ADVANCE: Alzheimer’s Disease VisuAlization of brain Connectivity

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Abstract
Alzheimer’s disease is commonly associated with neuron loss and consequent difficulty in forming memories, resulting in a negative impact on people’s quality of life. In fact, with the development of Alzheimer’s, the functional and metabolic connections between different regions of the brain go through several changes. Brain connectivity in an approach in which the brain is studied in a sophisticated manner looking for structural and functional relations between brain regions, developing tools for the analysis, classification and visualization of brain connectivity. In the context of Alzheimer’s, it presents a great potential, allowing early diagnosis and treatment. Nevertheless, the data needed to perform brain connectivity analysis is usually obtained through neurological examinations, often unprocessed and difficult to interpret. Getting an overview of such data while allowing the specialists to understand the development of the disease would greatly improve current processes. We present an ongoing interactive visualization consisting of synchronized views that allow effective navigation and analysis of brain connectivity.

1. Introduction
Alzheimer’s is a chronic neurodegenerative disease, associated with memory loss, among other symptoms. Although it has no cure, an early diagnosis may help delay its evolution. Nowadays, Big Data on health is widely seen as the potential resource to reduce costs and improve results. Every day thousands of new medical data are generated and recorded. In fact, nowadays, medical data are constantly being collected and stored, without even the user realizing it. Obtaining these data can be made both in terms of medical tests, such as neurological examinations, doctor visits, tests, etc. The main problem for doctors is that such data are often unprocessed and the doctor has serious difficulties in extracting potentially relevant information from them. Alzheimer’s disease, in particular, is related to a set of alterations on the links between different areas of the brain. Brain Connectivity in an approach in which the brain is studied in a sophisticated manner looking for structural and functional relations between brain regions, developing tools for the analysis, classification and visualization of brain connectivity.

Information gathered using Brain Connectivity Analysis has been taken into account [RLF15]: Eleven different brain connectivity metrics have been measured, for 111 regions of the brain. Such metrics are: Cortical Thickness (CThk), Gray Matter Volume (GMV), Mean Diffusivity (MD), Fractional Anisotropy (FA), Number of fiber tracts (FiberConn), Standard Uptake Value (rSUV, cerebellum). The analysis of such metrics allows the establishment of four different stages of cognitive impairment: (i) Cognitive Normal Controls (CTRL); (ii) Early Amnestic Mild Cognitive Impairment (EMCI); (iii) Late Mild Cognitive Impairment (LMCI); (iv) Alzheimer’s Disease (AZ).

Even though these data are crucial for the analysis of Alzheimer’s disease, it mainly consist of textual and numerical information, very difficult to analyse and understand. A visualization that allows the representation of such data in a way that alleviates data interpretation [Mun14] and aids in the establishment of an early diagnosis will potential bridge this gap, working as a tool which complements diagnosis, potentially leading to a very important impact in patients’ quality of life.

This paper is organized as follows. While in section 2 we introduce relevant related work that situates our study, in section 3 we present the ADVANCE, our work on brain connectivity visualization, associated with Alzheimer’s. We then describe the formative evaluation we have performed to validate and further consolidate our work. Lastly, we draw some conclusions and guidelines we will follow in our ongoing research on the visualization of the stages leading to Alzheimer’s Disease.

2. Related Work
In general, IV can be a strategic component to achieve various objectives in the development of a medical system. We can arrange
these goals into three groups: Visually present the medical data in a more intuitive manner, easy to learn, recognize, browse and to manage; Visually, increase the possibility of making diagnoses with them, therapeutic, managing patient data, and the curing process which would otherwise be difficult to observe; Avoid information overload and allow members of the clinical staff dominate larger amounts of information.

Several approaches for the visualization of medical patient records have been proposed, aiming at summarizing large amounts of data, thus helping to predict, anticipate and relate diseases, and new systems are likely to emerge, such as the Electronic Health Record (EHR) that is adopted widely and is increasing all over the world. The frequent paradigm is to organize patient records along the time axis, in which health records are distinguished by their inherent aspects, either by showing single patients’ or multiple patients’ records.

Single-patient record approaches show the data of a patient, or the data of a disease which has been identified. One of the most relevant is Lifelines [PMS’98]. This application is a pioneer on its context and was one of the first to assemble all patient’s records on a single screen. Its main objective is to gather all the information of a patient in a single interface, otherwise it would be dispersed in multiple interfaces. It makes it intuitive to analyze a patient’s clinical history. However, the display of the data of a single patient can be limited. Especially it becomes a challenge to show all this information at a time, which will eventually hinder the user’s view to find patterns or even see relations. For this type of approach, it is necessary to be very careful and accurately select what is viewed, in order to facilitate interpretation of the data.

