Integrative Visualization of Temporally Varying Medical Image Patterns

Jung Soh[1*], Mei Xiao[1], Thao Do[1], Oscar Meruvia-Pastor[2] and Christoph W. Sensen[1]

[1] Visual Genomics Centre, Faculty of Medicine, University of Calgary, 3330 Hospital Drive NW, Calgary, AB, T2N 4N1, Canada

[2] Department of Computer Science, Faculty of Science, Memorial University of Newfoundland, St. John's, NL, A1B 3X5, Canada

Summary

We have developed a tool for the visualization of temporal changes of disease patterns, using stacks of medical images collected in time-series experiments. With this tool, users can generate 3D surface models representing disease patterns and observe changes over time in size, shape, and location of clinically significant image patterns. Statistical measurements of the volume of the observed disease patterns can be performed simultaneously. Spatial data integration occurs through the combination of 2D slices of an image stack into a 3D surface model. Temporal integration occurs through the sequential visualization of the 3D models from different time points. Visual integration enables the tool to show 2D images, 3D models and statistical data simultaneously. As an example, the tool has been used to visualize brain MRI scans of several multiple sclerosis patients. It has been developed in Java™, to ensure portability and platform independence, with a user-friendly interface and can be downloaded free of charge for academic users.

1 Introduction

Tracking changes in disease patterns that appear in medical images is critical for the analysis of the pathology of neurologic diseases. Conventional MRI has become the preferred imaging method for the diagnosis of autoimmune diseases of the central nervous system, such as multiple sclerosis (MS). In MS patients, brain lesions form as the disease progresses [1][2]. The lesions can be observed as distinctively bright areas in MRI images [3][4].

Several neuroimaging tools exist, which allow the visualization of multiple 2D images and reconstructed surface models simultaneously, volume render the resulting 3D images and overlay segmented anatomical structures on the original 3D images [5][6]. However, none of these tools makes provisions for visually exploring changes of the disease patterns over time (such as the lesions that occur in MS patients). While changes in brain lesions over time have been studied before [7][8][9], none of these studies was presented in a format that allowed the user to visualize the changes in both 2D and 3D spaces, respectively.

In order to provide researchers with an efficient visualization tool for the observation of changing disease patterns, we have developed a software tool to visualize local and global changes recorded in image stacks of disease patterns, enabling the simultaneous display of 2D and 3D spaces. Our software package has been designed to be an integrative visualization tool, which utilizes 2D images and 3D models generated from other software packages, in a platform-independent framework. It was developed using the Java™ programming language to maximize portability and platform independence, with a user-friendly graphical user

* To whom correspondence should be addressed: jsoh@ucalgary.ca

doi:10.2390/biecoll-jib-2011-161

interface that makes the use of software self-explanatory, lowering the threshold for new users.

2 Methods

2.1 Image Pre-processing

Initially, a collection of MRI images obtained from a patient at different time points (one scan per month in our example) is pre-processed, to convert the stack of 2D images from the MRI scanner into a 3D surface model. The initial data analysis was completed using a combination of individual tools from two standard brain imaging software libraries: Analysis of Functional Neuroimages (AFNI, http://afni.nimh.nih.gov/afni) [10][11] and Functional MRI of the Brain (FMRIB) Software Library (FSL, http://www.fmrib.ox.ac.uk/fsl/fsl/list.html) [12]. All collected DICOM image files were converted to the NIFTI format (http://nifti.nimh.nih.gov). The required processing steps include: (i) brain extraction; (ii) registration of different scans; (iii) brain segmentation into different tissue types; and (iv) lesion segmentation.

Brain model extraction from the images was completed on the high-resolution T1-image dataset using the FMRIB Brain Extraction Tool (BET, http://www.fmrib.ox.ac.uk/analysis/research/bet), followed by manual clean-up via the Draw Dataset plug-in from AFNI. Default settings for BET were used for standard brain extraction. Fractional intensity thresholds were varied across scans to obtain the most accurate brain extraction for each individual subject. A trained operator then performed a manual clean-up of the images in order to remove all labelled voxels that did not constitute brain tissue and add all unlabelled voxels considered to be brain tissue.

