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The Perfect Neuroimaging-Genetics-Computation Storm: Collision of Petabytes of Data, Millions of Hardware Devices and Thousands of Software Tools

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Abstract

The volume, diversity and velocity of biomedical data are exponentially increasing providing petabytes of new neuroimaging and genetics data every year. At the same time, tens-of-thousands of computational algorithms are developed and reported in the literature along with thousands of software tools and services. Users demand intuitive, quick and platform-agnostic access to data, software tools, and infrastructure from millions of hardware devices. This explosion of

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[*] Some of the data used in preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.ucla.edu). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in analysis or writing of this report. A complete listing of ADNI investigators can be found at: http://adni.loni.ucla.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf. http://pipeline.loni.ucla.edu

information, scientific techniques, computational models, and technological advances leads to enormous challenges in data analysis, evidence-based biomedical inference and reproducibility of findings.

The Pipeline workflow environment provides a crowd-based distributed solution for consistent management of these heterogeneous resources. The Pipeline allows multiple (local) clients and (remote) servers to connect, exchange protocols, control the execution, monitor the states of different tools or hardware, and share complete protocols as portable XML workflows. In this paper, we demonstrate several advanced computational neuroimaging and genetics case-studies, and end-to-end pipeline solutions. These are implemented as graphical workflow protocols in the context of analyzing imaging (sMRI, fMRI, DTI), phenotypic (demographic, clinical), and genetic (SNP) data.

Keywords

aging; pipeline; neuroimaging; genetics; computation solutions; workflows; IBS; pain; Parkinson's disease; Alzheimer's disease; shape; volume; analysis; big data; visualization

Introduction

Process understanding is frequently the core research question in many biomedical, health and environmental applications. As we rarely know the exact process characteristics, we collect data (observations) which is used as proxy of the underlying physiological, physical or environmental phenomena. As such, the observed information (data) becomes the pivotal aspect of the scientific inquiry. The data variability, complexity and heterogeneity directly affect the scientific inference, accuracy of the results and reproducibility of findings.

Three data characteristics make contemporary biomedical data different, challenging and powerful. These are the data *volume* (size), typically in the petabyte range (1PB = 10^{15} bytes), data *heterogeneity*, including (un)formatted, ASCII/Binary, (un)structured, and the data *velocity*, or data *derivative*, which captures the change, transfer, and discovery of raw and derived data [1-3].

Table 1 illustrates the Kryder's law for exponential increase of the volume of data [4]. Using two decades of data, this law predicts that the density of information on hard drives, areal density, increases by a factor of 1,000 every 10-11 years. This storage rate increase is driven by the rapid expansion of data volume and velocity and translates into doubling of data size each 12-13 months. Both Moore's and Kryder's laws indicate similar exponential increase (of computational power and data storage, respectively) over time [5].

There are thousands of software tools for acquisition, processing, storage/databasing, service, migration, mining, analysis, visualization, annotation, and *data-driven process understanding*. For example, the field of biomedical imaging includes hundreds of different types of image processing algorithms and filters. For each type of process, there may be dozens of concrete software products (instance implementations). More specifically, the Neuroimaging Informatics Tools and Resources Clearing House (NITRC) [16] lists over 500 openly shared neuroimaging software tools. For each openly shared tool, there may be dozens proprietary or less commonly used analogues. Similarly, in genomics and bioinformatics there are over 200 data and cloud computing service providers, and hundreds of public, private and non-profit organizations that provide thousands of stand-alone tools [17]. Resource organization, classification, discovery, traversal and utilization of these software products require flexible human and machine interfaces [18].

Another computational challenge is the proliferation of millions of hardware devices. According to Cisco [19], by the end of 2012, the number of mobile-connected devices will exceed the number of people on Earth and there will be over 10 billion mobile-connected devices in 2016; i.e., there will be more than 1.3 mobile devices per capita worldwide. These include phones, tablets, laptops, handheld gaming consoles, e-readers, in-car entertainment systems, digital cameras, and “machine-to-machine modules.” There is a clear need for bridges between these mobile devices and for efficient connections to distributed databases, clients, servers, compute-nodes, web-services, variety of interfaces.

Methods

The LONI Pipeline environment (http://Pipeline.loni.ucla.edu) [20, 21] is a graphical workflow middleware providing an interface to computational libraries, informatics resources, computational expertise and cloud services (e.g., cloud data storage, cloud computing services). The Pipeline facilitates the design, validation, execution, monitoring and sharing of advanced heterogeneous computational protocols as graphical workflows. It also mediates the tool discovery and interoperability and provides distributed computing infrastructure for *en masse* data processing. The Pipeline's user-friendly interface enables access to disparate data, services, hardware infrastructure, computational expertise and cloud computing services [20].

Alternative infrastructures to the Pipeline environment that also facilitate visual informatics and computational genomics include Taverna [22], Kepler [23], Triana [24], Galaxy [25], AVS [26], VisTrails [27], Bioclipse [28], KNIME [29], NyPipe [30], PSOM [31] and others. The choice of a workflow environment depends on the specific research domain, scientific application and computational need. The Pipeline environment provides some advantages over the alternative architectures. These include distributed client-server architecture, an array of scheduler grid plug-ins, external lightweight data manager, easy incorporation of new software tools and libraries, and dynamic workflow design, validation, execution, monitoring and dissemination of complete end-to-end computational solutions [32].

