

# **This is Your Brain on Disk: The Impact of Numerical Instabilities in Neuroscience**

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## Dedication

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To the family, friends, teammates, conference buddies, and mentors who supported me in not only starting this journey, but keeping me sane and taken care of throughout it. I don't know where I would be otherwise, but because of all of you, I feel like I'm exactly where I'm supposed to be.

An extra thank you to Charlie for keeping me going while I dealt with a curveball to my health in wrapping this up. She made sure I was fed, loved, sane, and somehow even happy despite everything.

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First and foremost, I would like to thank my supervisors Tristan Glatard and Alan Evans for all of the guidance, support, wisdom, and encouragement they have given me over the years. I came into this program without strong direction but knowing that I wanted to impact science on a larger scale than just answering a specific question that interested me. Alan played the matchmaker and connected me with Tristan, who had similar goals to my own. Ever since, I have had the pleasure of working with both of them across a range of scales: Alan providing our eye-in-the-sky view, and Tristan getting down in the weeds with me on details. With their distinct strengths and perspectives but common optimism and positive outlook, I couldn't have asked for a better pair of advisors.

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## Abstract

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Neuroimaging, a field focused on understanding structure and function within the brain, has evolved into a discipline of computational science. In recent years, through the collection and evaluation of rich and descriptive datasets, countless studies have explored the possible utility of Magnetic Resonance Imaging data of the brain and began the development of relationships between them and phenotypic information such as disease, sex, stage of development, and more. Like many modern scientific disciplines, however, the reliability of these relationships depends on the trustworthiness and openness of methods used in their generation. With an increasing awareness on issues of reproducibility, preliminary explorations in neuroimaging have led to some skepticism regarding the robustness of findings. In some cases, these issues can be resolved through the federated sharing of datasets or the harmonization of software tools. In others, the sensitivity or stability of underlying numerical algorithms used to process the complex and high dimensional datasets may lead to unexpected variability. While impactful differences have been observed in neuroimaging across scientific teams, methods, toolboxes, or even the operating system of the computer being used, no studies have enabled or characterized the effect that machine error has on findings. Throughout this thesis I have developed infrastructure for high performance computing environments to enable the large scale numerical analysis of neuroimaging experiments, and used it to evaluate the role that numerical uncertainty in computing plays in the reproducibility or stability of results. Focusing on the application of mapping connections between brain regions, called structural connectomics, I perturbed the generation of networks and subsequently evaluated the observed variability to characterize the impact of small numerical errors as they accumulate over the course of an analysis. I found that not only do unavoidable computational errors have a considerable impact on results, but that they can in some cases be so significant as to obscure individual differences in maps of connectivity. This finding importantly demonstrates a best-case bound of error and its propagation throughout scientific pipelines. Moving beyond the perturbation of error, efforts to interpret the observed variability as a feature of a given analysis rather than a flaw showed that not only did this variability increase the reliability of datasets, but

it ultimately could be harnessed to produce stronger and more generalizable brain-phenotype relationships. The combination of these results importantly demonstrates that computational errors inherent to pipelines lead to impactful differences in a set of neuroimaging analyses. Whether that impact is for better or worse, however, depends entirely on whether these errors are being considered and accounted for, or ignored. Alongside the execution of these analyses, this thesis presents tools and a schematic which can be followed for the further exploration of numerical uncertainty and the role it may play in our understanding of the brain.

## Résumé

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Je ferais la traduction après avoir complété le résumé en anglais...

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## 1 Introduction

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In an age of big data and an ever growing landscape of –omics, the structure and function of the brain is being increasingly explored through connectomics. Brain maps, called connectomes, are constructed as networks in which areas of the brain are related to one another through properties of interest<sup>1</sup>, such as their morphology, connectivity, or function. These areas, also called regions of interest or vertices, and the properties or edges connecting them are intentionally flexible, allowing the brain networks to describe a limitless range of scales and organisms. While the connectome derived from a section of mouse brain may summarize the synapses between neurons found in an Electron Microscopy image<sup>2</sup>, the construction of a similar map from humans *in vivo* is limited to data collected through non-invasive imaging techniques, primarily Magnetic Resonance Imaging (MRI), and may summarize the global connectivity of the brain<sup>3–5</sup>.

Though the resolution of a typical MRI is approximately  $1,000,000\times$  less precise than an Electron Microscope image<sup>6</sup> which may show true cellular connectivity, MRI techniques allow for the capture of entire brains without harming the subject and can be measured over time to observe network evolution. While regions would be defined in the MRI case as macro-scale brain areas (often  $1\text{mm}^3$  or larger in size<sup>7</sup>), the edges between them can be defined as similarity in structure<sup>8–10</sup>, function<sup>11–13</sup>, or connectivity<sup>3,14,15</sup>. Exploring these networks can inform the development of biomarkers<sup>9,15</sup>, models of disease progression<sup>16,17</sup>, and potentially identify targets for medical intervention<sup>18,19</sup>.

In recent years, several large consortia such as the UK BioBank<sup>20</sup>, the Human Connectome Project<sup>21</sup>, and the Consortium of Reproducibility and Reliability<sup>22</sup> have made it their mission to capture and share brain imaging data from thousands of individuals which can be used to construct maps and explore the brain. However, connectomes are not an automatic result of these images. The estimation of brain networks relies on complex image processing software tools and scientific pipelines<sup>5,23</sup>, including the denoising and alignment of images, tissue classification and segmentation, and modelling or relating connectivity or function across regions. The orchestration and design of these pipelines has considerable impact on the derived maps and their application<sup>24,25</sup>. In the absence of ground-truth to evaluate the accuracy of

results generated from these tools, it is essential to understand their robustness to minor perturbations (e.g. small amounts of noise). This consistency (or possible lack thereof) has recently become under scrutiny across brain imaging<sup>26–28</sup>, necessitating a shift in the focus of researchers with an increasing emphasis on reproducibility.

While findings may on occasion be irreproducible as the result of p-hacking (i.e. the modification of analyses in search for significant results), it is often due to much more innocent means such as an inability to re-execute a previous workflow<sup>29</sup>, software errors<sup>28</sup>, system upgrades<sup>30</sup>, or the underlying stability of algorithms<sup>27</sup>. While the existence of these problems is becoming increasingly understood and accepted, their impact on the validity scientific claims or models in neuroimaging has remained largely uncharacterized.

The objective of this thesis is to understand the role that instability plays in the reproducibility of results, and develop methods around this exploration which enable higher quality and more easily reproducible claims in neuroimaging. To this end, I have:

- (i) developed a software library which facilitates and records provenance for the parallel execution, re-execution, visualization, and error detection of neuroimaging pipelines and datasets in high performance computing or cloud environments;
- (ii) developed and evaluated various methods for perturbing pipelines and observing the numerical instabilities inherent to structural connectome estimation;
- (iii) quantified the impact of numerical instability on a set of neuroimaging analyses measuring absolute change, dataset reliability, network topology, and the robustness of a brain-phenotype relationship; and,
- (iv) improved the quality and generalizability of modelling a brain-phenotype relationship through the aggregation of connectomes in a perturbation-augmented dataset.

Ultimately, in collaboration with my co-authors, I created a piece of computational infrastructure

which was used to facilitate the execution of pipelines consuming several CPU-decades for the induction of numerical instabilities in neuroimaging pipelines. I characterized the significant impact of these instabilities in various analytic contexts, and proposed a method for leveraging instabilities in machine learning applications which improves the generalizability of learned models. This thesis not only sheds light on this impactful issue in neuroimaging, but it presents a method for further exploration on the trustworthiness of scientific tools and results more generally. My work also demonstrates how scientific workflows can immediately benefit from explorations of numerical stability by leveraging the variability inherent to workflows to reduce bias in models of brain structure. This thesis is manuscript based, meaning that each of the four body-chapters is an exact copy of either a published or under-review manuscript.

## **1.1 Contributions to Original Knowledge**

I have developed and contributed to several tools, methods, and experiments which increase the accessibility of deploying and evaluating neuroimaging pipelines at scale. I have demonstrated the utility of these tools to explore and characterize the stability of neuroimaging pipelines. Below, I summarize original contributions in each of these areas.

### **Software Contributions**

Extending the Boutiques command-line descriptive framework<sup>31</sup>, for which I am a co-maintainer, I developed Clowdr<sup>32</sup> to enable the rapid deployment of scientific workflows across cloud and high performance computing resources. This tool is publicly available and has effectively been used on the Amazon Web Services cloud, Compute Canada, and Dell EMC resources, orchestrating decades of compute cycles over the resources in a matter of hours. As workflows in neuroimaging often rely on prebuilt and containerized dependencies through Docker or Singularity, I created Fuzzy (<https://github.com/verificarlo/fuzzy>), a curated collection of scientific libraries which were recompiled and instrumented to allow the stability evaluation of the contained tools. These environments use Verificarlo<sup>33</sup> to instrument libraries with Monte Carlo Arithmetic<sup>34</sup>. The precompiled libraries include: Python, Cython, BLAS, LAPACK, Libmath. The efficacy of the perturbations induced through these tools has been demonstrated for neuroimaging

applications through several experiments mentioned in the following paragraph.

## **Scientific Contributions**

The software contributions above were developed out of necessity for the exploration of the stability of neuroimaging analyses. First, I created and demonstrated the Fuzzy environments as an effective method for inducing instabilities in neuroimaging pipelines, and situated these instabilities with respect to other forms of perturbation<sup>35</sup>. In this paper, I demonstrated the considerable variability present in a structural connectome estimation pipeline solely due to numerical uncertainty. I applied this technique to study the stability of a set of typical network neuroscience experiments and characterized the effect of instabilities on each of a test-retest, network topology, and phenotypic classification setting<sup>36</sup>. This work illustrates the significant impact that numerical instabilities play in all levels of downstream analysis, spanning the reliability of comparisons across subjects, to the lack of reliability in individual network features, and ultimately the modelling of relationships between connectivity and phenotypic information (in this case, Body Mass Index). The final chapter of my thesis focused on the aggregation of unstable derivatives and their impact on the performance and generalizability of machine learning classifiers tasked with learning brain-phenotype relationships. The findings of this paper showed that dataset augmentation through Monte Carlo Arithmetic leads to the development of more stable and performant classifiers, and has significant implications on the development of robust neuroimaging biomarkers, as well as the potential to increase the benefit gained from additional data collection. Together, these contributions bridge the gap between numerical analysis and neuroimaging, providing novel insights into the reliability of tools, their results, and their ultimate application in understanding brain structure.

## **1.2 Contributions of Authors**

I was responsible for the experimental design, data processing, analysis, interpretation of results, and the majority of writing for each manuscript. Specific co-author contributions to each chapter are summarized below.

### **Ch.I – A Serverless Tool for Platform Agnostic Computational Experiment Management**

I designed and developed the tools, experiments, and figures, and wrote the majority of the manuscript. Shawn T. Brown, Tristan Glatard, and Alan C. Evans supported the design and development processes, edited the manuscript, and provided valuable feedback. Tristan Glatard and Alan C. Evans jointly supervised this project.

### **Ch.II – Comparing Perturbation Models for Evaluating Stability of Neuroimaging Pipelines**

I was responsible for the experimental design, tool development, data processing, analysis, interpretation, and the majority of writing. All authors contributed to the revision of the manuscript. Pablo de Oliveira Castro, Pierre Rioux, Eric Petit, and Shawn T. Brown all provided software development support. Alan C. Evans and Tristan Glatard supported the development process and jointly supervised this project.

### **Ch.III – Numerical Instabilities in Analytical Pipelines Lead to Large and Meaningful Variability in Brain Networks**

I was responsible for the experimental design, data processing, analysis, interpretation, and the majority of writing. All authors contributed to the revision of the manuscript. Yohan Chatelain, Pablo de Oliveira Castro, and Eric Petit were responsible for Monte Carlo Arithmetic tool development and software testing. Ariel Rokem, Gaël Varoquaux, and Bratislav Misic contributed to experimental design and interpretation. Tristan Glatard contributed to experimental design, analysis, and interpretation. Tristan Glatard and Alan C. Evans were responsible for supervising and supporting all of my contributions.

### **Ch.IV – Data Augmentation Through Monte Carlo Arithmetic Leads to More Generalizable Classification in Connectomics**

I was responsible for the experimental design, data processing, analysis, interpretation, and the majority of writing. All authors contributed to the revision of the manuscript. Yohan Chatelain and Ali Salari provided feedback on the experimental design. Tristan Glatard and Alan C. Evans contributed to experimental design, analysis, interpretation, and jointly supervised this project.



## 2 Background

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In this section I will first define and discuss the state of reproducibility in science across a range of domains, and explore several specific examples. Next, I will discuss the role that software reusability and numerical stability play in these problems, and advances which have been made in each of these fields. I will then approach neuroimaging, with a brief overview of the field and commonly used methods that are of relevance, finally presenting several case studies in neuroimaging to demonstrate the necessity of exploring numerical stability in this space.

### 2.1 Scientific Reproducibility

At the heart of science is the ability for researchers to build upon previous work, incrementally advancing a given field of research<sup>37,38</sup>. Despite being accepted as a cornerstone for progress, there is not a fully unified vocabulary around this practice<sup>39–41</sup>. Definitions have emerged to serve specific communities tackling issues of reproducibility, such as The Association for Computing Machinery which defines reproducibility as the ability to re-obtain a measure with stated quality and precision using an identical experimental setup when carried out by a different team in a different location<sup>42</sup>. In the case of life sciences, this definition has limited use since the samples being measured (e.g. human participants) or equipment used (e.g. exact imaging apparatus from the same manufacturer) is difficult or impossible to replicate. In these cases, a distinction in the level of reproducibility is often drawn with milestones corresponding to the ability to reproduce the methods used, the ability to obtain the same or equivalent results, and the ability to draw equivalent inferences from the results obtained<sup>39</sup>.

In an effort to increase clarity around this topic and handfuls of overlapping definitions, there have been recent efforts to visualize the intentions and slight conceptual differences across each<sup>40</sup>. Here, a distinction is made from reproducibility and replicability. Reproducibility in this case is defined as the ability to exactly re-run the analysis using the existing data and tools, but is performed by a unique analyst. Replicability then describes the ability to successfully re-do the experiment, including new data collection,

experimenters, and software, but ultimately arriving at the same claim. These definitions have practical value in the life sciences as they allow for the differentiation between a claim remaining unchanged in either the same or differing experimental configurations and equipment. The definitions presented here, often referred to colloquially as “Peng’s Reproducibility”, will be those referred to throughout this thesis.

In addition to the definitions of reproducibility and replicability accepted above, I will refer to an additional term in this space: reusability, which simply refers to the ability of being able to “hit go” on the analysis subsequent to its original execution. This definition closely matches a definition of reproducibility mentioned above, but no analog exists within the Peng framework, so it is added here for clarity.

With a rich and growing space of conceptual frameworks through which reusability, reproducibility, and replicability can be evaluated, it is perhaps self-evident that the level of trustworthiness across many disciplines has recently become a topic of interest. I will now introduce the so-called “Reproducibility Crisis”, an umbrella phrase which captures this movement, and highlight its relevance in both psychological and neurological sciences, serving as motivation for the work carried out in this thesis.

## **2.2 The Reproducibility Crisis**

The reproducibility of findings has long been a topic of concern to researchers in the life sciences<sup>43–46</sup>. However, several recent initiatives have brought this somewhat fringe topic into an area of broad concern. In 2015, the Open Science Collaboration<sup>47</sup> organized an attempted replication of 100 recent research papers in psychology. Their result, showing that approximately two-thirds of the studies failed to replicate, was swept up by mainstream media and proclaimed a crisis.

In an effort to characterize the so-called crisis, Nature conducted a survey of 1,500 scientists across a wide range of disciplines, probing their beliefs about the reproducibility of science in their field. This study found that 90% of respondents felt that their field was in some level of crisis<sup>48</sup>, and studies exploring possible causes or proposing solutions to the so-called crisis have continued to trend in the years since. Unsurprisingly, this phenomenon has been characterized from a number of different directions, even within a given discipline. In neuroscience, for example, statistical power has long been believed to be a

key culprit for irreproducibility<sup>49</sup>; a meta-analytic study of findings in literature estimated a median power of 21%. This work, however, assumed the robustness of data and methods used throughout the studies, and performed a purely statistical evaluation, so any inconsistencies in the analytical methods used may in reality lead to an even lower statistical power across published results.

In neuroimaging, studies began to dive deeper into the intermediate processing methods and explored their compounded effect on null hypothesis significance testing. A study evaluating the accuracy of significance testing frameworks within commonly used libraries for the analysis of functional MRI (fMRI) data found that under certain conditions false-positive rates were as high as 70%<sup>28</sup>. While the presentation of this result may misleadingly construe an inflated significance of these errors (see associated letters<sup>ab</sup> and correction<sup>c</sup>), undeniable attributes of these findings are both that a) there is considerable variability in the quality of tools under certain conditions and b) there are often-dramatic differences between supposedly-equivalent software libraries. The impact that cross-library differences have on analytical workflows was well summarized in an attempted replication of experiments on real fMRI datasets<sup>24</sup>, which showed that not only do the tools produce qualitatively different results, but could sometimes lead to diverging conclusions.

In all cases of limited reproducibility presented above, analyses were chosen to be evaluated explicitly because they could be re-executed across slightly different conditions. While all published methods, such as software written to produce the result associated with a given paper, would continue to function in an ideal world, in practice this is not the case. A study exploring published papers in computer science found that of 600 papers which were analyzed, approximately only 200 were able to weakly replicate<sup>29</sup>. In many cases, this was due to inadequate description of the specific implementations, environments, or how tools were applied, while in others, it was likely due to the commonly accepted phenomenon of “Software Aging”<sup>50</sup>. Regardless of the specific causes, this inability to re-execute workflows makes claims derived from these workflows irreproducible at the most fundamental level. Prior to exploring possible numerical

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<sup>a</sup><https://www.pnas.org/content/114/17/E3368>

<sup>b</sup><https://www.pnas.org/content/114/17/E3370>

<sup>c</sup><https://www.pnas.org/content/113/33/E4929>

underpinnings behind reproducibility, it is essential to ensure the reusability of analyses. The following section will discuss advances made prior to this thesis which facilitate the construction and distribution of re-executable scientific workflows.

## **2.3 Software Reusability**

There are a number of factors which limit the re-executability or reuse of scientific workflows, including incomplete specification of processing detail or lack of data and tool availability<sup>51</sup>. While the public sharing and dissemination of data may not always be possible in the life sciences due to concerns around ethics or the informed consent of participants<sup>52,53</sup>, there exist practical guides which can help researchers overcome this hurdle in certain cases (e.g. for neuroimaging<sup>54</sup> and psychology<sup>55</sup>). Given that ethical barriers should not exist limiting the reusability of software, this section will focus on tangible efforts which have been made to increase the re-executability of scientific pipelines.

### **2.3.1 Virtual Environments**

The configuration of tools and software environments is a necessary step prior to the execution of computational workflows. While authors set up their computational environments prior to carrying out experiments, these configurations are often left undocumented in published manuscripts, leaving readers with the daunting task of determining what versions of libraries were used and their dependencies<sup>56</sup>. However, this is not only an inconvenience but becomes scientifically troublesome when considering the reality that distinct software versions by design lead to incrementally different interfaces and results<sup>57</sup>. In programming languages such as Python<sup>58</sup>, packages may contain information strictly defining their requirements. However, these definitions are limited to capturing the dependencies written within the same language, and are often written with version “bounds” (i.e. requires package X with version  $\geq 1.0$ ), to simplify the interoperability between libraries.

Traditionally, the issue of environment configuration has been solved through the use of Virtual Machines (VMs)<sup>59</sup>. VMs are a method for packaging and sharing tools that are pre-installed in an executable environment which can be run across computers. A drawback of these machines is that they

are often require considerable storage and computational overhead, as they contain complete operating systems which must be launched in virtualized hardware, limiting their portability. Over the last few years, techniques for the virtual encapsulation of tools have shifted towards a “container” approach, which does not suffer from similar overheads. Container environments, made accessible primarily through Docker<sup>60</sup> and Singularity<sup>61</sup>, rely on the Linux kernel and other libraries of the host operating system, leading to smaller bundles that are less computationally expensive to run. While containers are not a perfect solution that guarantee reusability<sup>d</sup>, they are an important advancement which greatly increases the ability to distribute and consume scientific software, and provide a salve against the problem of software aging.

### **2.3.2 Tool & Analysis Descriptions Standards**

Beyond tool configuration, the most fundamental components of re-executability are a clear characterization of the tool(s) being run and the arguments or inputs provided to them. Despite this, there is no universally accepted description standard for software. In practice, grassroots standards often emerge by necessity in a given domain, and gain local adoption. In the case of neuroimaging, such standards include Brain Imaging Data Structure applications (BIDS apps)<sup>62</sup> and Boutiques<sup>31</sup>, each of which takes a distinct approach to this problem.

The Brain Imaging Data Structure defines an organization standard for neuroimaging datasets, with the goal of lowering the barrier to their sharing, interpretation, and inter-operation<sup>63</sup>. Accordingly, the BIDS app standard emerged as a *prescriptive* standard that dictates how tools should interact with these datasets<sup>62</sup>. This standard requires that a set of base arguments must be supported and accepted by tools: the location of the dataset, the location at which outputs should be placed, and the analysis level (e.g. for the analysis of an individual versus the analysis of a group). This standard also prescribes several optional arguments, such as allowing for the indication of a subset of subjects selected for analysis. However, a key limitation of this standard is that beyond the initial prescription of arguments there is no definition or description of how subsequent arguments that may be relevant for a given tool should be defined or

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<sup>d</sup>Due to problems which may arise by violating some of the best-practices described here: <https://developers.redhat.com/blog/2016/02/24/10-things-to-avoid-in-docker-containers/>

documented. The BIDS app standard dramatically simplifies performing an analysis pipeline with default behaviour, but this lack of additional description and no provenance definition to keep analysis records makes it an incomplete solution for software re-use when implemented at the barest level.

Boutiques facilitates re-executability through a *descriptive* standard which requires software developers to create a rich metadata record summarizing the arguments and function of their tools<sup>31</sup>. This standard supports a wide range of command-line tools, and is supported by a library which directly manages the execution of described tools alongside validation of inputs (e.g. ensuring two mutually-exclusive options are not provided) and provenance capture. However, while the added complexity of Boutiques leads to more rich descriptions and facilitates more complete tool re-use, this complexity also makes the standard considerably less accessible.

Other standards have been developed around neuroimaging which promote the capture of rich execution records, such as the NeuroImaging Data Model<sup>64</sup>, or foster the construction of workflows and the distributed execution of tools, such as CBRAIN<sup>64</sup>, LONI Pipeline<sup>65</sup>, and Nipype<sup>66</sup>. While these tools provide a rich set of features and techniques to improve the re-executability of software, prior to this thesis there was no single tool in the neuroimaging space which harmonized software virtualization, command-line tool descriptions, and provenance capture that supported the iterative development and deployment of analysis pipelines across high performance computing systems.

## **2.4 Numerical Stability**

In cases where the re-execution of software can be attempted and reproduction of claims can be tested, there are myriad possible sources of observed variability between results. While some of these may be avoided when following best practices<sup>67</sup>, such as the dependence of an analysis on a pseudo-random number, there are algorithmic properties which may persistently affect outcomes and would benefit from characterization. One such property is the numerical stability of an algorithm or tool<sup>68</sup>. While there are various theoretical and empirical techniques used for evaluating stability, each conceptually refers to stability as measure of sensitivity to small perturbations. Issues in stability emerge for one of two

reasons: the evaluation of poorly conditioned functions (i.e. those containing or nearby singularities), or the accumulation and propagation of numerical error<sup>68</sup>.

In the case of poorly conditioned functions, instability may often be detected both theoretically and empirically. One such measure for evaluating this is the “condition number” of a matrix or function<sup>69</sup>. While the mathematical form can be simplified for different contexts (i.e. matrices or linear functions), its general definition ultimately describes the worst-case error in the output for a relative change in input, as that change to input asymptotically approaches 0<sup>69</sup>. This allows functions to be evaluated with respect to their sensitivity to minor perturbations of their inputs, where a smaller condition number refers to smaller effect of perturbations.

While the condition number of a function can in some cases refer to its practical robustness to perturbations, it ultimately does not consider implementation so more accurately refers to how “easy” a function is to evaluate. In doing so, the condition number relates two distinct components of the stability of a problem: the forward error and backward error. The forward error is defined as the deviation of an output from the true result, while the backward error is defined as the smallest change to an input such that the theoretical result matches the empirical result<sup>68</sup>. The condition number is bounded by a relationship of these values, such that it will always be greater than or equal to the ratio of the forward error to the backward error<sup>69</sup>. In practice, forward and backward error are often combined into a measure of mixed stability which evaluates how closely a solution matches another when the input is perturbed slightly. In the case of problems where there is no ground-truth solution (e.g. alignment of an image to a template) it is impossible to explore the forward error independently, while the backward error may be evaluated in certain cases (e.g. if the approximation of a ground-truth alignment exists). Given that there is no guarantee that the backward error is measurable for an arbitrary problem, the mixed stability is commonly evaluated.

While in some cases it is possible to compute measures of stability analytically, is difficult for all but linear and differentiable systems<sup>70</sup>, neither of which can be assumed to be the case in complex scientific pipelines. In these cases, as well as when exploring the role of numerical errors in the stability of an

algorithm, numerical analysis<sup>71</sup> approaches can be used.

## 2.5 Numerical Analysis

Unlike in the analytical setting discussed above, the propagation and accumulation of numerical error is a largely empirical problem. This problem inevitably arises from the digital representation of non-integer data through the IEEE-754 floating point standard<sup>72</sup>. The representation of data in this format consists of three components: sign, exponent, and mantissa. These components are analogous to the traditional use of scientific notation in which the sign indicates whether the number is positive or negative, the exponent indicates the order of magnitude of the digits, and the mantissa contains the digits themselves. This standard is powerful given its ability to represent both large and small numbers with considerable precision. In the case of single precision numbers (32-bit floats), the sign, exponent, and mantissa are each allocated 1, 8, and 23 bits, respectively<sup>72</sup>.

Alongside the ability to represent both large and small numbers in the same bit space comes the caveat of two impactful types of imprecision when involved in floating point arithmetic: roundoff error and catastrophic cancellation<sup>73</sup>. Roundoff error, the loss of information in the location(s) following the least significant bit, can be caused due to any arithmetic operation on finite floating point numbers. This occurs when an operation results in more digits that belong in the mantissa than can be stored<sup>73</sup>. Conversely, catastrophic cancellation occurs when subtracting similar numbers. Results in both a larger portion of the mantissa containing non-significant 0 values populated beyond where either of the original values contained information, and the promotion of remaining significant bits that are possibly due to noise from previous errors, amplifying the numerical error further<sup>73</sup>. For example, consider a system with 4 decimal digits of precision which is tasked with evaluating the following expression:  $(2.126 + 100.2) - 102.1$ . The addition would first be evaluated, and rounding error would be introduced in the truncation of 102.226 to 102.2. While the result still has 4 significant digits of information, the subtraction will return the value 0.100, which contains only a single significant digit of information.

The handling of all floating point operations according to the IEEE-754 standard is deterministic



which importantly allows programs to repeatably obtain the same results<sup>72</sup>. However, when the repeated evaluation of floating point operations is unaccounted for by software developers or users, this also leads to the masking of propagated numerical errors within software. Stochastic arithmetic is an approach used to study the impact of numerical errors that emerged throughout floating point arithmetic<sup>74,75</sup>. In this approach, errors associated with operations are treated as random variables. One such example is stochastic rounding, in which the results of operations are considered to exist as both rounded-up and rounded-down quantities with equal validity. Considering this method, let alone any possible other model for error in the stochastic arithmetic context, the results of each operation can be successively perturbed to either setting and the exhaustive space of all possible terminal results from an algorithm can be described (though in many cases, this would result in far too many conditions to actually realize). Another example of stochastic arithmetic is Monte Carlo Arithmetic (MCA)<sup>34</sup>. MCA approaches stochastic arithmetic using a Monte Carlo<sup>76</sup> framework in which algorithms or software pipelines are repeatedly evaluated and each floating point operation throughout the execution is randomly perturbed. By repeating the evaluation of a pipeline using MCA, it is possible to obtain a distribution of equally plausible results at a configurable machine precision. Several libraries have been developed which support the instrumentation of arbitrary tools with MCA<sup>33,77</sup>, making it a technique which can be readily introduced to a wide array of pipelines for exploring numerical stability. A major caveat of this technique is the large computational overhead. As instrumented through Verificarlo<sup>33</sup>, MCA increases the run-time of floating point operations by approximately 100×, and may require 10s – 100s of runs to well sample the distribution of plausible results<sup>78</sup>. As scientific pipelines are not solely built of floating point operations in practice, resulting slowdowns may be considerably less dramatic when instrumented with MCA. Regardless, the repeated execution of perturbed analyses unavoidably increases the run-time of experiments according to the number of simulations performed.

While MCA allows for the perturbation of pipelines, the results cannot be evaluated in the conditioning context introduced above since the change in inputs is unknown, as perturbation happens iteratively throughout the pipeline. It here becomes useful to consider stability a measure of precision; while stability

and precision “have nothing to do with accuracy”<sup>70</sup>, they can serve as valuable measures of consistency. One measure of precision applicable in this context is the number of significant digits<sup>34</sup>. While there are distinct context-appropriate formulas which have varying underlying assumptions about the error<sup>79</sup>, Parker<sup>34</sup> first defined this in an MCA context as a function of the ratio between the mean and variance across simulations. In practice, this allows for the identification of which digits are unchanging across perturbations, and the construction of a margin of error around results. In contexts such as neuroimaging, performing MCA perturbations and evaluating the number of significant digits is particularly attractive as this method does not require a) a differentiable model of the given algorithm or pipeline, or b) an expected ground-truth result. Prior to this thesis the estimation of significant digits through MCA had not been applied to the study of stability in neuroimaging pipelines.

