0.02 [95%
CI: -0.08 to 0.03]). The ECD (3-weeks) group interaction term is significant ($P < 0.001$), and
190 despite not reaching significance, there was a tendency for CSP to be reduced over time in
sympathectomy group (-0.05; 95% CI: -0.10 to 0.00). Moreover, both terms are negative,
192 which is consistent with **Figure 2B** where the time course for these two groups are relatively
flat. We could formally test this using appropriate contrasts. One could also perform *post*
194 *hoc* tests to establish treatment effect differences at each measurement time (**Figure 2A**),
but one would need to correct for multiple comparisons (not implemented here). Neither
196 group admitted a significant main treatment effect relative to the control group. Code to fit
this model using the R statistical software package are shown in the **Appendix**.

198 Since the data are consistent with a linear growth-like pattern, one might consider
comparing a summary statistic approach. For example, a comparison of the slopes (see
200 **Table S2**) would reveal whether there was a significant difference in the rate of change in
CSP between groups. A Kruskal-Wallis test applied to the 4-groups of slopes suggests a
202 significant difference (**Table 2, Figure 2C**), with the median slopes (first, third quartiles)
being 0.098 (0.086, 0.104), -0.003 (-0.012, -0.002), 0.054 (0.024, 0.125), and -0.009 (-0.021
204 to 0.089) in the control, ECD (3-weeks), ECD (0-weeks), and sympathectomy groups,
respectively.

206

DISCUSSION

208 Despite RM-ANOVA being a common choice for analysing repeated measures in the
EJCTS and ICVTS, there are many alternative approaches. Linear mixed models represent the
210 most sophisticated of the models discussed, and are more amenable to real-world clinical
data as opposed to highly controlled experimental study designs. Hence, there have been
212 calls for some time to abandon less versatile methods [7]. The integration of these model
fitting methods into routine statistical software therefore removes a major barrier to
214 applied researchers. Moreover, one can extend mixed models to incorporate more flexible
correlation structures [13], non-continuous outcomes (e.g. binary), and non-linear
216 outcomes [14]. In some cases, there might be multivariate longitudinal data (multiple
repeated measures outcomes), which may even be correlated with a time-to-event
218 outcome, giving rise to so-called *joint models* [9,15]. On the other hand, two-stage
approaches offer a simpler—both mathematically and intuitively—approach that can
220 provide insight into data profiles and complement more rigorous modelling approaches. We
only addressed a subset of the methodological tools available. Other such methods have not
222 been discussed here, including generalised estimating equations, MANOVA [7], generalised
least squares [10], and empirical Bayes [8].

224 Despite repeated measures data being routinely collected at follow-up, particularly
in long-term observational studies, the situation of only analysing baseline (preoperative)
226 and a single postoperative value—typically the last follow-up measurement—remains
commonplace in the EJCTS and ICVTS, even though this may not be the most appropriate
228 method. Whatever the choice of methodology employed, it is essential that the data, study
design, methods, supporting assumptions, and any post hoc analyses are well described and
230 justified to facilitate reproducibility, to provide opportunity for readers to critique the
analysis [16], and to avoid misinterpretation due to overlapping terminology [8]. Graphs are
232 a highly effective way of summarising and presenting repeated measures data; however, it
is essential that they are presented on common axes scales, appropriately summarised and
234 described (e.g. defining any error bars) [4]. Nonetheless, figures such as those shown in
Figure 2A should be avoided. It is important to consider distributional assumptions (e.g.
236 normality in the RM-ANOVA) or that the growth-curve is approximately linear if calculating
it as a summary measure. When these assumptions are violated, transformations or
238 alternative models might be considered. In addition, we recommend more thought is given
to sample size determination during study design [17].

240

DECLARATIONS

242 **Conflicts of interest:** none to declare.

Data availability: the laboratory experiment data is provided in Grizzle and Allen [12], and
244 downloaded from supplementary data files of Davis [18] at
<http://www.springer.com/gb/book/9780387953700> [accessed 5th August 2017].

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296

298 **FIGURE LEGENDS**

300 **Figure 1. Panel A:** a graphical representation of a linear mixed effects model. The mean
trajectories of two hypothetical patients (A and B; coloured lines) and the mean trajectory
302 averaged over the complete sample of patients (black line) are shown. **Panel B:** longitudinal
study dataset exploring the long-term profile of rate of left ventricular mass regression with
304 time after aortic valve replacement with a stentless or a homograft valve. Smoothed lines
represent average profiles stratified by valve type, estimated using the LOESS method. Data
306 originally analysed in Lim et al. [19].

