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N4U

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Table of Contents

1 Executive Summary

Work package 6 (WP6) is in charge of finding, implementing and assessing algorithms to be available to end-users. The activities of the WP6 Algorithm Specification & Management belong to the Services Area (SA) and are spread over the entire 42 months duration of the project. These activities are strongly interlinked with the activities of the Network Area (NA) and Joint Research Area (JRA). Work of WP6 relates to tasks that started at month 1 of the neugrid4you (N4U) project and will continue for the whole duration of the project. In addition to algorithm specification, management and implementation, WP6 is responsible for the three Analysis Challenges in N4U, of which Analysis Challenge 2 (AC2) focuses on assessing algorithms for the automatic detection of white matter lesions in MRI images. This second deliverable, D6.2, reports on the plan and progress made so far in AC2. For AC2, N4U is fortunate to have the close cooperation of MAGNIMS, an European organization dedicated to the study of magnetic resonance in multiple sclerosis. MAGNIMS has contributed heavily to the design of AC2 and, supplied the data sets to be analysed. N4U, in close co-operation with MAGNIMS, will coordinate the statistical analysis of the results of the algorithms and the resulting publication in an academic journal. Also, N4U will be primarily responsible for implementing and running the algorithms (WP6) and organising the data sets (WP7).

2 Introduction

The aim of AC2 is to objectively compare existing algorithms for voxelwise segmentation of the MRI images of white matter (WM) lesions in the brains of multiple sclerosis (MS) patients. AC2 – referred to as "MUSCAT" by the end-user MAGNIMS – is ultimately aimed at improving image analysis methods specifically for MRI images of lesions in white matter in the brain with a particular emphasis on MS.

MAGNIMS (http://www.magnims.eu/)stands for MAGNetic resonance In Multiple Sclerosis and is a European organization dedicated to improving the MRI imaging of MS patients. The following members of MAGNIMS have agreed to work with N4U on AC2.

Hugo Vrenken – VU University Medical Center, Amsterdam

Mark Jenkinson – FMRIB Centre, Oxford

Marco Battaglini – University of Siena

So far, automated methods have failed to convince experts that they can replace the current manual segmentation methods even though manual segmentation is a tedious and labor intensive task. AC2 aims to facilitate the further development and optimization of such methods. As an important first step, an objective head-to-head comparison between existing methods and manual segmentation is required. In order to perform this comparison, several pieces are needed including MRI data, manual segmentation of the data to provide a "gold standard" for comparison, segmentation algorithms implemented on neuGRID, and an infrastructure that can run these demanding analyses. For AC2 we currently have many of these pieces in place and are in the process of completing the rest of them before running the algorithms on the data and comparing the results. Conditional on the approval of the authors, all of the algorithms implemented for AC2 will be available to all N4U end-users at the completion of AC2 and will be published in an academic publication.

2.1 Intended readership

This document is intended to be read by:

- All responsible for the management of AC2 and other partners in N4U that will be involved in the study
- MAGNIMS, the end-user organization that is working closely with N4U on AC2
- Users, user representatives, and other interested parties

2.2 Specifications

This document is required under WP6 of N4U DoW and is to be submitted by June 30th, 2013.

AC2 fulfils several goals of N4U as a whole and WP6 in particular. As MAGNIMS, in co-operation with N4U, is designing the study, selecting the algorithms and data sets, and taking care of the data analysis, it satisfies one of N4U requirements of having the N4U design driven by the end-user. Also, AC2 requires the installation of several new algorithms useful for the detection of lesions in white matter on neuGRID that will be available for all end-users. One of these algorithms has been recently developed in a university and neuGRID is demonstrating its ability to distribute algorithms for authors who do not have the resources to do so themselves. The results of AC2 will also provide a comparison of the new algorithms that will be available to end-users. While the data sets used in AC2 are to be kept strictly confidential in the near term, demonstrating N4U capability to do so, N4U hopes to get permission from their owner to eventually make them available to all end-users.

3 Data Sets

There will be three data sets used in AC2 – referred to as Dataset 1, Dataset 2 and LADIS. N4U already has possession of all three data sets and informal permission to use all three in AC2. N4U is in the process of formalizing these agreements.

We have been allowed by MAGNIMS to use two datasets consisting of MRI scans of multiple sclerosis patients where all the lesions have been manually segmented, and images from healthy control subjects.

Dataset 1: Dual echo (PD&T2) and MPR – 61 MS patients and 67 controls

Dataset 2: 2D FLAIR and T1W – 98 MS patients and 79 controls

In addition to the two MS data sets we will include a third data set, referred to as the LADIS data set, to address the issue of white matter lesions in older healthy individuals. These data were generated as part of the FP5 LADIS project (http://www.unifi.it/LADIS/). As with the two MS data set, the LADIS data set includes manually segmented lesions that provide a "gold standard" against which to compare the automatic methods.