The main types of computational tools available in the Pipeline library include software for neuroimaging and genetics data processing and visualization. For each of these types there are 3 categories of resources – data, atomic modules, and workflows. These resources can be explored via the Pipeline Navigator (http://pipeline.loni.ucla.edu/explore/library-navigator/) and can be tested via the guest-access Pipeline Web-Start server (http://pipeline.loni.ucla.edu/PWS). Many interesting end-to-end computational workflow solutions (pipelines) are documented online (http://pipeline.loni.ucla.edu/explore/pipeline-workflows/). There are also many video tutorials, screencasts, and training materials (http://

pipeline.loni.ucla.edu/learn/basic-videos/), which illustrate the basic and advanced features of the pipeline client-server architecture, and the protocols for workflow design, execution and management.

Neuroimaging Processing Tools

There are several hundred atomic neuroimage processing tools, from a variety of software suites available in the LONI pipeline library, **Figure 1.A**. These tools may be used for analysis of structural brain images (e.g., AFNI [33], ROBEX [34], MDT Atlasing [35, 36], BrainParser [37], SVPASEG [38, 39], AIR [40], FSL [41], BrainSuite [42], SSMA [43, 44], ANTS [45], ITK [46], MINC [47]), functional brain data (e.g., FLIRT [48], AFNI [33], WAIR [49], Matlab [50]), diffusion data (e.g., DTK [51], DIRAC [52], MiND [53]), statistical analyses (e.g., R [54], GAMMA [55], SOCR [56, 57], SPM [58, 59]), shape and surface modeling (e.g., sulcal analysis [60], local and global shape analyses [32], shape mapping DHM [61], FreeSurfer surface extraction, and cortical thickness [62, 63]).

Informatics and Genomics Computational Library

The breadth of genomics tools available as pipeline modules and workflows is illustrated by the variety of sequence alignment solutions [20], **Figure 1.B**. Some different categories of informatics and genomics computing software tools available in the Pipeline library include: sequence alignment (Mosaik [64], MAQ [65], PERM [66], BWA/BWA-SW [67, 68], Bowtie [69], Novoalign [70], SOAPv2 [71], BLAST [72]), indexing (mrFAST/mrsFAST [73]), genome-wide association studies (GWASS [74], PLINK [75]), basic and advanced quality control (SAMTools [76], GATK [77]), CNV calling (CNV/CNVR [78, 79]), annotation (Artemis [80]), *de novo* assembly (Trinity [81], Velvet [82]), molecular biology (EMBOSS [83]), population genetics (GENEPOP [84]), and many others.

Backend Pipeline Servers

Pipeline web-start server (PWS) uses Java Web-Start technology enabling guest users to test the LONI Pipeline application from a web browser without the installation of either a pipeline client or a server. The PWS server provides access to all of the functions and features included in the downloadable version. PWS is accessible via an anonymous guest login or user-authentication to connect to remote Pipeline servers, e.g., http://ucla.in/GRSc8a. Several alternative Pipeline servers provide secure access-controlled connections to independent computational infrastructures. Examples include LONI Genomics Server (Genomics.loni.ucla.edu, 1TB RAM/40-core), Cranium Server (Cranium.loni.ucla.edu, 16GB RAM/core, 1,200 cores) and Medulla Server (Medulla.loni.ucla.edu, 24GB RAM/core, 4,300 slots). The Distributed Pipeline Server infrastructure (http://pipeline.loni.ucla.edu/DPS) facilities the deployment of independent disparate Pipeline services on available hardware resources, including Amazon EC2 (http://pipeline.loni.ucla.edu/products-services/pipeline-server-on-ec2/).

Big Data

Modern protocols for imaging and genetics data collection generate enormous amounts of data. **Table 2** illustrates some of the data-management, storage and processing challenges associated with common neuroimaging and genetics analysis protocols. **Figure 2** shows an example of the multi-channel imaging brain data typically acquired in traumatic brain injury studies.

Applications and Results

To demonstrate the Pipeline management of heterogeneous neuroimaging, genetics, phenotypic and clinical data, and the diversity of computational data processing tools available through the Pipeline library, we have chosen three complementary applications. These include studies of imaging-based genome-wide association, hippocampal morphometry, persistent pain and irritable bowel syndrome. Each of these three applications demonstrates exemplary solutions to the resource-scalability and processing-efficiency challenges related to the data complexity (size, heterogeneity and velocity), software tools interoperability and diversity of hardware devices. Specifically, these case-studies demonstrate (1) how seemingly incongruent imaging, phenotypic and clinical data can be jointly processed and analyzed in an integrated computational workflow protocol; (2) how pipeline workflows can wrap independent software tools to make them interoperate; and (3) how these data and computational resources (tools and services) can be accessed via different client devices (e.g., desktop or laptop computers or mobile devices running different operating systems and browser configurations).

ADNI Imaging-Genetics GWAS Study

The Alzheimer's disease data used in this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.ucla.edu). ADNI is the result of efforts of many co-investigators from a broad range of academic institutions and private corporations, and subjects have been recruited from over 50 sites across the U.S. and Canada. The initial goal of ADNI was to recruit 800 subjects but ADNI has been followed by ADNI-GO and ADNI-2.For up-to-date information, see www.adni-info.org.

