DETECTION AND SUPPRESSION OF
MESIAL TEMPORAL LOBE EPILEPSY

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*We also certify that written approval has been obtained for any proprietary material contained therein.
DEDICATIONS

To my wife Sheela, for her unconditional love and support, she showed me life should be an adventure!

To my parents, for their love and patience for a son, who has not always been the best son.
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Detection and Suppression of Mesial Temporal Lobe Epilepsy

Abstract

by

YUANG TANG

Epilepsy is a complex neurological disease that affects more than 50 million people worldwide. Mesial temporal lobe epilepsy (MTLE) is the most common and refractory form of epilepsy. In this study, we present potential new therapies for the treatment of MTLE. First, we present a novel low frequency electrical stimulation paradigm, as a possible therapeutic treatment, for status epilepticus originating from the hippocampus as well as MTLE seizures. The paradigm utilizes the hippocampal commissure, as a unique stimulation target, to simultaneously influence large portions of the bilateral hippocampal network. In order to assess the efficacy of the proposed stimulation paradigm, an acute rat model of MTLE status epilepticus is developed, using bilateral micro-injections 4-Aminopyridine into the hippocampal structure. In animals that received stimulation, an 88% reduction in the powers of the bilateral epileptiform activity is achieved when compared to the control group. In addition, the stimulation paradigm is also shown to entrain the hippocampal network’s spontaneous epileptiform activity and disrupt the synchrony between the epileptiform activity within two sides of the hippocampi. Along with the low frequency stimulation paradigm, we also present a automated seizure detection algorithm. An effective automated seizure detector can reduce the significant human resources necessary for the care of patients suffering from epilepsy and offer improved
solutions for closed-loop therapeutic devices such as implantable electrical stimulation systems. While numerous detection algorithms have been published, an effective detector in the clinical setting remains elusive. In this study, a novel detector is proposed based on a support vector machine assembly classifier (SVMA). Each member of the SVMA is trained with a different set of weights between the seizure and non-seizure data and the user can selectively control the output of the SVMA classifier. The algorithm can improve the detection performance compared to traditional methods by providing an effective tuning strategy for specific patients. The proposed algorithm also demonstrates a clear advantage over threshold tuning. When compared with the detection performances reported by other studies using the publicly available epilepsy dataset hosted by the University of BONN, the proposed SVMA detector achieved the best total accuracy of 98.72%.
CHAPTER 1

INTRODUCTION
1.1 Epilepsy

Epilepsy is a complex disease that involves a broad range of symptoms. It is the most common neurological disorder that affects more than 50 million people worldwide (Slutzky, Cvitanovic et al. 2003). Among them, 30% receive little benefit from current antiepileptic drug treatments (AED) (Andrade, Zumsteg et al. 2006). Patients diagnosed with epilepsy suffer from recurrent epileptic seizures that are detrimental to the health and the quality of life of the individuals. According to definitions proposed by the International League Against Epilepsy (ILAE) and the International Bureau for Epilepsy (IBE), an epileptic seizure is a transient occurrence of signs and/or symptoms due to abnormally excessive or synchronous neuronal activity in the brain (Fisher, van Emde Boas et al. 2005). Epilepsy is a disorder of the brain characterized by 1) an enduring predisposition to generate epileptic seizures and 2) the neurobiological, cognitive, psychological, and social consequences due to this condition. Epilepsy itself increases the risk of accidents and sudden unexpected death (Tomson, Nashef et al. 2008). The diagnosis of epilepsy requires the occurrence of at least one non-provoked epileptic seizure. Epilepsy is not a specific disease or a single syndrome but rather a broad category of symptom complexes arising from disordered brain functions that themselves may be secondary to a variety of pathologic processes.

1.2 Mesial temporal lobe epilepsy

Mesial temporal lobe epilepsy (MTLE) is the most frequent form of epilepsy and is characterized by seizures that initiate in the mesial temporal limbic structures of the brain. The seizures may have a limited spread (simple partial seizures) or they may invade other regions of the cortex (complex partial seizures)(Sadler 2006). Onset of the seizures typically occurs in the
latter half of the first decade of life, with increased incidence of complex partial seizures. The characteristic clinical semiology of the seizures is comprised of abdominal, autonomic or emotional auras. The lateralizing clinical signs can be attributed to the typical spreading of seizures from mesial temporal structures with expression of, e.g. automatism, contralateral hand dystonia and postictal aphasia on the dominant-side speech functions (Lüders 2008).

