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Precision of Lead-Point with Support Vector Machine Based Microelectroneurosensor Recording of Subthalamic-Nucleus Neurons of Human Brain During Deep brain Stimulation in Parkinson`s Disease

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Abstract - *Though, even though, structural organization provides some evidences and indications (the clues) as to what capacity might be the function of basal-ganglia (BG) circuits in Parkinson`s Disease (PD) patients, albeit the inference of function from anatomical structure is exploratory or investigative. One investigative approach to studying-the-function of an area of the central nervous system (CNS) in particular substantia-nigra (SN) of the human-brain is to acquire the subthalamic-nuclei (STN) neurons with a vector supportive machine "extracellular micro-electro-neuro-sensors recording (MER) system" in locally anesthetized PD patients. Other approaches involve inferences of neuronal-signaling from imaging studies of blood-flow and metabolism, or of changes in gene expression. By sampling the signal of a part of the human-brain during behavior, one can gain some insight into what role that part might play in performance-behavior. Neurons within different basal ganglia nuclei have characteristic baseline discharge patterns that change with movement. In this study, we followed the MER approach with vector-support machine learning. We preprocessed the MER signals for improving signal-to-noise ratio (S/NR). In our study, we find that MER gives proof of correct-positioning of microelectrode (microchips), and ensures precise-identification of STN and confines and establishes its exact coordinates in a more scientific-objective way. MER boosts the safety, accuracy and efficacy of DBS-chip implementation. Hence, MER confirms presence of anomalous STN neurons. MER can confirm clear position of microchip (microelectrode) and strengthen the confidence of the neurosurgeons that they are in the right-target. Availability of MER results in a vast data vis-□-vis functioning on neurons positioned-deep in the brain may further help in extrication esoteric — cryptic of brain.*

Key Words: *Deep Brain Stimulation (DBS); Microelectroneurosensor or Microelectrode Recording (MER); Subthalamic-nucleus (STN); Parkinson's disease (PD)*

1. INTRODUCTION

Human brain is a complex dynamic organ encompass ensemble of billions of trillions of neuronal cells. Neural signals of such brain cells are massively curved data streams control information about the understanding brain activity. Specifically, movement and movement intentions are encoded in the motor cortex, cerebral cortex and brainstem regions. Basal ganglion is central area of the brain with distinct circuits that link many parts of brain (Figure 1).

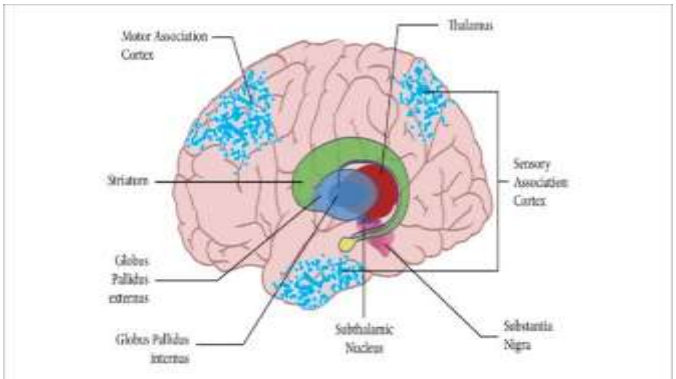


Figure 1. The cortical-surface with an overlay of the basal-ganglia and thalamus.

The blue-dots on the cortical-surface signify the neuronal activity for a notional-emulation. This emulation is conceptual and intangible and the active neural-net-works (NNWs) instantiating the emulation are in higher-level motor and sensory association areas of the brain.

Its functional architecture is parallel in nature and characteristic of the organization within each individual circuit. It is interlinked with several neurons of cerebral cortex, thalamus, brainstem, and at several other areas of brain coupled with a variety of functions, such as motor learning, control-of-voluntary motor movements, procedural-learning, routine behaviors' of habits (bruxisms), eye-movements, action, cognition, emotion and most of the higher order perceptual abilities and motor controls and thoughts, language and problem solving [1]-[41], etc.

Experimental—studies to date [1]-[41] shown that the basal-ganglia exert an inhibitory influence on a number of motor neuron systems, and that a release of this inhibition permits a motor neuron to become active. The behavior

switching that takes place within basal ganglia is influenced by voluminous signals (massive data) of motor neurons from many components of the brain, including prefrontal cortex which plays a fundamental key role in executive functions. Its functional architectures parallel in nature, consists of sub-cortical-nuclei (SCN) in the brains of vertebrates situated at forebrain, caudate nucleus, putamen, globus pallidus and substantia-nigra (SN) (Figure 1 above) that are complex-neural-structure correlated with motoneuron function. It receives afferents from motor cortex and drives efferent's to thalamus cortex, controls motorneuron impulses from cortex to spinal-cord.

1.1. Design of the Human Motor Control System

The motor control system is a complex neural system with a myriad of pathways. One of its output pathways consists of the ensemble of α-motoneurons which activates the skeletal muscle-fibres. One way to study this output pathway in humans is to record the 'motor unit potentials' ("if a sufficiently strong stimulus, e.g., if an electric shock is applied to whatsoever to the part of a nerve or muscle fiber, it will give rise to an excitation, the main manifestation of which there is a great rapid varied variation of the membrane potential (due to change in the ion permeability of the membranes), which is known as the action-potential' can be registered by two methods: by means of sensors (electrodes) applied to the outer surface of an extra-cellular fiber, and by means of a intra microelectrode introduced into the protoplasm—intracellular associated with firings of individual motor units (MU's) or motor neurons by means of indwelling ('needle' or 'wire') electrodes placed in a target and/or specific muscle [12]. A block diagram of the human motor control system is shown (Figure 2).

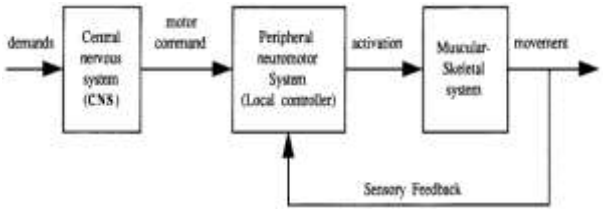


Figure 2. A simplified block diagram of the human motor control system

The control of voluntary movements has three stages: planning, initiation and execution, which are performed by different brain regions. The planning of a movement begins in the cortical association areas, while the actual initiation of the movement occurs in motor cortex. In addition to cortical association areas, the BG and Cerebellum are involved in planning. Just as a FYI at this stage, I came across this animation of basal ganglia circuitry (including neurotransmitters/ lesions) is useful for researching Parkinson's disease. The alpha motor neurons in the brainstem and spinal cord are responsible for the execution of the movement. The cerebellum is responsible for fine-tuning movements; therefore it is involved in both planning and execution. A simplified design of the block diagram of the human motor control system is shown in Figure 3.