## 2.6 Neuroimaging Data & Pipelines

Understanding the structure and function of the brain has long been a topic of exploration<sup>80</sup>, and neuroimaging enables this exploration *in vivo* in humans. Modern neuroimaging techniques rely on complex image acquisition techniques, such as Magnetic Resonance Imaging (MRI)<sup>81</sup>, Electroencephalography (EEG)<sup>82</sup>, or Magnetoencephalography (MEG)<sup>83</sup>. Each imaging modality has unique strengths and weaknesses, which has led to the adoption of multimodal methods for brain image analysis<sup>84,85</sup>. Even within a given imaging paradigm acquisition protocols may be designed to highlight different features of the brain. In the case of MRI, commonly used contrasts highlight brain structures (e.g. T1w<sup>86</sup>, T2w<sup>87</sup>), activity (e.g. BOLD<sup>88</sup>), or the diffusion of water in the brain (e.g. DWI<sup>89</sup>). Each of these techniques provides a unique look at the structure and function of the brain, and neuroimaging pipelines often consider one-or-more of these modalities at once<sup>23,90</sup>. For the purpose of this thesis, I will focus on evaluating the analysis of a diffusion imaging method towards the reconstruction of structural connectivity maps, or, connectomes.

Diffusion weighted imaging, DWI, is an imaging method that can be used for the identification of connective tissue (white matter tracts) within the brain<sup>91,92</sup>. These images are acquired by imposing directed magnetic gradients to the brain, which encourages the re-alignment of water molecules. The

directed gradients are swept across a  $180^\circ$  range, ultimately providing a series of images which can be jointly interpreted to identify the directional diffusion of water, and therefore alignment of axonal fibers<sup>93</sup>. The identification and modelling of this tissue allows for the estimation of brain networks and subsequent comparison of their features<sup>3</sup>, which may be relevant for understanding a number of neurological conditions<sup>16,17,94,95</sup>. The analysis of DWI data typically makes use of both structural and diffusion images<sup>90,96</sup>, and the use of these images can be conceptually decoupled into two components: pre-processing and modelling.

**Pre-processing** While distinct datasets and libraries may present slight deviations in the pre-processing of data, I will here describe the backbone of a widely applicable and community-accepted pre-processing workflow<sup>96–98</sup> and briefly discuss the rationale behind each component. The required data for the pre-processing workflow described here is: a set of 4-D diffusion images and associated acquisition parameters, a structural T1w image, and a template reference image (such as the ICBM152 template<sup>99</sup>). The diffusion images are first de-noised and aligned to one another alongside the removal of structured eddy-current artifacts<sup>100</sup> commonly found in the images. The structural image is then aligned to the template and a single reference diffusion volume separately via an affine registration<sup>101</sup>, and an optional non-linear registration may be subsequently applied between the structural image and template<sup>96</sup>. The transformations are combined such that there exists a mapping from the template space to the subject-specific diffusion space so that images can be meaningfully compared via brain region atlases (or parcellations) and tissue masks defined in the template space. These atlases can be transformed and applied to the diffusion image in subsequent modelling. Optionally, subject-specific tissue masks may also be generated from the structural image and transformed into the space of the diffusion image<sup>102</sup>.

**Modelling** Depending on the quality of the diffusion data (such as the resolution of diffusion directions sampled), various diffusion models may be appropriate for specific data<sup>103–105</sup>. Regardless of the specific techniques used at each stage, there are three components in the modelling workflow which lead to the generation of connectomes: fitting of a diffusion model, fiber tractography, and mapping fibers to a

parcellation<sup>14,98,106,107</sup>. Diffusion models seek to assign a direction or directions of water diffusion to each voxel within the image. These models range in complexity from 6-component tensors to orientation distribution function (ODF) histograms on the order of 100 components<sup>104</sup>. Higher order ODF models require higher fidelity data, but are necessary for many tractography algorithms. Tractography is applied following the evaluation of a diffusion model, and involves tracing the local estimates of diffusion or “flow” to form larger tracts of coherent connectivity<sup>108</sup>. Across the many available tractography algorithms, they can be conceptually grouped into two categories: deterministic and probabilistic models<sup>103</sup>. Deterministic models assign flow based on the single direction of maximum diffusion for each voxel, whereas probabilistic models assign fiber probabilities rather than making a unique decision. Finally, fiber streamlines are used to assign edges in a network. Regions of the network are often defined by a parcellation, such as the common Desikan-Killianey-Tourville<sup>109</sup> atlas, and edges correspond to tracts which connect them. The weights of edges are often defined as either a feature of the tracts, such as the average strength of diffusion across tracts, or the total number of tracts between regions. The networks are often stored in an adjacency matrix format, such that an  $N \times N$  matrix would correspond to a connectome constructed using an  $N$ -region parcellation, and contain non-zero values at location  $(i, j)$  to indicate a connection between regions  $i$  and  $j$ .

Over the last several decades there has been considerable advancement in the methods presented above, leading to higher quality maps of the brain<sup>110</sup>. Despite this, the inherent difficulty of this task and profound lack of ground-truth results in many contexts has limited the accuracy of models and the field is known to suffer from an issue of “false-positives”<sup>111–113</sup>. While there is regular debate on the usefulness of connectomes for this reason, it is worth stating that this thesis is unaffected by the outcome or validity of this debate. The evaluations performed throughout this thesis assess the numerical stability of processing tools, an analog of precision, which can serve as an informative and descriptive statistic regardless of the underlying accuracy of models being evaluated.

## 2.7 Evidence of Instability in Neuroimaging

In an effort to tie together the previous explorations of reproducibility and stability to neuroimaging, I will conclude this section with a summary of studies which shed light on these issues in the context of brain imaging. Examples of issues in reproducibility have arisen in neuroimaging across all operational scales from differences in experimental configuration across teams to numerical sensitivity with respect to minor numerical perturbations.

As neuroimaging is a relatively young and quickly growing field, there co-exist many libraries and tools which have been designed to accomplish similar tasks in parallel. Depending on the local preferences and expertise, scientists may elect to use one process over another at any stage throughout their analysis. In practice, this may lead researchers to many distinct answers to the same question. This effect of “researcher’s degrees of freedom” was recently explored for the dissection of white matter bundles derived from Diffusion MRI<sup>114</sup>. Independent teams from 42 centres were tasked with the segmentation of 14 tracts on a shared dataset using their method of choice (including manual, semi-automatic, or fully-automatic approaches). This study revealed that the variability introduced across teams was larger than any other source of variability in the experiment, and proposed that a reduction in analytical heterogeneity was necessary for the field to progress<sup>114</sup>. A similar study exploring the variability across teams in the context of a set of task-based fMRI experiments found that not only did no two teams of the 70 included use the same technique, but that findings were in considerable disagreement across groups<sup>115</sup>. Across 9 tested hypotheses, on average 20% of the teams arrived at different conclusions from the majority, clearly demonstrating the impact of analytical flexibility on the generation of consistent results. Interestingly, the two aforementioned studies which explored the variability across teams came to differing conclusions: while in the case of diffusion, the authors recommend removing heterogeneity in this technique, in the functional case this broad characterization of the space was deemed an essential building block.

The variability observed across these distinct-but-similar pipelines was likely introduced not at a single point, but at various stages within the pipelines. In the case of non-linear registration, for example, a

comparison of 14 commonly-used methods in neuroimaging were compared and showed produced a wide range of results<sup>25</sup>. Not only did this evaluation demonstrate that no-two methods were equivalent, it demonstrated that no single method was universally more performant than the others. Even when an effort is made to match workflows as closely as possible across libraries, considerable differences have been found in the terminal results. When replicating a series of fMRI experiments using the three most commonly used analysis libraries, the location and strength of brain activations were found to vary considerably<sup>24, 116</sup>. These inconsistencies may be the result of methodological differences in some cases (e.g. the possible use of global signal regression<sup>117</sup>), while in others they may be due to implementation differences or software bugs. When evaluating the statistical testing frameworks in these same libraries, false-positive rates were found to peak at 70% in some cases when reporting a p-value of 0.05<sup>28</sup>, and further demonstrated that the conditions under which each method performed the best was variable across tools. We can see from these studies that not only do differences exist across tools at each stage of analysis pipelines, but also that each tool has a unique relationship between the quality of their performance and the data being used. The extreme variability-in-variability that we observe might be due to underlying numerical properties of the algorithms, and must be explored on a tool-by-tool basis.

The stability of neuroimaging pipelines has begun to be explored in specific use-cases through the perturbation of data or libraries prior to processing. In the case of Diffusion MRI, the stability of tensor models were studied analytically and validated experimentally<sup>118</sup>. In this study, the stability of each tensor reconstruction was first evaluated and found to contain considerable variability in stability across algorithms, ranging from nearly 1 (relatively stable) to nearly 10 (highly unstable). The models were then tested across a range of operating points, and showed a tight relationship between the observed variability and the theoretical conditioning<sup>118</sup>. Importantly, this work clearly demonstrated that experimental variability may serve as a proxy for theoretical conditioning. This work also illustrated an often overlooked feature of variability: that the stability of models varies across the space of inputs, and thus any evaluation of stability is inextricably linked to both the tool and data being used.

Another exploration of stability through experimental perturbation compared two tools for cortical and

sub-cortical surface estimation<sup>27</sup>. In this experiment, grey matter surfaces were estimated from a single image using two toolboxes. Subsequently, the intensity of a single voxel within the white matter (centre of the Corpus Callosum) of the image was amplified by 1% of its original value, and the tools were re-run. This analysis showed significant differences between not only the original and perturbed surfaces, but showed non-uniformity in the variability across cortical structures that was distinct for each tool<sup>27</sup>. This study importantly sheds light on the reality that variability introduced to a workflow may affect the results in unexpected ways. The fact that the minor perturbation of a single voxel buried within white matter may lead to a significant change in the estimation of grey matter matter surfaces suggests that a more thorough exploration of perturbations and associated variability may be required to fully understand the behaviour of these pipelines.

Though the magnitude of differences observed in the above cases is perhaps surprising, it may have been expected in all scenarios to observe some non-zero amount of variability. However, differences in results have also been observed in neuroimaging when changing operating system<sup>30,119</sup> or even padding an image with a row of empty voxels<sup>120</sup>. This array of findings clearly demonstrates the relevance of characterizing numerical stability in the context of neuroimaging both due to the abundance of cases in which numerical inconsistencies have been observed and the general lack of characterization of this effect. This thesis begins with enabling the rapid and provenance rich deployment of neuroimaging workflows, and uses this platform to dig deep into the induction and evaluation of numerical instabilities, the impact of instability on analytical workflows, and concludes with an exploration of how the observed variability may be harnessed as a *feature* rather than a bug.

# Ch.I: A Serverless Tool for Platform Agnostic Computational Experiment Management

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## Abstract

Neuroscience has been carried into the domain of big data and high performance computing (HPC) on the backs of initiatives in data collection and an increasingly compute-intensive tools. While managing HPC experiments requires considerable technical acumen, platforms, and standards have been developed to ease this burden on scientists. While web-portals make resources widely accessible, data organizations such as the Brain Imaging Data Structure and tool description languages such as Boutiques provide researchers with a foothold to tackle these problems using their own datasets, pipelines, and environments. While these standards lower the barrier to adoption of HPC and cloud systems for neuroscience applications, they still require the consolidation of disparate domain-specific knowledge. We present Clowdr, a lightweight tool to launch experiments on HPC systems and clouds, record rich execution records, and enable the accessible sharing and re-launch of experimental summaries and results. Clowdr uniquely sits between web platforms and bare-metal applications for experiment management by preserving the flexibility of do-it-yourself solutions while providing a low barrier for developing, deploying and disseminating neuroscientific analysis.

## Ch.I - 1 Introduction

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The increasing adoption of distributed computing, including cloud and high-performance computing (HPC), has played a crucial role in the expansive growth of neuroscience. With an emphasis on big-data analytics, collecting large datasets such as the Consortium for Reliability and Reproducibility<sup>1</sup>, UK-Biobank<sup>2</sup>, and Human Connectome Project<sup>3</sup> is becoming increasingly popular and necessary. While these datasets provide the opportunity for unprecedented insight into human brain function, their size makes non-automated analysis impractical.

At the backbone of science is the necessity that claims are reproducible. The reproducibility of findings has entered the spotlight as a key question of interest, and has been explored extensively in psychology<sup>4</sup>, neuroimaging<sup>5,6</sup>, and other domains<sup>7,8</sup>. Computational experiments must be re-executable as a critical condition for reproducibility, and this bare minimum requirement becomes increasingly challenging with larger datasets and more complex analyses. While sharing all code and data involved may appear a compelling solution, this is often inadequate for achieving re-runability or reproducibility of the presented findings and models<sup>8</sup>. When re-executable applications fail to reproduce findings, there is a gray area where the source of errors are often unknown and may be linked to misinterpretation of data, computing resources or undocumented execution details, rather than scientific meaning.

As a result, new tools and standards have emerged to aid in producing more reusable datasets and tools, and thereby more reproducible science. The Brain Imaging Data Structure (BIDS)<sup>9</sup> and the associated BIDS apps<sup>10</sup> prescribe a standard for sharing and accessing datasets, and therefore, increasing the accessibility and impact of both datasets and tools. This standard includes the definition of file organization on disk, as well as key-value pairs of metadata information in JavaScript Object Notation (JSON) files, and assigns specific meaning to command-line arguments to be used when processing these datasets. The Boutiques framework<sup>11</sup> provides a standard for software documentation in a machine-interpretable way, allowing the automation of tool execution and evaluation. These descriptions fully encapsulate the runtime instructions for a given tool in JSON-files, and are appropriate for a majority of command-line applications. Software containerization initiatives such as Docker<sup>12</sup> and Singularity<sup>13</sup> facilitate execution consistently across arbitrary computing environments with minimal burden on the user.

Web-platforms such as OpenNeuro<sup>14</sup>, LONI Pipeline<sup>15</sup>, and CBRAIN<sup>16</sup> simplify the analysis process further by providing an accessible way to construct neuroscience experiments on commonly used tools and uploaded-datasets. These systems deploy tools on HPC environments and record detailed execution

information so that scientists can keep accurate records and debug their workflows. Tools such as LONI's provenance manager<sup>17</sup>, Reprozip<sup>18</sup>, and ReCAP<sup>19</sup> capture system-level properties such as system resources consumed and files accessed, where tools supporting the Neuroimaging Data Model (NIDM)<sup>20</sup>, a neuroimaging-specific provenance model based on W3C-PROV<sup>21</sup>, capture information about the domain-specific transformations applied to the data of interest.

The initiatives enumerated above have synergistic relationships, where each solves a small but significant piece of the larger puzzle that is computational and scientific reproducibility and replicability. However, the learning curve associated with adopting each of these technologies is considerable, leveraging them in an impactful way is difficult, and certain applications may benefit from different approaches so these learning curves may have to be paid multiple times. For instance, interoperability is mainly valuable in contexts which there is a large variety of datasets or tools, and provenance may be of importance to identify the impact of an underlying system on a processing or modeling task. We present Clowdr, a lightweight tool which ties these approaches together so that researchers can minimize the learning burden and lower the barrier to develop, perform, and disseminate reproducible, interoperable and provenance-rich neuroscience experiments.

## **Ch.I - 2 Emergent Technologies in Reproducible Neuroscience**

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Conducting reproducible analyses in neuroscience requires many complementary facets, building on technologies which are commonly adopted as *de facto* standards.

### **Ch.I - 2.1 Data and Code Interoperability**

Due in part to its simplicity and active public development community, BIDS<sup>9</sup> has become an increasingly prominent data organization format in neuroimaging. This standard makes use of the Nifti file format<sup>22</sup> and human-readable JSON files to capture both imaging and subject-specific metadata. An important benefit of this data organization is the ability to launch data processing pipelines in the form of BIDS applications<sup>10</sup>, which expose a consistent set of instructions compatible with the data organization. Together, these complementary standards are suitable for performing a large variety of neuroimaging experiments. In contexts where tools have heterogeneous interfaces, or data organizations are custom-built for a particular context, the Boutiques<sup>11</sup> framework allows the rich description of a pipeline such that tool execution, validation, and exploration can be automated. These descriptors include the command-line structure to be populated as well as rich parameter descriptions and interactions, such as mutually exclusivity or

dependence, such that complicated data interactions required or forbidden by the tool can be accounted for.

### **Ch.I - 2.2 Software Virtualization**

While virtual machines have long been used for deploying analysis pipelines with complex dependencies in heterogeneous environments, software containers have recently emerged as lighter-weight alternatives suitable for transient data processing applications. Docker<sup>12</sup> provides this functionality across all major host operating systems, but is often not supported by HPC centers due to security vulnerabilities<sup>23,24</sup>. Singularity<sup>13</sup> addresses the security risks of Docker, but currently only supports Linux operating systems, filling the niche of containerization on shared computing resources. A detailed comparison in the context of medical imaging can be found in<sup>25</sup>.

### **Ch.I - 2.3 Workflow Engines**

Custom scientific pipelines can be composed in Python with Nipype<sup>26</sup>, Dask<sup>27</sup>, Pegasus<sup>28</sup>, Toil<sup>29</sup>, or several other tools which facilitate the modular interaction of complex independent processing stages. While the underlying tasks in Nipype, Dask, and Toil are defined in Python, Pegasus uses a Domain Specific Language (DSL) for representing tasks, increasing the barrier for defining tasks but ultimately increasing their portability. While Nipype is a widely used tool in neuroimaging and has many readily-defined interfaces available for researchers, the others require non-insignificant development to describe interfaces for common neuroimaging applications such as FSL<sup>30</sup> or MRtrix<sup>31</sup>. PSOM<sup>32</sup> and Scipipe<sup>33</sup> are functionally similar to Nipype but have been developed for GNU Octave/MATLAB and Golang, respectively. Several domains have more specialized tools which accomplish similar feats in their area of interest. These include Pypet<sup>34</sup>, Neuromanage<sup>35</sup>, Arachne<sup>36</sup>, and others which facilitate the automation of modeling and simulation workflows using tools such as Neuron<sup>37</sup>. For an in depth look at other tools in this space please refer to<sup>34</sup> and<sup>35</sup>. Each of these tools enables the construction of dependency graphs between pipeline components, and allow the deployment either to cluster scheduling software, multiple processing threads, and in some cases computing clouds. These tools primarily function through programmatic interfaces, though LONI pipeline<sup>15</sup>, OpenMOLE<sup>38</sup>, and Galaxy<sup>39</sup> provide both DSL and graphical user interfaces. Many of these tools also embed provenance capture, fault-tolerance features, and data tracking to avoid recomputations across similar executions. While each of these tools is a powerful and attractive option for creating workflows, they remain complex and potentially overkill when launching atomic single-step analyses, prebuilt pipelines, or analysis software developed in a different language than

the workflow engine of choice.

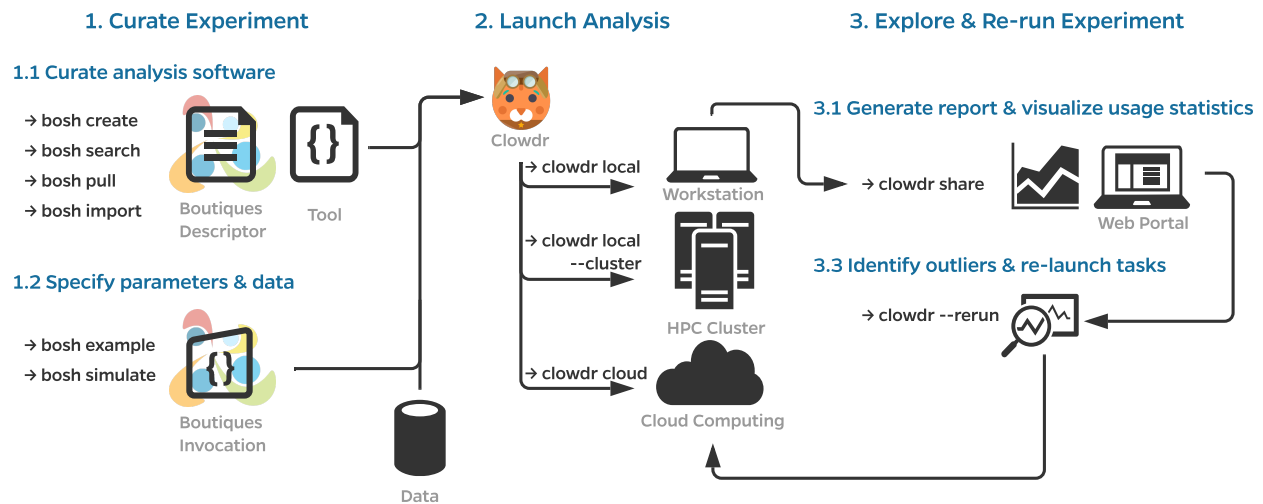
### **Ch.I - 2.4 Provenance**

Building on the W3-PROV<sup>21</sup> standard for data provenance metadata put forth by the World Wide Web Consortium, NIDM<sup>20</sup> is a standard which represents a processing and data provenance graph specific to neuroimaging analyses. While this standard is machine-interpretable and interoperable-by-design, supporting it currently requires tight integration with analysis pipelines. In LONI pipeline, a provenance model exists which includes detailed records of data use and file lifecycle<sup>17</sup>, which is designed to inform data consumers what types of analyses can be and have been performed with the data in question; this tool is tightly coupled with the LONI pipeline ecosystem. The ReCAP<sup>19</sup> project has been developed to evaluate the resource consumption of arbitrary pipelines on the cloud and can aid in cloud-instance optimization. While this tool has potential for a large impact in designing both cost effective and scalable analyses, there is considerable overhead as it manages executions through a persistent server and workflow engine. While various other libraries exist to monitor some piece of data or compute provenance, Reprozip<sup>18</sup> is perhaps the most exciting as it uniquely captures records of all files accessed and created throughout an execution, which allows for the creation of rich file dependency graphs. The limitation of this technique is that it requires data of interest to be written to disk, as opposed to managed in memory, which may not always be the case in some applications.

### **Ch.I - 2.5 Web Platforms**

Increasing the portability and accessibility of launching large scale analyses, web platforms such as CBRAIN<sup>16</sup>, LONI pipeline<sup>15</sup>, and OpenNeuro<sup>14</sup> provide science-as-a-service where users can upload and process their data on distant computing resources. Additionally, these platforms provide an accessible and immediate way to share the results produced from experiments with collaborators or the public. These tools provide incredible value to the community and allow the deployment of production-level pipelines from the web, but they are not suitable for prototyping analyses or developing pipelines, and it is cumbersome to run these services on a lab's own resources. In addition, monolithic Web interfaces are only suitable for a certain type of use-cases and high-level users, while developers or computer-savvy users prefer to rely on modular command-line tools and libraries.

## Ch.I - 3 The Clowdr Microtool



**Figure Ch.I - 1.** Clowdr Workflow. **(1)** Prior to launching an analysis with Clowdr, users must curate the analysis tools and their inputs. For the sake of portability, Clowdr supports both native and containerized applications described in the Boutiques format. Several tools exist in Boutiques which simplify the adoption/creation or execution of tools and are enumerated in **(1.1,1.2)**, respectively. **(2)** Scientists can then launch their analysis with Clowdr either locally, on HPC systems, or computing clouds. Possible workflows could involve the tuning of hyperparameters locally on a subset of the dataset of interest, and ultimately deploying the analysis at scale using the same arguments, or sweeping hyperparameter values on an HPC system. **(3)** After execution, summary reports can be produced by Clowdr **(3.1)** and visualized through a custom web portal enabling filtering by both execution properties and parameters, facilitating outlier detection and comparison across executions. Identified outliers, such as failures, incomplete tasks, or those which consumed more resources than expected can be re-run through Clowdr without having to regenerate any of the information previously provided. Clowdr facilitates the development, deployment, and debugging of analyses in a closed-loop provenance-rich microservice.

While the technologies enumerated above are essential pieces toward reproducible neuroscience, they are largely isolated from one another and place a large burden on researchers who wish to adopt all of these best practices. Clowdr leverages these tools to increase the deployability, provenance capture, and shareability of experiments. In summary, Clowdr:

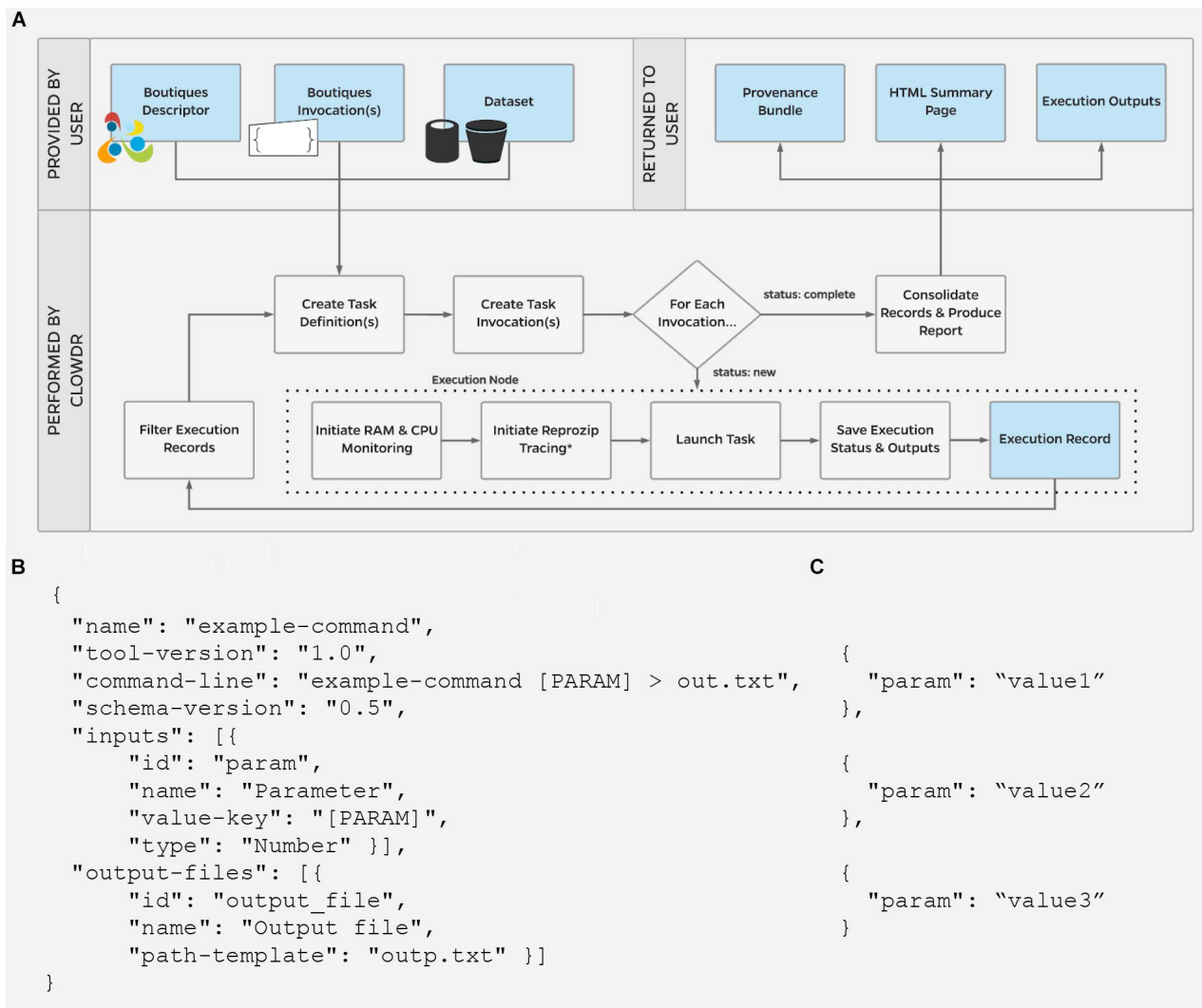
i is tightly based on Boutiques and is BIDS-aware, supporting both arbitrary pipelines and providing

an accessible entrypoint for neuroimaging;

- ii executes both bare-metal workflows and Docker or Singularity virtualized pipelines through Boutiques on local, HPC, and cloud resources;
- iii supports the parallelized batch deployment and redeployment of pipelines constructed with workflow-engines, while being agnostic to programming language and construct;
- iv captures system-level provenance information (i.e., CPU and RAM usage), supports Reprozip, and internal provenance captured by arbitrary pipelines such as NIDM; and
- v supports the deployment of both development- and production-level tools without an active server, and provides a web-report for exploring and sharing experiments.

A typical workflow using Clowdr is summarized in Figure Ch.I - 1. While a Clowdr experiment follows the same workflow as traditional experiments, beginning with tool and data curation through prototyping, deployment, and exploration, there are several considerable benefits provided by Clowdr over traditional approaches. In particular, Clowdr is based on the rich Boutiques framework for tool description and execution, ensuring that documentation, parameter definitions, and real-world parameter values accompany the tool at all times. Clowdr also treats all computing systems the same, from the users perspective, so transitioning from local development of analyses to at-scale systems is seamless, which minimizes errors made during this transition. Clowdr also provides a visualization portal for exploring executions and filtering either based on parameter values or runtime statistics, allowing for quality control of the execution in addition to commonly used quality control of processed derivatives themselves.

Figure Ch.I - 2 shows the execution lifecycle within Clowdr. Starting from user-provided Boutiques descriptor (B) and invocation(s) (C), and access to any required datasets, Clowdr begins by identifying a list of tasks to launch. For a new experiment, tasks are identified in one of three main ways: (1) a one:one mapping from a list of invocations, (2) a one:many mapping from a single invocation in which parameter(s) have been specified for sweeping during execution, or a BIDS-specific, and (3) one:many mapping from a single invocation for a BIDS app, which will iterate upon the participant- and session-label fields, and described in the BIDS app specification<sup>10</sup>. Experiments can be re-run, and determine the task-list based on whether a full, failure-only, or incomplete-only re-execution is desired. Once the task-list is determined, Clowdr creates an independent invocation which explicitly defines the arguments used in each task.



