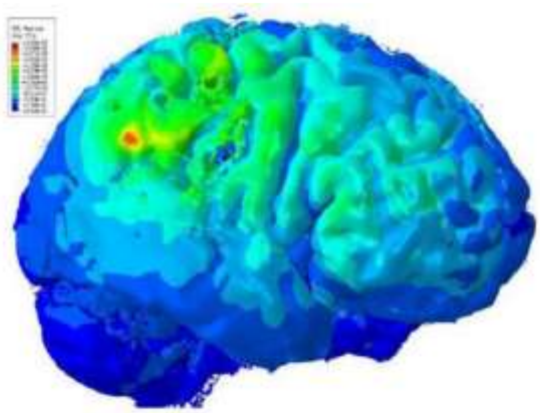
HPC Cloud Simulation

of Direct Current Brain Stimulation in Schizophrenia

An UberCloud Experiment



With Support From:

UberCloud Case Study 200

http://www.TheUberCloud.com

March 10, 2018

Welcome!

The UberCloud* Experiment started in July 2012, with a discussion about cloud adoption in technical computing and a list of technical and cloud computing challenges and potential solutions. We decided to explore these challenges further, hands-on, and the idea of the UberCloud Experiment was born, and since then generously supported by Hewlett Packard Enterprise and INTEL.

We found that especially small and medium enterprises in manufacturing would strongly benefit from technical computing in HPC centers and in the cloud. By gaining access on demand from their desktop workstations to additional and more powerful computing resources in the cloud, their major benefits became clear: the **agility** gained by shortening product design cycles through shorter simulation times; the superior **quality** achieved by simulating more sophisticated geometries and physics, and by running many more iterations to look for the best product design; and the **cost** benefit by only paying for what is really used. These are benefits that obviously increase a company's innovation and competitiveness.

Tangible benefits like these make computing - and more specifically technical computing as a service in the cloud - very attractive. But how far are we from an ideal cloud model for engineers and scientists? At first we didn't know. We were facing challenges like security, privacy, and trust; traditional software licensing models; slow data transfer; uncertain cost & ROI; lack of standardization, transparency, cloud expertise. However, in the course of this experiment, as we followed each of the 200 teams closely and monitored their challenges and progress, we've got an excellent insight into these roadblocks, how our teams have tackled them, and how we are now able to reduce or even fully resolve them.

Schizophrenia is a serious mental illness characterized by illogical thoughts, bizarre behavior/speech, and delusions or hallucinations. This **UberCloud Experiment #200** is based on computer simulations of non-invasive transcranial electro-stimulation of the human brain in 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 sponsored by Hewlett Packard Enterprise and Intel. The current work represents an initial effort to demonstrate 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.

This project won the prestigious international 2018 Innovation Excellence Award from Hyperion and the HPC User Forum Steering Committee!

We want to thank all team members for their continuous commitment and contribution to this exciting project, and our main sponsors **Hewlett Packard Enterprise** and **INTEL** for generously supporting all the 200 UberCloud experiments.

Wolfgang Gentzsch and Burak Yenier

) UberCloud is the online community & marketplace where engineers and scientists discover, try, and buy Computing Power as a Service, on demand. Engineers and scientists can explore and discuss how to use this computing power to solve their demanding problems, and to identify the roadblocks and solutions, with a crowd-sourcing approach, jointly with our engineering and scientific community. Learn more about UberCloud **HERE.*

Team 200

HPC Cloud Simulation of Direct Current Brain Stimulation in Schizophrenia

> *"Advania's HPC Cloud servers with Abaqus in an UberCloud container empowered us to run numerous complex configurations of sensitivity electrode placement."*

Figure 1: Illustration of transcranial Direct Current stimulation device.