4 Algorithms

MAGNIMS has currently selected three algorithms for automatically segmenting white matter lesions for inclusion in AC2 but may request additional algorithms be included in the future. N4U currently has 2 of the three algorithms running at a basic level. N4U is working to finalizing the two algorithms and implementing a third.

As described in a recent position paper by the MAGNIMS group (Vrenken et al. J Neurol, 2013), a fairly large number of methods for WM lesion segmentation have been described, but only a small number is (easily) available to users. Therefore, the collaborative N4U-MUSCAT effort on MS WM lesion segmentation will actively approach developers of algorithms that are considered suitable, based on their requirements and the characteristics of the data made available by MAGNIMS.

Based on availability and the characteristics of the data at least the following three methods will be included in the comparison.

CASCADE A new algorithm written at the Karolinska Institutet in Stockholm, as well as being evaluated in AC2, will be available to N4U end-users. The author has provided a copy to N4U which we have running after some effort including recompiling. The author is working on an improved version which we will implement as soon as available. N4U has informal approval from the author to include CASCADE in AC2 and make it available to N4U end- users and formal approval is being arranged.

Lesion-TOADS An established software tool, downloadable from the internet, designed for segmenting MS lesions. It requires about 8GB per job and 30 minutes to run. Lesion-TOADS is distributed as a plugin for MIPAV software. MIPAV is Java based software developed by NIH for both visualization and processing and can read a variety of file formats used in medical imaging. Currently N4U has Lesion-TOADS running under MIPAV in an interactive mode. Work is progressing on running MIPAV in command line mode so it can be run under neuGRID. Once MIPAV is fully operational on neuGRID, it will be available to run other MIPAV plugins in addition to Lesion-TOADS. Lesion-TOADS and MIPAV are free for use for academic research.

EMS A white matter lesion segmentation algorithm based on expectation maximization, that can be downloaded from the internet. It is run under SPM which in turn runs under MATLAB. SPM is available free of charge to academic researchers. While the standard version of MATLAB has license fee per copy, most MATLAB code can be compiled to an executable form that can be run with a free licence on computers such as the neuGRID infrastructure. N4U has some experience compiling MATLAB to executables and will gain additional experience with EMS that will be available for other algorithms. Also, as EMS requires SPM, and SPM is a widely used, neuGRID will also make SPM available. Implementation of the EMS algorithm within the N4U infrastructure is in its early stages.

5 Analysis of Results

We will analyse the performance of the automated segmentation algorithms by comparing their output to the manual "gold standard" labels. This will include a comparison at the voxel level to generate false positive and false negative fractions, and assess whether any of these algorithms currently is good enough to replace manual lesion segmentation. If computational resources are sufficient, we will also perform a statistical analysis called leave-one-out cross-validation to analyse the performance of the training-data based methods in more detail. Results of these analyses will be published in a scientific publication.

6 Conclusion

The three algorithms included in AC2 so far should take no more than a few hours to run on each individual patient's scans. The proposed setup of analyses allows us to ensure on-time delivery of results, and expand to even more advanced analyses if resources are sufficient. Also, many infrastructure issues have been resolved in AC1 and will not be issues in AC2. However, the algorithms to be included in AC2 are less widely used than the FreeSurfer and FSL algorithms used in AC1, and thus will likely require substantially more effort. Thus in AC2, as compared to AC1, the effort will likely be shifted from computational effort and infrastructure to algorithm implementation.

7 References

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8 Annex I Technical Requirements

The second year Analysis Challenge AC2 is tackling an important problem in the field of biomarkers in white matter lesions – particularly in the areas of MS and aging.

The following list of technical challenges were largely completed in the preparation and running of AC1. However, AC2 will provide additional exercise of some of these technical abilities - which are all essential for N4U to meet its goals.

1) Reliable distribution of the executable and supporting files of algorithm scripts to those already installed on individual clusters. With the intent to maintain all N4U algorithm scripts on N4U for as long as possible, it will likely have hundreds or thousands of algorithms and scripts to support. – AC2 requires additional algorithms to be installed.

2) Reliable distribution of the executable and supporting files of algorithm scripts to a new cluster. – Accomplished in AC1 but additional algorithms will need installation in AC2.

3) The ability of ExpressLane to restart were it left off in the list of jobs to be completed within an ExpressLane jobs file. – Completed in AC1.

4) An effective strategy to manage the range of memory requirements for a particular algorithm script in combination with a range of image volume sizes. Letting the user have easy control of memory requirements seems to be the best strategy. – Completed in AC1 but considering more robust and flexible implementation for AC2.

5) Handling the large number files that occasionally will be written to the output storage unit simultaneously because many different jobs happen to finish at about the same time and making sure few if any files are lost.- Implemented in AC1.

6) Organisation and format of the image volume files, including naming conventions, so algorithm scripts can run on as many different N4U data sets as possible. – Data sets for AC2 need to be added.

7) Efficiently manage the intellectual property rights of algorithms and data sets. – AC2 has additional algorithms and data sets that need IPR issues resolved.

