Large Scale Digital Atlases in Neuroscience
The ALLEN Institute for Brain Science Resources

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ABSTRACT

Imaging in neuroscience has revolutionized our current understanding of brain structure, architecture and increasingly its function. Many characteristics of morphology, cell type, and neuronal circuitry have been elucidated through methods of neuroimaging. Combining this data in a meaningful, standardized, and accessible manner is the scope and goal of the digital brain atlas. Digital brain atlases are used today in neuroscience to characterize the spatial organization of neuronal structures, for planning and guidance during neurosurgery, and as a reference for interpreting other data modalities such as gene expression and connectivity data. The field of digital atlases is extensive and in addition to atlases of the human includes high quality brain atlases of the mouse, rat, rhesus macaque, and other model organisms. Using techniques based on histology, structural and functional magnetic resonance imaging as well as gene expression data, modern digital atlases use probabilistic and multimodal techniques, as well as sophisticated visualization software to form an integrated product. Toward this goal, brain atlases form a common coordinate framework for summarizing, accessing, and organizing this knowledge and will undoubtedly remain a key technology in neuroscience in the future. Since the development of its flagship project of a genome wide image-based atlas of the mouse brain, the Allen Institute for Brain Science has used imaging as a primary data modality for many of its large scale atlas projects. We present an overview of Allen Institute digital atlases in neuroscience, with a focus on the challenges and opportunities for image processing and computation.

Keywords: Digital atlas, neuroscience, mouse, human, standardization

1. DIGITAL ATLASING AND THE ALLEN BRAIN ATLAS

The field of digital atlases is extensive, and includes high quality brain atlases of the mouse, rat, rhesus macaque, human, as well as several other model organisms. In addition to atlases based on histology, magnetic resonance imaging and positron emission tomography, modern digital atlases use gene expression, connectivity, and probabilistic and multimodal techniques, as well as sophisticated visualization software. Today digital brain atlases are used in neuroscience to characterize the spatial organization of neuronal structures, for planning and guidance during neurosurgery, and as a reference for interpreting other data modalities such as gene expression or proteomic data. One of the ultimate aims of neuroscientific enquiry is to gain an understanding of the brain and how its workings relate to the activities from behavior to consciousness. Toward this goal, brain atlases form a common coordinate framework for summarizing, accessing, and organizing this knowledge and will undoubtedly remain as a critical-path technology in the future.

With the advent of high throughput molecular biology it has been possible to use large scale gene expression profiling as a component of digital brain atlas. Several approaches have been taken to spatially identify gene expression in the mammalian central nervous system on a genomic scale. Of the many techniques including *in situ* hybridization (ISH), microarray, quantitative-PCR, and digital sequencing, colorimetric non-radioactive ISH offers amongst the best alternatives for visualization of spatial localization of signal in its original setting. Whereas radioactive ISH has been cited to have higher sensitivity for genes expressed at lower levels and a stronger signal-to-noise ratio than non-radioactive probes, the benefits of colorimetric ISH for anatomic and tissue recognition as well as morphological cell characteristics is strong. These latter qualities are essential in the development of image registration, mapping, and visualization techniques enabling quantitative cross gene comparison.

In 2001, Paul Allen, co-founder of Microsoft, assembled a group of leading scientists to discuss the future of neuroscience and what could be done to accelerate neuroscience research. During these discussions the idea emerged that

a genomic scale 3D atlas of gene expression in the mouse brain would be of great use to the neuroscience community [1]. Of the potential possible techniques the project would ultimately use a technique for mapping gene expression developed by Gregor Eichele and colleagues at the Max Planck Institute for Biophysical Chemistry in Goettingen, Germany. This technique uses colorimetric ISH to map gene expression and designs gene specific probes that bind to mRNA within sectioned but intact brain tissue thereby profiling gene expression and preserving spatial context. An example is shown in **Figure 1a** below together with image viewing application in **Figure 1b.** The figure shows hybridization expression signal in layer 5 of the cortex as well as several other regions. These image viewing tools are freely available at www.brain-map.org
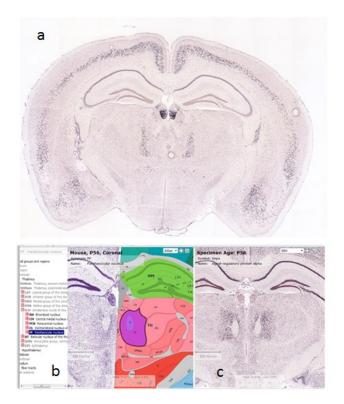

