4th September 2019

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Editorial Office

Journal of The Royal Society Interface

6-9 Carlton House Terrace

London

SW1Y 5AG

Dear Madams/Sirs,

Please find included with this submission to the Journal of The Royal Society Interface our manuscript, “A Monte Carlo method to estimate cell population heterogeneity”.

Determining and quantifying sources of cellular heterogeneity is crucial for a swathe of applications, ranging from biotechnological processes to therapeutics. Mathematical models of cellular heterogeneity can be used to investigate the sources of variation present in experimental data. By fitting these models to observations, it is possible to test different hypotheses about the origin of cellular variation. The current approaches to fitting mathematical models to the individual-cell-level data produced by experiments are, however, complex. They also require the investigator to specify the number of subpopulations of cells – groups of individual cells that share dynamics – *a priori*. Here, we introduce a computational sampling method named ``Contour Monte Carlo" for estimating mathematical model parameters from such data, which is straightforward to implement and does not require cells be assigned to predefined categories. As such, we suggest our method may be a widely applicable tool for analysing the types of individual cell observations produced from laboratory experiments.

In this paper, we suppose a mathematical model based on ordinary differential equations with idiosyncratic parameter values for each cell, which can generate cell population heterogeneity. We then introduce a Monte Carlo based framework for fitting these models to cell population ``snapshot’’ data – the type of observations produced from laboratory experiments like flow cytometry. Our framework is Bayesian, although is distinct from the framework used in more traditional Bayesian analysis because the snapshot data are assumed to be probability densities, rather than raw data. We then apply this framework to perform inference on three systems that have been investigated for this purpose elsewhere in the literature. The Julia code that generated our results is publicly available, which, we hope, encourages others to apply our method to their own problem.

All authors have made a significant contribution to the work and have agreed to submit the paper in its current form to the Journal of The Royal Society Interface. I can also confirm that the research has not been (and will not be) submitted simultaneously to another journal, in whole or in part.

Finally, we would like to suggest the following people as potential reviewers of our manuscript:

* Edmund Crampin, University of Melbourne, [edmund.crampin@unimelb.edu.au](mailto:edmund.crampin@unimelb.edu.au)
* Jan Hasenauer,  ICB, Helmholtz Zentrum München, [jan.hasenauer@uni-bonn.de](mailto:jan.hasenauer@uni-bonn.de)
* Julio R Banga, IIM-CSIC, Vigo (Spain), [julio@iim.csic.es](mailto:julio@iim.csic.es)
* Luis Tenorio, Colorado School of Mines, [ltenorio@mines.edu](mailto:ltenorio@mines.edu)
* Jari Kaipio, Deparment of Mathematics, University of Auckland, New Zealand, [jari@math.auckland.ac.nz](mailto:jari@math.auckland.ac.nz)
* Michael Stumpf, Department of Life Sciences, Imperial College, [m.stumpf@imperial.ac.uk](mailto:m.stumpf@imperial.ac.uk)

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

Yours sincerely,

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