308 **Figure 2. Panel A:** a so-called 'dynamite plot' showing the mean (height of bars) longitudinal
measurement values for different treatment groups at each measurement time, together
310 with the standard deviation (SD; error bar: ± 1 SD). Kruskal Wallis rank-sum tests comparing
the outcome between the four treatment groups: # = $P < 0.1$, * = $P < 0.05$, ** = $P < 0.01$, *** =
312 $P < 0.001$. **Panel B:** serial measurements of coronary sinus potassium (CSP) (mEq/L) from four
groups of dogs. Each translucent line represents a single dog, whilst line colours denote
314 treatment group. Mean profiles (bold lines) are overlaid to summarise the average group
trajectories. **Panel C:** a graphical display of the summary statistic slopes method, estimated
316 by fitting separate linear regression lines to each dog (cf. Panel A) and extracting the
estimated slopes. The slopes for each treatment group are summarised here as boxplots.

Table 1. Methodologies for analysing repeated measures data, their advantages and disadvantages, and some software options.

Method	Advantages	Disadvantages	Software
Two-stage methods	<ul style="list-style-type: none"> • Analysis is based on familiar univariate analysis methods • Data summary methods may facilitate interpretation, e.g. AUC and rate of change are well-understood concepts in biomedicine research • Multiple summary methods can be used 	<ul style="list-style-type: none"> • Can be difficult to specify the correct summary statistic in advance • Reduced data summary statistics are relatively less efficient • Reduced data summary statistics can lose information or fail to capture features of the time course • Summary methods not readily implemented in statistical software, but the summary measures are generally rudimentary to calculate • Missing data can result in sample bias 	<ul style="list-style-type: none"> • Standard tests for independent groups (e.g. <i>t</i>-test, ANOVA, Mann-Whitney <i>U</i>-test, Kruskal-Wallis test) are standard in all statistics software packages • Summary statistics can be calculated ‘by hand’ or using a simple programme written in a spreadsheet or statistics package
RM-ANOVA	<ul style="list-style-type: none"> • Includes the data at all time points • Simple to implement, and conceptually an extension of the ubiquitous ANOVA 	<ul style="list-style-type: none"> • Requires complete data on each subject • Depends on restrictive sphericity assumption, which is highly questionable for longitudinal data • Cannot handle mistimed / unbalanced measurements • Results provide limited information on how the groups differ, often requiring <i>post hoc</i> analyses 	<ul style="list-style-type: none"> • SPSS: ‘General Linear Model: Repeated Measures’ • SAS: PROC GLM • R: aov, Anova (in the car¹ package), ezANOVA (in the ez² package) • Stata: anova
LMMs	<ul style="list-style-type: none"> • Includes the data at all time points • Missing data can be straightforwardly handled if missing (completely) at random • Allows flexible modelling of the time effect 	<ul style="list-style-type: none"> • Implementation and complexity of fitting is relatively more difficult • Assumptions can be harder to assess 	<ul style="list-style-type: none"> • SPSS: ‘Mixed Models’ • SAS: PROC MIXED • R: lme (nlme³ package) or lmer (lme4⁴ package)

¹ Fox J, Weisberg S (2011). *An R Companion to Applied Regression*, Second Edition. Thousand Oaks CA: Sage.

² Lawrence MA (2016). ez: Easy Analysis and Visualization of Factorial Experiments. R package version 4.4-0. <https://CRAN.R-project.org/package=ez>

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⁴ Bates D, Maechler M, Bolker B, Walker S (2015). Fitting Linear Mixed-Effects Models Using lme4. *Journal of Statistical Software*, 67(1), 1-48.

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- Permits unbalanced data with greatly different numbers of measurements per subject
 - Allows for time-varying covariates
 - Permits estimation of individual trends
 - Can be augmented with more complex covariance structures that captures more features of the correlation patterns, and hierarchically
-

- Stata: `xtmixed`

320 **Table 2.** Results from analysis of laboratory experiment longitudinal data.

Linear mixed effects model^a				
	Estimate	SE	95% CI	P
Intercept	4.05	0.17	(3.72 to 4.37)	<0.001
Group				
ECD (3-weeks)	-0.44	0.23	(-0.90 to 0.03)	0.064
ECD (0-weeks)	-0.33	0.24	(-0.82 to 0.17)	0.19
Sympathectomy	-0.32	0.23	(-0.80 to 0.15)	0.18
Time (mins)	0.08	0.02	(0.05 to 0.12)	<0.001
Time * ECD (3-weeks)	-0.09	0.03	(-0.14 to -0.04)	<0.001
Time * ECD (0-weeks)	-0.02	0.03	(-0.08 to 0.03)	0.43
Time * Sympathectomy	-0.05	0.03	(-0.10 to 0.00)	0.054
Summary statistic (Kruskal-Wallis rank-sum tests)				
	df		χ^2	P
Slope	3		8.53	0.036
Final value	3		11.14	0.011

322 **Notation:** CSP–coronary sinus potassium; SE–standard error; CI–confidence interval; ECD–extrinsic cardiac denervation; df–degrees of freedom; χ^2 –chi-square statistic.

^a Fitted by restricted maximum likelihood.