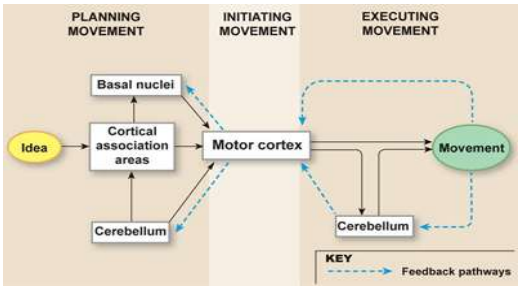


Figure 3. Design of the Human Motor Control System

A slightly different way of considering the human motor control system circuit design is shown in Figure 4.

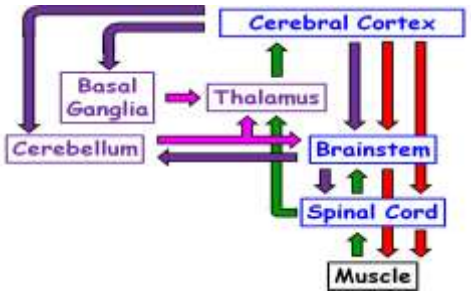


Figure 4. Human motor control system circuit design

The primary motor pathway is from the cortex to the brainstem (corticobulbar tract) and spinal cord (corticospinal tracts). The lateral corticospinal tract conveys commands to the body (think playing the piano, tap dancing). The anterial corticospinal tract controls trunk muscles (think using a hula-hoop, "core" exercises). All 3 levels (cortex, brainstem and spinal cord) receive inputs from sensory receptors. In addition, feedback loops involving two additional independent subcortical systems (the Cerebellum and the BG) modulate activity at the brainstem and cortical levels. Note that there are no direct connections between the cerebellum and the basal ganglia and the final common pathway .Thinking of motor control as having 3 separate levels is useful when trying to understand spinal shock, and decorticate and decerebrate rigidity

1.2. Brain

Brain is a dynamic organ [12], [39]-[41]. It continuously adapts in response to changes in the external and internal environments. This property of the brain, called brain plasticity, facilitates recoveries from and damages to the brain, spinal cord or peripheral nerves injuries. One of the goals of the research is to understand how organization of the somatosensory and the motor areas of the brain are affected by spinal cord damages and/or injuries. This

knowledge will help understand how ability of the brain to undergo reorganization can be used for better recoveries from damages and injuries [39]-[41]. Due to spinal cord injuries, sensory information from parts of the body below level to the lesion does not reach the brain. Neurons in the somatosensory cortex that no longer receive sensory inputs get reactivated by the remaining uninjured inputs. Such reorganization can facilitate behavioural recoveries and also affect perceptual abilities and motor control leading to phantom sensations [39]- [41]. So, our research is also focused on determining the nature and extent of such reorganization, and the properties and mechanisms that underlie such changes. These issues can be addressed using *in vivo* models of partial spinal cord injuries. In order to help recoveries from spinal cord injuries we are investigating use of stem cells and neural precursor cells. We are also developing brain-machine interface devices to help patients with injuries [40], [41].

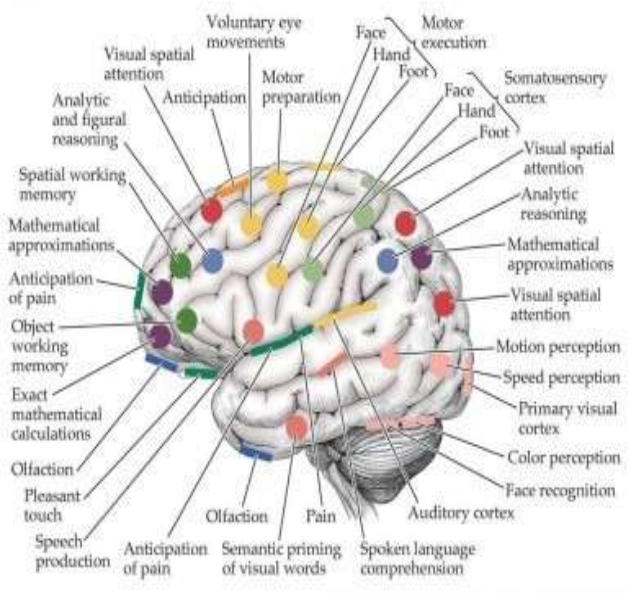


Figure 5 Behavioral science, psychology, social work and mental health information (excerpted from modern research methods, real psycho. tumblr.com).

Human brain is a complex dynamic organ consisting of billions of trillions of neuronal cells. The substantia nigra is an important organ of the brain. Basal ganglion (BG) is an important part of the brain which is parallelly connected circuitry with substantia-nigra SN). When SN stops functioning, the Parkinson problem arises due to dopamine (a chemical messenger) receptors (cells) damage and also injury and/or damage of the BG. Therefore, one approach for studying the function of substantia-nigra (SN) is to acquire the STN neurons with microelectrode recording (MER, also called micro-electro-neuro-sensor-recording). Brain scientists [17], [23], [24] developed the deep brain stimulation of the subthalamic nucleus (STN-DBS), a stereotactic-functional neuro-surgical procedural technique that reduces tremors and restores motor function in patients with advanced Parkinson's disease.

Two Nobel Scientists, namely, Mahlon R DeLong at the Emory University School of Medicine (Emory, America), formulated a new model for the brain's circuitry and exposed a fresh target for this illness [17], and simultaneously Alim Louis Benabid at the Joseph Fourier University (Grenoble, France) devised an effective and reversible intervention that remedies neuronal-misfirings [23], [24]. The duo invented the development of deep brain stimulation (DBS) of subthalamic nucleus (STN) - a surgical method for Parkinson`s Disease to restore and increase motor function. Benabid designed and developed and employed the MER system for STN-neuronal data acquisition (i.e., STN signal recordings) especially for the identification of the "signal-patterns" (or "signatures") with which he visualized the complete STN thoroughly [12]. The problem with targeting subthalamic nucleus is that it is a small diamond shaped biconvex lens structure and not clearly identified on the MRI due to lack of contrast between the STN and the surrounding structures [8], [9]. The STN can be visualised on the MRI but other methods such as Lozano's technique where a position 3 millimetre (3 mm) lateral to the superolateral border of the red nucleus is targeted have been studied and found to be effective areas for stimulation [10]

As the MRI techniques are not absolutely perfect, use of electrophysiological techniques such as microelectrode recording – the MER system ("micro-electro-neuro-signal-recording system) from the subthalamic nucleus as well as intra-operative stimulation have helped in visibly differentiating the STN [5]-[12], [13]-41]. MER can identify subthalamic neurons by their characteristic bursting pattern and their signals clearly identify the nucleus form the surrounding structures [12], [41]. On table stimulation is studied to ensure that there is optimal-benefit with the least dyskinesias (side-effects) and this is the final test to ensure the correct targeting of the STN.