After the brain extraction, the FMRIB Linear Image Registration Tool (FLIRT, http://www.fmrib.ox.ac.uk/analysis/research/flirt) was used to register each subject's brain to the MNI152 1mm brain template (http://neuro.debian.net/pkgs/fsl-atlases.html) [12]. This step allowed the cross-subject comparison and facilitated accurate tissue segmentation. FLIRT default settings were used with the MNI152 1mm brain as the reference image. With these settings, FLIRT registered the image using an Affine 12 parameter model and Tri-Linear interpolation. Each patient's complete set of scans was subsequently registered together. This step was necessary to enable meaningful comparisons when visualizing changes in MS lesions within a patient over time. The first scan for each patient was used as the reference for the registration of all subsequent scans of the same patient.

To build the anatomical context of the brain, in which the MS lesions were found, we performed segmentation of the MRI scans to retrieve the following tissue types: ventricular cerebrospinal fluid (CSF), cortical grey matter, and sub-cortical tissue. The FMRIB Automated Segmentation Tool (FAST, http://www.fmrib.ox.ac.uk/analysis/research/fast) was used to segment the extracted MNI152-registered image. Default settings were used, with the exception of binary segmentation being selected. The image was segmented for three tissue classes, which produced grey matter (GM), white matter (WM) and cerebrospinal fluid (CSF) masks. The CSF mask was modified by a trained operator using AFNI to exclude all CSF outside of the ventricles. The GM mask was also modified using AFNI to include only cortical GM (i.e., excluding T1 "black hole" lesions within white matter). The third mask included the subcortical white matter and subcortical grey matter structures and was modified using AFNI to remove any remaining vasculature or non-subcortical tissue. The segmented images were then registered to subject space.

Hyperintense MS lesions were manually segmented from the FLAIR (Fluid Attenuated Inversion Recovery) images in AFNI by a trained operator. Lesions were first identified and

traced roughly, after which a threshold based on voxel intensity was applied to define the borders of the lesions more clearly. The resulting image was subsequently modified to include any missing areas and to exclude any hyperintense regions that were not lesions. T2 FRFSE (Fast Relaxation Fast Spin Echo) images were used to confirm lesions identified on FLAIR and were consulted frequently, since lesions that were not as clear on the FLAIR images, could be quite apparent on T2 FRFSE images, particularly in the *pons* and *cerebellum* regions of the brain. Lesion segmentation in subject FLAIR space was later upsampled to T1 space, in order to be able to compare occurrence of lesions within the segmented brain.

2.2 Visualization Data Flow

Once the segmentation procedures were completed, we were able to reconstruct the corresponding 3D models from the stacks of masked images. Using the Marching Cubes algorithm available from the Visualization Toolkit (VTK) [13], we produced the 3D surface-based models for the cortex, sub-cortex, CSF and lesions for each MRI scan. These 3D models, when overlaid together, provided a cohesive brain context in which the lesions could be visualized.

Figure 1 shows the flow of data in our visualization software, as applied to the observation of MS white matter pathology.

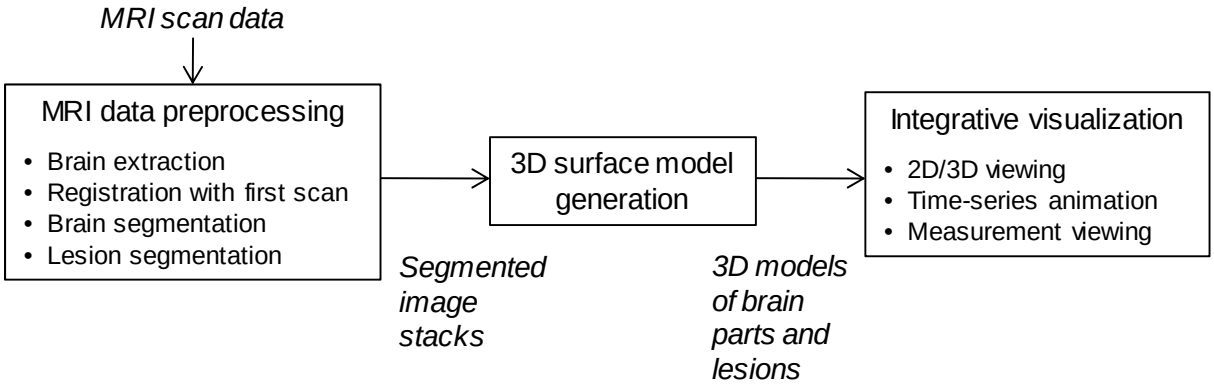

Figure 1: Simplified data flow in integrative visualization of time-varying disease patterns. Multiple scans of the same patient are done at different time points to observe the changes over time through the time-series animation.