Regarding the visualization of multiple patients’ records in parallel, all the approaches group patients’ data in order to allow them to be viewed side-by-side. The parallel data visualization helps doctors find records that are similar, or else, differences between a target record and it is even possible to align all events on a sentinel event and thus be able to detect events that happened before, events that are occurring and events that arose after the sentinel event. There is also the possibility that an application only focuses in comparing medical data associated with a disease, and that’s what TimeSpan [LPK’16] proposes. It is a visualization tool aiming at a better understanding of the time aspects of the Stroke treatment process in order to support exploratory analysis of time and multidimensional data of stroke patients. Its interface consists of an interactive hybrid view of temporal data comprised of multiple views. Another interesting application is PhenoBlocks [GHC’16], which compares phenotypes among patients. Phenotypes are observable and measurable deviations of what is seen about the morphology of the human body. The overview is achieved through radial bar charts (sunburst visualization) to view the phenotypes in common. Data of a patient is always in focus and in this view, the user can see information about a specific phenotype. In an area, beside may be other data of similar patients already grouped by disease, previously set by researchers, wherein each row corresponds to a disease, these rows are sorted by a greater similarity with information in focus from top to bottom. Each cell represents an abnormality, the chart layers help simulate phenotypes hierarchy (inside out). This type of approach provides a simple, but effective way to quickly explore the data and look for potential temporal patterns in several records. When aligned in relative time intervals, they can be compared easily, allowing users to see the details around all sentinel events. By showing various data of patients with the same characteristics, it is possible to compare, allowing users to view interactively, see correlations and causes more directly, which may enable physicians to see the effects and results more easily. However, this view must allow powerful mechanisms for data selection and filtering in order to potentiate a thorough analysis of the presented data.

There are in fact many ways of displaying medical data that has been stored over time. Almost all applications use temporal data, which is crucial when considering the development of pathologies. For the first category, it can be concluded that the main feature used with most consensus is the overview, which makes sense because it is the main objective proposed for the category: to view all data of a patient or a disease in question, on a single screen and not have to resort to various interfaces for the information. For the second category, the overview state meets consensus. Another state that gathers consensus is to be able to filter the data and this is because the purpose of the cluster itself is to visualize multiple data in parallel, which means that a large amount of data from several patients will be seen and should therefore be possible to filter, making the view clearer to the user, so that he can find patterns in events or causes of certain events. Two articles/app can be highlighted: TimeSpan [LPK’16] and PhenoBlocks [GHC’16]. The latter is particularly relevant, in which with the data of a target patient, it is possible to view similar patients, thus being able to help the user find patients with similar problems.

3. Visualizing Alzheimer’s Disease

In order to create a meaningful visualization, an iterative and incremental approach has been followed. After a first learning phase, low-fidelity prototypes were developed aiming at ideas how the dashboard of ADVANCE would be. Target users validated them, helped to clarify some questions and generated new ideas, having as a central point that, since the focus is on the representation of the connectivity between brain areas, the main idioms of the dashboard would be a connectogram and some focused data as well as second plan would always be visible to enable comparison.

3.1. ADVANCE

ADVANCE’s layout is divided into three areas, on the left (Figure 1 A) there is a control panel, that enables control over many functions and interactivity with the idioms.

At the center (Figure 1 B) there is a connectogram with the data of a patient (Focus Connectogram).

The right side (Figure 1 C) is subdivided into three areas, which are collapsible and expandable for further flexibility. On the top (Figure 1 C.1) there are several smaller connectograms, (Mini-Connectograms) which enable easy comparisons between connectograms. In the middle (Figure 1 C.2) there is a Circle Matrix showing the aforementioned data in a more detailed perspective. At the bottom (Figure 1 C.3) there is one more matrix-like idiom, showing the connections between the brain areas and the number of fibres connecting these areas.
3.2. Connectograms

A connectogram represents the data of a patient among the four possible stages of the disease.

The information of metrics is included, represented by layers. Each corresponds to one metric and has a slice and colour associated. Each slice represents one area of the brain among the 111 possible, and the intersection of a layer with a slice (a cell) corresponds to the measured value for that patient (Figure 2).

The colour is used to help visualize how the cell interacts with the others of the same metric and is normalized using linear interpolation, considering maximum and minimum values for the corresponding metric (Figure 3).

