Large Deep Neural Networks for MS Lesion Segmentation

Juan C. Prieto.[a], Michele Cavallari.[b], Miklos Palotai[b], Alfredo Morales Pinzon[b], Svetlana Egorova[b], Martin Styner.[a], Charles R.G. Guttmann.[b]

[a]NIRAL, UNC, Chapel Hill, NC, United States; [b]CNI, Brigham and Women's Hospital, Boston, MA, United States;

ABSTRACT

Multiple sclerosis (MS) is a multi-factorial autoimmune disorder, characterized by spatial and temporal dissemination of brain lesions that are visible in T2-weighted and Proton Density (PD) MRI. Assessment of lesion burden and is useful for monitoring the course of the disease, and assessing correlates of clinical outcomes.

Although there are established semi-automated methods to measure lesion volume, most of them require human interaction and editing, which are time consuming and limits the ability to analyze large sets of data with high accuracy. The primary objective of this work is to improve existing segmentation algorithms and accelerate the time consuming operation of identifying and validating MS lesions.

In this paper, a Deep Neural Network for MS Lesion Segmentation is implemented. The MS lesion samples are extracted from the Partners Comprehensive Longitudinal Investigation of Multiple Sclerosis (CLIMB) study. A set of 900 subjects with T2, PD and a manually corrected label map images were used to train a Deep Neural Network and identify MS lesions. Initial tests using this network achieved a 90% accuracy rate. A secondary goal was to enable this data repository for big data analysis by using this algorithm to segment the remaining cases available in the CLIMB repository.

Keywords: Deep learning, multiple sclerosis MS, segmentation, large scale

1. INTRODUCTION

Multiple sclerosis (MS) is a multi-factorial autoimmune disorder, in the development of which both genetic and environmental factors play a role.[1] It is characterized by the focal inflammation and breakdown of the myelin which protects nerve fibers in the central nervous system resulting in focal lesions that appear in multiple places within the central nervous system. MS lesions are visible in T2-weighted MR sequences as hyperintensities and in Proton Density (PD) images.[2]

Recent MS lesion segmentation approaches include deep convolutional encoder networks using convolutional and deconvolutional layers. The novelty of this method relies on learning patterns from entire images, in contrast to patch based methods that require patch selection and extraction. MS lesion segmentation is done by segmenting the underrepresented classes in the network.[3] Other approaches are focused in learning spatial features and using multi-channel 3D MR images with labeled (pre-segmented data).[4]

While there are well established algorithms for MS lesion segmentation, most of them require human interaction and editing. Using recent classification techniques there is the possibility to improve existing methods. Deep Learning algorithms extract high-level, complex abstractions of the data. A key benefit of these types of algorithms is that by increasing the number of samples to train the network, the classification accuracy improves when the network is presented with new cases.[5] Even though Deep learning algorithms have excellent results in classification tasks, one of the major drawbacks for MS lesion classification is related to the number of samples that are used to train the network. In other words, the number of MS lesions samples is much lower than the number of samples drawn from the surrounding WM tissue. This is known as "The Class Imbalance Problem". To address this issue, we use a lesion frequency map generated from the subject population. The MS lesion detection will be limited to regions with a frequency higher than 20.

Further author information: (Send correspondence to J.C.P)
J.C.P.: E-mail: jprieto@med.unc.edu

The primary objective of this work is to improve existing methods of MS lesion segmentation using vast amounts of MS lesion samples to train a deep neural network. The neural network presented here was trained using data from the Partners Comprehensive Longitudinal Investigation of Multiple Sclerosis (CLIMB) study. CLIMB has a large repository of labeled images with manually corrected MS lesions. The following section explains the methods used to train the deep neural network. The network is trained using multi-channel data proton density (PD) and T2 weighted images.

The following section explains the materials used to generate the image samples to train the network.

2. MATERIALS

The Partners Multiple Sclerosis center has over 3000 patients enrolled in the CLIMB study at the Brigham and Womens Hospital. Patient follow-up has an average of 2.6 (SD 2.8) years. All CLIMB patients have a diagnosis of MS as defined by the 2005 McDonald criteria.

