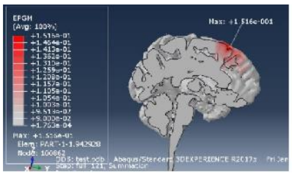 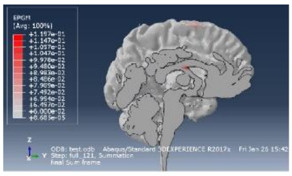 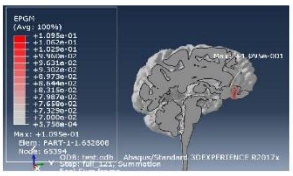 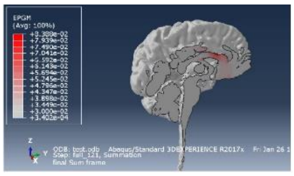

Dassault, NIMHANS, and UberCloud Foster Innovative Non-Invasive Neuro-Stimulation of the Brain to Treat Schizophrenia, with High Performance Computing

By Wolfgang Gentzsch, President and Co-Founder of the UberCloud, March 29, 2018

Abstract: In a series of challenging high performance computing applications in the Life Sciences, UberCloud's HPC Containers have been packaged recently with several scientific workflows and application data to simulate complex phenomena in human's heart and brain. As the core software for these HPC Cloud experiments we are using the (containerized) Abaqus solver running in a fully automated multi-node HPE environment in the Advania HPC Cloud.

Treatment of Schizophrenia is complex, lengthy, and often risky

The brain is the most complex organ of the human body and it therefore follows that it's disorders such as schizophrenia are equally complex. Schizophrenia is a complex chronic brain disorder that affects about one percent of the world's population. When schizophrenia is active, symptoms can include delusions, hallucinations, trouble with thinking and concentration, and lack of motivation. Schizophrenia interferes with a person's ability to think clearly, manage emotions, make decisions and relate to others. Symptoms include hearing internal voices, having false beliefs, disorganized thoughts and behavior, and being emotionally flat. These symptoms may leave a person feeling fearful and withdrawn. Their disorganized behavior can be perceived as incomprehensible or frightening to others.

Often, schizophrenia cannot be treated successfully by using just one type of medicine. Therefore, a range of treatments including drugs are available and the key to a successful outcome is to find the right combination of the right drugs and the right talking therapies for the individual patient. Different people will respond differently to different treatments. Finding the right treatment regime can be a very lengthy process and finding the right medication at the right dose alongside the most useful talking therapy can take a lot of time.

As an alternative to drugs, Deep Brain Stimulation (DBS) is being applied to treat schizophrenia, involving implanting electrodes within certain areas of the brain to produce electrical impulses that regulate abnormal impulses in a patient's brain. But this treatment is intrusive and comes with a certain risk for potential complications such as stroke, cerebrospinal fluid (CSF) leakage, bleeding, etc. Other drawbacks are that not every patient can afford DBS surgery considering their individual health conditions and high-cost medical procedures.

A New Method: Non-Invasive Direct Current Stimulation

In recent years, so-called transcranial Direct Current Stimulation (tDCS) has been introduced which is a new form of non-invasive neurostimulation that is used to safely treat a variety of clinical conditions including depression, obsessive-compulsive disorder, migraine, and central and neuropathic chronic pain. tDCS involves the injection of a weak (very low amperage) electrical current to the head through surface electrodes to generate an electric field that selectively modulates the activity of neurons in the cerebral cortex of the brain. While the precise mechanism of tDCS action is not yet known, extensive neurophysiological research has shown that direct current electricity modifies neuronal cross-membrane resting potentials and thereby influences neuronal excitability and firing rates.

Figure 1: Illustration of transcranial Direct Current stimulation device. Courtesy Bipolar Network News.

Stimulation with a negative pole (cathode) placed over a selected cortical region decreases neuronal activity in the region under the electrode whereas stimulation with a positive pole (anode) increases neuronal activity in the immediate vicinity of the electrode. In this manner, a tDCS device as shown in the picture may be used to increase cortical brain activity in specific brain areas that are under-stimulated or alternatively to decrease activity in areas that are overexcited. Research has shown that the effects of tDCS can last for an appreciable amount of time after exposure. The benefit of tDCS treatment for the patient is administered with the subject fully conscious and uses very small electric currents that are unable to induce a seizure, constrained to the cortical regions, and can be focused with relatively high precision. Moreover, tDCS is inexpensive, lightweight, and can be conducted anywhere.