While the exact composition of the limbic system is different depending on the literature, common structures are shared within them. One such description of the limbic system includes the hypothalamus, anterior thalamus, cingulate cortex, amygdala, and the hippocampus the center of the limbic system. An illustration of the limbic system is shown in fig. 1. Patients suffering from MTLE exhibit mesial temporal sclerosis (MTS) characterized by segmental pyramidal cell loss in the CA1 and CA3 regions of the hippocampal structure (Blumcke 2008). However whether the hippocampal sclerosis is the cause of seizures is unclear. It has been shown that MTLE patients often experienced early insults during infancy such as prolonged complex febrile convulsions, status epilepticus, CNS infection or trauma. Following the early traumas, these patients may undergo a significant latent period free from epileptic seizures before the characteristic unprovoked recurrent MTLE seizures develop (French, Williamson et al. 1993). One possibility is that these initial insults may cause hippocampal sclerosis, over time that leads to the progression of recurrent MTLE seizures and it’s been observed that surgical removal of the hippocampal sclerosis often suppressed further epileptic seizure activity. Regardless of the relationship between hippocampal sclerosis and epileptic seizures, the hippocampus is a key structure in seizure generation and propagation in MTLE (Chang and Lowenstein 2003; Vonck, Boon et al. 2005; Parrent and Almeida 2006; Tellez-Zenteno, McLachlan et al. 2006; Boon, Vonck et al. 2007). The first objective of this thesis is to design and implement a model of
MTLE status epilepticus in vivo. This model can be used to evaluate new treatment paradigms that can control hippocampal status epilepticus which may lead to new therapies, both for adult MTLE patients, as well as early stage status epilepticus and potentially prevent MTLE development later in life.

1.3 Hippocampus

The hippocampus maintains the central position of the limbic system. Its neurons are densely packed and form a distinctive laminated structure. The hippocampus has substantial projections to other structures of the limbic system and the cortex including the septum, entorhinal cortex, amygdala, thalamus, and the hypothalamus. These projections are presented in fig.2 The anatomy of the hippocampus consists of four sub regions: the dentate gyrus (DG); Cornu Ammonis regio superior (CA1); Cornu Ammonis regio inferior (CA3) and the subiculum. A cross-section image of the human hippocampus, depicting the listed regions, is shown in fig.3 along with the major connections within the hippocampal structure and the entorhinal cortex. Each region of the hippocampus is distinguished by the characteristics of their principle cells and their connections. Interestingly, the four regions are functionally connected in a mostly sequential manner with the DG projecting to principle cells in the CA3 region via the mossy fiber axons, the CA3 projects to the CA1 region via the Schaeffer collateral axon fibers and the CA1 projects to the subiculum. This stepwise connection pathway of the hippocampus is commonly referred to as the “trisynaptic pathway.” The major inputs into the hippocampus arise from the entorhinal cortex that synapses on neurons in the dentate gyrus via the perforant path. The major outputs of the hippocampus originate in the CA1 and subiculum regions with the entorhinal cortex as one of their major targets completing a feedback loop. The CA3 region is
sometimes described as the “Pace Maker” of the hippocampus. It outputs to the CA1 region and subsequently the subiculum via the schaffer collaterals. It also has feedback projections to the dentate gyrus. Unlike other regions, neurons in the CA3 region make numerous excitatory synapses on neighboring CA3 neurons. A significant portion of these neurons exhibit rhythmic, bursting activity that is, in part due to the presence of large numbers of calcium channels in their dendrites. Calcium influx through these channels can result in prolonged depolarization, during excitation, and generate additional action potentials. However, these activities are curtailed by nearby GABAergic inhibitory interneurons that exert a strong influence in the CA3 region. Published evidence suggests that rhythmic activity seen in CA3 is linked to the spontaneous interictal spikes and is crucial in ictal seizure suppression (David Amaral 2007).

1.4 Hippocampal commissures

The details above describe the neuro-anatomy of a single hippocampus. The hippocampal structure actually consists of two bilateral hippocampi and we now present a description of the connections between the bilateral hippocampi. In the mammalian telencephalon, there exist three distinct commissure systems: the corpus callosum; the anterior commissure and the hippocampal commissure. The hippocampal commissure consists of two separate fiber tracts: the dorsal hippocampal commissure (DHC) and the ventral hippocampal commissure (VHC). While the human hippocampal commissure system is very similar to that of other primates, there are significant differences compared with the hippocampal commissure system in rats (Amaral, Insausti et al. 1984; Gloor, Salanova et al. 1993).

In the rat hippocampal formation, the major communications across the two hippocampi are carried out via the significant VHC. The VHC consists primarily of fibers originating from
neurons in the CA3 region that synapses on the neurons within the contralateral CA1 region and fibers originating from the dentate gyrus that synapses to homotopic regions of the contralateral dentate gyrus. The DHC in the rat mainly carry projections from the entorhinal cortex to the contralateral entorhinal cortex, entorhinal cortex to the contralateral dentate gyrus and subicular complex to the contralateral entorhinal cortex (Amaral, Insausti et al. 1984). These rat hippocampal commissural connections are summarized in fig.4a.

