ASH: an Automatic pipeline to generate realistic and individualized chronic Stroke volume conduction Head models

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ASH: an Automatic pipeline to generate realistic and individualized chronic Stroke volume conduction Head models

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Abstract

Objective. Large structural brain changes, such as chronic stroke lesions, alter the current pathways throughout the patients' head and therefore have to be taken into account when performing transcranial direct current stimulation simulations. *Approach.* We implement, test and distribute the first MATLAB pipeline that automatically generates realistic and individualized volume conduction head models of chronic stroke patients, by combining the already existing software SimNIBS, for the mesh generation, and lesion identification with neighborhood data analysis, for the lesion identification. To highlight the impact of our pipeline, we investigated the sensitivity of the electric field distribution to the lesion location and lesion conductivity in 16 stroke patients' datasets. *Main results.* Our pipeline automatically generates 1 mm-resolution tetrahedral meshes including the lesion compartment in less than three hours. Moreover, for large lesions, we found a high sensitivity of the electric field distribution to the lesion conductivity value and location. *Significance.* This work facilitates optimizing electrode configurations with the goal to obtain more focal brain stimulations of the target volumes in rehabilitation for chronic stroke patients.

1. Introduction

Stroke is the leading cause of long-term adult disability worldwide. According to the World Health Organization, one out of six people suffers from a stroke [17]. During a stroke, a deficit in oxygen supply due to either a hemorrhage or an infarction causes damage to a certain brain area, lesioning the tissue. In 80% of the cases, the motor cortex is involved [15].

Transcranial direct current stimulation (tDCS) is one of the therapeutic interventions aiming at stimulating the reorganization of the motor cortex to improve motor impairments and enhance recovery. TDCS is considered a viable tool due to its limited side-effects, safety, availability, portability and relatively low costs [16]. During tDCS, anodal and cathodal electrodes are placed on the scalp and a low-intensity direct current, commonly between 0.5 and 2 mA, is delivered and conducted by head tissues. It has been reported that cortical regions exposed to higher electric field strength are more likely to modulate [5]. Therefore, in motor stroke rehabilitation, for example, it is crucial to target the motor cortex precisely and with a sufficiently strong electric field.

So far, literature shows mixed findings regarding stroke patients' response to tDCS brain stimulation [16, 24]. Targeting the correct cortical area by identifying the optimal electrode configuration is indeed still a challenge in tDCS and in brain stimulation in general [12]. Volume conduction effects, which

are subject-dependent, determine the current pathways throughout the head and will be affected by large structural brain changes, such as stroke lesion, in terms of lesion location and conductivity, which is so far unknown or inconsistent throughout literature [3, 25, 26].

Simulations with volume conduction models that include the lesion compartment might, therefore, improve and guide tDCS stroke rehabilitation. Furthermore, fulfilling safety margins, i.e. the maximal electric field strength distribution which is safe to induce in the head, can be secured via simulations. Here, we present a pipeline that enables performing safety and tolerability tests on the skin of the participant [4], as well as in the brain tissue.

There are several software tools dedicated to simulating brain stimulation [11, 19, 23]. In our study, we focused on SimNIBS [23]. SimNIBS is a free and open-source software package for the simulation of non-invasive brain stimulation, which allows calculating the electric field induced by transcranial magnetic stimulation (TMS) and transcranial electric stimulation[9] in a realistic head model. SimNIBS uses the finite element method to simulate brain stimulation and therefore requires volumetric meshes. However, by default, stroke lesions are not automatically included in the volumetric meshes created by modeling tools such as SimNIBS. Lesion compartments can be identified from MRI scans either by dedicated software tools like [14, 22], or manually by researchers. A disadvantage of manual identification is that it is highly time-consuming and rater-dependent.

