Reproducible, generalizable, and scalable analytic software for large neuroimaging datasets

Dissertation Proposal Defense

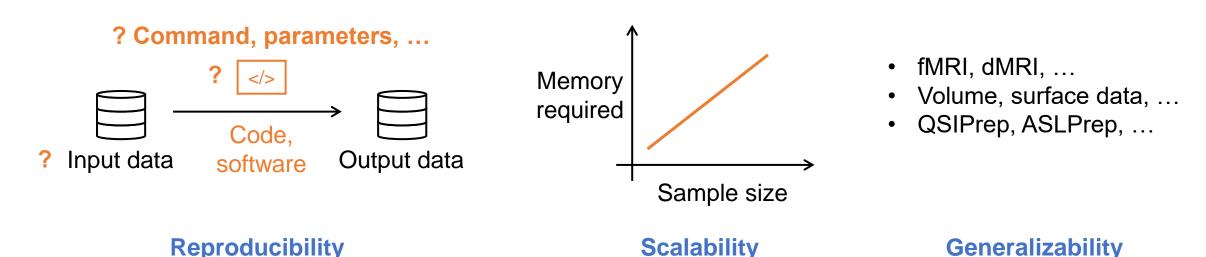
Chenying Zhao

April 1st, 2022



Overview – The challenge: Reproducibility in large-scale neuroimaging research

- Reproducibility crisis in neuroscience and neuroimaging, esp. with large-scale datasets
 - Fully reproducible research requires a full audit trail of data processing; however existing tools are not user-friendly
 - Memory intensive for e.g., mass-univariate hypothesis testing
 - Analytic tools are often not generalizable for various image types, data types and processing methods.



Overview – Proposed solutions

To develop reproducible, generalizable, and scalable analytic software for large neuroimaging datasets

- Aim 1: To develop and release an open-source software package for reproducible image processing at scale.
- Aim 2: To develop and release a generalizable, memory-efficient, open-source R package for mass-univariate hypothesis testing of large neuroimaging datasets.

Outline

- Aim 1: Software for reproducible image processing at scale
- Aim 2: Memory-efficient, generalizable software for statistical analysis
- Software development

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- Aim 2: Memory-efficient, generalizable software for statistical analysis
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Outline: Approach for Aim 1

To develop and release an open-source software package for reproducible image processing at scale

- Approach for Aim 1:
 - Background
 - BIDS and BIDS apps
 - Method for data provenance tracking using DataLad
 - Workflow and functionality of proposed software
 - Compatibility with computing cluster management systems
 - Evaluation data and details

Aim 1 – Background Reproducibility crisis in neuroimaging studies

Even with the same data, different analytical methods and tools can lead to discordant results:

H1 cluster 3 (P_{yes} = 0.14) H1 cluster 1 ($P_{\text{ves}} = 0.38$) H1 cluster 2 ($P_{\text{ves}} = 0.29$) Ground truth HARDI DET HARDI PROBA DTI DET **Functional** MRI: Botvinik-Nezer et al., Nature 2020 100/0% (OL/OR) 53/44% 85/185% 90/263% Hard Diffusion MRI: 100/0% 37/30% 52/67% 79/95% POPT Hard Maier-Hein et al., Nat Comm 2017 100/0%

48/53%

89/104%

26/6%

Aim 1 – Background Large-scale neuroimaging datasets can enhance statistical power

- Human Connectome Project
 - Young adult (n=1,200)
 - Development (n=1,300)
- Philadelphia Neurodevelopmental Cohort (PNC, n=1,601)
- Healthy Brain Network (n=5,000)
- UK Biobank (n=40,000+)
- ...

Aim 1 – Background Challenges in reproducibly processing large-scale datasets and emerging solutions

- Large-scale datasets:
 - © enhance statistical power
 - 😊 complexity, heterogeneity, and huge sample size
- Emerging solutions:



Code version control tools

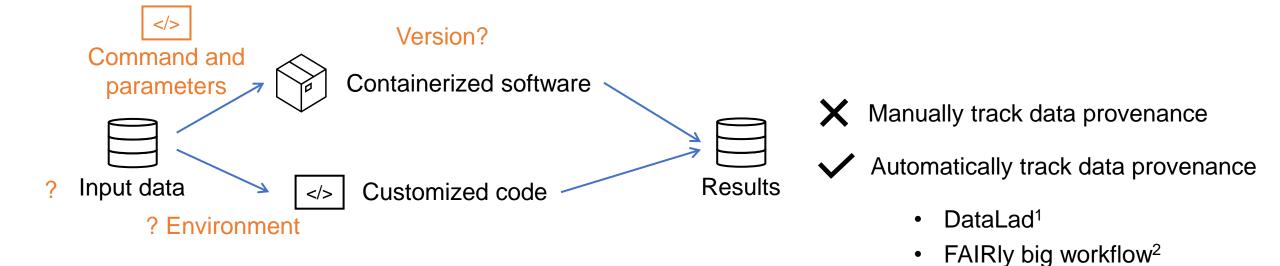


Portable containers



High performance computing (HPC) clusters

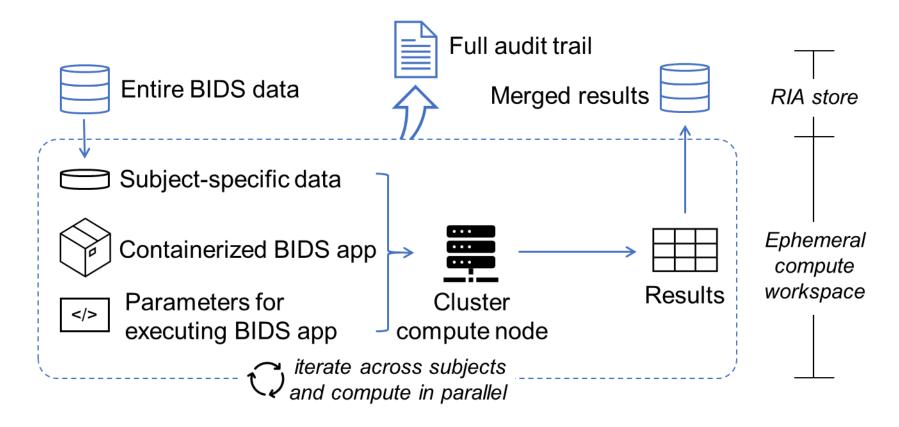
Aim 1 – Still, there are obstacles... Complete reproducibility with automatic data provenance tracking



- However, not practical for most academic investigators
 - Numerous steps and DataLad functions
 - Highly customized code

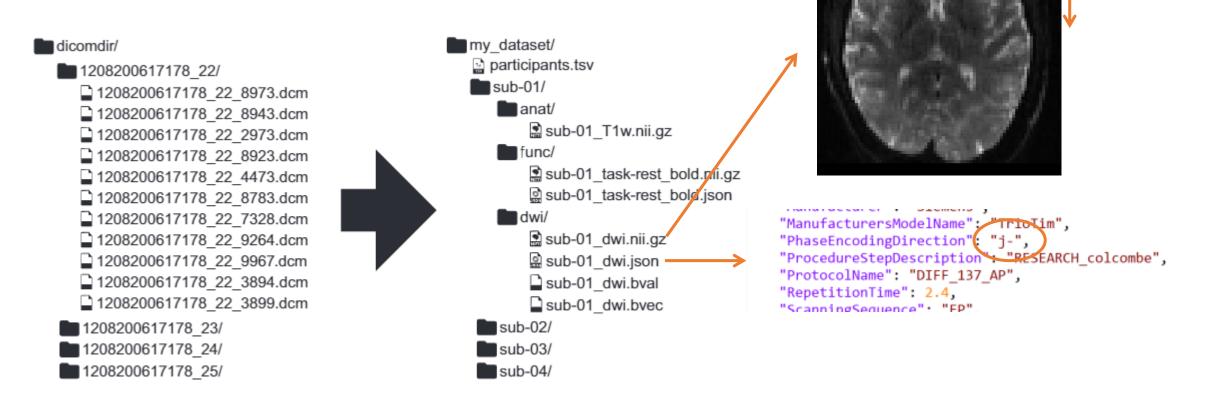
Aim 1 – Proposed software: BABS

Proposed software package: BIDS-App Bootstrap (BABS)



Aim 1 – BIDS and BIDS apps What is Brain Imaging Data Structure (BIDS) format?