In the human hippocampal commissures, there is a dramatic reduction in the VHC. However, the DHC remains a sizable tract that is morphologically very similar to other primates (Gloor, Salanova et al. 1993). An illustration of major human hippocampal commissural pathways is shown in fig.5b. While the human DHC is anatomically significant, its physiological function remains a debate. Electrical stimulation studies by Wilson et al. suggest the DHC have little functional value. In the study, 74 epileptic patients were bilaterally implanted with 3 to 6 electrodes that are aimed at various regions of the limbic system. Single pulse stimulations of 100us duration, 05 to 5mA amplitude are delivered to each electrode while evoke potentials are measured from both the ipsilateral and contralateral electrodes. 78% of the implanted electrodes evoked identifiable responses from various ipsilateral recording sites, while no identifiable responses were seen in the contralateral recordings. However paired pulse stimulation of the subicular region did evoke readily identifiable responses in the contralateral entorhinal cortex. These responses seem to have an all or none mechanism and Wilson suggests a possible “gating” process is thus associated with the activation of the DHC. The study concluded that the inability to record identifiable responses in the contralateral electrodes during single pulse stimulation suggests a lack of functionality for the DHC (Wilson, Isokawa et al. 1990; Wilson, Isokawa et al. 1991).
In a separate study, Gloor et al. presented data that suggest the human DHC is a functional pathway and is actively involved in the spread of temporal lobe seizure from one hemisphere to the other. 53 patients diagnosed with complex temporal lobe epilepsy, were selected to study their pattern of seizure spread. Electrodes were strategically implanted in the patients. A total of 220 seizures were analyzed and categorized into four types of seizure propagation patterns. Of the four types of seizure spread patterns to the contralateral hemisphere: type I, II, III exhibit seizure propagation patterns that are best explained through the dorsal hippocampal commissure, which further suggest the dorsal hippocampal commissure in humans is a functional pathway (Gloor, Salanova et al. 1993).

1.5 Treatments

Once diagnosed, combinations of AED treatments are used in an effort to suppress the epileptic seizures. Unfortunately, for patients suffering from MTLE, only 11% to 25% of the population achieves complete remission from seizures with AED treatments. The remaining patients often develop intractable epilepsy that may become more elaborate over time (Engel 1996) and lead to further neuronal damage (Salmenpera, Kalviainen et al. 2001) and impaired cognitive performance and behavioral abnormalities (Oyegbile, Dow et al. 2004). For these patients surgical intervention is considered.

Studies have shown that 65% to 70% of selected MTLE patients that undergo appropriate surgical resection of the epileptic focus become seizure free, usually with the additional aid of an AED treatment (Zumsteg, Andrade et al. 2006). However, surgical intervention is invasive and irreversible and can lead to detrimental side effects such as memory loss, speech deficits, hemiparesis, dysphasia and hemianopsia (Blume and Parrent 2006). Besides these possible risks,
not all MTLE patients are good candidates for surgery. Individuals diagnosed with bilateral temporal disorder or multiple epileptic foci are generally not considered. Due to the inadequacies of the current treatments, significant research is now underway to find novel therapeutic solutions for MTLE with electrical stimulation being at the forefront of the promising new methodologies.

1.6 Alternative Treatments

Neurostimulation is a novel treatment option, mainly for those epilepsy patients who cannot benefit from AED treatments. It has the advantage of reversibility, adjustability and is less invasive compared surgical resections. Vagal nerve stimulation (VNS) is the only approved stimulation therapy in clinical use so far and shows a median reduction in seizures of 35-45% (Morris and Mueller 1999). The role of electrical brain stimulation is currently under intensive clinical research; and different targets such as the thalamus (Andrade, Zumsteg et al. 2006), the subthalamic nucleus (Chabardes, Kahane et al. 2002) and direct stimulation of the epileptic focus are being evaluated. In small clinical series, direct stimulation of the hippocampus in TLE has demonstrated potential efficacy in controlling seizures without memory deterioration (Boon, Vonck et al. 2007; Velasco, Velasco et al. 2007). These studies utilize high frequency (>50Hz) electrical stimulation largely based on the therapeutic effects, achieved with high frequency stimulations (DBS), on patients suffering from movement disorders such as Parkinson’s. Overall these studies have reported mixed results.