The details of the MRI data pre-processing and 3D surface model generation stages are listed in Table 1.

2.3 User Interface

The pre-processed images (in TIFF format) as well as the 3D surface models (in OBJ format) were used as the basis for development of the new visualization software. This visualization software is designed to facilitate simultaneous display of 2D slices and 3D graphical models, alongside each other. The main frame contains three separate areas: a panel for displaying 2D slice images, a panel for displaying 3D models and a panel for displaying statistical charts. In a typical use scenario, a user would load multiple image stacks corresponding to scans of one patient at different time points (each stack being a collection of TIFF format images), in order to be able to visually compare these. Similarly, the user would load several 3D lesion models representing the same patient at different time points (several OBJ files would be loaded). In addition, loading a 3D anatomical reference model, such as a head model or cortex model (in OBJ format) can help to put the lesion models into a proper anatomical context. For example, a head model can be constructed using head contours extracted from a stack of MRI images.

To compare different stacks, users can assign colours to the 2D image stacks and hide/unhide selected stacks. It is also possible to modify the colour and transparency of the 3D models, so that 3D objects at different depths can be observed simultaneously.

Processing stage			Tool(s) used	Input	Output	Automated ?
Major	**Minor**	**Detailed**				
MRI data pre-processing	Brain extraction	Semi-automated extraction	BET	T1	Skull-stripped (SS) T1	Semi-automated
		Manual cleanup	AFNI			
	Registration	Registration to MNI152 1mm brain	FLIRT	SS T1, T2, FLAIR	SS T1, T2, FLAIR registered to MNI152 and first scan	Automated
		Registration to first scan (for each subject)				
	Brain segmentation	Automated segmentation	FAST	Registered SS T1	Cortical, subcortical, CSF masks on T1	Semi-automated
		Manual cleanup	AFNI			
	Lesion segmentation		AFNI	FLAIR	Lesion masks on FLAIR	Manual
3D surface model generation			VTK Marching Cubes algorithm	Lesion masks	3D lesion models	Automated
				Cortical masks	3D cortical models	
				Subcortical masks	3D subcortical models	
				CSF masks	3D CSF models	

Table 1: Detailed processing stages of MRI data pre-processing and 3D surface model generation. For each stage, the tools used, input data, and output data are listed.

Figure 2 shows the main graphical user interface of the visualization software. Multiple 2D image stacks can be loaded onto the 2D display panel (left) and multiple 3D models onto the 3D display panel (right). Within the interface, a 2D stack and a 3D model are visually linked side by side for easy referencing in either direction. At the bottom of the interface is another panel for the display of statistical information such as the change in lesion volume over time.

Java™ is a widely used high-level programming language, designed to be platform independent. Our software is written in Java, so that it can be deployed on any computing platform, including even virtual reality environments such as the CAVE Automated Virtual Environment [14]. The whole software package can be distributed as a *jar* (Java Archive) file and can be run using different operating systems, as long as Java version 1.6 (or higher) is installed. VTK is one of the most widely used toolkits in medical image visualization. It provides abundant classes for 2D/3D image visualization and processing. Several medical

image visualization packages, such as 3D slicer [15], DataViewer3D [16], and OsiriX [17], use VTK as the rendering engine for model rendering. Because of its well-documented algorithms and active community support, we adopted VTK as our main visualization framework.