The aim of our study is to implement, test, and distribute an automatic MATLAB-based pipeline, ASH (an automatic pipeline to generate realistic and individualized chronic stroke volume conduction head models), that provides a realistic and individualized volumetric mesh of chronic stroke patients. ASH is SimNIBS compatible, makes use of lesion identification with neighborhood data analysis (LINDA) to automatically identify the lesion, and can facilitate large-scale group-analysis in stroke patients. In addition, to demonstrate the impact of our pipeline, we conducted tDCS simulations in SimNIBS on data from 16 stroke patients to show the sensitivity of the electric field distribution to the lesion location and lesion conductivity.

2. Methods

In this section, we describe: (1) the dataset used in the study; (2) the MATLAB pipeline that automatically generates volume conduction head models for chronic stroke patients; (3) the SimNIBS tDCS simulations.

[9] https://simnibs.github.io/simnibs/build/html/index.html.

2.1. The dataset

In this study, we analyzed T1-weighted (T1w) MRI scans of 16 chronic stroke patients. The first MRI scan (subject 401) was obtained in a previous study [8] and was acquired with a 3T scanner (GE Discovery MR750). The other 15 subjects were scanned at the Donders Centre for Cognitive Neuroimaging with a 3T MAGNETOM Prisma or a 3T MAGNETOM PrismaFit scanner. The anonymized MRI scans of the latter group are available online as a Donders Data Sharing Collection [27], together with the output data of this study and the MATLAB code. MRIs of the 15 subjects were acquired under the approval of the Ethics Committee 'CMO regio Arnhem-Nijmegen' (NL58437.091.17). Written informed consent was received from each chronic stroke patient.

2.2. The pipeline

The MATLAB-based automatic pipeline we introduce requires as input a T1w MRI of the subject and generates a realistic and individualized volumetric mesh which includes the lesion compartment of a chronic stroke patient. As already mentioned, the ASH pipeline uses the SimNIBS [23] and LINDA [22] software toolboxes. A sketch of the pipeline is visualized in figure 1 and its application requires the four following steps:

(Step 1) MRI data selection: To create individualized models, SimNIBS requires a T1-weighted image. T2-weighted images are optional but highly recommended. LINDA requires a T1-weighted image only; therefore, we used anonymized, defaced and realigned (to RAS orientation) T1w MRI scans.

(Step 2) Segmentation and meshing of the whole head: The T1w MRI is processed by SimNIBS, generating a tetrahedral volumetric mesh with six homogeneous and isotropic compartments: scalp, skull, eyes, cerebrospinal fluid (CSF), gray matter, and white matter. In particular, we utilize the SimNIBS function *headreco* with the option *cat* that leads to the use of SPM12 [21] with the extension library CAT12 [9] for the segmentation routine. Segmentations with CAT12 have a more accurate reconstruction of the cortical gray and white matter.

(Step 3) Segmentation of the lesion: Since the segmentation and meshing of the lesion compartment are not performed by SimNIBS, we use LINDA. LINDA is a neuroimaging toolkit for the automatic segmentation of chronic stroke lesions based on machine learning techniques [22]. LINDA requires a T1w MRI as input and generates a volumetric mask of the lesion.

(Step 4) Generation of the final mesh: The volumetric mesh generated in step 2 is modified to incorporate the lesion compartment generated in step 3. To do so, the mesh elements whose centroids are within the lesion mask are relabeled as 'lesion'. In addition, we make sure that the resulting lesion compartment