The efficacy of using low frequency electrical stimulations (<10Hz) to suppress epileptic activity has been studied in a number of animal experiments. Durand and Warman have shown,
in an *in-vitro* preparation, the ability of a single precisely placed electrical pulse to reset of annihilate a developing or ongoing seizure (Durand and Warman 1994). Repetitive low frequency supra threshold stimulation has also been shown to control epileptic activity in a number of *in vitro* studies. 1Hz electrical stimulation, mimicking the interictal spiking frequency observed in the slice preparation, is able to prevent the formation of ictal activity (Jerger and Schiff 1995; Barbarosie and Avoli 1997; Avoli 2001; D'Arcangelo, Panuccio et al. 2005). These findings support the proposal that certain interictal spiking may actually interfere with the generation of ictal events (Swartzwelder, Lewis et al. 1987; Jensen and Yaari 1988). There is also significant evidence, in *in vivo* preparations, where low frequency stimulation delivered prior to amygdale targeted kindling stimulation, is able to greatly increase the threshold of seizure formation and decrease the incidence of kindled seizures (Goodman, Berger et al. 2005; Carrington, Gilby et al. 2007). **The second objective of this paper is to design a low frequency electrical stimulation paradigm, specifically for treating MTLE, the most refractory and difficult to control for of epilepsy.**

### 1.7 Epileptic Seizure Detection

Depending on the mechanism of epileptic seizure suppression, novel treatments such as electrical stimulation may be delivered only when an epileptic seizure onset is detected. In order to implement such a close loop therapeutic system, an automated seizure detection algorithm is necessary. Such a system can be used to monitor patient vitals continuously and deliver therapeutic stimulation only when epileptic seizure onset is detected. However the utility of such a detector goes beyond just controlling a close loop therapeutic device. One of the most important aspects epilepsy treatment is the monitoring of patient EEG health. An accurate
automated seizure detection algorithm can provide an objective measure of the patients EEG health that can be used to (1) help diagnose patients with non-epileptic seizures or epileptic seizures that physicians find difficult to classify; (2) evaluate the effectiveness of various treatments such as AED therapies; (3) monitor patients in emergency care units and epilepsy centers. This patient population often suffers from severe episodes of seizures and must be monitored continuously by trained physicians. An effective seizure detection algorithm can not only provide valuable information regarding the seizures but also reduce the patient care load for the physician. (Stefan and Hopfengartner 2009) The third objective of this thesis is to implement a robust seizure detection algorithm that offers patient specific tuning.

1.8 Thesis Objectives and Organization

Objective I. Design and characterize an in vivo model of MTLE status epilepticus in rats.

Hypothesis: It is our hypothesis that continuous bilateral micro-injections of high concentration [20mM] 4-Aminopyridine (4-AP) can induce persistent bilateral epileptic activity in the hippocampal structure.

Rational: In this study, we focus on the treatment of MTLE with electrical stimulation. To verify the efficacy of the electrical stimulation paradigm to suppress MTLE seizures, an experimental model of MTLE is needed. Patients with MTLE can exhibit multiple seizure foci that can exist in both sides of the hippocampal structure, thus the in vivo model of MTLE should have bilateral epileptic activity. 4-AP have been used extensively to generate epileptiform
activity in various experimental preparations and high concentrations of continuous bilateral 4-AP micro-injections should induce epileptic activity in both sides of the hippocampal structure. The experimental MTLE model should also generate persistent epileptiform activity, mimicking status epilepticus, because (1) it is the most severe form of seizures and is the most difficult to treat; (2) clinical evidence suggest adult MTLE patients often experience status epilepticus during infancy and that these early insults may lead to MTLE later in life. As such, controlling this early stage status epilepticus may be a preventative measure for the development adulthood MTLE.

**Experimental Protocol:**

Bilateral micro-injections of [20mM] 4-AP solutions are continuously injected into the hippocampal structure of anesthetized rats. In order to monitor the epileptiform activity generated, recording electrodes are placed bilaterally into the CA3 region of the hippocampal structure. The epileptiform activity are characterized by

1. visual inspection of the percent duration of the epileptiform activity for each side of the hippocampal structure.
2. the average power of the epileptiform activity within a given time window for each side of the hippocampal structure.
3. and the epileptiform morphology including the interictal spiking frequency quantified using STFT.

The experimental MTLE model should generate consistent epileptiform activity, both interictal and ictal like waveforms, for the duration of 7 hours which is the length of the stimulation experiments.
Objective II. Design and verify a low frequency electrical stimulation paradigm for the suppression of bilateral MTLE status epilepticus

_Hypothesis:_ It is our hypothesis that 5Hz electrical stimulation of the ventral hippocampal commissure (VHC) can suppress bilateral status epilepticus.

_Rational:_ Low frequency electrical stimulation has been shown to suppress epileptiform activity in a number of studies. To determine the exact stimulation frequency, we utilize published evidence suggesting interictal spiking activity suppresses ictal events and set the stimulation frequency to the interictal spiking frequency, observed in the model of MTLE status epilepticus, obtained in objective I. The VHC is a novel stimulation target. Due to its substantial projections to both sides of the hippocampal structure and its densely packed structure, a single stimulation electrode placed at the VHC, can simultaneously deliver influential electrical stimulation to majority portions of both sides of the hippocampal structure. This characteristic of the VHC may lead to powerful suppression of hippocampal seizures.

