14th July 2020

Professor Mark Chaplain  
Co-Chief Editor  
Journal of Theoretical Biology

Dear Professor Chaplain,

Please find included with this our revised manuscript, “A Monte Carlo method to estimate cell population heterogeneity from cell snapshot data” and point-by-point responses to reviewers’ comments.

The reviewers’ comments were extremely helpful, and the manuscript is much improved from this feedback. Unfortunately, two of the authors were keenly involved in the UK’s Covid response, so had to divert attention from this paper to perform these duties. This, and the quite substantial changes to the manuscript detailed below, is why it took such a time for us to adequately respond to the reviewers’ comments. Nonetheless, we apologise for not asking the editor for an explicit extension.

One key addition to the manuscript was incorporating a real data example: the process of finding then analysing these new data took quite some time. This was mainly because all existing papers that we’ve found in the literature analyse either purely synthetic data or laboratory data that is not freely available. Thanks to one of the reviewer’s comments though, we found such an example, and this addition is included in S4.4. Undertaking the analysis for this piece was illuminating and, we believe, has substantially improved the paper. We also hope that, by including explicit references to this open source data, it will encourage other members of the mathematical biology community to use it to benchmark their methods.

Another important addition to the manuscript was discussion of the Chan et al. (2016) paper suggested by reviewer 1. Reading this paper made us aware of an alternative class of method available for dealing with population substructure determination in single cell “snapshot” experiments. Their method looks only at population averages at each time point whereas our method looks at distributions, and so we argue that our approach is superior in this respect. It was important to consider such approaches in our discussion of the literature, however, and we are thankful to the reviewer for highlighting this study.

Otherwise, our point by point responses (and additions to the manuscript resulting from these) has led to a manuscript which is improved and easier to parse for a reader.

We hope that you will find our amended manuscript suitable for consideration for publication and look forward to hearing from you in due course.

Yours sincerely,

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