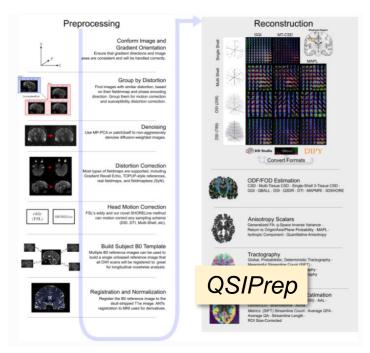
BIDS includes images + their metadata in sidecar JSON files:

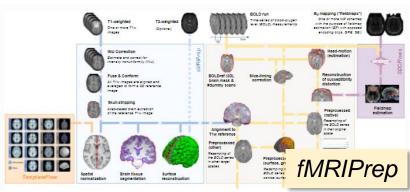


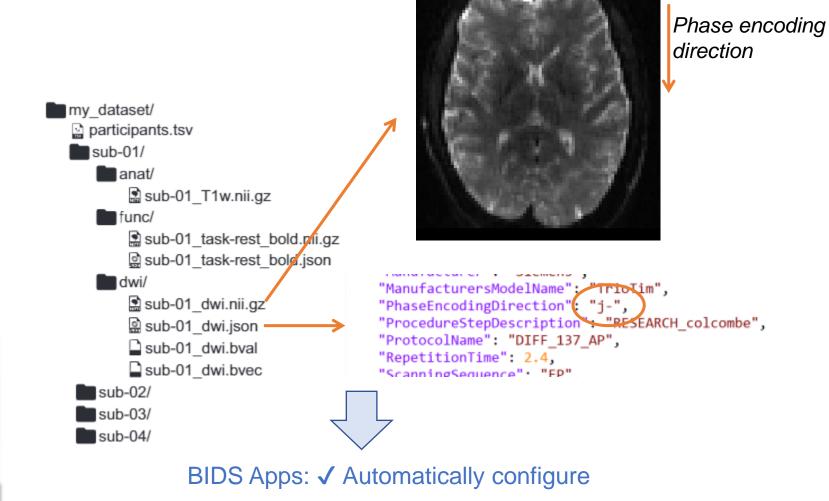
Phase encoding

direction

Aim 1 – BIDS and BIDS apps What are BIDS apps?



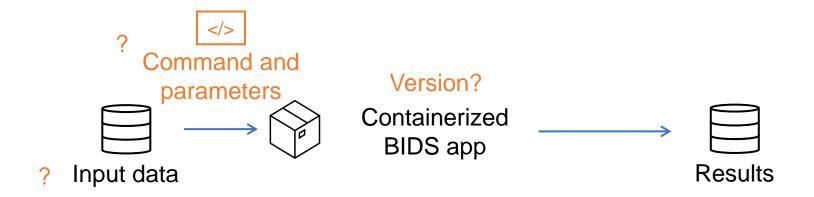




√ Containerized

Aim 1 – BIDS and BIDS apps What is lacked for complete reproducibility?

Applying containerized BIDS apps enhances reproducibility, however...

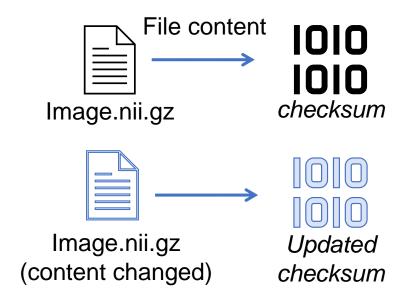


BABS will fill this gap and maximize reproducibility

Aim 1 – Method for data provenance tracking using DataLad Data version control







- No matter how large the file is
- (sensitive) contents in the file cannot be retrieved from the checksum

Aim 1 – Method for data provenance tracking using DataLad Functions in DataLad

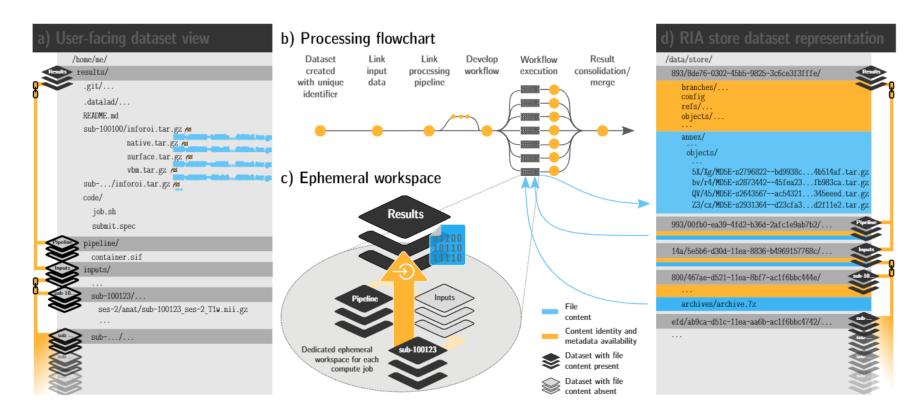
 DataLad provides machine-readable, re-executable provenance record

Example provenance record:

```
commit e035f896s45c9fac70cn7cc4dbd0dad43907755p
         ane Doe <j.doe@fz-juelich.de>
AuthorDate Wed Feb 10 18:05:30 2021 +0100
Commit: | Jane Doe < j.doe@fz-juelich.de>
CommitDate: Wed Feb 10 18:05:30 2021 +0100
[DATALAD RUNCMD] Compute sub-6025043/ses-2
  === Do not change lines below ===
   "cmd": singularity exec -B {pwd} --cleanenv code/pipeline/.datalad/
          environments/cat/image sh -e -u -x -c [...]'
   "dsid": "8938de76-0302-45b5-9825-3c6ce3f3fffe".
   "exit": 0,
   "extra inputs": [
   "code/pipeline/.datalad/environments/cat/image"
   "inputs'
    "inputs/ukb/sub-6025043/ses-2/anat/sub-6025043 ses-2 T1w.nii.gz",
   "code/cat standalone batch.txt",
   "code/finalize job outputs.sh"
    "sub-0025043/ses-2"
   "." :"bwa":
  ^^^ Do not change lines above ^^^
sub-6025043/ses-2/inforoi.tar.gz | 1 +
sub-6025043/ses-2/native.tar.gz | 1 +
sub-6025043/ses-2/surface.tar.gz | 1 +
sub-6025043/ses-2/vbm.tar.gz | 1 +
4 files changed, 4 insertions(+)
```

Aim 1 – Workflow of BABS

- BABS will follow the workflow of FAIRly big framework
 - FAIR = findability, accessibility, interoperability, and reusability
 - FAIRly big is a DataLad-based framework for reproducible processing of large-scale datasets.
 - This facilities a full audit trail for processing data at scale



