BrainQuake: an open-source Python toolbox for Stereo-EEG analysis

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Abstract

Intracranial stereo-electroencephalography (SEEG) is broadly used in pre-surgical evaluation of intractable epilepsy, due to its high temporal resolution in neural activity recording and high spatial resolution within suspected epileptogenic zones. Neurosurgeons or technicians should face the challenge of conducting a workflow of post-processing operations with multi-modal data (e.g. MRI, CT, EEG) after an implantation surgery, including brain surface reconstruction, electrode contact localization, and SEEG data analysis. Several software or toolboxes have been developed to take one or more steps in the workflow but without an end-to-end solution. In this article, we introduce BrainQuake, an open-source Python software, integrating modules and pipelines in surface reconstruction, electrode localization, ictal and inter-ictal SEEG analysis, and final visualizations, each of which is highly automated with a user-friendly graphical user interface (GUI). BrainQuake also supports remote communications with a public server, which is facilitated with automated and standardized preprocessing pipelines, high-performance computing power, and data curation management to provide a time-saving and compatible platform for neurosurgeons and researchers.

1 Introduction

Nearly 30% of the patients with epilepsy eventually develop to intractable patients who are resistant to anti-epileptic drugs (Kwan and Brodie 2000). To these patients, intracranial stereo-electroencephalography (SEEG), firstly developed by Talairach and Bancaud at Hopital Sainte Anne, Paris (Bancaud et al. 1965), is now a common clinical approach to consider about. SEEG aims at identifying the epileptogenic zones (EZ) (Rosenow and Lüders 2001) in suspicious area of one's brain by implanting depth electrodes and capturing the abnormal neural activities, followed by a resection or thermocoagulation surgery (Cossu et al. 2015; Shu Wang et al. 2020). During this procedure, a large number of neurodata with multiple modalities occur. Pre-surgical MRI T1 structural image and CT image after the implantation surgery can respectively be taken as information for brain surface reconstruction and SEEG electrode localization (Behrens et al. 1994; Dykstra et al. 2012). Neural activities before the resection surgery are recorded with SEEG electrodes for EZ localization and lesion analysis, usually lasting for two weeks. The neural activity acquired during the two-week SEEG recording is vital to the presurgical planning (Cossu et al. 2015) and also of great value to the brain research (Zhang et al. 2019; Akkol et al. 2021). However, how to exploit the large amount of multi-modal neurodata and manage them effectively remains a problem to be solved.

SEEG Electrode localization procedure using co-registered MR and CT images provides neurosurgeons with accurate anatomical positions of the implanted electrode contacts (Dykstra et al. 2012). The traditional and broadly used method of electrode contact localization mostly depends on visual checking and manual operations (Darcey and Roberts 2010). After registration of MR and CT images, technicians view the CT image slice by slice, locating highlighted contact voxels and mapping the positions onto the MRI (Darcey and Roberts 2010). Trouble occurs since every patient may have 100 contacts implanted in average and one should check the slices back and forth for a contact centroid, which is a complicated and time-consuming task. Several previous works have proposed semi-automated methods (Narizzano et al. 2017; Hamilton et al. 2017; Blenkmann et al. 2017; Qin et al. 2017; Li et al. 2019) trying to improve the effectiveness and precision of electrode contact localization. 3D Slicer's SEEGA extension applies an algorithm of center-of-mass convergence for the contact segmentation step (Narizzano et al. 2017; Arnulfo et al. 2015), which shows great feasibility and robustness in locating contacts along each electrode shaft. However, this method requires a prior manually-defined fiducial file of the planned starting and ending points of each electrode and an additional presurgical CT scanning. Another study (Qin et al. 2017) inherits the convergence algorithm and develops a workflow of preprocessing steps trying to reduce the required input. This workflow includes MRI and CT registration, masking, eroding, and clustering steps, but still needs to insert several pause points for visual checking and manual adjustments. Another toolbox (Blenkmann et al. 2017) implements k-means clustering algorithm to segment contacts along each electrode, in which the voxels of each electrode should be carefully thresholded, otherwise the contacts may not be completely segmented.