**Figure Ch.I - 2. (A)** Clowdr Data Flow. Beginning with a user-supplied tool descriptor **(B)** and parameter invocation(s) **(C)**, Clowdr identifies unique tasks to launch and wraps each with usage and log monitoring tools, to ultimately provide a rich record of execution to the user alongside the expected output products of the experiment. Clowdr ultimately produces an HTML summary for users to explore, update, filter, and share the record of their experiment. In the above schematic, blue boxes indicate data, where gray indicate processing steps. \*External reprozip tracing is supported on limited infrastructures, as running virtualized environments within a trace capture requires elevated privileges which may be a security risk on some systems.

At this stage, Clowdr distributes tasks to the Cloud system or local cluster scheduler being used for deployment. Presently Clowdr supports the SLURM scheduler and Amazon Web Services (AWS) cloud through their Batch service with adoption of more platforms ongoing. Each task is launched through



a Clowdr-wrapper, which initializes CPU and RAM monitoring and triggers Reprozip tracing prior to launching the analysis itself. Reprozip tracing has limited support in conjunction with containerized analyses on HPC systems due to potential security issues. Reprozip is built upon the Linux command “ptrace,” which traces processes to monitor or control them. To eliminate the potential risk of using this tool, it is common for systems to disallow the tracing of administrator-level processes. The requirement of limited administrator privileges by Singularity (during the creation of multiple user namespaces) and Docker (for interacting with the daemon) makes encapsulating these tools within the restricted ptrace scope not possible on many shared systems. For more information on the specific conditions in which these technologies can be made to interoperate please view the GitHub repository for this manuscript, linked below.

Upon completion of the analysis, Clowdr bundles the system monitored records, standard output and error, exit status, and any other information collected by either the tool itself or the Boutiques runtime engine, and concludes its execution. Once the experiment has begun, Clowdr provides the user with the Clowdr provenance directory which will be updated automatically as executions progress.

The researcher can monitor the provenance directory using the Clowdr share portal (Figure Ch.I - 3), which provides a web interface summarizing the task executions. Once the analysis concludes, the figures on this web page and the associated metadata can be saved and serve as a record of the experiment either for evaluation or dissemination alongside published results.

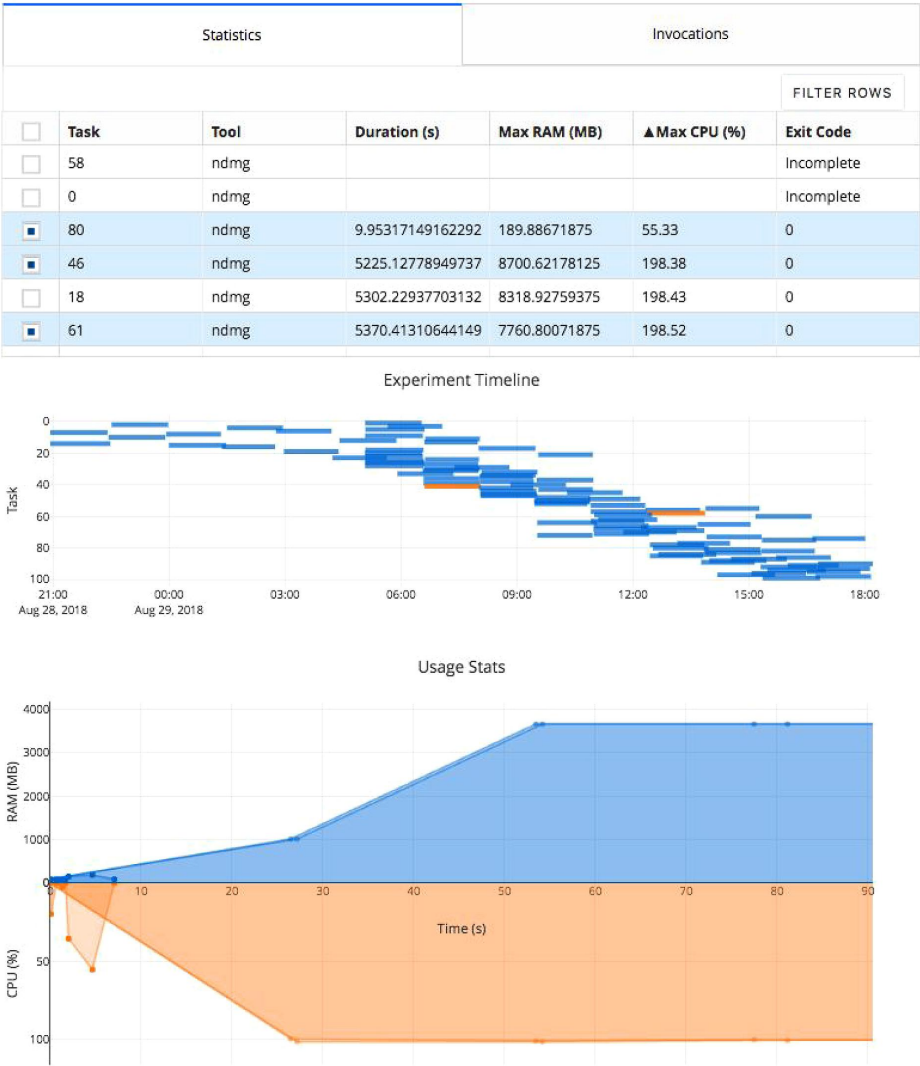
The Clowdr package is open-source on GitHub<sup>41</sup>, and installable through the Python Package Index.

## **Ch.I - 4 Performing Experiments With Clowdr**

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Here, we explore an experiment in which we used Clowdr to process the Human Connectome Project (HCP)<sup>3</sup> dataset with a structural and functional connectome estimation pipeline, ndmg<sup>40</sup>. The records of this experiment, and materials and instructions that can be used to reproduce a similar analysis with Clowdr using the publicly available DS114 BIDS dataset<sup>14</sup> and the example BIDS application<sup>10</sup> can be found on Github at: <https://github.com/clowdr/clowdr-paper>. Specific packages and their versions for both experiments can be found at the end of this manuscript.

As summarized above, performing an analysis with Clowdr requires the creation of a Boutiques descriptor summarizing the pipeline of interest, an invocation containing the parameters to supply to this pipeline on execution, and curation of the data to be processed. There are several utilities in Boutiques



**Figure Ch.I - 3.** Clowdr Experiment Viewer. Experiments launched with Clowdr can be monitored and both progress and runtime statistics explored. The page is produced using Plotly Dash to produce highly interactive plots and tables, enabling rich filtering, rescaling, and exploration of executions. The table can be toggled to present summary statistics about experiment execution or invocation parameters identifying parameters used for each task in the experiment. The subsequent Gantt plot shows the timeline of executed tasks in the experiment, where those selected for visualization in the usage plot below are highlighted. The final plot in this view shows the memory and processing footprint throughout all selected tasks. Selection and filtering may be done by value in the tables or selection in the task timeline. In this example, several tasks did not complete and one appeared to exit after 10 s erroneously. The Clowdr portal enables quick identification of these outliers, and the table view can be switched to identify more information such as parameters pertaining to the executions of interest. For more information about the pipeline being executed in particular, please see<sup>40</sup>.

which aid in this setup process, including to automatically generate a descriptor and sample inputs from a tool, and can be explored in the associated documentation<sup>11</sup>.

Clowdr experiments can be launched locally, on cluster, or submitted to cloud resources. In each case, invocations and task definitions are created locally, and then the jobs are run serially, submitted to a cluster queue, or pushed to cloud storage and called remotely. The commands used in Clowdr to launch these commands are the local, local with the cluster switch, and cloud modes, respectively. Upon completion of each tasks, summary files created by Clowdr can be either inspected manually or consolidated and visualized in the web with the Clowdr share command (Figure Ch.I - 3).

The share tool, launchable on any computer with access to the experiment, creates a lightweight web service displaying summary statistics and invocation information from the experiment, including memory usage, task duration, launch order, and log information. The visualizations provided are filterable and sortable, enabling users to interrogate and identify outliers in their experiment, explore potential sources of failure, and effectively profile the analysis pipeline in use. The modified figures can be downloaded from this interface, serving as accessible records of execution.

In the example above, the HCP dataset has been processed using a pipeline performing image denoising, registration, model fitting, and connectivity estimation, all of which are commonly used processing steps in neuroimaging. For more information on this pipeline, please see<sup>40</sup>.

In this experiment the table has been filtered to show several tasks which appeared spurious in their execution compared to the others. We can see that several tasks failed to complete and one appeared to terminate in significantly less time than the others. After identifying these tasks and exploring the time series' to see at what stage of processing the job failed (in this case, immediately), we can investigate parameter selections used in each and attempt the re-execution of these jobs using the local or cloud command with the rerun switch in Clowdr. Clowdr provides a layer of quality control on executions, in addition to that which is regularly performed by researchers on their datasets, which provides immediate value when identifying task failures which otherwise may be difficult to identify, especially in cases which intermediate and terminal derivatives are written to the same location, which can often be the case with transformations estimated by registration pipelines, for example.

While the share tool currently requires maintaining an active server, the plots can be exported statically and it is in the development roadmap to enable exporting the entire web page as static files, as discussed here: <https://github.com/plotly/dash/issues/266>. Since the record created by Clowdr is stored in the machine-readable and JSON format, researchers can easily extract their records and

integrate it into other interfaces that suit their application.

## Ch.I - 5 Discussion

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Clowdr addresses several barriers to performing reproducible neuroscience. Clowdr experiments consist of enclosed computational environments, versioned-controlled Boutiques-described tools with explicit usage parameters, rich execution history, and can be re-executed or distributed with minimal effort. Clowdr provides an accessible interface for initially running analyses locally, and translating them seamlessly to HPC environments. The rich record keeping provided with Clowdr is system-agnostic resulting in uniformly interpretable summaries of execution. As a Python library, Clowdr can be used as a module in a larger platform, or directly as a command-line tool.

Clowdr uniquely packages an executable tool summary, parameters, and results together, in a language- and tool-agnostic way, and therefore, greatly increases the transparency and shareability of experiments. Importantly, this adds clarity to experimental failures and documents the hyper-parameter tuning process of experiments, which has been historically largely undocumented in literature<sup>42</sup>.

There are several axes upon which the value of Clowdr can be discussed. In particular: lines of code written, time spent, and the ultimate re-runability of analyses. While these remain subjective areas for comparison, we can conceptually consider a workflow dependent on Clowdr to those constructed with traditional scripting, workflow engines (WEs), and software-as-a-service (SaaS) platforms.

Where Clowdr has been built upon tools and standards to provide users with a series of single-commands for launching and managing analyses, accomplishing a similar result with traditional scripting would take considerably more lines of code and time. Similarly, where command-line execution may be similar in complexity to tools developed with WEs, their integration within tools requires substantial development and is only practical in cases for which there is a WE written in the same language as the underlying application. SaaS platforms provide a similar type of abstraction to Clowdr, where tools are treated as black-box objects, but come with the added overhead of maintaining complex database architectures, often complex integration of tools, and primarily restrict access through web-based interfaces which leads to reduced flexibility for the user.

The clear benefit of Clowdr is in the simplicity it provides for identifying outliers or failed tasks and either re-launching specific subsets of an analysis or the entire experiment. Clowdr records and visualizes detailed logging information about executions and the specific instructions which were used, which isn't

guaranteed in either traditional scripting or WE-based applications. To replicate this feature across these systems, tools which (1) record execution instructions, (2) identify parameters used for parallelization, (3) produce summary plots, and (4) reconstruct and (5) re-execute instructions would require development.

While SaaS platforms often contain these features, an additional limitation of large platforms is that they are often designed for consumers of widely adopted tools consumers rather than tool developers. Clowdr fills the void between these types of pipeline deployments by providing a programmatic tool-independent method for managing job submission and collecting provenance across multiple architectures and enabling the rapid prototyping of analyses.

Several immediate applications of the provenance information captured by Clowdr include the benchmarking of tools, and resource optimization during the selection of cloud resources, as was done in<sup>19</sup>. While the value of comparing provenance records has not been demonstrated here, other studies such as<sup>43</sup> have demonstrated the efficacy of leveraging provenance information to identify sources of variability or instability within pipelines.

Future work includes adopting a W3C-PROV compatible format for Clowdr provenance records, increasing the machine-readability and interoperability of these records with other standards such as NIDM. Integrating the reports produced by Clowdr with a system such as Datalad would allow for record versioning and more strictly enforce the complete reporting of experiments. Clowdr will also continually be extended with greater testing and support for more HPC schedulers, clouds, and provenance capture models.

## **Tools and Versions**

The following is a list of tools and data used in this manuscript, and their respective versions. The architecture and analysis presented for the Clowdr package corresponds to version 0.1.0. The key Python packages and specific versions tested are: boutiques (version 0.5.12), boto3 (1.7.81), botocore (1.10.81), slurmpy (0.0.7), psutil (5.4.7), pandas (0.23.4), plotly (3.1.1), and plotly dash (0.24.1), including dash-core-components (0.27.1), dash-html-components (0.11.0), dash-renderer (0.13.0), dash-table-experiments (0.6.0), and flask (0.12.2). Executions were tested locally using Docker (17.12.0-ce), and on Compute Canada's Cedar high performance cluster using Singularity (2.5.1-dist). The Docker container used for ndmg can be found on Docker hub as neurodata/m3r-release (0.0.5), which contains ndmg (0.1.0-f). The Singularity container used was pulled and dynamically created from this Docker hub endpoint. The dataset use was a subset of the HCP 1200 collection<sup>3</sup>.

## Author Contributions

GK designed and developed the tools, experiments, and figures, and wrote the majority of the manuscript. SB supported the design and development processes, and edited the manuscript and provided valuable feedback. TG provided insight and contributed to the design and development of the tools and experiments, and contributed to writing the manuscript. AE edited the manuscript and provided valuable feedback. TG and AE jointly supervised this project.

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## Conflict of Interest Statement

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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## Ch.II: Comparing Perturbation Models for Evaluating Stability of Neuroimaging Pipelines

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**Abstract**

With an increase in awareness regarding a troubling lack of reproducibility in analytical software tools, the degree of validity in scientific derivatives and their downstream results has become unclear. The nature of reproducibility issues may vary across domains, tools, datasets, and computational infrastructures, but numerical instabilities are thought to be a core contributor. In neuroimaging, unexpected deviations have been observed when varying operating systems, software implementations, or adding negligible quantities of noise. In the field of numerical analysis these issues have recently been explored through Monte Carlo Arithmetic, a method involving the instrumentation of floating point operations with probabilistic noise injections at a target precision. Exploring multiple simulations in this context allows the characterization of the result space for a given tool or operation. In this paper we compare various perturbation models to introduce instabilities within a typical neuroimaging pipeline, including i) targeted noise, ii) Monte Carlo Arithmetic, and iii) operating system variation, to identify the significance and quality of their impact on the resulting derivatives. We demonstrate that even low-order models in neuroimaging such as the structural connectome estimation pipeline evaluated here are sensitive to numerical instabilities, suggesting that stability is a relevant axis upon which tools are compared, alongside more traditional criteria such as biological feasibility, computational efficiency, or, when possible, accuracy. Heterogeneity was observed across participants which clearly illustrates a strong interaction between the tool and dataset being processed, requiring that the stability of a given tool be evaluated with respect to a given cohort. We identify use cases for each perturbation method tested, including quality assurance, pipeline error detection, and local sensitivity analysis, and make recommendations for the evaluation of stability in a practical and analytically-focused setting. Identifying how these relationships and recommendations scale to higher-order computational tools, distinct datasets, and their implication on biological feasibility remain exciting avenues for future work.

## Ch.II - 1 Introduction

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A lack of computational reproducibility<sup>1</sup> has become increasingly apparent in the last several years, calling into question the validity of scientific findings affected by published tools. Reproducibility issues may have numerous sources of error, including undocumented system or parametrization differences and the underlying numerical stability of algorithms and implementations employed. While containerization can mitigate the extent of machine-introduced variability, understanding the effect that these sources of error have on the encapsulated numerical algorithms remains difficult to explore. In simple cases where algorithms are differentiable or invertible, it is possible to obtain closed-form solutions for their stability. However, as software pipelines grow, containing multiple complex steps, using non-linear optimizations and non-differentiable functions, the stability of these algorithms must be explored empirically.

As neuroscience has evolved into an increasingly computational field, it has suffered from the same questions of numerical reproducibility as many other domains<sup>2</sup>. In particular, neuroimaging often attempts to fit alignments, segmentations, or models of the brain using few samples with variable signal to noise properties. The nature of these operations leaves them potentially vulnerable to instability when presented with minor perturbations in either the data themselves or their processing implementations. The independent evaluation of atomic pipeline components may be feasible in some cases, as was done by Skare et al. in<sup>3</sup>. Here, the authors computed the theoretical conditioning of various tensor models used in diffusion modeling, and compared these values to the observed variances in tensor features when fit on simulated data. While approaches like the above provide valuable insights to algorithms and their implementations independently, the impact of these stepwise instabilities within composite pipelines remains unknown. Even if one were able to evaluate each step within a pipeline, identifying the impact these instabilities may have on a result when composed together, both structurally and analytically, remains practically difficult to evaluate. Additionally, as datasets grow in size, the adoption of High Performance Computing environments becomes a necessity. These environments are highly heterogeneous in terms of hardware, operating systems, and parallelization schemes, and this heterogeneity has been shown to compound with these instabilities and impact results<sup>4</sup>.

Various forms of instability have been observed in structural and functional magnetic resonance (MR) imaging, including across operating system versions<sup>4</sup>, minor noise injections<sup>5</sup>, as well as dataset or implementation of theoretically equivalent algorithms<sup>6,7</sup>. These approaches may have practical applications in decision making, such as deciding which tool/implementation should be used for an experiment.

However, they are relatively far removed from the underlying numerical instabilities being observed. Recent advances in numerical analysis allow for the replacement of floating point operations with Monte Carlo Arithmetic simulations<sup>8</sup> which inject a random zero-bias rounding error to operations for a target floating-point precision<sup>8,9</sup>. This method can be used for evaluating the numerical stability of tools by wrapping existing analyses<sup>9</sup> and providing a foothold for scientists wishing to explore the space of their pipeline's compound instabilities<sup>10</sup>.

In this paper we explore the effect of various perturbations on a typical diffusion MR image processing pipeline through the use of i) targeted noise injections, ii) Monte Carlo Arithmetic, and iii) varying operating systems to identify the quality and severity of their impact on derived data. This evaluation will inform future work exploring the stability of these pipelines and downstream analyses dependent upon them. The processing pipeline selected for exploration is Dipy<sup>11</sup>, a popular tool that generates structural connectivity maps (connectomes) for each participant. The pipeline accepts de-noised and co-registered images as inputs, and then performs two key processing steps: tensor fitting and tractography. We demonstrate the relative impact that each of the tested perturbation methods has on the resulting connectomes and explore the nature of where these differences emerge.

## **Ch.II - 2 Methods**

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All processing described below was run using servers provided by Compute Canada. Software pipelines were encapsulated and run using Singularity<sup>12</sup> version 2.6.1. Tasks were submitted, monitored, and provenance captured using Clowdr<sup>13</sup> version 0.1.2-1. All code for performing the experiments and creating associated figures are available on GitHub at <https://github.com/gkiar/stability> and <https://github.com/gkiar/stability-mca>, respectively.

### **Ch.II - 2.1 Dataset and pre-processing**

The dataset used for processing is a 10-session subset of the Nathan Kline Institute Rockland Sample dataset (NKI-RS)<sup>14</sup>. This dataset contains high fidelity structural, functional, and diffusion MR data and is openly available for research consumption. The 10 sessions used were chosen by randomly selecting 10 participants and selecting their alphabetically-first session of data. This data was preprocessed prior to the modelling evaluated here using a standard de-noising and image alignment pipeline<sup>15</sup> built upon the FSL toolbox<sup>16</sup>. The steps in this pipeline include eddy current correction, brain extraction, tissue segmentation, and image registration. The boundary between white and gray matter was obtained by computing the

difference between a dilated version of the white matter mask and the original. Data volumes at this stage of processing are four-dimensional and variable in spatial extent (first three dimensions) with a fixed number of diffusion directions (fourth dimension), totalling approximately  $100^3 \times 137$  voxels in each case.

## Ch.II - 2.2 Modeling

After pre-processing the raw diffusion data using FSL, structural connectomes were generated for an 83-region cortical and sub-cortical parcellation<sup>17</sup> using Dipy<sup>11</sup>. A six-component tensor model was fit to the diffusion data residing within white matter. Seeds were generated in a  $2 \times 2 \times 2$  arrangement for each voxel within the boundary mask, resulting in 8 seeds per boundary voxel. Deterministic tracing was then performed using a half-voxel step size, and streamlines shorter than 3-points in length were discarded as spurious. Once streamlines were generated they were traced through the parcellation. Edges were added to the graph corresponding to the end-points of each fiber, and were weighted by the streamline count. This pipeline was implemented in Python, including a few components in Cython, and relies on the Numpy library for a large proportion of operations. Each resulting network is a square connectivity matrix of  $83 \times 83$  edges, as shown in Fig. Ch.II - 1. This pipeline was chosen as it is both common and simple relative to many alternatives.

## Ch.II - 2.3 Stability Evaluation

Targeted and Monte Carlo perturbation modes were tested 100x per image. Noise was represented by percent deviation of the Frobenius norm of a resulting connectome from the corresponding reference (no noise injection). A deviation of 50% indicates that the norm of the difference between the noisy and reference networks is 50% the size of the norm of the reference graph. This is formalized below in Eq. (1):

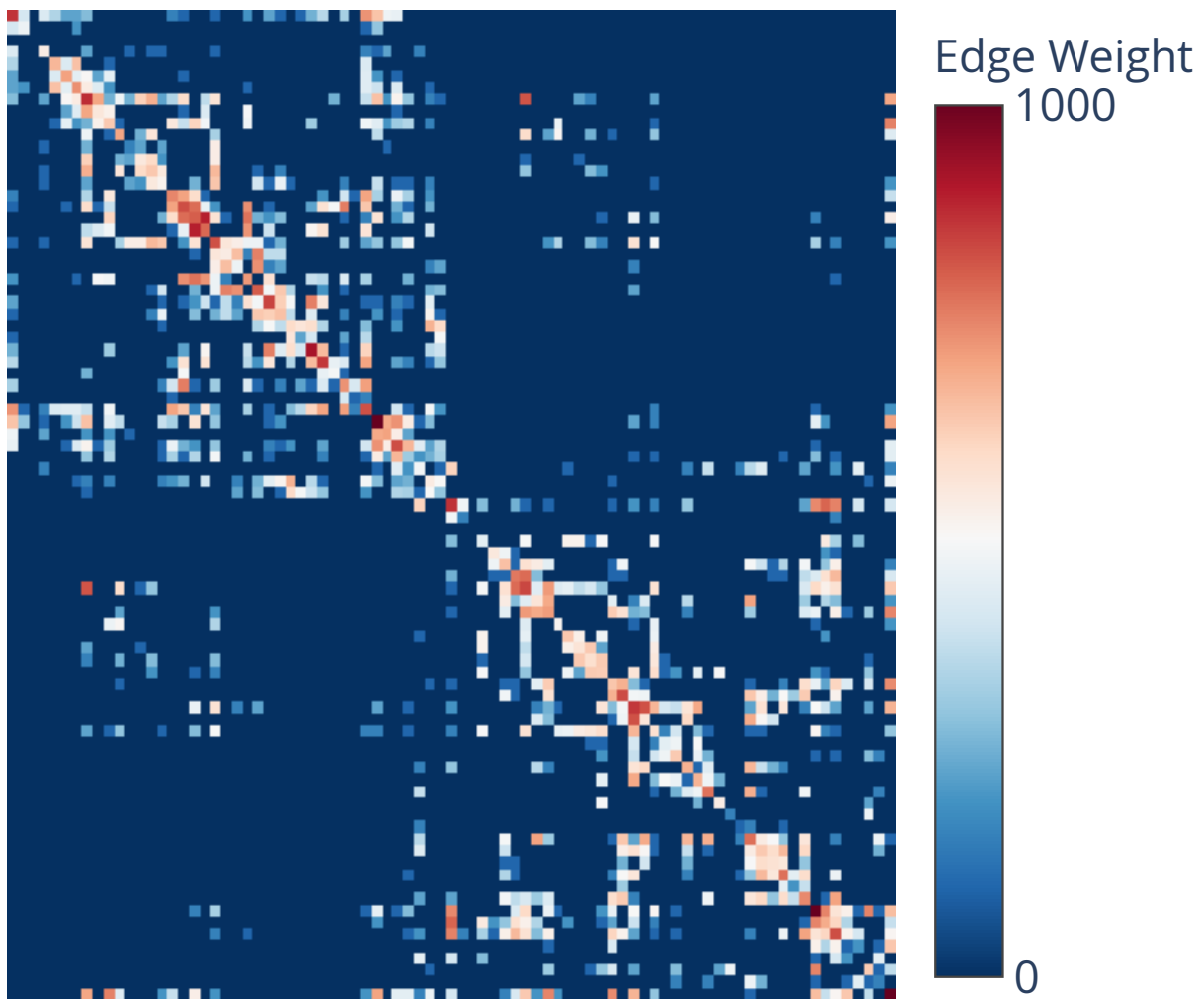
$$\%Dev(A,B) = \sqrt{\sum_{i=1}^m \sum_{j=1}^n |a_{ij} - b_{ij}|^2} / \sqrt{\sum_{i=1}^m \sum_{j=1}^n |a_{ij}|^2}, \quad (1)$$

where  $A$  is the reference graph,  $B$  is the perturbed graph, and  $a_{ij}$  is an element therein at row  $i$  and column  $j$ .

The perturbation methods evaluated, presented below, are summarized in Table Ch.II - 1.

## Ch.II - 2.4 Subject-Level Variation

Comparison between subjects will be used as a reference error. If the differences observed by other methods are similar in magnitude to the subject-level difference, then the validity of the processed



**Figure Ch.II - 1. Example connectome.** Each row and column corresponds to a region within the brain, and the intersection a connection between them. If no connection is found between regions, the edge strength is zero. If a streamline is found to connect two regions, the weight is incremented by 1. The resulting weights are the sum of all observed connections for every streamline traced within a brain image.

networks for use in downstream phenotypic analysis becomes questionable as subjects cannot be reliably distinguished from one another. This error is computed as the pairwise distance between all 10 subjects included in this cohort.

## Ch.II - 2.5 Targeted Noise

The goal of targeted noise was to inject data perturbations sufficiently small that the resulting images would be indistinguishable from the original. This is meant to test the lower-bound of noise sensitivity for processing pipelines. The type of targeted noise used here will be referred to as 1-voxel noise and is similar to the method employed in<sup>5</sup>. In our case, the intensity of a single voxel in the defined range will be scaled based on a scaling factor. The voxels modified in this case were randomly generated within the mask of brain regions being modeled by the pipeline.

The two modes of 1-voxel noise injection tested here were: a) a single voxel per entire image of size  $(X, Y, Z, D)$  (approximately  $100^3 \times 137$  for all images), or b) a single voxel per 3D volume of size  $(X, Y, Z)$  (approximately  $100^3$  for all images), and are referred to as “single” and “independent” modes, respectively. While the number of perturbed voxels in the independent case is approximately 100 times larger, the intensity of magnification was consistent as in both cases the original voxel intensities were doubled.

## Ch.II - 2.6 Monte Carlo Arithmetic

Verificarlo<sup>10</sup> is an extension of the LLVM compiler which automatically instruments floating point operations at build-time for software written in C, C++, and Fortran. Once compiled with Verificarlo, the Monte Carlo emulation method and target precision can be set as environment variables. For all simulations a rounding error on the least significant floating point bit in the mantissa (bit 53) was introduced. The simulations were computed using the custom QUAD backend which is optimized to reduce computation time over the traditional mcalib MPFR backend leveraging GNU’s multiple precision library<sup>9</sup>. Noise through Verificarlo can be injected as “Precision Bounded”, simulating floating point cancellations, “Random Rounding”, simulating only rounding errors on computation, and “MCA”, which includes both of these modes. A particularity of the Random Rounding mode is that it only injects rounding noise on inexact floating-point operations (i.e. operations that have a rounding error in IEEE-754 at the target precision). Therefore, RR mode preserves the original exact operations, it is a more conservative noise simulation. We used both the RR and MCA modes of simulation.

Verificarlo was used to instrument tools in two modes we will refer to as “Python” and “Full Stack”. In the Python instrumentation, the core Python libraries were recompiled with Verificarlo as well as any subsequently installed Cython libraries. In the Full Stack instrumentation, BLAS and LAPACK were also recompiled, meaning that Numpy, a dominant Python library for linear algebra, was also instrumented. The Full Stack implementation did not run successfully using the MCA mode. We suspect that some libraries



require exact floating-point operations or are sensitive to cancellation errors, so only the Random Rounding (RR) mode was able to be evaluated for the Full Stack. These instrumentations took approximately 10 hours for the authors to refine, and the images are available on DockerHub at [gkiar/fuzzy-python](https://gkiar/fuzzy-python).