Background – Still, there are obstacles... Impractical adoption of existing effort

```
1#!/bin/bash
                                           28 # datalad containers - run executes
2 # fail on any issue, show commands
                                           29 # the "cat" computational pipeline.
                                           30 # specified inputs are auto-obtained,
3 set -e -u -x
4 # name arguments for readability
                                           31 # specified outputs are saved with
5 dssource="$1"
                                           32 # provenance record
                                           33 datalad containers-run \
6 pushgitremote="$2"
7 subid="$3"
                                               -m "Compute subject ${subid}" \
                                               -n cat \
9 # obtain the analysis dataset, which
                                               --explicit \
10 # also tracks the required inputs
                                               --output "${subid}" \
11 datalad clone "${dssource}" ds

    "inputs/ukb/${subid}/*T1w.nii.gz"

12 cd ds
                                           39 "<container invokation arguments>"
14 # register location for result
                                           40 # END OF APPLICATION-SPECIFIC CODE
15 # deposition, separate from the input
16 # source for performance reasons only
                                           42 # push result file content to the
                                           43 # configured "storage-remote"
17 git remote add outputstore

→ "$pushgitremote"

                                           44 datalad push --to storage-remote
19 # all job results will be put into
                                           46 # push branch with provenance records
20 # a job-specific, dedicated branch
                                           47 # needs a global lock to prevent
21 git checkout -b "job-$JOBID"
                                           48 # write conflicts
                                           49 flock "$DSLOCKFILE" git push
23 # START OF APPLICATION - SPECIFIC CODE

    outputstore

24 # pull down input data manually,
25 # only needed for wildcard-based file
                                           51 # log entry to mark non-error exit
26 # selection in the next command
                                           52 echo SUCCESS
27 datalad get -n "inputs/ukb/${subid}"
```

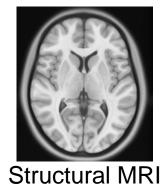
- FAIRly big framework is not userfriendly
- Long scripts
 - Numerous steps ...
 - Numerous DataLad functions ...

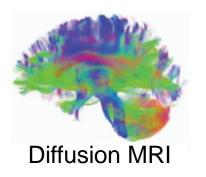
Part of the full script

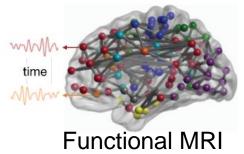
Wagner et al., bioRxiv 2021

Background – Still, there are obstacles... Poor generalizability of existing effort

Image types

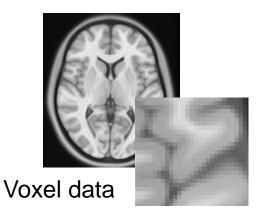


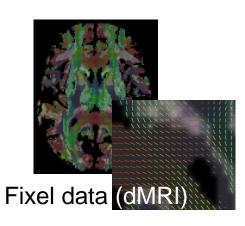


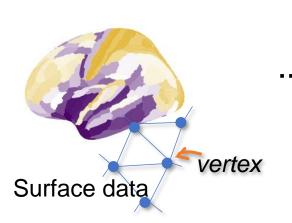


• • •

Data types







Processing methods and software

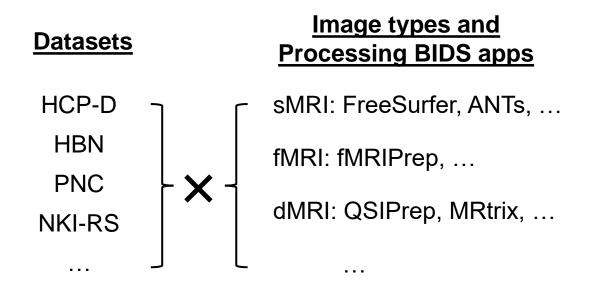


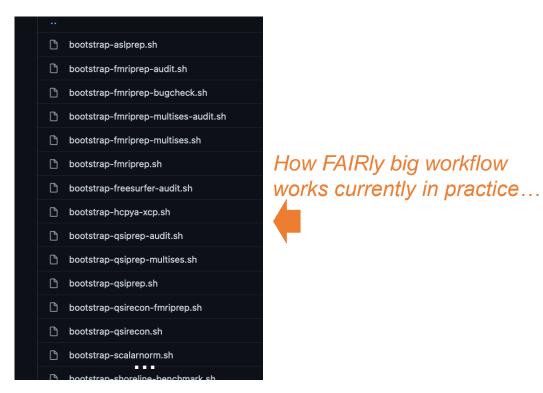




- -

Aim 1 – Still, there are obstacles... Poor generalizability of existing effort

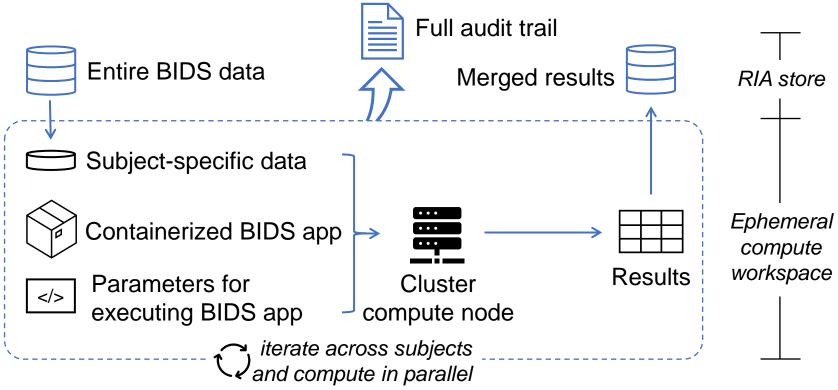




Numerous customized scripts for various BIDS apps and datasets

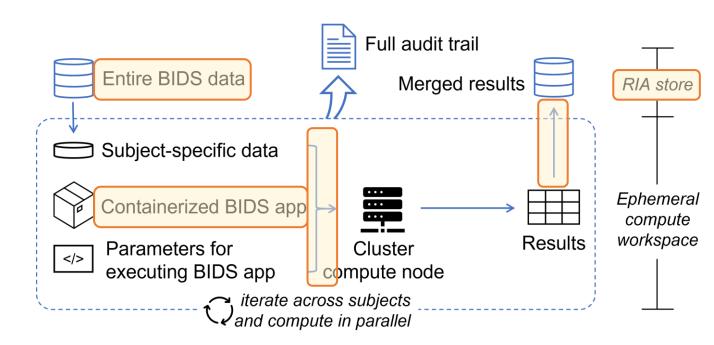
BABS will be user-friendly, generalizable software

Aim 1 – Workflow of BABS

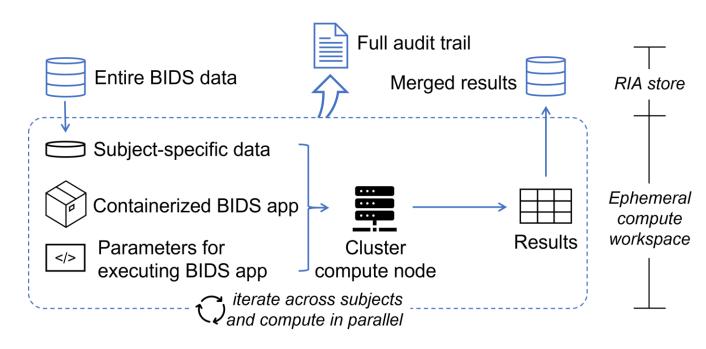


- ✓ All provenance tracked
- ✓ Fully reproducible rerun
- ✓ Generalizability: not depending on specific information of BIDS dataset and app

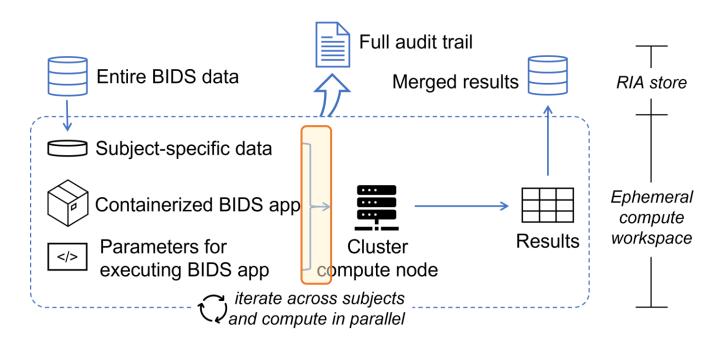
- babs-init: initialize necessities for each run
 - Create RIA store
 - Ask DataLad to start to track data provenance
 - Automatically generate the scripts that will later be used internally
- babs-check-setup
- babs-submit
- babs-status
- babs-merge
- babs-unzip