In clinical SEEG data analysis, doctors are mainly concerned about the effect of a few episodes of ictal data for the location of epileptic foci. Channels with relatively early abnormal activity during the seizure often indicate the epileptic foci. A previous work defined an Epileptogenicity Index (EI) using the onset of high-frequency energy to predict the onset area(Bartolomei, Chauvel, and Wendling 2008). However, in some cases, the onset period may not be captured to provide sufficient diagnostic information. In contrast to only a few seizures during the monitoring period, most of the SEEG signals recorded are seemingly normal inter-ictal data. The sporadic abnormal activities in the inter-ictal interval, such as spikes or high frequency oscillations (HFO), can be used as plausible pathological markers of epileptic zone. Because the intracranial EEG recording of a patient consumes huge storage, recording an 80-channel intracranial EEG at a sampling rate of 2000 Hz for 24 hours may generate a data volume of about 50G. It is time-consuming for surgeons to extract sparse inter-ictal pathological activities from long-term SEEG. Under the condition that inter-ictal data is frequently deleted or cannot be traversed by surgeons, it is rarely to be fully utilized. Therefore, there is an urgent need to detect abnormal activities in vast of inter-ictal SEEG data to condense pathological information and to reduce clinicians' workload. Both HFO activities (Navarrete et al. 2016) and spike detection algorithms (Barkmeier et al. 2012) have been developed based on waveform morphology, but indexation methods that efficiently extract inter-ictal epileptic discharge events are yet to be developed. In addition, the performance of current inter-ictal event detection methods heavily depends on the manual selection of the parameters (Remakanthakurup Sindhu, Staba, and Lopour 2020).

After electrode localization and data analysis, cortical surface reconstruction is an essential following step for better visualization. The reconstruction procedure has been developed by several previous works (Dale, Fischl, and Sereno 1999; Fischl 2012; Zöllei et al. 2020; Henschel et al. 2020).

Freesurfer group releases tools and pipelines publicly (Fischl 2012). They built a reconstruction pipeline, 'recon-all', covering from preparatory operations like motion correction and skull-stripping, to final steps like segmentation and cortical parcellation. Several subsequent works have also proposed advanced reconstruction tools, specifically, 'infant-freesurfer' (Zöllei et al. 2020) for covering all ages of subjects and 'fast-surfer' deep learning pipeline (Henschel et al. 2020) for solving the time-consuming problem. However, Freesurfer software and its advanced tools can only be executed on Linux-based operating systems. Virtual machine configuration and the usage of terminal-lines can be troublesome for some windows users. And there is often a lack of local computing power for a rapid surface reconstruction in the clinical setting.

Here we present BrainQuake, an open-source Python software, providing epilepsy surgeons with tools and integrated pipelines of surface reconstruction, electrode contact localization, and ictal and inter-ictal SEEG analysis for pre-surgical evaluations. The integration aims at automatically executing the whole workflow with fewer input files and fewer pause points. BrainQuake is designed as an end-to end, highly automated, time-saving software, free to be downloaded and compatible to both Linux and Windows OS. With a comprehensive data processing platform established, surgeons can take the most advantage of neurodata and make reliable pre-surgical evaluations for those epilepsy patients. We hope this software can be helpful to clinical practice and human neuroscience studies using SEEG.

2 Materials and Requirements

2.1 Software Overview

BrainQuake is an open-source Python software for image and SEEG data processing of refractory epilepsy patients. BrainQuake consists of four modules: surface module, electrode module, ictal module, and inter-ictal modules (**Figure 1**). The surface module is used for surface reconstruction of the patient's MRI T1 image. We incorporate a GUI, a client-server communication mode, a public server with powerful GPUs, and a data curation system, which can ensure that users share a time-saving, private, and stable data preprocessing pipeline. The electrode module consists of a pipeline to locate and anatomically label the SEEG electrode contacts using both pre-operative T1 image and post-operative CT image. The ictal module and inter-ictal module make an analysis of the recorded SEEG data and then pinpoint the suspicious seizure onset zones (SOZ) using Epileptogenicity Index (EI) and High Frequency Events Index (HI), respectively. Finally, BrainQuake provides a comprehensive result visualization of individualized patient's 3D brain surface, with SEEG contacts and SOZ predictions projected on it. We develop GUIs for all these modules (**Figure 2**) and tutorials can be found along with installation packages.

2.2 Data

2.2.1 Subjects

Stereo-electroencephalography electrodes, or intracranial depth electrodes, were used in human subjects undergoing epilepsy surgical treatment. We analyzed data from five patients who were temporarily implanted with SEEG electrodes (8-16 contacts per electrode, 2mm diameter and 3.5mm center-to-center spacing). Intracranial EEG was continuously recorded for two weeks in average and MRI and CT images were respectively acquired before and after the implantation operation. The surgeries were conducted in Department of Neurosurgery and Epilepsy Center, Tsinghua Yuquan Hospital. Data collection and scientific workup were approved by its Institutional Review Board.