CLIMB subjects have a clinic visit every six months with a complete neurological examination, including each patients expanded disability status score (EDSS), body mass index (BMI) and other clinical variables. The routine protocol for the image acquisition includes a PD image with echo time (ET) 30, pixel spacing $0.9375, 0.9375, 3$ and repetition time (RT) 3000. A T2-weighted image is acquired with 80 ET, equal pixel spacing and 3000 TR. A T1 weighted image is also available pre and post gadolinium injection.

To train the network, the PD and T2 images are used. Both of these images are inherently co-registered. A label map for these images was generated by an automatic segmentation method and the lesions were validated, and corrected by an imaging expert.

The following section explains the methods used generate the samples and train the deep neural network.

3. METHODS

To generate the PD/T2 image samples, all images will be registered to the MNI-152 atlas. In order to reduce registration artifacts that appear when images from different modalities are registered, a PD/T2 template will be generated using 20 randomly chosen subjects from the population. The generated template will be registered to the MNI-152 atlas. All subjects will be registered to the PD/T2 template. Once the registration is completed, a frequency map is generated using the manually corrected label maps from each subject.

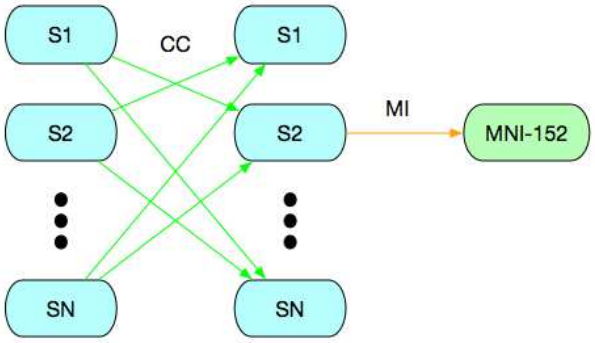
3.1 Template generation

To generate the template we chose 20 subjects randomly from the population. Using a multi-modal registration (PD, T2), each subject is registered between each other using the Advance Normalization tools (ANTS). A cross-correlation metric is chosen for the registration between subjects.

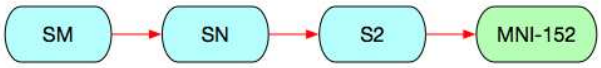
One subject S_r is randomly chosen and a multi-modal registration (PD, T2) is registered to the MNI-152 atlas. The metric chosen for this registration is cross correlation. Figure 3 shows the registration scheme.

Each subject is transformed to the MNI atlas space, i.e., $S_M -> S_N -> S_r -> MNI$. In total 400 images are generated for PD and 400 for T2. The templates ares generated by averaging them.

The PD and T2 templates generated with this procedure will be used to register each subject to the MNI atlas space. The following section explains how a lesion frequency map is generated once all subjects are registered to the MNI-atlas space.



(a) Subject registration



(b) Concatenate transformations

Figure 1. a) Each PD and T2 image is registered between each subject. A random subject is chosen and both PD and T2 are registered to the MNI atlas. b) Each resulting registration is concatenated in order to have each subject in the MNI atlas space. In total, there are 400 PD and T2 images. The template is generated by averaging them.

Figure 2. Registration scheme for a subject with multiple time points. Each time point is registered to the previous one. The first time point is registered to the MNI template. The PD/T2 images are interpolated using BSplines while the label map is interpolated with Nearest Neighbor.

3.2 Frequency map generation

A frequency map is generated using the manually corrected label maps for each subject. Each time point T_n within a subject is registered to the time point T_{n-1}. The first time point is registered to the templates generated in the previous section. The registration scheme is shown in Figure 2.

A subject label map $Sl_{\hat{n}}$ is generated using an 'OR' operation across time points, i.e., the lesions for a given subject won't be counted more than once if the MS lesion is present in more than one time point.