The UberCloud Experiment #200

In the last six years UberCloud has performed 200 cloud experiments with engineers and scientists and their complex applications. This latest HPC cloud experiment is based on computer simulations of a novel non-invasive transcranial electro-stimulation of the human brain to treat schizophrenia. The experiment has been collaboratively performed by the National Institute of Mental Health & Neuro Sciences in India (NIMHANS), Dassault SIMULIA, Advania, and UberCloud, and generously sponsored by Hewlett Packard Enterprise and Intel. The current work demonstrates the high value of computational modeling and simulation in improving the clinical application of non-invasive transcranial electro-stimulation of the human brain in schizophrenia.

NIMHANS is India's premier neuroscience organization involved in clinical research and patient care in the area of neurological and psychiatric disorders. Since 2016, Dassault Systemes has been collaborating with NIMHANS on a project to demonstrate that computational modeling and simulation can improve the efficacy of Transcranial Direct Current Stimulation (tDCS), a noninvasive clinical treatment for schizophrenia. Successful completion of the first stage of this project has already raised awareness and interest in simulation-based personalized neuromodulation in the clinical community in India.

Our project demonstrates an innovative method that can stimulate deep inside the brain non-invasively/non-surgically, using multiple electric fields applied from scalp. This procedure can precisely activate selective regions of the brain **leaving minimal risk and also making it affordable to all**.

The method that is adopted here is called "Temporal Interference" (TI), where we are forcing two alternating currents (transcranial Alternating Current Stimulation: tACS) at two different high-frequency electric fields towards the brain via pairs of electrodes placed on the scalp. Neither of the individual alternating fields is enough to stimulate the brain because the induced electric field frequency is much higher than the neuron-firing frequency; hence the current simply passes through tissue medium with no effect. However, when two alternating current fields intersect deep inside the brain, a pattern of interference is created which oscillates within an 'envelope' at a much lower frequency i.e. difference between two high-frequencies, which is commonly referred to as "beat frequency", which would stimulate a neural activity in the brain. **With this method clinicians can precisely target regions of the brain without affecting major part of the healthy brain!**

It is anticipated that "Temporal-Interference" stimulation has great potential to treat a large number of neurological disorders. However, it is required to be personalized for an individual depending upon the type of disease targeted and inter-individual variation in brain morphology and skull architecture. Since each patient's brains can be vastly different, an optimal electrode placement needs to be identified on the scalp in order to create Temporal-Interference at specific regions of the brain for an effective outcome. For instance, in Parkinson's disease, thalamus and globus pallidus would most likely be the regions to create Temporal-Interference to regulate electrical signals and there by activating neurons to reduce the tremor in the patients.

The power of multi-physics technology on the Advania Cloud Platform allowed us to simulate the Deep Brain Stimulation by placing two sets of electrodes on the scalp to generate Temporal-Interference deep inside the grey matter of the brain, as presented in the Figure 2 workflow. However, a basic level of customization in post processing was required in making this methodology available to the clinician in real time and also reduce overall computational effort, where doctors can choose two pre-computed electrical fields of an electrode pair to generate temporal interference at specific regions of the grey matter of the brain. Nevertheless, the technique proposed here can be extended to any number of electrode pairs in future.