It is possible to group the brain areas by groups (tags). To accommodate that characteristic we provide filtering mechanisms: there is a layer in the interior of the focus connectogram that enables the user to hide all the cells associated with this tag in order to focus attention in other brain areas. Furthermore, a caption (external layer) is displayed with the name of the areas and a set of visual connectors representing the links between them may be added/removed to the Focus Connectogram. The cells can be highlighted by metrics or tags.

The control panel allows the adjustment of this view. For instance, it is possible to hide/show and reorder the metrics (layers) over this idiom through a list of checkboxes. When hovering one of the items on the list a highlight of the metric data is made on the connectogram, enabling the user to track changes. For a more detailed analysis, it is also possible to change the height of the layers in the Focus Connectogram with a slider.

When hovering a cell, a tooltip shows information of which brain region the respective tag belongs to, as well as its numeric value.

Also, every time that the cells are hidden through the internal layer associated to tags or displayed by the control panel (list of hidden tags), the colour of the visible cells is recalculated according to available information. Every time the mouse goes over the layer of tags, the ones belonging to that tag are highlighted.
As previously mentioned, brain connection is represented using visual links. These are color coded using a linear gradient ranging from blue to red (cold/warm). Blue corresponds to 0 fibers, while the color red is assigned to the total number of fibers coming out of a brain area. Thus, it is immediately perceivable to the users which areas comprise a higher number of connections: the ones whose visual links are depicted in colors closer to red. The rule to codify the colour of the ribbon is as follows: first, an estimate of the total number of fibers coming out of a brain area is made, to which we associate the red colour. Then, it is viewed how many fibers come out of a ribbon that comes out of an area and then is calculated the colour of the edge of the ribbon between 0 and the total number of fibers, and in the other edge of the ribbon, the same is done, but for the corresponding area (Figure 4).

3.3. Circle Matrix
This idiom was created after discussion with context experts who highlighted the importance of individual data to be visualized with more detail. As a result, we created a Circle Matrix, depicted in Figure 5.

This idiom is made up of two areas. The first consists of a headline for the name of metrics, which had a fixed position. The second area, below the headline, contains the information of the selected layers in the connectograms, represented by lines, each one having maximum seven vertical lines with the information of the respective metrics.

Every time a cell is clicked in a connectogram all the information of the cells of that row are converted into a new line in this idiom, made up of several circles, one for each metric.

The size of the circle is calculated dynamically i.e. every time a new line (selected brain area) is added/removed, each column has the colour of the metric used in connectograms: the lowest values have a lighter tone (higher brightness) and the highest have a darker one (lower brightness). The radius is directly proportional to the value of the metric.

3.4. Connection Matrix
Since a considerable amount of information is depicted in the Connectograms, it is difficult to explore brain connections in detail only by using this artifact. Hence, a means of enabling a detailed analysis of such information in a coordinated manner is extremely relevant.

The Connection Matrix allows the individual analysis of connections between particular brain areas, complementing the connectograms (Figure 6). A matrix-like approach has been followed, allowing simultaneous comparison between different regions. It consists of a fixed headline and an matrix-like area below to visualize the selected information. The headline textually presents the name of the brain areas and the tag group. Several lines represent the areas that have been selected on a Connectogram. Each line contains 111 rectangles, representing the areas to which the corresponding region can be connected. When a cell is selected on a connectogram, a new line is added, in the same manner as the Circle Matrix.
Using this idiom, it becomes easier to verify which are the connected areas: the rectangles presenting a grey shade. Rectangle brightness is inversely proportional to the number of fibres connecting an area to another: while white represents the number 0, darker shades are related to a higher number of fibers (Figure 7).

It is also possible to hide the rectangles associated to a tag through the headline at the top of each line. When that happens, all colours are recalculated. Furthermore, to keep track of information throughout the visualization, every time the mouse hovers a tag, corresponding rectangles are highlighted. In order to take advantage of the available space, while still providing detailed information, a magnifying lens was added which activates every time the mouse cursor hovers one of the rectangles, showing the number of fibres connecting that region. It also depicts the name of the area and shows the same information for its neighbouring rectangles (Figure 8).

When the highlight of the cells belonging to a metric is made in a Connectogram, the same metric is also highlighted in the remaining Connectograms.

Similarly, when a cell associated to a tag is highlighted on the tags’ layer, that action will produce an effect on all the other views. The same occurs when the cells associated to a metric are hidden/shown and reordered.