Figure 1. (a*) In-situ* hybridization image of a gene Etv1 (Ets Variant 1), a transcription factor that modulatse biological processes like cell growth, angiogenesis, migration, proliferation and differentiation. This gene expresses in the brain in layer 5 of the cortex shown as a band in . (b) Using the digital atlas and image viewing technology available www.brain-map.org this gene can viewed together with drawings of anatomy for cross comparison and localization of expression signal.

Since the initial public release of the data in December 2004, approximately 50,000 users worldwide access the Allen Brain Atlas resources each month. In addition to using these atlases as a standard to verify gene expression patterns and study particular genes of interest, scientists have mined the atlases to search for marker genes in various brain regions associated with diseases, identify different cell type markers, delineate brain regions, and compare gene expression data across species. Other uses of the resources also include leveraging the experimental methods, probes, and transgenic tools and technologies developed by the Allen Institute to inform and design new experiments. Over time the Allen Institute has expanded its products to provide a unique online public resource integrating extensive gene expression data, connectivity data and neuroanatomical information with powerful search and viewing tools for the adult and developing brain in mouse, human and non-human primate The standardized features in the web applications allow users to search and mine the various data sets. Features include simple and more advanced methods for gene searches based on correlation of expression patterns [2], colorimetric and fluorescent ISH image viewers, graphical displays of ISH,

microarray and RNA sequencing data, and an interactive reference atlas viewer The downloadable Brain Explorer software enables 3D navigation of anatomy and gene expression across several datasets. All of the Allen Brain Atlas resources can be accessed through the Allen Brain Atlas data portal at www.brain-map.org.

The use of anatomy independent grid based methods has allowed for the development of anatomy independent correlation based searches. An analogous and dual problem is viewed from the spatial context and one can ask for a given spatial location, how does gene expression at that location vary in the spatial neighborhood of that location? While neuroanatomists have used gene expression data to guide their understanding of brain architecture for some time, only more recently have integrated studies over large classes of genes been possible [3,8]. If data are spatially mapped, these two fundamental questions connecting gene expression and anatomy are dual to each other and one can develop powerful tools to navigate between lists of correlated genes and delineations of anatomic regions. These concepts are well illustrated with two tools from the Allen Brain Atlas, *NeuroBlast* (**Figure 2**) and the *Anatomic Gene Expression Atlas* (**Figure 3.**)
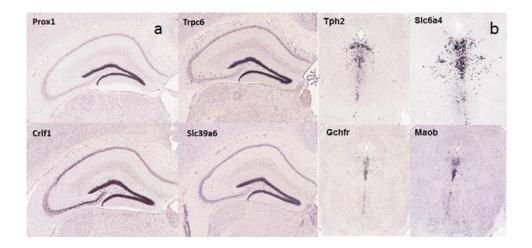

Figure 2. (a) *In-situ* hybridization image of a gene Prospero Homeobox 1(*Prox1*) and three other genes whose expression pattern is highly correlated with *Prox1, Trpc6, Crlf1,* and *Slc39a6*. These genes are found by utilizing anatomy independent grid searching (*NeuroBlas*t) methods resulting from large scale data mapping in the Allen Brain Atlas. (b) Similar search for high correlates of Tryptophan Hydroxylase 2 (*Tph2*) finds other genes (*Slc6a4*, *Gchfr*, *Maob*)implicated in serotonin system of the hind brain region.

