UNIVERSITY OF ARKANSAS

College of Engineering
Department of Biomedical Engineering

Ariel I. Mundo
120 Engineering Hall
University of Arkansas
Fayetteville, AR 72701

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Dear Dr. Marta Garcia-Fiñana,

My coauthors and I wish to submit a new manuscript entitled "Using generalized additive models to analyze biomedical non-linear longitudinal data" to be considered for publication in *Statistical Methods in Medical Research*. We confirm that this work is original, and that the manuscript is not currently under consideration for publication elsewhere.

In biomedical longitudinal studies, longitudinal data (repeated measures in different groups) is typically analyzed using the repeated measures analysis of variance (rm-ANOVA) or linear mixed models (LMEMs). However, both models require several assumptions to be valid, particularly in that they expect a *linear* trend of the data. As we show in the manuscript, multiple studies in biomedical research across different areas (oncology, wound healing, antibody expression, etc.) have shown that is rather frequent the case where the data is non-linear, which limits the use of rm-ANOVA and LMEMs. In our manuscript we summarize in a clear way the limitations of rm-ANOVA and LMEMs in the context of biomedical longitudinal research and present the theory and application of generalized additive models (GAMs) as a suitable class of models to analyze non-linear data. We have taken special care to make our work accessible by avoiding complex mathematical derivations, relying on simple and clear language and visual representations to reinforce the theoretical aspects of GAMs.

Furthermore, our manuscript uses simulated data (using reported non-linear trends in the biomedical literature) to provide a basic workflow to computationally implement different GAMs models using R, and we share our code and data in a GitHub repository (https://github.com/aimundo/GAMs-biomedical-research) to make our work reproducible and accessible to the biomedical community.

We believe that this manuscript should be of interest to readers in all areas of biomedical research where longitudinal data is collected, and we also consider that our work is appropriate for *Statistical Methods in Medical Research* as it focuses on statistical methods and their implementation in biomedical research with an emphasis on reproducibility and accessibility.

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

Ariel I. Mundo
Graduate Research Assistant
aimundo@uark.edu

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Corresponding Author:
Timothy J. Muldoon, M.D., Ph.D.
University of Arkansas
Department of Biomedical Engineering
Fayetteville, AR, USA 72701
tmuldoon@uark.edu
(479) 575-5324

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