



# THE COMPUTERWORLD HONORS PROGRAM

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## CASE STUDY

LOCATION:  
*Los Angeles, California,  
United States*

YEAR:  
*2006*

STATUS:  
*Laureate*

CATEGORY:  
*Science*

NOMINATING COMPANY:  
*Sun Microsystems*

### ORGANIZATION:

UCLA's Laboratory of Neuro Imaging (LONI)

### PROJECT NAME:

Brain Database

### Summary

The complex relationships governing genotype, phenotype and behavioral interactions can only be understood by integrating a variety of data from multiple measurements on large cohorts of subjects. For example, studying the genetics and environmental effects on the human brain require pooling and integration of large amounts of imaging, behavioral, psychiatric and physiologic data.

Contemporary neuroscience research, training and clinical applications demand new paradigms for managing, processing and visualizing multi-dimensional, multi-resolution and heterogeneous phenotypic, genotypic and imaging brain data. Such endeavors utilize increasingly complex research methodologies that require vast computational resources and a plethora of data sources and software tools. Existing ad-hoc approaches fall short in providing the neuroscience community with a flexible, extensible and user-friendly environment that simplifies the creation, management, dissemination and validation of these scientific analyses. The data flow and processing Pipeline Execution Environment, developed by the Laboratory of Neuro Imaging (LONI), addresses this need, dramatically improving the efficiency of research by allowing scientists to focus on science, instead of the mundane, arduous tasks of data management and processing.

### Introductory Overview

The LONI Pipeline Execution Environment is a platform-agnostic, Java-based graphical execution environment that modularizes software tools in a given analysis. These modules are interconnected according to function and dependencies, allowing data to automatically "flow" from parent to child; execution of data-independent modules are automatically parallelized. The Pipeline provides a secure, unified and intuitive framework for the integration of neuroscientific data, software algorithms and tools, and data processing and analysis protocols and a uniform interface to heterogeneous tools for data modeling, analysis and visualization. When compared to the traditional command-line execution of software tools that often have a large number of arcane parameters, the Pipeline's graphical data flow model dramatically simplifies complex scientific analyses.



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### Benefits

The LONI Pipeline Execution Environment improves communication, results validation and replication as research pipelines and associated data can be packaged and easily distributed to collaborators. Its intuitive GUI design minimizes the learning curve associated with designing complex, heterogeneous analyses and the XML module description framework facilitates additions of new tools into the pipeline library. Furthermore, the application's client-server functionality provides the neuroimaging community with access to sites with vast computational resources, facilitating integration and processing on a massive scale with 1,000's of subjects processed simultaneously through the same protocol. All client-server communications is AES-encrypted for security.

The end result—the Pipeline Execution Environment's research-centric approach represents a fundamental paradigm shift in data management, analysis and interpretation of neuroscientific data. Scientists, now, have more time to dedicate to science and research.

Examples of specific neuroscientific applications of the LONI Pipeline Execution Environment:

a. Methamphetamine and the Brain. In a recent study, we constructed and applied a pipeline using multidimensional modeling techniques to reveal, for the first time, how methamphetamine affects brain structure. This study is now expanding into broader collaborative work targeting drug addiction over time. The work focuses on new methods for detecting therapeutic response through longitudinal scanning of methamphetamine addicts with functional (PET) and structural (MRI) data.

b. HIV/AIDS. Our recent study focused on how AIDS affects several brain regions like the caudate, hippocampus, cerebellum, and the entire brain cortex. The findings are important from a general scientific standpoint as the detected brain deficits directly relate to immune system deterioration and help explain the typical profile of declining brain function in AIDS. They reveal, quantitatively and in 3D visual format, the brain systems impacted by AIDS. Using a new brain mapping technique, we identified the brain regions that are most vulnerable to the virus. We found that thinning of the language cortex correlated with immune system deterioration measured via blood levels of CD4+ T-lymphocytes. Specific patterns of tissue loss – with up to 15% loss visualized in the association areas of the brain—correlated with cognitive and motor deficits. Based on this work, it is therefore now feasible to associate T-lymphocyte cell depletion, and cognitive impairment, with specific brain deficit patterns visualized with MRI. These quantitative MRI-based maps reveal the pattern of damage caused by HIV in the brain. These pipeline-enabled mapping techniques can be powerfully applied to gauge HIV disease progression and response to anti-retroviral therapy, even prior to the onset of dementia or opportunistic infections. This work has led to the establishment of a consortium to pool AIDS neuroimaging data, and we have broadened our collaborations to include neuroimaging collaborators at several national centers.