2.2.2 Example Data

We provide 5 sets of sample data so that one can follow the data format and file structure and go through the procedures in BrainQuake. Sample data is available at https://doi.org/10.5281/zenodo.5494990, including MRI T1 image and CT image in nifti-1 type, and recordings of ictal and inter-ictal EEG data for each sample. The file structure is shown in **Figure 3**. Freesurfer 'recon-all' results are also included since we use some of those intermediate files in our modules. Two separate directories, BrainQuake dataset and freesurfer dataset, will be configured during the initialization of software.

2.2.3 Operating Requirements

The codes are divided into client part and server part. Computers running either Linux, Mac OS X or Windows should be able to run the client Python GUI code. For the server part, it should be running on Linux or Mac OS X, since Freesurfer works only on Linux. We recommend users install the client GUI code and communicate with a public server we provide and leave all the time-consuming works to it. Essential processed data for functional modules in BrainQuake can be downloaded from the server. If facilitated with a Linux-based server at local, one can still download and install the server code and run the whole pipeline within their own workspace. The software should be run on Python 3.6 or higher. To support the Python GUI, users need to install the following third-party software packages: socket, scikit-learn, scipy, nibabel, matplotlib, mayavi. At the remote server side, freesurfer (v6 or higher) and docker should be properly installed as well as the packages mentioned above. Full installation tutorials can be found on https://github.com/HongLabTHU/Brainquake.

3 Methods

3.1 Image Processing Modules

3.1.1 Surface Module

Freesurfer provides a complete pipeline, 'recon-all', for surface reconstruction which is compiled with abundant tools like skull-stripping, image registration, cortical reconstruction and segmentation, etc. More time-saving or specific pipelines like 'Fast-surfer' (Henschel et al. 2020) and 'infant-freesurfer' (Zöllei et al. 2020) are released in recent years. We integrate all those pipelines in the provided server, and provide processing options in the surface module GUI so that users no longer need to deal with the terminal when using 'recon-all' or wait too long for a reconstruction result, since the server is facilitated with GPUs and the average processing time is 3.5h for 'recon-all' and only 30min for 'fast-surfer' and 'infant-surfer'. Windows users need not configure a virtual machine for installing freesurfer locally since our server can undertake all the preprocessing works.

3.1.2 Electrode Module

Either processed manually or semi-automatically, the main idea of electrode contact segmentation is to identify the brightest voxels in a CT image as contact positions along each depth electrode. To conduct an autonomous pipeline of contact segmentation, we should make the best use of the image properties. BrainQuake's electrode module requires input data of only a post-surgical CT NIFTI image and a result package of surface reconstruction. The pipeline in the module includes three parts: image preprocessing, electrode clustering, and contact recognition. (**Figure 4**)

3.1.2.1 Preprocessing

Before we can autonomously identify any electrode or contact, we must ensure that the image contains only intracranial area of a brain, since the skulls, teeth, or some electrode supports outside the brain are hard to be distinguished from the electrodes based on the voxel value difference of a CT image. In the preprocessing step, we register the CT with the standardized MR image generated in the surface module. This registration step uses FSL 'flirt' (Jenkinson et al. 2012), which is done after surface reconstruction in the surface module. Then the registered CT can be masked with a skull-stripped MR image in the surface data package to remove the extracranial part of CT data since they are now in the same coordinate. At this time, the CT image contains only the information about the intracranial brain and the electrodes, the two of which show a great difference in their voxel value ranges. Electrode voxels are much brighter in the image so they can be extracted simply by thresholding. (**Figure 4A**)

3.1.2.2 Hough Transform and Gaussian Mixture Model

After extracting the electrode voxels into point clouds (**Figure 4B**), we need to identify the electrodes' number and axes, and label each voxel into different electrode clusters. This step is completed in most of the previous works by clustering algorithm with manual adjustment. In BrainQuake, we develop a method of combining 3D Hough Transform, a pattern recognition algorithm, and Gaussian Mixture Model, a clustering algorithm, to label voxels into different electrode cluster (**Figure 5**).