_Experimental Protocol:_

To study the effect of the proposed stimulation paradigm on the epileptiform activity in the experimental model of MTLE status epilepticus, two groups of animals are formed: the control group and the stimulation group. For the control group, bilateral micro-injections of 4-AP are used to generate bilateral MTLE status epilepticus like activity in the hippocampal structure, characterized by objective I. Seven hours of bilateral epileptic activity, from the CA3
regions of the hippocampal structure, are recorded for each animal. For the stimulation group, the same experimental MTLE status epilepticus model is applied to each animal, however during hours 2, 4 and 6, each animal will also receive a 30 min 5Hz stimulus train delivered via the VHC. The stimulation intensity is set to the stimulation current that evoked the maximum antidromic potential recorded with the CA3 recording electrodes. To compare the epileptiform activity between the control group and the stimulation group, we quantify the severity of the epileptiform activity using the percent duration of epileptiform activity/hour and average power for each of the seven hours. But before we can obtain an accurate epileptic signal power, we must first remove the stimulation artifacts along with the evoked physiological responses.

To quantify the accuracy of the artifact removal methodology to eliminate artifacts while maintaining the epileptiform activity, the same stimulation paradigm is applied to healthy animals in the absence of 4-AP injections. These stimulation trains can then be combined with epileptiform activity obtained from the control group to form a test dataset for the artifact removal algorithm. The algorithm is applied to the test dataset and a recovered version of the original control epileptiform activity is obtained. The correlation between the recovered epileptiform activity and the original epileptiform activity along with their difference in average power can be used to quantify the efficacy of the artifact removal algorithm.

To quantify the efficacy of epileptic seizure suppression during stimulation, the signal power and percent duration of epileptiform activity, for the hours 2, 4, 6, between the control group and the stimulation group is compared for each side of the hippocampal structure. Statistical significance can be measured with student $t$-test for each pair of comparisons.

To investigate the possibility of epileptic seizure suppression post stimulation, the percent duration and signal power of epileptiform activity, for hours 3, 5, 7, between the control group
and the stimulation group is compared for each side of the hippocampal structure. Again statistical significance is measured with student $t$-test for each pair of comparisons.

To quantify the difference in epileptic seizure suppression between the three sessions of stimulation, during stimulation, the signal power of the epileptiform activity during hours 2, 4, 6 of the stimulation group are compared with each other for each side of the hippocampal structure. Statistical significance is analyzed using one-way ANOVA. If significant difference exists, then post-hoc Tukey Kramer test is used to determine individual differences.

To quantify the difference in epileptic seizure suppression between the three sessions of stimulation, post stimulation, the signal power of the epileptiform activity during hours 3, 5, 7 of the stimulation group are compared with each other for each side of the hippocampal structure. Statistical significance is analyzed using one-way ANOVA. If significant difference exists, then post-hoc Tukey Kramer test is used to determine individual differences.

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**Objective III.** Design and implement a robust seizure detection algorithm that offers patient specific tuning.

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**Hypothesis:** It is our hypothesis that an epileptic seizure detector constructed from an assembly of SVM classifiers, each trained with a different weighting ratio between seizure data and non-seizure data, can offer the end user easy patient specific tuning and achieve superior classification performance.
**Rational:** Patients suffering from epilepsy exhibit a variety of EEG morphologies. This characteristic makes the ability for a static classifier to achieve good performance for every patient difficult. Instead, a detector that can be tuned for individual patients should offer better performance. However, the method of tuning is also important; traditional tuning methods of varying the detection threshold are easy but do not take into account the available information in the training data and can lead to unpredictable results. Other more complex methods of adjusting different classifier parameters are not suited for clinical use where the end users are not experts in machine learning. So in this study, we present a detector that provides easy tuning by training an assembly of SVM classifiers each trained to offer more sensitivity or specificity. The end user can tune the detector, for each patient and achieve higher performance, by simply choosing a specific SVM classifier within the assembly.

**Experimental Protocol:**

In order to accurately compare the proposed SVM assembly detector with other published methods, the publically available epileptic seizure dataset from the University of BONN is used. The following measures are used to quantify the effectiveness of the detector.

1. Sensitivity
2. Specificity
3. Total Accuracy
4. Detection Delay

The proposed algorithm is compared with other detection algorithms published with the same dataset along with threshold tuning results of a similarly trained SVM classifier.
These conclude the objectives of this thesis. The remaining sections of this thesis are organized as the following. In chapter 2, the *in vivo* model of MTLE status epilepticus is presented along with the results for the low frequency electrical stimulation paradigm using the experimental model. In chapter 3, details of the SVM assembly epileptic seizure detection algorithm including its performance measures are presented. In chapter 4, concluding remarks regarding the results of each objective are presented along with possible future directions. During my research, I also worked on a Multi-scale SVM classifier algorithm. When the algorithm was finished, it was realized that a nearly identical algorithm was published in (Nick Kingsbury 2005). So this work was never published and the results are presented in Appendix A.
1.9 FIGURE CAPTIONS

**Figure 1.1:** Structures of the Limbic system.

**Figure 1.2:** Output projections of the hippocampus.

**Figure 1.3:** Cross section of the hippocampus. The Dentate Gyrus (DG) projects to the CA3 cell layer via the mossy fibers. The CA3 cell layer projects to the CA1 cell layer via the Schaffer collateral (SC). The CA1 cell layer projects to the Entorhinal cortex via the Perforant Path (PP).