The Alzheimer's Disease Neuroimaging Initiative (ADNI) [94-96] data was screened and from 589 study participants, 188 qualified for an Alzheimer's Disease (AD) diagnosis at baseline, 401 had mild cognitive impairment (MCI). Among them, 9 were early-onset (EO) AD (Male: 4, Female: 5) and 27 were early-onset MCI (Male: 15, Female: 12). Subjects (ages 55 to 65) were divided into two groups: EO-AD and EO-MCI. Individual ADNI genotype and imaging data were downloaded and merged to form a single dataset containing genome-wide information for 36 individuals. Genetic analysis, including quality control, were performed using PLINK version 1.09. All the genetic processing was done via the LONI Pipeline environment. The 20 most significant single nucleotide polymorphisms (SNPs) were chosen by Manhattan plot and were associated with specific neuroimaging biomarkers. The structural ADNI data (1.5T MRI) was parcellated using BrainParser, and the 15 most important neuroimaging markers were extracted by the Global Shape Analysis (GSA) Pipeline workflow.

The goal of this application is to demonstrate the use of the pipeline environment for genome-wide association study (GWAS) using early-onset ADNI data including cognitive impairment measures, neuroimaging and genetics biomarkers. After standard SNP quality control [97, 98], the raw SNP data (630K SNPs) was reduced to 360K SNPs. A new pipeline workflow was designed to integrate the global shape analysis, tensor-based morphometry and SOCR multivariate regression analyses. The results of the automated pipeline workflows included significant correlations between SNPs and various neuroimaging biomarkers in the EO subjects and discriminated between EO-AD and EO-MCI cohorts, **Figure 3**. A connectomics diagram can be used to illustrate the strength of the associations between the 15 derived neuroimaging biomarkers and the top 20 SNP genetic markers. In this case-study, the small sample-size (N=36) has a negative effect on the (statistical) power to detect significant associations between the biomedical imaging markers (e.g., regional volume and shape metrics) and the genetic traits (SNPs/chromosomes). However, the same computational pipeline workflows can be used to analyze similarly larger cohorts (e.g., N>700), where sufficient power may be available to detect interactions between imaging and genetics effects (after Bonferonni correction for multiple testing). The imaging, genetics and clinical data used in this example were directly imported into the Pipeline workflow environment from the ADNI database using the Pipeline's IDAGet module. This pipeline workflow protocol can be designed on one client, and execution may be initiated on a user-specified pipeline server from another pipeline client, and the workflow progress, and final result inspection, may be monitored or examined on a different client device.

Genetic Associations with Hippocampal Function and Shape

A recent study investigated the genetics effects (single-nucleotide polymorphisms, SNP, associated with FKBP5 gene regulation, rs1360780) related to attention, behavioral, and hippocampal morphometrics [99]. The FKBP5 gene regulates glucocorticoid receptor sensitivity and is associated with hypothalamic-pituitary-adrenal axis functioning and stress-related psychiatric disorders [100]. In this cross-sectional study using fMRI/MRI, African American cohort of adults (N = 103) separated into 2 groups by genotype: Group 1 included carriers of the rs1360780 T allele, associated with increased risk for posttraumatic stress disorder; Group 2 included non-carriers. The study used the local shape analysis pipeline workflow to identify attention bias toward threat ($F_{1,90}$=5.19, p=0.02), and revealed alterations in the hippocampal shape for TT/TC compared with the CC genotype groups. **Figure 4** shows part of the computational protocol implemented as a pipeline workflow and the exemplary result from this morphometric analysis.

Persistent Pain and Irritable Bowel Syndrome (IBS)

A UCLA IRB approved study recruited 328 female normal controls (NC) and IBS subjects. A diagnosis of IBS was made using the ROME III symptom criteria [101, 102] based on the assessment by one of 4 gastroenterologists experienced in the diagnosis of functional bowel disease and the exclusion of organic disease. A subject's medical history and physical examination were obtained by a gastroenterologist. IBS patients with all types of predominant bowel habit were included. Subjects with a history of any chronic functional symptom or syndrome, or symptoms suggestive of disordered mood or affect, by history or by questionnaire, were excluded. In addition, potential subjects are excluded if by either history or questionnaire they a) have a serious medical condition or are taking medications which may interfere with interpretation of the brain imaging or physiological measures (other than IBS); b) have an ongoing major psychiatric diagnosis or psychotropic medication use over the past 6 months (subjects are not excluded for lifetime incidence of psychiatric disorder, or for intake of low dose tricyclic antidepressant for non-psychiatric indication); c) have a positive symptom score on the Hospital Anxiety and Depression Scale consistent with depression or anxiety d) do excessive physical exercise (i.e., marathon runners).

Brain images were obtained from all 328 subjects (107 IBS, 221 NC) using 1.5 and 3T MRI scanners [103]. We collected phenotyping data on catastrophizing (Coping Strategies Questionnaire) [104], early life trauma (Early Trauma Inventory) [105], state anxiety and depression (Hospital Anxiety and Depression Scale) [106], health status (12-Item Short-Form Health Survey) [107], trait anxiety scores (State Trait Anxiety Inventory) [108] and IBS symptom severity and duration (Bowel Symptoms Questionnaire) [109].

As a first step for shape-based neuroimage analysis, we reconstruct surface representation of anatomical structures of interest. Then, we analyze both cortical and subcortical structures. The cortical surfaces, including both white matter and pial surfaces, are reconstructed from T1-weighted MR images using FreeSurfer [110]. For sub-cortical structures, we applied the LONI BrainParser [37] to automatically segment the T1-weighted MR image into fifty-six regions. Using masks generated by BrainParser, accurate surface representations of the segmented regions are reconstructed with a novel algorithm we developed recently. This tool can remove segmentation artifacts without volume shrinkage and guarantees all surfaces guaranteed have the correct topology. All surfaces are represented as triangular meshes with spherical topology. The global shape analysis (GSA) pipeline workflow was used to identify regional differences between the NC and IBS subjects using the 56 regions of interest (ROIs) on 6 different volumetric and shape metrics (average mean curvature, surface area, volume, shape index, curvedness, and fractal dimension). **Figure 5** shows the 3 steps in this analysis (data inputs, pipeline workflow and results of regional group differences).