c. Williams Syndrome. Williams Syndrome (WS) is a rare genetic condition estimated to occur in 1/20,000 births which causes facial abnormalities, medical and developmental deficits. Last year we also began mapping the profile of deficits in Williams syndrome using the Pipeline Execution Environment. We produced the first detailed maps revealing how Williams Syndrome impacts the human cerebral cortex. Using the Pipeline and applying novel brain mapping techniques and statistically averaging cortical thickness maps from 166 brains, we detected and mapped a sharply delimited region of language cortex with increased cortical thickness and



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gyral complexity. The isolated, thickened cortical region in language areas is remarkable because Williams subjects show remarkable strengths in language function. It is, therefore, a significant lead in the neuroscience of Williams Syndrome as it reveals the cortical territory affected by the genetic deletion. The affected sector of language cortex is 5-10% thicker and has higher complexity. The resulting 3D maps are the first to link a known genetic deletion (here located in chromosome 7q11.23), specific anomalies of cortical thickness, and behavior, in any disorder. Because the region of 5-10% thicker cortex and increased gyral complexity is circumscribed, the maps also provide new leads for neuroimaging and molecular work on WS. The findings visualize cortical zones where the WS genetic deletion selectively disrupts gyrification, shedding light on the anatomical scope and timing of the structural deficits in utero, and their behavioral and cognitive sequelae. Discovering the territory affected clarifies which systems develop abnormally in Williams Syndrome; importantly, these cortical deficits are linked with cognitive differences and can be mapped in living patients. This is clearly advantageous for detecting how genes control the development of the human cortex, but also for clinical prognosis, and for understanding the underlying mechanism of Williams Syndrome.

d. Time-Lapse Map of Brain Development. In a longitudinal study of brain development, which charts the trajectory of human brain development using MRI, we created the first dynamic map of brain changes that occur in childhood and adolescence. This project scanned 13 children with brain MRI every 2 years for 10 years. We developed new mathematics based on random effects models and cortical pattern matching to map the pattern of gray matter changes in the human cortex over time, resulting in a time-lapse animation of human cortical development. Brain development was tracked and visualized across the age range 4 through 21 in a spatiotemporally-detailed time-lapse sequence. The resulting time-lapse "movies" reveal that:

- higher-order association cortices mature only after lower-order somatosensory and visual cortices whose functions they integrate;
- phylogenetically older brain areas mature earlier than newer ones. We also began direct comparisons of this time-lapse sequence with several other large pediatric populations scanned longitudinally: children with (1) autism, (2) bipolar disorder and childhood-onset schizophrenia;
- direct comparison of these disease processes with normal cortical development is shedding light on these neuro-developmental disorders.

Our scientific collaboration is now focusing on developing the mathematics to compare developmental trajectories from abnormally developing children with the normative database, focusing on childhood onset schizophrenia and bipolar illness.

### The Importance of Technology

Coupling the LONI Pipeline Execution Environment with an effective, robust implementation of information technology will dramatically increase its efficacy and value to the neuroimaging community. Currently, grid functionality has been integrated into the Pipeline, combining the ease-of-use offered by the execution environment with the job management features of SUN Grid Engine. Complex, heterogeneous analyses can now be built in the execution environment and submitted natively to distributed computing resources via SUN Grid Engine, dramatically simplifying job submission and management. This functionality vastly improves the parallel nature of the LONI Pipeline by allowing vertical parallelization on symmetrical multiprocess-



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ing supercomputers as well as horizontal parallelization on compute clusters, both automatically handled by the Grid Engine. With this configuration, the Pipeline facilitated the development of an algorithm to measure cortical complexity by building fractal dimension measures from parametric models of the human cortex. The analysis required disparate software toolsets running on heterogeneous computational resources. We implemented a set of nonlinear partial differential equations that induced a grid on arbitrary sectors of the human cortex and analyze their frequency content. We used this algorithm and reported that the complexity of the cortex was found to be greater in women than men. The anatomic validity of the measure was further confirmed in a collaborative study of Williams Syndrome, summarized above, in which the pattern of cortical thinning and increased gyrification was mapped.