**Figure 1.4:** Connections of the hippocampal commissural fibers in primates and rats.
1.8 FIGURES

Figure 1.1
Figure 1.2
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CHAPTER 2

An electrical stimulation paradigm for the suppression of seizures in a model of MTLE status epilepticus.
2.1 ABSTRACT

Mesial temporal lobe epilepsy (MTLE) is the most common and refractory form of epilepsy. Patients diagnosed with MTLE often experience status epilepticus during infancy. It is postulated that this initial trauma is the root cause of MTLE development later in life. In this study, we present a novel low frequency electrical stimulation paradigm, as a possible therapeutic treatment, for status epilepticus originating from the hippocampus as well as MTLE seizures. The paradigm utilizes the hippocampal commissure, as a unique stimulation target, to simultaneously influence large portions of the bilateral hippocampal network. In order to assess the efficacy of the proposed stimulation paradigm, an acute rat model of MTLE status epilepticus is developed, using bilateral micro-injections 4-Aminopyridine into the hippocampal structure. In animals that received stimulation, an 88% reduction in the powers of the bilateral epileptiform activity is achieved when compared to the control group. In addition, the stimulation paradigm is also shown to entrain the hippocampal network’s spontaneous epileptiform activity and disrupt the synchrony between the epileptiform activity within two sides of the hippocampi. In conclusion, the proposed electrical stimulation paradigm shows promise both as a novel treatment for status epilepticus during infancy as well as for adult patients suffering from recurrent MTLE seizures.
2.2 INTRODUCTION

Epilepsy is the most common neurological disorder affecting more than 50 million people worldwide. Patients with this disease suffer spontaneous seizures that are debilitating to the everyday life of the individual. Of these patients, 30% receive little benefit from current antiepileptic drug treatments (AED) and experience recurrent epileptic seizures (Nadkarni, LaJoie et al. 2005). Mesial temporal lobe epilepsy (MTLE) accounts for the majority of these cases. MTLE is the most frequent form of epilepsy, unfortunately it is also the most resistant to current AED treatments (Andrade, Zumsteg et al. 2006). Of the MTLE patient population, only 11% to 25% experience complete remission from seizure episodes with AED applications (Blume 2006). For the remaining patients, surgical intervention is the alternative. Studies have shown that 50% to 70% of selected MTLE patients that undergo appropriate surgical resection of the epileptic focus become seizure free, usually with the additional aid of an AED treatment (Spencer 2002; Zumsteg, Andrade et al. 2006). While mesial temporal lobe lobotomy, when applied judiciously, is a therapeutically effective treatment option for MTLE, it is invasive, irreversible and can lead to detrimental side effects such as memory loss, speech deficits, hemiparesis, dysphasia, and hemianopsia (Blume and Parrent 2006). In addition, not all MTLE patients are good candidates for surgery. Individuals diagnosed with bilateral temporal disorder or multiple epileptic foci are generally not considered (Wheatley 2006; Boex, Seeck et al. 2011). These factors motivate the continuation of research to find alternative therapies.

Electrical stimulation of the epileptic brain is a potential therapy that can greatly benefit epilepsy patients that have exhausted AED treatment options and still suffer from persistent seizures. The interests in using electrical stimulation of the brain to treat epilepsy have greatly increased recently due to the success of deep brain stimulation (DBS) in ameliorating various
movement disorders such as Parkinson’s disease. While the exact mechanism of DBS remains a mystery, the palliative results are significant with little evidence of adverse side effects (Durand and Bikson 2001; Schrader, Stern et al. 2006; Jobst 2010; Lega, Halpern et al. 2010; Rahman, Abd-El-Barr et al. 2010; Zhong, Yu et al. 2011). Electrical stimulation offers several advantages over surgical intervention: (1) it is less invasive; (2) it is reversible; (3) the treatment protocol be easily customized to fit the needs of individual patients (Sunderam, Gluckman et al. 2010). A number studies have been published studying the therapeutic effect of electrical stimulations on MTLE patients experiencing refractory seizures, using both high frequency electrical stimulations ($\geq$130Hz) (Tellez-Zenteno, McLachlan et al. 2006; Boon, Vonck et al. 2007; Velasco, Velasco et al. 2007; Boex, Seeck et al. 2011) and low frequency electrical stimulations (1 to 10Hz) (Chkhenkeli, Sramka et al. 2004; Kinoshita, Ikeda et al. 2005) and have reported promising results. None of the studies reported any observable side effects due to the electrical stimulations and one study found that higher stimulation amplitudes are needed for effective seizure suppression (Boex, Seeck et al. 2011). While the results of these studies are promising, the achievable seizure suppression effectiveness of current electrical stimulation protocols does not measure up to those achieved by surgical intervention (Rolston, Desai et al. 2011). Thus there still exists the need for further research into novel electrical stimulation paradigms for epileptic seizure suppression.