MEET THE TEAM

End Users – Dr. Ganesh Venkatasubramanian, G. Bhalerao, R. Agrawal, S. Kalmady (from NIMHANS), and G. Umashankar and Karl D'Souza (from Dassault Systemes).
Software Provider – Dassault/SIMULIA (Tom Battisti, Matt Dunbar, Karl D'Souza) providing Abaqus 2017 software and support.
Resource Provider – Advania Cloud in Iceland (represented by Aegir Magnusson and Jon Tor Kristinsson), with access and support for the HPC server from HPE.
HPC Cloud Experts – Fethican Coskuner, Ender Guler, and Wolfgang Gentzsch from the UberCloud, providing novel HPC software container technology for ease of Abaqus cloud access and use.
Experiment Sponsor – Hewlett Packard Enterprise, represented by Bill Mannel and Jean-Luc Assor, and Intel.

USE CASE: TRANSCRANIAL DIRECT CURRENT BRAIN STIMULATION

Schizophrenia is a serious mental illness characterized by illogical thoughts, bizarre behavior/speech, and delusions or hallucinations. This UberCloud Experiment #200 is based on computer simulations of non-invasive transcranial electro-stimulation of the human brain in 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 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.

Transcranial Direct Current Stimulation (tDCS): A new neuro-stimulation therapy

While well-known deep brain stimulation involves **implanting** electrodes within certain areas of the brain producing electrical impulses that regulate abnormal impulses, transcranial Direct Current Stimulation (tDCS) is a new form of **non-invasive** neuro-stimulation that may be used to safely treat a variety of clinical conditions including depression, obsessive-compulsive disorder, migraine, and central and neuropathic chronic pain. TDCS can also relieve the symptoms of narcotic withdrawal and reduce cravings for drugs, including nicotine and alcohol. There is some limited evidence that tDCS can be used to increase frontal lobe functioning and reduce impulsivity and distractibility in persons with attention deficit disorder. TDCS has also been shown to boost verbal and motor skills and improve learning and memory in healthy people. TDCS involves the injection of a weak (very low amperage) non-alternating electrical current to the head through **surface electrodes** to generate an electromagnetic field that selectively modulates the activity of neurons in the cerebral cortex of the brain.

The exact mechanism of tDCS is not clear but extensive neurophysiological research has shown that direct current (DC) electricity penetrates the skull and outer layers of the cortex to modify neuronal cross-membrane resting potentials and thereby influence the level of neuronal excitability and modulate firing rates.

Stimulation with the negative pole (cathode) placed over a selected cortical region will decrease neuronal activity under the electrode whereas stimulation with the positive pole (anode) will increase neuronal activity under the electrode. In this manner, tDCS may be used to increase cortical brain activity in specific brain areas that are under aroused or alternatively 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.

tDCS may sound similar to electroshock or electroconvulsive therapy (ECT) but it is quite different. ECT is done under anaesthesia and applies electrical currents a thousand times greater than tDCS to cause a seizure. ECT drastically affects the functioning of the entire brain and can result in significant adverse effects, including memory loss. Transcranial DC stimulation uses only very small electric currents that cannot set off a seizure and is far more selective in its effects. TDCS only influences the area of the cortical brain directly beneath the electrode.

tDCS may work in a way that is somewhat similar to transcranial magnetic stimulation (TMS) but is still quite different. In TMS, the brain is penetrated by a powerful pulsed magnetic field that causes all the neurons in the targeted area of the brain to fire in concert. After TMS stimulation stops, depending on the frequency of the magnetic pulses, the targeted region of the brain is either turned off or on. TMS devices are quite expensive and bulky which makes them difficult to use outside a hospital or large clinic. TMS can also set off seizures, so must be medically monitored. Where tDCS is quite different from TMS is that it only affects neurons that are already active—it does not cause resting neurons to fire. Moreover, the effects of tDCS appear to be limited to the cortex of the brain, whereas TMS can penetrate to deeper brain structures.

HPC BRAIN SIMULATION IN THE ADVANIA CLOUD

The National Institute of Mental Health and Neuro Sciences (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-SIMULIA 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 project will dramatically increased interest in simulation-based personalized neuromodulation in the clinical community.