1. Literature Survey

1.1. Parkinson`s Disease

Parkinson's disease (PD), perhaps best known for its tremor, slows and stiffens movements. From the 1940s through the 1960s, surgeons battled the ailment by annihilating regions of the brain, chosen more by heuristics trial and error method than by a clear understanding of neural-misbehavior. The so-called lesions created by these operations often delivered spectacular and stable effects, counteracting the tremor and, to some extent, other features of PD. Even slight misplacement, however, brought complications rather than benefits. Such damage was permanent, as dead tissue could not be revived.

The 1960s broke open a new treatment for PD and largely dismissed the surgical era. Scientists established that the malady arises from insufficient quantities of the neurotransmitter dopamine in an area of the brain that controls movement, the basal ganglia. By the end of the decade, the late George Cotzias (Lasker Clinical Medical Research Award, 1969) had reported dramatic improvements in PD patients who received a carefully tuned regimen of oral L-dopa, the metabolic precursor of dopamine. The medication honeymoon, however, can wear off. After long-term administration, the drug induces severe involuntary movements in some individuals. Only small windows of the day remain in which patients experience neither PD features nor their manifestations (so called the signs and symptoms) nor these disturbing effects.

1.2. Provocative pathways

When DeLong began his experimental research, in the late 1960s, the basal ganglia had been implicated in movement, particularly because defects there were associated with illnesses such as PD in which motor disturbances (like turbulent fluctuations and/or oscillations in the membranes) feature prominently and significantly. Little was known, however, about how exactly the BG contribute to movement. To find out, DeLong implanted small tiny microchips (i.e., micro-electro-neuro-sensors or/ microelectrodes into monkeys' brains and measured the activity of specific neurons in the basal ganglia while the animals performed trained actions. He thus matched neurons with tasks; some influenced, for instance, the direction, size, or speed of arm, leg, or facial movements. In this way, he mapped out the organization of the so-called motor-circuit (Figures 6 and 7). Figure 6 shows the virtual picture of the DBS implanted sensors in the PD brain

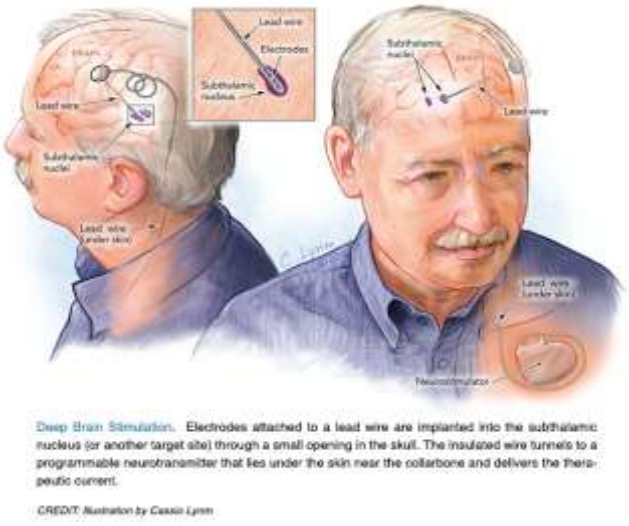


Figure 6: virtual picture of the DBS implanted sensors in the PD brain

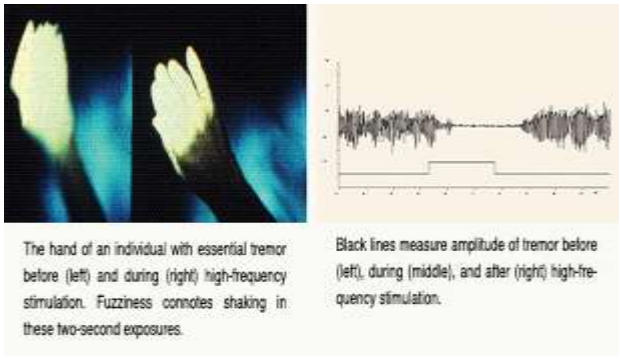


Figure 7. Essential tremor and its amplitudes

Based on his own experimental-investigative work and that of others as well as existing anatomical—structural information [17]-[23], [24]. DeLong proposed a model in which basal ganglia neurons operate in separate circuits. Multiple pathways originate from distinct centres' in the cerebral cortex, run through the basal ganglia, and wind up back where they started; the circuits work alongside one another and allow parallel processing of emotions, thoughts, and motor functions. This work provided insights into the well-established observation that cognitive and emotional problems accompany many motor disorders that stem from basal ganglia failings. Furthermore, the findings supplied a new framework for exploring how BG components malfunction in various illnesses, including PD. Although dopamine loss clearly causes the disease's motor perturbations, the associated changes in basal ganglia activities were unclear. DeLong's model—which included detailed maps of stimulatory and inhibitory signals through the basal ganglia—offered ideas. For example, the final stop in the motor circuit of the basal ganglia is a structure that sends restraining orders onward, thereby suppressing other parts of the motor system. Anything that causes superfluous activity at that site might generate the symptoms that characterize PD.

1.3. From Addicts to Insights

In the early 1980s, sporadic outbreaks of a syndrome that mimics Parkinson's disease started occurring among drug addicts and scientists traced it to a chemical, MPTP, which was contaminating some batches of "synthetic heroin." Administration of the compound to monkeys reproduced the key clinical and pathological features of PD, and thus offered a powerful new tool for studying the illness. DeLong seized upon the opportunity. A part of the basal ganglia called the subthalamic nucleus drives the inhibitory output signal, and in 1987, DeLong reported that MPTP triggers neurons in the subthalamic nucleus of monkeys to fire excessively. Perhaps, DeLong reasoned, the over exuberant signals quash motor activity in PD. If so, inactivating the subthalamic nucleus might ameliorate some of the illness's worst symptoms. He then did an experiment that would transform PD treatment subsequently. He administered MPTP to two monkeys; as

usual, they gradually slowed down until they sat motionless, their muscles stiffened, and they developed tremors. DeLong then injected a second toxic chemical that inactivated the subthalamic nucleus. Within one minute, the animals began to move. Gradually, their muscles loosened and the tremors ceased. These findings strongly supported the hypothesis that hyperactivity in the subthalamic nucleus underlies PD symptoms.

