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Dear Dr. Rizopoulos,

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 *Biostatistics*. We confirm that this work is original, and that the manuscript is not currently under consideration for publication elsewhere.

A frequent observation of longitudinal biomedical studies is that the evolution of the response over time is non-linear. However, the models typically used by biomedical researchers in such situations are either the repeated measures analysis of variance (rm-ANOVA) or linear mixed models (LMEMs). Because both rm-ANOVA and LMEMs expect a *linear* trend of the data, the inference obtained from these models is unreliable when they are used in non-linear longitudinal data. This is a critical issue that we address in our manuscript, where we also present generalized additive models (GAMs) as a suitable class of models to analyze non-linear longitudinal data in biomedical research.

We believe our work satisfies two of the publishing criteria from *Biostatistics* because it: 1) Presents an innovative application of statistical methodology (GAMs, which are commonly used in ecology) to address a substantive problem in biomedical sciences and 2) Critically reviews an area of statistical methodology relevant to biomedical science applications (we summarize in a clear way the limitations of rm-ANOVA and LMEMs in the context of biomedical longitudinal research and contrast them with the advantages of GAMs).

Of notice, we have taken special care to make our work accessible to biomedical researchers by avoiding complex mathematical derivations, relying on simple and clear language and visual representations to reinforce the theoretical aspects of GAMs, and to highlight the unreliable inference that rm-ANOVA and LMEMs produce when used on non-linear longitudinal data. We also provide a basic workflow to computationally implement GAMs (via R) using simulated data that follows reported trends in the literature. 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 readers in all areas of biomedical research where longitudinal data is collected, and to a broader audience that seeks the implementation of novel statistical methods in medical or biomedical research.



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

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