The *NeuroBlast* facility is a search tool to help identify genes with similar 3D spatial gene expression profiles. While searching for genes that express in a given anatomic region is a natural approach, greater search power may sometimes be obtained by starting with a particular expression pattern and inquiring whether there exist other genes with a similar pattern of expression. As each ISH experiment will result in its own specific gene expression profile, *NeuroBlast* uses a particular image series as input rather than simply the gene name or accession number. For an input seed image series obtained through the ABA, *NeuroBlast* computes a similarity metric (Pearson's correlation) between the gene expression of the input series seed and every other image series ranking each series by the score. As a second complementary tool, the *Anatomic Gene Expression Atlas* (*AGEA*) is a novel, relational atlas revealing the genetic architecture of the adult C57BL/6J mouse brain [3,4] based on spatial correlations across expression data for thousands of genes in the Allen Brain Atlas (ABA). *AGEA* includes three discovery tools for examining neuroanatomical relationships and boundaries: (1) 3D expression-based correlation maps, (2) a hierarchical transcriptome-based parcellation of the brain, and (3) a

facility to retrieve from the ABA specific genes exhibiting enriched expression in local correlated domains. The utility of this atlas is illustrated by analysis of genetic organization in the thalamus, striatum and cerebral cortex. *AGEA* is a publicly accessible online computational tool integrated with the ABA (http://mouse.brain-map.org/agea).
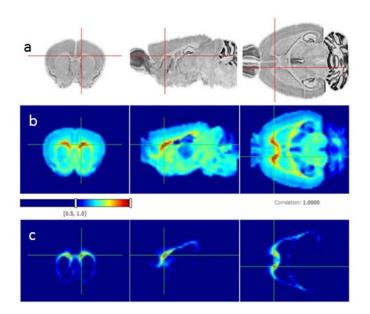

Figure 3. The *Anatomic Gene Expression Atlas* identifies highly correlated regions of gene expression in the rostral migratory stream (RMS). The RMS is a specialized migratory route found in the mouse brain along which neuronal precursor cells that originate in the subventricular zone of the brain migrate to reach the olfactory bulb. Its significance lies in the ability to refine and change an animals sensitivity to smells. The RMS provides an example of neurogenesis in the adult brain. This structure is especially enhanced in the rodent brain and is visible using the AGEA tool. Two unbiased representations of correlative gene expression are shown, in (a) RMS including midbrain, pallidum, hypothalamus, and amygdala, and in (b) detail showing the RMS alone.

2. LARGE SCALE INFORMATICS PIPELINES

Large scale informatics pipelines have been developed to process and manage the volumes of data produced. Large scale gene expression studies in the mammalian brain offer the promise of understanding the topology, networks and ultimately the function of its complex anatomy, opening previously unexplored avenues in neuroscience. High-throughput methods permit genome-wide searches to discover genes that are uniquely expressed in brain circuits and regions that control behavior. Previous gene expression mapping studies in model organisms have employed situ hybridization (ISH), a technique that uses labeled nucleic acid probes to bind to specific mRNA transcripts in tissue sections. A key requirement for this effort is the development of fast and robust algorithms for anatomically mapping and quantifying gene expression for ISH. The Allen Institute employs an informatics pipeline for automatically mapping expression profiles of ISH data which is fully automated and adaptable to other organisms and tissues. Our automated

study of over 20,000 genes has indicated that at least 78.8% are expressed at some level in the adult C56BL/6J mouse brain. The Allen Brain Atlas (ABA) informatics pipeline [4] addresses the challenge of automating the mapping of 3-D gene expression patterns on a genomic scale. The primary goal of the pipeline is to acquire and process data on the expression of individual genes in a fashion that will enable online anatomic structural search, visualization, and data mining of ISH imagery. A secondary goal is to develop tools to facilitate visual and computational discovery.

The prototypic informatics automated pipeline, illustrated in **Figure 4**, consists of modules supporting the following functions:

- Image preprocessing, including tile stitching and direct compression into JPEG2000 format,
- Image storage and indexing,
- Access to a novel online digital reference atlas for the adult C56Bl/6J mouse brain,,
- 3-D image reconstruction and deformable registration to bring the ISH images into a common anatomic framework,
- Signal detection and estimation for segmentation of expressing cells and tissues,
- Compilation of gene expression results over 3-D regions and presentation in an online searchable database,
- Visualization tools for examining 3-D expression patterns of multiple genes in anatomic regions.
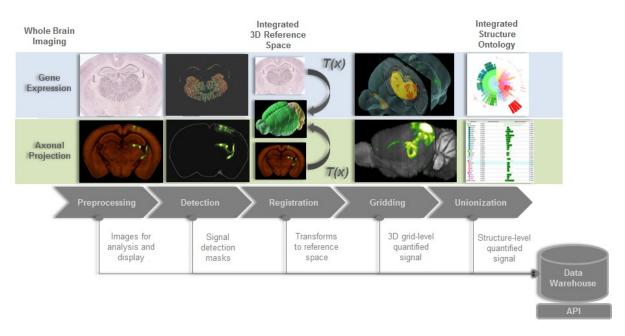