When the cells associated to a tag are shown/hidden, and the action was triggered either by the layer of tags on the Focus Connectogram or the Circle Matrix, that action will produce an effect on all the Connectograms and the Connection Matrix. It should be noted that if the visual connectors are visible on the Focus Connectogram, they will be redrawn and their colours recalculated, according to the current information. When the mouse cursor hovers the tags’ layer, the visual connectors will come out of the areas associated to those tags and are highlighted. On the other hand, when hovering any visual connector, a highlight is made and a tooltip is shown with the name of the origin and destination of that connection, as well as the number of corresponding fibres.

When a cell is selected in either of the Connectograms, an arc is created around all the cells of that brain area. This mechanism generates new information to be added to the Circle Matrix and the Connection Matrix. It is possible to eliminate new information (lines) created on these views, which will affect the other views. In this case the corresponding line is eliminated both from the Circle Matrix and the Connection Matrix and the surrounding arc is eliminated from the Focus Connectogram.

It is also possible to exchange the Focus Connectogram with any Mini Connectogram, enabling the user to visualize another patient’s data with more detail.

An option of dividing the focus connectogram in half, placing two connectograms side by side, is available, in order for the user to make comparisons more easily (Figure 10).
3.6. Architecture

The ADVANCE architecture (Figure 11) consists of a web application architecture, with particular aspects regarding information visualization. It was designed and programmed, so that it could grow easily in the future, an object-oriented language was used, which would facilitate the introduction of new functionality, new animations, new languages, etc.

4. Demonstration of Potential

In this section we present the potential of ADVANCE in revealing patterns and validating context knowledge.

Figure 12 shows a pattern for the regions associated with a tag, which for all three patients always have the highest value.

In the figure 13 it is visualized the potential in having created a program C# that cleans the false positives of the data.

According to the validation of knowledge that is known by the scientific community, the ventricles of a patient with AZ have a higher volume than a healthy person, in Figure 14 we can see data of three healthy people compared with data from three patients already diagnosed with Alzheimer’s disease and this situation is clearly visible.
4.1. Divulgation

ADVANCE has already been shown to the public in some moments, allowing its dissemination to the scientific community, which validates its relevance.

A poster was presented at the conference 9WBME (http://wbme.fc.ul.pt), for which an abstract was also submitted. This was highlighted as one of the top three in the conference.

ADVANCE was also shown at an event in Porto (http://healthportugal.com/noticias/hcps-meetings-with-health-innovation-improving) by IBEB, which had a very positive critique, leading to the submission of an abstract for the PSMR2017 (http://www.psmr2017.pt) conference. It was also accepted to be presented at that conference, to be held from 29 to 31 May.

Recently there was a contact with Nicolás F. Lori (PhD.) from Argentina (http://www.inecoorono.org) by IBEB, which was shown ADVANCE, and showed an interest in seeing their magnetic resonance images visualized in ADVANCE.

It will be integrated into the Neuropsychad (http://www.neuropsychad.com) startup created by IBEB elements.

5. Validation

The ADVANCE evaluation consisted of two stages of testing: The first (Tests with Users) ADVANCE was used by users without any connection to the medical field, with this test is intended to measure the usability of the app. The protocol was as follows: there was first a short presentation where it was described what the job consisted of and what it was for, then a small demonstration of ADVANCE’s capabilities was showing its capabilities and what it visualizes with the help of some examples, in the next part the users would have to perform a set of tasks in order to test the usability of ADVANCE. A set of tests were performed, subdivided into several tasks that the user would have to perform with ADVANCE, then the execution time that each user took to complete the task and the number of errors in each task until getting to the answer that was intended.

1. For the metric \( fa \) what is the group of regions (tag) that has more similarities between the 4 patients presented in the visualization?
2. Can you identify for the patient focus what the highest value of the \( fa \) metric is and which region of the brain it belongs to?
3. Tell which patient has the lowest value for the region of the previous question?
4. For the P0N patient, by viewing only the BasalGanglia region group and CorpusCollusum, say to which region or regions of CorpusCollusum all their fibers are connected to a region Of BasalGanglia?
5. Only using the focus connectogram for the P0N patient, tell how many regions the Optic-Chiasm region group is bound when only the ‘Others’. BasalGanglia And CorpusCollusum are visible?
6. For the patient P1N, say the regions referring to the tags RH ctx and LH Ctx have very similar values, eventually highlighting, only visualizing the clus metric?
7. Make a comparison only between P0N and P0EMCI and viewing the AGMV metric with the regions associated with tag BasalGanglia, say a big difference between the two that stands out, referring to the values that the regions of the brain obtained?
8. Only by visualizing the data of the region-to-region connections of the patients P0N P0EMCI P0LMCI P0N for region cxt-liparsopercularis, does it have some connection to a region of Ctx-rh?

