July 23, 2018

Re: Revision of Manuscript No. 39544
Title: Tunable structure priors for Bayesian Rule Learning for knowledge integrated
Biomarker Discovery

We thank you for your interest in our research and appreciate the peer-review report. We were happy to receive such positive comments and useful suggestions to help improve the quality of our manuscript. Accordingly, we have made revisions to our manuscript and provided responses below to each reviewer. We hope that we have addressed all the concerns that were pointed out to us.

Please note that the following requests (as commented in the manuscript) do not apply to our article, since it predominantly discusses the development of a computational method and its evaluation using public data: (a) IRB statement, (b) Statistics review, and (c) IACUC statement. The statistics review is not deemed necessary since the authors are already considered to be statisticians as they have advanced degrees in that or related fields and have had previous publications in related areas of this manuscript.

We look forward to final acceptance and publication of our article in your esteemed journal.

Thanking you.
Best regards,

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Reviewer 1:
"The simpler is best to clinical doctor."

Our response:
Thank you for your positive feedback of our manuscript. Since, this is primarily a paper in statistics and computational methods, section 2 of the manuscript may have been hard to read by a clinician. We have attempted to simplify this section by including hypothetical examples from biomedicine each time we introduce a notation, to better explain our method and its implementation by providing context. We hope that the revised manuscript will be more readable to a clinical doctor.

Reviewer 2:
"The manuscript is very well written and useful for the researcher in the field of oncology."

Our response:
Thank you for your encouraging feedback. We have made a few more revisions that we hope has further improved the quality of our manuscript.

Reviewer 3:
"This is a research article that investigate the use of an extension of Bayesian Rule Learning (BRL), a model learning algorithm, to explain the input dataset. "Informative structure priors" (i.e., prior knowledge about the dataset) were included in the model learning process and the degree of incorporation of these structure priors was controlled by a λ hyperparameter. The effect of λ on the operation of the algorithm and the predictive performance was investigated using a simulated dataset and an authentic lung cancer prognostic biomarker dataset.   The study is interesting and it may provide new insights about practical considerations in using model learning algorithm for explaining dataset.   I have a few more specific comments. (1) Section 2: Is the term "structure priors" commonly used in the field of model learning? More detailed definition and explanation will be beneficial for readers not in the field.   (2) Section 2.2.1.3: The methods of model learning using different classifiers were compared in the study. The so-called state-of-the-art classifiers should be described in more detail.   (3) Discussion: A key message from the study is that prior knowledge about the dataset can be incorporated into the extension of BRL in model learning to improve the interpretation of the data. How can we assure that this will not introduce bias into the model learning process? (4) Throughout the manuscript, past tense should be used."

Our response:
Thank you for your positive and encouraging feedback. We also thank you for your helpful comments. We have revised our manuscript to address your concerns. Specifically—

1) Yes, the term 'structure priors' is commonly used in Bayesian statistics. We noticed that we had used the term twice before we had formally introduced this term in section 2.1.2. This may have contributed to the confusion. In our revised manuscript, we have removed these usages until we define it. For the audience with other backgrounds, we have additionally included a reference that can help readers to gain deeper understanding of structure priors (Koller et al., 2009, section 18.3.6.1).
2) In the revised manuscript, we have now better described the state-of-the-art classifiers in section 2.2.2.3 (please also note that we had also numbered them incorrectly in the previous version of the manuscript).
3) Thank you for bringing the issue of bias to our attention. It is an important detail we hadn't addressed in the original manuscript. We have now added a paragraph at the end of the Results and Discussion section to discuss how bias can be introduced into structure priors if specified incorrectly. We have cautioned the reader to avoid this.
4) We have revised the entire manuscript to use past tense.