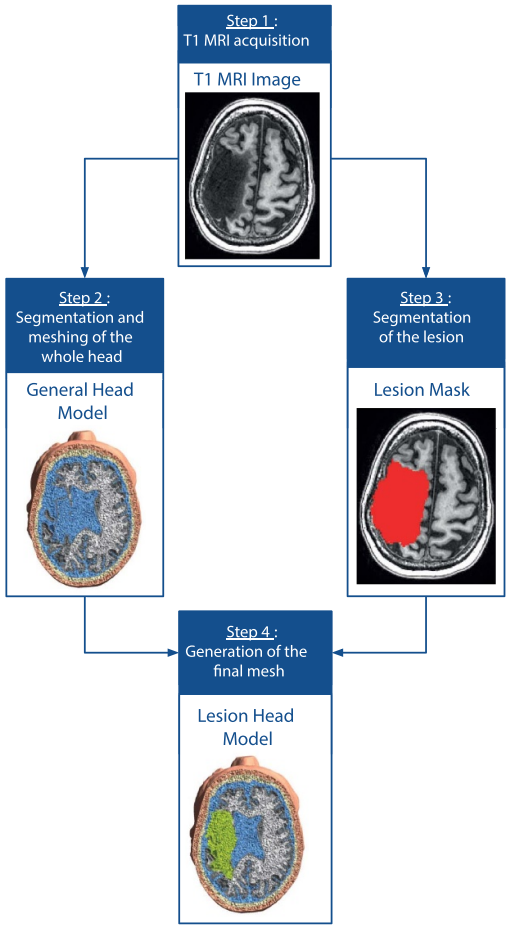

Figure 1. Sketch of the automatic pipeline. White background indicates input/output, blue background steps.

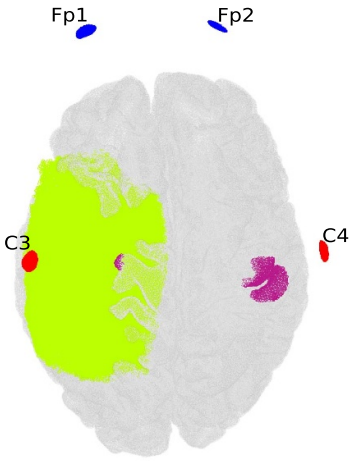

Figure 2. Visualization of the volume conduction models used in the simulations for subject 401. In purple, the tDCS target volumes (i.e. gray matter elements within a 1 cm sphere around the center of the left- and right-hand motor cortex) are depicted, the lesion volume is visualized in green. The ipsi- and contra-lesional electrode configurations, C3-Fp2 and C4-Fp1, respectively, are shown (in red the anodes C3 and C4, and in blue the cathodes Fp1 and Fp2).

does not contain elements of the scalp, skull, or eye compartments.

The steps described above are implemented in MATLAB scripts which can be found online at the ASH GitHub page[10] and at the Donders repository [27].

2.3. TDCS simulations

To investigate the influence of the lesion conductivity and location on the induced electric field, we performed and compared several tDCS simulations in SimNIBS on the datasets of 16 stroke patients. For each stroke subject, we created two head models:

- a General Head Model without a lesion, based on the output of SimNIBS (step 2)
- a Lesion Head Model, based on the output of our pipeline (step 4).

For both models, the conductivity values of healthy tissues were the default values used in SimNIBS (scalp = 0.465 S m^{-1}, skull = 0.01 S m^{-1}, eyes = 0.5 S m^{-1}, CSF = 1.654 S m^{-1}, gray matter = 0.275 S m^{-1} and white matter = 0.126 S m^{-1}). It is visible from figure 1 (step 1) that the lesion is made of inhomogeneous tissue and we can presume that it contains a combination of white matter, gray matter, and CSF (see MRI scans of figures 1A and B in [18]). For this reason, in the Lesion Head Model, 16 different lesion conductivity values between 0.126 and 1.654 S m^{-1} (i.e. the conductivity of the white matter and CSF, respectively) were assigned.

Subsequently, we performed tDCS simulations in SimNIBS. Two tDCS electrode pairs at C3-Fp2 and at C4-Fp1 were selected for the ipsi- and contra-lesional primary motor cortex stimulation, respectively (see figure 2), following, for example [2]. We visually identified and marked the 'target volumes' for the tDCS stimulation as the center of the left- and right-hand motor cortex (the so-called hand knob) from the T1w MRI or from the gray matter model of each chronic stroke patient. Next, the left and right tDCS target volumes were defined as all the gray matter elements within a 1 cm sphere around the center of the left- and right-hand motor cortex. In figure 2, both the target volumes (in purple) and the lesion (in green) are visualized for subject 401. We therefore computed and visualized the maximum values of the simulated electric field strength (E_{max}) both in the General Head Model and the Lesion Head Model, with varying lesion conductivity values (figure 5). In addition, we calculated the relative difference in percentage of the E_{max} between the General Head Model and the Lesion Head Model, with varying lesion conductivity values (figure 5, percentages in black).