Although effective and inexpensive, conventional tDCS therapies can stimulate only shallow regions of the brain such as prefrontal cortex and temporal cortex regions. These therapies cannot really penetrate deep inside the brain. There are many other neurological disorders which need clinical interventions deep inside the brain such as thalamus, hippocampus and subthalamus regions in Parkinson's, Autism, and Memory Loss disorders. The general protocol in such neurological disorders is to treat patients with drugs and in some cases, patients may be recommended to undergo highly invasive surgeries. This would involve drilling small holes in the skull, through which the electrodes are inserted to the dysfunctional regions of the brain to stimulate the region locally as shown in Figure 2. This procedure is called as "Deep Brain Stimulation", in short DBS. However, DBS procedure has potential complications such as stroke, cerebrospinal fluid (CSF) fluid leakage, bleeding, etc. Other drawbacks are that not every patient can afford DBS surgery considering their individual health conditions and high cost medical procedures.

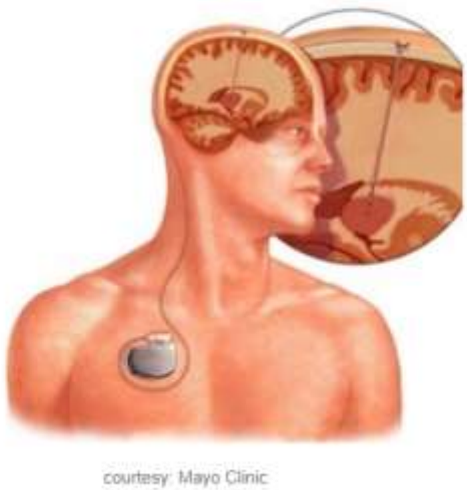


Figure 2: invasive surgeries involve drilling small holes in the skull, through which the electrodes are inserted to the dysfunctional regions of the brain to stimulate the region locally.

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**.

Background

The method that is adopted here is called "Temporal Interference" (TI), where we are forcing two alternating currents (transcranial Alternating Current Stimulation: tACD) 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 neurons-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 with 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 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.

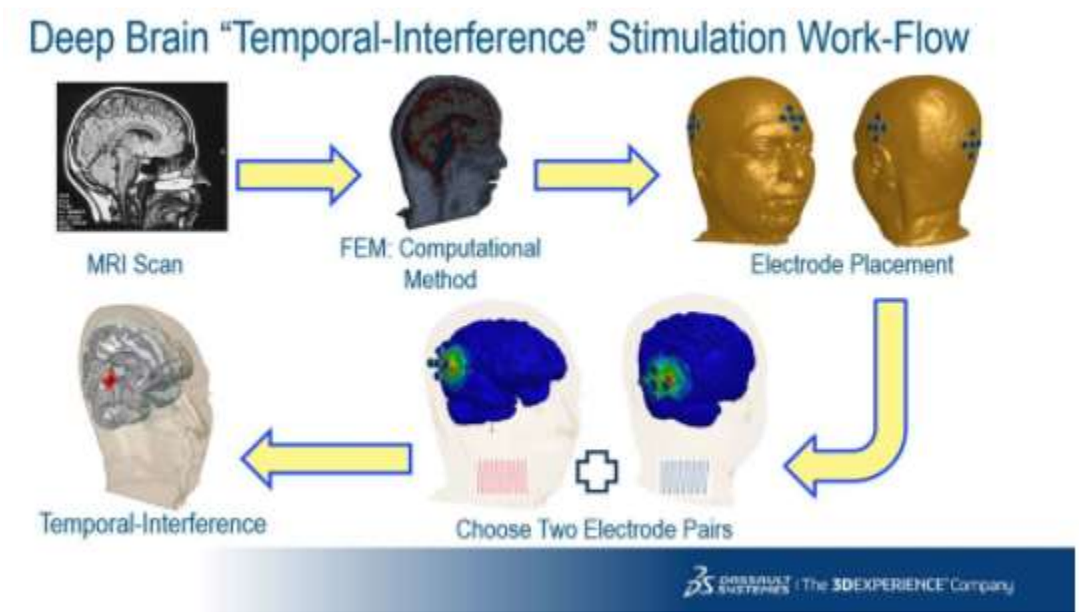


Figure 3: The workflow for the Virtual Deep Brain Stimulation on a human head model.

