Bayesian statistics for repeated measures

Their application and use in biomedical research

Ariel Mundo, John Tipton, Timothy Muldoon

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/Introduction Background ==

The study of the temporal changes in a variable of interest (a longitudinal analysis) is a question that has been analyzed extensively in biomedical research. Typically, measurements are taken across multiple timepoints on the same subject(s) within a group. Examples of this type of approach include clinical studies on cancer breast and neck cancer(Sio et al. 2016; Kamstra et al. 2015), 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). Whereas this type of study presents advantages over a cross-sectional study in the number of subjects required to achieve a certain statistical power, its ability to provide a time-correlated view of the phenomenon of interest, and, the potential to explore multiple relationships between different variables, the statistical analysis of such data is more challenging and requires careful consideration.

Biomedical researchers typically employ a $frequentist$ approach to analyze longitudinal data. Such type of analysis is a hypothesis test using the *analysis of variance over repeated measures* (repeated measures ANOVA or rm-ANOVA). Although the usual approach, rm-ANOVA is subject to multiple conditions to be valid, some of which are not easily verifiable. Moreover, this approach restricts the inferences it can extract from a longitudinal study, particularly when the data does not follow a linear trend (Figure 1. with line and "wiggly plot"), due to the inherent nature of the model and its limitations .Examples of such type of data are found in studies of tumor response to radio/chemotherapy in multiple models and clinical settings [(Vishwanath et al. 2009)]. Therefore, this study has three goals: a) Present in an amenable and practical manner the requisities of a $frequentist$ approach over longitudinal data and how these limit the analysis b) present a different area of statistical analysis for longitudinal biomedical data $Bayesian Statistics$, which does not use *p-values*, and is less restrictive thereby allowing a statical analysis that is based on the data itself. c)Iimplement 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.

- 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.

- 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)

References

Chavalarias, David, Joshua David Wallach, Alvin Ho Ting Li, and John PA Ioannidis. 2016. "Evolution of Reporting P Values in the Biomedical Literature, 1990-2015." *Jama* 315 (11): 1141–8.

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.

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.

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."

Sio, Terence T, Pamela J Atherton, Brandon J Birckhead, 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.