Normal clustering algorithms randomly pick some centroids in CT image, classify the voxels into clusters, and calculate the new centroid of each cluster. After multiple iterations, theoretically, voxels belonging to the same electrode can be assigned to the same cluster. But clustering algorithm is strongly dependent on the initial selection of centroids. With an improper initialization of the random centroids, the true distribution of electrode clusters can be difficult to estimate. There is a high probability that you would get a locally optimal clustering result, definitely requiring a manual intervention here to fix it, for example, to merge some of the clusters to form a real electrode or to split two or more electrodes in the same cluster.

Our method fixes this issue by adding a Hough transform before clustering. Hough Transform is a common method used in computer vision or digital image processing (Illingworth and Kittler 1988). It can be used to detect a certain class of shapes in an image automatically. The main idea of Hough

Transform is that for a specific shape, we choose a set of parameters and create a parameter space. For example, the parameter we usually use to describe circles can be center and diameter, while the parameter of 2D lines can be slope and intercept. Suppose we have a raw image with a mixture of dots on it. Each dot will vote in the parameter space for every possible parameter set they can contribute to. Positions in the space with the highest votes are recognized as the parameter sets describing the most obvious shape in the raw image. In our case, SEEG electrodes in a CT image are a combination of line-shaped objects in 3D space. The parameter space is established to represent the line direction (horizontal orientation and altitude) and the distance between the coordinate origin and the line.

Firstly, we transform those voxels into point clouds (**Figure 5A**). Then, we apply a 3D line Hough Transform to detect line-shaped trajectories (Jeltsch, Dalitz, and Pohle-Fröhlich 2016; Dalitz, Schramke, and Jeltsch 2017) in the point clouds, returning centroid and axis direction of each electrode cluster. At this stage, we get a set of approximate but not precise results representing the position of each cluster (**Figure 5B**), which can be a good set of prior knowledge to start clustering. After that, we use Gaussian Mixture Model (Reynolds 2009; Pedregosa et al. 2011) to assign each point to the electrode cluster it belongs to, since the point clouds can be viewed as a mixture of different line-shaped 3D Gaussian kernels (**Figure 5C**). After a successful clustering, the axes directions of electrodes can be regressed (Pedregosa et al. 2011). This combinatory method makes use of both electrode geometric prior and voxel distribution in a CT image, which shows great accuracy and robustness in our experiments.

3.1.2.3 Contact Segmentation

In the contact segmentation step, we manage to recognize the brightest voxels along each electrode cluster, which are viewed as the contacts' positions. We first define the head tip, or what we call 'target contact', of the electrode. With respect to a cluster of point clouds in the image space, it is easy to approximately locate the target of this line-shaped cluster, since the target position is always nearer to the space center (i.e. the brain center) than the tail position. After finding out the start point of this cluster, we iteratively calculate the center-of-mass (Arnulfo et al. 2015) of the surrounding image voxels within a restricted volume with respect to the real contact size. The position of this mass center can converge to the true target contact position within 1-2 iterations because the start point is already much close to it. The remaining contacts can be recognized using a similar iterative procedure: take a small step (the step size is provided by the true size of the adjacent interval distance along the electrode, 3.5mm in our cases) along the cluster's axis direction from the previous contact; calculate the mass center around the new position and converge to the next contact. (**Figure 4D**)

3.1.2.4 Validation Method of Electrode Localization

We used two methods to validate the results of the electrode module, visual inspection of the electrode positions and quantitative measurements of the electrode contact distribution. The recognized contacts were projected onto the 2D slice of the fusion of MR and CT images. Then we scanned through all these slices and visually checked if the electrodes and the highlighted electrode shaft on CT slices were overlapped.

To quantitatively estimate the accuracy of contact localization, we must define a gold standard of contact positions and then estimate the contact deviation error one by one. Usually, a group of clinical experts should be invited to view through all those image slices and mark the contact positions manually. However, due to the occurrence of artifacts for each contact in the CT images, one may find it tough to segment those contacts since the adjacent contact pairs are usually merged. Thus, we cannot trust the manual segmentation results as a gold standard. Here we estimate two indirect metrics, axis-contact distance (i.e. distances between contacts and their estimated shaft axis), and inter-contact distance of each pair of adjacent contacts (Narizzano et al. 2017; Arnulfo et al. 2015). Both of the metrics are based on the geometric properties of the SEEG electrodes. Contacts along the same electrode shaft must be line-shaped regressed and the deviation distance must be close to 0 mm. The electrodes we used have a fixed distance of 3.5 mm between each pair of adjacent contacts, so the inter-contact distance must be distributed like a Gaussian with a mean of 3.5 mm and a trivial variance as much as possible.