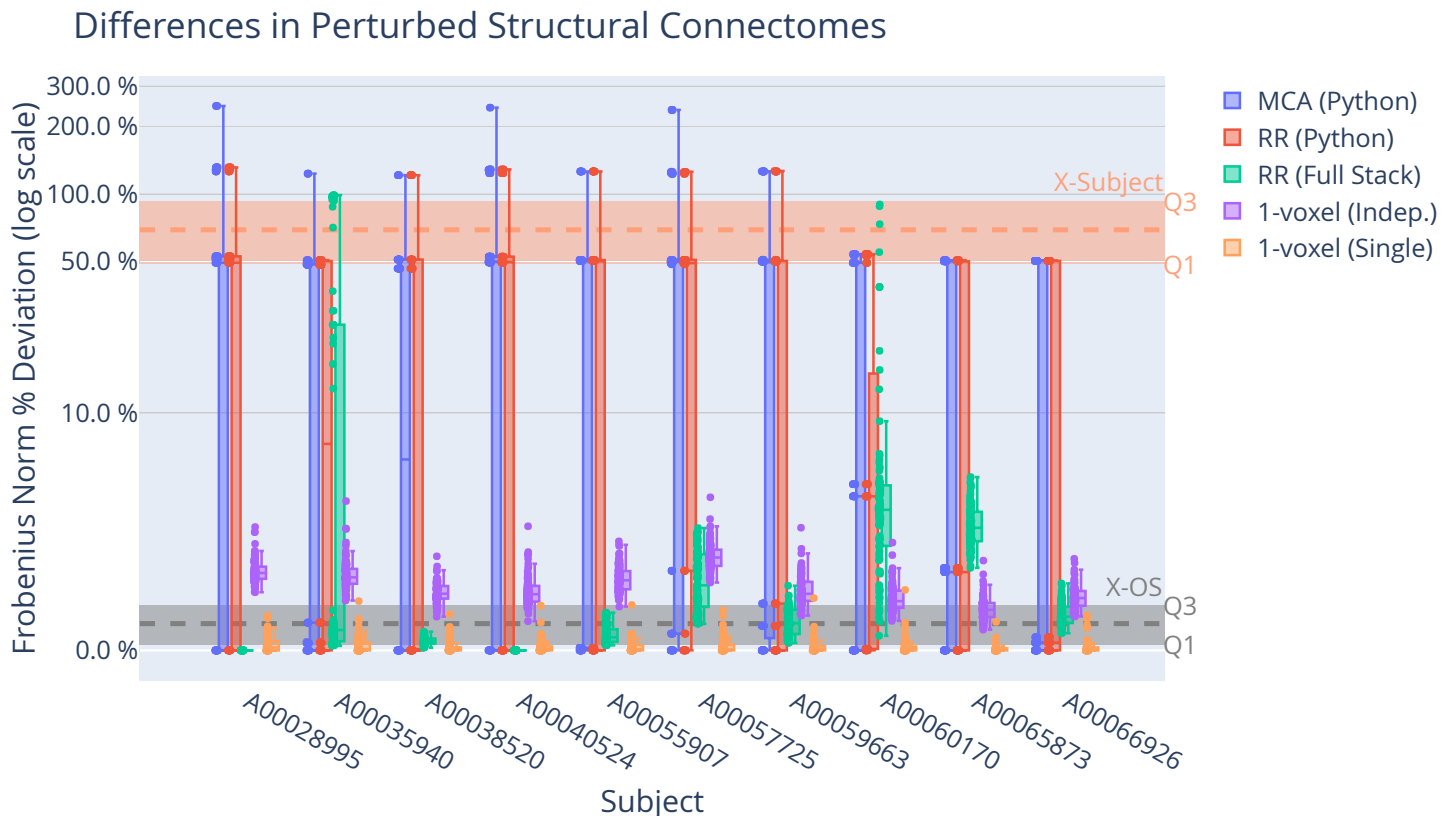
## Ch.II - 2.7 Operating System Variation

Operating system noise was evaluated across Alpine Linux 3.7.1 and Ubuntu 16.04. Alpine is a lightweight distribution which comes with minimal packages or libraries, and Ubuntu is a popular Linux distribution with a large user and development community. Alpine was chosen as its lightweight nature makes it an efficient choice for the packaging and distribution of libraries in containers for scientific computing, reducing the overhead of shipping code towards data sources. Ubuntu was chosen due to its high adoption and community support by major libraries. While Alpine comes with a minimal set of libraries, a core difference between these systems as noted by DistroWatch (<https://distrowatch.com/>) is their dependence on a different version of the Linux kernel. While numerical differences between operating systems are likely the result of compilers<sup>18</sup> and installed libraries, the purpose of testing across operating systems explicitly rather than combinations of specific tools is to re-create a real-world setting in which typical scientific users observe numerical differences across equivalent high-level pipelines.

Ubuntu was used as the base operating system for all simulations other than this comparison. The variability observed across operating systems was aggregated across participants and included as a reference margin of error.

**Table Ch.II - 1.** Description of perturbation modes

| Permutation | Description  |
|-------------|--|
| X-Subject   | Pairwise comparison of sessions based on <b>Subject ID</b> .   |
| 1-voxel     | Intensity value doubled for either <b>Single</b> (one voxel in entire 4D volume) or <b>Independent</b> (one voxel per 3D sub-volume) voxels. |
| MCA         | Simulation of all floating point operations in <b>Python</b> (Python and Cython-compiled libraries).   |
| RR          | Simulation of all rounding operations in <b>Python</b> or the <b>Full Stack</b> (BLAS, and LAPACK, Python and Cython-compiled libraries).    |
| X-OS        | One of <b>Ubuntu 16.04</b> or <b>Alpine 3.7.1</b> .  |



**Figure Ch.II - 2. Comparison of perturbation modes.** As evaluated by the percent deviation from reference in the Frobenius Norm of a resulting connectome, each of the 10 processed subjects were re-processed 100 times for each perturbation method. We see that the MCA and RR (Python) methods resulted in distinct modes for the outputs in all cases reaching extreme deviations equivalent to cross-subject variation. The RR (Full Stack) method shows high variability across subjects, and only reaching cross-subject variation in the case of 2 subjects. The 1-voxel methods result in considerably less deviation from reference, and are more consistent across subjects than the RR (Full Stack) method.

## Ch.II - 2.8 Aggregation of Simulated Graphs

To structurally evaluate each simulation setting, connectomes were aggregated within setting and subject combinations. Several aggregation methods were explored to preserve various sensitivity and stability properties across the aggregated graphs. In each case, the operations are performed edge-wise, so the aggregated graph is not guaranteed to be single graph in the set of perturbed graphs. The aggregation operations are the edge-wise mean and the  $0^{th}$  (min),  $10^{th}$ ,  $50^{th}$  (median),  $90^{th}$ , and  $100^{th}$  (max) %-iles. The mean aggregate will include a non-zero weight for every edge which appears in at least one simulation, and the  $0^{th}$  and  $100^{th}$  %-iles will include the lowest and highest observed weight for every

edge, respectively. The 90<sup>th</sup>, 50<sup>th</sup>, and 10<sup>th</sup> %-iles increasingly aggressively filter edges based on their prominence across simulations. The combination of percentile aggregates also enable isolation of the most spurious edges, such as by taking the difference of maximum and minimum aggregates. A volatile aggregate was created to this effect which consists of edges which are found in the maximum aggregate but not the minimum aggregate. Note that in this case, the weight for these edges is not implied and can be defined as an alternative function of the graph collection, such as mean, but as the weight does not appear when comparing binary edges, no recommendation for this weighting is made here.

## Ch.II - 3 Results

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All perturbation modes were applied to either the input data or post-processing pipeline described in the Section [Ch.II - 2.2](#), and were evaluated according to Eq. (1).

### Ch.II - 3.1 Perturbation Induced Differences

Fig. [Ch.II - 2](#) shows the percentage deviation for each simulation mode on 10 subjects. Introduced perturbations show highly-variable changes in resulting connectomes across both the perturbation model and subject, ranging from no change to deviations equivalent to difference typically observed across subjects. For the 10 subjects tested, we see that the Python-instrumented MCA and RR pipelines resulted in the largest deviation from the reference connectome. In these cases we also see that the results are modal, where each subject has discrete states that may be settled in, some of which result in deviations comparable to subject-level noise. This modality is likely due to minor differences introduced at crucial branch-points which then cascaded throughout the pipeline. This hypothesis is supported by observing that the Full Stack implementation with RR perturbations shows a continuous distribution of differences that are highly variable in intensity, ranging from no deviation to subject-level in some cases for some subjects, which are explored in Section [Ch.II - 3.2](#).

The 1-voxel independent mode unsurprisingly produces larger changes than the 1-voxel single mode. These changes are larger than or comparable to operating system variability, respectively, resulting in small deviations from the reference, and are relatively minor in comparison to the extremes observed with Monte Carlo Arithmetic. Operating system deviations are very low or even zero in some cases. In all perturbation settings we can see that there is large variability both across simulations on the same data and across subjects.

### Ch.II - 3.2 Progression of Deviations in a Continuous Setting

In the case of subject A00035940, the Full Stack RR perturbations led to a continuous distribution of outputs, ranging in difference from none to subject-level from the reference. Fig. Ch.II - 3 explores the progression of these deviations by visualizing the difference-connectome for samples along various points of this distribution. In the center we show the reference connectome, and surrounding it the difference graph for a simulated sample with labelled *%Dev* from this reference. In this case, we can see a progression of structurally consistent deviations. In particular, edges corresponding to regions in the left hemisphere become increasingly distorted (bottom-right portion of the connectome), whereas the within-hemisphere connectivity for the right hemisphere (top-left portion) remains largely intact in all cases except the extreme difference case. We notice in all cases that the connectivity between regions is decreasing until the edges disappear entirely. While this behaviour is not consistent across all subjects, this observation suggests a peculiarity in the quality of data in this region for the subject in question. This could be due to artifacts caused by motion or other factors, ultimately reducing the stability of modeling connectivity in this region.

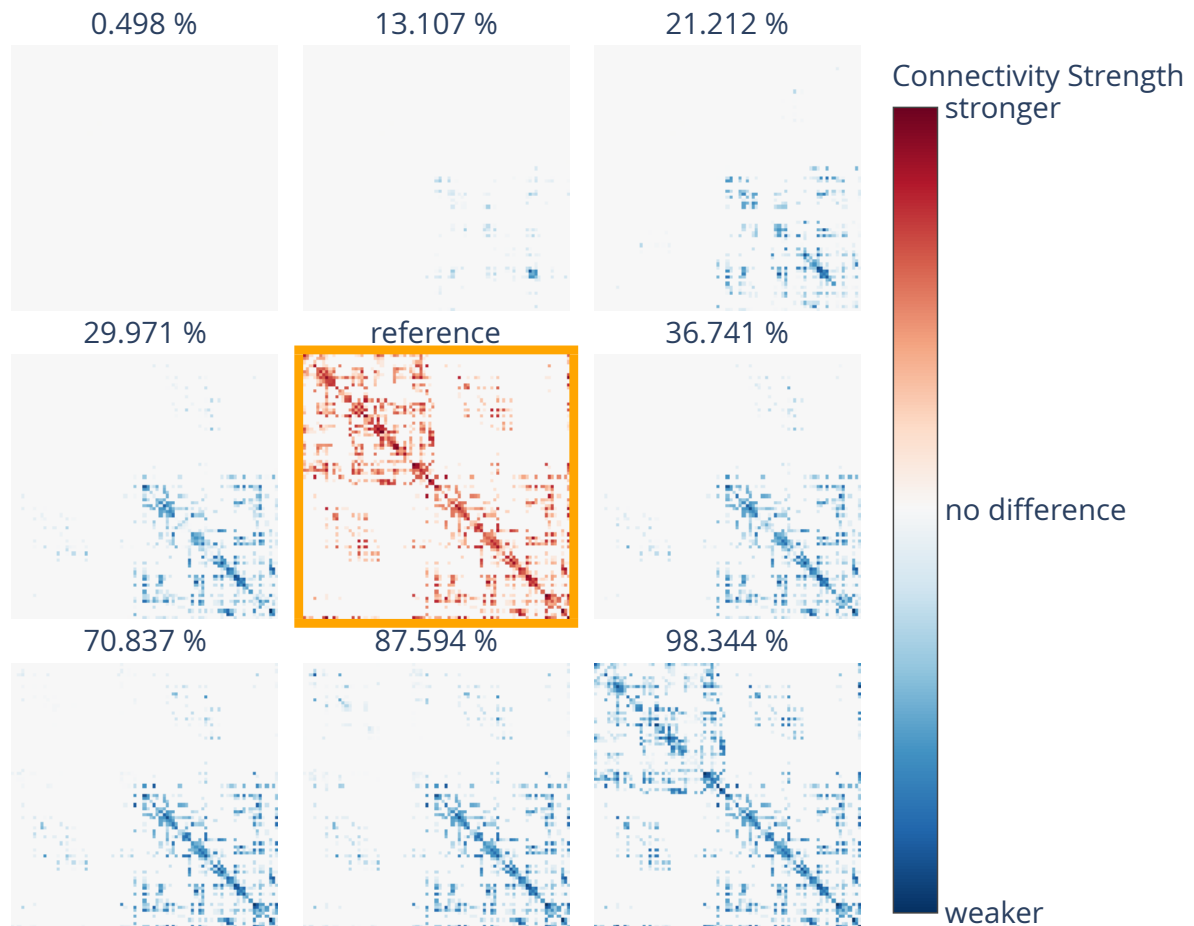
### Ch.II - 3.3 Structural Properties of Introduced Perturbation

While the case investigated above notably showed a significant degradation of regional signal quality for Full Stack RR noise in a single subject, Fig. Ch.II - 4 explores the relative change in connectivity from the reference for each perturbation mode and subject. Edges in the presented graphs are weighted by their standard deviation across all simulations for that participant, and coloured as positive or negative deviations based on whether the mean weight for all simulations was greater or lower than the reference weight, respectively. All edges with a standard deviation of 0 across all simulations were greened out for clarity.

For the Python instrumented MCA and RR implementations, edge weight was generally inflated non-specifically for existing edges in the reference connectome for all subjects. The Full Stack RR implementation shows significant variability across subjects, where the number of affected edges ranges from none to all. In each case where there exists some deviation, intensities appear to be spatially linked, suggesting the differences may be due to variable quality in the underlying data. In this case, Monte Carlo Arithmetic may have served to shed light on poor signal-to-noise properties present within regions of the images being modelled.

For 1-voxel noise, the differences introduced across independent injections impacted a larger portion

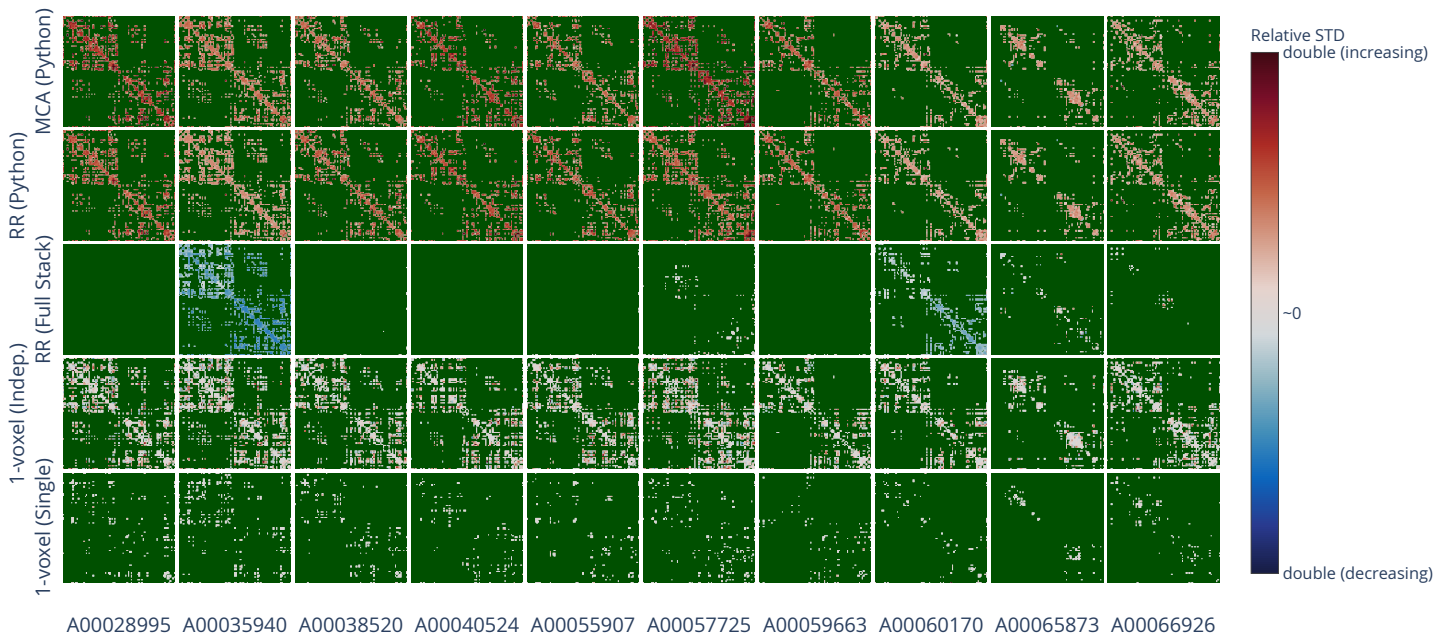
## Error-Induced Deviations from Reference Connectome



**Figure Ch.II - 3. Structure of Deviations.** Shown in increasing deviation from left–right and top–bottom, with the reference in the centre, are the difference connectomes observed for the RR (Full Stack) perturbations of subject A00035940. In this case, the left hemisphere (bottom-right portion of the graph) begins to degrade quickly, eventually reaching an almost complete loss in signal.

of edges than single injections, unsurprisingly. By design (i.e. injection at random locations for each simulation), the deviations appear non-specifically spatially distributed. However, 1-voxel noise could be modified to spatially constrain the location for noise injection regionally, allowing the evaluation of modelling for particular sub-structures within the images.

Structural Differences Across Perturbation Modes and Subjects



**Figure Ch.II - 4. Perturbation introduced structural differences.** The variance of each edge is shown relative to the reference edge strength, and coloured either red or blue based on the mean perturbed weight was higher or lower than that of the reference, respectively. Edges which experienced no variation were coloured as green to be distinct from all edges which experience any variation.

### Ch.II - 3.4 Aggregation Across Simulations

For each simulation method there existed a graph nearly identical to the reference, but the variability introduced by these simulations were highly variable both in terms of the method of perturbation used and the dataset being processed. The aggregation of the simulated graphs into a consensus graph allows features of this variation to be encoded implicitly in connectomes which may be used for downstream analyses. Fig. Ch.II - 5 shows the relative percentage of added and missing edges for each setting across all subjects using a variety of such aggregation methods.

By aggregating the simulated connectomes in a variety of methods, the resulting edges would be a product of applying some filter to the set of observed edges, and succinctly represented in a single graph. While minor deviations in one edge may reduce the strength of connectivity between two strongly linked regions, the addition of a connection between two regions which were previously unconnected may be significant in one aggregation method but ignored in another. In the case of the above example, despite the strength of connectivity remaining low between the newly connected nodes many graph theoretic

measures rely on binarized graphs and may be considerably affected, such as the degree.

We notice that the 1-voxel independent (i.e. single voxel per 3D volume) method shows the most variability across each aggregation method. Where all of the MCA-derived methods perturb the pipeline non-locally, both epsilon-level methods add local noise at arbitrary locations. This distinction seems to manifest in more widely added or knocked-out edges for the 1-voxel cases, as the location of noise may have considerable impact on a multitude of nearby fibers, where MCA methods have a zero-bias noise globally, meaning all deviations from the reference are spurious and due to numerical error rather than the introduction of a systemic change that sheds light on an underlying cascading instability.

Unsurprisingly, the only aggregation method which shows considerable amount of both new and missing edges is the volatile technique, which takes edges that exist in the binary difference of 100<sup>th</sup> and 0<sup>th</sup> percentile graphs, eliminating all extremely stable edges from the graph (i.e. those which exist for the reference and all simulations). While the mean sparsity of the reference graphs is 0.30, meaning 30% of possible connections have non-zero weight on average, the sparsity of the volatile aggregates ranges from 0.005 to 0.130, or, the aggregates contain between 2.5% and 43.0% the number of edges as the reference graphs.

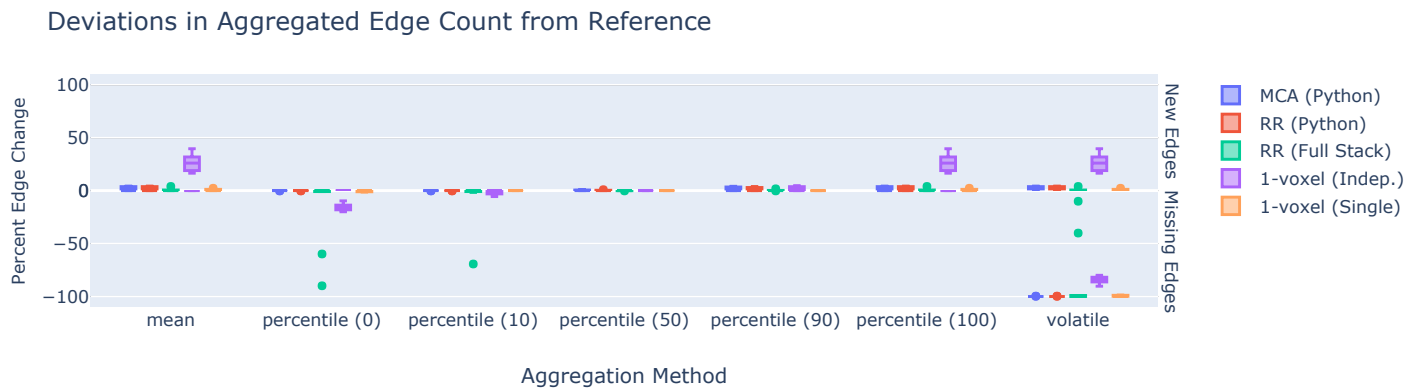
## **Ch.II - 3.5 Comparison of Simulation Performance**

While the application of each perturbation model tested sheds light on different properties of pipeline stability, the resource consumption of these methods has significant bearing when processing data in the context of a real experiment often consisting of dozens to hundreds of subjects worth of data. In this experiment, a single unperturbed pipeline execution took approximately 20 minutes using 1 core and 6 GB of RAM. Fig. Ch.II - 6 shows the relative Time-on-CPU for a single simulation of each method tested, relative to the reference task with no instrumentation. For Monte Carlo Arithmetic instrumented executions, we expect to see a considerable increase in computation time as additional overhead is added to each floating point operation. In the case of 1-voxel noise it is expected to see a minor increase in computation time as the perturbed data volumes were generated at runtime, reducing the data redundancy on disk.

The Python MCA and RR modes show a slight increase in computation time to the reference task, whereas the Full Stack version approaches a nearly 7× slowdown, on average. This discrepancy further supports the hypothesis stated above that floating point logic implemented directly in Python, without the use of Numpy or external libraries, account for a minor portion of the total floating point operations.



As Verificarlo has been shown to increase the runtime of floating point operations by approximately  $100\times$ , this result suggests that the pipeline evaluated here is largely I/O limited. In the case of 1-voxel perturbations, we see a slowdown approximately equivalent to that of the Python instrumentation, not exceeding a  $2\times$  increase. Across all executions approximately 2000 CPU hours were consumed. While this is a small workload in the context of HPC, the required resources quickly reach the order of CPU years after extrapolating to the entire NKI-RS dataset or others in neuroimaging.



**Figure Ch.II - 5. Gain and loss of edges in aggregation of simulations.** The relative gain and loss of edges is shown for each aggregation method and perturbation method in terms of binary edge count. The volatile aggregation is the difference between percentile (100) and percentile (0) aggregates, and is contains all edges which do not appear in every graph. The volatile set of edges for each of MCA (Python), RR(Python), RR (Full Stack), 1-voxel (independent), and 1-voxel (single) contain 2.5%, 2.5%, 18.5%, 43.0%, and 1.7% of the number of edges found in the reference, respectively. In the worst case, 1-voxel (independent), this means that the existence of nearly half the edges in the graph fail to have consensus across the simulations.

## Ch.II - 4 Discussion

We have demonstrated through the application of multiple perturbation methods how noise can be effectively injected into neuroimaging pipelines enabling the exploration and evaluation of the stability of resulting derivatives. These methods operate by either perturbing the datasets or tools used in processing, resulting in a range of structurally distinct noise profiles and distributions which may each provide value when exploring the stability of analyses. While 1-voxel noise is injected directly into the datasets prior to analysis, MCA and RR methods iteratively add significantly smaller amounts of noise to each operation



performed.

In the case of partial (Python) instrumentation with MCA and RR, distinct and considerably distinct modes emerged in all tested subjects. We hypothesize that software branching likely played a role leading to this unexpected result. As the majority of numerical analysis in Python is traditionally performed using the Numpy library, and therefore BLAS and LAPACK, it is possible that the error introduced by Python was allowed to cascade throughout the pipeline without correction, until the next Python branch point occurred and this repeated, eventually growing to the often subject-level differences observed. These modes would then be the result of a small number of instrumented numerically-sensitive operations, leading to a bounded set of possible outcomes of an otherwise deterministic process. It is possible that these distinct modes could serve as upper-bounds for the deviation due to instabilities within a pipeline, and is an area for further exploration. Future work will also more closely instrument libraries with functionality that will enable the identification of crucial branch points, as this functionality is already present within Verificarlo. The identified crucial branch points could be leveraged for the re-engineering of pipelines with more stable behaviour, and potentially shed light on new “best practices”.

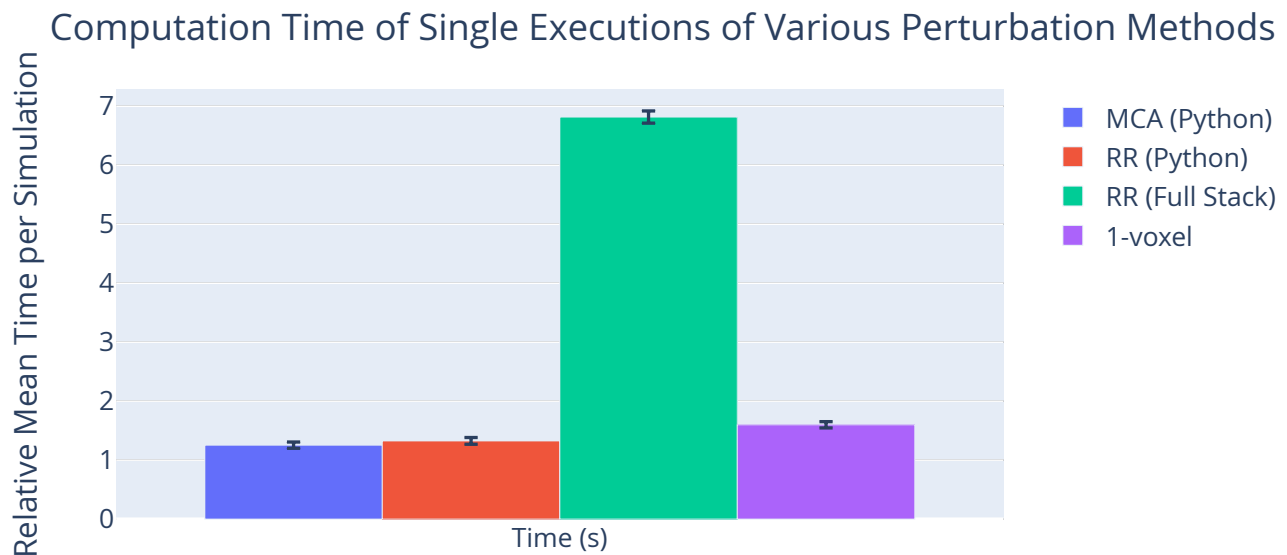
An exciting application of MCA and RR (Python) analyses in cases where pipeline modification is not feasible is the generation of synthetic datasets. Using each mode or an aggregated collection of modes as samples in the MCA-boosted dataset could potentially increase the statistical power of analyses for datasets which may suffer from small samples, or be used to increase the robustness of derivatives by bagging the results using an appropriate averaging technique for the simulated derivatives.

While the Python instrumentation with MCA and RR resulted in derivative modes, the Full Stack instrumentation with RR produced a continuous distribution of derivatives which were often less distinct from the reference results. Extending the hypothesis posited above, this continuous set of results may be due to a law of large numbers effect emerging when performing a considerable number of small perturbations, leading to a normalized error distribution and effectively a self-correction of deviations. Future work will test this hypothesis and consider the relationship between the fraction of instrumented floating point operations and modality, as well as through the incremental profiling and evaluation of tools for the comparison of intermediate derivatives and their deviation from a reference execution. These experiments have potential to provide more insight into the origin of instabilities in scientific pipelines and identify rich optimization targets.

As the significance of RR (Full Stack) perturbation was highly variable across participants, this technique could also be used for automated quality control, flagging high-variance subjects for further

inspection or exclusion from analyses. From the top level, inspecting the regional degradation of signal across these perturbations as shown in Fig. Ch.II - 3, researchers could lead a targeted interrogation of their raw datasets to identify underlying causes of signal loss. Conversely, investigating which low-level BLAS operations contribute to the observed instabilities will allow researchers to clarify the link between ill-conditioning and so-called “bad data” directly within their pipelines. Upon characterizing this relationship it would be valuable to identify the point (if any) at which targeted N-voxel perturbations become equivalent to MCA-induced variability, bridging the Uncertainty Quantification and Numerical Analysis approaches.

