

Bayesian statistics for longitudinal studies in biomedical research

Their application and use in biomedical research

Ariel Mundo*

Timothy J. Muldoon[†]

John R. Tipton[‡]

Paper outline

The paper Introduction has been updated, proposed sections appear at the end of the document as well as an initial graph.

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

*Department of Biomedical Engineering, University of Arkansas, Fayetteville

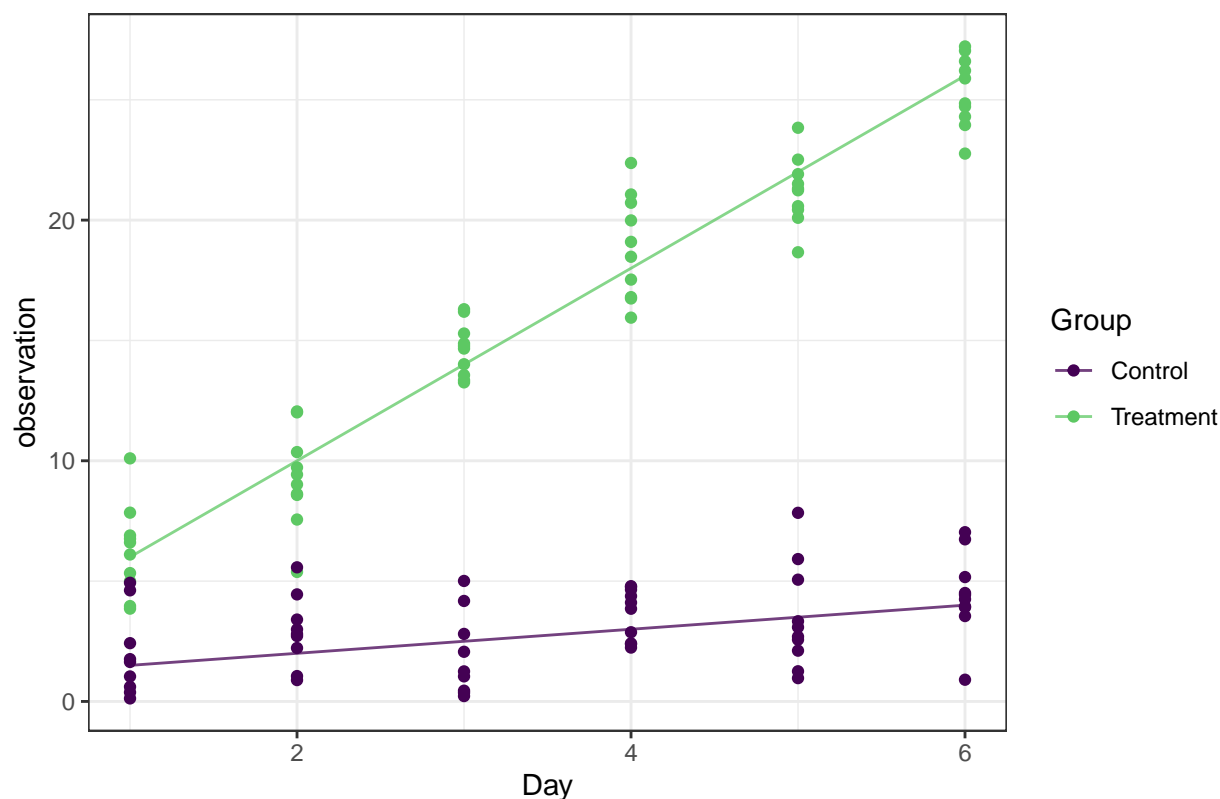
[†]Department of Biomedical Engineering, University of Arkansas, Fayetteville

[‡]Department of Mathematical Sciences, University of Arkansas, Fayetteville

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 (rm-ANOVA) 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.

Simulated linear time-varying responses



- Section 1: Challenges presented by longitudinal studies: Missing observations, and correlation between measurements. How rm-ANOVA is limited by missing observations, and how both rm-ANOVA and LMEMs are limited with data that does not follow a linear trend (equations for both situations and the fit they produce.)
- Section 2: Bayesian statistics as an alternative approach. Gentle presentation of Bayes theorem *with*

a biomedical-related example(!) Advantages over ANOVA and how inference works. Argue that while it is not commonly used in the biomedical arena, it is a more accurate and flexible approach.

- Section 3: Present the implementation of a spline-fitted model in R, using data simulated from (Vishwanath et al. 2009)

