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Cicerone: stereotactic neurophysiological recording and deep brain stimulation electrode placement software system

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Summary

Stereotactic neurosurgery and neurophysiological microelectrode recordings in both humans and monkeys are typically done with conventional 2D atlases and paper records of the stereotactic coordinates. This approach is prone to error because the brain size, shape, and location of subcortical structures can vary between subjects. Furthermore, paper record keeping is inefficient and limits opportunities for data visualization. To address these limitations, we developed a software tool (Cicerone) that enables interactive 3D visualization of co-registered magnetic resonance images (MRI), computed tomography (CT) scans, 3D brain atlases, neurophysiological microelectrode recording (MER) data, and deep brain stimulation (DBS) electrode(s) with the volume of tissue activated (VTA) as a function of the stimulation parameters. The software can be used in pre-operative planning to help select the optimal position on the skull for burr hole (in humans) or chamber (in monkeys) placement to maximize the likelihood of complete microelectrode and DBS coverage of the intended anatomical target. Intra-operatively, Cicerone allows entry of the stereotactic microdrive coordinates and MER data, enabling real-time interactive visualization of the electrode location in 3D relative to the surrounding neuroanatomy and neurophysiology. In addition, the software enables prediction of the VTA generated by DBS for a range of electrode trajectories and tip locations. In turn, the neurosurgeon can use the combination of anatomical (MRI/CT/3D brain atlas), neurophysiological (MER), and electrical (DBS VTA) data to optimize the placement of the DBS electrode prior to permanent implantation.

Keywords: Neuromodulation; movement disorders; Parkinson's disease; neurostimulation; electrical stimulation; electrode; stereotactic neurosurgery; surgical planning.

Stereotactic neurosurgery and deep brain stimulation

Stereotactic neurosurgery has been used in research for over one hundred years and it has gained acceptance into clinical practice since the 1950s [15]. The precision of target localization using stereotactic frames has improved since the inception of image-guided (MRI and CT) methods based on internal landmarks [17, 22, 27]. However, even with the increased accuracy of image-guided stereotactic targeting, it is often necessary to use neurophysiological microelectrode recordings (MER), and electrical stimulation to confirm and further explore the target [12, 13, 18, 26, 30]. In turn, stereotactic neurosurgical procedures typically require the integration of anatomical, neurophysiological, and electrical data to enable the neurosurgeon to make the most informed decisions possible.

Stereotactic neurosurgery is particularly relevant to deep brain stimulation (DBS). Over the last two decades DBS has evolved from a highly experimental technique to a well established therapy for a range of medically refractory neurological disorders [2]. To date, the most effective application of DBS technology is for the treatment of movement disorders. Surgical interventions for movement disorders have a long history, beginning with early studies that used lesions to eliminate activity in localized brain regions. Surgeons using stimulating/recording electrodes for target confirmation during ablative surgery found that high-frequency stimulation ($\sim$100 Hz) of the brain had behavioral outcomes similar to lesioning [3]. This realization transformed the world of functional neurosurgery, and DBS has become the surgical intervention of choice for Parkinson's disease (PD), essential tremor, and dystonia. In addition, DBS shows promise in the treatment of other neurological disorders such as epilepsy, obsessive-compulsive disorder, Tourette's syndrome, and depression. Currently the most common DBS procedures are for PD and they depend on precise localization and electrode insertion into the globus pallidus internus (GPi) or subthalamic

nucleus (STN), small structures deep within the basal ganglia.

In current clinical practice, MRI-based surgical navigation systems are used in concert with stereotactic frame systems to target the nucleus of interest and select the initial electrode trajectory for DBS surgeries [7–10, 16, 21, 28, 29]. The anatomical target is identified by direct visualization of the nucleus in the MRI and/or a brain atlas co-registered with the MRI [24]. The stereotactic coordinates of the anatomical target are calculated relative to the fiducial markers of the stereotactic frame present in the image. In turn, the mechanical adjustments of the frame system can be calibrated to enable a surgical trajectory that follows the desired path [26]. Many believe that accurate placement of DBS electrodes for a maximal therapeutic outcome requires neurophysiological definition of the anatomical borders of the nucleus and identification of areas where stimulation causes side effects [23, 25]. Therefore, the target area is commonly explored with several microelectrode penetrations during which extracellular unit recording and microstimulation data are collected.

The final DBS electrode placement is selected after a review of the gathered anatomical and neurophysiological data. This crucial decision is often based on paper records which are inefficient and limit opportunities for data visualization. Traditional 2D brain atlases are typically used to estimate electrode position with respect to the anatomy by superimposing the atlas over plots of the microelectrode recording data. However, these atlas slices are not customized to each patient and they are often spaced at large and irregular intervals, so the closest available slice may not accurately capture the neuroanatomy of the given electrode trajectory. This is especially true when the surgical trajectory is at an oblique angle relative to the sagittal and coronal planes used in 2D brain atlases. More importantly, the fundamental purpose of DBS is to modulate neural activity with applied electric fields, but current neurosurgical navigation systems do not allow for visualization of the spread of stimulation.

To address these limitations, we developed the Cicerone software system for stereotactic neurosurgical planning, neurophysiological data collection, and deep brain stimulation visualization. This research tool integrates the vast array of data used in the implantation of DBS electrodes, with the goal of improving the therapeutic outcome of the surgery. Cicerone provides interactive 3D visualization of co-registered MRI/CT images, subject-specific 3D anatomical brain atlas, and neurophysiological data from microelectrode recordings. Furthermore, it displays predictions of the volumes of tissue that would be activated by DBS for any given electrode position and orientation in the brain. Cicerone can be used to define a pre-operative target location and trajectory for the DBS electrode placement and help select the location on the skull for burr hole (in humans) or chamber (in monkeys) placement. Intra-operatively, Cicerone allows entry of the microdrive coordinates and MER data, enabling real-time interactive visualization of the electrode location in 3D relative to the surrounding anatomy. In addition, the user can simultaneously visualize the DBS electrode and its predicted stimulating effects in relation to the neuroanatomy and neurophysiology. In turn, stereotactic placement of the DBS electrode can be optimized prior to permanent implantation with the combination of anatomical, neurophysiological, and electrical data.

Cicerone was developed to integrate the various data sets used in our scientific analysis of human and monkey DBS research studies. The human and monkey versions of Cicerone are conceptually similar, but due to differences in the surgical procedures they have been developed as two separate software applications. Both systems were written using VTK (Visualization Toolkit; Kitware, Clifton Park, NY) and Tcl/Tk (Tool Command Language; http://tcl.sourceforge.net) making them portable across platforms, including Windows. Version 1.0 of Cicerone is self-contained on a single CD, and auto-installs on a PC similar to any traditional Windows software. Cicerone is currently a research tool and not commercially available or intended for clinical use outside of IRB approved studies. Individuals interested in using Cicerone in their own research are encouraged to contact CCM.

Human Cicerone

The Cicerone system was developed to address three issues. First, improve the intra-operative management of MER data. Second, provide the neurosurgeon with the ability to interactively visualize the stimulating influence of the DBS electrode in the target location before permanent implantation. Third, provide a common visualization platform to simultaneously analyze the anatomical (MRI/CT/3D brain atlas), neurophysiological (MER), and electrical (DBS VTA) data pertinent to the surgery.

In general, the MRI/CT scans with the stereotactic fiducial makers necessary for a human DBS procedure are acquired on the day of the surgery. Therefore, we