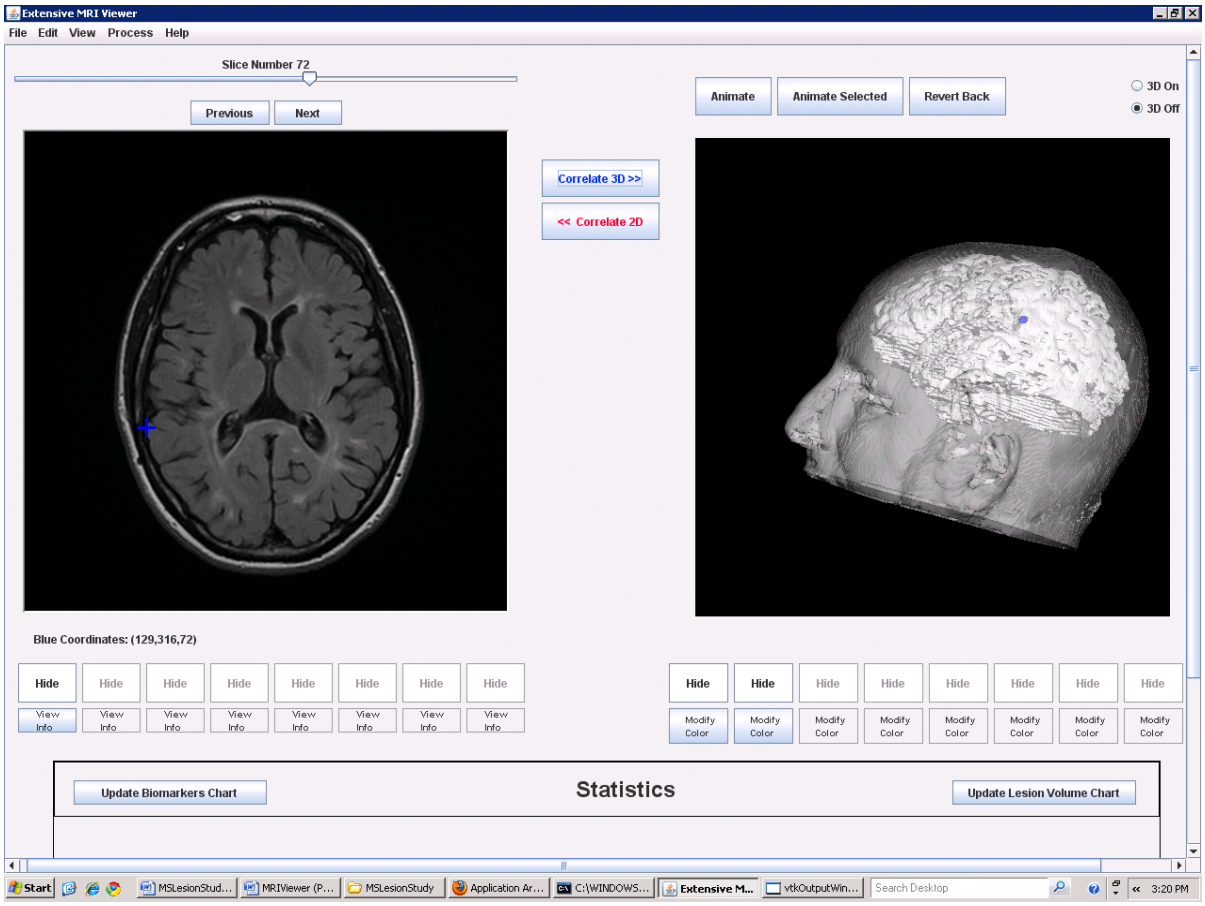

Figure 2: Main frame of the visualization software, which contains a 2D display panel (left), a 3D display panel (right), and a statistical chart display panel (bottom).

3 Results

3.1 Experimental Data

To apply the visualization software to a clinical problem, we used T1, T2, and T2 FLAIR MRI images of MS patients as the source of the MRI data. The patients for this study were recruited from the Dalhousie MS Research Unit. All patients in the study provided informed consent following procedures approved by the Research Ethics Board of the Capital District Health Authority, Halifax, Nova Scotia, Canada (Brain Connectivity and Executive Functioning in MS: CDHA-RS/2009-137, Version 1.2, March 11, 2009). The subjects were each scanned six times, at monthly intervals. The MRI scans for each patient has been pre-processed and corresponding sets of 3D models have been generated, as described in the Methods section above.

3.2 Visualization of Time-Series Image Patterns

After loading multiple 3D-lesion models of a patient, we were able to observe the changes in their shape, position, and size by visualizing the lesion models in several ways. Figure 3 shows a case where multiple lesion models from different time points were loaded and viewed

simultaneously. Images and 3D models from different time points are differentiated by distinct colours, both in the 2D and 3D panels, respectively. The 2D panel shows the overlay of lesion masks on the same numbered slice from the MRI scans of a patient. The 3D panel shows the 3D lesion models reconstructed from the corresponding scans. To aid in the comprehension of the changes that occurred, the software could also be used to compute the lesion volumes and display them as a chart. The measurement could be performed over entire set of lesion models, or only on the selected portion of the models (as indicated by the white box in Figure 3). The software was also used to measure the trend of changes in the pattern between scan sessions of a patient and plot it as a graph. For example, the lesion volume was be measured by counting the number of voxels in the 3D lesion model. This was in turn accomplished by summing up the counts of pixels in all the 2D lesion masks that comprise the 3D models of the lesion.