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 3 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.

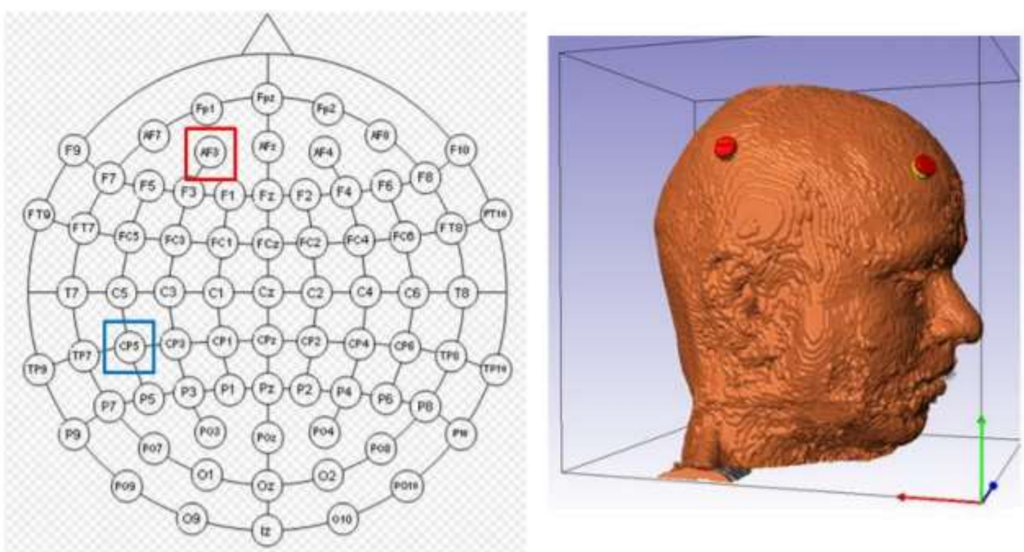


Figure 4: International 10/10 convention (left) showing anode AF3 (red) and cathode CP5 (blue); subject-specific model (right).

After a satisfactory 3D head/brain model was developed, electrode placement was performed with Simpleware® ScanIP and ScanCAD modules using the 10/10 international convention with the anode at AF3 and the cathode at CP5 (Figure 4). Finally, a high-resolution tetrahedral FE mesh (element size = 1mm3) was generated using the ScanIP and ScanFE modules.

A high-fidelity finite element human head model was considered including skin, skull, CSF, sinus grey & white matter, which demanded high computing resources to try various electrode configurations. Access to HPE's Cloud system at Advania and SIMULIA's Abaqus 2017 code in an UberCloud software container empowered us to run numerous configurations of electrode placements and sizes to explore new possibilities. This also allowed us 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 our inhouse workstations and HPC systems.

The results demonstrated in the Figure 5 video/picture 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 subparietal sulcus.