1.4. High Frequency, High hopes

Across the Atlantic, Benabid [ ] had also been tackling neurological disorders, and he was perturbed. In a throwback to the pre-L-dopa era, the trickiest patients—those who did feebly with long-term pharmaceutical treatment—would wind up in the operating room. Benabid craved a new tool—something safer that would quiet the most disabling symptoms of PD. One day in 1987, he was about to create a lesion in a person with essential tremor, a condition that causes trembling in various parts of the body. He was targeting a component of the thalamus that contributes to tremors. As usual, the patient was awake so Benabid could test whether he had located the right tissue; he inserted a probe into the spot that he intended to lesion and sent an electrical-pulse to ensure that perturbing this site did not generate undesired-effects. Usually he delivered 50 Hz frequency, but he decided to find out what would happen if he augmented the frequency. Just below 100 Hz, something unexpected occurred: The tremor stopped. The patient became tranquil; Benabid thought that he had caused unintended muscle-contraction. He switched off the stimulus and contrite for his gaffe—erratic variable. Bur the patient told him not to contrite, as it was the first time in many years that his hand had not shaken (Figure 7). Benabid repeated the procedure, with the same outcome. Furthermore, when he withdrew the current, the tremor recurred. The effect, therefore, was reversible. Benabid realized he was onto something exciting. Deep brain stimulation had been used for more than two decades to treat pain, but no one had dialled up the frequency. Later that year, he tried the same approach for PD patients. In addition, he implanted a device that was on the market for pain relief and delivers constant stimulation. Some of the individuals benefited from the procedure, and no complications occurred. In 1991, Benabid reported that high-frequency stimulation could be deployed bilaterally in people with essential tremor and PD; this strategy reduced tremor on both sides of the body. The gains were long lasting, and adverse effects were mild; furthermore, any undesired outcomes could be reversed by reducing stimulation.

Although the technique quelled tremors, Benabid knew that this symptom was not the one that most debilitated people with PD. Perhaps high-frequency stimulation of brain areas other than the thalamus (i.e., the subthalamic nucleus) would alleviate the more troublesome aspects of the illness such as slowness of movement and rigidity, he reasoned. In this state of mind, Benabid read DeLong's report that damage to the subthalamic nucleus wipes out multiple symptoms of PD in animals. This site was not an attractive target: Lesioning procedures and spontaneous lesions had established decades earlier that, when things went wrong, violent flailing could result. By that time, however, Benabid had performed high-frequency stimulation of the thalamus and other brain regions' in more than 150 patients. He was confident that he would cause no harm in the subthalamic nucleus; if necessary, he could remove the electrode. In 1995, Benabid reported results from the first humans who received bilateral, high-frequency stimulation of the subthalamic nucleus—three people with severe PD. The treatment suppressed slowness of movement and muscle rigidity. Eight years later, he confirmed and extended these results in a study of individuals who had undergone the procedure five years earlier. The surgery restored motor skills, suppressed tremor, and improved the ability to conduct normal activities of daily living. Furthermore, people were able to slash their dosage of L-dopa and related medications, which reduced associated complications. In 2002, the US Food and Drug Administration (FDA) approved high-frequency stimulation of the subthalamic nucleus for treating advanced Parkinson's disease. The method is not a cure, and it does not reverse all aspects of the malady. In particular, speech and cognition continue to decline. Many questions remain about the mechanism of this intervention. It might jam or replace inappropriate circuit activity. Regardless how it works, surgeons are using high-frequency deep brain stimulation to combat an ever-growing number of sites and diseases: essential tremor, dystonia—a condition of involuntary muscle contractions—and even psychiatric illnesses. The FDA approved its use for obsessive-compulsive disorder in 2009, and scientists are investigating applications for drug-resistant depression and Tourette syndrome. Through their open-minded explorations and willingness to challenge dogma, Benabid and DeLong have delivered extraordinary medical innovations to humankind. By reaching deep into the brain, they have soothed some of the most troubling conditions that corrupt it.

Parkinson’s disease is the second most common neurodenerative disease which is characterised by the convolution of tremor, rigidity, Bradykinesia and postural instability. The search for optimal cure is on for the past 2 centuries since the time it was first discovered by James Parkinson [1]. The main pathology of Parkinson’s disease is present in the nigrostriatal system which is characterised by the degeneration of the dopaminergic neurons in the substantia nigra pars compacta. Substantia nigra pars compacta is a part of the basal ganglia which modulates the cortex and helps in fine tuning motor activities. There are two dopaminergic pathways involved form the striatum to the thalamus and the cortex- direct pathway which leads to stimulation of the cortex and the indirect pathway which inhibits the cortex. The dopaminergic supply from the substantia nigra pars compacta acts by D1 receptors which activate the direct

pathway and the D2 receptors which inhibit the indirect pathway. Absence of these neurons leads to an increased firing from the subthalamic and globus pallidal interna neurons which lead to increased inhibition of the thalamic neurons and cortex and overall reduced movement. [2] Figure 8 depicts the normal functioning of basal ganglia and the abnormality in idiopathic Parkinson's disease.

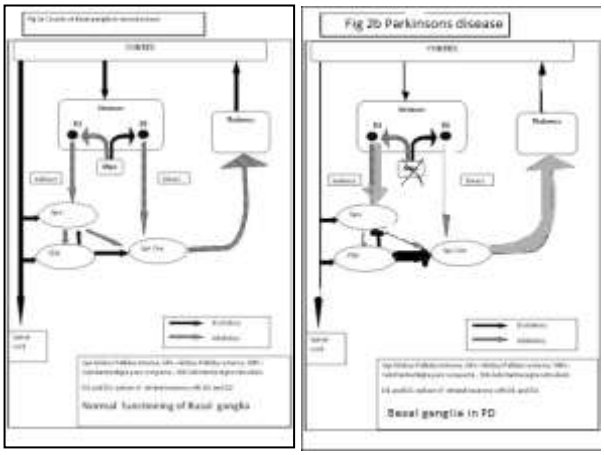


Figure 8. Normal control functioning of basal ganglia and the abnormality in idiopathic Parkinson's disease.