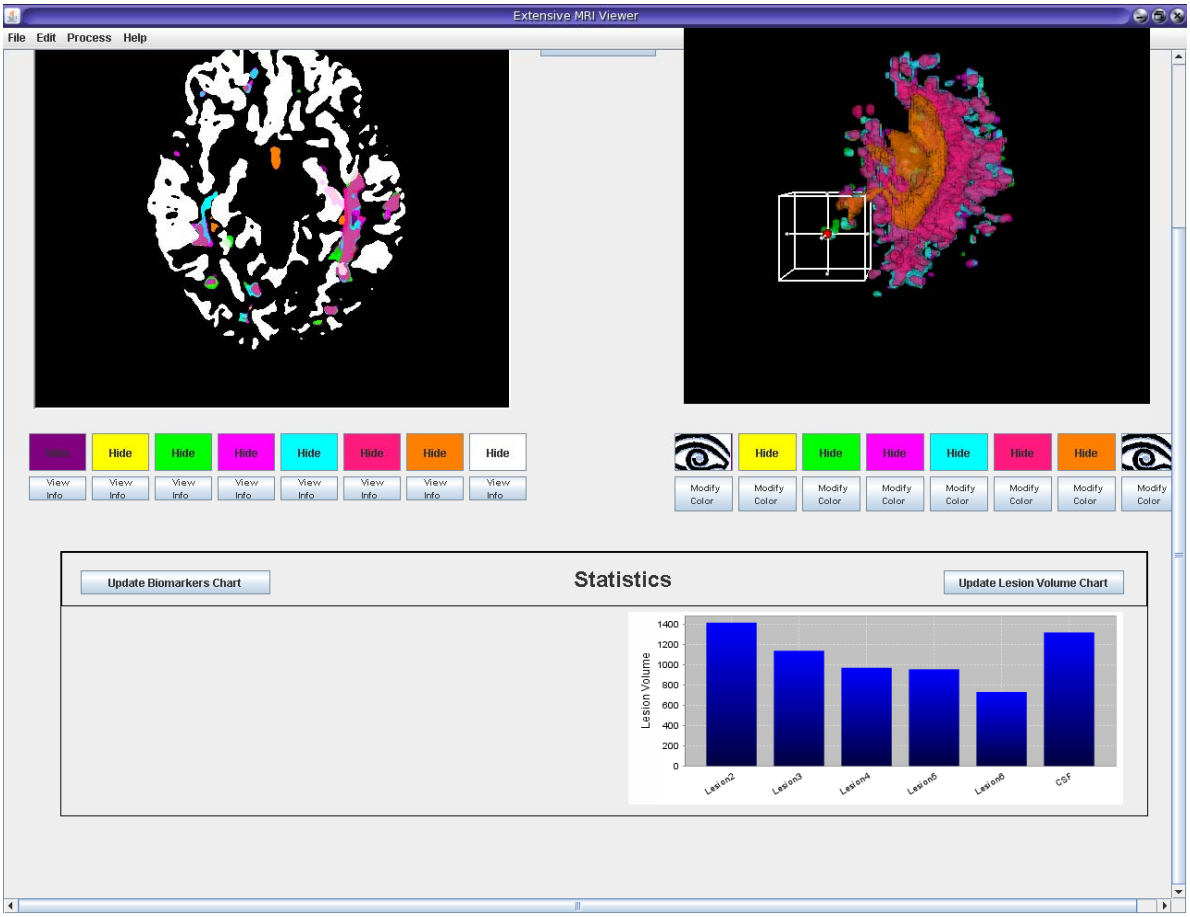

Figure 3: Visualizing lesions extracted from multiple scan sessions. 2D stacks of lesion masks and 3D lesion models are loaded and shown together, distinguished by unique colors.

Alternatively, the changes in the lesions over time could also be shown sequentially as an animation. We were able to observe that MS lesions can grow, shrink, appear, disappear and reappear over time. Their overall appearance is highly irregular and their pattern of evolution is very difficult to characterize. However, access to multiple MRI scans of one patient, acquired over a time period, provided opportunities to visualize lesion changes as a time-series animation and eliminated the need for the user to show and hide lesion models one after another. As shown in Figure 4, using our visualization tool, we were able to overlay a selected brain model to achieve a better sense of the spatial orientation of the lesions. With each lesion model uniquely coloured and reconstructed from a separate scan, the animation provided us with an intuitive perception of the magnitude and location of temporal changes of the brain lesions in an individual patient.