Figure 4. The Allen Institute informatics pipeline is an automated and semi-automated digital processing system for an algorithmic approach to publishing image and non-image neuroscience data including components for preprocessing, signal detection, registration and alignment, anatomic structural summary and gridding. Final data are stored and cross referenced for ready web deployment as well as use for external users through an API.

3. STANDARDIZED ATLASES

Mapping neuroscience and clinical data into a common frame of reference allows scientists and physicians to compare results between populations and individuals. A central reason for standardization is that multiple and diverse brain

specimens can be transformed into a standard framework that maximizes understanding their similar features. Another is that it allows identification of how unique or unusual features in a particular brain may differ from an average population. With the advanced image processing capabilities of modern computer technology, digital atlases can serve as the framework building standard atlases and to traverse the brain and information linked to it. One consideration in standardizing brain atlases is the type of coordinate system.

A vision and key steps that led to the creation of a digital mouse brain atlas framework for sharing data was developed by the International Neuroinformatics Coordinating Facility (INCF, www.incf.org) in what is known as Waxholm Space (WHS); named in honor of the group's first meeting location in Sweden in 2009.) Waxholm Space consists of multiple ultra-high resolution MRI scans of the standard laboratory mouse and simultaneous Nissl histology for those same brains. A supporting web-based Digital Atlasing Infrastructure enables the integration of data from genetic, anatomical and functional studies. Three major online mouse brain resources -- the Allen Mouse Brain Atlas, the Edinburgh Mouse Atlas Project, and the Cell Centered Database from UCSD) -- are now integrated with the INCF Digital Atlasing Infrastructure and therefore working together. This interoperability will facilitate future research as well as increase the value of previously acquired data. The INCF Digital Atlasing Project is a collaborative open access project with contributors on several continents. The Allen Reference atlas (**Figure 5**) and supporting atlases are fully consistent with the INCF vision in providing a centralized atlas infrastructure and annotation. Recently with the acquisition of high throughput imaging systems these atlases have been enhanced for greater detail and flexibility. The third generation reference atlas is comprised of an average of over 1200 mouse brain specimens with detailed annotation in both hemispheres.
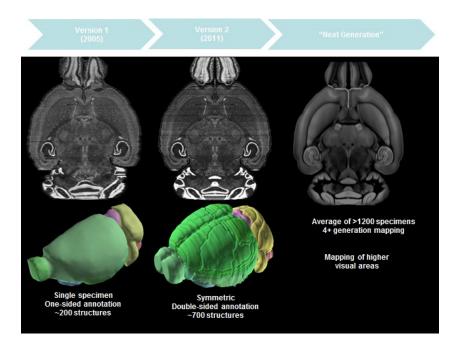

Figure 5. Three generations in the evolution of the Allen Institute atlas infrastructure. The first consisted of a hemisphere annotation of a single specimen at the level of about 200 structures. Further detail was added and the symmetrically annotated. In the most recent version as a scan of over 1200 individual mouse brains was accomplished and deformable registered to produce a strong population average. In addition select annotation of higher visual areas of the mouse are being added.