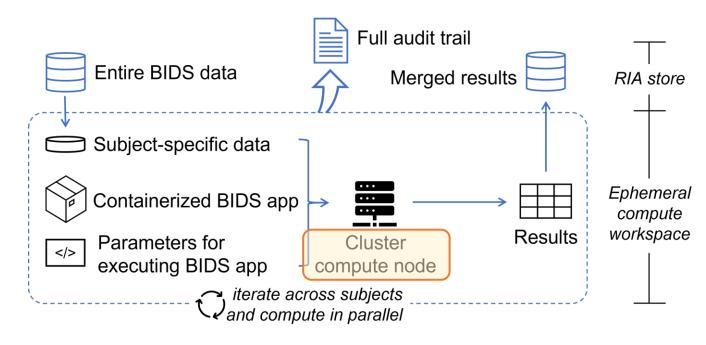
- babs-init: initialize necessities for each run
- babs-check-setup: check all necessaries are correctly set up by babs-init
- babs-submit
- babs-status
- babs-merge
- babs-unzip



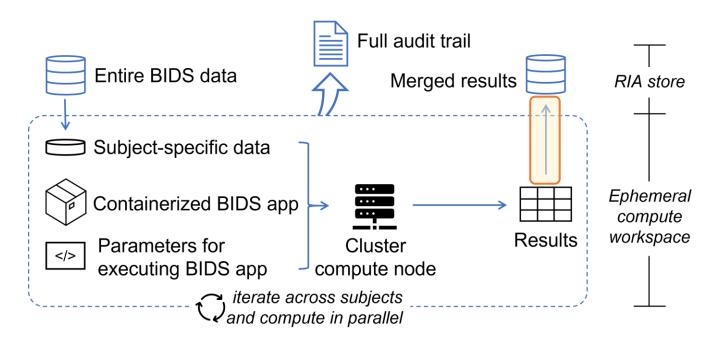
- babs-init: initialize necessities for each run
- babs-check-setup: verify that data and container configuration is appropriate
- babs-submit: submit the jobs to be executed in parallel on cluster compute nodes. Options include:
 - submitting only one subject for testing
 - submitting all subjects but excluding the subjects with successful outputs
- babs-status
- babs-merge
- babs-unzip



- babs-init: initialize necessities for each run
- babs-check-setup: verify that data and container configuration is appropriate
- babs-submit: submit the jobs to be executed in parallel on cluster compute nodes
- babs-status: easily check all jobs' status, and it allows users to automatically resubmit the jobs if failed or stalled
- babs-merge
- babs-unzip

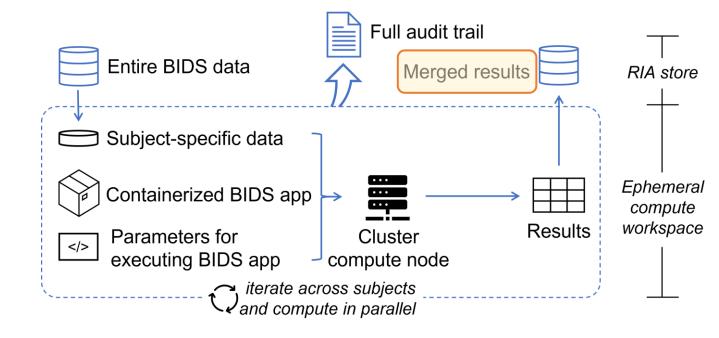


- babs-init: initialize necessities for each run
- babs-check-setup: verify that data and container configuration is appropriate
- babs-submit: submit the jobs to be executed in parallel on cluster compute nodes
- babs-status: easily check all jobs' status and automatically resubmit if needed
- babs-merge: merge results and provenance from all jobs. Results are now compressed at the RIA store.
- babs-unzip



- babs-init: initialize necessities for each run
- babs-check-setup: verify that data and container configuration is appropriate
- babs-submit: submit the jobs to be executed in parallel on cluster compute nodes
- babs-status: easily check all jobs' status and automatically resubmit if needed
- babs-merge: merge results and provenance from all jobs
- babs-unzip: allow users to decompress the zipped data and only get the requested files

- ✓ Parsimonious set of commands
- ✓ Generalizable functionality of BABS
 - any BIDS dataset
 - any BIDS-app
- ✓ Fully reproducible way with complete provenance tracking



Aim 1 – Compatibility with computing cluster management systems

 There are various management systems for clusters, and the commands for job scheduling can vary across systems:

C	luste	r
	•••	
	•••	
	•••	

User Commands	SGE	Slurm
Job submission	qsub [script_file]	sbatch [script_file]
Job deletion	qdel [job_id]	scancel [job_id]
Job status by job	qstat -u * [-j job_id]	squeue [job_id]

- Design of BABS: will be compatible with Slurm and SGE
- Test of BABS: on Slurm and SGE systems, using
 - Slurm cluster through collaborations with University of Minnesota
 - SGE-based CUBIC system at Penn Medicine

Aim 1 – Evaluation data and details BIDS data and app

- Input BIDS data: large-scale diffusion MRI (dMRI) from Reproducible Brain Charts (RBC) effort
 - Four datasets with different dMRI acquisition protocols
 - In total n=6,372 dMRI

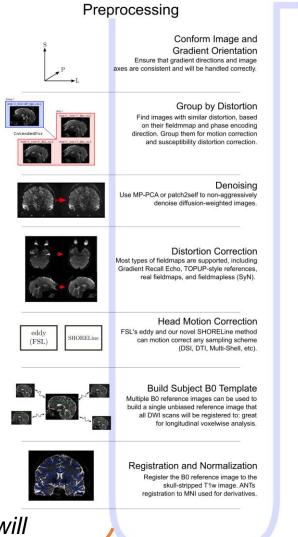
	dMRI				
Datasets	Sample size (n)	Resolution	b-values (s/mm²)	Number of directions	
Philadelphia Neurodevelopmental Cohort (PNC) ¹	1409	1.875x1.875x2 mm	1000	64	
Healthy Brain Network (HBN) ²	2151	1.8mm isotropic	1000, 2000	64	
NKI Rockland Sample (NKI-RS) ³	2169	2mm isotropic	1500	137	
Human Connectome Project - Development (HCP-D) ⁴	643	1.5mm isotropic	1500, 3000	185	
Total	6372				

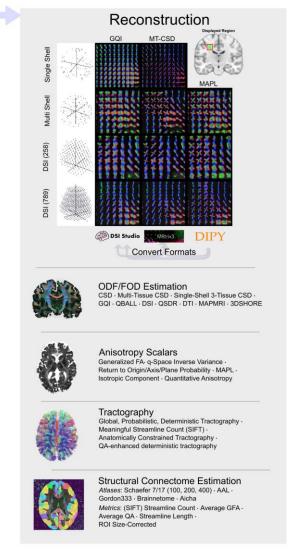
¹Satterthwaite et al., Neurolmage 2014; ²Alexander et al., Sci Data 2017;

³Nooner et al., Front Neurosci 2012; ⁴Somerville et al., Neurolmage 2018

Aim 1 – Evaluation data and details BIDS data and app

- Containerized BIDS app: QSIPrep
 - For dMRI preprocessing + reconstruction
 - Can process the dMRI with nearly all sampling schemes