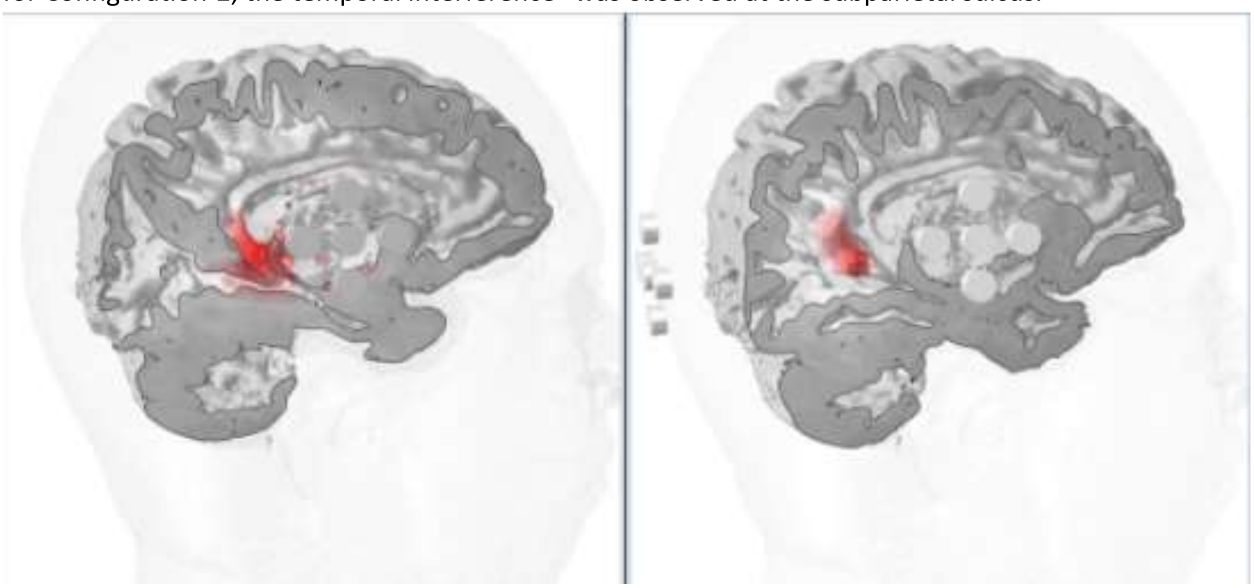


Figure 5: The results show the sensitivity of the temporal-interference region deep inside the brain based on electrode placement on the scalp.

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. Simultaneously, we would be working towards streamlining the methodology which can be used by clinicians and also explore next steps in performing design exploration studies on DASSAULT's 3DEXPERIENCE Platform. We would be positioning the Temporal Interference workflow to other Neurosciences Institutes and thereby expanding our presence in the field of Neurosciences.

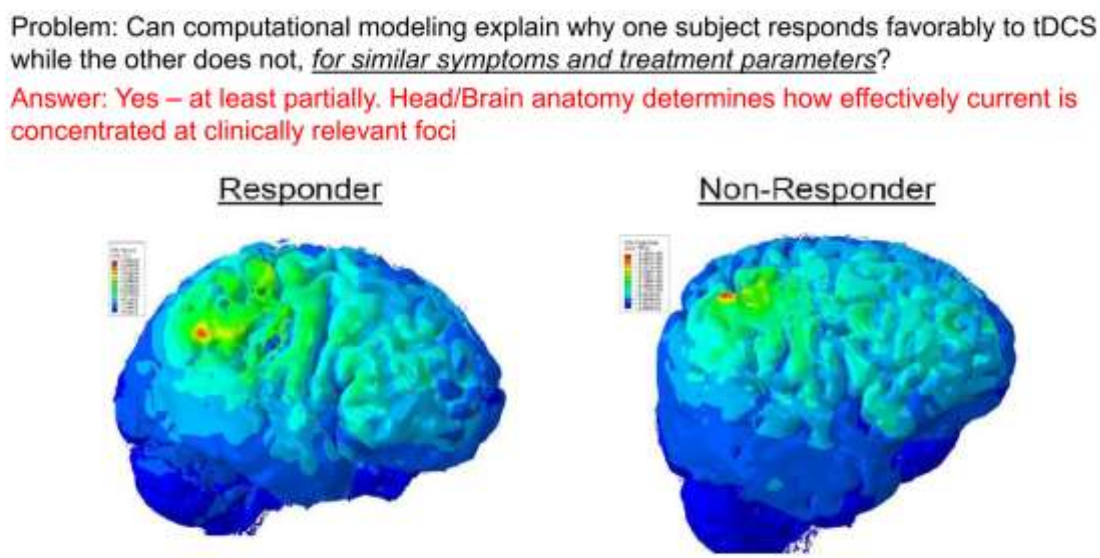


Figure 6: Image-based Finite Element Modeling results, for so-called Responder versus Non-Responder (3M nodes. 17M elements. Electrostatic analysis. Element type: DC3D4E. Isotropic conductivity, different for each region).