As a further analysis, we studied the relation between the absolute relative difference in E_{max} and the volume (in cm^3) of the lesion (figure 6).

[10] https://github.com/mcpiastra/ASH.

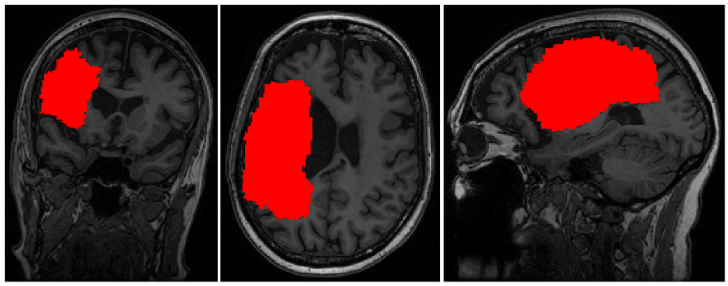

Figure 3. Coronal, axial and sagittal slice of the lesion mask (in red) identified by LINDA overlayed to MRI scan (in grayscale) of subject 401.

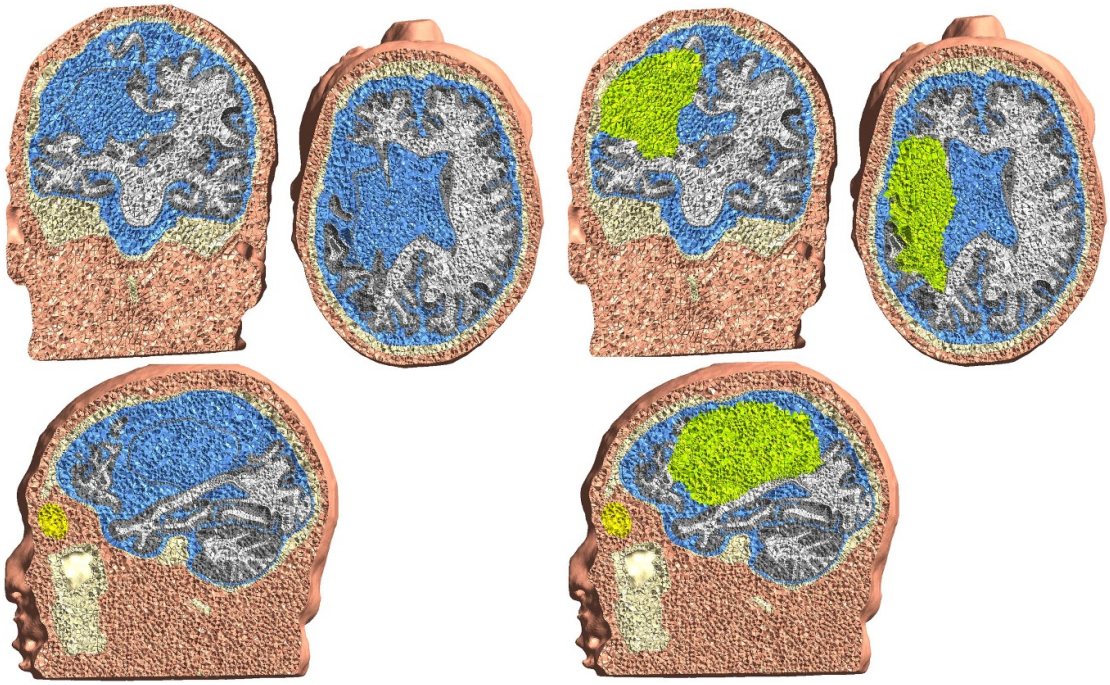

Figure 4. Clipped tetrahedral mesh of the General Head Model (on the left) and the Lesion Head Model (on the right) of subject 401 in the coronal, axial and sagittal plane. The lesion compartment is depicted in green.