3.2 SEEG Data Analysis Modules

3.2.1 Ictal Module

For ictal data, clinicians mainly focus on the areas where pathological activity occurs earlier, and the EI index is used to predict the SOZ (Bartolomei, Chauvel, and Wendling 2008). Based on this, the epileptogenicity index (EI) module of the software in this article mainly predicts the SOZ by quantifying the time of high gamma energy change of each channel during the onset of the seizure, as well as the strength of energy changes (Zhao et al. 2019). Specifically, first, we select a piece of normal baseline data and a piece of target data containing the initial process of seizure. The baseline data is used to normalize the target data and a threshold of starting is calculated for each channel. When the target data of each channel exceeds its corresponding threshold, the abnormal activity starting time of each channel is then decided. After the onset time of each contact is sorted, the reciprocal of the rank is taken as time coefficient (TC) (**Figure 6A**). Then we calculate the average energy of each channel in a short period after the earliest starting time of all channels as the per-channel energy coefficient (EC). The epilepsy index is obtained by multiplying the time coefficient with the energy coefficient and taking the square root of it, which is used to describe the degree of epileptogenicity of each contact.

3.2.2 Inter-ictal Module

Previous work on SEEG inter-ictal data found that both HFO and spike are reliable biomarker of seizure onset zone (SOZ), while HFO has better specificity for SOZ than spikes (Roehri and Bartolomei 2019; Shuang Wang et al. 2017). The HFO sub-category, 80-250 Hz ripple component, is relatively more common than a higher frequency component (Shuang Wang et al. 2013). This frequency band can also take into account the spike activity which is similar to a full-band signal (Roehri et al. 2017; Cai et al. 2021). Therefore, for the inter-ictal data, we extract the pathological activity by detecting the short-term abnormal energy enhancement in the band of 80-250 Hz, providing an efficient indexation method through unified energy detection. Specifically, first, we use the Hilbert transform to extract the energy envelope in the 80-250 Hz band of the signal. We calculate the median value of the whole envelope (global) and the median value of each contact (local) to combine them as a synergistic threshold for each contact. The time range when the threshold is exceeded is marked as abnormal activity (**Figure 6B**). When the interval between two adjacent abnormal activities is too small, they are considered to belong to the same event and merged, and abnormal activities of too short duration are excluded. Finally, the number of abnormal activities (High Frequency Events Index, HI) calculated for each channel is used as an index to measure each contact's relative likelihood of being in the SOZ.

4 Results and Validation

We processed all four functional modules using MRI/CT images and SEEG data acquired from 5 epilepsy patients. The time required for surface reconstruction was either around 0.5h using Fast-surfer or 3.5h using Freesurfer recon-all on the public server (40 cores, 2.1 GHz, 64 GB RAM). The preprocessing step in the electrode module for each subject is around 15min, mostly spent on image registrations of MRI and CT using FSL 'flirt' command. Contact localization consumes only 30sec for each subject in average. A 70sec-length inter-ictal SEEG costs around 40sec for EI calculation, and a 3min-length inter-ictal data costs around 70sec for HI calculation.

4.1 Electrode Module Validation

We processed 46 electrodes with 454 contacts implanted in 5 patients in total. During visual inspection, all 46 electrodes were perfectly matched with the highlighted electrode shaft artifacts on CT images (**Figure 7AB**). For quantitative validation, we estimated two metrics, axial offset and inter-contact distance error, to measure whether the recognized contacts' distributions obey the geometric rules of the SEEG electrode. In statistics, 95% of the contacts were less than 0.1 mm deviating from their axes (**Figure 7C**). By subtraction of 3.5mm (real inter-contact distance) mean, the inter-contact distance error was distributed around 0 mm with a Gaussian-like distribution. 95% of the contact distance fell in the range of 3.5±1 mm and 50% of the contact distance fell in the range of 3.5±0.3 mm (**Figure 7D**). These two estimates show comparable results with 3D Slicer's CPE Module (Narizzano et al. 2017).