Conclusions

Although there are a number of useful software discovery and navigation frameworks [18, 111, 112], the protocols for tool interoperability continue to present significant biomedical computing challenges. There are considerable design differences between independent software suites. Furthermore, the varieties of computer programming languages for algorithm implementation, the substantial diversity of compilers and optimization strategies, and the gamut of hardware resources present additional hurdles in biomedical computing. Mediating these computational issues, coping with the enormous amounts of incongruent data, and handling a wide spectrum of devices require a paradigm shift of how we manage, process, interrogate and utilize biomedical and health related data.

The evidence is clear that we are in the front of an enormous storm of exponentially increasing wave of data, processing power and resource diversity. Multidisciplinary science efforts, technologies like Hadoop [113], OpenStack [114], Elastic Cloud Computing [115], Pipeline workflow systems [32, 116] and super high-bandwidth networking [117, 118] will be critical for riding this storm and uncovering novel biomedical knowledge. Embracing the *science interactome* (the multidisciplinary interactions between biomedical, computational and basic scientific areas, which often lead to new discoveries) will also be essential for establishing, maintaining and expanding the cyclical flow from Biomedical Challenges ↔ Scientific Models ↔ Data Analysis ↔ Computational Infrastructure ↔ Sustainable Education.

In this manuscript, we presented evidence of the rapid increase of the volume, diversity and velocity of biomedical data (e.g., neuroimaging and genetics [119-121]), and the growth of computational models, algorithms, software tools, services and electronic devices that manipulate these data [122-124]. There is evidence that software tool expansion always occurs within the limits of the available hardware infrastructure [125]. This close connection between the Moore's law for increase of computational power facilitates the observed expansion of new and more powerful software tools (e.g., Software as a Service (SaaS) [126], Platform-as-a-Service (PaaS) [127]). For example, in 1993, Windows NT OS 3 consisted of 5-million lines of code, which 10-years later grew 10-fold to 50-million lines in Windows, Server OS 2003 [128]. Similarly, from 2000 to 2007, the Linux Debian OS grew from 59-million to 280-million lines of code [129]. Web and mobile applications, or webapps, are software systems running on portable devices, which have significantly grown since 2005 into a multi-billion dollar business [130]. The explosion of webapp software development can be measured in terms of pure source code, usage of third-party APIs, and historical data. Studies of lines of code in specific areas indicate that over the past few decades there is an exponential increase of software development efforts [131, 132]. This advancement of the software tool capabilities in turn pushes the introduction of more efficient and omnipotent hardware devices (e.g., Infrastructure as a Service (IaaS) and Virtual Machines (VMs) [133]).

The Pipeline workflow environment is one of many solutions that provide a distributed and platform-independent management of heterogeneous resources using dispersed clients and servers, elaborate exchange protocols, and flexible mechanisms for control, execution, monitoring and sharing of complete computational protocols. We demonstrated three advanced end-to-end computational pipeline solutions for neuroimaging, genetics and computational morphometry. These solutions are implemented as graphical workflow protocols in the context of analyzing imaging (sMRI, fMRI, DTI), phenotypic (demographic, clinical), and genetic (SNP) data.

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As of September 2013, the Laboratory of Neuro Imaging (LONI) will be relocated to the University of Southern California (USC). Thus, some of the URL links, web-page references, and internet resources cited throughout this manuscript may be relocated to appropriate subdomains under http://www.loni.usc.edu. If you find broken links or defunct URLs please contact help@loni.usc.edu.

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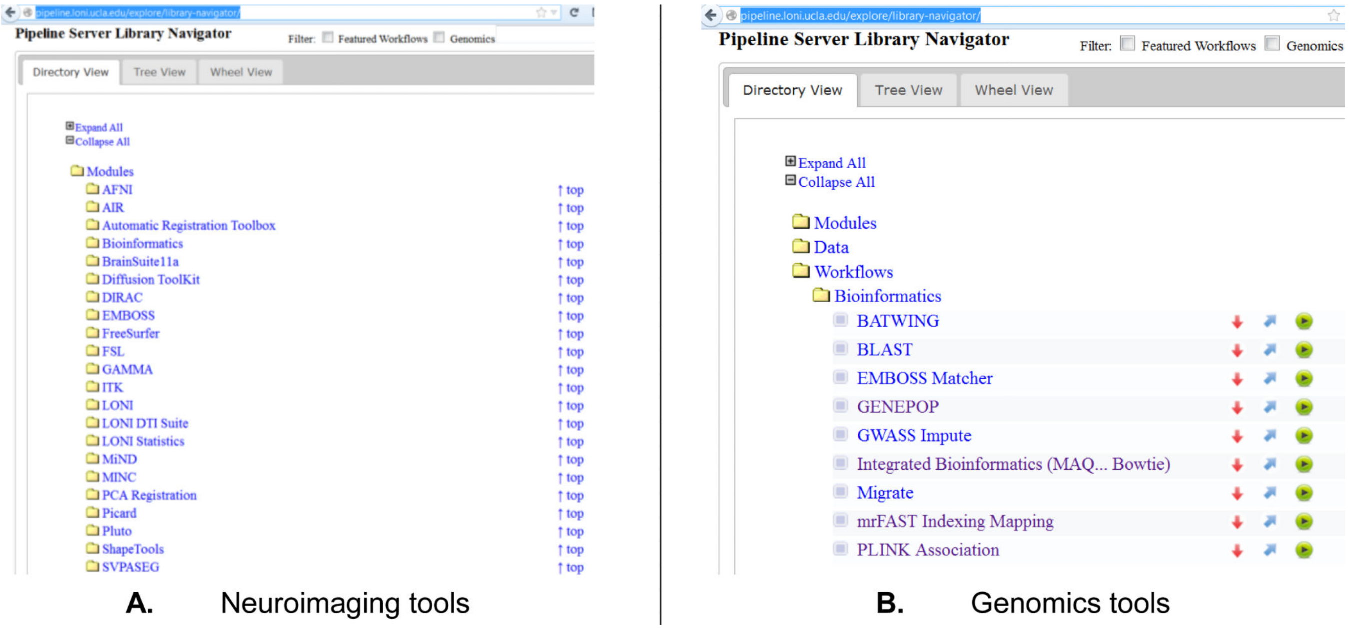