Finally, to verify the fulfillment of safety margins, we computed the maximum of the electric field strength in the whole gray matter volume among all subjects.

3. Results

3.1. Pipeline results

Our pipeline generated meshes with approximately 3.5 million tetrahedral elements for each subject. The size of the lesion varied considerably throughout subjects, i.e. from a lesion of ≈183 cm^3 (subject 401) to one of ≈3 cm^3 (subject 44 and 53). More precisely, the 16 lesion volumes, i.e. the sum of volumes of the tetrahedral elements labeled as 'lesion', range from 2.6 to 183 cm^3, with a median of ≈38 cm^3 and interquartile range of ≈90 cm^3. Figure 3 shows a coronal, axial, and sagittal slice of the lesion mask generated by LINDA overlaying the MRI scan (output of step 3) for subject 401. The lesion mask, in red, has a volume of ≈183 cm^3.

Furthermore, in figure 4 the clipped General Head Model and Lesion Head Model of subject 401 are visualized in the coronal, axial and sagittal plane, showing the stroke lesion mesh in the left hemisphere (in green).

All the calculations were done both on a workstation and on a personal laptop. The workstation is operated with version 16.04 of Ubuntu with 128 GB of RAM and an Intel Xeon W-2155 CPU. One full computation took less than 2 h. In 86 min, the General Head Model was generated by SimNIBS; in 19 min the lesion mask was created by LINDA; the generation of Lesion Head Model took less than a second and one tDCS simulation with SimNIBS took around 1 min. The personal laptop has version 20.04 of Ubuntu with 15 GB of RAM and an Intel Core i7-8650U CPU.

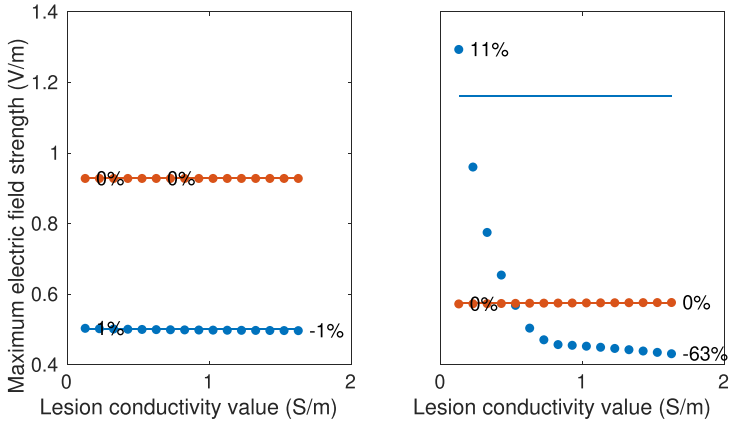

Figure 5. Maximum values of the electric field strength in the target volume, for the ipsi-lesional (in blue) and contra-lesional (in orange) stimulations, when the General Head Model (continuous line) and the Lesion Head Model (dotted line) is used to perform the simulations, for varying lesion conductivity values, for the subject with the smallest stroke lesion (subject 44; left) and with the largest stroke lesion (subject 401; right). The maximum and minimum percentage relative difference in percentage between the electric field strength computed with the different head models is displayed. For the ipsilesional stimulation, results differ considerably between the two subjects.

