Globalink Research Award
Research Proposal

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1. Student statement of interest *(approximately 0.5 pages)*
Working with Dr. Camille Maumet's team at the Institut national de recherche en informatique et en automatique (INRIA, Rennes, France) will have a hugely positive impact on the trajectory and outputs of my Ph.D. Dr. Maumet has significant experience with both provenance-tracing and the analysis and comparison of popular fMRI pipelines, both of which are essential to the success of my project. I will be able to learn state-of-the-art approaches to managing computational experiments and their results, and methods for evaluating the significance of variability among outputs. Without a collaboration with Dr. Maumet, I would take significantly longer to learn these methods and would not be able to easily translate my work from diffusion MRI to functional MRI applications, which is the dominant modality in the field.

The success of this project will have a huge impact on my career as a researcher. My goal is to become a professor at a Canadian institute, in which I will continue to work on evaluating the trustworthiness of scientific claims, and will attempt to generalize the work I develop here to other disciplines. This career trajectory will only be possible with understanding of state of the art methods in comparing tools and datasets across multiple domains, a skill which will be taught to me by Dr. Maumet. I am extremely excited for the prospect of this award and believe that the tools I will learn throughout this collaboration will be invaluable both for colleagues at my home institution and the community at large once the research conducted as a result of this collaboration becomes published.

2. Research proposal *(1.5 to 2.5 pages single spaced excluding timeline and cited literature)*

2.1 Background and review of relevant prior work

In recent years there has been a growing focus on evaluating the reproducibility of scientific findings. With a large, confused, and growing lexicon of definitions in this space, reproducibility can briefly be described as the ability for a researcher to successfully reproduce their own findings, while replicability refers to the ability of other researchers using similar means to arrive at the same conclusions [1]. Meta-analyses have been performed across several domains of science [2]–[4] which have shown that a significant proportion of claims fail to replicate, posing a significant problem for science.

In neuroimaging this issue has been explored with respect to the impact that analysis tools themselves have on claims and their replicability. In functional Magnetic Resonance Imaging (fMRI) selection of software tool has been shown to produce different results [5], and in structural MRI the stability of two software packages with respect to minor data perturbations

has been evaluated [6]. Currently, there lacks a joint evaluation of tool stability and it relative impact to selection.

In numerical analysis, a condition number describes the stability of a function or matrix, where a larger value indicates a more significant change in output with respect to input, or, lower stability. This is represented functionally as the ratio of the relative change in the output of the system to the to the ratio of relative change in input data. While this conditioning can be computed directly for differentiable functions or linear matrices, in the case of complex processing pipelines performing multiple independent steps on high dimensional data, obtaining closed-form solutions is intractable. However, by performing known perturbations to unprocessed data, we can obtain an empirical estimate of tool conditioning based on the relative variance of input data and produced derivatives.

2.2 Objectives of the project

In my Ph.D. thesis I plan to characterize the stability of neuroimaging tools in the context of diffusion and functional MRI. Leveraging the publicly-available Consortium of Reproducibility and Reliability (CoRR) dataset [7] consisting of similar data collected across multiple sites, I will evaluate the stability of commonly-used analysis pipelines (FSL [8], MRTrix [9], Dipy [10]) with respect to perturbations in input data.

While this conditioning can provide insights into the stability of tools, it can also be applied across independent datasets and tools to serve as a proxy for the generalizability of derivatives between selections, and importantly identify the impact that a given dataset or tool may have on the obtained results. During this project abroad I will:

1. Identify target algorithms and tools in f-MRI for evaluation of numerical stability. These algorithms should be both commonly-used and sufficiently simple that theoretical conditioning of the functions can be evaluated and compared to empirical estimates.

2. Characterize the significance of result instability in the within- and across-tool settings. This will be evaluated using test-retest reliability as well as techniques demonstrated and developed by Dr. Maumet.

2.3 Significance of the project

The successful completion of my proposed project has the potential to shed light on the effect that numerical instabilities have on neuroimaging analyses, and identify a significant dependence between scientific claims and the tools used to generate them. Given the current climate of scientific research amidst the “reproducibility crisis,” it is more important than ever to identify which scientific results are trustworthy. My work on evaluating the stability of neuroimaging tools and parameter settings will provide a resource for researchers to cross-

reference when 1) designing experiments, 2) reading published results, and c) comparing claims.