### Originality

Accurate identification of brain tissue and cerebrospinal fluid in a whole-head MRI is a critical first step in many neuroimaging studies. Automating this procedure eliminates intra- and interrater variance and greatly increases throughput for a labor-intensive step. Many available procedures perform differently across anatomy and under different acquisition protocols. We have addressed this challenge again using the LONI Pipeline Execution Environment by developing a Brain Extraction Meta-Algorithm (BEMA). This algorithm uses the pipeline to execute many extraction algorithms and a registration procedure in parallel to combine the results in an intelligent fashion and obtain improved results over any of the individual algorithms. Using an atlas space, BEMA performs a coordinate-wise analysis of training brain data to determine the optimal Boolean combination of extraction algorithms to produce the most accurate result for a given voxel. This allows the provided extractors to be used differentially across anatomy, increasing both the accuracy and robustness of the procedure. We tested BEMA using a variety of the registration methods. Training was performed on the MRI scans of 136 subjects from five separate datasets with different acquisition parameters on separate scanners. Testing was performed on 135 separate subjects from the same data sets. BEMA outperformed the individual algorithms, as well as interrater results from a subset of the scans, when compared with the mean Dice coefficient, a rating of the similarity of output masks to the manually defined gold standards.

The LONI Pipeline Execution Environment is the first instance of a flexible, distributed and secure processing environment for computational analysis and interpretation of neuroscience data. Its modular architecture integrates novel software engineering techniques like client-server TCP/IP communications, AES encrypted communications using the Diffie-Hellman encryption algorithm, Grid engine integration via SUN Microsystem's Java DRMAA bindings and SUN Grid Engine and automated process management. The environment also provides the first comprehensive ontological description of software libraries, algorithms and computational tools for data processing. The Pipeline environment may be invoked using batch scripting or via graphical user interface.



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### Success

We commenced the development of the LONI Pipeline Execution Environment in 2001 and since then, we have met all of our original goals with the Pipeline now fully operational. This includes a uniform interface to heterogeneous tools for data modeling, analysis and visualization; improve communication, results validation and replication; provide a computational infrastructure to the community; allow data integration and processing on a massive scale. In the development process, we have discovered many new challenges and have set our new goals for the future.

The LONI Pipeline Execution Environment v1 is widely distributed in the neuroimaging community. The software has been downloaded approximately 800 times and supports several hundred active users. The latest version, LONI Pipeline Execution Environment v3, is currently in the beta stage of development.

Andrew S. Fox, from University of Wisconsin-Madison, said "... I would like to recommend that users develop and manipulate their pipelines using the LONI Pipeline Processing Environment and execute their processes on multiple computers." (<http://brainimaging.waisman.wisc.edu/~fox/loni2condor.html>).

Russell Frisby, Johns Hopkins University said "the LONI Pipeline processing environment, a java powered graphical user interface that enables numerous, heterogeneous programs to run seamlessly in sequence or in parallel without the aid of intermediate adapter programs." (<http://www.npaci.edu/Outreach/PACI-REU/reports03/finals/FrisbyREU2003.pdf>).

Biomedical computation, visualization, imaging & informatics resources manual of the NIH National Center for Research Resources: "The LONI Pipeline Processing Environment was developed to address [these needs] by providing a simple, platform-independent, visual programming interface that allows the linking together of many independently developed analysis programs into a processing pipeline." ([http://nbcr.sdsc.edu/pub/NCRR\\_booklet.pdf](http://nbcr.sdsc.edu/pub/NCRR_booklet.pdf)).

Jorge Jovicich, Harvard University, said: "[BIRN Portal] biological workflow component has been added that incorporates the LONI Pipeline, FreeSurfer, 3D Slicer and JViewer."

([http://www.nbirn.net/Publications/Newsletter/birning\\_issues\\_vol1\\_issue3.pdf](http://www.nbirn.net/Publications/Newsletter/birning_issues_vol1_issue3.pdf)).

The need for a robust tool for computational neuroscience has been widely recognized by the neuroscience community and there are several initiatives to achieve this in different forms. The LONI Pipeline Execution Environment is the most commonly used and referenced utility for building population-based and disease-specific digital brain atlases, for training of research investigators and for fostering efficient communication of biomedical information.

### Difficulty

There are four computational neuroscience challenges that we faced in this project. They included brain mapping of degenerative disorders, modeling maturation of brain structure and function, establishing relations between phenotype and genotype in schizophrenia, and developing a mouse model for multiple sclerosis in humans. These challenges were addressed using different mathematical and statistical models, however, the practical technological and visualization tools employed to obtain our findings were all based on the same foundational computational infrastructure.



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The major technological challenges that we had to overcome to complete this project were the absence of powerful computational infrastructure and the difficulties associated with transitioning from the old script-based data analysis protocols to the new interactive Pipeline graphical environment. Our computational infrastructure needs were met by acquiring a heterogeneous Grid system from SUN Microsystems, Dell and SGI.