4. AN ATLAS OF CONNECTIONS

Several independent projects to map the connectome of the laboratory mouse at the mesoscale have been recently launched. Among these projects the Allen Institute embarked on a large-scale effort to develop a regional and cell type specific three-dimensional connectivity map. The Allen Mouse Brain Connectivity Atlas (**Figure 6**) uses a combination of normal and genetically modified mice together with genetic tracing approaches and a high-throughput serial 2-photon tomography system to image the labeled axons throughout the entire brain. High resolution coronal images are sampled every 100 μm (0.1mm) resulting in a 750-GB dataset per brain. These datasets are all registered into a common 3D reference space or reference space with high spatial fidelity allowing for quantitative analyses. Unlike other atlases from the Allen Institute, this atlas focuses on the identification of neural circuitry that governs behavior and brain function. Axonal projections from regions throughout the brain are mapped into a common 3D space using a standardized platform to generate a comprehensive and quantitative database of inter-areal and cell type-specific projections. By also adopting genetic tracing approaches, this Connectivity Atlas offers a reproducible framework to facilitate future efforts in probing circuit functions. The majority of the image sets are single injections into spatially distinct regions, but a subset of these are repeated injections into the same cortical and subcortical regions. The spatial mapping facilitates informatics based approaches to virtual 3D tractography as shown in **Figure 7**.
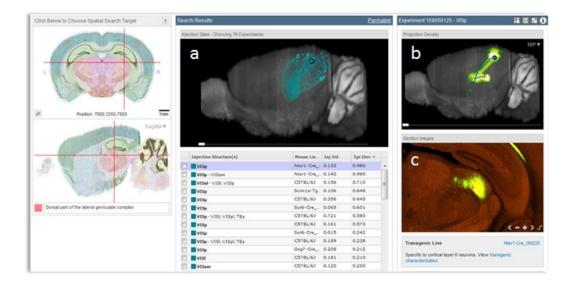

Figure 6. Allen Mouse Connectivity atlas search portal showing reference atlases, injection experiments and image results. Users can browse by injection or projection site and compare data with other resources and the Connectivity Atlas is consistent with these applications.
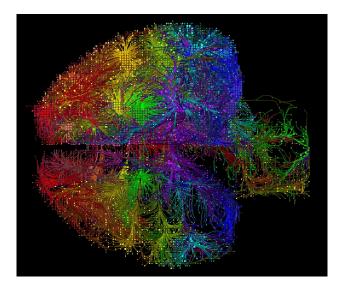
Figure 7.   Connecitivty projections from 21 cortical injections in the right hemisphere showing contralateral projections. The image processing involves virtual tractrography based on projection signal.   Images such as this can be displayed in the Brain Explorer application.

5.   HUMAN BRAIN ATLASING

Extending this work to humans, The Allen Human Brain Atlas was made public in May 2010 and was the first anatomically and genomically comprehensive, three dimensional map of the human brain. This atlas was created to enhance research in many neuroscience research fields including neuropharmacology, human brain imaging, human genetics, neuroanatomy, and genomics.. The atlas is also geared toward furthering research into mental health disorders, such as Alzheimer's disease, autism, schizphrenia and depression, and brain injuries.

Human brains share a consistent genetic blueprint, and possess enormous biochemical complexity. Gene expression studies show that 84% of all genes are expressed somewhere in the human brain and in patterns that are substantially similar from one brain to the next [10]. The analysis of differential gene expression and gene co-expression relationships demonstrates that brain-wide variation strongly reflects the distributions of the major cell classes such as neurons, oligodendrocytes, astrocytes and microglia, all of which are essential to brain function (**Figure 8**). Interestingly, the neocortex displays a relatively homogeneous transcriptional pattern, but with distinct features associated selectively with primary sensorimotor cortices and with enriched frontal lobe expression. Most notably, the spatial topography of the neocortex is strongly reflected in its molecular topography-the closer two cortical regions, the more similar their transcriptomes. In **Figure 9** this relationship is made quantitatively precise in that cortical regions more proximal are shown to have more closely related genetic profiles.
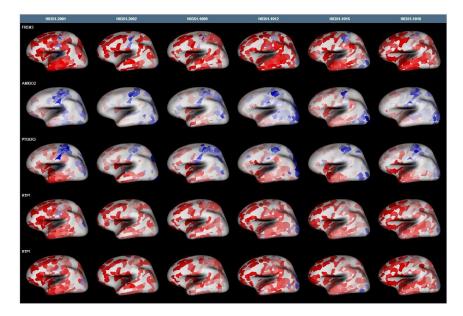
Figure 8. Data from the Allen Human Brain Atlas shown in the downloadable Brain Explorer application. Search for genes showing differential expression between the frontal and occipital lobes of the cortex and projected to an inflated cortical representation minimizing differences of gyri and sulci between 6 patients. Searches such as this can be performed in the downloadable Brain Explorer application.