pipeline.loni.ucla.edu/explore/library-navigator/

Pipeline Server Library Navigator

Filter: □ Featured Workflows □ Genomics

Directory View | Tree View | Wheel View

⊞Expand All
⊟Collapse All

Modules
- AFNI ↑ top
- AIR ↑ top
- Automatic Registration Toolbox ↑ top
- Bioinformatics ↑ top
- BrainSuite11a ↑ top
- Diffusion ToolKit ↑ top
- DIRAC ↑ top
- EMBOSS ↑ top
- FreeSurfer ↑ top
- FSL ↑ top
- GAMMA ↑ top
- ITK ↑ top
- LONI ↑ top
- LONI DTI Suite ↑ top
- LONI Statistics ↑ top
- MiND ↑ top
- MINC ↑ top
- PCA Registration ↑ top
- Picard ↑ top
- Pluto ↑ top
- ShapeTools ↑ top
- SVPASEG ↑ top

A. Neuroimaging tools

pipeline.loni.ucla.edu/explore/library-navigator/

Pipeline Server Library Navigator

Filter: □ Featured Workflows □ Genomics

Directory View | Tree View | Wheel View

⊞Expand All
⊟Collapse All

Modules
Data
Workflows
- Bioinformatics
  - BATWING
  - BLAST
  - EMBOSS Matcher
  - GENEPOP
  - GWASS Impute
  - Integrated Bioinformatics (MAQ... Bowtie)
  - Migrate
  - mrFAST Indexing Mapping
  - PLINK Association

B. Genomics tools

Figure 1.

Examples of classes of tools available in the Pipeline computational library.

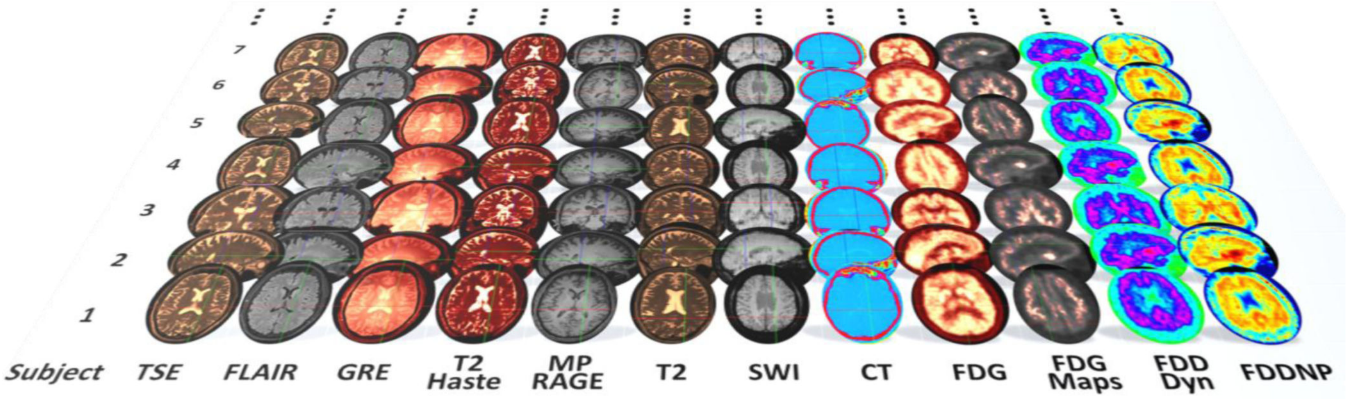
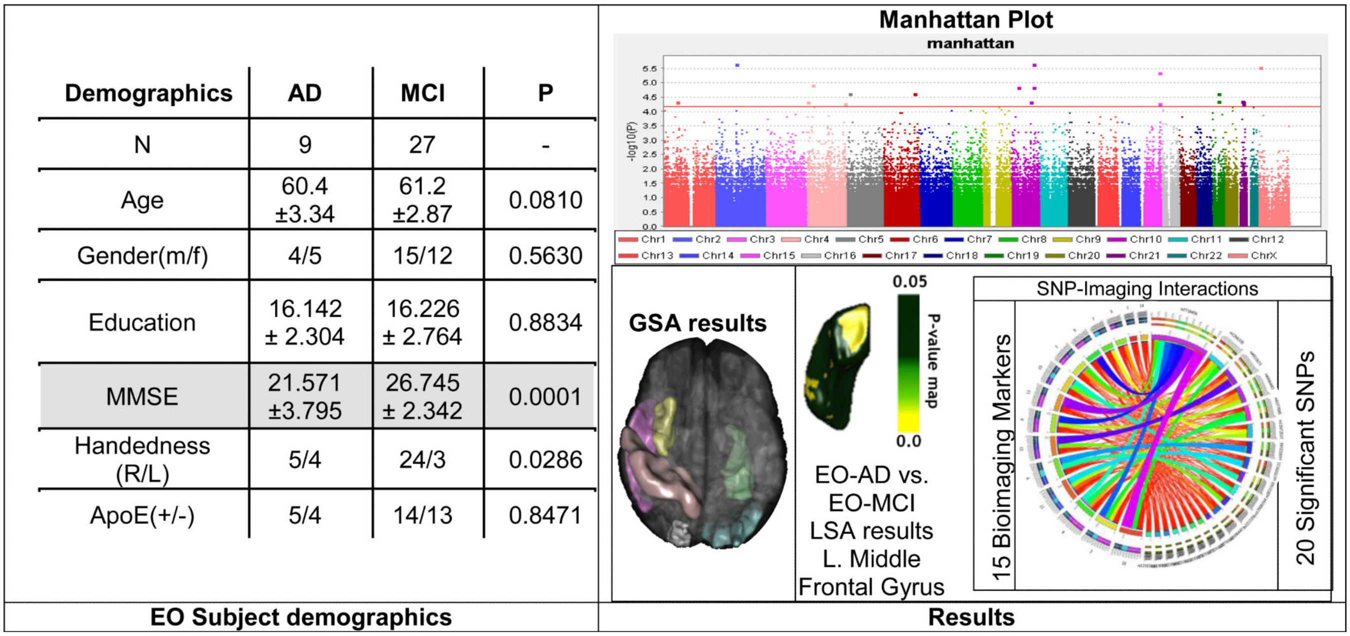