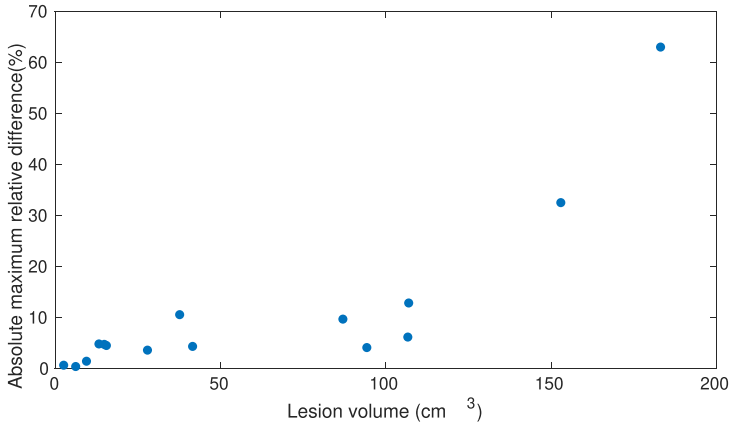

Figure 6. Relation between volume of lesions and absolute maximum relative difference between E_{max} for the General Head Model and the Lesion Head Model in the ipsilesional target volume, for each subject. The larger the volume of lesion is, the higher the relative difference.

One full computation took less than 3 h. In approx 90 min, the General Head Model was generated by SimNIBS; in approx 80 min, the lesion mask was created by LINDA; the generation of Lesion Head Model took less than a minute and one tDCS simulation with SimNIBS took around two minutes.

3.2. TDCS simulation results

We visualized E_{max} only for subjects 44 and 401, since they have the smallest and largest lesions (≈3 and 183 cm^3, respectively). Figure 5 shows that the results for the ipsi- and contra-lesional stimulations differ considerably, for both subjects. For the contralesional stimulation, variations of the E_{max} are very limited, as well as the relative difference values, for both subjects. By contrast, for the ipsilesional stimulation, results differ considerably between the two subjects. For subject 44 there is almost no difference E_{max} when the General Head Model or the Lesion Head Model is used, independently from the lesion conductivity. However, for subject 401, the E_{max} decreases with increasing lesion conductivity value. The E_{max} ranges from 1.29 to 0.43 V m^{-1} for the Lesion Head Model, and 1.16 V m^{-1} for the General Head Model, corresponding to relative differences of 11% and −63%, respectively.

Figure 6 demonstrates a trend between lesion volumes and maximum relative difference between E_{max} for the General Head Model and the Lesion Head Model. The larger the lesion volume is, the higher the relative difference. In particular, for lesions larger than approximately 10 cm^3 the absolute maximum relative difference exceeds 5%.

Finally, we found that the maximum of the electric field strength in the whole gray matter volume among all subjects to be 6.56 V m^{-1}.

4. Discussion

In this study, we implemented, tested and distributed the first automatic MATLAB-based pipeline that provides a realistic and individualized volumetric mesh of chronic stroke patients. The pipeline is SimNIBS compatible and is available at the ASH GitHub page[11], the data and code are publicly available as a Donders Data Sharing Collection [27]. In addition, we demonstrated the relevance of our pipeline by conducting tDCS simulations in SimNIBS with data from 16 chronic stroke patients. We compared the electric field distribution resulting from a volume conduction head model where the lesion compartment is neglected, and the one from a volume conduction head model where the lesion is included, with varying conductivity values, in each subject.

Several findings in our study underline that individualized analysis including the presence of a large stroke lesion is crucial in brain stimulation simulations. Firstly, we showed that, for lesions larger than 10 cm^3, the absolute maximum relative difference exceeds 5%. Moreover, it can be seen that when the lesion is modeled as CSF, as done so far in most studies (e.g. in [6, 13, 18]), there might be a remarkable difference (up to 63 percentage points, see figure 5) from the scenarios that use a different lesion conductivity value.