The advent of treatment with initial levodopa followed by the armamentarium of various drugs but the medical treatment is fraught with appearance of various side effects such as dyskinesias (side-effects) and on-off phenomenon. The dopaminergic drive in normal patients is a continuous one and oral medications however cannot completely mimic the normal state with drug concentrations changing from trough to peak levels based on the time of consumption. Initial ablative surgeries performed during the 1950s targeting the globus pallidus interna and thalamus improved with the onset of stereotactic surgery and deep brain stimulation techniques. This involves inhibition of the brain structures with high frequency oscillations usually of the frequencies ranging from 130 to 190 Hz. This high frequency inhibition of neurons in two structures –subthalamic nucleus and globus pallidus interna has improved symptoms in patients with Parkinson's disease and has become the standard of care in advanced disease. [3,4] Further, on head to head comparison of the therapeutic options, a recent study has shown that DBS is more effective than the best medical therapy in improving "on" time without troubling dyskinesias by 4.6h/day, motor function in 71% vs 36% on medical therapy, and in quality of life, 6 months after surgery.[5,6]. Of the two, subthalamic nucleus (STN) stimulation is associated with more drug reduction compared to globus pallidal stimulation. Subthalamic nuclei deep brain stimulation (STN DBS) involves placing two leads, one in each subthalamic nucleus with a pulse generator placed under the skin on the chest. The surgery is performed under stereotactic guidance –i.e., a stereotactic frame is placed on the head and the nucleus is identified on the magnetic resonance imaging (MRI) of the brain and the co-ordinates are obtained in the vertical and the horizontal planes, then with the help of these co-ordinates the leads are placed through a small hole on the scalp. For optimal therapeutic efficacy of DBS, it is imperative to have accurate electrode lead placement. [7] A small deviation in the electrode positioning may cause it to be misplaced in the surrounding structures such as the corticospinal tract, red nucleus, ocumulotor nerve and other structures. Improper targeting may lead to various side effects such as speech disorders, visual deficits with diplopia (the double vision), ocular deviations or motor stiffness [7]-[11].

1.5. Support Vector Machine Based Microelectroneurosensor Recording (MER) Analysis

One of the most effective treatments for PD is deep brain stimulation (DBS) of the subthalamic nucleus (STN). The procedure involves the surgical implantation of stimulating electrodes into the STN and provides a unique opportunity to record *in vivo* the related neuronal activity, through microelectrode recordings (MERs) of high spatio—temporal resolution. However, the optimal placement of the stimulation electrode continues to be a challenge, possibly due to the neuroanatomic variability within the STN sensorimotor area [7].

Microelectroneurosensor or microelectrode recording (so called MER) have been used before to enhance our understanding of how STN neurons function and classify possible mechanisms for DBS in PD. MER-based algorithms have also been developed to categorize and detect the sensorimotor area within the STN by using both the high and low-frequency content of the recorded signals [21]. The high frequencies of the MER signal include both the electrical action potentials from neurons located closest to the electrode tip (typically at a distance of less than 100μm –300μm) as well as smaller sub-noise level spikes from nearby neurons known as "background-unit-activity" designated as BUA. The combinations of these two signals are referred to as "multiunit-activity" referred to as MUA. The lower frequencies of the MER signal correspond to the local field potential called LFP potentials, which reflect the cumulative activity of a population of neurons within a better diameter from the electrode tip (around 0.5mm–3mm). So far, most of the MER based analyses of the STN have focused by a series of scientists [7]-[21] on the gross automatic detection of the STN borders [26]-[28].

Jose et.al [42] studied in a total of 118 PD patients with advanced state of PD and showed that it is possible to estimate the human labeling of DBS microelectrode-recordings of STN region, with an average accuracy of least 92.8% using multinomial logistic classifier, trained with the first 25 principal components (PCs) of the extracted features, from the dataset composed of 1000 signals from 4 PD patients.

Amirnovin et al [11], [18] conducted the study on microelectrode-signal-recording (MER) in targeting subthalamic-nuclei (STN) in 40 Parkinson candidates (i.e., Parkinson diseased subjects). The predicted location (with the preoperative deep brain stimulation with the magnetic resonance imaging, DBS MRI) was used in 42% of the cases; however, in the remaining 58% of the cases it was modified through MER (MER with STN-DBS). By applying MER technique, an average pass through the subthalamic-nucleus (STN) of 5.6 mm was attained and evaluated to 4.6 mm if the central-tract was selected as per the MR-imaging. Application of microelectrode-recording augmented the path through the subthalamic-nuclei by 1 mm, increasing the likelihood of implanting the microelectrodes with the deep brain stimulator squarely in the STN, which is relatively an elfin or petite target. Bour et al [21] studied the outcome of MER in 57 PD patients with STN-DBS and deduced the following inferences. For the subthalamic-nucleus, the central-trajectory was chosen for inserting-microelectrodes in 50% of the cases, the channel selected had the longest segment of STN with the MER activity in 64% of STN DBS cases. In case the central electrode was selected for embedding the innocuous micro electrode, this was also the channel with the best microrecording in 78% for STN. The final electrode-position or electrode-point in the STN, if not placed in the central-channel, was often more lateral than medial to the computed—evaluated target ten percent (10%, i.e., 10 patients / 98 patients) lateral; six percent (6%, i.e., 6/98) medial and frequently more anterior 24% (i.e., 22/98) than posterior 10% (10/98). The mean and standard deviation (SD) of the deepest contact-point with respect to the magnetic resonance imaging (MRI)-based target for the STN was 2.1 mm ± 1.5mm.

The goals of our study was to unveil the significance of intraoperative microelectrode recordings of neural signals and elucidate their predictive role in terms of the response to STN-DBS, to identify the MER signal characteristic discharge patterns (or signatures) of STN that correlate with improved symptoms of PD as well as movement-related activity (MRA), to experimentally investigate the correlation of microrecording with the final-tract chosen during bilateral subthalamic-nuclei deep brain stimulation.

The best trajectory was considered as the one with the longest STN recordings and detectable MRA and finally to quantify the efficacy of MER with STN DBS using principal components based tracking method. The surgical procedure for placing the stimulating microelectrode in the track MERs has a 1-mm precision, both horizontally and vertically [9]. Intraoperative current stimulation (60μs pulse width, 130 Hz frequency, 0.5- to 5.0 volts amplitude) verified the short-term clinical improvement and identified possible side effects.

Although anatomical structural organization provide some clues as to what might be the function of basal ganglia circuits in PD patients, albeit the inference of function from anatomical structure is exploratory. One investigative approach to studying-the-function of an area-of-the-CNS in particular substantia-nigra (SN) is to acquire the STN neurons with extracellular MER in locally anesthetized PD patients [12]-[15]. Other approaches involve inferences of neuronal signaling from imaging studies of blood flow and metabolism, or of changes in gene expression. By sampling the signal of a part of the brain during behavior, one can gain some insight into what role that part might play in behavior. Neurons within different basal ganglia nuclei have characteristic baseline discharge patterns that change with movement [16], [17]. In this study, we followed the MER approach. Keeping this in mind, a retrospective study was carried out at Tertiary Care NIMS Hospital and research center (Hyderabad, Telangana State TS, South India) with a dedicated movement disorder unit in Neurology department of NIMS and biomedical eng. Twelve subjects with diagnosis of PD as per United Kingdom Parkinson disease society brain bank criteria are included in the study.