Figure 2.

Traumatic brain injury (TBI) studies demonstrate the diversity of the neuroimaging data in clinical applications. Imaging modalities included in many TBI studies include: TSE: Turbo-Spin-Echo magnetic resonance imaging (MRI); FLAIR: Fluid Attenuated Inversion Recovery MRI; GRE: Gradient-Recalled-Echo (MRI); T2 Haste: Half-Fourier Acquisition Single-Shot Turbo Spin-Echo MRI; MP RAGE: Magnetization-Prepared Rapid Acquisition with Gradient Echo (MRI); T2: T_2-weighted MRI; SWI: Susceptibility Weighted Imaging (MRI); CT: Computed Tomography; FDG: Fludeoxyglucose Positron Emission Tomography (PET); FDG Maps: Statistical maps of Fludeoxyglucose; FDDNP: 2-(1-{6-[(2-[F-18]fluoroethyl)(methyl)amino]-2-naphthyl}ethylidene)malononitrile PET imaging.



Demographics	AD	MCI	P
N	9	27	-
Age	60.4 ±3.34	61.2 ±2.87	0.0810
Gender(m/f)	4/5	15/12	0.5630
Education	16.142 ± 2.304	16.226 ± 2.764	0.8834
MMSE	21.571 ±3.795	26.745 ± 2.342	0.0001
Handedness (R/L)	5/4	24/3	0.0286
ApoE(+/-)	5/4	14/13	0.8471

EO Subject demographics

Figure 3.

Early Onset (EO) ADNI Imaging-Genetics GWAS Study using the pipeline environment.