The frequency map is generated by simply adding $Sl_{\hat{i}}$ across all subjects in population.

The following section explains the neural network architecture used for MS lesion segmentation.

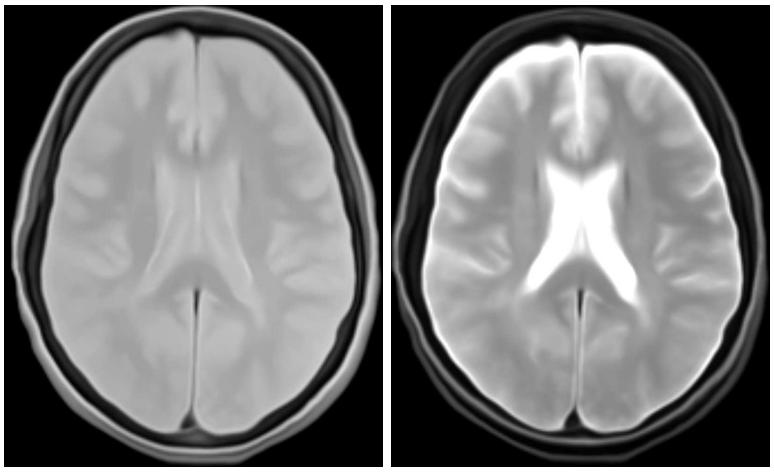
$$\hat{Sl}_i = \|_j^{Tp_i} LM_j \tag{1}$$

$$FM = \sum_i^n \hat{Sl}_i \tag{2}$$

3.3 Deep neural network

To build the network, the TensorFlow* (TF) framework was used. TF is an open source software library for machine learning tasks. The network was trained for two classes MS lesion and white matter (WM). After examination of the CLIMB database, 6000 time points were found with available label maps.

*https://www.tensorflow.org/



(a) Average PD (b) Average T2

Figure 3. Average templates generated using 20 randomly selected patients.

3.3.1 MS lesion samples

The images were sampled using the label maps and constraining the search region with in the frequency map generated in the previous section. The minimum threshold used for the frequency map was empirically chosen and set to 20.

The average lesion size is 2.6 voxels width/height with standard deviation of 2.8. We chose a patch size of $[11, 11, 11]$ to extract samples from the data. From each timepoint, MS lesion samples and WM samples were extracted. In total, 320000 samples were drawn (160000 MS and 160000 WM). An additional 40000 samples were chosen for validation purposes, these samples were not used during training.

3.3.2 Network architecture

The network was setup with 9 layers. 2 convolutional layers with pooling plus 5 fully connected layers. Each layer uses rectified linear units to connect the output of one layer to the next.

The last layer uses a softmax function to generate the probability for each class. The network was trained with a Gradient Descent Optimizer using an exponential decay function for the learning rate. The starting learning rate was set at e^{-9}.

While training, dropout with rate 0.5 was used to avoid over fitting and increase the classification accuracy. The network was optimized using batches of samples with size 64 and 20000 iterations.

The following section shows the results of this deep neural network.

4. RESULTS

Figure 3 shows the generated templates for PD and T2 images. Figure 4 shows the generated frequency map as explained is section 3.2.

Figure 5 shows two samples of MS lesions and WM displayed as RGB images (the contrast in the images has been modified, the PD density image is set in the red channel and the T2 is set in the green channel). All the samples have been projected in two dimensions using principal component analysis (PCA). PCA finds the linear lower-dimensional representation of the data such that the variance of the reconstructed data is preserved. This plot shows a red and blue cross, they represent the centroids obtained from analyzing the data using KMeans clustering algorithm[6] (the centroids do not correspond to the centroids of the two classes). The data points shown in magenta correspond to MS lesions while the WM are shown in cyan.

These MS and WM samples are used to train the network. 170000 samples from each class are randomly chosen and shuffled in order to train the network.