In this study, we investigate a low frequency (5Hz) electrical stimulation paradigm, targeting the hippocampal commissure fiber tract, for the suppression of long-lasting bilateral hippocampal seizures in rats, as a model of bilateral MTLE status epilepticus. The long-lasting hippocampal seizures are generated via periodic bilateral micro-injections of 4-Aminopyridine solutions into the rat hippocampal structure. We focus on the suppression of status epilepticus
because (1) it is the most intense, detrimental and difficult to control form of epileptic seizures and (2) Patients suffering from MTLE often experience febrile status epilepticus (SE) during their infancy, followed by a long silent period, before their condition evolves into clinical MTLE years later (Ohtsu, Oguni et al. 2002). One hypothesis is that the SE episodes are the cause of the hippocampal sclerosis commonly found in MTLE patients, which in turn leads to MTLE later in life. With this in mind, an electrical stimulation protocol, that can suppress hippocampal status epilepticus, can be applied not only as a treatment for adult MTLE patients but also as a possible treatment for status epilepticus during infancy and possibly prevent the formation of MTLE later in life. The proposed stimulation paradigm utilizes the hippocampal commissure, to simultaneously deliver influential electrical stimulation to large portions of both sides of the hippocampi. While the functionality of the hippocampal commissures in humans has been open to debate (Wilson, Isokawa et al. 1990; Wilson, Isokawa et al. 1991; Gloor, Salanova et al. 1993) we have demonstrated the ability to excite the dorsal hippocampal commissure by direct electrical stimulation, and recorded bilateral evoked potentials in the hippocampi of a human subject (MZ Koubeissi 2009). The frequency of stimulation, for this study, is set to mimic the spontaneous periodic spiking activity observed within the animal preparation. This design solution is based on several past findings. Chaos control strategies have shown success in entraining epileptic spiking events in in-vitro slice preparations (Horgan 1994; Schiff, Jerger et al. 1994; Slutzky, Cvitanovic et al. 2003). The essence of these studies is to use electrical stimulation to control the spiking interval, forcing the hippocampal network to spike at a particular interval or unstable periodic orbit UPO. In epilepsy, periodic low frequency spiking events, such as interictal spiking, are often observed. Following the logic of chaos control, these natural spiking frequencies exhibited by the epileptic hippocampus may be possible fixed points
that when stimulated at these frequencies, the hippocampal network can be entrained. Also in studies done by Avoli et al., 1Hz electrical stimulation approximating the interictal spiking frequency present in the CA3 region of the hippocampus suppressed epileptic seizures in a 4-AP model of MTLE \textit{in-vitro} (Barbarosie and Avoli 1997; Avoli 2001).

In the following sections, we first detail the protocols used to generate the acute animal model of MTLE status epilepticus, used in this study, along with the methods of data acquisition and signal processing. We then present the findings, regarding the various effects of proposed electrical stimulation paradigm, by comparing the animals that received stimulation verse the control animals. Finally we discuss the significance of the results presented in this study.
2.3 METHODS

2.3.1 Surgical procedures.

All procedures in this study are approved by the Institutional Animal Care and Use Committee, Case Western Reserve University Cleveland. Adult male Sprague Dawley rats weighing between 300 to 400 grams are anesthetized with urethane (1.5 g/kg, i.p.). The animals are then secured via a stereotaxic apparatus. The body temperatures of the animals are maintained at 37°C with a heating pad. Incisions are made along the rostro-caudal axis above the skull. Seven holes are drilled through the skull for the placement of the necessary devices, shown in fig. 2.1, their locations relative to the bregma are: the stimulation electrode (S) (AP -1.0 mm, ML 0.5 mm); the ground screw opposite to the stimulation electrode placement (AP -1.0 mm, ML 1.0 mm); bilateral recording electrodes placed in the CA3 regions of the hippocampus (AP -3.0 mm, ML 3.0 mm); bilateral micro-syringe placements (AP -5.0 mm, ML 4.0 mm) and the reference screw (AP 3.0mm, ML 2.0mm). The placement accuracy of the VHC stimulation electrode (Stim) and the two recording electrodes (LR, RR) placed in the CA3 cell layer of the hippocampus are determined by observing their recorded evoked potentials. When placed correctly, a stimulus pulse delivered to the VHC evokes large bilateral CA3 antidromic potentials at LR and RR. In fig. 2.1, a 700uA pulse, with 100us duration, is delivered to the VHC via the stimulation electrode. The resulting CA3 potentials are characteristic of antidromic activation with delays < 2.5 ms between the stimulus artifacts and their evoked potentials. For accurate positioning of the micro-syringes, recording electrodes are inserted into the holes created for LsM and RsM and their depth adjusted until the CA1 cell layer is reached, verified by strong
evoked orthodromic potentials also shown in fig. 2.1. The recording electrodes are then removed and replaced by micro-syringes (LmS, RmS) placed at the same locations.

