Reviewer's report

Title: Dynamic prediction of repeated events data based on landmarking model: application to colorectal liver metastases data

Version: 0 Date: 27 Jun 2018

Reviewer: Krithika Suresh

Reviewer's report:

The objective of this manuscript is to produce dynamic predictions of recurrent and terminal events using longitudinal patient histories. The authors propose the use of dynamic pseudo-observations (DPOs) within a landmarking framework. At each landmark time, the authors compute a DPO for the each of the events of interest in a multinomial framework. They then fit a generalized linear model with a logit link function on the DPOs to model the effects of the baseline covariates and time-dependent covariate values. Since the covariate effects can be expected to vary smoothly with landmark time, a landmark dataset is constructed and a landmark supermodel with logit link is fit. Estimation is conducted using an generalized estimating equation approach. The dynamic event probabilities can be directly computed using the inverse link function. The authors investigate the prediction bias and efficiency of the DPOs at baseline in a finite sample.

The development of this problem in a multinomial framework with DPOs is an interesting extension in the dynamic prediction literature. The benefits of this method should be highlighted with a direct description of the advantages of the use of DPOs and this method over existing approaches for addressing dynamic prediction with recurrent events. Also, the model description should be placed in the body of the manuscript to improve clarity. Mainly, the manuscript should demonstrate the predictive performance of the method using simulation studies and/or by assessing the predictive ability in the application. There needs to be further investigation into how it performs with increasing landmark times, and even perhaps a comparison with an alternative method.

Specific comments:

Line 70: Although it is unrealistic for the terminal and recurrent events to be independent marginally, it is commonly assumed that they are independent conditional on the frailty. Perhaps provide a clinical example or reference of when it would not make sense for the recurrent and terminal to be independent conditional on the frailty, or describe while it does not make sense in the application presented in this paper.

Line 76: Although the authors discuss current landmarking literature, they fail to cite literature on dynamic prediction that deals with recurrent events in a landmarking or joint modeling
framework (e.g., Musoro et al. 2016; Maugan et al. 2013, etc.). It would be interesting to note the advantages of the proposed method compared to approaches taken in other papers.

Line 92: The phrase "incomplete censoring data" is not clear here, and the general description of DPOs should be made clearer and the reason for using the approach should be emphasized here.

Line 152: It would be helpful to describe how the "landmark dataset" is structured, and what landmark times individuals will contribute data at based on their recurrence and death status.

Line 201: The model equation from Appendix B and description of estimation should be in the main body of the paper. This would provide a better idea of how the model was implemented, how the data was structured, and would provide context of what a "supermodel" is.

Line 216: Due to the purpose of the paper being the dynamic prediction of recurrent and terminal events, it would be interesting and helpful to have the Simulation Study include an evaluation of how well the method does in predicting outcomes. It would be useful to see results not just at t=0 but at future time points to demonstrate how well it uses the dynamic information available.

Lines 335-338: Not clear why this is an advantage. The supermodel can be extended to accommodate baseline hazards that are also a smooth function of landmark time. Some clarification is required here.

Lines 343-349: Discussion paragraph is not clear. It would be helpful to provide a reference or further description here.

Line 358: "Prediction bias" refers to the prediction bias for DPOs; however, this statement may falsely imply that there is no prediction bias for predicted probabilities of events, which has not been demonstrated in the simulation study.

The paper requires editing for grammar and sentence structure to improve clarity.

Minor comments:

Line 61: Include a reference for dynamic prediction models for recurrent events data.

Line 64: Clarify "during following repeated events".

Line 74: The wording "latter context" is confusing.

Line 77: "present dynamic prediction model": The model has not yet been described.

Line 85: Define "landmarking time".

Line 90-91: Move the DPO literature review to after the introduction on DPOs.
Line 95: Include reference for using DPOs to estimate state occupation probabilities

Line 139: Replace "indictors" with "indicators"

Line 141: The phrase "whole subjects" is unclear

Line 210: Since "supermodel" is a defined model, provide a reference or model equation in body of paper.

There are two 2.4 Sections (Line 216, Line 254)

It will be easier to follow if the "Simulation studies" and the "Application" were separated and the Results for each directly followed in the same section.

Line 234: It is unclear what "recorded event times data (n=100)" is referring to

Application: How was death due to other causes handled? Was any model selection performed?

Line 378: Capital "J" is not defined. Only lower case "j" was defined previously (Line 104)

Table 5: Clarify whether "1 time" in the table heading refers to "1 recurrence"

Do the authors mean "efficiency" instead of "efficacy"?

References:


Are the methods appropriate and well described?  
If not, please specify what is required in your comments to the authors.

Yes

Does the work include the necessary controls?  
If not, please specify which controls are required in your comments to the authors.

Unable to assess

Are the conclusions drawn adequately supported by the data shown?  
If not, please explain in your comments to the authors.

Yes

Are you able to assess any statistics in the manuscript or would you recommend an additional statistical review?  
If an additional statistical review is recommended, please specify what aspects require further assessment in your comments to the editors.

I am able to assess the statistics

Quality of written English  
Please indicate the quality of language in the manuscript:

Needs some language corrections before being published

Declaration of competing interests  
Please complete a declaration of competing interests, considering the following questions:

1. Have you in the past five years received reimbursements, fees, funding, or salary from an organisation that may in any way gain or lose financially from the publication of this manuscript, either now or in the future?

2. Do you hold any stocks or shares in an organisation that may in any way gain or lose financially from the publication of this manuscript, either now or in the future?

3. Do you hold or are you currently applying for any patents relating to the content of the manuscript?

4. Have you received reimbursements, fees, funding, or salary from an organization that holds or has applied for patents relating to the content of the manuscript?

5. Do you have any other financial competing interests?

6. Do you have any non-financial competing interests in relation to this paper?
If you can answer no to all of the above, write 'I declare that I have no competing interests' below. If your reply is yes to any, please give details below.

I declare I have no competing interests

I agree to the open peer review policy of the journal. I understand that my name will be included on my report to the authors and, if the manuscript is accepted for publication, my named report including any attachments I upload will be posted on the website along with the authors' responses. I agree for my report to be made available under an Open Access Creative Commons CC-BY license (http://creativecommons.org/licenses/by/4.0/). I understand that any comments which I do not wish to be included in my named report can be included as confidential comments to the editors, which will not be published.

I agree to the open peer review policy of the journal