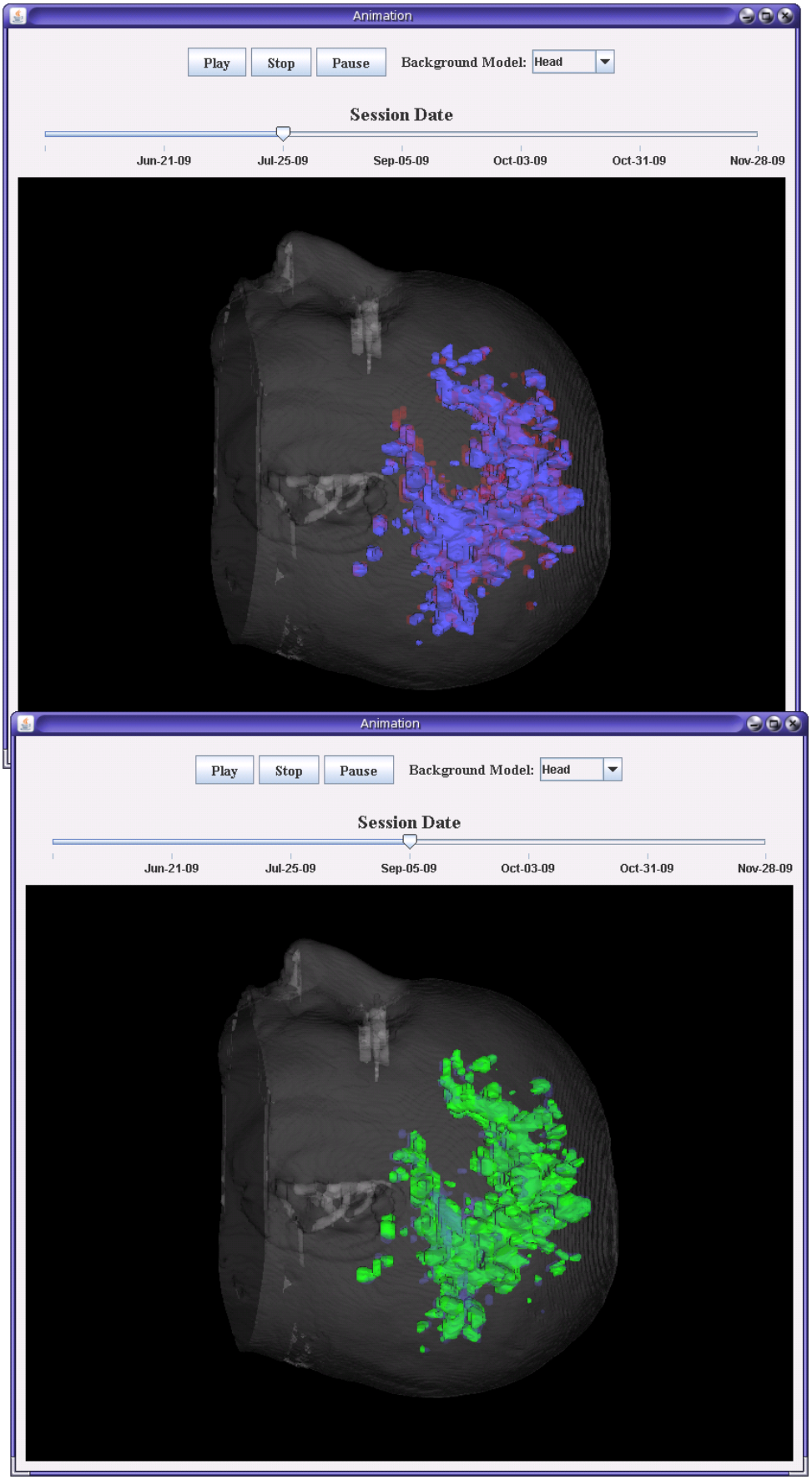

Figure 4. Animating changes in lesions over time. Two lesion models reconstructed from two scans acquired over time are shown. The slider bar shows the actual date of the scan. Different colors represent different time points, such that temporal changes between successive scans are elucidated.