4.2 SEEG Analysis Validation

To evaluate the accuracy of predicting SOZ using EI and HI indices, the clinician's selection of patients' SOZ electrode contacts was used as the ground truth. The receiver operator curve (ROC) and the corresponding area under the curve (AUC) were further used to evaluate the consistency between the index-based prediction and the clinical diagnosis. The average AUC of EI and HI on 5 patients are 0.83 and 0.80 respectively (with EI of S2 excluded) (**Figure 8**). We can see that on patient S1, both EI and HI have achieved excellent SOZ prediction results. The AUC value of S2 based on EI is close to 0.5 and has no predictive effect, while the predictive effect based on HI reaches 0.92, which is very accurate. When the seizure data cannot provide sufficient diagnostic information, the inter-ictal data can be used to provide auxiliary information for the SOZ location, showing indispensible value of inter-ictal SEEG data. Finally, displaying SOZ predictions on reconstructed cortical volume is convenient for clinicians to verify with other evidence (**Figure 8C**).

5 Conclusion and Discussion

Intracranial SEEG data provide abundant electrophysiological information from the human brain for surgical planning and brain research. With the prevalence of SEEG recording in recent years, vast of neurodata has been generated while researchers are exploring a way to make the best use of it. The challenge lies in both the fusion of multi-modal neurodata and intensive computation during SEEG analysis. Here we have introduced a self-sustained Python toolbox - BrainQuake, integrating multiple approaches to form a complete solution. For structural data, electrode module and surface module provide fast and automated pipelines for surface reconstruction and electrode localization, with only raw MRI T1 and CT images needed for processing. For functional data, ictal and inter-ictal modules exploit the long range of SEEG data and provide a pre-surgical estimation of seizure onset zones. Blending structural and functional results, we provide neurosurgeons a comprehensive tool for surgical planning. Neuroscientists who are using SEEG to study the human functions will also be benefited from our toolbox.

The electrode localization approach implemented in BrainQuake divides the problem into two parts, a global level of electrode clustering and a local level of contact segmentation. BrainQuake innovates in the level of automatic electrode voxel clustering. Semi-autonomous methods require either additional messages of input or a graphical user interface to complete this process, the efficiency and user experience of which highly depends on the quality of images and preprocessing steps. Our algorithm, the combination of 3D Hough Transform and Gaussian Mixture Model, managed to take advantage of both geometric prior and graphical information embedded in CT images. Hough Transform helps to detect the geometric characteristic of the objects in the image. Whatever the image resolution is high or low, electrode shafts are always straight and highlighted from the background, so a pattern recognition algorithm can surely be used to analyze the image. To our knowledge, this valid and useful geometric property has never been exploited in any other electrode localization method before. Hough Transform makes electrode shafts be recognized automatically, although it may not return us a precise result. The recognized directions may deviate a little bit from the shaft, or a recognized centroid may not be in the exact center of the true electrode. However, the result can be rather close to the true state, which is a good starting point to initialize the clustering algorithm. Thus, we remove the complicated manual intervention and the pipeline consumes much less time than previous tools. As for the subsequent step of single electrode's contact segmentation, the algorithm of center-of-mass convergence (Arnulfo et al. 2015) has shown valid and reliable results. In our pipeline we apply this algorithm to each electrode one by one after electrode clustering and acquire the precise contact coordinates. The processing time from clustering to segmenting consumes only 30sec in average.

The automatic SOZ prediction methods usually use the onset order of high-frequency activity at each contact during seizure or the specific distribution of abnormal activity during inter-ictal period as pathological features (Bartolomei, Chauvel, and Wendling 2008; Navarrete et al. 2016; Barkmeier et al. 2012) These methods have already been integrated into some software independently (Colombet et al. 2015; Tadel et al. 2011). Though seizure data is considered to be more relevant to SOZ prediction, it may be difficult to be captured or not provide enough information for diagnosis. On the contrary, large amount of inter-ictal SEEG have not fully utilized. The pathological information extracted from long-term data may also have a good predictive power on SOZ and is more immune to noise than ictal data. As shown in our results, HI derived from inter-ictal data was a good supplement to the EI based on ictal data. However, the processing of long-term data also brings the challenge of computing power. The progress in the field of deep learning has led to the development of high-performance parallel computing. The acceleration capability of GPU may be a solution to the problem of massive SEEG data high-load computing. At present, the mechanisms of seizures and inter-ictal discharges are still unclear, and they may reflect different aspects of th**e** epileptic network (Jiruska et al. 2017; Grinenko et al. 2018). In this article, we provide efficient methods for extracting information about these two types of epilepsy activities so that clinicians can compare the consistency or divergency between them. This may serve as a platform for exploring the causal relationship between these two states, and ultimately better guide clinical diagnosis.