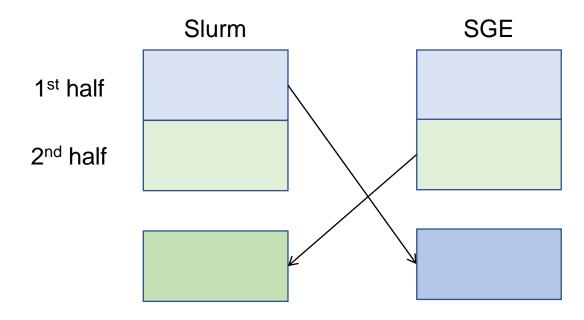


Preprocessed data will also be used in **Aim 2**

QSIPrep

Aim 1 – Evaluation data and details Evaluation details

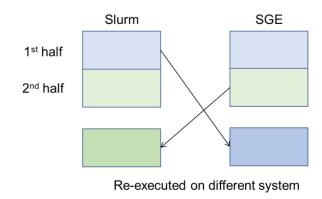
- 1. Compatibility with both cluster systems: BABS will be applied to all datasets on both Slurm and SGE systems
- 2. Reproducibility and capability of capturing full process provenance even for dataset at scale:
 - To perform a split-half cross-validation:



Re-executed on different system

Aim 1 – Evaluation data and details Evaluation details: split-half cross-validation

- 2. To demonstrate the **reproducibility and capability** of capturing full process provenance even for dataset at scale: To perform a split-half cross-validation:
 - To compare the differences between the output connectivity matrices from original run and rerun
 - Expect that there is minimal difference



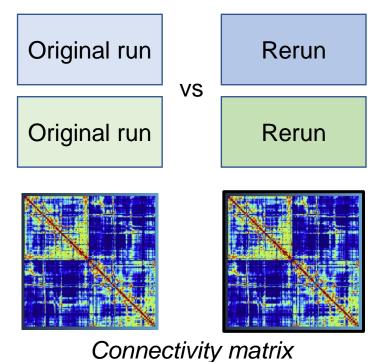


Figure adapted from: Baum et al., Neurolmage 2018

Outline

- Aim 1: Software for reproducible image processing at scale
- Aim 2: Memory-efficient, generalizable software for statistical analysis
- Software development

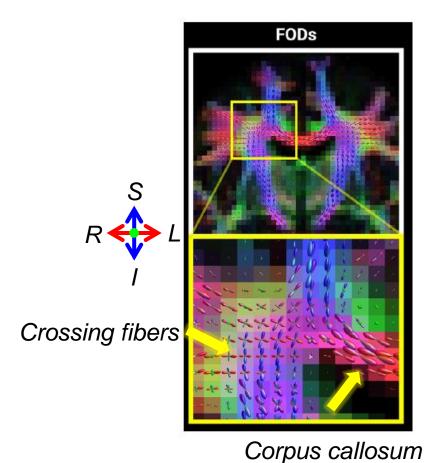
Outline: Approach for Aim 2

To develop and release a generalizable, memory-efficient, open-source R package for massunivariate hypothesis testing of large neuroimaging datasets

Approach for Aim 2:

- Background
- Method for efficient memory
- Workflow and functionality of proposed software
- Evaluation data and details
- Application of GAMs to developmental datasets
- Generalizability and extensibility

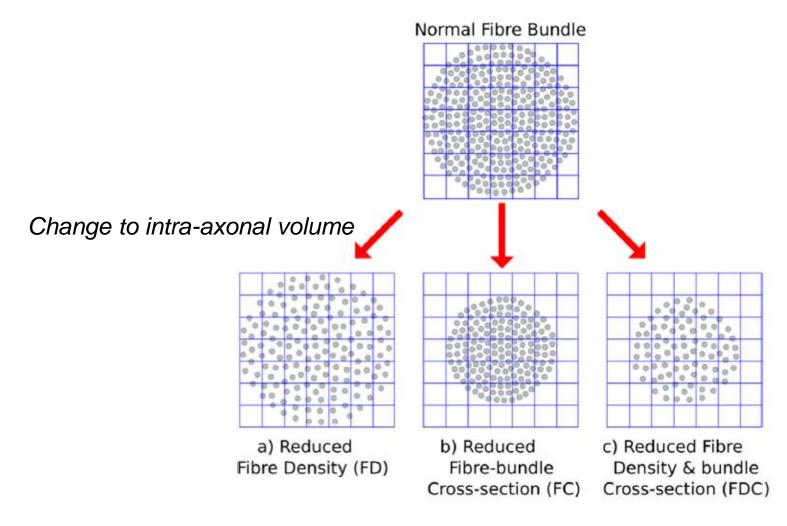
Aim 2 – Background: What is fixel data?



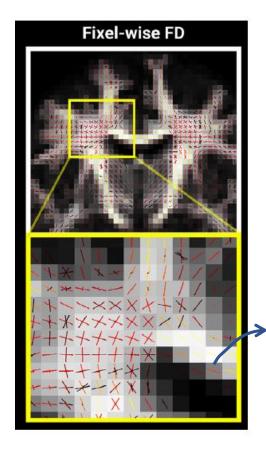
FOD, fiber orientation distribution FD, fiber density

"Fixel": an individual <u>fi</u>ber population within a vo<u>xel</u>

Aim 2 – Background: What is fixel data? Fixel-wise metrics



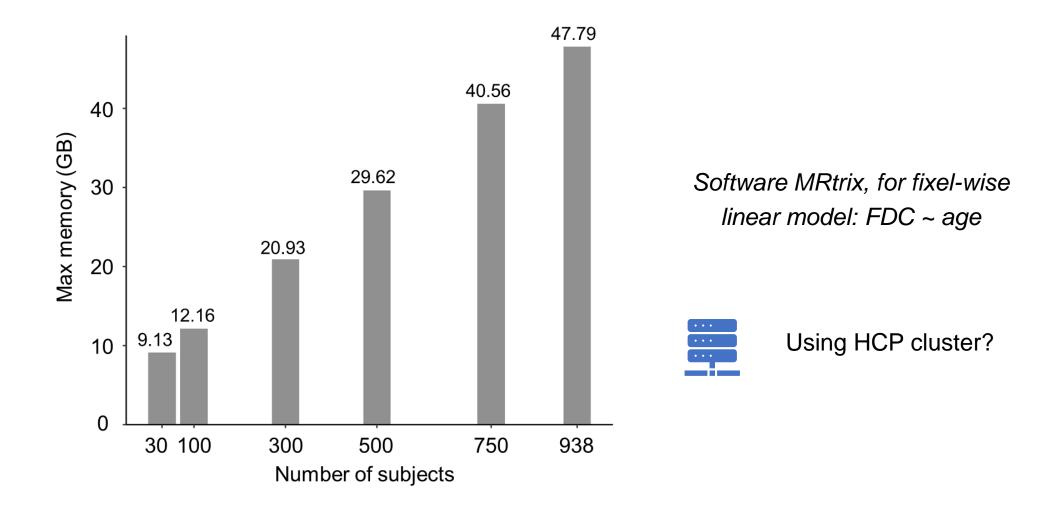
Aim 2 – Background: Mass-univariate hypothesis testing



Does fixel-wise FD change over development?

→ To perform a mass-univariate hypothesis testing:
 @ each fixel, test FD ~ age

Aim 2 – Background Challenge #1: Intensive memory requirement for large-scale dataset



Aim 2 – Background

vertex data

Sydnor et al., Neuron 2021

Challenge #2: No consistent statistical analysis tool generalized across image types

Voxel data age Consistent statistical analysis tool? Fixel data age Surface

vertex

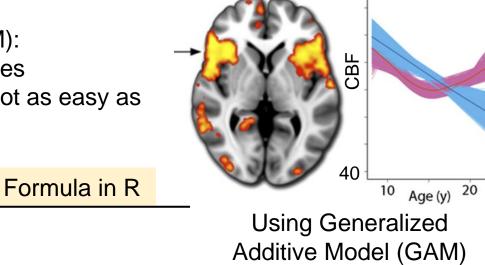
age

39

Aim 2 – Background

Challenge #3: Users cannot easily model nonlinear age effects with current tools

- Lifespan age effects are often nonlinear
- Current tools often only support generalized linear model (GLM):
 - Limited flexibility: not supporting GAM with penalized splines
 - Generating design matrix and contrast matrix for GLM is not as easy as writing a formula in R



Satterthwaite et al., PNAS 2014

age

21.50

Design matrix

Contrast matrix

21.75 20.50 20.50 20.92 20.92

intercept sex

0 1

lm(): FD ~ age + sex

GAM

Linear regression

???