9 Annex II Toolbox Portfolio Update

The N4U DoW requires an update on the current status of the algorithms available to end-users as part of this deliverable. As outlined in the DoW, part of WP6's responsibility is to integrate, test, validate and document new algorithms, pipelines and toolkits as requested by end-users. The DoW also requires the Toolbox Portfolio report will contain details of algorithms that are available for Production or under consideration.

The most commonly requested algorithm by end-users is unquestionably FreeSurfer/ReconAll. This is likely because (1) ReconAll is one of the most widely accepted algorithms for measuring brain atrophy measures in the literature and is widely used to study Alzheimer's disease and (2) it takes 1 to 4 days to run on each subject. As recent studies have 100's to 1000's of subjects few research institutions have both the computational resources and expertise to process this amount of data in a reasonable time. neuGRID offers a relatively quick and easy solution to this processing challenge.

A major part of the effort in deploying algorithms was improving the ExpressLane interface for running the algorithms and tuning the neuGRID infrastructure so it could run the algorithms efficiently. ExpressLane improvements included such features as optional pickup and delivery of a user's data from their computer on a job by job basis. Infrastructure tuning included such things as improving the bandwidth to the FBF DACs so it was no longer the bottleneck in ReconAll jobs and matching the memory allocation to the requirements of ReconAll.

ExpressLane scripts fall into two classes: official and custom. Official scripts are supplied by neuGRID, implement a few widely used algorithms, are readily available to all users, and have been tested. They also provide examples from which users can develop custom scripts.

In contrast, custom scripts are intended for much more limited use, often tailored to a particular task of an end-user. For example, an end-user may wish to run ReconAll with a slightly different set of options than the official script. In this case, an end-user can copy and modify an official ReconAll script and modify it for their particular needs. Therefore, a few official scripts, with the possibility of modification provide, with a little effort, a vast array of scripts tailored to the end-users needs.

Two "official" scripts are available to run ReconAll in neuGRID:

nG+FreeSurfer+5.3.0+ReconAll+v01.script

nG+FreeSurfer+5.3.0+ReconAllLong+v01.script

with the longitudinal version measuring the change in hippocampal volume between two time points.

Four additional official scripts include

nG+FSL+5.0.4+FirstMulti+v01.script

nG+FSL+5.0.4+FirstHippo+v01.script

nG+FSL+5.0.4+SienaX+v01.script

nG+FSL+5.0.4+Siena+v01.script

which implement standard FSL algorithms that measure hippocampal volume, whole brain volume and percentage change in brain volume.

In addition, the official scripts can also run under ExpressLane via a graphical user interface (GUI) for those users who prefer the GUI alternate to ExpressLane's standard command line interface.

9.1 Software Packages

The wide variety of the algorithms available in FSL and FreeSurfer, beyond those available via the neuGRID official scripts, are also available to those users of neuGRID who are comfortable with modifying FSL and FreeSurfer scripts. As most users of FSL and FreeSurfer in the research community run FSL and FreeSurfer via scripts we expect many users will create custom script by modifying neuGRID official scripts. The many algorithms implemented in FSL and FreeSurfer for fMRI, diffusion tensor imaging and many other applications, are currently easily accessible to end-users with a basic knowledge of editing scripts.

As two of the most widely used software packages in neuroscience, the most recent updates, FSL 5.0.4 and FreeSurfer 5.3.0, are installed on neuGRID and available for use by end-users. As several updates to both packages have been released in the last year, N4U has made it priority to install significant updates within weeks of release.

Other software packages also installed on neuGRID, but have only seen limited use by end-users, are:

R-2.13.1-1.sl5 – a public domain statisical package

brainvisa-3.2.1 – toolbox for segmentation of T1-weighted images

civet-200906 – cortical segmentation, release by the Montreal Neurological Institute.

texlive-2012 – text manipulation software with useful graphing campa

octave-3.0.5-1.el5 – semicompatible public domain version of MatLab

spm-8_r4667 – Implementation of the SPM package

Less frequently used packages are only updated on the request of end-users.

9.2 Works in progress

In addition to the algorithms deployed on the neuGRID infrastructure above several additional algorithms are at various points of development.

AdaBoost, which measures the hippocampal volume from MRI images of the brain, has been implemented and extensively tested under ExpressLane on more than a thousand MRI scans. Adaboost is in the final stages of deployment on neuGRID. AdaBoost is currently unique under ExpressLane, as it actually transfers the images to the LONI infrastructure in the United States to calculate the hippocampal volume, and the resulting volumes and other output are transferred back to ExpressLane for output.

BBSI, with its 40GB executable, is currently providing a major challenge to neuGRID infrastructure. We have recently managed to run it on the neuGRID infrastructure and are looking into ways to have it run more efficiently.

CASCADE, **Lesion-TOADs and EMS** are in AC2 are described in the main text of this document.

LDDMM measures the shape of the hippocampus and uses the segmentation of the hippocampus generated by FreeSurfer as input. It installation has been requested by end-users and we are currently working with the author to obtain a copy of the executables and arrange the IPR.