

Bayesian statistics for repeated measures

Their application and use in biomedical research

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Paper outline

I have been thinking that this type of paper probably does not need a relatively long introduction as the one I did for *JBO*. Below are some of my ideas on how to tackle this paper, your comments would be appreciated. Please keep in mind that I have started to write the Background/Intro part, and just have ideas on how to go from there

Background

A longitudinal study is defined as that where a variable of interest is measured repeatedly in a group (or groups) of subjects. In biomedical research, this type of study is preferred when the intention is to observe the evolution of the effect of treatment (or treatments) across time, rather than analyzing the information at a single timepoint (a cross-sectional study). Clinical examples of this approach in biomedical research include studies on breast and neck cancer (Sio et al. 2016; Kamstra et al. 2015), where in the first case weekly measurements of skin toxicities in breast cancer patients with radiation-induced dermatitis were taken for up to 8 weeks, and mouth opening in head and neck cancer patients was measured at 6, 12, 18, 24 and 36 months after radiotherapy (RT) in the latter. Similar examples are found in studies of tumor response (Roblyer et al. 2011; Tank et al. 2020; Pavlov et al. 2018; Demidov et al. 2018), antibody expression (Ritter et al. 2001; Roth et al. 2017), and cell metabolism (Jones et al. 2018; Skala et al. 2010). From a statistical standpoint, a longitudinal study presents advantages over a cross-sectional approach: it requires a lower number of subjects to reach a certain statistical power, and besides the previously mentioned time-effect evolution, it allows to determine the intra-variability of the response between different subjects (Guo et al. 2013; Fitzmaurice, Laird, and Ware 2012).

Researchers have typically employed a *frequentist* approach to analyze longitudinal data. Such type of analysis is based on a hypothesis test using the *analysis of variance over repeated measures* (repeated measures ANOVA or rm-ANOVA). However, a rm-ANOVA analysis not only assumes that the data fulfills certain requisites such as constant variance across measurements (which is frequently unjustified) and complete observations from each subject (Schober and Vetter 2018; Gueorguieva and Krystal 2004), but it also requires the use of *post hoc* analyses which inflate the false positivity rate (Liu, Cripe, and Kim 2010). Recently, *linear mixed effects models* (LMEMs) have started to be used by certain groups to analyze longitudinal data (Vishwanath et al. 2009; Skala et al. 2010). Generally speaking, LMEMs incorporate both *fixed* and *random* effects making them more flexible than rm-ANOVA as they can work with missing observations, and they allow to model the covariance of the parameters in different manners (West, Welch, and Galecki 2014).

However, the nature of LMEMs and rm-ANOVA restrict the inferences they can extract from a longitudinal study when the data does not follow a linear trend (Figure 1. with line and “wiggly plot”), because the model in both cases does not allow for a consistent fit with the trend of the data. This particular non-linear behavior in longitudinal data has been reported in particular in studies that measure tumor response to radio/chemotherapy in preclinical and clinical settings (Vishwanath et al. 2009; Roblyer et al. 2011; Tank et al. 2020; Skala et al. 2010; Demidov et al. 2018), and wound healing and metabolism (Jones et al. 2018; Grice et al. 2010; Young and Grinnell 1994). In such circumstances, even if a *p-value* with “significance”

($p < 0.05$) is obtained, the model lacks predictive power and this compromises the extent of the inferences that can be derived from the analysis.

In contrast to the *frequentist* rm-ANOVA and LMEM analysis, *Bayesian statistics* represent a relatively new field that does not rely on *p-values* and hypothesis test to analyze information. Bayesian statistics can work with missing observations, allow the data (and not an underlying assumed distribution) to determine the outcome in regard to significance and are able to expand the comparisons and inferences derived from the analysis. On the other hand, the shift that Bayesian theory represents from the traditional statistical view in research and the set of computational tools required for the implementation of this type of models have limited their use in the biomedical research community. Based on this, the goals of this study are: a) to present the limitations of a *frequentist* approach over longitudinal data, and demonstrate how these limitations in turn affect the results of the analysis b) introduce in a practical and amenable manner the theory of Bayesian statistics highlighting its applicability to biomedical research and c) Implement b) over a set of simulated data that matches previously reported trends in longitudinal biomedical studies. With an emphasis on reproducibility by providing the code and dataset used, this will provide biomedical researchers a clear view of the advantages of Bayesian statistics for the analysis of longitudinal data.

```
rm(list=ls())
library(ggplot2)
library(splines)
dt<-seq(1,6,0.1)
y<-2*dt+1
z<-rnorm(y,mean=y,sd=3)
q<-0.01*dt^6-0.2*dt^5+0.2*dt^4+1
zq<-rnorm(q,mean=q,sd=10)
ab<-as.data.frame(cbind(dt,z,zq))

# x<-seq(0.6,500)
# knots <- c(0.25, 0.5, 0.75)
# theta <- c(0.6, 0.1, 0.5, 0.2, 0.8, 0.3)
# basis<-bs(x,knots=3,degree=1)
# y.spline<-basis %*% theta
#
#
# ggplot(data=ab,aes(x=dt,y=z))+geom_point()
# ggplot(data=ab,aes(x=dt,y=zq))+geom_point()
```

- Paragraph 2: Challenges presented by longitudinal studies. Missing observations, and correlation between measurements. Limitations that these items raise for the traditional ANOVA methods of analysis.
- Paragraph 3: Bayesian statistics as an alternative approach. Advantages over ANOVA and what inference can be made from it. Argue that while it is not commonly used in the biomedical arena, this paper aims at showing the implementation in an amenable manner to analyze non-linear trends in data.

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- Recap on repeated measures ANOVA and the requisites that it needs to work properly -Sphericity -Variance-covariance matrix -Explain the *true* meaning of a *p-value* and why it is not what researchers commonly think it is
 - Gentle introduction to Bayesian statistics -How it works -What advantages it has over ANOVA -What a confidence interval means probabilistically

(Chavalarias et al. 2016)

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