In regard to the PD symptoms prediction and feature extractions, Kyriaki Kostoglou, et.al [8] hypothesized that a data informed combination of features extracted from intraoperative MER which can predict the motor improvement of PD patients undergoing DBS surgery. Sang Jin Kim, et.al, [9] hypothesized that STN-DBS will improve long term potential (LTP) like plasticity in motor cortex of PDs. Zuan He [11] hypothesized that DBS works by reducing the level of synchronization among the neuronal firing patterns within the target site and proposed a desynchronization-based closed strategy for the generation of DBS input (nonlinear delay feedback stimulation NDFS). Sabato S, et.al. [20] Investigated the therapeutic mechanisms of HF DBS in PD by developing a computational simulation model of cortico-BG thalamo-cortical loop in controls and Parkinson conditions under the effects of DBS at some frequencies. Further they found that the DBS infused in the loop educes subtle neural changes that travel along multiple pathways with different latencies meet in striatum. In a US based study [20], [21], high frequency (HF) DBS is clinically recognized surgical therapy to treat Parkinsonian movement disorders, but its mechanisms remain hazy. Recent hypotheses imply that the therapeutic value of HF-DBS stalks from enhancing the regularity of the firing patterns in basal ganglia. The main objective and utilization of the of the vector VSM machine based MER system is to characterize the STN neurons/neural signals of the subcortical-structures of the human brain during DBS for the classification purposes during experimental investigations in our study for making diagnostic analysis and to deduce the inferences to be drawn in our proposed work.

2. Aims and Objectives

The aim is to study the correlation of computer aided support vector machine based microelectroneurosensor/ microelectrode recording (MER) system with the final tract chosen during bilateral subthalamic-nuclei deep brain stimulator (STN-DBS) performed at a specialized centre in South India.

3. Methods

A retrospective study was carried out at a tertiary care hospital with a dedicated computer science and biomedical engineering and movement disorder unit from South India. 46 patients with diagnosis of PD as per United Kingdom Parkinson disease society brain bank criteria were included. All the patients were willing to undergo the procedure and fulfilled the following criteria to be eligible for STN-DBS i.e., they had disease duration of 6 years or more, good response to levodopa, able to walk independently in drug "on" state and had normal cognition. All PD patients who were wheelchair or bed bound, had dementia or severe psychiatric disturbances were excluded.

3.1. Computer Assisted Stereotactic Functional Neurosurgery

3.1.1. Magnetic Resonance Imaging (MRI) Targeting

The problem with targeting subthalamic nucleus is that it is a small biconvex structure and not clearly identified on the MRI due to lack of contrast between the STN and the surrounding structures. (8,9) The STN can be visualized on the MRI but other methods such as Lozano's technique where a position 3 mm lateral to the superolateral border of the red nucleus is targeted have been studied and found to be effective areas for stimulation. [10] As the MRI techniques are not absolutely perfect, use of electrophysiological techniques such as microelectrode recording from the subthalamic nucleus as well as intra-operative stimulation have helped in clearly demarcating the STN.

Microelectrode recording can identify subthalamic neurons by their characteristic bursting pattern and their signals clearly identify the nucleus form the surrounding structures. On table stimulation is studied to ensure that the there is optimal benefit with the least side effects and this is the final test to ensure the correct targeting of the STN. All these techniques are normally used in combination during targeting, although the individual role of each modality is still unknown

3.1.2. Stereotactic Functional Neurosurgery

Surgery was performed in all by a qualified neurosurgeon. Stereotactic functional targets were acquired using a specialised system with a stereotactic frame Cosman Roberts Wells (called CRW) which has a luminant magnetic resonance localiser. The targeting was performed according to Lozano's technique – 2mm sections are taken parallel to the plane of anterior comissure-posterior commissure line and at the level with maximum volume of red nucleus, STN is targeted at 3 mm lateral to the anterolateral border of red nucleus.

The co-ordinates are entered into stereo-calc software which gives the co-ordinates of the STN. Neuro navigation software –Framelink is also used to compute the course of the microchips (the electro-neuro-sensors, i.e., electrodes) and to avoid vessels. The surgery was performed with two drawl or burr holes on the two-sides of the PD brain, i.e., the PD brains right hemisphere (BRH) and left hemisphere (BLH) based on the co-ordinates. Five channels are introduced with the central channel representing the MRI target while medial (nearer the centre) and lateral (away from the centre) are placed in the x-axis while anterior(front) and posterior (back) are placed in the y-axis to cover an area of 5 mm diameter.

3.2. Deep Brain Stimulator

A number of advances have been taken lay in the field of neuromodulation especially for neurodegenerative advanced idiopathic Parkinson`s disease (PD) which includes investigating novel structural-targets, humanizing-pioneering and frontier-technology. At present, subthalamic-nuclei (STN) are the best and key-target for PD-surgery. For this malady, deep brain stimulation (DBS) is the well suited therapy for cardinal motor-symptoms detection, principally reducing-tremors and motor-fluctuations and restoring and increasing the motor functioning. DBS is a procedure during which an electrode is surgically implanted in the brain. The electrode is connected to a wire, which sits under the skin and terminates at a neurostimulator [Figure 9].

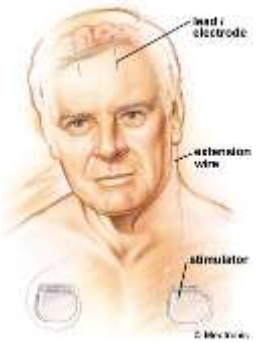


Figure 9. DBS microelectroneurosensor (microelectrode) and the neurostimulator

The neurostimulator contains a battery operated current source that injects current to the tip the electrode. The current impulses can be targeted in such a way that they are able to alter the electrical activity in the diseased brain to alleviate some of the motor symptoms in Parkinson`s and also to suppress seizures in Epilepsy patients (i.e., epileptic seizure patients). Basically, DBS is a

neurosurgical treatment that stimulates the brain with electrical signals, is applied to treat PD and an ever-increasing list of neurological disorders. Despite growing numbers of applications, DBS is at a virtual technological languish owing to several features: some degree of choice of stimulus waveforms, ability to stimulate on a sole position with bungling use of battery power (cause "energy is a constraint resource in battery"). The solitary acceptable key in input is a periodic or sporadic train of quadrangle pulses applied in an extremely tiny region of the brain (a few millimetre`s). Even though some degree of customization and custom –built program is allowable (e.g., change of pulse width, frequency, amplitude, etc), the resultant signals—waveforms hog-tied to generate—produce a ample selection of controlled responses from the targeted neural system, restraining the patient's behaviours. It is likely that the curative-impact of such steady periodic stimulation stems from restoring the pathological rhythmic basal ganglia (BG) output seen in PD with stimulant—tonic, high frequency (HF) firing. This augmented movement stops neurons from modulating action in their adjoining neighbouring structures producing an "information-lesion" within the vicinity. HF stimulation provides medical benefits (PD motoric-symptoms reversal) when the targeted region is immensely pathological, yet comes amid major charges: prolonged physical programming of the signal, veto adjustment to patient's needs, frequent surgical battery proxy, and prevalent sway to near cognitive loops with probable adverse face effects.