 $qam(): FD \sim s(age) + sex$

Aim 2 – Proposed software: ModelArray

Current challenges in mass-univariate hypothesis testing for large-scale datasets:

- 1. Scalability: Massive memory resources needed by large datasets
- 2. Generalizability: No consistent statistical analysis tool generalized across data types
- 3. User-friendly: Users cannot easily model nonlinear age effects with current tools

To address these challenges, I propose to develop **ModelArray**, a generalizable, memory-efficient, open-source R package for mass-univariate hypothesis testing of large neuroimaging datasets.

Aim 2 – Method for efficient memory

- HDF5 file format:
 - An HDF5 file (.h5) stores large dataset hierarchically and provides fast data access.
- R package DelayedArray:
 - Accessing and analyzing data without loading the entire data into memory

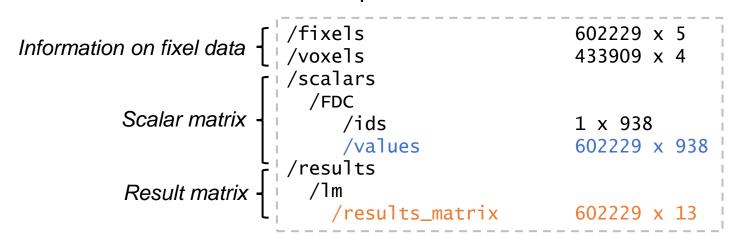
File size on the disk:

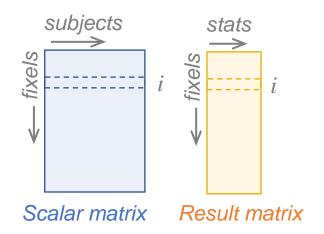


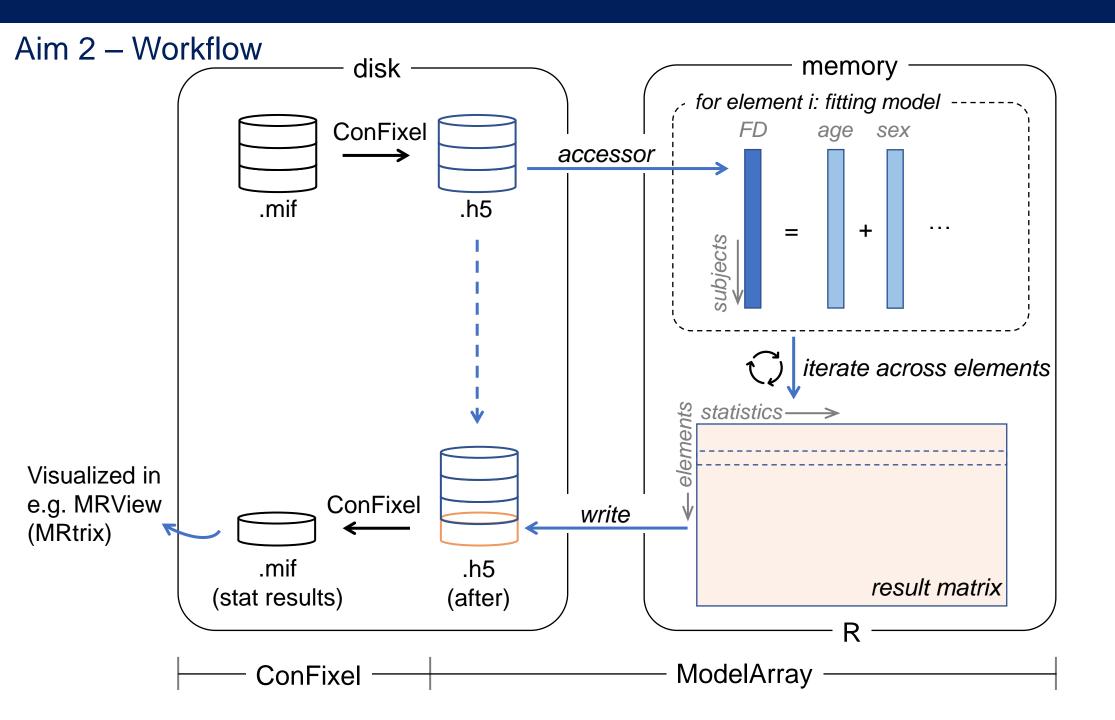
2.5 GB

- # in-memory size in R:
- > object.size(fixelarray)
- > 15584 bytes

An example .h5 file for fixel data:



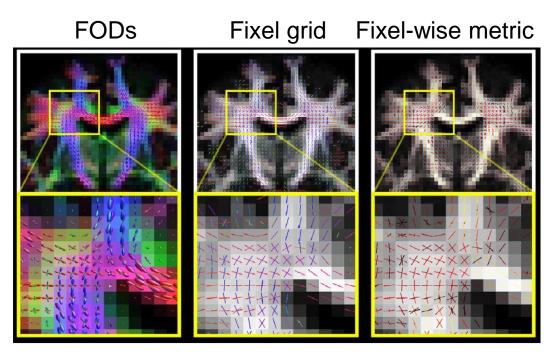




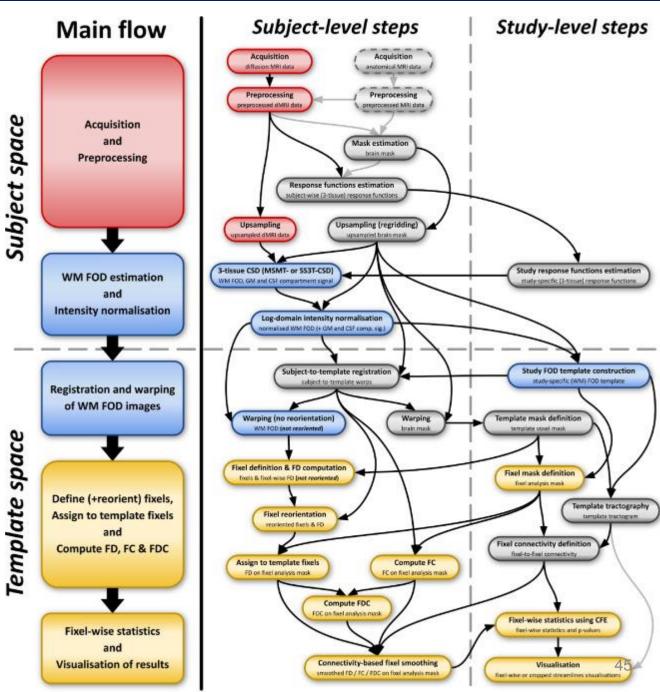
Aim 2 – Functionality of ModelArray Example script of the whole procedure of running ModelArray in R

```
> library(ModelArray)
> filename <- "example.h5"</pre>
> modelarray <- Modelarray(filename, scalar_types = "FDC")</pre>
> phenotypes <- read.csv("example.csv")</pre>
# Linear model:
> lm.outputs <- ModelArray.lm(FDC~age, modelarray, phenotypes, "FDC")</pre>
# Generalized additive model (GAM):
> gam.outputs <- ModelArray.gam(FDC~s(age)+sex+motion, modelarray, phenotypes, "FDC")
> writeResults(filename, df.output=lm.outputs, analysis_name="lm")
> writeResults(filename, df.output=gam.outputs, analysis_name="gam")
```