HPC Cloud Hardware and Results

During the final production phase, we have run 42 simulations to study whether a drug causes arrhythmias or not. With all these changes we were able to **speed up one simulation by a factor of 27** which then (still) took 40 hours using 160 CPU cores on Advania's HPC as a Service (HPCaaS) hardware configuration built upon HPE ProLiant servers XL230 Gen9 with 2x Intel Broadwell E5-2683 v4 with Intel OmniPath interconnect. We observed that the model scaled without a significant loss of performance up to 240 compute cores, making the 5-node sub-cluster of the Advania system an ideal candidate to run these compute jobs. In these simulations, we applied the drugs by blocking different ionic currents in our cellular model, exactly replicating what has been observed before in cellular experiments. For each case, we let the heart beat naturally and see if the arrhythmia is developing.

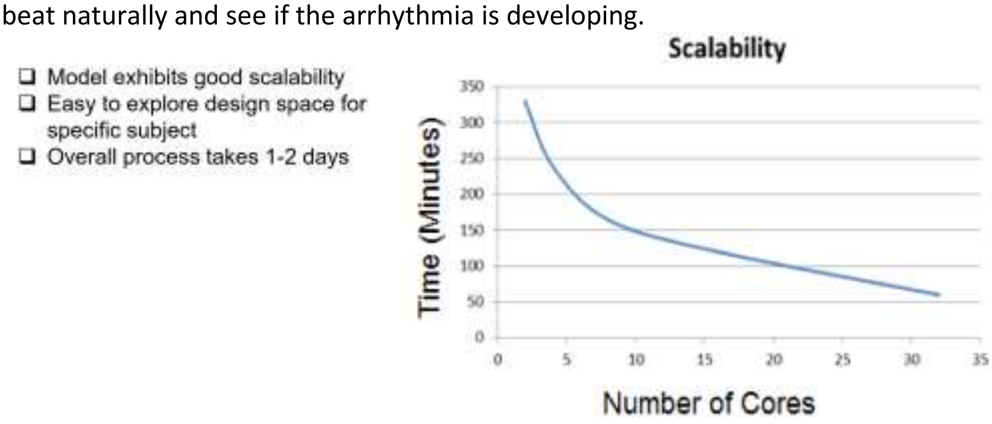


Figure 7. Selected results for Image-based Finite Element Modeling with good scalability.

We ran 26 different Abaqus jobs on the Advania/UberCloud HPC cluster – each representing a different montage (electrode configuration). Each job contained 1.8M finite elements. For comparison purposes, on our own cluster with 16 cores, a single run took about 75min (solver only) whereas on the UberCloud cluster a single run took about 28min (solver only) on 24 cores. Thus, we got a significant speedup of about 2x running on UberCloud/Advania.