The tasks were created to verify if ADVANCE fulfilled the objectives we defined, in this case to measure usability.

In the end a small questionnaire (SUS) was also carried out to test the usability of ADVANCE at the end of the tests, a small debriefing was performed. The results obtained were quite positive at both the statistical and feedback level by test users. At the statistical level, it is perceived that the tasks were increasing in complexity, that on average, all users take similar time to solve the tasks, sometimes finding some users who have more difficulties in some tasks that give rise to the outliers visible in the boxplots (Figure 15). At the level of the questionnaire with SUS, it had a result (77.13) above the average (68) [B∗96], users found ADVANCE not very complex, in terms of difficulty to use, they also classified ADVANCE only with positive answers, did not think that ADVANCE presented inconsistencies at functionality level. At feedback level on the part of the users, it was always extremely positive. A lot of feedback was given to the ADVANCE interface and features that could change. Some examples:

- There would be a connectogram for a metric in question, where the layers would represent the patients and the slices remained
the regions of the brain. This idea emerged in order to easily compare metric data for a set of patients:

- Place a line between the two connectograms when they are side by side, so that the user realizes well that there are two connected connectograms in that display mode.

In a second stage, some case studies were performed, in which ADVANCE was tested by users connected to the area of neuroscience in order to measure the utility, the same protocol was used from the previous step, except for the part of the accomplishment of the tasks. To test the utility of ADVANCE, two case studies were carried out, this time with professionals from the area, in our case there were three people linked to IBEB in which their work area / study is linked to neuroscience. For these cases, users did not have tasks to perform, they were able to explore ADVANCE at will, trying to validate context knowledge. At the end, a small debriefing was performed. At the final debriefing and throughout the user’s exploration of ADVANCE, some aspects were commented on to improve and reinforce the positive aspects. One example: Would be able to extract information from the interface (values / prints).

With these two types of tests that complement each other, we have been able to test whether the ADVANCE features are well implemented, if the user can interact with the interface and validate context knowledge. The tests allowed us to accurately measure the usefulness and usability of ADVANCE. The feedback obtained from the study participants was very important, not only in the detection of problems in the application, but also in suggestions for their resolution. The test user sample (20) was the ideal one to be able to measure the usability, a very interesting classification was obtained in the SUS (77.13) and it is expected that this classification will improve with the introduction of the new functionalities obtained through user feedback. It should also be noted that several meetings were held with IBEB throughout development, where feedback had repercussions at the ADVANCE interface. Case studies have proven that it is possible to validate context knowledge and find patterns in the data.

6. Conclusions and Future Work

Alzheimer’s disease is common in our society and often becomes a critical illness, resulting in a very negative impact on the quality of life of patients. Nowadays, medical data is constantly collected and stored, without even the user realizing that it is happening. Obtaining this data can be done in terms of medical examinations, such as neurological examinations.

Using the principles of Cerebral Connectivity, it is possible to study the structural and functional relationships between the brain regions, enhancing early diagnosis and treatment. However, the data collected is often numeric, unprocessed and difficult to analyze. VI is able to take in large amounts of data and extract new information from them, being able to visualize patterns that are important and help gain valuable insight into the context of it.

ADVANCE is an interactive visualization for the presentation of such data associated with the brain that allows effective navigation as well as an analysis of the data. It is an interface, which relies on multiple interconnected views, offering different perspectives on the same data, allowing the user to check the context knowledge, while making patterns immediately evident. In a first phase of development, with only the real visualization of the data represented by the IBEB connectograms, they gave as feedback that they had never seen the data all together and they are in fact very similar, showing the potential interface only at a very early stage of development. An iterative and incremental development was followed. At the end, a set of tests was carried out, in which users connected to the area of neuroscience validated knowledge of the context and also managed to point out guidelines for future work. ADVANCE consists of a visualization that allows validating contextual knowledge and finding patterns in the data, it has been validated by people who move in the context of use, will potentially have a practical application as a diagnostic aid, is a relevant work in the area of neuroscience, which has been widely publicized and presented at conferences.

Throughout the many meetings that were held with the IBEB, new ideas were always coming up, some were soon added, others were not high priorities and were kept in the background and others saved for future work. One of the main ideas was to be able to visualize statistical data in such a way, as to make comparisons easily, for example, to create a connectogram with statistical data and to make comparisons. In the last phase, the user is allowed to upload their own data to ADVANCE and later to create login areas, for each user to have access to their data, with the implementation of these functionalities, ADVANCE can give further information about Alzheimer’s disease and improve diagnosis and treatment.

References