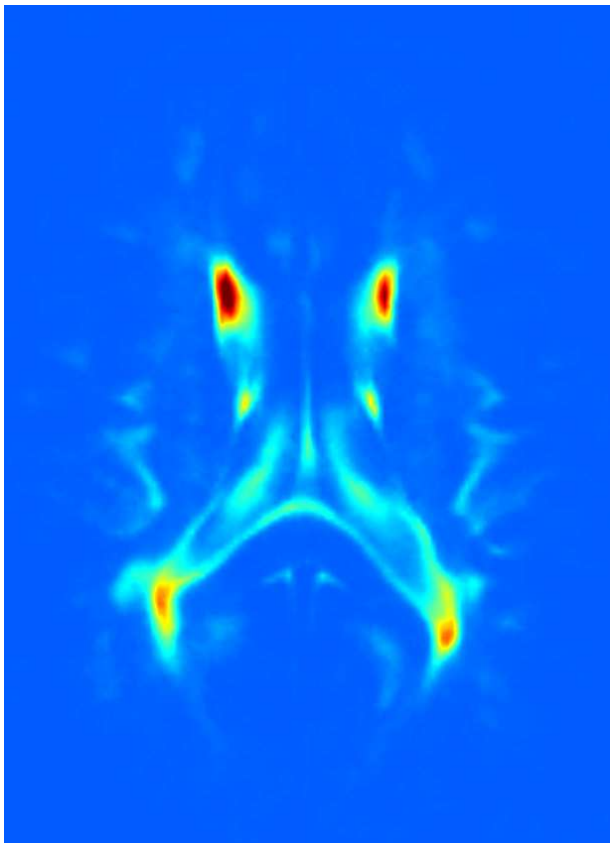


Figure 4. Frequency map for MS lesions. The blue color show low frequencies and the red color high frequency regions for MS lesions. The maximum number in the frequency map is 886.

(a) MS Lesion (b) WM (c) PCA projection (d) Zoom in in the PCA

Figure 5. a) MS Lesion and b) WM image sample. RGB images, the PD is on the red channel and the green channel represents the T2 image. The contrast has been modified in these images to show the features of the MS lesion compared to the WM. c) All the samples are analyzed using principal component analysis and projected to the two dimensional plane. d) Zoom in the upper level of the projection.