In contrast to our study, in the literature, ([6, 13, 18]) the lesion is usually delineated by hand and filled with CSF, thus leading to potentially inaccurate models. Lesion delineation by hand, currently considered as the gold standard, is indeed often conducted by researchers who are not radiologists nor neurologists and might not have been trained. Therefore, it might change from rater to rater, and it requires up to several hours per lesion/patient. Consequently, large-scale group-analyses are hampered. The pipeline we propose in this study is fully automatic, easy-to-use, fast, and integrated into already existing state-of-the-art software toolboxes such as SimNIBS and LINDA. In addition, there are scenarios where the lesion is not a CSF-filled cavity, nor a homogeneous tissue. See, for example, figure 1 (step 1) and figure 1(A) of [18]. Shunting effects caused by the presence of additional CSF of the lesion volume in the head model, or ignoring the inhomogeneity of the lesion, might, therefore, alter the electric field distribution both in the whole gray matter volume and in the target volumes. An incorrect model of such a large structural brain change can thus lead to ineffective and uncontrolled tDCS rehabilitation treatments. Our work indicates such huge variation and suggests, therefore, that more effort should be taken in order to estimate the lesion conductivity value. Our present and future work can actually facilitate such an estimation. We plan to build lesion head models for patients on which we apply current by tDCS and record the resulting scalp potentials by using EEG electrodes. The estimate for lesion conductivity will be the value that minimizes the difference between recorded and model potentials [20].

Our simulations are fulfilling the safety margins, since the maximal E_{max} in the gray matter throughout all 16 subjects resulting from our study is 6.56 V m^{-1}, i.e. one order of magnitude lower than the limit indicated in [1]. In general, only coarse indications are present in the literature and many investigations are still ongoing. Nevertheless, in [1], they indicate a range of 6.3–13 A m^{-2}, which corresponds to 19–39 V m^{-1} in the gray matter, like the one in which brain injury could occur in animals [1].

The lesion compartment resulting from our pipeline is not necessarily connected, since we do not modify the original mesh not containing the lesion. Isolated lesion mesh elements might lead to unwanted high potential values due to conductivity jumps, especially when the CSF conductivity is assigned to the lesion compartment. Nevertheless, we do not expect our results and conclusions to be affected by such cases, since the target volumes are not necessarily overlapping with the lesion compartments. In order to obtain connected lesion compartments with smooth boundaries, one option is to include the lesion mask prior to the meshing procedure. This would require a more intense modification of the SimNIBS code by the user, which will hamper the usability. In addition, in our study, we did not want to change the geometrical properties of the models, i.e. the mesh, but only the number of compartments in the model, i.e. with and without the lesion.

Recent literature increasingly highlights the necessity of an individualized volume conduction head model in brain stimulation simulations [7, 10]. By testing our pipeline with data from 16 chronic stroke patients, we could show the high impact of the lesion conductivity on the simulation results, already for lesions 10 cm^3 large. Both in this line of work and in clinical practice, the ultimate goal is the individual electrode configuration optimization, in order to control the electric field distribution in both the gray matter and target volumes and to guarantee the fulfillment of the current safety margins. Our work fits perfectly in this context in that it provides a preliminary step needed to conduct large-scale group-analysis in stroke rehabilitation.

5. Conclusion

A fully automated, easy-to-use, open-source, and fast MATLAB-based pipeline that provides a realistic and individualized volumetric mesh of chronic stroke lesions is implemented, tested and distributed.

[11] https://github.com/mcpiastra/ASH.

The pipeline embeds the already existing software toolboxes SimNIBS and LINDA and leads to more accurate and controlled tDCS (and TMS) simulations in SimNIBS for stroke rehabilitation studies. Within this work, we showed the high sensitivity of the electric field distribution to the lesion conductivity value and location, by running tDCS simulations in data of 16 chronic stroke patients. This work facilitates lesion conductivity value estimation, which will increase the accuracy of brain stimulation simulations, ultimately allowing optimization of electrode configuration and therefore more focal stimulations of the target volumes, while guaranteeing the fulfillment of safety margins.

Data availability statement

The data that support the findings of this study are openly available at the following URL/DOI: https://doi.org/10.34973/5752-rf24.

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