The following study gives an interesting insight into pathophysiology if electrical stimulation with deep brain stimulator.

All this year's Louis Benabid in his experiment stressed that continuous stimulation does not damage the cells. Hence, DBS has no side effect.

The above study emphasizes that continuous stimulation reactivates cells and prevents apoptosis. Hence it has potential benefits of altering the disease process [22]. This has been observed clinically in our patient population. Patients who underwent DBS had a longer survival and better quality of life compared to their counterparts who had medical management in only.

3.3. Microelectroneurosensor Recording (MER)

Intra-operative recording was performed in all 5 channels. All five micro-neuro-sensors are slowly passed through the STN and recording is performed from 10mm above to 10 mm below the STN calculated on the MRI. Stimulation of adjacent functional regions cause adverse effects like involuntary muscle movements. So, the raw and filtered STN signals with EMG involuntary muscle movements obtained through while observing the local field potential (EMG muscle-movements) during STN recording is shown in Figures 10 and 11.

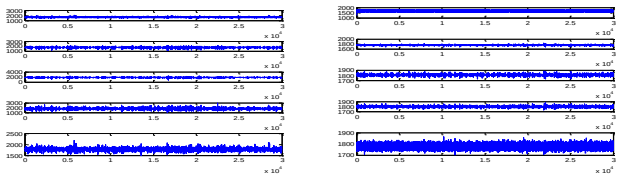
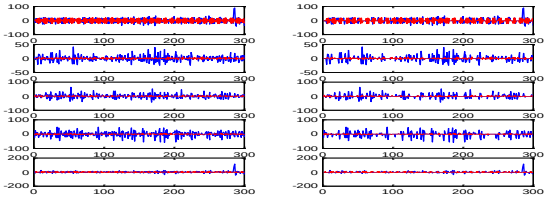


Figure 10. Stimulation of adjacent functional regions of involuntary muscle movement signals (the noised local field potentials). Their corresponding filtered STNs recordings are shown in Figure 11.



11. Filtered Observation of filtered Local field potentials during STN Recordings

STN IS identified by a high noise with a large baseline and an irregular discharge with multiple frequencies. Figure 12 shows the microelectrode recording which is obtained from the STN

Figure 12 –Picture of the microelectrode recording –the panel in the top left shows recording in a single level in a single channel; the panel in the bottom left shows the recording in the central channel over 11 mm and shows the typical firing pattern with irregular firing and broad baseline noted from -1.00 level; the top right shows the typical histogram frequency and the Fast Fourier

Transformation (FFT) graphs of a typical STN neuron; the bottom right shows the same in a linear fashion

The channel with maximum recording and the earliest recording were recorded on both sides. Intra-operative test stimulation was performed in all channels from the level at the onset of MER recording. Stimulation was done at 1mv, 3mv to assess the improvement in Bradykinesia (slowness of movement), rigidity and tremor. Appearance of Dyskinesias (side effects like non motor symptoms) was considered to be associated with accurate targeting. Side effects were assessed at 5mv and 7mv to ensure that the final channel chosen had maximum improvement with least side effects. Correlation was assessed between the aspects of MER and the final channel chosen in 46 patients (92 sides).

4.4 Machine Learning Techniques

We will be applying the artificial intelligence based machine-learning techniques in order to personalize the evidence-based DBS implantation procedure and we will be validating the DBS patients in the future work. Currently, the intraoperative STN localization is based on the neurologist's empirical assessment of the electrode location [26] and, hence, does not guarantee optimal motor improvement, given the neurophysiological and anatomical variability of the STN. The main goal of our study was to reveal the significance of intraoperative microelectrode recordings of neural signals and elucidate their predictive role in terms of the response to STN-DBS. We will be applying the principal components analysis, KL-transform for the data reduction and followed by the clustering methods for the classifying the clusters.

4. Results and Discussion

4.1. Results

Forty-six patients were included in this study with their mean age of 58.1 + 9.1 years with mean disease duration of 8.8 + 3.64 years. Out of 5 channels, STN microelectrode recordings were detected in 3.5 +1.1 on right side and 3.6 +1.04 on left side. Figure 13 shows the percentage of people with the number of channels showing microelectrode recording.

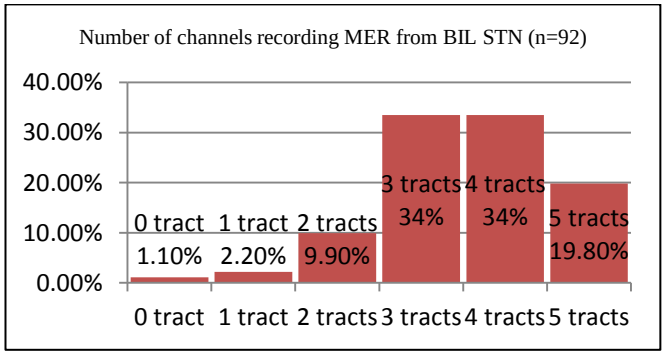


Figure 13. % of people with the number of channels showing microelectrode recording.

Final tract selected were most commonly central seen in 42.3% followed by anterior in 33.7%. Concordance of final tract with the channel having the highest recording was 58.7%, with channel showing maximum width of recording was 48% and with either was 64%. Absence of any recording in the final tract chosen was seen in 6.52%. Out of the six patients, one patient had no recording and lead was placed in central channel. Two patients had medial, 2 anterior and 2 central channels as their final tract. This was selected based on macrostimulation.

