**College of Engineering**
*Department of Biomedical Engineering*

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Dear Editors-in-Chief,

My co-authors and I wish to submit a new manuscript titled "Generalized additive models to analyze biomedical non-linear longitudinal data in R: Beyond repeated measures ANOVA and Linear Mixed Models" to be considered for publication as a "Tutorial in Biostatistics" in *Statistics in Medicine*. We confirm that this work is original, and that the manuscript is not currently under consideration for publication elsewhere.

The motivation of our work is that in many cases, the evolution of the response over time is non-linear in longitudinal biomedical studies. However, the statistical models typically employed by biomedical researchers in such situations are linear, the two most commonly used being the repeated measures analysis of variance (rm-ANOVA) or linear mixed models (LMEMs), which produce unreliable inference and estimates in such cases. In our manuscript, we address the limitations of rm-ANOVA and LMEMs when used in non-linear data in a way that we believe is accessible to the biomedical research community at large.

At the same time, we present generalized additive models (GAMs) as a powerful class of methods to analyze non-linear data. Because these models are not commonly used in biomedical research, we provide the basic theoretical aspects of GAMs and their implementation in R using simulated data that follows trends of tumor oxygenation in the literature, while providing a basic workflow for model selection in an accompanying Appendix. To make our work reproducible and accessible to the biomedical community, we share the code and data in a GitHub repository (https://github.com/aimundo/GAMs-biomedical-research).

We believe that this manuscript should be of interest to the readers of *Statistics in Medicine* that work with longitudinal data, and to a broader audience that seeks the implementation of novel statistical methods in medical or biomedical research.

Thank you for your consideration, and please do not hesitate to contact us if you require further information.

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