The differences observed when performing 1-voxel perturbations were often comparable in magnitude to the variation introduced across Operating Systems. As OS noise is not controlled and may differ greatly



**Figure Ch.II - 6. Computation time for each perturbation method.** Shown in relative time to the reference execution, plotted is the average execution time for the perturbation methods. MCA and RR (Python) have a small increase in computation time per run, as few floating point operations were instrumented in these settings. The RR (Full Stack) method has nearly a  $7\times$  slowdown. In this case, all floating point operations were instrumented, but the slowdown of less than the estimated  $100\times$  would suggest that the bulk of computation time is not spent on floating point arithmetic. The 1-voxel implementations had a minor slowdown due to the regeneration of data prior to pipeline execution. In every case, the real-world slowdown is  $S\times$  larger, where  $S$  is the number of simulations, in this case 100.

among distributions, package updates, etc., it is likely an insufficiently descriptive evaluation method, and should be used as a reference alongside others. The level of control made available through 1-voxel perturbations in terms of both locality and strength of noise makes it a flexible option that could potentially be used to target known areas of key importance for subsequent analyses. Due to the fact that these perturbations introduce a minor change to input images, this method could also be used for estimating global pipeline stability in a classical sense (i.e. conditioning).

While each of the perturbation modes showed distinct differences with respect to the magnitude and continuity of their induced deviations, Fig. Ch.II - 4 illustrates that the structure of these deviations was also highly variable across both perturbation method and data. This suggests different applications and use cases for each perturbation method. While MCA and RR Python implementations impact connectomes globally, these could be applied to generate synthetic datasets. Full Stack RR is highly variable with respect to dataset, suggesting possible applications in quality control, granted further work is performed to more fully understand the effect observed between this and the Python-only case. Both 1-voxel methods add noise locally, and can test the sensitivity of specific pipeline components or regions of interest to variation. Other methods, such as automatic differentiation, could also be explored as possible avenues leading towards an understanding of the end-to-end conditioning of pipelines.

In addition to generating unstable derivatives which could be looked at or analyzed independently, this type of perturbation analyses enables the aggregation of derivatives. As is summarized in Fig. Ch.II - 5, the method by which graphs or edges are aggregated can drastically change the construction of resulting graphs. While the mean and max (i.e. 100<sup>th</sup> percentile) methods both retain all edges that have appeared in even a single graph, the minimum (0<sup>th</sup> percentile) and other low-percentile aggregations require a stricter consensus of edges for inclusion in the final graph. A benefit of performing multiple aggregations is the composition of graphs with complex edge composition, such as the most volatile edges, as is shown in the final column of Fig. Ch.II - 5. While the binary edge count in the composite graphs varies in each of these methods, it is unclear how derived graph statistics will be affected, and that remains an exciting question for further exploration.

From a resource perspective, each of the perturbation methods evaluated requires multiple iterations to get a sense of the pipeline stability or build aggregates, here taken as 100 iterations. Though the MCA-based methods have the obvious disadvantage of extra computational overhead within each execution cycle of the pipeline, the noise-injection methods do not increase the computation time for a single pipeline execution itself but in this case added computational burden for the generation of synthetic data

dynamically, reducing the redundancy of stored images on disk. While Verificarlo has been demonstrated to account for an approximately  $100\times$  slowdown in floating point operations<sup>10</sup>, the largest slowdown observed in this pipeline is approximately a factor of 7, as shown in Fig. Ch.II - 6. This suggests that the bulk of time on CPU for this pipeline is not spent on floating point operations, but perhaps other operations such as looping, data access, or manipulation of information belonging to other data types. While this slowdown is observed for the the Full Stack implementation, the Python-only implementation is negligibly slower than the reference execution, suggesting that even fewer of the floating point logic is directly written in Python. The slowdown in the 1-voxel setting is of a similar scale to that of the Python-only implementation, with the slowdown likely caused by the addition of 2 read and 1 write operations to the pipeline's execution (reading of simulation parameters and original image, application of simulation, and subsequent writing of perturbed image to temporary storage). Note that the figures shown in Fig. Ch.II - 6 are for a single simulation, and real relative CPU time in each case would be  $100\times$  larger for the experimental application of these methods.

The work presented here demonstrates that even low order computational models such as a 6-component tensor used in diffusion modelling are susceptible to noise. This suggests that stability is a relevant axis upon which tools should be compared, developed, or improved, alongside more commonly considered axes such as accuracy/biological feasibility or performance. The heterogeneity observed across participants clearly illustrates that stability is a property of not just the data or tools independently, but their interaction. Characterization of stability should therefore be evaluated for specific analyses and performed on a representative set of subjects for consideration in subsequent statistical testing. Additionally, identifying how this relationship scales to higher-order models is an exciting next step which will be explored. Finally, the joint application of perturbation methods with more complex post-processing bagging or signal normalization techniques may lead to the development of more numerically stable analyses while maintaining sensitivity that would be lost in traditional approaches such as smoothing.

## **Ch.II - 5 Conclusion**

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All pipeline perturbation methods showed unique non-zero output noise patterns in low-order diffusion modeling, demonstrating their viability for exploring numerical stability of pipelines in neuroimaging. MCA and RR (Python) instrumented pipelines resulted in a wide range of variability, sometimes equivalent to subject-level differences, and are recommended as possible methods to estimate the lower-bound of

stability of analyses, generation of synthetic datasets, and possible identification of Python-introduced critical branch points. RR (Full Stack) perturbations resulted in continuously distributed connectomes that were highly variable across datasets, ranging from negligible deviations to complete regional signal degradation. We provisionally recommend the use of RR (Full Stack) noise for automated quality control and identifying global pipeline stability. While 1-voxel methods result in considerably smaller maximum deviations than the MCA-based methods, they are far more flexible and enable evaluating the sensitivity of pipelines to minor local data perturbations. While the MCA-based methods are more computationally expensive than direct 1-voxel noise injections, the slowdown was found to be less significant in practice than the  $100\times$  scaling factor estimated per floating point operation, presumably due to a significant portion of the pipeline computation time being spent on data management or string and integer processing rather than the constant use of floating point arithmetic.

In all cases, while tool instrumentation enables the parallelized simulation of a particular set of instructions, the aggregation of the simulated graphs is an essential component of the downstream analyses both when exploring the nature of instabilities or developing inferences upon the pipeline's derivatives. We recommend a percentile approach to aggregation, where the threshold can be adjusted based on the desired robustness of the resulting graphs. An advantage of percentile approaches is also that composite aggregates can be formed, isolating edges based on their prevalence across simulations. Further exploration of the distribution of perturbed results should be performed to conclude on the relevance of the aggregation used, as the desired aggregate should be close to the expected value of the distribution.

While both MCA and random-injection simulations are computationally expensive in that they require the evaluation of many simulations, they provide an opportunity to characterize processing modes that may emerge when analyzing either noisy datasets or unstable tools. This work also highlighted an important relationship between the noise properties of an incoming dataset and the tool, validating the need to jointly evaluate the stability of tool–dataset combinations.

Where this work demonstrates a range of numerical variation across minor changes in the quality of data or computation, it does not address the analytic impact of these deviations on downstream statistical approaches. This open question, as well as the relative impact of normalization techniques on this process, present avenues for research which will more clearly place these results in a biologically relevant context, allowing characterization of the functional impact of the observed instabilities.

## Acknowledgments

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# Numerical Instabilities in Analytical Pipelines Lead to Large and Meaningful Variability in Brain Networks

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## Abstract

The analysis of brain-imaging data requires complex processing pipelines to support findings on brain function or pathologies. Recent work has shown that variability in analytical decisions can lead to substantial differences in the results, endangering the trust in conclusions<sup>1–7</sup>. We explored the instability of results by instrumenting a connectome estimation pipeline with Monte Carlo Arithmetic<sup>8,9</sup> to introduce random noise throughout. We evaluated the reliability of the connectomes, their features<sup>10,11</sup>, and the impact on analysis<sup>12,13</sup>. The stability of results was found to range from perfectly stable to highly unstable. This paper highlights the potential of leveraging induced variance in estimates of brain connectivity to reduce the bias in networks alongside increasing the robustness of their applications in the classification of individual differences. We demonstrate that stability evaluations are necessary for understanding error inherent to scientific computing, and how numerical analysis can be applied to typical analytical workflows. Overall, while the extreme variability in results due to analytical instabilities could severely hamper our understanding of brain organization, it also leads to an increase in the reliability of datasets.

The modelling of brain networks, called connectomics, has shaped our understanding of the structure and function of the brain across a variety of organisms and scales over the last decade<sup>11, 14–18</sup>. In humans, these wiring diagrams are obtained *in vivo* through Magnetic Resonance Imaging (MRI), and show promise towards identifying biomarkers of disease. This can not only improve understanding of so-called “connectopathies”, such as Alzheimer’s Disease and Schizophrenia, but potentially pave the way for therapeutics<sup>19–23</sup>.

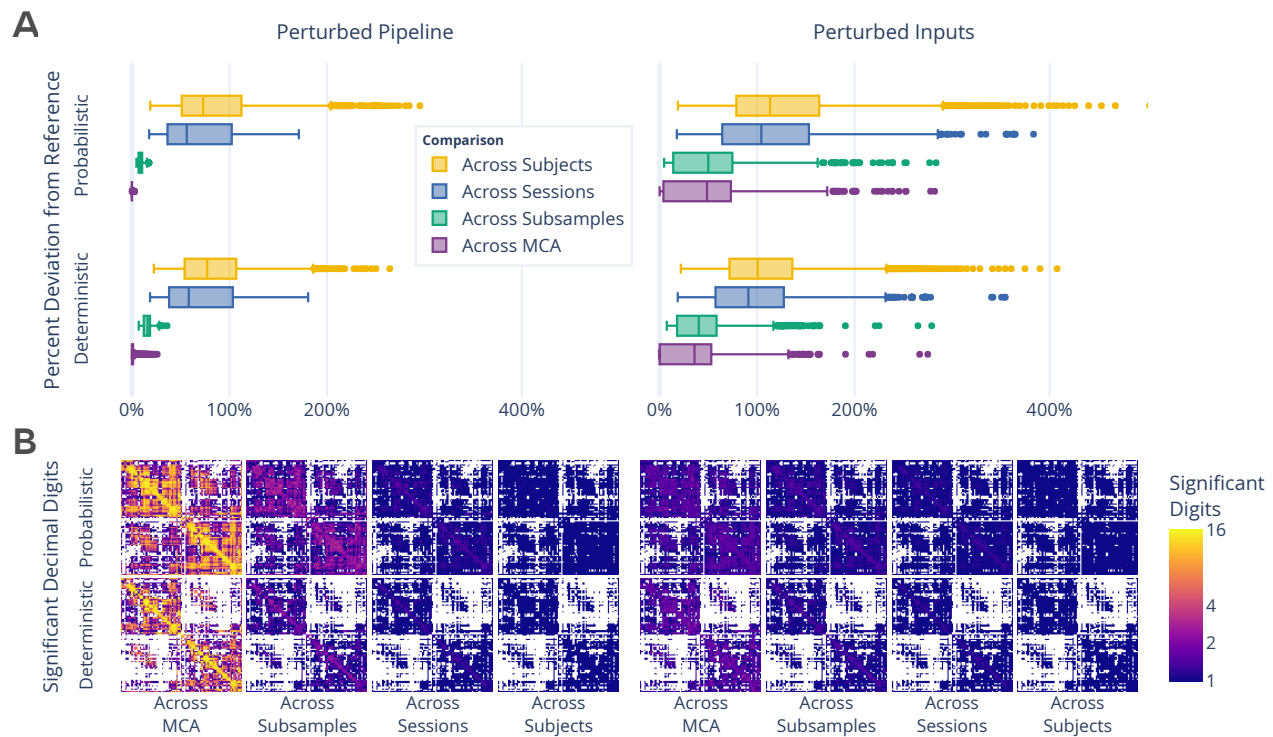
However, the analysis of brain imaging data relies on complex computational methods and software. Tools are trusted to perform everything from pre-processing tasks to downstream statistical evaluation. While these tools undoubtedly undergo rigorous evaluation on bespoke datasets, in the absence of ground-truth this is often evaluated through measures of reliability<sup>24–27</sup>, proxy outcome statistics, or agreement with existing theory. Importantly, this means that tools are not necessarily of known or consistent quality, and it is not uncommon that equivalent experiments may lead to diverging conclusions<sup>1, 5–7</sup>. While many scientific disciplines suffer from a lack of reproducibility<sup>28</sup>, this was recently explored in brain imaging by a 70 team consortium which performed equivalent analyses and found widely inconsistent results<sup>1</sup>, and it is likely that software instabilities played a role.

The present study approached evaluating reproducibility from a computational perspective in which a series of brain imaging studies were numerically perturbed such that the plausibility of results was not affected, and the biological implications of the observed instabilities were quantified. We accomplished this through the use of Monte Carlo Arithmetic (MCA)<sup>8</sup>, a technique which enables characterization of the sensitivity of a system to small perturbations. We explored the impact of perturbations through the direct comparison of structural connectomes, the consistency of their features, and their eventual application in a neuroscience study. Finally we conclude on the consequences and opportunities afforded by the observed instabilities and make recommendations for the roles stability analyses may play towards increasing the reliability of brain imaging research.

## **Ch.III - 1 Graphs Vary Widely With Perturbations**

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Prior to exploring the analytic impact of instabilities, a direct understanding of the induced variability was required. A subset of the Nathan Kline Institute Rockland Sample (NKIRS) dataset<sup>29</sup> was randomly selected to contain 25 individuals with two sessions of imaging data, each of which was subsampled into two components, resulting in four collections per individual. Structural connectomes were generated with



**Figure Ch.III - 1.** Exploration of perturbation-induced deviations from reference connectomes. **(A)** The absolute deviations, in the form of normalized percent deviation from reference, shown as the across MCA series relative to Across Subsample, Across Session, and Across Subject variations. **(B)** The number of significant decimal digits in each set of connectomes as obtained after evaluating the effect of perturbations. In the case of 16, values can be fully relied upon, whereas in the case of 1 only the first digit of a value can be trusted. Pipeline- and input-perturbations are shown on the left and right, respectively.

canonical deterministic and probabilistic pipelines<sup>30,31</sup> which were instrumented with MCA, replicating computational noise at either the inputs or throughout the pipelines<sup>4,9</sup>. The pipelines were sampled 20 times per collection and once without perturbations, resulting in a total of 4,200 connectomes.

The stability of connectomes was evaluated through the deviation from reference and the number of significant digits (Figure Ch.III - 1). The comparisons were grouped according to differences across simulations, subsampling of data, sessions of acquisition, or subjects. While the similarity of connectomes decreases as the collections become more distinct, connectomes generated with input perturbations show considerable variability, often reaching deviations equal to or greater than those observed across individuals or sessions (Figure Ch.III - 1A; right). This finding suggests that instabilities inherent to these pipelines may mask session or individual differences, limiting the trustworthiness of derived connectomes.

While both pipelines show similar performance, the probabilistic pipeline was more stable in the face of pipeline perturbations whereas the deterministic was more stable to input perturbations ( $p < 0.0001$  for all; exploratory). The stability of correlations can be found in Supplemental Section [Ch.III - S1](#).

The number of significant digits per edge across connectomes (Figure [Ch.III - 1B](#)) similarly decreases across groups. While the cross-MCA comparison of connectomes generated with pipeline perturbations show nearly perfect precision for many edges (approaching the maximum of 15.7 digits for 64-bit data), this evaluation uniquely shows considerable drop off in performance across data subsampling (average of  $< 4$  digits). In addition, input perturbations show no more than an average of 3 significant digits across all groups, demonstrating a significant limitation in the reliability independent edge weights. Significance across individuals did not exceed a single digit per edge in any case, indicating that only the magnitude of edges in naively computed groupwise average connectomes can be trusted. The combination of these results with those presented in Figure [Ch.III - 1A](#) suggests that while specific edge weights are largely affected by instabilities, macro-scale network topology is stable.

## Ch.III - 2 Subject-Specific Signal is Amplified While Off-Target Biases Are Reduced

**Table Ch.III - 1.** The impact of instabilities as evaluated through the separability of the dataset based on individual (or subject) differences, session, and subsample. The performance is reported as mean Discriminability. While a perfectly separable dataset would be represented by a score of 1.0, the chance performance, indicating minimal separability, is  $1/\text{the number of classes}$ .  $H_3$  could not be tested using the reference executions due to too few possible comparisons. The alternative hypothesis, indicating significant separation, was accepted for all experiments, with  $p < 0.005$ .

| Comparison                | Chance | Target | Reference Execution |       | Perturbed Pipeline |       | Perturbed Inputs |       |
|---------------------------|--------|--------|---------------------|-------|--------------------|-------|------------------|-------|
|                           |        |        | Det.                | Prob. | Det.               | Prob. | Det.             | Prob. |
| $H_1$ : Across Subjects   | 0.04   | 1.0    | 0.64                | 0.65  | 0.82               | 0.82  | 0.77             | 0.75  |
| $H_2$ : Across Sessions   | 0.5    | 0.5    | 1.00                | 1.00  | 1.00               | 1.00  | 0.88             | 0.85  |
| $H_3$ : Across Subsamples | 0.5    | 0.5    |                     |       | 0.99               | 1.00  | 0.71             | 0.61  |

We assessed the reproducibility of the dataset through mimicking and extending a typical test-retest experiment<sup>26</sup> in which the similarity of samples across multiple measurements were compared to distinct samples in the dataset (Table [Ch.III - 1](#), with additional experiments and explanation in Supplemental

Section [Ch.III - S2](#)). The ability to separate connectomes across subjects (Hypothesis 1) is an essential prerequisite for the application of brain imaging towards identifying individual differences<sup>18</sup>. In testing hypothesis 1, we observe that the dataset is separable with a score of 0.64 and 0.65 ( $p < 0.001$ ; optimal score: 1.0; chance: 0.04) without any instrumentation. However, we can see that inducing instabilities through MCA improves the reliability of the dataset to over 0.75 in each case ( $p < 0.001$  for all), significantly higher than without instrumentation ( $p < 0.005$  for all). This result impactfully suggests the utility of perturbation methods for synthesizing robust and reliable individual estimates of connectivity, serving as a cost effective and context-agnostic method for dataset augmentation.

While the separability of individuals is essential for the identification of brain networks, it is similarly reliant on network similarity across equivalent acquisitions (Hypothesis 2). In this case, connectomes were grouped based upon session, rather than subject, and the ability to distinguish one session from another was computed within-individual and aggregated. Both the unperturbed and pipeline perturbation settings perfectly preserved differences between cross-sectional sessions with a score of 1.0 ( $p < 0.005$ ; optimal score: 0.5; chance: 0.5), indicating a dominant session-dependent signal for all individuals despite no intended biological differences. However, while still significant relative to chance (score: 0.85 and 0.88;  $p < 0.005$  for both), input perturbations lead to significantly lower separability of the dataset ( $p < 0.005$  for all). This reduction of the difference between sessions of data within individuals suggests that increased variance caused by input perturbations reduces the impact of non-biological acquisition-dependent bias inherent in the brain graphs.

Though the previous sets of experiments inextricably evaluate the interaction between the dataset and tool, the use of subsampling allowed for characterizing the separability of networks sampled from within a single acquisition (Hypothesis 3). While this experiment could not be evaluated using reference executions, the executions performed with pipeline perturbations showed near perfect separation between subsamples, with scores of 0.99 and 1.0 ( $p < 0.005$ ; optimal: 0.5; chance: 0.5). Given that there is no variability in data acquisition or preprocessing that contributes to this reliable identification of scans, the separability observed in this experiment may only be due to instability or bias inherent to the pipelines. The high variability introduced through input perturbations considerably lowered the reliability towards chance (score: 0.71 and 0.61;  $p < 0.005$  for all), further supporting this as an effective method for obtaining lower-bias estimates of individual connectivity.

Across all cases, the induced perturbations showed an amplification of meaningful biological signal alongside a reduction of off-target signal. This result appears strikingly like a manifestation of the

well-known bias-variance tradeoff<sup>32</sup> in machine learning, a concept which observes a decrease in bias as variance is favoured by a model. In particular, this highlights that numerical perturbations can be used to not only evaluate the stability of pipelines, but that the induced variance may be leveraged for the interpretation as a robust distributions of possible results.

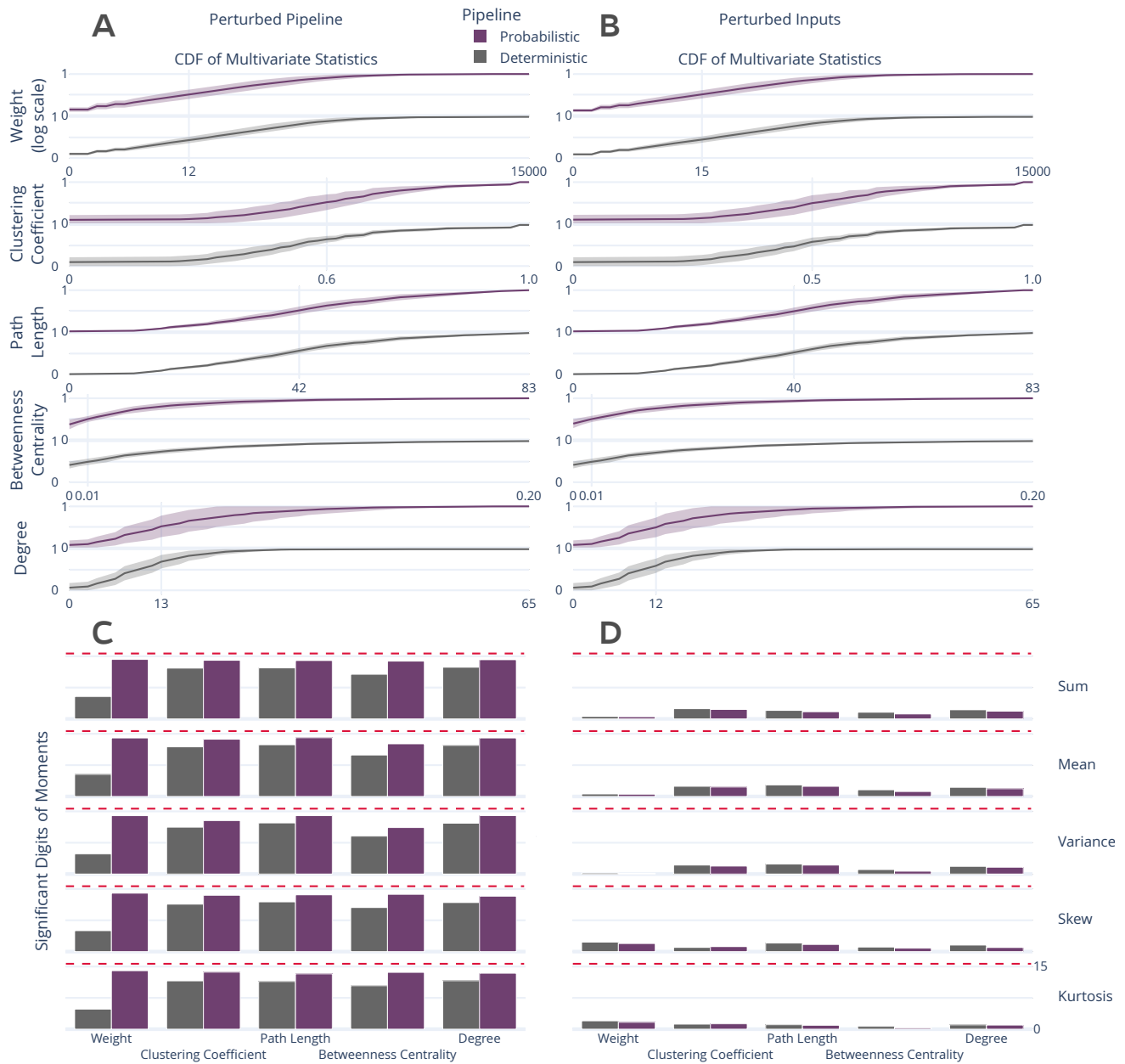
### **Ch.III - 3 Distributions of Graph Statistics Are Reliable, But Individual Statistics Are Not**

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Exploring the stability of topological features of connectomes is relevant for typical analyses, as low dimensional features are often more suitable than full connectomes for many analytical methods in practice<sup>11</sup>. A separate subset of the NKIRS dataset was randomly selected to contain a single non-subsampled session for 100 individuals, and connectomes were generated as above.

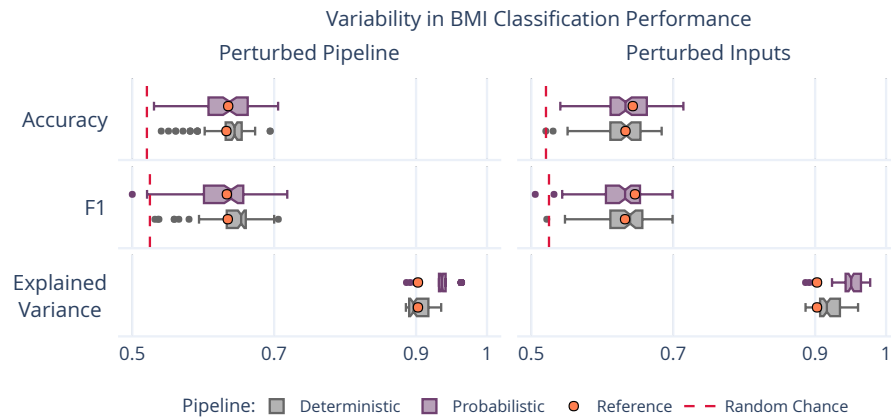
The stability of several commonly-used multivariate graph features<sup>10</sup> was explored in Figure Ch.III - 2. The cumulative density of the features was computed within individuals and the mean density and associated standard error were computed for across individuals (Figures Ch.III - 2A and Ch.III - 2B). There was no significant difference between the distributions for each feature across the two perturbation settings, suggesting that the topological features summarized by these multivariate features are robust across both perturbation modes.

In addition to the comparison of distributions, the stability of the first 5 moments of these features was evaluated (Figures Ch.III - 2C and Ch.III - 2D). In the face of pipeline perturbations, the feature-moments were stable with more than 10 significant digits with the exception of edge weight when using the deterministic pipeline, though the probabilistic pipeline was more stable for all comparisons ( $p < 0.0001$ ; exploratory). In stark contrast, input perturbations led to highly unstable feature-moments (Figure Ch.III - 2D), such that none contained more than 5 significant digits of information and several contained less than a single significant digit, indicating a complete lack of reliability. This dramatic degradation in stability for individual measures strongly suggests that these features may be unreliable as individual biomarkers when derived from a single pipeline evaluation, though their reliability may be increased when studying their distributions across perturbations. A similar analysis was performed for univariate statistics and can be found in Supplemental Section Ch.III - S3.



**Figure Ch.III - 2.** Distribution and stability assessment of multivariate graph statistics. (A, B) The cumulative distribution functions of multivariate statistics across all subjects and perturbation settings. There was no significant difference between the distributions in A and B. (C, D) The number of significant digits in the first 5 five moments of each statistic across perturbations. The dashed red line refers to the maximum possible number of significant digits.

## Ch.III - 4 Uncertainty in Brain-Phenotype Relationships



**Figure Ch.III - 3.** Variability in BMI classification across the sampling of an MCA-perturbed dataset. The dashed red lines indicate random-chance performance, and the orange dots show the performance using the reference executions.

While the variability of connectomes and their features was summarized above, networks are commonly used as inputs to machine learning models tasked with learning brain-phenotype relationships<sup>18</sup>. To explore the stability of these analyses, we modelled the relationship between high- or low- Body Mass Index (BMI) groups and brain connectivity<sup>12,13</sup>, using standard dimensionality reduction and classification tools, and compared this to reference and random performance (Figure Ch.III - 3).

The analysis was perturbed through distinct samplings of the dataset across both pipelines and perturbation methods. The accuracy and F1 score for the perturbed models varied from 0.520 – 0.716 and 0.510 – 0.725, respectively, ranging from at or below random performance to outperforming performance on the reference dataset. This large variability illustrates a previously uncharacterized margin of uncertainty in the modelling of this relationship, and limits confidence in reported accuracy scores on singly processed datasets. The portion of explained variance in these samples ranged from 88.6% – 97.8%, similar to the reference, suggesting that the range in performance was not due to a gain or loss of meaningful signal, but rather the reduction of bias towards specific outcome. Importantly, this finding does not suggest that modelling brain-phenotype relationships is not possible, but rather it sheds light on impactful uncertainty that must be accounted for in this process, and supports the use of ensemble modeling techniques.



## Ch.III - 5 Discussion

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The perturbation of structural connectome estimation pipelines with small amounts of noise, on the order of machine error, led to considerable variability in derived brain graphs. Across all analyses the stability of results ranged from nearly perfectly trustworthy (i.e. no variation) to completely unreliable (i.e. containing no trustworthy information). Given that the magnitude of introduced numerical noise is to be expected in typical settings, this finding has potentially significant implications for inferences in brain imaging as it is currently performed. In particular, this bounds the success of studying individual differences, a central objective in brain imaging<sup>18</sup>, given that the quality of relationships between phenotypic data and brain networks will be limited by the stability of the connectomes themselves. This issue was accentuated through the crucial finding that individually derived network features were unreliable despite there being no significant difference in their aggregated distributions. This finding is not damning for the study of brain networks as a whole, but rather is strong support for the aggregation of networks, either across perturbations for an individual or across groups, over the use of individual estimates.

**Underestimated False Positive Rates** While the instability of brain networks was used here to demonstrate the limitations of modelling brain-phenotype relationships in the context of machine learning, this limitation extends to classical hypothesis testing, as well. Though performing individual comparisons in a hypothesis testing framework will be accompanied by reported false positive rates, the accuracy of these rates is critically dependent upon the reliability of the samples used. In reality, the true false positive rate for a test would be a combination of the reported confidence and the underlying variability in the results, a typically unknown quantity.