References

- Demidov, Valentin, Azusa Maeda, Mitsuro Sugita, Victoria Madge, Siddharth Sadanand, Costel Flueraru, and I Alex Vitkin. 2018. “Preclinical Longitudinal Imaging of Tumor Microvascular Radiobiological Response with Functional Optical Coherence Tomography.” *Scientific Reports* 8 (1): 1–12.
- Fitzmaurice, Garrett M, Nan M Laird, and James H Ware. 2012. *Applied Longitudinal Analysis*. Vol. 998. John Wiley & Sons.
- Grice, Elizabeth A, Evan S Snitkin, Laura J Yockey, Dustin M Bermudez, Kenneth W Liechty, Julia A Segre, NISC Comparative Sequencing Program, and others. 2010. “Longitudinal Shift in Diabetic Wound Microbiota Correlates with Prolonged Skin Defense Response.” *Proceedings of the National Academy of Sciences* 107 (33): 14799–14804.
- Gueorguieva, Ralitza, and John H Krystal. 2004. “Move over Anova: Progress in Analyzing Repeated-Measures Data Andits Reflection in Papers Published in the Archives of General Psychiatry.” *Archives of General Psychiatry* 61 (3): 310–17.
- Guo, Yi, Henrietta L Logan, Deborah H Glueck, and Keith E Muller. 2013. “Selecting a Sample Size for Studies with Repeated Measures.” *BMC Medical Research Methodology* 13 (1): 100.
- Jones, Jake D, Hallie E Ramser, Alan E Woessner, and Kyle P Quinn. 2018. “In Vivo Multiphoton Microscopy Detects Longitudinal Metabolic Changes Associated with Delayed Skin Wound Healing.” *Communications Biology* 1 (1): 1–8.
- Kamstra, JI, PU Dijkstra, M Van Leeuwen, JLN Roodenburg, and JA Langendijk. 2015. “Mouth Opening in Patients Irradiated for Head and Neck Cancer: A Prospective Repeated Measures Study.” *Oral Oncology* 51 (5): 548–55.
- Liu, Chunyan, Timothy P Cripe, and Mi-Ok Kim. 2010. “Statistical Issues in Longitudinal Data Analysis for Treatment Efficacy Studies in the Biomedical Sciences.” *Molecular Therapy* 18 (9): 1724–30.
- Pavlov, Mikhail V, Tatiana I Kalganova, Yekaterina S Lyubimtseva, Vladimir I Plekhanov, German Yurievich Golubyatnikov, Olga Y Ilyinskaya, Anna G Orlova, et al. 2018. “Multimodal Approach in Assessment of the Response of Breast Cancer to Neoadjuvant Chemotherapy.” *Journal of Biomedical Optics* 23 (9): 091410.
- Ritter, Gerd, Leonard S Cohen, Clarence Williams, Elizabeth C Richards, Lloyd J Old, and Sydney Welt. 2001. “Serological Analysis of Human Anti-Human Antibody Responses in Colon Cancer Patients Treated with Repeated Doses of Humanized Monoclonal Antibody A33.” *Cancer Research* 61 (18): 6851–9.
- Roblyer, Darren, Shigeto Ueda, Albert Cerussi, Wendy Tanamai, Amanda Durkin, Rita Mehta, David Hsiang, et al. 2011. “Optical Imaging of Breast Cancer Oxyhemoglobin Flare Correlates with Neoadjuvant Chemotherapy Response One Day After Starting Treatment.” *Proceedings of the National Academy of Sciences* 108 (35): 14626–31.
- Roth, Eli M, Anne C Goldberg, Alberico L Catapano, Albert Torri, George D Yancopoulos, Neil Stahl, Aurélie Brunet, Guillaume Lecorps, and Helen M Colhoun. 2017. “Antidrug Antibodies in Patients Treated with Alirocumab.”
- Schober, Patrick, and Thomas R Vetter. 2018. “Repeated Measures Designs and Analysis of Longitudinal Data: If at First You Do Not Succeed—Try, Try Again.” *Anesthesia and Analgesia* 127 (2): 569.

- Sio, Terence T, Pamela J Atherton, Brandon J Birkhead, David J Schwartz, Jeff A Sloan, Drew K Seisler, James A Martenson, et al. 2016. “Repeated Measures Analyses of Dermatitis Symptom Evolution in Breast Cancer Patients Receiving Radiotherapy in a Phase 3 Randomized Trial of Mometasone Furoate Vs Placebo (N06c4 [Alliance]).” *Supportive Care in Cancer* 24 (9): 3847–55.
- Skala, Melissa C, Andrew Nicholas Fontanella, Lan Lan, Joseph A Izatt, and Mark W Dewhirst. 2010. “Longitudinal Optical Imaging of Tumor Metabolism and Hemodynamics.” *Journal of Biomedical Optics* 15 (1): 011112.
- Tank, Anup, Hannah M Peterson, Vivian Pera, Syeda Tabassum, Anais Leproux, Thomas O’Sullivan, Eric Jones, et al. 2020. “Diffuse Optical Spectroscopic Imaging Reveals Distinct Early Breast Tumor Hemodynamic Responses to Metronomic and Maximum Tolerated Dose Regimens.” *Breast Cancer Research* 22 (1): 1–10.
- Vishwanath, Karthik, Hong Yuan, William T Barry, Mark W Dewhirst, and Nimmi Ramanujam. 2009. “Using Optical Spectroscopy to Longitudinally Monitor Physiological Changes Within Solid Tumors.” *Neoplasia* 11 (9): 889–900.
- West, Brady T, Kathleen B Welch, and Andrzej T Galecki. 2014. *Linear Mixed Models: A Practical Guide Using Statistical Software*. CRC Press.
- Young, Patty K, and Frederick Grinnell. 1994. “Metalloproteinase Activation Cascade After Burn Injury: A Longitudinal Analysis of the Human Wound Environment.” *Journal of Investigative Dermatology* 103 (5): 660–64.