2.4 Timeline showing which task will be done when to achieve each objective.
While at INRIA, the timeline for research will be as follows:

2018/04/01-05/01: My project will begin by learning the fMRI tool landscape. Dr. Maumet's team has worked extensively with the execution and evaluation of fMRI-based processing tools. The first month of this exchange will involve a large degree of knowledge exchange in which I am introduced thoroughly to processing tools, the steps involved, common failure-modes, implicit assumptions, and current exploration of the stability and reproducibility within this space.

05/01 - 06/01: Alongside learning about the fMRI processing pipelines and their steps, we will identify potential algorithms to compute closed-form solutions for condition and investigation for sources of instability. We will then compute the closed form solutions for these tools, and compute their empirical stability estimates.

06/01 - 07/01: Finally, we will compute and compare the stability of tools with that of subsequent claims made across both a) different datasets using the same tool, and b) the same dataset using a different tool. These two questions will lend themselves towards understanding the generalizability or transitivity of findings across both data and software selections.

2.5 Cited literature

[1] P. Patil, R. D. Peng, and J. Leek, "A statistical definition for reproducibility and replicability," bioRXiv , Jul. 2016.
[2] Open Science Collaboration, "PSYCHOLOGY. Estimating the reproducibility of psychological science," Science , vol. 349, no. 6251, p. aac4716, Aug. 2015.
[3] K. A. Baggerly and K. R. Coombes, "DERIVING CHEMOSENSITIVITY FROM CELL LINES: FORENSIC BIOINFORMATICS AND REPRODUCIBLE RESEARCH IN HIGH-THROUGHPUT BIOLOGY," Ann. Appl. Stat. , vol. 3, no. 4, pp. 1309–1334, 2009.
[4] J. P. A. Ioannidis, "Why most published research findings are false," PLoS Med. , vol. 2, no. 8, p. e124, Aug. 2005.
[5] A. Bowring, C. Maumet, and T. E. Nichols, "Exploring the Impact of Analysis Software on Task fMRI Results," bioRXiv , Mar. 2018.
[6] A. Salari, L. Scaria, G. Kiar, and T. Glatard, Numerical error propagation in the HCP structural pre-processing pipelines . 2018.
[7] X.-N. Zuo et al. , "An open science resource for establishing reliability and reproducibility in functional connectomics," Sci Data , vol. 1, p. 140049, Dec. 2014.
[8] M. Jenkinson, C. F. Beckmann, T. E. J. Behrens, M. W. Woolrich, and S. M. Smith, "FSL," Neuroimage , vol. 62, no. 2, pp. 782–790, Aug. 2012.
[9] J. D. Tournier and F. Calamante, "MRtrix: diffusion tractography in crossing fiber regions," International Journal of , 2012.
[10] E. Garyfallidis et al. , "Dipy, a library for the analysis of diffusion MRI data," Front. Neuroinform. , vol. 8, p. 8, Feb. 2014.

3. Interaction

While in Dr. Maumet's lab, I will be working closely with her and her colleagues. I will sit in her lab and see her daily through regular working interactions. My project will begin with mentorship on functional neuroimaging and processing. Once comfortable with these processing methods, Dr. Maumet will show me in detail the type of analyses her team has developed and performs on comparing the variability across tools and datasets. We will have weekly meetings in which we evaluate our progress, set milestones for the upcoming week, and modify our roadmap to ensure we effectively complete the research objectives.

4. Collaborations

4.1 Does this project build on an existing international collaboration?

No

4.2 Does this project create potential for future collaborations?

Yes

4.3 Please describe briefly the existing, planned or future collaboration.

While I have discussed research projects with Dr. Maumet through various conferences and workshops, no formal collaboration exists between my home institute and her group. Following this exchange, we will have an ongoing collaboration based upon the characterization of tool stability research that we will be working on together. While significant local expertise is available in this study for structural and diffusion imaging, Dr. Maumet will be an invaluable collaborator to extend this work to fMRI.