When performing these experiments outside of a repeated-measure context, such as that afforded here through MCA, it is impossible to empirically estimate the reliability of samples. This means that the reliability of accepted hypotheses is also unknown, regardless of the reported false positive rate. In fact, it is a virtual certainty that the true false positive rate for a given hypothesis exceeds the reported value simply as a result of numerical instabilities. This uncertainty inherent to derived data is compounded with traditional arguments limiting the trustworthiness of claims<sup>33</sup>, and hampers the ability of researchers to evaluate the quality of results. The accompaniment of brain imaging experiments with direct evaluations of their stability, as was done here, would allow researchers to simultaneously improve the numerical stability of their analyses and accurately gauge confidence in them. The induced variability in derived brain networks may be leveraged to estimate aggregate connectomes with lower bias than any single

independent observation, leading to learned relationships that are more generalizable and ultimately more useful.

**Cost-Effective Data Augmentation** The evaluation of reliability in brain imaging has historically relied upon the expensive collection of repeated measurements choreographed by massive cross-institutional consortia<sup>34,35</sup>. The finding that perturbing experiments using MCA both increased the reliability of the dataset and decreased off-target differences across acquisitions opens the door for a promising paradigm shift. Given that MCA is data-agnostic, this technique could be used effectively in conjunction with, or in lieu of, realistic noise models to augment existing datasets. While this of course would not replace the need for repeated measurements when exploring the effect of data collection paradigm or study longitudinal progressions of development or disease, it could be used in conjunction with these efforts to increase the reliability of each distinct sample within a dataset. In contexts where repeated measurements are collected to increase the fidelity of the dataset, MCA could potentially be employed to increase the reliability of the dataset and save millions of dollars on data collection. This technique also opens the door for the characterization of reliability across axes which have been traditionally inaccessible. For instance, in the absence of a realistic noise model or simulation technique similar to MCA, the evaluation of network stability across data subsampling would not have been possible.

**Shortcomings and Future Questions** Given the complexity of recompiling complex software libraries, pre-processing was not perturbed in these experiments. Other work has shown that linear registration, a core piece of many elements of pre-processing such as motion correction and alignment, is sensitive to minor perturbations<sup>7</sup>. It is likely that the instabilities across the entire processing workflow would be compounded with one another, resulting in even greater variability. While the analyses performed in this paper evaluated a single dataset and set of pipelines, extending this work to other modalities and analyses is of interest for future projects.

This paper does not explore methodological flexibility or compare this to numerical instability. Recently, the nearly boundless space of analysis pipelines and their impact on outcomes in brain imaging has been clearly demonstrated<sup>1</sup>. The approach taken in these studies complement one another and explore instability at the opposite ends of the spectrum, with human variability in the construction of an analysis workflow on one end and the unavoidable error implicit in the digital representation of data on the other. It is of extreme interest to combine these approaches and explore the interaction of these scientific degrees of freedom with effects from software implementations, libraries, and parametric choices.

Finally, it is important to state explicitly that the work presented here does not invalidate analytical pipelines used in brain imaging, but merely sheds light on the fact that many studies are accompanied by an unknown degree of uncertainty due to machine-introduced errors. The presence of unknown error-bars associated with experimental findings limits the impact of results due to increased uncertainty. The desired outcome of this paper is to motivate a shift in scientific computing – both in neuroimaging and more broadly – towards a paradigm which favours the explicit evaluation of the trustworthiness of claims alongside the claims themselves.

## **Ch.III - 6 Methods**

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### **Ch.III - 6.1 Dataset**

The Nathan Kline Institute Rockland Sample (NKI-RS)<sup>29</sup> dataset contains high-fidelity imaging and phenotypic data from over 1,000 individuals spread across the lifespan. A subset of this dataset was chosen for each experiment to both match sample sizes presented in the original analyses and to minimize the computational burden of performing MCA. The selected subset comprises 100 individuals ranging in age from 6 – 79 with a mean of 36.8 (original: 6 – 81, mean 37.8), 60% female (original: 60%), with 52% having a BMI over 25 (original: 54%).

Each selected individual had at least a single session of both structural T1-weighted (MPRAGE) and diffusion-weighted (DWI) MR imaging data. DWI data was acquired with 137 diffusion directions; more information regarding the acquisition of this dataset can be found in the NKI-RS data release<sup>29</sup>.

In addition to the 100 sessions mentioned above, 25 individuals had a second session to be used in a test-retest analysis. Two additional copies of the data for these individuals were generated, including only the odd or even diffusion directions (64 + 9 B0 volumes = 73 in either case). This allowed for an extra level of stability evaluation to be performed between the levels of MCA and session-level variation.

In total, the dataset is composed of 100 downsampled sessions of data originating from 50 acquisitions and 25 individuals for in depth stability analysis, and an additional 100 sessions of full-resolution data from 100 individuals for subsequent analyses.

### **Ch.III - 6.2 Processing**

The dataset was preprocessed using a standard FSL<sup>36</sup> workflow consisting of eddy-current correction and alignment. The MNI152 atlas<sup>37</sup> was aligned to each session of data, and the resulting transformation was applied to the DKT parcellation<sup>38</sup>. Downsampling the diffusion data took place after preprocessing

was performed on full-resolution sessions, ensuring that an additional confound was not introduced in this process when comparing between downsampled sessions. The preprocessing described here was performed once without MCA, and thus is not being evaluated.

Structural connectomes were generated from preprocessed data using two canonical pipelines from Dipy<sup>30</sup>: deterministic and probabilistic. In the deterministic pipeline, a constant solid angle model was used to estimate tensors at each voxel and streamlines were then generated using the EuDX algorithm<sup>31</sup>. In the probabilistic pipeline, a constrained spherical deconvolution model was fit at each voxel and streamlines were generated by iteratively sampling the resulting fiber orientation distributions. In both cases tracking occurred with 8 seeds per 3D voxel and edges were added to the graph based on the location of terminal nodes with weight determined by fiber count.

The random state of the probabilistic pipeline was fixed for all analyses. Fixing this random seed allowed for explicit attribution of observed variability to Monte Carlo simulations rather than internal state of the algorithm.

### Ch.III - 6.3 Perturbations

All connectomes were generated with one reference execution where no perturbation was introduced in the processing. For all other executions, all floating point operations were instrumented with Monte Carlo Arithmetic (MCA)<sup>8</sup> through Verificarlo<sup>9</sup>. MCA simulates the distribution of errors implicit to all instrumented floating point operations (flop). This rounding is performed on a value  $x$  at precision  $t$  by:

$$inexact(x) = x + 2^{e_x - t} \xi \quad (1)$$

where  $e_x$  is the exponent value of  $x$  and  $\xi$  is a uniform random variable in the range  $(-\frac{1}{2}, \frac{1}{2})$ . MCA can be introduced in two places for each flop: before or after evaluation. Performing MCA on the inputs of an operation limits its precision, while performing MCA on the output of an operation highlights round-off errors that may be introduced. The former is referred to as Precision Bounding (PB) and the latter is called Random Rounding (RR).

Using MCA, the execution of a pipeline may be performed many times to produce a distribution of results. Studying the distribution of these results can then lead to insights on the stability of the instrumented tools or functions. To this end, a complete software stack was instrumented with MCA and is made available on GitHub at <https://github.com/gkiar/fuzzy>.

Both the RR and PB variants of MCA were used independently for all experiments. As was presented in<sup>4</sup>, both the degree of instrumentation (i.e. number of affected libraries) and the perturbation mode have an effect on the distribution of observed results. For this work, the RR-MCA was applied across the bulk of the relevant libraries and is referred to as Pipeline Perturbation. In this case the bulk of numerical operations were affected by MCA.

Conversely, the case in which PB-MCA was applied across the operations in a small subset of libraries is here referred to as Input Perturbation. In this case, the inputs to operations within the instrumented libraries (namely, Python and Cython) were perturbed, resulting in less frequent, data-centric perturbations. Alongside the stated theoretical differences, Input Perturbation is considerably less computationally expensive than Pipeline Perturbation.

All perturbations targeted the least-significant-bit for all data ( $t = 24$  and  $t = 53$  in float32 and float64, respectively<sup>9</sup>). Simulations were performed 20 times for each pipeline execution. A detailed motivation for the number of simulations can be found in<sup>39</sup>.

### **Ch.III - 6.4 Evaluation**

The magnitude and importance of instabilities in pipelines can be considered at a number of analytical levels, namely: the induced variability of derivatives directly, the resulting downstream impact on summary statistics or features, or the ultimate change in analyses or findings. We explore the nature and severity of instabilities through each of these lenses. Unless otherwise stated, all p-values were computed using Wilcoxon signed-rank tests.

#### **Ch.III - 6.4.1 Direct Evaluation of the Graphs**

The differences between simulated graphs was measured directly through both a direct variance quantification and a comparison to other sources of variance such as individual- and session-level differences.

**Quantification of Variability** Graphs, in the form of adjacency matrices, were compared to one another using three metrics: normalized percent deviation, Pearson correlation, and edgewise significant digits. The normalized percent deviation measure, defined in<sup>4</sup>, scales the norm of the difference between a simulated graph and the reference execution (that without intentional perturbation) with respect to the norm of the reference graph. The purpose of this comparison is to provide insight on the scale of differences in observed graphs relative to the original signal intensity. A Pearson correlation coefficient<sup>40</sup> was computed in complement to normalized percent deviation to identify the consistency of structure and not just intensity

between observed graphs.

Finally, the estimated number of significant digits,  $s'$ , for each edge in the graph is calculated as:

$$s' = -\log_{10} \frac{\sigma}{|\mu|} \quad (2)$$

where  $\mu$  and  $\sigma$  are the mean and unbiased estimator of standard deviation across graphs, respectively. The upper bound on significant digits is 15.7 for 64-bit floating point data.

The percent deviation, correlation, and number of significant digits were each calculated within a single session of data, thereby removing any subject- and session-effects and providing a direct measure of the tool-introduced variability across perturbations. A distribution was formed by aggregating these individual results.

**Class-based Variability Evaluation** To gain a concrete understanding of the significance of observed variations we explore the separability of our results with respect to understood sources of variability, such as subject-, session-, and pipeline-level effects. This can be probed through Discriminability<sup>26</sup>, a technique similar to ICC<sup>24</sup> which relies on the mean of a ranked distribution of distances between observations belonging to a defined set of classes. The discriminability statistic is formalized as follows:

$$Disc. = Pr(\|g_{ij} - g_{i'j'}\| \leq \|g_{ij} - g_{i'j'}\|) \quad (3)$$

where  $g_{ij}$  is a graph belonging to class  $i$  that was measured at observation  $j$ , where  $i \neq i'$  and  $j \neq j'$ .

Discriminability can then be read as the probability that an observation belonging to a given class will be more similar to other observations within that class than observations of a different class. It is a measure of reproducibility, and is discussed in detail in<sup>26</sup>. This definition allows for the exploration of deviations across arbitrarily defined classes which in practice can be any of those listed above. We combine this statistic with permutation testing to test hypotheses on whether differences between classes are statistically significant in each of these settings.

With this in mind, three hypotheses were defined. For each setting, we state the alternate hypotheses, the variable(s) which were used to determine class membership, and the remaining variables which may be sampled when obtaining multiple observations. Each hypothesis was tested independently for each pipeline and perturbation mode, and in every case where it was possible the hypotheses were tested using the reference executions alongside using MCA.

$H_{A1}$ : Individuals are distinct from one another

Class definition: *Subject ID*

Comparisons: *Session (1 subsample), Subsample (1 session), MCA (1 subsample, 1 session)*

$H_{A2}$ : Sessions within an individual are distinct

Class definition: *Session ID | Subject ID*

Comparisons: *Subsample, MCA (1 subsample)*

$H_{A3}$ : Subsamples are distinct

Class definition: *Subsample | Subject ID, Session ID*

Comparisons: *MCA*

As a result, we tested 3 hypotheses across 6 MCA experiments and 3 reference experiments on 2 pipelines and 2 perturbation modes, resulting in a total of 30 distinct tests.

### Ch.III - 6.4.2 Evaluating Graph-Theoretical Metrics

While connectomes may be used directly for some analyses, it is common practice to summarize them with structural measures, which can then be used as lower-dimensional proxies of connectivity in so-called graph-theoretical studies<sup>11</sup>. We explored the stability of several commonly-used univariate (graphwise) and multivariate (nodewise or edgewise) features. The features computed and subsequent methods for comparison in this section were selected to closely match those computed in<sup>10</sup>.

**Univariate Differences** For each univariate statistic (edge count, mean clustering coefficient, global efficiency, modularity of the largest connected component, assortativity, and mean path length) a distribution of values across all perturbations within subjects was observed. A Z-score was computed for each sample with respect to the distribution of feature values within an individual, and the proportion of "classically significant" Z-scores, i.e. corresponding to  $p < 0.05$ , was reported and aggregated across all subjects. The number of significant digits contained within an estimate derived from a single subject were calculated and aggregated.

**Multivariate Differences** In the case of both nodewise (degree distribution, clustering coefficient, betweenness centrality) and edgewise (weight distribution, connection length) features, the cumulative density functions of their distributions were evaluated over a fixed range and subsequently aggregated across individuals. The number of significant digits for each moment of these distributions (sum, mean, variance, skew, and kurtosis) were calculated across observations within a sample and aggregated.



### Ch.III - 6.4.3 Evaluating A Brain-Phenotype Analysis

Though each of the above approaches explores the instability of derived connectomes and their features, many modern studies employ modeling or machine-learning approaches, for instance to learn brain-phenotype relationships or identify differences across groups. We carried out one such study and explored the instability of its results with respect to the upstream variability of connectomes characterized in the previous sections. We performed the modeling task with a single sampled connectome per individual and repeated this sampling and modelling 20 times. We report the model performance for each sampling of the dataset and summarize its variance.

**BMI Classification** Structural changes have been linked to obesity in adolescents and adults<sup>41</sup>. We classified normal-weight and overweight individuals from their structural networks (using for overweight a cutoff of  $\text{BMI} > 25^{13}$ ). We reduced the dimensionality of the connectomes through principal component analysis (PCA), and provided the first  $N$ -components to a logistic regression classifier for predicting BMI class membership, similar to methods shown in<sup>12,13</sup>. The number of components was selected as the minimum set which explained  $> 90\%$  of the variance when averaged across the training set for each fold within the cross validation of the original graphs; this resulted in a feature of 20 components. We trained the model using  $k$ -fold cross validation, with  $k = 2, 5, 10$ , and  $N$  (equivalent to leave-one-out; LOO).

### Ch.III - 6.4.4 Data & Code Provenance

The unprocessed dataset is available through The Consortium of Reliability and Reproducibility ([http://fcon\\_1000.projects.nitrc.org/indi/enhanced/](http://fcon_1000.projects.nitrc.org/indi/enhanced/)), including both the imaging data as well as phenotypic data which may be obtained upon submission and compliance with a Data Usage Agreement. The connectomes generated through simulations have been bundled and stored permanently (<https://doi.org/10.5281/zenodo.4041549>), and are made available through The Canadian Open Neuroscience Platform (<https://portal.conp.ca/search>, search term "Kiar").

All software developed for processing or evaluation is publicly available on GitHub at <https://github.com/gkpapers/2020ImpactOfInstability>. Experiments were launched using Boutiques<sup>42</sup> and Clowdr<sup>43</sup> in Compute Canada's HPC cluster environment. MCA instrumentation was achieved through Verificarlo<sup>9</sup> available on Github at <https://github.com/verificarlo/verificarlo>. A set of MCA instrumented software containers is available on Github at <https://github.com/gkiar/fuzzy>.



### Ch.III - 6.5 Author Contributions

GK was responsible for the experimental design, data processing, analysis, interpretation, and the majority of writing. All authors contributed to the revision of the manuscript. YC, POC, and EP were responsible for MCA tool development and software testing. AR, GV, and BM contributed to experimental design and interpretation. TG contributed to experimental design, analysis, and interpretation. TG and ACE were responsible for supervising and supporting all contributions made by GK. The authors declare no competing interests for this work. Correspondence and requests for materials should be addressed to Tristan Glatard at [tristan.glatard@concordia.ca](mailto:tristan.glatard@concordia.ca).

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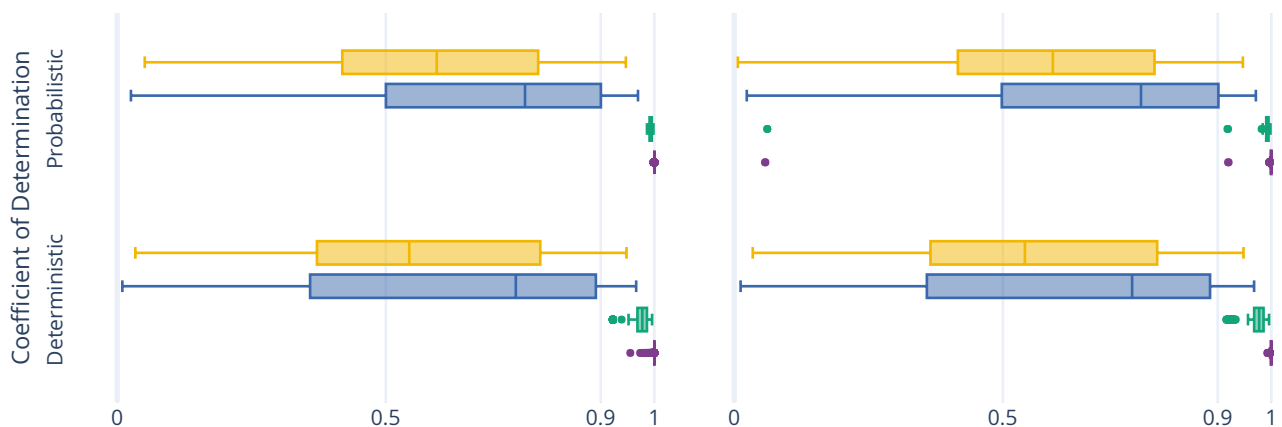
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## Ch.III - S1 Graph Correlation

The correlations between observed graphs (Figure Ch.III - S1) across each grouping follow the same trend to as percent deviation, as shown in Figure Ch.III - 1. However, notably different from percent deviation, there is no significant difference in the correlations between pipeline or input instrumentations. By this measure, the probabilistic pipeline is more stable in all cross-MCA and cross-directions except for the combination of input perturbation and cross-MCA ( $p < 0.0001$  for all; exploratory).

The marked lack in drop-off of performance across these settings, inconsistent with the measures show in Figure Ch.III - 1 is due to the nature of the measure and the graphs. Given that structural graphs are sparse and contain considerable numbers of zero-weighted edges, the presence or absense of an edge dominated the correlation measure where it was less impactful for the others. For this reason and others<sup>44</sup>, correlation is not a commonly used measure in the context of structural connectivity.



**Figure Ch.III - S1.** The correlation between perturbed connectomes and their reference.

## Ch.III - S2 Complete Discriminability Analysis

**Table Ch.III - S1.** The complete results from the Discriminability analysis, with results reported as mean  $\pm$  standard deviation Discriminability. As was the case in the condensed table, the alternative hypothesis, indicating significant separation across groups, was accepted for all experiments, with  $p < 0.005$ .

| Exp. | Subj. | Sess. | Samp. | Reference Execution |                 | Perturbed Pipeline |                 | Perturbed Inputs |                 |
|------|-------|-------|-------|---------------------|-----------------|--------------------|-----------------|------------------|-----------------|
|      |       |       |       | Det.                | Prob.           | Det.               | Prob.           | Det.             | Prob.           |
| 1.1  | All   | All   | 1     | 0.64 $\pm$ 0.00     | 0.65 $\pm$ 0.00 | 0.82 $\pm$ 0.00    | 0.82 $\pm$ 0.00 | 0.77 $\pm$ 0.00  | 0.75 $\pm$ 0.00 |
| 1.2  | All   | 1     | All   | 1.00 $\pm$ 0.00     | 1.00 $\pm$ 0.00 | 1.00 $\pm$ 0.00    | 1.00 $\pm$ 0.00 | 0.93 $\pm$ 0.02  | 0.90 $\pm$ 0.02 |
| 1.3  | All   | 1     | 1     |                     |                 | 1.00 $\pm$ 0.00    | 1.00 $\pm$ 0.00 | 0.94 $\pm$ 0.02  | 0.90 $\pm$ 0.02 |
| 2.4  | 1     | All   | All   | 1.00 $\pm$ 0.00     | 1.00 $\pm$ 0.00 | 1.00 $\pm$ 0.00    | 1.00 $\pm$ 0.00 | 0.88 $\pm$ 0.12  | 0.85 $\pm$ 0.12 |
| 2.5  | 1     | All   | 1     |                     |                 | 1.00 $\pm$ 0.00    | 1.00 $\pm$ 0.00 | 0.89 $\pm$ 0.11  | 0.84 $\pm$ 0.12 |
| 3.6  | 1     | 1     | All   |                     |                 | 0.99 $\pm$ 0.03    | 1.00 $\pm$ 0.00 | 0.71 $\pm$ 0.07  | 0.61 $\pm$ 0.05 |

The complete discriminability analysis includes comparisons across more axes of variability than the condensed version. The reduction in the main body was such that only axes which would be relevant for a typical analysis were presented. Here, each of Hypothesis 1, testing the difference across subjects, and 2, testing the difference across sessions, were accompanied with additional comparisons to those shown in the main body.

**Subject Variation** Alongside experiment 1.1, that which mimicked a typical test-retest scenario, experiments 1.2 and 1.3 could be considered a test-retest with a handicap, given a single acquisition per individual was compared either across subsamples or simulations, respectively. For this reason, it is unsurprising that the dataset achieved considerably higher discriminability scores.

**Session Variation** Similar to subject variation, the session variation was also modelled across either both or a single subsample. In both of these cases the performance was similar, and the finding that input perturbation reduced the off-target signal was consistent.

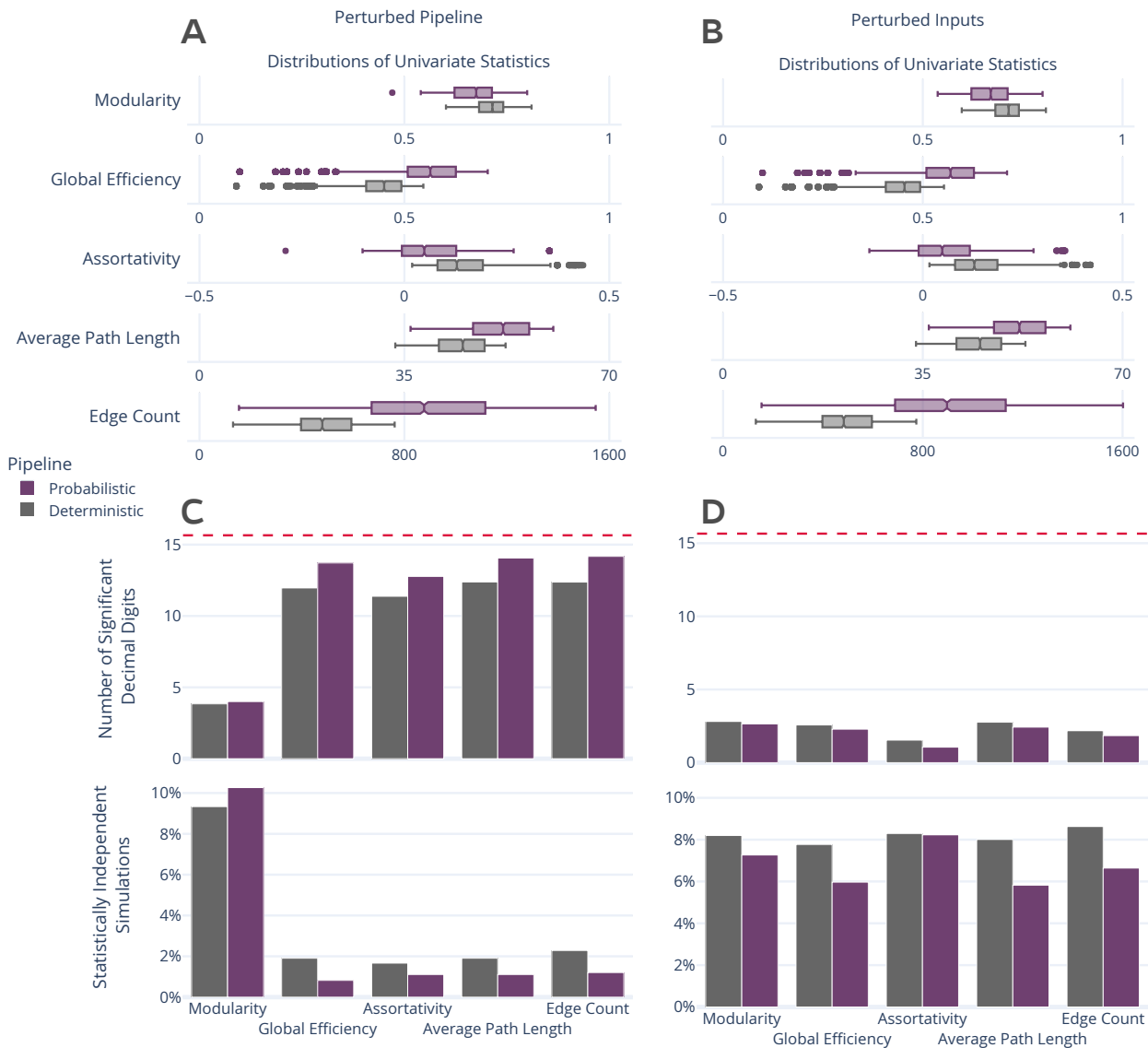
## Ch.III - S3 Univariate Graph Statistics

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Figure Ch.III - S2 explores the stability of univariate graph-theoretical metrics computed from the perturbed graphs, including modularity, global efficiency, assortativity, average path length, and edge count. When aggregated across individuals and perturbations, the distributions of these statistics (Figures Ch.III - S2A and Ch.III - S2B) showed no significant differences between perturbation methods for either deterministic or probabilistic pipelines.

However, when quantifying the stability of these measures across connectomes derived from a single session of data, the two perturbation methods show considerable differences. The number of significant digits in univariate statistics for Pipeline Perturbation instrumented connectome generation exceeded 11 digits for all measures except modularity, which contained more than 4 significant digits of information (Figure Ch.III - S2C). When detecting outliers from the distributions of observed statistics for a given session, the false positive rate (using a threshold of  $p = 0.05$ ) was approximately 2% for all statistics with the exception of modularity which again was less stable with an approximately 10% false positive rate. The probabilistic pipeline is significantly more stable than the deterministic pipeline ( $p < 0.0001$ ; exploratory) for all features except modularity. When similarly evaluating these features from connectomes generated in the input perturbation setting, no statistic was stable with more than 3 significant digits or a false positive rate lower than nearly 6% (Figure Ch.III - S2D). The deterministic pipeline was more stable than the probabilistic pipeline in this setting ( $p < 0.0001$ ; exploratory).

Two notable differences between the two perturbation methods are, first, the uniformity in the stability of the statistics, and second, the dramatic decline in stability of individual statistics in the input perturbation setting despite the consistency in the overall distribution of values. It is unclear at present if the discrepancy between the stability of modularity in the pipeline perturbation context versus the other statistics suggests the implementation of this measure is the source of instability or if it is implicit to the measure itself. The dramatic decline in the stability of features derived from input perturbed graphs despite no difference in their overall distribution both shows that while individual estimates may be unstable the comparison between aggregates or groups may be considered much more reliable; this finding is consistent with that presented for multivariate statistics.



**Figure Ch.III - S2.** Distribution and stability assessment of univariate graph statistics. (A, B) The distributions of each computed univariate statistic across all subjects and perturbations for Pipeline and Input settings, respectively. There was no significant difference between the distributions in A and B. (C, D; top) The number of significant decimal digits in each statistic across perturbations, averaged across individuals. The dashed red line refers to the maximum possible number of significant digits. (C, D; bottom) The percentage of connectomes which were deemed significantly different ( $p < 0.05$ ) from the others obtained for an individual.



# Data Augmentation Through Monte Carlo Arithmetic Leads to More Generalizable Classification in Connectomics

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## Abstract

Machine learning models are commonly applied to human brain imaging datasets in an effort to associate function or structure with behaviour, health, or other individual phenotypes. Such models often rely on low-dimensional maps generated by complex processing pipelines. However, the numerical instabilities inherent to pipelines limit the fidelity of these maps and introduce computational bias. Monte Carlo Arithmetic, a technique for introducing controlled amounts of numerical noise, was used to perturb a structural connectome estimation pipeline, ultimately producing a range of plausible networks for each sample. The variability in the perturbed networks was captured in an augmented dataset, which was then used for an age classification task. We found that resampling brain networks across a series of such numerically perturbed outcomes led to improved performance in all tested classifiers, preprocessing strategies, and dimensionality reduction techniques. Importantly, we find that this benefit does not hinge on a large number of perturbations, suggesting that even minimally perturbing a dataset adds meaningful variance which can be captured in the subsequently designed models.

## Ch.IV - 1 Introduction

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The application of machine learning has become commonplace for the identification and characterization of individual biomarkers in neuroimaging<sup>1</sup>. Models have been applied to discriminate between measures of brain structure or function based upon phenotypic variables related to disease<sup>2–4</sup>, development<sup>5</sup>, or other axes of potential consequence<sup>6,7</sup>.

These models often build representations upon processed imaging data, in which 3D or 4D images have been transformed into estimates of structure<sup>8</sup>, function<sup>9</sup>, or connectivity<sup>10</sup>. However, there is a lack of reliability in these estimates, including variation across analysis team<sup>11</sup>, software library<sup>12</sup>, operating system<sup>13</sup>, and instability in the face of numerical noise<sup>14</sup>. This uncertainty limits the ability of models to learn generalizable relationships among data, and leads to biased predictors. Traditionally, this bias has been reduced through the collection and application of repeated-measurement datasets<sup>15,16</sup>, though this requires considerable resources and is not feasible in the context of all clinical populations.