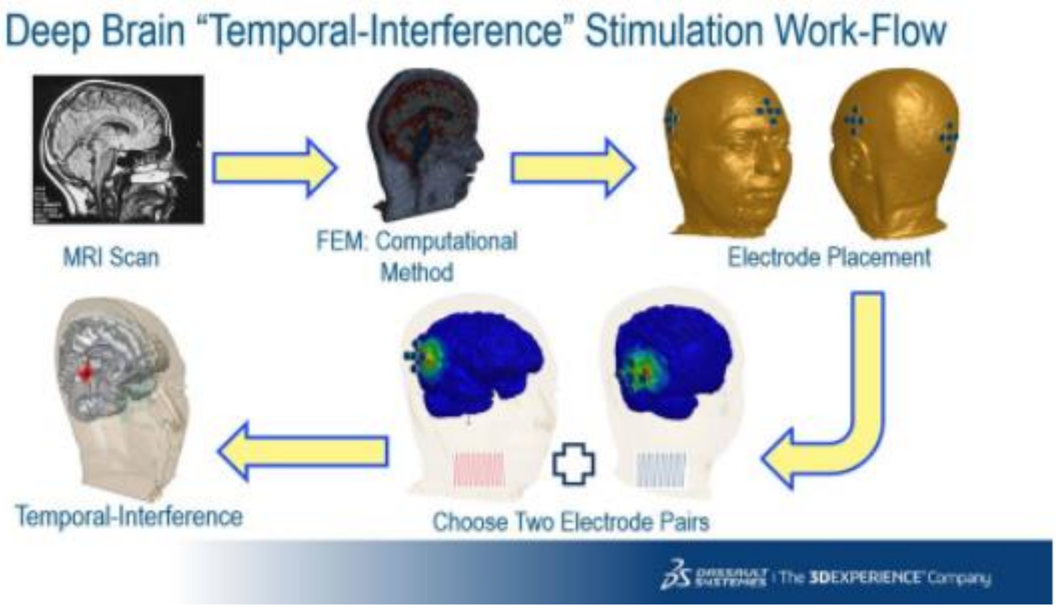

Figure 2: The workflow for the Virtual Deep Brain Stimulation on a human head model. Courtesy Dassault Systemes.

A high fidelity finite element human head model was considered including skin, skull, cerebro-spinal fluid, sinus grey & white matter, which demanded high-performance computing resources to try various electrode configurations. Access to HPE's high performance computing infrastructure in the Advania Cloud and SIMULIA's Abaqus 2017 code packaged in an UberCloud HPC container empowered the researcher to run numerous configurations of electrode placements and sizes to explore best possible electrode placement. This also allowed to study the sensitivity of electrode placements and sizes in the newly proposed method of Temporal-Interference in Deep Brain stimulation **which was not possible before** on the user's inhouse workstations and HPC systems.

The results demonstrated in Figure 3 is for two sets of electrical fields superimposed to produce "Temporal Interference":

- Configuration-1: Electrical fields generated from electrodes placed on the left and right side of pre-temporal region of the scalp.
- Configuration-2: Electrical fields generated from electrodes placed on the left of the pre-temporal and rear occipital region of the scalp.

In Configuration-1, the "temporal interference" was observed at the right hippocampus region, whereas for Configuration-2, the temporal interference" was observed at the sub-parietal sulcus.

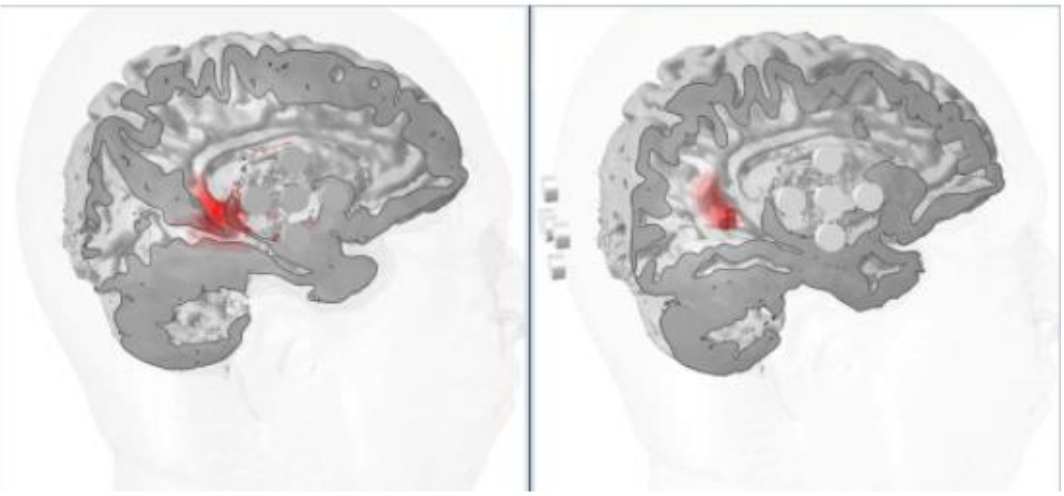

Figure 3: The results show the sensitivity of the temporal-interference region deep inside the brain based on electrode placement on the scalp.