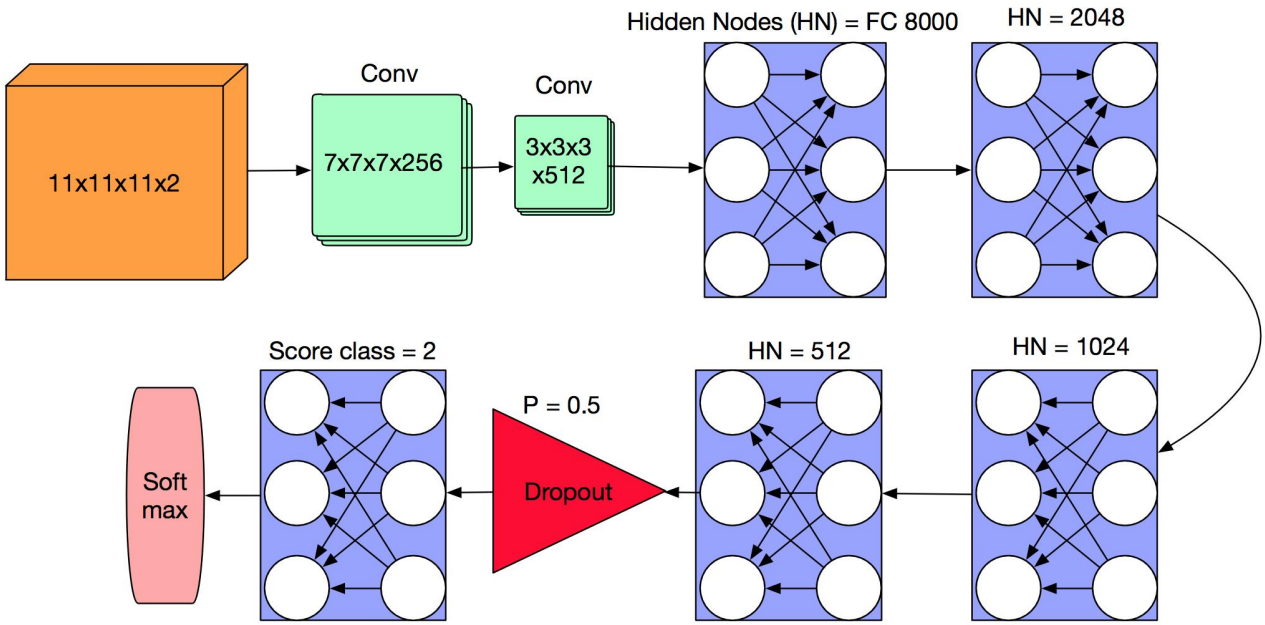


Figure 6. Network architecture created for MS lesion classification. The network consists of two convolutional layers plus 5 fully connected layers. The output of each layer uses a rectified linear function (RELU). A dropout layer is used with a probability of 0.5. The last layer uses a softmax function to turn the outputs into probabilities.

Figure 6 shows the network architecture build for this classification task.

Figure 7 shows the evolution of the cross entropy loss during the optimization and the training accuracy of correctly classifying a MS sample or a WM sample. Figure 8 shows some kernels learned by the first convolutional layer.

During the optimization, the accuracy of the network reached a maximum of 82% of accuracy. This network is tested with using 40000 samples images that were never used to train the network. The classification accuracy was 84%.

5. CONCLUSIONS

Initial tests using this network achieved a 84% accuracy rate. Future work will include another class to detect chronic "black hole" lesions. This type of lesions are characterized by their hypointensity appearance on T1-weighted images, after the injection of a gadolinium based contrast agent. By studying these lesions in a cross sectional study, we aim to demonstrate that the ratio of chronic lesions to overall T2 lesion load is significantly higher in areas of low compared to high normative blood perfusion. In longitudinal analysis, we aim to demonstrate that the regions susceptible to the formation of destructive "black holes" progressively extend to areas of higher normative perfusion, reflecting impaired perfusion with age.

ACKNOWLEDGMENTS

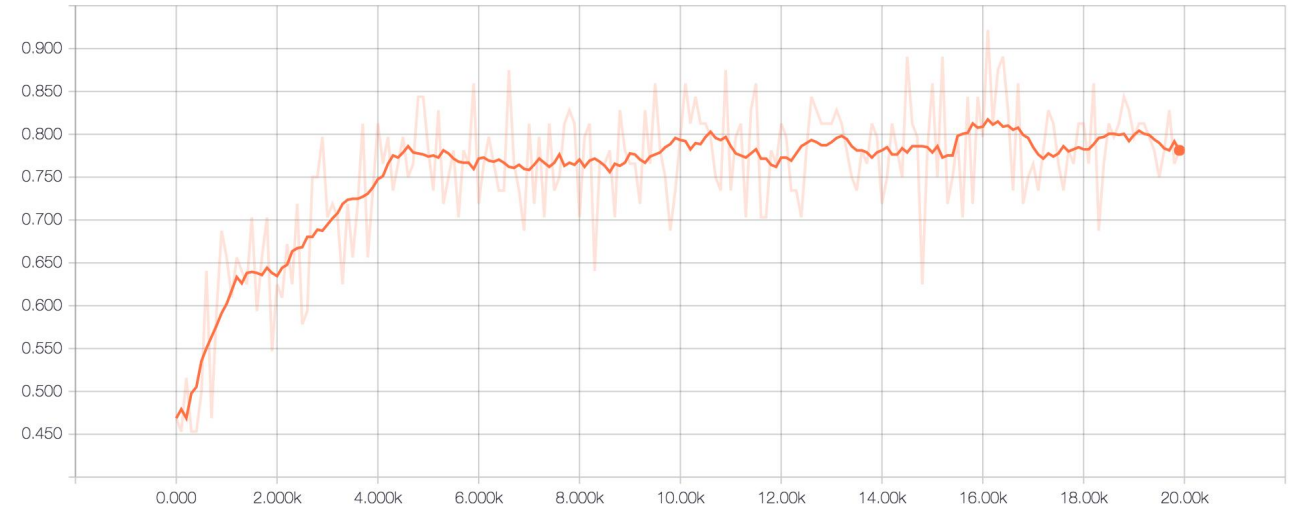
J.C. Prieto and M. Cavallari are supported by Research Fellowship Award from Mallinckrodt Pharmaceuticals.