Perturbation methods which inject small amounts of noise through the execution of a pipeline, such as Monte Carlo Arithmetic (MCA)<sup>17,18</sup>, have recently been used to induce instabilities in structural connectome estimation software<sup>19</sup>. Importantly, this technique produces a range of equally plausible results, where no single observation is more or less valid than the others – including those which were left unperturbed. While sampling from a set of perturbed connectomes may have an impact on learning brain-phenotype relationships<sup>14</sup>, there remains potential for leveraging the distribution of perturbed results to augment datasets in lieu of increasing sample sizes or performing repeated measurements.

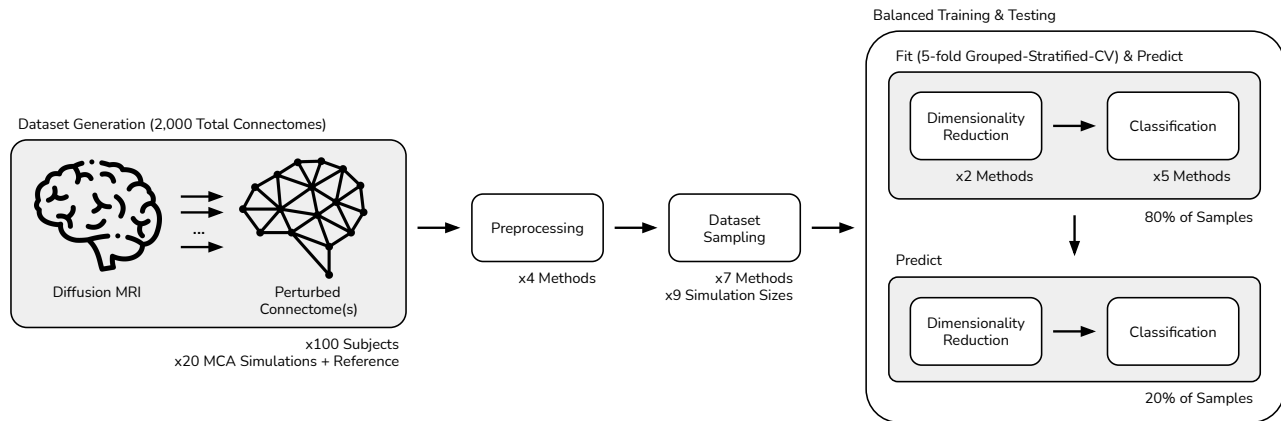
Using an existing collection of MCA-perturbed structural connectomes<sup>20</sup>, we trained classifiers on networks sampled from the distribution of results and evaluated their performance relative to using only the unperturbed networks. We evaluate several techniques for resampling the networks, and compare classifiers through their validation performance, the performance on an out-of-sample test set, and the generalizability of their performance across the two. We demonstrate the efficacy of using MCA as a method for dataset augmentation which leads to more robust and generalizable models of brain-phenotype relationships.

## Ch.IV - 2 Materials & Methods

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The objective of this study was to evaluate the impact of aggregating collections of unstable brain networks towards learning robust brain-phenotype relationships. We sampled and aggregated simulated networks

within individuals to learn relationships between brain connectivity and individual phenotypes, in this case age, and compared this to baseline performance on this task. We compared aggregation strategies with respect to baseline validation performance, performance out-of-sample, and generalizability. The experimental workflow is visualized in Figure Ch.IV - 1.



**Figure Ch.IV - 1.** Experiment workflow. MCA-simulated connectomes were previously generated for 100 subjects, 20 times each. The resulting dataset of 2,000 connectomes were independently preprocessed using one of 4 techniques. The dataset was then sampled according to one of 7 dataset sampling strategies and using one of 9 possible number of MCA simulations per subject. The dataset was split into balanced training and testing sets, and fed into the models. The models consisted of one of 2 dimensionality reduction techniques prior to classification using one of 5 classifier types. The models were fit and made predictions on the training set prior to making predictions on the test set.

All developed software and analysis resources for this project have been made available through GitHub at <https://github.com/gkpapers/2020AggregateMCA>.

## Ch.IV - 2.1 Dataset

An existing dataset containing Monte Carlo Arithmetic (MCA) perturbed structural human brain networks was used for these experiments<sup>20</sup>. The perturbations introduced for the generation of brain networks in this dataset were at the level of machine-error, simulating expected error over a typical pipeline execution. This dataset contains a single session of data from 100 individuals ( $100 \times 1 \times 1$ ). The derived brain networks were generated with a probabilistic structural connectome estimation pipeline<sup>21</sup> using a fixed random seed, and minimal Monte Carlo Arithmetic (MCA) perturbations were added to all Python-implemented operations throughout the pipeline<sup>17,18</sup>. Each sample was simulated 20 times, resulting in 2,000 unique

graphs. Further information on the processing and curation of this dataset can be found here<sup>14</sup>.

This collection enabled the exploration of subsampling and aggregation methods in a typical learning context for neuroimaging<sup>22,23</sup>. Exploring the relationship between the number of simulations and performance further allows for MCA-enabled resampling to be evaluated as a method of dataset augmentation.

As the target for classification, individual-level phenotypic data strongly implicated in brain connectivity was desired. Participant age, which has consistently been shown to have a considerable impact on brain connectivity<sup>24–27</sup>, was selected and turned into a binary target by dividing participants into adult ( $> 18$ ) and non-adult groups (68% adult).

## **Ch.IV - 2.2 Preprocessing**

Prior to being used for this task, the brain networks were represented as symmetric  $83 \times 83$  adjacency matrices, sampled upon the Desikan-Killiany-Tourville<sup>28</sup> anatomical parcellation. To reduce redundancy in the data, all edges belonging to the upper-triangle of these matrices were preserved and vectorized, resulting in a feature vector of 3,486 edges per sample. All samples were preprocessed using one of four standard techniques:

**Raw** The raw streamline count edge-weight intensities were used as originally calculated.

**Log Transform** The  $\log_{10}$  of edge weights was taken, and edges with 0 weight prior to the transform were reset to 0.

**Rank Transform** The edges were ranked based on their intensity, with the largest edge having the maximum value. Ties were settled by averaging the rank, and all ranks were finally min-max scaled between 0 and 1.

**Z-Score** The edge weights were z-scored to have a mean intensity of 0 and unit variance.

## **Ch.IV - 2.3 Machine Learning Pipelines**

The preprocessed connectomes were fed into pipelines consisting of two steps: dimensionality reduction and classification. Dimensionality reduction was applied using one of two methods:

**Principal Component Analysis** The connectomes were projected into the 20 dimensions of highest variance. The number of components was chosen to capture approximately 90% of the variance present within the dataset.

**Feature Agglomeration** The number of features in each connectome were reduced by combining edges according to maximum similarity/minimum variance using agglomerative clustering<sup>29</sup>. The number of resulting features was 20, to be consistent with the number of dimensions present after PCA, above.

After dimensionality reduction, samples were fed into one of five distinct classifiers as implemented through scikit learn<sup>30</sup>:

**Support Vector Machine** The model was fit using a radial basis function (RBF) kernel, L2 penalty, and a balanced regularization parameter to account for uneven class membership.

**Logistic Regression** A linear solver was used due to the relatively small dataset size. L2 regularization and balanced class weights were used, as above.

**K-Nearest Neighbour** Class membership was determined using an L2 distance and the nearest 10% of samples, scaling with the number of samples used for training.

**Random Forest** 100 decision trees were fit using balanced class weights, each splitting the dataset according to a maximum of 4 features per node (corresponding to the rounded square root of 20 total features).

**AdaBoost** A maximum of 50 decision trees were fit sequentially such that sample weights were iteratively adjusted to prioritize performance on previously incorrectly-classified samples, consistent with<sup>31</sup>.

The hyperparameters for all models were refined from their default values to be appropriate for a small and imbalanced dataset. The performance for all pipeline combinations of preprocessing methods, dimensionality reduction techniques, and models using the reference (i.e. unperturbed) executions in the dataset ranged from an F1 score of 0.64–0.875 with a mean of 0.806; this evaluation was performed on a consistent held-out test set which was used for all experiments, as described in a following section. This set of models was chosen as it includes i) well understood standard techniques, ii) both parametric and non-parametric methods, iii) both ensemble and non-ensemble methods, and iv) models which have been commonly deployed for the classification of neuroimaging datasets<sup>2–4,6,7,24,32,33</sup>.

## Ch.IV - 2.4 Dataset Sampling

A chief purpose of this manuscript involves the comparison of various forms of aggregation across equivalently-simulated pipeline outputs. Accordingly, the dataset was resampled after preprocessing but prior to dimensionality reduction and classifiers were trained, evaluated, and combined according to the

following procedures:

**Reference** Networks generated without any MCA perturbations were selected for input to the models, serving as a benchmark.

**Truncate** The number of significant digits<sup>17</sup> per-edge was calculated using all simulated networks, and the edge weights in the reference graph were truncated to the specified number of digits. Importantly, this is the only method used which deliberately squashes the variance observed across simulations.

**Jackknife** The datasets were repeatedly sampled such that a single randomly chosen observation of each unique network was selected (i.e. derived from the same input datum). This resampling was performed 100 times, resulting in the total number of resamplings being  $5\times$  larger than the number of unique observations per network, ensuring a broad and overlapping sampling of the datasets.

**Median** The edgewise median of all observations of the same network were used as the samples for training and evaluation.

**Mean** Similar to the above, the edgewise mean of all observations for each network were computed and used as input data to the classifiers in both collections.

**Consensus** A distance-dependent average network<sup>34</sup> was computed across all observations of each network. This data-aware aggregation method, developed for structural brain network analysis, preserves network properties often distorted when computing mean or median networks.

**Mega-analysis** All observations of each network were used simultaneously for classification, increasing the effective sample size. Samples were organized such that all observations of the same network only appeared within a single fold for training and evaluation, ensuring double-dipping was avoided.

**Meta-analysis** Individual classifiers trained across jackknife dataset resamplings, above, were treated as independent models and aggregated into an ensemble classifier. The ensemble was fit using a logistic regression classifier across the outputs of the jackknifed classifiers to learn a relationship between the predicted and true class labels.

The robustness and possible benefit of each subsampling approach was measured by evaluation on a subset of all MCA simulations, including 9 distinct numbers of simulations, ranging from 2 to 20 simulations per sample. Combining the dataset sampling methods, the set of simulations, preprocessing

strategies, dimensionality reduction techniques, and classifier models, there were 2,520 perturbed models trained and evaluated next to 40 reference models.

## Ch.IV - 2.5 Training & Evaluation

Prior to training models on the brain networks, 20% of subjects were excluded from each dataset for use as an out-of-sample test dataset for all experiments. With the remaining 80% of subjects, cross validation was performed following a stratified grouped  $k$ -fold approach ( $k = 5$ ). In this approach, samples were divided into training and validation sets such that the target variable was proportionally represented on each side of the fold (stratified), conditional upon all observations from the same individual, relevant for the mega-analysis dataset sampling method, falling upon the same side of the fold (grouped). This resulted in 5 fold-trained classifiers per configuration, each trained on 64% of the samples and validated on 16%, prior to each being tested on the remaining 20% of held-out samples. All random processes used in determining the splits used the same seed to remove the effect of random sampling.

Classifiers were primarily evaluated on both the validation and test (out-of-sample) sets using F1 score, a standard measure for evaluating classification performance. The generalizability of predictions was defined as:

$$G = 1 - |F1_{test} - F1_{validation}| \quad (1)$$

where a score of 1 (maximum) indicates the equivalent performance across both the validation and test sets, and a lower score (minimum of 0) indicates inconsistent performance. The absolute change in performance was used in Eq. 1, resulting in a score which penalizes spurious over-performance similarly to under-performance. This is a desired attribute of the measure as all inconsistency, whether due to chance or model fit, is undesirable when applying a classifier out-of-sample.

Differences in F1 score and generalizability for perturbed experiments with respect to their reference were used to measure the change in performance between for each dataset sampling technique, and statistical comparisons were made through Wilcoxon Signed-Rank tests.

## Ch.IV - 3 Results

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The figures and findings presented in this section represent a summary of the complete experiment table which consists of performance measures and metadata for all 2,560 models tested. The complete



performance table alongside the table of significant differences, are made available through the GitHub repository.

### Ch.IV - 3.1 Data Resampling Improves Classification

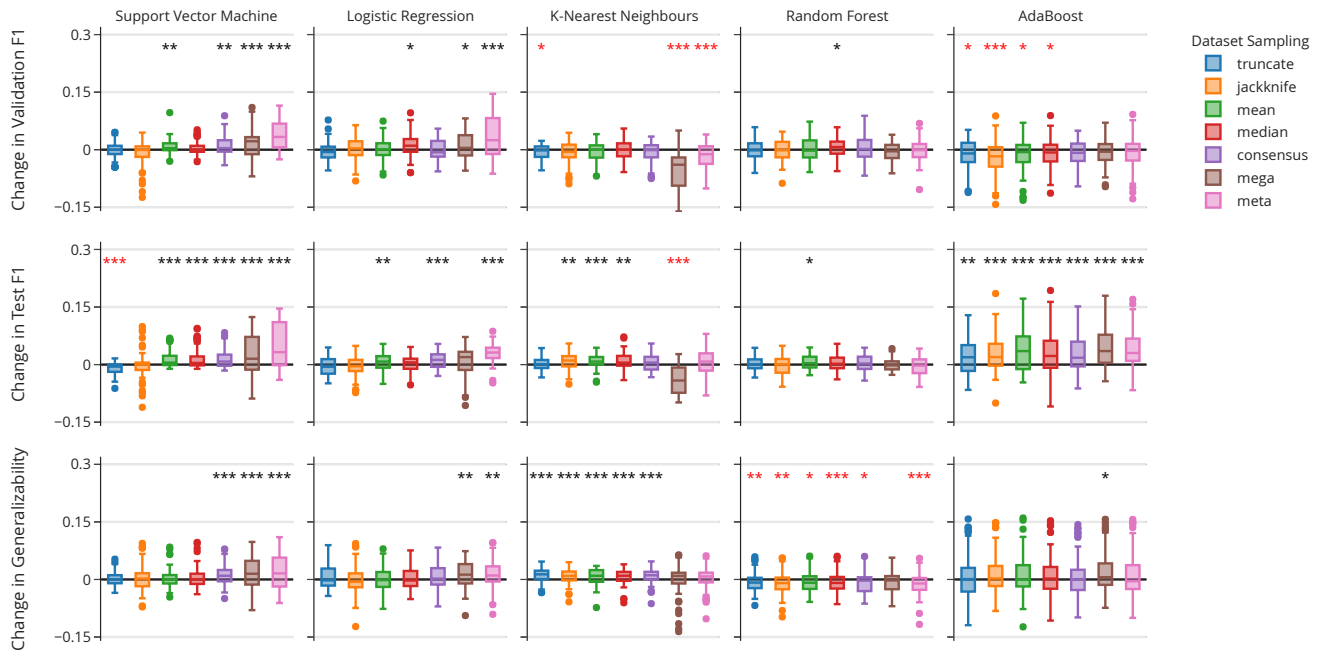
The overall performance of each subsampling method is summarized in Table Ch.IV - 1. The change in performance was measured in both cases as a change in F1 score on the validation set, the change in F1 score on the test set, and the change in overall generalizability, a measure which summarizes the similarity between validation and test performance for a given model.

**Table Ch.IV - 1.** Statistically significant change in performance. Red values indicate significant decline in performance, black values indicate improvement, and empty cells indicate no change. A single star represents  $p < 0.05$ , and each additional star is an additional order of magnitude of significance.

| Dataset Sampling | Validation | Test | Generalizability |
|------------------|------------|------|------------------|
| Truncate         | **         |      |                  |
| Jackknife        | **         | **   |                  |
| Mean             |            | ***  |                  |
| Median           |            | ***  |                  |
| Consensus        |            | ***  | *                |
| Mega-Analysis    | *          | *    | ***              |
| Meta-Analysis    | **         | ***  | *                |

Across all classifier types it was found that consensus, mega-, and meta-analytic approaches outperformed other dataset resampling methods, as each of these methods led to improved testing performance and generalizability. The only method which did not improve performance at all was the truncation resampling approach. This method was distinct from the others in that the variance observed across simulations was used to estimate and squash variance in the reference network, whether other approaches captured the variance. The finding that truncation hurts performance importantly suggests that the variability across the observed networks is biologically meaningful and contains signal.

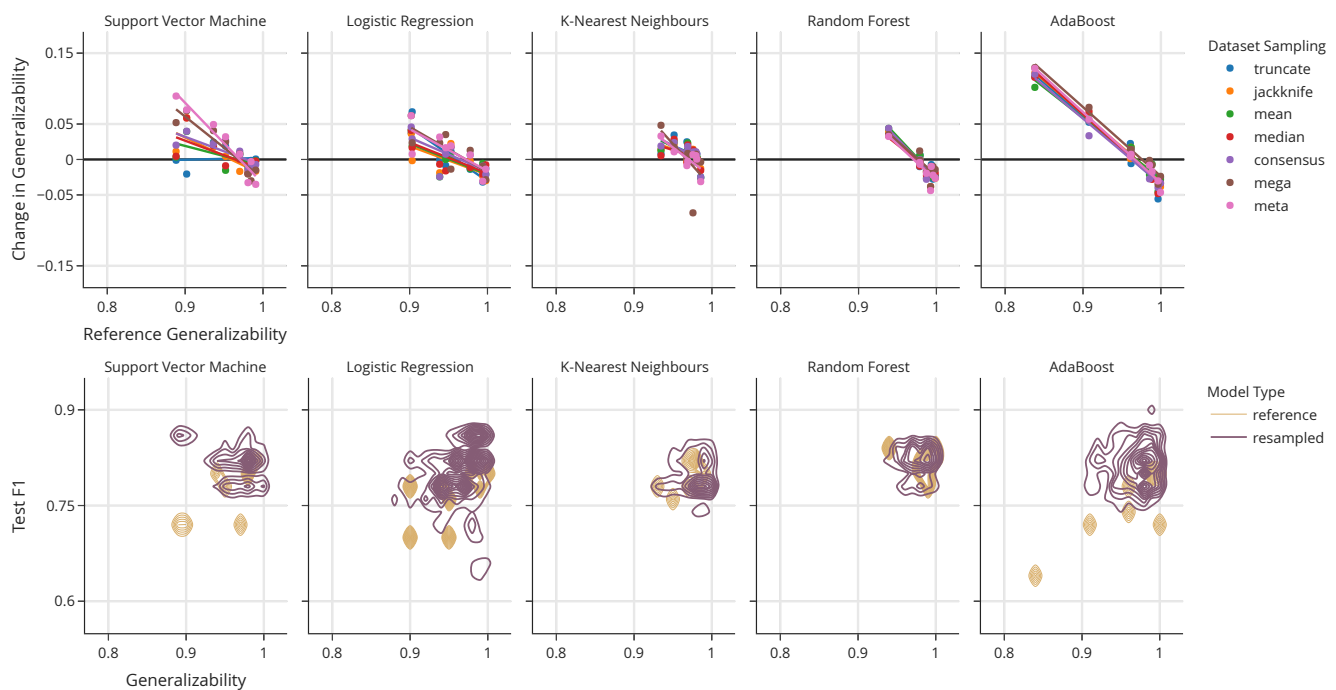
The change in performance for each model and dataset sampling technique is shown in Figure Ch.IV - 2. The support vector machine and logistic regression models improve across each of the three measures for a variety of dataset sampling techniques, suggesting that the addition of the MCA-perturbed samples improves the training, testing, and overall generalizability of these classifiers.



**Figure Ch.IV - 2.** Relative change in classifier performance with respect to classifier type and dataset sampling strategies as measured by change in F1 score on the validation set (top) or test set (middle), as well as the generalizability of performance (bottom). Each star annotation indicates an order of magnitude of statistically significant change, beginning at 0.05 for one star and decreasing from there, with those in black or red indicating an increase or decrease due to resampling, respectively.

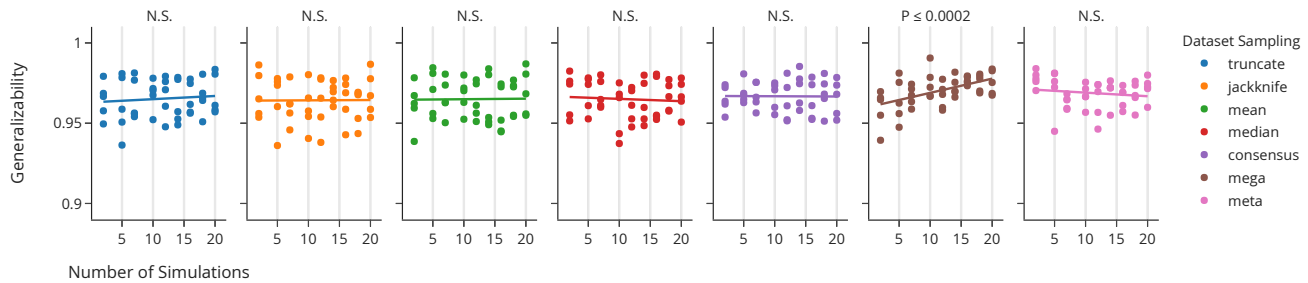
Distinctly, k-nearest neighbours (KNN) and AdaBoost classifiers experienced minimal change in validation and often saw their performance decline. However, the improvement of these classifiers on the test set suggests that resampling reduced overfitting in these classifiers. In the case of KNN, this translates to improved generalizability, while in the case of AdaBoost generalizability was largely unchanged, suggesting that the model went from underperforming to overperforming after dataset resampling. The unique decline in performance when using the mega-analytic resampling technique on KNN classifier is suggestive of poor hyper-parameterization, as there is a strong relationship between the performance and the ratio of the number of samples in the dataset to the  $k$  parameter of the model. At present this parameter was scaled linearly with the number of MCA simulations used, however, it is both possible that an improved scaling function exists or that the model performance degrades with large sample sizes making it a poor model choice given this resampling technique.

The random forest classifiers uniquely did not see a significant change in validation or testing performance across the majority of resampling techniques. However, these classifiers did experience a significant decrease in the generalizability of their performance, meaning that there was a larger discrepancy between training and testing performance in many cases. This distinction from the other models is possibly due to the fact that random forest is a simple ensemble technique which takes advantage of training many independent classifiers and samples them to assign final class predictions, allowing this approach to form more generalizable predictions, and thus the addition of more data does not significantly improve performance further. While AdaBoost is also an ensemble method, the iterative training of models with increasing emphasis on difficult samples allows for the added variance in those samples to play an increasingly central role in the construction of class relationships, and thus more directly takes advantage of the added variability in samples.



**Figure Ch.IV - 3.** Relationship between generalizability and resampling. Top: change in the generalizability of classifiers with respect to the reference generalizability. Each data point represents the mean change in generalizability for all models using the same preprocessing and dimensionality reduction techniques for a given classifier and dataset sampling strategy. Bottom: contour density distributions of generalizability and F1 scores across all models for both reference and resampled training.

While certain combinations of preprocessing, dimensionality reduction, and classifiers performed



**Figure Ch.IV - 4.** The generalizability of classifiers using each dataset sampling technique with respect to the number of MCA simulations. Each number of simulations was sampled a single time, to avoid artificial skewing of the dataset due to the inclusion of “higher” or “lower” quality samples; a single drawing of each split mimics a true perturbation experiment context.

more harmoniously than others, there was no significant relationship between the performance of any single resampling method and preprocessing or dimensionality reduction technique. Overall, the above results show that dataset augmentation through MCA-perturbed pipeline outputs may be an effective way to improve the performance and generalizability of non-ensemble classifiers tasked with modeling brain-phenotype relationships, both within and out of sample, especially when variance is captured rather than removed.

### Ch.IV - 3.2 Resampling Leads to Consistent Performance

To better characterize the the benefit of resampling, the relationship between the magnitude of improvement and the baseline performance of the classifier were further explored (Figure Ch.IV - 3). We found that the increase in the generalizability of a classifier was inversely related to the baseline generalizability (Figure Ch.IV - 3; top). In other words, the less generalizable a classifier was originally, the more its generalizability improved (significant at  $p < 0.05$  for all dataset sampling strategies and classifier other than KNN). There were several situations in which the generalizability of models were noted to decrease, however, though this only occurred for models with high generalizability scores (all  $> 0.935$ ). Importantly, the relative change in generalizability shifts scores towards a single “mode”, suggesting a less biased estimate of the true generalizability of performance on the task, and mitigating both under- and over-performance due to chance.

When exploring the relationship between F1 and generalizability (Figure Ch.IV - 3; bottom), it becomes apparent that even for the majority of models which may not have improved performance along

both axes, either their generalizability or F1 score is improved. While an ideal classifier would reside in the top-right of the shown plots, the dataset resampling techniques consistently shift the distributions in this direction and often improve classifiers along one or both of these axes. Importantly, the variance in performance across both measures is significantly decreased, suggesting that resampling leads to more reliable and reproducible classifiers.

### **Ch.IV - 3.3 Number of Simulations is Largely Unimpactful**

While we previously noted an increase in classifier performance due to perturbation-enabled dataset resampling, it was important to explore the relationship between the number of simulated samples and performance (Figure Ch.IV - 4). There was no relationship between the number of independent simulations and performance, as measured by either F1 or generalizability, for all dataset resampling techniques other than mega-analysis. In the case of the mega-analytic approach, however, there was a significant positive relationship between the number of samples used and the generalizability of performance, though there remained no increase in F1 score. The mega-analysis approach is the only approach which changes the number of samples being provided directly to the classifiers, thus mimics an increase in sample size for traditional experiments. While outlying samples may play a small role in many of the proposed forms of resampling, or non-existent in the median case, the mega analytic approach treats all simulations with equal importance as unique samples in the dataset. In this case, the relationship we observe is consistent to what one might expect when increasing the number of samples.

## **Ch.IV - 4 Discussion**

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The numerical perturbation of analytic pipelines provides a unique, data-agnostic, and computationally unintrusive method for dataset augmentation. Using a technique such as MCA, samples can be simulated across an array of controlled executions and used to enrich datasets with a range of plausible results per sample. We demonstrate that this method of dataset augmentation can be used to improve the training, testing, and generalizability of classifiers.

Through the training and evaluation of 2,560 models combining varying strategies for preprocessing, dimensionality reduction, classifier, and resampling, we found consistent improvement across all measured axes. Interestingly, while there was a statistically significant improvement when using many dataset resampling techniques, there was no significant improvement in the performance, and in fact a reduction, using the truncation resampling method as is shown in Table Ch.IV - 1. This result importantly

demonstrates that the added variability in results obtained through MCA is meaningful and signal-rich itself, and an important determination of performance is the inclusion of this variability.

While the non-ensemble methods benefited most obviously from the dataset resampling strategies, where both F1 and generalizability were often improved, the results presented in Figure Ch.IV - 3 demonstrate that variability in performance across both of these axes was reduced across all classifier configurations. While a reduction in the variability of performance is desirable in itself, this figure also illustrates that the performance of resulting models converges around the more performant models in the case of all classifiers. The reduction in variability also results in models which differed less significantly when looking across classifier types.

Although performance was improved by the integration of MCA simulated samples, performance was not significantly related to the number of simulations used in any case other than the mega-analytic resampling strategy. The independence of performance and number of simulations is encouraging, as a key limitation for using Monte Carlo methods is the often extreme computational overhead. The ability to use a small number of simulations and achieve equivalent performance through the majority of resampling techniques allows for significantly better performance without added data collection and only a theoretical doubling the sample processing time. The benefit of increasing the number of simulations in the mega-analytic case could be considered an analog to increasing the sample size of an experiment. While the range of simulations used here demonstrated a consistent improvement in generalizability, there will be a plateau in performance, either at a perfect score or, more likely, before this is reached. Further work is required for characterizing the relationship between the performance of mega-analytic resampling and the number of simulations, though it is likely that this relationship will be domain-specific and dependent on other experimental design variables such as the number of features per sample.

While our study shows that classifiers with poorer baseline performance benefit more from augmentation, an important limitation of this is the operating point to which that claim remains true. For example, it is unlikely that the trend observed here for a task with a mean reference performance of 0.81 would hold across models operating with reference performance near chance or near perfect. Characterizing the behaviour of this technique across a range of classification contexts and performances would shed light on whether this technique could be applied globally or if it is limited to making “good” models better.

It is a well understood problem that small sample sizes lead to uncertainty in modeling<sup>35</sup>. This is generally planned for in one of two ways: the collection of vast datasets, as is the case in the UK-BioBank which strives to collect samples from half a million individuals<sup>15</sup>, or the collection of repeated

measurements from the selected samples, as is the case in the Consortium of Reliability and Reproducibility which orchestrates multiple centres and scanners, each collecting multiple acquisitions<sup>16</sup>. In either case, the additional data collection by these initiatives is both financially and temporally expensive and leads to unintended confounding effects associated with time of day<sup>36</sup>, weather<sup>37</sup>, or other off-target variables that may be poorly described in the resulting dataset<sup>38</sup>.

While the results presented here provide strong evidence in favour of dataset augmentation through numerical perturbations, the improvement from these methods has not been directly compared to additional data acquisitions in this experiment due to the limited sample size of the available perturbed dataset<sup>20</sup>. Previous studies exploring the effect of sample size on neuroimaging classification tasks have shown that variability in performance decreases with sample size<sup>39</sup>, where a doubling of sample size from 100 to 200 approximately corresponded to halving the uncertainty in performance<sup>35</sup>. However, this decrease in variability is often accompanied by a decrease in out of sample performance in practice<sup>40</sup>. A meta-analysis across 69 studies showed that increasing sample size was negatively related to out-of-sample performance<sup>41</sup>, where accuracy was noted to decline by approximately 5% in a similar doubling from 100 to 200 samples, suggesting that a major contribution of increasing sample size in neuroimaging is a reduction in overfitting which must occur prior to a possible boost in performance. Our finding that MCA-based dataset augmentation reduced overfitting and improved upon baseline performance is encouraging, and suggests that models trained using such perturbed datasets may benefit more from increased data collection.