Aim 2 – Evaluation of ModelArray Data: dMRI fixel data from RBC



Fixel-wise metric: FDC (combination of FD and FC, more sensitive)



Figures adapted from Dhollander et al., Neurolmage 2021

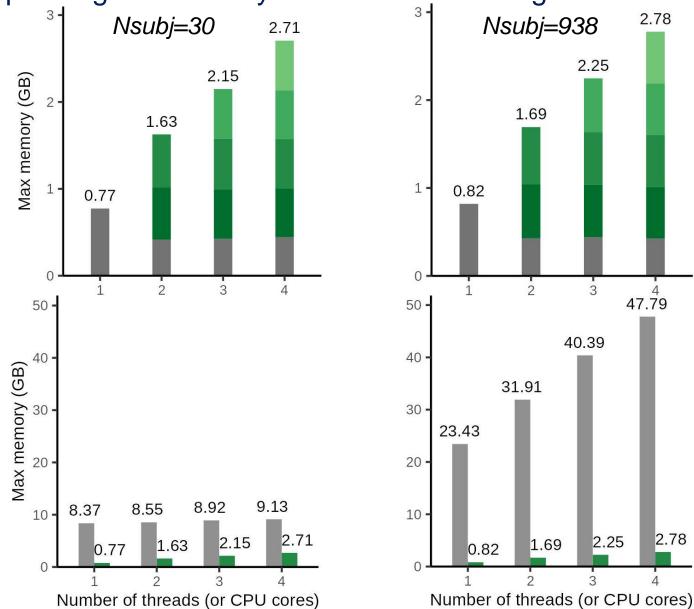
Aim 2 – Evaluation of ModelArray

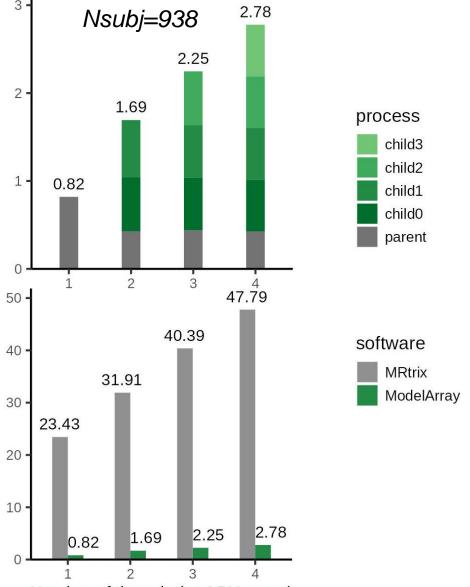
- Evaluations:
 - Memory profiling
 - Runtime profiling
- Evaluation details:
 - Will compare to primary existing tool for fixel-wise statistical analysis: the function "fixelcfestats" in MRtrix¹.
 - Will evaluate on a standalone computer with Linux system to avoid interference from other users.
 - Will use simple linear model: FDC ~ age

Aim 2 – Evaluation of ModelArray Memory profiling **CPU** child process i parent process child process j memory Figure adapted from: https://www.blasbenito.com/post/02 child process k _parallelizing_loops_with_r/ \$ htop 10652 chenying 0 1135M 1:25.39 R --no-echo --nochild processes -0 1135M 1:25.40 R --no-echo --no-r parent process ->

Memory usage will be captured by Working Set Size (WSS) Tools for Linux

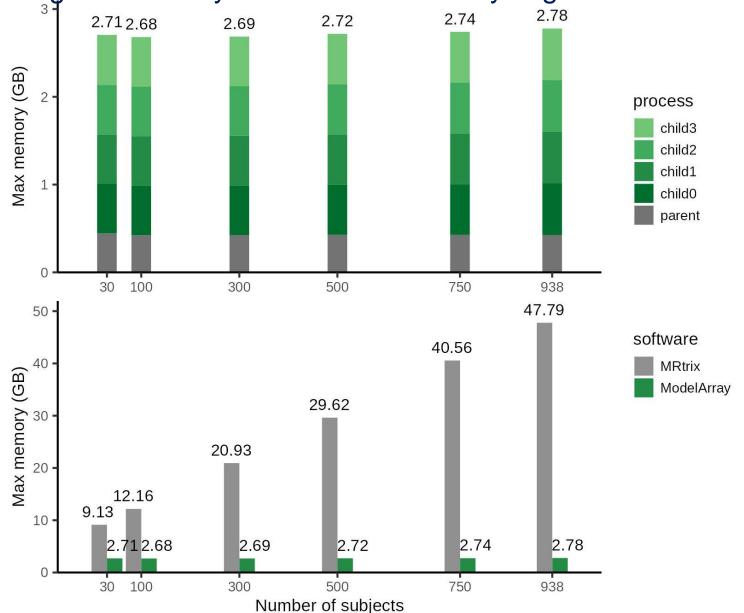
Aim 2 – Evaluation of ModelArray Memory profiling: Preliminary results – when using different number of threads (or CPU cores)





Aim 2 – Evaluation of ModelArray

Memory profiling: Preliminary results – when analyzing different number of subjects



parallelization factor = 4

- 4 CPU cores requested for ModelArray
- 4 threads requested for MRtrix

Aim 2 – Application of GAMs to developmental datasets Methods

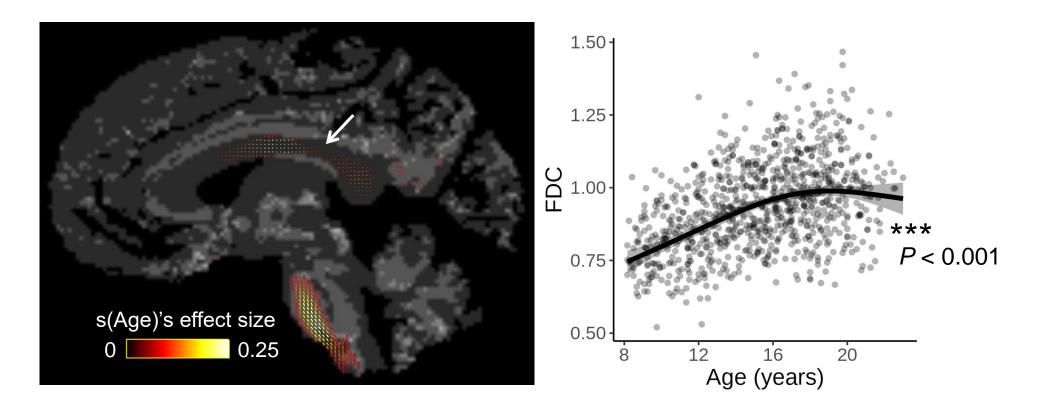
• I will also demonstrate the use of GAMs in ModelArray for modelling nonlinear developmental effects with penalized splines:

$$FDC \sim s(Age) + sex + motion$$

- *motion*: mean relative volume-to-volume displacement of 7 b=0 images
- Effect size = $R_{full}^2 R_{reduced}^2$

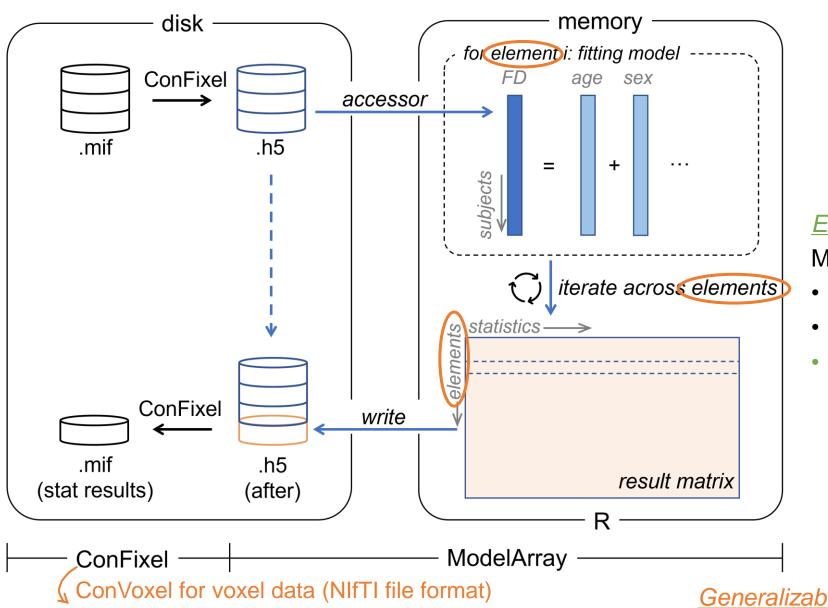
$$\uparrow$$
 $FDC \sim sex + motion$

Aim 2 – Application of GAMs to developmental datasets Preliminary data: nonlinear age effect in adolescent development