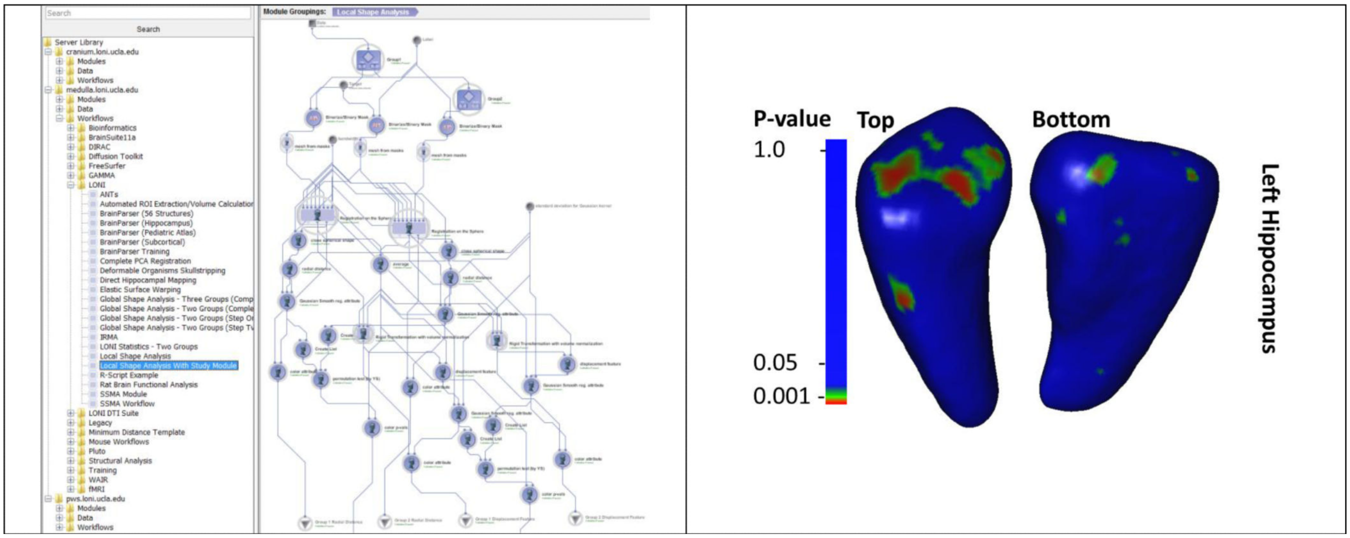
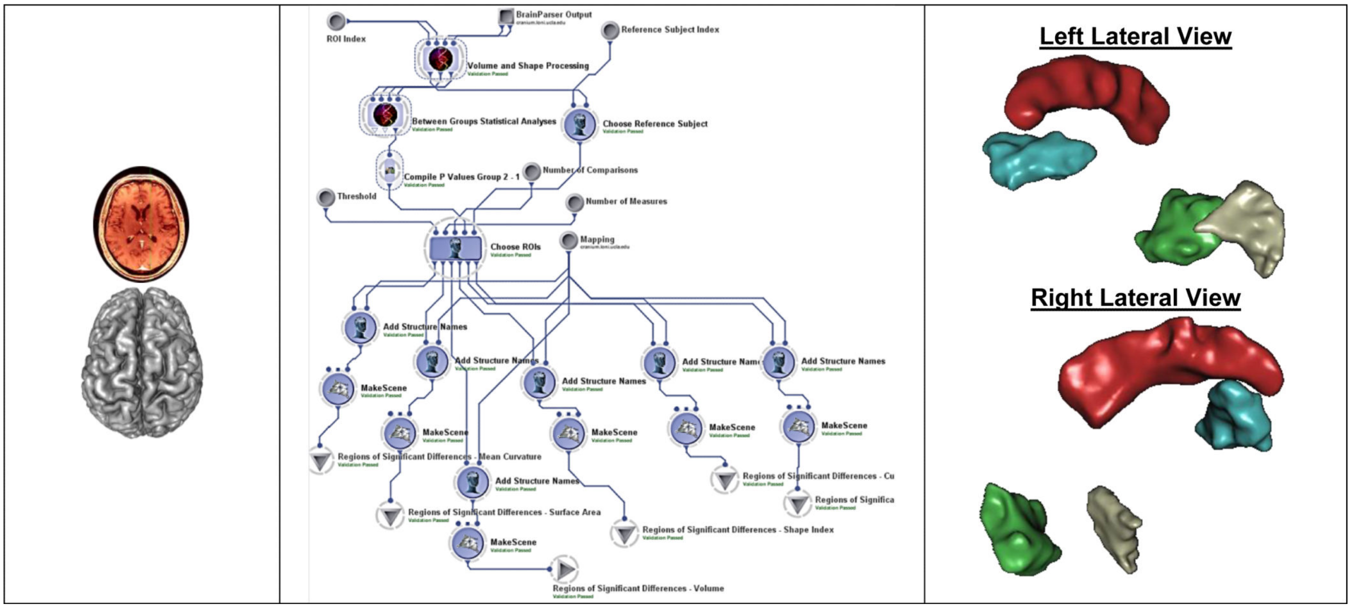

Search
Search
Server Library
cranium.loni.ucla.edu
Modules
Data
Workflows
medulla.loni.ucla.edu
Modules
Data
Workflows
Bioinformatics
BrainSuite11a
DIRAC
Diffusion Toolkit
FreeSurfer
GAMMA
LONI
ANTs
Automated ROI Extraction/Volume Calculatior
BrainParser (56 Structures)
BrainParser (Hippocampus)
BrainParser (Pediatric Atlas)
BrainParser (Subcortical)
BrainParser Training
Complete PCA Registration
Deformable Organisms Skullstripping
Direct Hippocampal Mapping
Elastic Surface Warping
Global Shape Analysis - Three Groups (Comp
Global Shape Analysis - Two Groups (Comple
Global Shape Analysis - Two Groups (Step Or
Global Shape Analysis - Two Groups (Step Tv
IRMA
LONI Statistics - Two Groups
Local Shape Analysis
Local Shape Analysis With Study Module
R-Script Example
Rat Brain Functional Analysis
SSMA Module
SSMA Workflow
LONI DTI Suite
Legacy
Minimum Distance Template
Mouse Workflows
Pluto
Structural Analysis
Training
WAIR
fMRI
pws.loni.ucla.edu
Modules
Data
Workflows
Module Groupings: Local Shape Analysis
P-value
1.0
0.05
0.001
Top
Bottom
Left Hippocampus

Figure 4.

Example of using the pipeline environment to complete a neuroimaging genetics study of FKBP5 gene (rs1360780) association with attention, measured through behavioral response (dot probe task) and hippocampal morphometrics. The superior and inferior vies of the hippocampal surface map illustrate the vertex locations, on the mean left hippocampus, where FKBP5 carriers (group 1) and non-carriers (group 2) showed significant shape differences.


BrainParser Output
ROI Index
Reference Subject Index
Volume and Shape Processing
Between Groups Statistical Analyses
Choose Reference Subject
Compile P Values Group 2 - 1
Number of Comparisons
Threshold
Number of Measures
Choose ROIs
Mapping
Add Structure Names
MakeScene
Regions of Significant Differences - Mean Curvature
Regions of Significant Differences - Surface Area
Regions of Significant Differences - Shape Index
Regions of Significant Differences - Cu
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Regions of Significant Differences - Volume
Validation Passed
Left Lateral View
Right Lateral View

Figure 5.