Based on this insight, the team is now continuing to work towards studying various electrode placements in targeting different regions of the brain. While preliminary results look promising, the team will be working closely with NIMHANS in validating the method through further research on this topic and experimentation. In parallel, the team is also working towards streamlining the methodology such that it can easily be used by clinicians.

HPC Cloud Hardware and Results

We ran 26 different Abaqus jobs on the Advania HPC cluster – each representing a different montage (electrode configuration). Each job contained 1.8M finite elements. For comparison purposes, on the user's own server with 16 cores, a single run took about 75min whereas on the UberCloud cluster a single run took about 28min on 24 cores. Thus, we got a significant speedup of about 2x running in the cloud. With this cloud approach, in the future, it will be possible to run many different electrode placement simulations in parallel, thus dramatically speeding up the search for the optimal electrode placement for an individual patient, with the final goal to perform such a search in (almost) real time. In addition, during this cloud experiment, the Abaqus 2017 software container has always been accessible through the user's browser, from anywhere, on demand, for any kind of interactive and batch work, and for remote visualization of the simulation results.

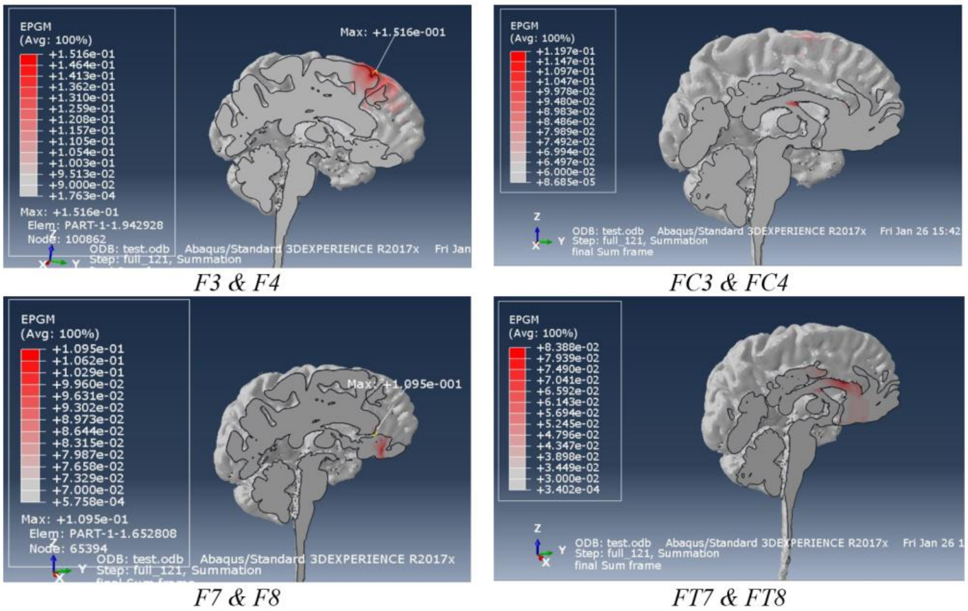

Figure 4: Localization of the peak Electrical Potential Gradient value in Abaqus for different combinations of electrodes.

CONCLUSION

In the recent times, the Life Sciences community has come together better than ever before, to collaborate and leverage new technologies for the betterment of health care and improved medical procedures. The application discussed here **demonstrates a novel method for "Deep Brain Stimulation" in a non-invasive way which has the potential to replace some of the painful/high risk brain surgeries such as in Parkinson's disorders.**

The huge benefits of these computational simulations are that they **(i)** predict the current distribution with high resolution; **(ii)** allow for patient-specific treatment and outcome evaluation; **(iii)** facilitate parameter sensitivity analyses and montage variations; and **(iv)** can be used by clinicians in an interactive real-time manner.

However, there is still a lot of work to be done in collaboration with the Doctors/Clinicians at NIMHANS and other Neurological Research Centers on how this method can be appraised and fine-tuned for real time clinical use.

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About UberCloud

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