Dynamic Risk Prediction Using Longitudinal Biomarkers of High Dimensions – Response to Reviewer 2' Comments

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Dear Reviewer,

Thanks again for your comments. Your comments are in italics and our responses to your specific concerns are given below in blue, and edited text in the revised version of the manuscript has also been marked with blue.

Reviewer 2 Comments: (Comments to the Author in italics):

"1. I disagree with the authors' description of landmarking because in the landmarking approach also the time origin is set to zero at each landmark time. The difference as I understand it is that in landmarking the landmark time does not have to coincide with the biomarker measurement time, and so landmark times are always common across subjects, irrespective of biomarker measurement times. Landmarking typically uses a last observation carried forward for the biomarker measurement at the landmark time."

Response: There are two types of landmarking. One is "unconditional" landmarking as described in van Houwelingen (2007); van Houwelingen and Putter (2008, 2012). The other one is the partly conditional (PC) landmarking in Maziarz et al. (2017). The "unconditional" landmarking doesn't reset the time origin at each landmark time, while PC resets the time.

This statement is also described in Maziarz et al. (2017), on page 2 " Similar approaches based on the idea of a landmark time without setting starting times to s were considered (van Houwelingen, 2007; van Houwelingen and Putter, 2012)."

2. *"In the authors response to my comment 2 they explain how the situation where different subjects have different measurement times could be accommodated. But my comment referred to the situation where different biomarkers have different measurement times, e.g. biomarker 1 has measurement times s_{1ij} and biomarker 2 has measurement times s_{2ij}. Could the method also handle this scenario?"*

Response: Sorry for the misunderstanding. The proposed method can not handle the

scenario when different biomarkers are measured at different times. We have added this point in the last paragraph of the Discussion section as below:

"If biomarkers are measured at different time points, we can impute the missing data at pre-specified landmark times, using the Last Observation Carried Forward or the predicted random effects based on estimates from a linear mixed effects model as described in Maziarz et al. (2017)"

2. *" I am still unsure how the survival model used to generate the simulated data is a piecewise exponential model. In the equation for λ_i on p10 we see that λ_i depends on $W_{1i}(t)$,$W_{2i}(t)$ and $W_{3i}(t)$. According to the equations at the bottom of p9, $W_{1i}(t)$ and $W_{2i}(t)$ are smooth functions in t, which suggests that λ_i varies with t across time. This is inconsistent with the authors response that λ_i is constant within measurement time intervals. Please could the authors also clarify whether the same survival model is used to generate survival times and to analyse the simulated data. "*

Response: We agree with the reviewer and clarified the paragraph as below:

"Survival times are linked to the latent longitudinal biomarkers via a piecewise exponential model assuming the rate is constant between two consecutive measurement times. In **Simulation Study 1**, the rate parameter in the exponential model is $\lambda_i(s_{ij}) = 0.02 \exp[0.5W_{1i}(s_{ij}) + 0.5W_{2i}(s_{ij}) + 0.5W_{3i}(s_{ij})]$ for time interval $[s_{ij}, s_{ij} + 6)$. For additional complexity in **Simulation Studies 2 and 3**, the rate parameter includes an interaction term, i.e., $\lambda_i(s_{ij}) = 0.02 \exp[0.5W_{1i}(s_{ij}) + 0.5W_{2i}(s_{ij}) + 0.5W_{3i}(s_{ij}) - W_{1i}(s_{ij}) \times W_{2i}(s_{ij})]$. "

Best regards,

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References

van Houwelingen, H. (2007) Dynamic prediction by landmarking in event history analysis. *Scandinavian Journal of Statistics*, **34**, 70–85.

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van Houwelingen, H. C. and Putter, H. (2012) *Dynamic Prediction in Clinical Survival Analysis*. Chapman Hall.

Maziarz, M., Heagerty, P., Cai, T. and Zheng, Y. (2017) On longitudinal prediction with time-to-event outcome: comparison of modeling options. *Biometrics*, **73**, 83–93.