3.3 Software Availability

Our visualization software is available as a free-of-charge download for academic use at http://www.visualgenomics.ca/~mxiao/research/MSLesionStudy.html, under the GNU Lesser General Public License (LGPL). The current version of the software has been tested on Unix Solaris 10 and Windows XP with .NET Framework 3.5. In order to run the program from our *jar* files, Java Version 1.6 (or higher) needs to be installed. The freely available tools ImageJ as well as shared (dynamically linked) libraries of VTK also have to be installed, from the links provided in the above URL for downloading the software. Detailed installation and the user guide are also available on the project website. The brain imaging software libraries AFNI and FSL, which have been used for the pre-processing of MRI images in our study, can be downloaded free of charge from the AFNI download page (http://afni.nimh.nih.gov/afni/download/afni/releases/latest) and the FSL download page (http://www.fmrib.ox.ac.uk/fsldownloads), respectively.

4 Discussion

Temporal changes in medical image patterns are important indicators of pathology. Several tools have been created to automatically detect these changes [5] and modelling of the changes by a mathematical time series has also been described [9]. However, these tools are essentially automated image analysis approaches that may not always correspond with decisions based on expert human observation. The advantages of our software include the ability to load various types of pre-processed images, such as those in NIFTI format, for image stacks or OBJ format for 3D models. While rendering of time-varying MS lesions has been done by some researchers [18], neither a graphical user interface nor animation capability was provided.

The focus of our software was the development of user-guided visualization methods, rather than in the development of a fully automated visual analysis toolkit. It is intended to be complementary to automatic change detection or curve fitting approaches and is designed to readily incorporate advances in these approaches into a format, which allows expert researchers and clinicians to view and interpret such data using a graphical interface. Both global and local changes in lesions can be visualized using our software. To display changes in lesions automatically, we use animation libraries available in Java to sequentially display models at different time points. The animation window provides full control over how to visualize the changing lesion models, so that patterns of changes can be intuitively understood. For example, we were also able to import these analyses, images and animation features into the CAVEman environment [19], which provides unique opportunities for 3D immersive visualization and manipulation of any compatible data collections, which change over time. Future work will include analyzing temporal changes and generating qualitative/quantitative descriptions of the observed global and local changes.

A predominant method of zooming into a 3D volume of interest has been to show the 3D object with a cut-away view defined by perpendicularly intersecting planes [5][15][16][20] [21]. This method can only be used to show the internal details with limited perspectives. In conditions such as MS, where patients exhibit a combination of dynamically changing and relatively static lesions that are often widespread, clinicians and researchers may be concerned with very specific regions of interest within the brain, depending on their clinical or research objectives. As our tool is oriented towards giving the user as much control as possible for visualization, we provide a method of volume selection. This method is not based on any superimposed anatomical atlas or computer-generated segmentations of the 3D space. Selecting a volume by a box widget lets the user set any volume enclosed by a box (such as

the small white box in Figure 3). The size, location, and orientation of the box can all be freely controlled by the user to fit the volume of interest as closely as possible. Within the selected volume, the user can then investigate changes in lesions.

Our visualization software was developed using the example of an investigation of patterns of MS lesions and their changes over time, as MS has been the subject of intensive studies using MRI methods since its introduction into the medical imaging field. Our software was designed to serve as a flexible and complementary package to existing conventional structural MRI image analyses that will assist clinicians and researchers in understanding the evolution of brain lesions within a particular patient over time.

Acknowledgements

This work was supported by Genome Canada/Genome Alberta, ASRA, WED, the Governments of Canada and of Alberta through WEPA, iCORE/Sun Microsystems Industrial Research Chair program, ANPI, and CFI. We thank Heather Angka, Carl Helmick, Jordan Fisk, John Fisk, and George Robertson for MRI data acquisition and processing.

References

[1] A, Bar-Or. Immunology of Multiple Sclerosis. Neurologic Clinics, 23:149-175, 2005.

[2] A. Prat, and J. Antel, 2005. Pathogenesis of Multiple Sclerosis. Current Opinion in Neurology, 18:225-230.

[3] M. Filippi and M. Rocca. Conventional MRI in Multiple Sclerosis. Journal of Neuroimaging, 17:3-9, 2007.