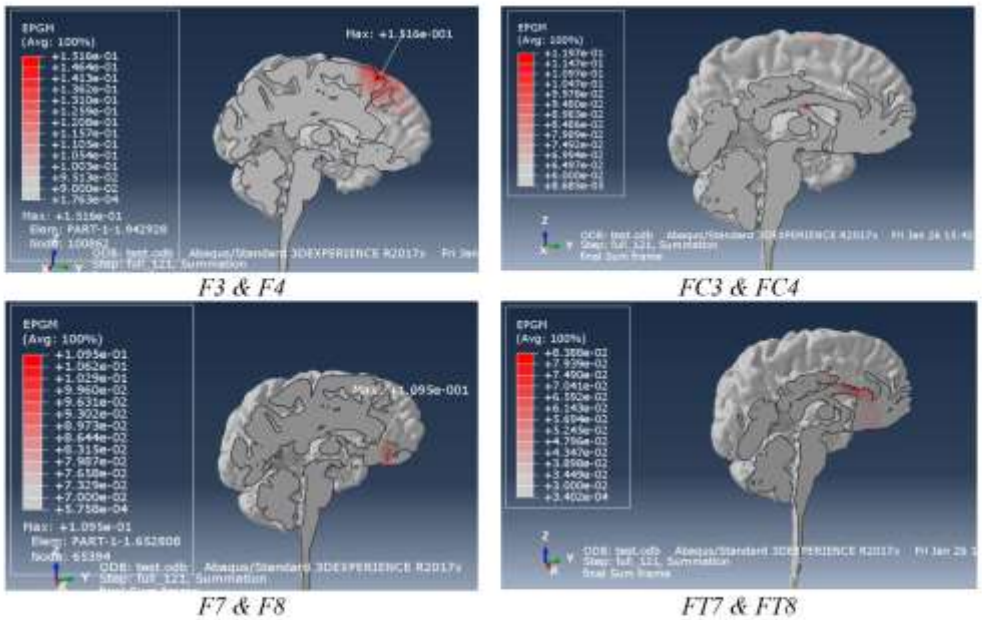


Figure 8: Localization of the peak Electrical Potential Gradient value in Abaqus for different combinations of electrodes.

However, an even bigger advantage now comes from performing these 26 different electrical simulations (which are independent of each other) all in parallel, with an overall speedup of 26, thus **reducing simulation time for the 26 simulations from previously 33 hours down to 28 minutes, a speed-up factor of 70 just by using cloud resources.** With this achievement, now, the patient would just wait for the simulation results, while the doctor identifies the best electrode configuration, and fine-tunes the patient's remote control, **all now in an ambulant treatment, ready for the masses!**

CONCLUSION

In the recent times, the Life Sciences community has come together than never 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 and expensive brain surgeries such as in Schizophrenia and Parkinson's disorders.**

The huge **benefits** of the computational simulations are that (i) they predict the current distribution with high resolution; (ii) allow for patient-specific (personalized) and quantifiable treatment; (iii) facilitate parameter sensitivity analyses and montage variations; and (iv) clinician can devise the most effective treatment protocol for a specific patient; and finally, this new method has the potential to replace some of the painful/high risk and expensive brain surgeries such as in Schizophrenia and Parkinson's disorders, into an affordable and ambulant treatment.

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.

Case Study Authors – G. Umashankar, Karl D'Souza, and Wolfgang Gentzsch

Thank you for your interest in our free and voluntary UberCloud Experiment !

If you, as an end-user, would like to participate in an UberCloud Experiment to explore hands-on the end-to-end process of on-demand Technical Computing as a Service, in the Cloud, for your business then please register at: http://www.theubercloud.com/hpc-experiment/.

If you, as a service provider, are interested in building a SaaS solution and promoting your services on the UberCloud Marketplace then please send us a message at https://www.theubercloud.com/help/.

2013 Compendium of case studies: https://www.theubercloud.com/ubercloud-compendium-2013/
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The UberCloud Experiments received several international Awards, among other:

- HPCwire Readers Choice Award 2013: http://www.hpcwire.com/off-the-wire/ubercloud-receives-top-honors-2013-hpcwire-readers-choice-awards/
- HPCwire Readers Choice Award 2014: https://www.theubercloud.com/ubercloud-receives-top-honors-2014-hpcwire-readers-choice-award/
- Gartner Cool Vendor Award 2015: http://www.digitaleng.news/de/ubercloud-names-cool-vendor-for-oil-gas-industries/
- HPCwire Editors Award 2017: https://www.hpcwire.com/2017-hpcwire-awards-readers-editors-choice/
- IDC/Hyperion Research Innovation Excellence Award 2017: https://www.hpcwire.com/off-the-wire/hyperion-research-announces-hpc-innovation-excellence-award-winners-2/
- 2018 - UberCloud Wins Multiple Awards: https://www.hpcwire.com/off-the-wire/ubercloud-wins-multiple-awards-for-hpc-innovation-and-best-use-of-hpc-in-the-cloud/

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