We gratefully acknowledge the support of NVIDIA Corporation with the donation of the Tesla K40 GPU used for this research.

REFERENCES

[1] Taylor, B. V., "The major cause of multiple sclerosis is environmental: genetics has a minor role-yes," *Multiple Sclerosis Journal* **17**(10), 1171–1173 (2011).

(a) Cross entropy loss



(b) Training accuracy

Figure 7. a) Cross entropy loss output of the network after each iteration. b) Training accuracy

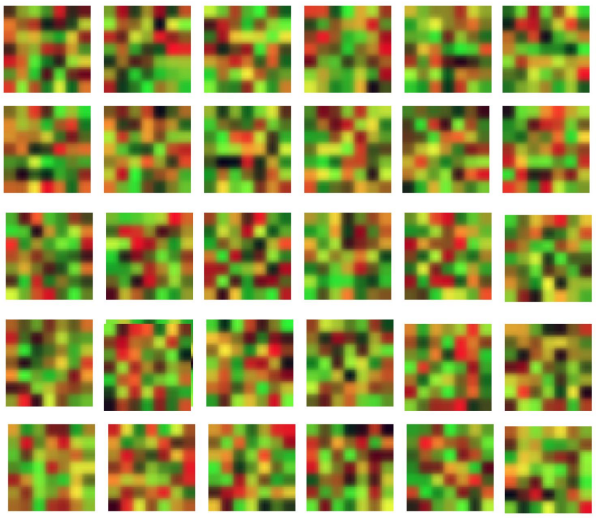


Figure 8. 20 randomly chosen kernels from the 256 kernels learned by the first convolutional layer.

[2] Simon, J., Li, D., Traboulsee, A., Coyle, P., Arnold, D., Barkhof, F., Frank, J., Grossman, R., Paty, D., Radue, E., et al., "Standardized mr imaging protocol for multiple sclerosis: Consortium of ms centers consensus guidelines," *American Journal of Neuroradiology* **27**(2), 455–461 (2006).

[3] Brosch, T., Yoo, Y., Tang, L. Y., Li, D. K., Traboulsee, A., and Tam, R., "Deep convolutional encoder networks for multiple sclerosis lesion segmentation," in [*International Conference on Medical Image Computing and Computer-Assisted Intervention*], 3–11, Springer (2015).

[4] Yoo, Y., Brosch, T., Traboulsee, A., Li, D. K., and Tam, R., "Deep learning of image features from unlabeled data for multiple sclerosis lesion segmentation," in [*International Workshop on Machine Learning in Medical Imaging*], 117–124, Springer (2014).

[5] Najafabadi, M. M., Villanustre, F., Khoshgoftaar, T. M., Seliya, N., Wald, R., and Muharemagic, E., "Deep learning applications and challenges in big data analytics," *Journal of Big Data* **2**(1), 1 (2015).

[6] Pedregosa, F., Varoquaux, G., Gramfort, A., Michel, V., Thirion, B., Grisel, O., Blondel, M., Prettenhofer, P., Weiss, R., Dubourg, V., Vanderplas, J., Passos, A., Cournapeau, D., Brucher, M., Perrot, M., and Duchesnay, E., "Scikit-learn: Machine learning in Python," *Journal of Machine Learning Research* **12**, 2825–2830 (2011).