4.2. Discussion

We assessed the role of microelectrode stimulation in selection of the final channel. Compared to the anatomical localisation based on MRI where the final tract was seen only in 42.3% the microelectrode recording was associated with final channel in 64 %. This is similar to a previous study wherein by using MER, an average pass through the STN of 5.6 mm was achieved compared to 4.6 mm if central tract was selected as per imaging [11]. MER by itself is not a complete tool to clearly distinguish—discriminate the optimal target as the line of the DBS lead may not correspond to the axis of the STN. Further the impedance of the microelectrode may vary as they may be influenced by the brain tissue and may not show a clear recording. Still MER definitely confirms the clear position of the electrodes and bolsters the confidence of the neurosurgeons that they are in the target. Further the availability of microelectrode recording results in a vast data regarding the functioning on the neurons situated deep in the brain and may help in further untying mysteries of the brain.

5. Conclusion and Future Work

The aim of this study was to decipher the predictive role of intraoperative neural signals in STN DBS response and provide scientific insights by revealing the most informative intraoperative MER features and extracting STN MER "patterns (or signatures)" associated with UPDRS improvement. We investigated the MER with STN high frequency DBS in PD, recorded the STN neural signals. Absence of any recording from STN in the final tract selected was noted in 6/92 (-6.52%). Out of six patients, 1 had no MER recording in any of the 5 channels and lead was placed in central channel. Two had medial, 2 anterior and 2 had central channels as their final tract. This was selected based on macrostimulation. In our study, we find that MER gives proof of correct-positioning of microelectrode, ensures accurate detection of STN precincts and determines its exact coordinates in a more objective way. MER enhances safety, accuracy and efficacy of DBS electrode implementation. Thus, MER confirms presence of abnormal STN neurons. Unperturbed MER definitely can confirm clear position of electrodes and bolsters the confidence of the neurosurgeons that they are in the target. Availability of MER results in a vast data regarding functioning on neurons situated deep in the

brain may further help in untying mysteries of brain. This study correlated MER signal multiunit activity features with DBS improvement. All this year's Dr Benabid in his experiment frazzled that incessant stimulation will not injure the cells. Therefore, DBS has no side effect. The above study emphasizes that continuous stimulation reactivates cells and prevents apoptosis. Thus, it has potential benefits of altering the disease-process. This has observed in our population. Patients who underwent DBS had a longer survival and better quality of life compared to their counterparts who had medical management in only. Microelectrode recording is useful to confirm the right path but has to be taken in consideration with effects on macrostimulation.

Future work involves implementing the STN neurons signals data (STN data) with the machine learning techniques in particular principal component analysis and clustering methods. Since the existing open loop DBS devices have the following disadvantages, such as, oonly some degree of customization is allowed (e.g., - change of pulse-width, amplitude, and frequency), Inefficient use of battery (we all know energy is a constrained resource in the battery), lengthy manual programming of the signal, no adaptation to patients needs, and frequent surgical - battery replacements and hence adaptive closed loop devices will be used in which the DBS parameters are automatically changed without any manual intervention.. Presently open loop deep brain stimulators are used in Parkinson disease in our country.

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BIOGRAPHIES

Venkateshwarla Rama Raju received the B.Sc.(Hon`s) Degree in Electronics in 1984 from Osmania University, post B.Tech (Hon`s) Degree in Computer Science & Engineering(CSE) with Artificial Intelligence – Robotics & Biomedical Engineering (AI&R, BME) specialization from University of Hyderabad (UoH) Central University(HCU) in 1988, M.Tech Degree in Computer Science & Technology with AI/NLP specialization from JNU New Delhi in 1992, PhD Degree in Transdiscipline Biomedical Eng & Neurology from Nizam`s Inst of Medical-Sciences(NIMS)Hospital (2009) all in India. He also pursued an Advanced masters MS Degree through research in Cognitive Science (AI/Medical-Neuroscience, Natural Language-and-Speech Processing, Speech-Technology & Auditory-Processing) at ILASH-Research Centre, Computer Science Dept, University of Sheffield(England,1994-95), M.Phil/D.Sc. Degree in Biomedical-Signal-processing from the Bioengineering-Transducers-Signal-Processing(BTSP) Research Group of University of Leicester (UoL) Dept of Engineering (England,1995-97), worked as Scientist/Engineer at Planning Commission (New Delhi) through Indian Engineering Services (IES), Research Fellow at UOS-and-UoL. Presently, he is a full Professor at CMRCET Hyderabad involved in developing and applying new estimation, systems and control-tools in order to: build computational simulation and statistical models of electrical-activity in neural-circuits affected by Parkinson`s disease(PD), understand electro-physiological-dynamics of neural-circuits in health/disease-states during DBS treatment, design more effective, adaptive, and safer DBS-strategies for neurological-neurodegerative-disorders; design new clinical/clinico-statistical-experiments, develop/apply systems-level mathematical-frameworks for modeling-and-controlling neuronal-network-activity in the brain with DBS, create a more intelligent-system for both placing-and-controlling the electrodes; implant an intelligent-chip that continuously measures-monitors neural-activity, and finally build an effective new cadre-of-researchers who bridge the training and thinking gaps toward major-advances in trans discipline neuroscience. He has over 200 papers published in national and international journals and over 15 chapters in various text books – IFMBE Springer Nature and Springer Forensics proceedings. He is a Professional member of different scientific societies of engineering medicine biology and computing: Life member of ISTE, senior member of IEEE (USA), British Computing Society (BCS, UK), LAM of Indian Academy of Neurology (IAN), life member of Indian Academy of Neurosciences (IANs), Member [# 46708] of International Parkinson Disease and Movement Disorders society (WI, USA), Neurological Society of India (NSI), member of Andhra Pradesh Neurology society and neuroscientists association, etc. He was granted [SR/CSRI/201/2016] by the Dept of Science & Technology (DST), Ministry of Science Technology, Govt of India, New Delhi. Our research areas also include, Human Motor Control: This research addresses the role of the peripheral neuromuscular system in the control of posture and movement. System identification methods are used to address the issues, such as, what are the mechanical properties of human joints and how do they vary under normal physiological conditions?, what mechanisms are responsible for generating the mechanical behavior; what are the relative roles of intrinsic muscle properties and reflex mechanisms? Both intrinsic and extrinsic flexor aspect of forearm and extensor and physiology of the upper limb, and what role do these mechanical properties play in the control of posture and movement? Biomedical engineering (BME) System Identification and Signal Analysis Methods - This research focuses on the development of tools and utilities and techniques for the biomedical signal analysis and system and their application to clinically diagnostic relevant problems. The emphasis is on practical methods for the identification of linear-time-varying and nonlinear systems within a continuous-time, nonparametric context. Current application areas includes, human motor control, respiratory monitoring for apnea detection/prediction, and automated decision support for effective medical diagnostics

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