Analyzing IBS/NC regional differences: (Left) raw sMRI data, (Middle) GSA workflow including data processing, surface reconstruction, 3D parcellation, and statistical analysis, (Right) Statistically significant ROI between-differences rendered as 3D scenes (left cuneus is green, and right angular gyrus is gray; the red cingulate gyrus and the blue insula are shown for orientation only).

Table 1

Rapid increase of the volume of neuroimaging and genetics data.

Volume of Data **MB = megabyte = 10^6 bytes, GB = gigabyte = 10^9 bytes,** **TB = terabyte = 10^{12} bytes, PB = petabyte = 10^{15} bytes**							**D. Computational Power (CPU transistor counts) Moore's Law**	**Years**
Single Cryo brain Volume 1600 cm^2					**B. Neuroimaging (annually)**	**C. Genomics (BP/Yr)**		
A. Voxel Resolution		**Gray Scale**		**RGB Color**	**200 GB**	**10 MB**	**1×10^5**	**1985-1989**
Size	Count	8bits	16bits	24bits	1 TB	100 MB	1×10^6	1990-1994
1cm	12×15×9	1620	3000	4860	50 TB	10 GB	5×10^6	1995-1999
1mm	120×150×90	1.62 MB	3.24 MB	4.86 MB	250 TB	1TB	1×10^7	2000-2004
100 µm	1200×1500×900	1.62 GB	3.24 GB	4.86 GB	1 PB	30TB	8×10^6	2005-2009
10 µm	12000×15000×9000	1.62 TB	3.24 TB	4.86 TB	5 PB	1 PB	1×10^9	2010-2014
1 µm	120000×150000×90000	1.62 PB	3.24 PB	4.86 PB	10+ PB	20+ PB	1×10^{11}	2015-2019 (estimated)

Legend:

A. Recent technological advances enable significant increases of the level of detail of optical imaging (e.g., cryotomographic brain images) into the micron (µm) resolution [6-8].

B. By 2012, there were 55PBs of neuroimaging data [9, 10], which may exaggerate the volume of neuroimaging data due to different publications sharing the same datasets. As of 2010, the Imaging Data Archive, a Laboratory of Neuro Imaging brain database, stored about 5×10^{15}B=5PBs data. Recent neuroimaging studies may generate 1.5 TB of data each week [11].

C. In 2011, the size of the genetics data is estimated to be 30TBs (based on 10,000 human genomes) [12, 13]. As the total number of complete human genomes sequenced by the end of 2011 worldwide was >10,000, this figure may be orders of magnitude smaller than the real genomics data size. Furthermore, data derived from genome sequencing of other species and ‘partial genomes’ (e.g., exome capture sequencing, RNA sequencing and chromatin immunoprecipitation sequencing) is not included in this estimate. By 2015 more than a 10^6 human genomes will be sequenced [12]. Assuming each genome takes about 10^{11}B (100GB) this translates into a total data volume of 10^{17}B (100PB). Some of the sequences may be whole-genome 100X depth/coverage acquisitions, and some may be acquired at lower depth.

D. Data volume may be increasing at a faster pace compared to the well-established growth of computational power, Moore's law [14, 15].

Table 2

Storage and processing of Big neuroimaging and genetics data.

N=1	Raw data: 10GB (e.g., 512 directional diffusion data) Derived: 100GB	100+ GB RAM 70+ hrs CPU	320GB (at 80X)	2+ TB RAM 100+ hrs CPU
D. Cohort Studies (N~100)	100GB – 1TB	1TB RAM 100's hrs CPU	3+ TB	2+ TB RAM 100's hrs CPU
Multi-site population wide studies (N>1,000)	1-10 TB	1+ TB RAM 1000's hrs CPU	30+ TB	2+ TB RAM 1000's hrs CPU
Longitudinal (Time ≥ 2)	> 5TB	> 2 TB RAM > 5,000 hrs CPU	---	---

Legend:

A. Relative to the mouse brain, the field of view of human brain imaging data is several orders of magnitude larger [85]. Diffusion imaging of mouse brain may reach 1.9 GB (7 × 512 × 256 × 256 points with real and imaginary parts, represented as 4 bits float numbers) [86], and correspondingly diffusion spectral or high-angular resolution images may exceed 10GB per human subject and session [8]. The Global Shape Analysis pipeline workflow [32] includes about 100 processing steps and depending on the server load and the number of subjects provided as input may take 7 days to complete on the LONI Pipeline Medulla cluster (4TB RAM, 3,000 slots).

B. Many computationally intensive neuroimaging processing tools require significant hardware resources including storage, memory and CPU cycles [21].

C. In 2011, many alternative commercial DNA sequencing platforms generated whole genome sequences of size 100-600GB [87], which require days of computations on powerful grid systems. For example, our experience shows that Trinity whole-genome *de novo* assembly [88, 89] takes over 14 days of calculations on the LONI Pipeline Genomics server (1.4TB RAM, 40-core).

D. The infrastructure needs of cohort-based and multi-institutional studies increase linearly with the increase of the number of cases that require processing. Thus, a brain study of 1,000 subjects (e.g., Chinese Probabilistic Brain Atlas [90], vGWAS [91]) or a computational genetics study of 1,000 whole-genome sequences (e.g., prostate cancer [92], autism spectrum disorder [93]) may require Terabytes of storage and extensive infrastructure for data management, processing and interrogation. Longitudinal neuroimaging studies add another layer of complexity, as these typically require baseline as well as several (1+) follow up scans, which increases proportionately the volume of the imaging data.