- Data: PNC dataset (n=938), aged 8-22 years
- Threshold: P value of s(Age) < 1x10⁻¹⁵
- GAM Formula: $FDC \sim s(Age) + sex + motion$

Aim 2 – Generalizability and extensibility of ModelArray



ConCifti for surface data (CIFTI grayordinate file format)

Extensibility:

Model fitting functions in ModelArray:

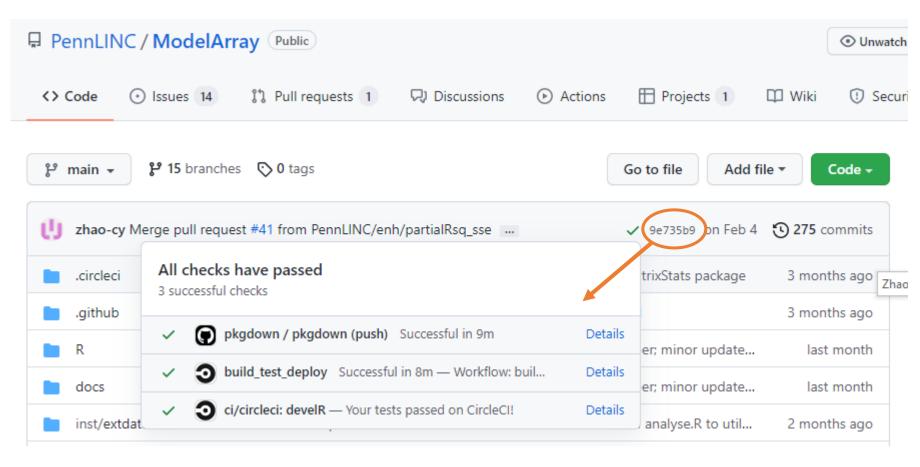
- ModelArray.lm() for linear model
- ModelArray.gam() for GAM
- ModelArray.new() for ?

I/O interface

Outline

- Aim 1: Software for reproducible image processing at scale
- Aim 2: Memory-efficient, generalizable software for statistical analysis
- Software development

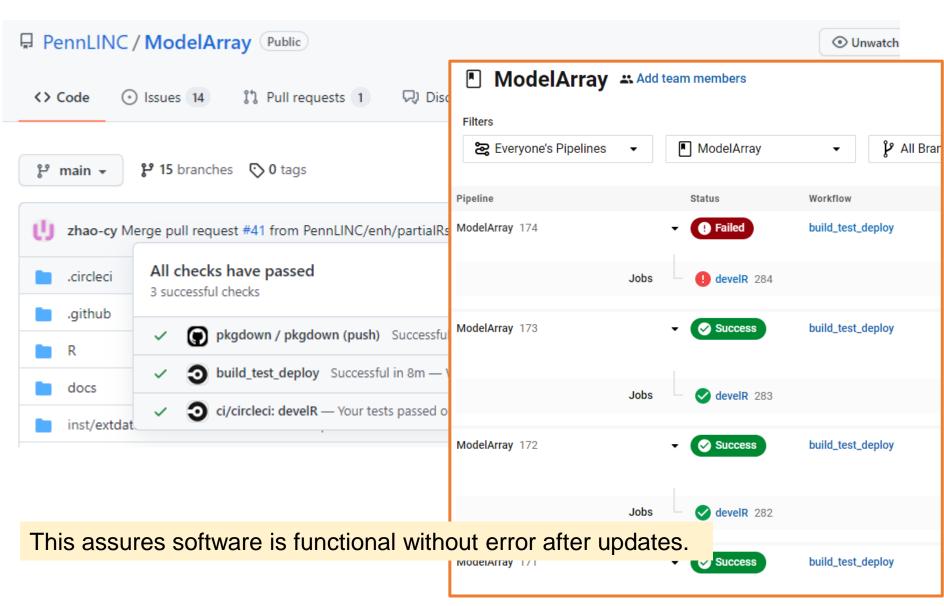
Software development Version control and CI testing







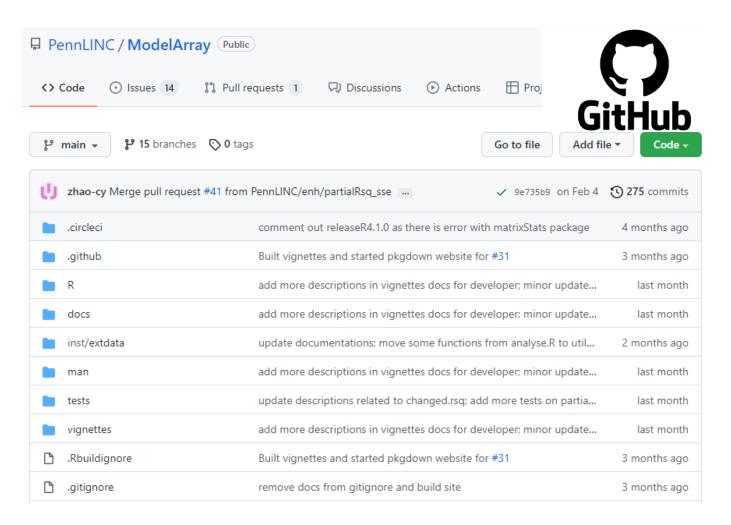
Software development Version control and CI testing







Software development Containerization and release



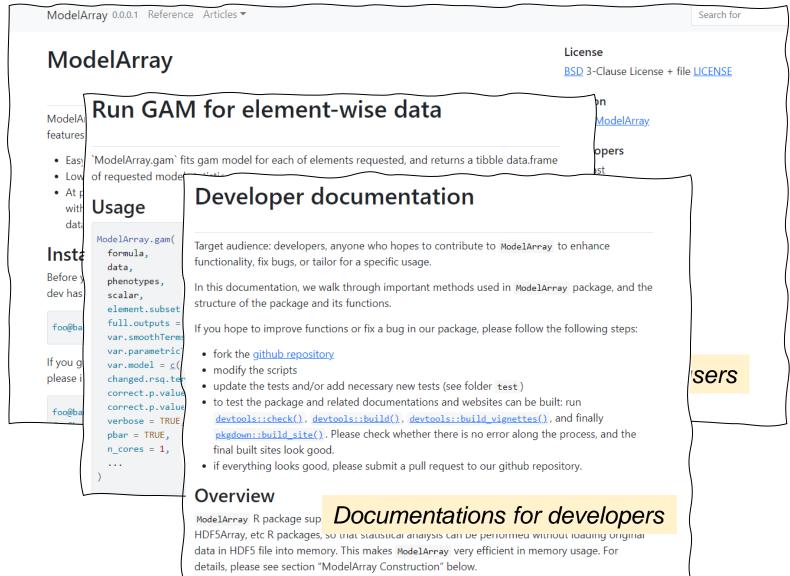


- Will build a container to enhance portability
- Will release on DockerHub

This workflow ensures both version control and frictionless portability.

Source code openly available on GitHub

Software development Comprehensive documentations



Thank you !!!