[4] C.H. Polman, S.C. Reingold, G. Edan, M. Filippi, H.P. Hartung, L. Kappos, F.D. Lublin, L.M. Metz, H.F. McFarland, P.W. O'Connor, M. Sandberg-Wollheim, A.J. Thompson, B.G. Weinshenker, and J.S. Wolinsky. Diagnostic Criteria for Multiple Sclerosis: 2005 Revisions to the "McDonald Criteria." Annals of Neurology. 58, 840-846, 2005.

[5] S. Huang, R. Baimouratov, P. Xiao, A. Ananthasubramaniam, and W.L. Nowinski. A Medical Imaging and Visualization Toolkit in Java. Journal of Digital Imaging, 19:17-29, 2006.

[6] R.B. Trelease and A. Rosset. Transforming Clinical Imaging Data for Virtual Reality Learning Objects. Anatomical Sciences Education, 1:50-55, 2008.

[7] M. Bosc, F. Heitz, J.P. Armspach, I. Namer, D. Gounot and L. Rumbachc. Automatic Change Detection in Multimodal Serial MRI: Application to Multiple Sclerosis Lesion Evolution. Neuroimage, 20:643-656, 2003.

[8] M. Filippi and R.I. Grossman. MRI Techniques to Monitor MS Evolution: The Present and the Future. Neurology, 58:1147-1153, 2002.

[9] D.S. Meier and C.R.G. Guttmann. MRI Time Series Modeling of MS Lesion Development. Neuroimage, 32:536-537, 2006.

[10] R.W. Cox. AFNI: Software for Analysis and Visualization of Functional Nagnetic Resonance Neuroimages. Computers and Biomedical Research, 29:162-173, 1996.

[11] R.W. Cox and J.S. Hyde. Software Tools for Analysis and Visualization of FMRI Data. NMR in Biomedicine, 10:171-178, 1997.

[12] S.M. Smith, M. Jenkinson, M.W. Woolrich, C.F. Beckmann, T.E. Behrens, H. Johansen-Berg, P.R. Bannister, M. De Luca, I. Drobnjak, D.E. Flitney, R.K. Niazy, J. Saunders, J. Vickers, Y. Zhang, N. De Stefano, J.M. Brady, and P.M. Matthews. Advances in Functional and Structural MR Image Analysis and Implementation as FSL. Neuroimage, 23:S208-S219, 2004.

[13] W. Schroeder, K. Martin and B. Lorensen. The Visualization Toolkit. Prentice-Hall, 2006.

[14] C.W. Sensen. Using CAVE® Technology for Functional Genomics Studies. Diabetes Technology and Therapeutics, 4:867-871, 2002.

[15] S. Pieper, B. Lorensen, W. Schroeder, R. Kikinis, R. The NA-MIC Kit: ITK, VTK, Pipelines, Grids and 3D Slicer as an Open Platform for the Medical Image Computing Community. Proc. IEEE Int. Symp. Biomed. Imaging, 698-701, 2006.

[16] A. Gouws, W. Woods, R. Millman, A. Morland, G. Green. DataViewer3D: An Open-Source, Cross-Platform Multi-Modal Neuroimaging Data Visualization Tool. Frontiers in Neuroinformatics, 3:9, 2009.

[17] A. Rosset, L. Spadola, O. Ratib. OsiriX: An Open-Source Software for Navigating in Multidimensional DICOM Images. Journal of Digital Imaging, 17:205-216, 2004.

[18] M. Tory, T. Möller and M.S. Atkins. Visualization of Time-Varying MRI Data for MS Lesion Analysis. Proceedings of the SPIE, 4319:590-598, 2001.

[19] J. Soh, A.L. Turinsky, Q.M. Trinh, J. Chang, A. Sabhaney, X. Dong, P.M.K. Gordon, R.P.W. Janzen, D. Hau, J. Xia, D.S.Wishart, and C.W. Sensen. Spatiotemporal Integration of Molecular and Anatomical Data in Virtual Reality Using Semantic Mapping. International Journal of Nanomedicine, 4:79-89, 2009.

[20] T. Heinonen, K. Visala, M. Blomqvist, H. Eskola, H. Frey. 3D Vsualization Library for Multimodal Medical Images. Computerized Medical Imaging and Graphics, 22:267-273, 1998.

[21] S.E. Mahmoudi, A. Akhondi-Asl, R. Rahmani, S. Faghih-Roohi, V. Taimouri, A. Sabouri, H. Soltanian-Zadeh. Web-Based Interactive 2D/3D Medical Image Processing and Visualization Software. Computer Methods and Programs in Biomedicine, 98:172-182, 2009.