BrainQuake is designed to be an auxiliary tool for epilepsy neurosurgeons and technicians, trying to convey a pre-surgical evaluation solution with blended functional and structural neurodata. Most of current software or toolboxes focus on one or a few steps, developing splendid algorithms or techniques for data processing, but in clinical practice, it is a cumbersome task to merge all kind of results into one system or coordinate. Also, several steps consume a large amount of time and effort to do repeated works, resulting in an inefficient working procedure. BrainQuake commits to freeing surgeons and technicians from tedious and time-consuming work, allowing them to concentrate on the steps which rely more on common sense and medical expertise that is short in machine algorithms. In the upcoming era of big neurodata, this kind of human-computer synergy is an efficient approach of data utilization, and we believe it will eventually promote the fields of both neurology and neuroscience.

6 Conflict of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

7 Author Contributions

BH, FC, KW conceived of the work; FC and KW designed the software; FC developed the surface module and the electrode module; KW and TZ developed the ictal module; KW developed inter-ictal module; FC, KW and BH contributed to drafting and revising the article; HW and WZ collected the experimental data.

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Figure 1. General overview of BrainQuake structure. BrainQuake is designed to analyze SEEG data, CT image and MRI T1 image. Ictal and inter-ictal modules are used to recognize suspect contacts within SOZs. Electrode module analyses graphic information from a CT image to locate the SEEG electrodes and contacts and project them onto the surface reconstructed by the surface module. Suspect contacts' locations are marked (blue) on the 3D plot of the surface and electrodes, giving a brief overview of the pre-surgical evaluation result.

Figure 2. GUIs of BrainQuake's main window and four functional modules. **(A).** BrainQuake main window; **(B).** Surface module; **(C).** Electrode module; **(D).** Inter-ictal module; **(E).** Ictal module.

Figure 3. File structures of two datasets implemented in BrainQuake. Temporary and final results are saved under each subject's folders.

Figure 4. The pipeline of electrode localization and contact segmentation procedures in the electrode module. **(A).** The preprocessing step includes image registration from a subject's raw CT to MRI (brain.mgz after surface reconstruction), skull-stripping of registered CT, and thresholding of electrodes in the CT data. **(B).** The coordinates of electrode voxels in the CT image after thresholding can be extracted and plotted, viewing as a mix of point clouds. **(C).** After a Hough Transform and Gaussian Mixture Model algorithm, the electrodes are clustered and marked by different colors. **(D).** Contact segmentation step: contact positions are recognized one by one by converging to the center of mass based on voxel values. Contact positions are marked as red asterisks. **(E).** The results of the contact segmentation pipeline are visualized on the 3D surface space.

Figure 5. Three examples of electrode point clouds been 3D Hough-transformed and then clustered using Gaussian Mixture Model. **(A).** The initial point clouds of electrodes are extracted from one's CT intracranial image after several preprocessing steps. **(B).** The centroids and directions (showing by the red arrows) of SEEG electrodes are detected by line's Hough Transform algorithm in 3D coordinates. **(C).** The clustered electrodes are marked by different colors, giving Gaussian Mixture Model and the prior knowledge of clusters' centroids and directions generated from **(B)**.

Figure 6. Methods of ictal and inter-ictal SEEG data analysis. **(A).** Onset time and energy during the initial stage of seizures are combined as EI. **(B).** Count of over-threshold high frequency events are used as HI.

Figure 7. Validation of electrode localizations. Visual checking of an example subject's electrodes and contacts projected onto one's CT image. The raw CT brain **(A)** shows electrode positions as highlighted line-shaped voxels. Our recognized electrodes (red spheres) are projected on **(B)**, showing that they are overlapped with each other. Contact positions are quantitatively estimated by two metrics, axis-contact distance and adjacent inter-contact distance error. **(C).** Axis-contact distance estimates the distribution of deviation distance between each contact and its regressed electrode shaft axis. **(D).** Adjacent inter-contact distance error estimates the distribution of distance between each pair of adjacent contacts.

Figure 8. Results of SEEG data analysis. **(A).** ROC and AUC results of SOZ prediction, based on EI. **(B).** ROC and AUC results of SOZ prediction, based on HI. **(C).** HI results of S2 (scale of contacts) and cortical reconstruction are displayed at the same time with clinical SOZ shown in red.