We have previously shown that differences in transcriptional patterns of distinct neocortical areas depend on the distance between these areas, although comparatively few genes show very high levels of differential expression in the neocortex [10]. To make this precise we profiled cortical 22 cortical regions using both microarray and RNA-seq technology. To assess the extent to which these more subtle expression relationships can be found using RNA-Seq as compared with microarray, we first performed ANOVA on all samples from these 22 neocortical areas. RNA-Seq identified 3524 genes differentially expressed ($p<0.05$, Bonferroni corrected), compared with 2411 identified using microarray intensities (**Fig. 9A**). RNA-Seq was found to improve the sensitivity of microarrays to detect differential expression by approximately 10%, even when comparing relatively similar tissue. It is important to note that more than half of these genes agreed between methods ($p<10^{-200}$), providing evidence of the high reliability of both methods.

To quantify the relationship between transcriptional and physical distance in these 22 regions, we selected the top 1000 genes differentially expressed using each method and used the intersecting 393 genes ($p<10^{-225}$) to apply multidimensional scaling (MDS) to these data. We first visualized this relationship by mapping the samples into two dimensions using MDS on gene expression values. Both mappings recapitulate the spatial topography of the neocortex with qualitatively nearly identical layout (**Fig. 9C**, inset; R=0.98) and at the same scale, suggesting that both microarray and RNA-Seq can extract comparable genetic distance relationships. To quantitatively measure this effect, following[10], we compared this embedding with the physical MNI [11] coordinates of each sample. This method finds the closest fit of the genetically based MDS representation and physical based MNI representation of samples. Although the goodness of fit between native and MDS coordinates shows a slight improvement in RNA-Seq (38.4%) relative to microarray (34.6%), the results are impressively comparable. Finally, we recapitulate that the transcriptional distance between pairs of regions (based on 3D MDS coordinates) increase with increasing physical distance in the brain (**Fig. 9D-E**), as previously described [10].
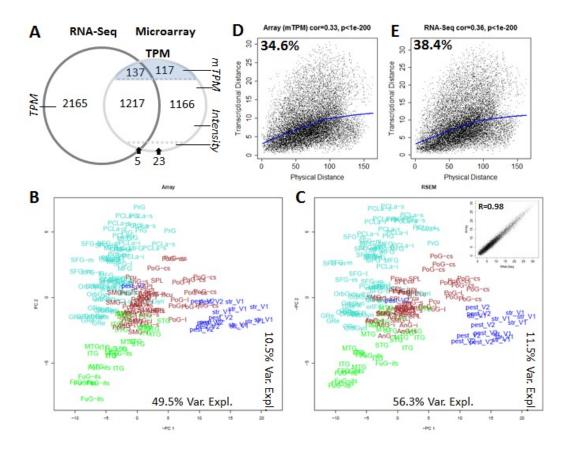
Figure 9: Spatial topography of the neocortex. A) Significant overlap in differentially expressed genes in neocortex identified using RNA-Seq and microarray, as identified with ANOVA. Blue shaded region shows additional genes identified using microarray after RNA-Seq scaling. B-C) Visualization in principal component space using multidimensional scaling (MDS), based on the top 393 genes, using microarray (B) and RNA-Seq (C), where distance between points reflects similarity in gene expression profiles. Each point represents a sample labeled with its region of origin and centered at the first two principal components. Colors correspond to lobe (turquoise = frontal; green = temporal; brown = physietal; blue = occipital). The percent variance explained from each component is shown, and accounts for 60% or more in both cases. Inset in C shows the correlation of transcriptional distances between each pair of regions in RNA-Seq compared with microarray is quite high. D-E) Correlation between transcriptional (based on 3D MDS [10], and physical (based on MNI coordinates) distance is quite high as measured by microarray (D) and RNA-Seq (E). Each dot represents a pair of samples, and all pairs are shown. The percent goodness of fit as well as the (Lowess) regression fit line are shown.

6. CONCLUSIONS

The development of digital brain atlases is now a major undertaking in neuroscience. While it may not be possible to systematically map each of the 100 billion neurons any time soon in any given individual brain, modern mapping techniques are providing atlases of remarkable resolution and functionality. Large-scale atlases of the brain are providing content to the neuroscience community through molecular, cellular, functional, and connectomic data. Given the complexity, diverse modalities, resolution, and scale of the brain there is much work to be done and consequently many opportunities within computational neuroinformatics.

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