A common issue in many machine learning contexts is the unbalanced nature of datasets. When using a nearest-neighbour classifier, for instance, a dramatic difference in the membership of each group could have significant impact on model hyper-parameters and performance. In contexts where balanced sampling is not possible, such as when considering a rare clinical population, perturbation-augmented datasets could be applied for realistic upsampling of data. In this case, a mega-analytic aggregation strategy could be used in which more simulations would be performed for members of the under-represented class, similar to the balancing of weights applicable to some models. This application is particularly important, as upsampling is often challenging in biological contexts where realistic simulation models are sparse.

## Ch.IV - 5 Conclusion

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This work demonstrates the benefit of augmenting datasets through numerical perturbations. We present an approach which leverages the numerical instability inherent to pipelines for creating more accurate and generalizable classifiers. While the approach and results demonstrated here were specifically relevant in the context of brain imaging, the data-agnostic method for inducing perturbations and off-the-shelf machine learning techniques used suggest that this approach may be widely applicable across domains. This work uniquely shows that numerical uncertainty is an asset which can be harnessed to increase the signal captured from datasets and lead to more robust learned relationships.

### Data & Code Availability

The perturbed connectomes were publicly available in a data resource previously produced and made available by the authors<sup>20</sup>. They can be found persistently at <https://doi.org/10.5281/zenodo.4041549>, and are made available through The Canadian Open Neuroscience Platform (<https://portal.conp.ca/search>, search term “Kiar”). All software developed for processing or evaluation is publicly available on GitHub at <https://github.com/gkpapers/2020AggregateMCA>. Experiments were launched on Compute Canada’s HPC cluster environment.

### Author Contributions

GK was responsible for the experimental design, data processing, analysis, interpretation, and the majority of writing. All authors contributed to the revision of the manuscript. TG and ACE contributed to experimental design, analysis, interpretation. The authors declare no competing interests for this work. Correspondence and requests for materials should be addressed to Gregory Kiar at [gregory.kiar@mail.mcgill.ca](mailto:gregory.kiar@mail.mcgill.ca).

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### 3 Discussion

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The work presented across the manuscripts contained within this thesis demonstrate the creation and application of infrastructure and methodology for the analysis of stability in neuroimaging pipelines, and demonstrate its application for both the study of robustness in an analytical context and the generation of more generalizable brain-phenotype relationships. These four manuscripts incrementally present the methods developed to perform a large scale evaluation of numerical stability in neuroimaging, each providing a foundation for the following studies. As a result, this thesis has led to the creation of both scientific software resources and considerable scientific advancement in the study of numerical stability in neuroimaging.

In the following sections I will discuss and interpret the findings as a whole and their implications on the field of structural connectomics. I will then discuss the relevance of extrapolating these conclusions to other domains of neuroimaging, including the analysis of both functional and structural images. Beyond discussing the implications of the results presented here, I will propose ways in which perturbation analyses may be further adopted in neuroimaging, and conclude with lessons learned both from my own pursuit of these projects and recommendations for the field at large.

#### 3.1 The Impact of Perturbing Structural Connectome Estimation

Throughout this thesis I have demonstrated that controlled perturbations serve as a viable and effective method to study the stability of structural connectome estimation pipelines. In each of the various methods tested in Chapter II, such as one-voxel noise injection, sparse Python-only Monte Carlo Arithmetic (MCA), or dense full-stack MCA, we noticed that the distinct nature of the perturbations in each case led to distinctly structured variability in the results. In the case of one-voxel perturbations, a small and localized form of noise, we noticed similarly localized changes in outputs. However, the MCA instrumentations led to outcomes with local, topographical, or scaling changes across different simulations of the same data. Perturbations with MCA were not only able to encapsulate similar effects and deviations as were

observed with the one-voxel methods, but the independence of the MCA method from the dataset, the lack of introduced bias, and the global perturbation of operations makes MCA a more scalable and generalizable technique for exploring instability. While I recommend the adoption of the MCA technique generally, one-voxel methods can serve as a valuable method for the local evaluation of instabilities, such as an evaluation of the sensitivity of an algorithm in a region that is difficult model, or in proximity to unavoidable contrast changes such as in the presence of a lesion or significant atrophy.

The two MCA environments used throughout this thesis differed considerably in both their construction and the resulting behaviour of tools. In the sparse setting, referred to across the manuscripts as either “Python-only” or “Input Instrumentation”, a considerably smaller set of libraries were instrumented with MCA. In this case, all floating point operations performed directly by Python or Cython-compiled code were perturbed. However, while the widely adopted NumPy<sup>121</sup> library is a Python-installed module, it remained largely uninstrumented as operations therein predominantly rely on the lower-level linear algebra libraries BLAS<sup>122</sup> and LAPACK<sup>123</sup>. In the dense setting, referred to as “Full-Stack” or “Pipeline Instrumentation”, BLAS, LAPACK, and NumPy were instrumented as well. As was confirmed by a minimal change in execution time, this distinction meant that the operations perturbed in the sparse configuration were not those doing the “heavy lifting” of image, matrix, or array manipulation, but only those doing more simple manipulations of data in the setup and recovery from these operations. This results in an important change to the MCA method as it was originally defined by Parker<sup>34</sup>: the few-and-far-between nature of perturbations both limits the law of large numbers<sup>124</sup>, making it likely that there exists bias in the introduced perturbations, and allows for the cascading of single perturbations without correction, amplifying this bias as a result. Given that the realizations of this bias is still random across executions, an unbiased sampling of the distribution of results may still be possible.

Across the two MCA instrumentations we observed similar bounds of the induced variability. This, alongside considerably reduced computational overhead in the sparse case, suggests that sparsely applied MCA could be a useful technique for approximating the bounds of pipeline variation as measured with dense (or, true) MCA. Just as the list of instrumented libraries in the sparse configuration is a strict subset

of those instrumented in the dense case, it holds that the set of possible perturbed results in the sparse configuration is a strict subset of the possible results in the dense case. This relationship is potentially powerful as this means that problems can undergo a preliminary and less computationally intense stability evaluation prior to being evaluated more densely. The coherence of results across the two perturbation configurations presented throughout Chapter III suggest that the sparse Input Instrumentation is a high quality estimator of the true MCA distribution. Figure Ch.III - 2 shows that the sample distributions of network statistics derived from the perturbed connectomes are unchanged across both MCA configurations, and Table Ch.III - 1 demonstrates the ability of both techniques to increase the reliability of the dataset. Uniquely, the connectomes resulting from the sparse MCA instrumentation contained less session- and acquisition-dependent signal than either the original dataset or the dense MCA results. With the specific cause of this result unknown, it is impossible to make a statement on the generalizability of the effect, however, given its potential significance in brain imaging, it is an area of extreme interest for future work.

The variability introduced by MCA also had considerable impact on the modelling of brain-phenotype relationships. In the case of both MCA instrumentation methods, Figure Ch.III - 3 shows how random sampling of the perturbed networks led to a distribution of performance (F1 score) on a BMI classification task that spanned an approximate range of  $\pm 0.10$  relative to performance using the reference (unperturbed) connectomes. The balance of performance about the original values lends credence to the interpretation of MCA derived connectomes as being sampled from the distribution of equally plausible results, some of which may contain “more” or “less” signal for a given task, and by extension, that the unperturbed connectomes are simply point-estimates of these distributions. Chapter IV demonstrates several techniques for considering the variability across these distributions of networks from the sparse-MCA setting on a similar classification task. While the majority of techniques used were designed to aggregate connectomes and aimed to capture variability, a single truncation strategy was tested which removed all non-significant bits of information across the distributions. When exploring these techniques, the truncation strategy was the only method which did not improve the performance of the models, and in fact made them worse, suggesting that the observed variability was not entirely to random fluctuation or noise, but that

the variation observed across perturbations contained meaningful signal. Each of the variance-capturing aggregation strategies led to improved performance of the classifiers, while three strategies also led to the improved generalizability of these classifiers as well (e.g. similarity between performance on validation and out-of-sample test sets). Interestingly, the three superior strategies each took a conceptually distinct approach to aggregation. Distance-dependent consensus averaging<sup>125</sup> is a technique for computing a group-wise average connectome that preserves the distributions of short- and long-range edges found in the original networks, a property that the smoother median- and mean-averaged graphs fail to preserve. The mega-analytic consideration of all perturbed connectomes treated each observed network as a sample in a repeated-measures dataset. This increased the dataset size by  $20\times$  in this case, and, importantly, all observations of each connectome were available and considered equally valid for the learning of class-dependent relationships. Unlike all other methods tested, the improvement of this method with Finally, the meta-analytic voting across classifiers was performed with the construction of a ensemble model which fit a Logistic Regression classifier across the outputs of each of the independently-trained jackknife classifiers. Each jackknife model was trained with no attempt to capture within-subject across perturbations, but rather sampled the space of possible population-level relationships by repeatedly considering single observations of each individual. These models were then considered as a forest, and a relationship was learned across their predictions and various levels of confidence. An important conceptual difference between this technique and the mega-analytic classification above is that each component classifier here performs a unique feature selection step, meaning that the different samplings may arrive at different features for classification. One attribute that each of these three techniques have in common over the other methods tested (jackknife classifiers, median, mean), is that more of the variance across perturbations was captured rather than either independently sampled or smoothed.

While I have yet to mention the Clowdr tool presented in Chapter I, it played an essential role in the execution of these experiments. Over the course of the four presented manuscripts, Clowdr has facilitated the launch, debugging, visualization, and provenance recording of over 20,000 cluster and cloud tasks, totalling 22 CPU-years worth of resources. While many tools exist to facilitate large scale deployments of



pipelines, Clowdr enables this for tools which are still in development while also providing a quick path to the FAIR<sup>126</sup> publication of tools and records through Boutiques<sup>31</sup>, or easy adoption of these tools in public-facing community platforms such as CBRAIN<sup>127</sup>.

The combination of results presented across my thesis, showing both the significance of numerical instabilities in structural connectome estimation and the utility of the associated variability, demonstrate that numerical analysis techniques such as MCA can serve as valuable tools towards studying and improving reproducibility in neuroimaging. Other efforts which have explored reproducibility from the angle of analytical flexibility<sup>2,115</sup> sample a broad and rich space of approaches and tool configurations that is not directly comparable to the techniques demonstrated here. Combining these approaches would be of extreme interest and lead to a far richer description of the uncertainty associated with certain tasks, processing techniques, or analytic questions more broadly, and could be used to inform comparison of results obtained across distinct libraries where such comparisons are currently impractical.

### **3.2 Extrapolating Conclusions Across Domains**

Throughout this thesis I have focused on the analysis of stability in the estimation of diffusion MRI-derived structural connectomes. Given this specific application, I do not make any strict claims about the generalizability of these findings on other domains of neuroimaging or beyond. However, if one wishes to participate in the thought experiment of forming a hypothesis about the stability of another domain, there are three components which must be considered: data, problem difficulty, and software quality. I will discuss what to look for in each of these components, and apply these questions to possible applications in structural and functional neuroimaging.

**Data** The quality and dimensionality of datasets have a considerable role on the stability of applied tools. Various attributes that contribute to this impact are the signal to noise ratio (SNR), resolution, sparsity, and image contrast. The impact of each of these features can be considered conceptually in the context of the curse of dimensionality<sup>2</sup>. For example, for a setting in which equivalent datasets vary only by the sparsity of entries, applied models will arrive at more stable solutions in the case of the more dense dataset<sup>128</sup>.



Similarly, if a dataset has a higher SNR relative to an otherwise equivalent neighbour, the dataset with the higher SNR will lead to more stable solutions. In the context of neuroimaging, the resolution and sparsity are relatively consistent across all MRI modalities, however, the SNR and quality of contrasts differ significantly. Structural imaging methods generally have higher SNR and sharper contrast<sup>86,87</sup> than either functional<sup>88</sup> or diffusion<sup>92</sup> sequences, suggesting that the analysis of structural images may lead to more robust results. However, if analysis methods have been developed with underlying assumptions about the SNR or smoothness of these images, then the associated tools may in fact be less stable in the face of perturbation.

**Problem Difficulty** The difficulty of a given problem can also be thought of as the model's complexity. The theoretical difficulty of robustly fitting a model can be evaluated by calculating its conditioning, as was discussed in Section 2.4. While this remains practically difficult to evaluate, a reality which served as a large motivation for this thesis, complexity can be coarsely estimated by considering both the dimensionality of input data and the number of parameters produced in the output. For example, a diffusion MRI dataset containing 135 diffusion directions will provide a more stable solution when fitting a 6 component tensor than an 60 component orientation histogram, barring any fatal algorithmic implementation errors. In reality, the difficulty of a pipeline is dependent on the specific steps, their sequence, and the specific algorithms chosen to accomplish them. While there are many stable diffusion tensor models<sup>118</sup>, it is possible that this area provides a best-case given that each voxel is modelled independently and the models themselves summarize relatively simple phenomenon. On the other hand, techniques for the correction of topological errors in brain surfaces, a common component of both structural and functional analyses, have been developed over several decades and range in complexity from manual proof-reading to fitting high dimensional transformations<sup>129</sup>. It is likely that there is considerable heterogeneity in the stability of these methods given the dramatic range in flexibility, complexity, and conceptual approach. Similar to image registration, simpler (e.g. affine) approaches will tend to be considerably more stable than their more complex (e.g. diffeomorphic non-linear) counterparts. This

balance between complexity or problem difficulty and stability is therefore a design decision which must be considered when constructing pipelines and, absent a context-specific evaluation, simpler methods should be preferred if variability in the results is undesired or the associated error will not be considered.

**Software Quality** There are many factors which determine the quality of software, though without explicit evaluation these can often best be approximated by meta-data properties of libraries. One such feature is the openness of a tool. Open science practices have recently been shown to lead to faster progress<sup>130</sup> and have been widely and effectively been adopted in both genomics<sup>131</sup> and for the ongoing COVID-19 pandemic<sup>132</sup>. Aside from the “two heads are better than one” argument, this is likely because software quality has been shown to decrease in a competitive market<sup>133</sup>, while open source software development typically fosters a collaborative environment. Another feature of library quality is modularity or size. Smaller libraries solving fewer independent problems are generally of higher quality<sup>133</sup>; this is often called the “worse is better” or New Jersey philosophy<sup>134</sup>. With these criteria in mind, the diffusion workflows evaluated here relied solely on open source implementations of thoroughly tested and peer-review published algorithms in DIPY<sup>135, 136</sup>, which makes the quality of software a likely best-case scenario. However, there exists considerable heterogeneity in both the openness and size of libraries across neuroimaging as a whole. While pipelines such as fMRIPrep<sup>23</sup> integrate functionality across a set of disparate libraries, it is likely that distinct branches therein will differ considerably in terms of their stability as a result. Both FreeSurfer<sup>137</sup> and CIVET<sup>138</sup>, two tools commonly used for the estimation of cortical surfaces from structural data, have been largely developed in separate silos. While these tools are more mature than either DIPY or fMRIPrep mentioned above, it has been shown that this maturity does not equate to a robustness to minor data perturbations<sup>27</sup> in either case. The estimation of software quality is undeniably the most difficult to perform from a surface level, making it imprudent to provide a general claim as to the expectation of which domains or analytic modalities may be more stable relative to others.

While this exercise could be conducted across arbitrary domains, if one had to make an *a priori* set of guidelines to follow it would unsurprisingly be that higher quality datasets, simpler problems, and more

open and widely tested code will generally lead to more consistently stable solutions<sup>e</sup>.

### 3.3 Future Directions in Operationalizing Perturbation Analysis

The initial aim of this thesis was to identify instabilities within neuroimaging pipelines. An exciting evolution of this plan was the finding that the variability arising from numerical perturbations may contain meaningful signal. This suggests that perturbation analysis is not only valuable as a tool for measuring the stability of algorithms or workflows, but that it can be applied far more flexibly to improve their quality. Considering this, next steps in this area could be categorized into two broad questions: *where* to perturb, and *what* to do with the induced variability. I will discuss different components of neuroimaging workflows which may benefit from perturbation analysis and identify several possible applications of the results for each. I will then more broadly discuss other applications for perturbation analysis and possible open questions as they may apply across each of these areas. Given that the intersection of numerical analysis and neuroimaging is in its infancy, many of these potential explorations remain as open questions that an interested reader could explore (or build a grant program around).

#### 3.3.1 Targets for Perturbation

Neuroimaging data undergoes considerable processing after collection, beginning with image reconstruction. Initiatives such as Gadgetron<sup>140</sup> provide scanner-agnostic MRI reconstruction algorithms in an effort to both improve the quality of these reconstructions and reduce cross-vendor variances. The perturbation of image reconstruction algorithms could be performed to identify which algorithms are the most robust across a set of manufacturers and scanner models. In addition to the identification of robust reconstruction methods, higher fidelity images could be generated through the ensemble of perturbed images, possibly achieving benefits like those found in High Dynamic Range image enhancement. Similarly, this could be applied to influence the development of vendor-neutral pulse sequences themselves<sup>141</sup>, and inform the adoption of stable data collection-and-reconstruction pairs.

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<sup>e</sup>This recommendation towards simplicity is not unlike the fact that simple or heavily regularized models are more generalizable in machine learning<sup>139</sup>.

Reconstructed images typically undergo numerous alignments, corrections, denoising steps, and modelling prior to their application in the modelling of structural or functional phenomena. These processing steps, such as image registration which is relevant across all modalities of neuroimaging, are often known to exhibit sensitivity to initial conditions or noise<sup>30</sup>, as was confirmed here. The perturbation of any of these components or entire workflows could be done to test the sensitivity of specific components to numerical error or identify unstable steps within pipelines.

Processed data are often terminally used in statistical testing or machine learning frameworks. Commonly used frameworks for testing hypotheses or fitting models often contain an element of randomness, such as Permutation Testing<sup>142</sup> or Stochastic Gradient Descent<sup>143</sup>. This tolerance and expectation of randomness likely makes them less susceptible to the errors associated with minor perturbations. However, feature selection, a typically deterministic process, is commonly performed on neuroimaging data prior to their application in these frameworks<sup>144</sup>. In cases where initialization of these features has considerable impact on their quality<sup>145</sup>, the perturbation of both the initializations and feature selection algorithm itself serves as an interesting avenue for exploration. It is possible that perturbing feature selection will lead to similarly meaningful variability as was observed here, which would have the considerable benefit of being much less computationally expensive than the perturbation of image processing steps.

### **3.3.2 Applications of Perturbations & Open Questions**

This thesis ultimately focused on two specific applications and interpretations of perturbation analyses: the evaluation of pipeline stability and the aggregation of unstable derivatives. There are many possible extensions to this work and distinct functions that MCA-based perturbations can enable from both the perspective of tool development and analysis. One such opportunity from the perspective of tool development is the localization of instabilities. VeriTracer<sup>146</sup> provides functionality to trace the execution of workflows and evaluate the propagation of numerical error throughout pipelines. By gradually improving or removing sources of instability within pipelines, it would be possible to construct workflows that are more robust to numerical error. A separate approach would be to introduce a mixed (declining) precision

model for data in pipelines. In this case, MCA could be used to estimate the number of significant bits at each node of a pipeline, and use this information to truncate the data and bit-space allotted to subsequent results accordingly. This approach would not only remove the compounding effect of numerical instabilities at each node (as defined at a context- and tool-appropriate resolution), but it would make explicit a priority for tool developers to err on the side of building simpler and more robust pipelines. In a preliminary exploration of this idea, I truncated the data associated with Chapter III after pre-processing was performed and found that a large portion of the induced variance in connectome construction was reduced in the sparse instrumentation case.

In cases where the re-engineering of pipelines is either non-feasible (e.g. closed source software) or not of interest, Chapter IV demonstrates that capturing the induced variability can improve the quality of derived results. An interesting comparison can be made here between pipeline variability and the Bias-Variance trade off<sup>147</sup>. Deterministic pipelines without perturbations will produce a single result with a single fixed (and biased) error. When perturbations are introduced, this error shifts from a single biased quantity to distinct errors with considerable variability. Rather than then considering any single result of the tool as the “true” result, we can model a series of results derived from the same data in the form of a *mean ± variance*, for example. This shift in perspective is powerful: statistics have long concerned themselves with accounting for measurement error in the collection of samples and developing robust measure for estimating population-level statistics. Adopting such techniques across perturbed observations will not only allow for more richly descriptive individual measures, but it will provide a quantitative value of measurement uncertainty which can be accounted for in subsequent testing and modelling efforts. This would enable the construction of a joint false-positive rate when combining the uncertainty in results and testing frameworks, and would lead to more reproducible findings.

Finally, a point which was mentioned here is the distinction between unique MCA instrumentations. The comparison between the two instrumentations explored here provides perhaps the simplest case for such a comparison: the sparse environment induced perturbations on a strict subset of the operations perturbed in the dense setting. However, when considering pipelines built upon different libraries, such as

the dependence of FSL<sup>148</sup> on many Libmath functions<sup>30</sup> versus the dependence of DIPY<sup>135</sup> on Python, these instrumentations become increasingly difficult to compare. In an extreme case where all floating point operations are instrumented with MCA for both pipelines, we can ignore this problem and state that true MCA is applied in both cases. This claim is fragile, however, as even if a single operation or function is unperturbed in either case, there is the possibility of either allowing for the unequal propagation of errors, or the unfair “skipping” of a highly (un)stable step; this picture becomes further muddled as instrumentations become even less dense. While this may not be a substantial issue in practice, as the variability of results will likely be explored within a given tool and subsequent stabilities could be compared, this problem of comparing instrumentations can arise within a pipeline, as well. For example, the instrumentation of the DIPY-constructed pipelines that were tested throughout this thesis was performed with Verificarlo<sup>33</sup>. Using this tool, BLAS, LAPACK, NumPy, the Python interpreter, and Cython libraries associated with DIPY were all re-built with MCA-logic introduced at the level of C or FORTRAN. If the instrumentation was instead introduced from the level of Python as function decorators, for example, experiments performed across the two versions would capture distinct and possibly non-overlapping variability. The relationship between distinct instrumentations in general is poorly understood, and there currently doesn’t exist a theoretical framework for their comparison. Development of such an understanding, possibly with roots in Set Theory<sup>149</sup>, would be an extremely interesting topic for further investigation that would increase the generalizability of findings derived from perturbation experiments.

### **3.4 Hindsight**

The final topic I would like to discuss is centred on hindsight. Throughout this project I have developed tools for scientific infrastructure, built pipelines from modular pre-existing components, adapted a numerical analysis framework to a new scientific domain, modelled instability in connectomes through a wide array of both commonly used and novel measures, and showed how numerical instability can be a useful property of software. This process has not only been punctuated by scientific outputs which found their ways into papers, but by failures and lessons, both pertaining to my own work and the field of

neuroimaging at large. I have published successes and failures from my Ph.D. on my website throughout my degree<sup>f</sup> in an effort to not repeat my own mistakes and allow others to learn from them. While making an effort to be brief, I feel it necessary to provide some considerations and advice that would be relevant both to my previous-self and possibly the field of neuroimaging as a whole. None of these reflections are intended to be perfect, but merely serve as some things to think about...

**Be Aware of the Cost of Computing** While this advice may at first provoke thought about funding and the cost of either building machines or using the cloud, I do not intend to refer to money, but energy. Scientific computing is an expensive endeavour: over the course of my thesis, I have consumed nearly 22 CPU-years worth of execution time for the project directly related to my thesis, and double that if considering collaborations. Even taking a lower-bound estimate, this means my experiments have consumed 4,000 kWh of electricity<sup>g</sup>. I have been fortunate to perform my research on computers residing in Quebec and Ontario, where my average rate of Carbon emissions at the time of writing was approximately 20 g CO<sub>2</sub>/kWh<sup>h</sup>. In this relatively green environment my research has produced 160 kg CO<sub>2</sub> emissions which, for reference, currently equates to an upper-bounded offset cost of approximately \$8.00<sup>i</sup>. If I had performed my experiments in another environment, such as through Amazon Web Services instances residing in the United States where the rate of Carbon emissions averages over 400 g CO<sub>2</sub>/kWh<sup>j</sup>, the total environmental footprint would increase 20-fold, which would amount to the same Carbon footprint as putting an extra car on the road for a year<sup>k</sup>! This is not meant as an endorsement for running analyses in Canada *per se*, but merely as a reminder that we should be aware of the impact that our experiments have on the world more broadly than just our papers. This is important so we can clearly evaluate which

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<sup>f</sup><https://gkiar.me/phd>

<sup>g</sup><https://www.top500.org/lists/green500/2019/11/>

<sup>h</sup><http://bit.ly/canada-energy-consumption>

<sup>i</sup><https://www.energysage.com/other-clean-options/carbon-offsets/>

[costs-and-benefits-carbon-offsets/](#)

<sup>j</sup><https://www.eia.gov/tools/faqs/faq.php?id=74>

<sup>k</sup>[https://www.nrcan.gc.ca/sites/www.nrcan.gc.ca/files/oe/pdf/transportation/](https://www.nrcan.gc.ca/sites/www.nrcan.gc.ca/files/oe/pdf/transportation/fuel-efficient-technologies/autosmart_factsheet_6_e.pdf)

[fuel-efficient-technologies/autosmart\\_factsheet\\_6\\_e.pdf](#)

experiments are worth doing and offset any distant harm we may cause.

**Keep Clear and Incremental Objectives** Over the last several years it has become clear to me that projects are rarely “complete”. There is always another experiment, figure, analysis, or interpretation that we can explore. However, the longer we follow these rabbit holes (which often provide their fair share of excitement), I have found it becomes gradually easier to lose sight of the original target or purpose. The experiments I presented in Chapter IV, for example, are a small subset of the models, conditions, and experimental permutations originally considered when aggregating connectomes. I did not exclude the others because of their outcomes, but because they failed to answer the question I sought out to explore. These incrementally distinct experiments were the result of asking new questions that brought me not only further from where I started, but into the territory of having answers that were ultimately uninterpretable because I hadn’t fully answered questions that they depended upon. I got momentarily swept up in where I wanted my project to lead eventually, rather than taking the time to fully understand where it was now. I suspect that I am not the only scientist to fall into this trap, and I believe the field of neuroimaging as a whole may have experience with it, at least in appearance. Despite regularly defining possible real-world applications and outcomes in papers, neuroimaging and fMRI in particular has received considerable criticism for lack of delivering on this promise<sup>150</sup>. While this criticism is perhaps unfairly harsh<sup>151</sup>, it remains that neuroimaging hasn’t yet become as relevant as may have once been anticipated. While I believe this is in part due to an academic curiosity taking the reins as I experienced, I think this in reality is more of an “image problem” due to conflation of the *eventual* objectives and those which are presently feasible and being built towards. By clearly defining and communicating our goals and the incremental objectives that must be met along the way, both as individual scientists and as a field, I suspect we’ll fall down fewer of these rabbit holes, and stop having to defend the reality that science is an incremental process that takes time.

**Avoid “Not Invented Here” Thinking** A point which I have mentioned repeatedly throughout this thesis is that there are a considerable number of libraries that have been built to accomplish similar tasks, often



in isolation. In fact, I committed this taboo myself during this thesis in Chapter I with the creation of Clowdr. I built this tool out of the necessity to run experiments in the particular way I had envisioned, and I did so largely from the ground-up. As a result, the code has at various points required development to function in new use cases, or become difficult to maintain as its sole core contributor. In retrospect, a more sustainable solution may have been for me to build my extension into an existing framework or library, such as Nipype<sup>66</sup>. While the creation of this tool was necessary and relevant for the completion of my thesis, if I built the extensions I needed in an existing ecosystem I would have not only gained the review and debugging support of its user and developer base, but also been able to provide a more accessible contribution to the community who were already familiar with a given environment. I believe the same could likely be said for many tools that have been built in neuroimaging (and likely science more broadly). Though I don't believe there should be a single solution for every challenge, I do think that maintaining a collaborate-first and compete-second perspective would not only reduce possible redundancies in this space, but would lead to higher quality and more sustainable contributions.

## 4 Conclusion

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The objective of this thesis was to explore and improve the robustness of results in neuroimaging. This process began with the development of a scalable library for the deployment, management, visualization, and provenance-rich capture of computational experiments. This tool significantly lowered the barrier to adopting high performance computing infrastructures for large neuroimaging experiments. With the computational backbone in place, I compared various perturbation methods for the evaluation of numerical instabilities in structural connectome estimation pipelines. Through perturbation of either the inputs directly or adding stochasticity to existing numerical error, I was able to demonstrate instability in structural connectome estimation that peaked at the level of observing cross-subject differences. Building upon this proof-of-concept for the effective perturbation of pipelines, I performed a series of experiments, comparisons, and evaluations of perturbed structural connectomes to quantify the analytical impact of the

induced instabilities. While individual estimates of connectivity and subsequently derived features varied considerably, in some cases retaining no signal, it became evident that the perturbation of connectome generation led to variability that both improved the reliability of the dataset and had potential for improving the downstream modelling of brain-phenotype relationships. In an effort to capture this variance, I tested several strategies for the aggregation of this variance across perturbed connectomes and evaluated their impact on the performance of several classifiers tasked with modelling a relationship between structural connectivity and age. I found that the aggregation of induced variability lead to more performant predictive models which were more generalizable to unseen data.

I believe that this thesis clearly demonstrates the impact that numerical instabilities may have on neuroimaging results, and provided a compelling solution to this problem that can be immediately adopted by the community. Alongside the characterization of instability in structural connectome estimation, the tools I developed increase the accessibility of the large scale application of numerical analysis and neuroimaging workflows. I began this thesis with the ambition of shedding light on important issues in neuroscience, and ultimately improving the trustworthiness of neuroimaging claims. I believe that the contributions presented here provide compelling evidence of both the impact of numerical error in neuroimaging and provide a glimpse of a hopeful future in the field when these challenges are faced head-on rather than swept under the rug.

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