2.3.2 Hippocampal status epilepticus generation.

Bilateral status epilepticus, originating from the hippocampal structure, are induced using micro-injections of normal artificial cerebral fluid (ACSF) containing [25mM] 4-aminopyridine (4-AP) via the implanted LmS and RmS. The normal ACSF consists of (in mM) 124 NaCl, 5 KCl, 1.25 NaH2PO4, 2 CaCl2, 1.5 MgSO4, 26 NaHCO2 and 2 g/L D-glucose. The injections are 1.0 ul at the start of the first hour and 0.5 ul during subsequent hours for a total of seven hours which comprises the entire duration of the experiment protocol. The injections are done at a rate of .1ul/min.

2.3.3 Stimulation and recording.

Parylene-C insulated tungsten electrodes (127 µm diameter, A-M Systems, Sequim, WA, USA) are used for recording the field potential from the hippocampi. For stimulation of the VHC, polyimide insulated tungsten electrodes (254 µm diameter, 1 mm tip exposure, A-M Systems) are used. Recorded signals are bandpass filtered 1 – 5 kHz and amplified 100 times using Model 1700 four-channel amplifiers (A-M Systems) before the signals are sampled at 20 kHz via a ML795 PowerLab/16SP data acquisition system (ADInstruments Inc., Colorado Springs, CO, USA) and stored on hard disk.

2.3.4 Experimental setup and analysis.

To study the effect of the proposed electrical stimulation protocol on the epileptic like seizure activities, the experimental animals are organized into two groups, the control group and
the stimulation group, with (n=15) animals in each group. Both group of animals received
periodic bilateral 4-AP micro-injections for seven hours, according to the protocol described in
hippocampal status epilepticus generation and the epileptic events recorded during the entire
period. For the animals in the stimulation group, 30 min of electrical stimulation is also
delivered to the VHC starting at the fifteenth minute of hours two, four and six. The stimulation
consisted of 5 Hz monophasic pulses, 100 µs in duration and amplitudes large enough to evoke
the maximum antidromic potentials recorded in the CA3 cell layer, ranging from 0.5 to 1.5 mA.

2.3.5 Stimulus artifact removal

In order to accurately compute the signal power due to spontaneous physiological activity
during stimulation, the stimulus pulse artifacts along with their evoked electrical responses
should be removed from the recordings. We have implemented an artifact removal algorithm
based on template subtraction. Let \( x(n), n = 1: N \) denote the recorded data of length N spanning
the entire duration of a stimulus pulse train. Let \( p_i, i = 1: I \), where \( I \) is the total number of
stimulus pulses, be the onset location of the \( i \)th stimulus pulse in \( x \). Then for each \( i \)th artifact, a
template window \( T_W_i \) is computed as

\[
T_W_i(k) = \frac{1}{150} \sum_{j=-75, j \neq i}^{i+75} x_{p_j+k-1}, k = 1: SI
\]

where \( SI = 4000 \) is the stimulation interval between two adjacent pulses. In essence, for each
artifact, we create an artifact template window by averaging the 75 artifacts before and after the
artifact set for removal. We can then reduce the stimulation artifacts along with their evoked
responses by subtracting the artifact template windows from the original data. In order to
determine the efficacy of this artifact removal method, a test signal, 30 min in duration, is
constructed by combining a 30 min data segment of consistent bilateral epileptic activity with a 30 min stimulus train. The stimulus train is obtained from a healthy animal preparation and consists mainly of the stimulation artifacts, their evoked responses and low levels of various noises. The artifact removal algorithm is then applied to the test signal to recover the original epileptic activity. An illustration of this process is shown in fig. 2.2. The test signal, formed from the combination of the original epileptic activity and the stimulus train, is typical of what is encountered during actual experimentation and the artifact removal algorithm is able to recover the majority of the original bilateral epileptic activity. To quantify the accuracy of the recovered epileptic signals, the 30 min recovered epileptic data is divided into 180 data segments each lasting 10 s. The Pearson’s correlation coefficient (R) is computed between each recovered data segment and its corresponding original data. The total %difference in signal power between the recovered data and the original data is also computed. Overall the average R values are (Left: 0.98±0.041 | Right: 0.99±0.030) and the %differences in power are (Left: 0.75% | Right: 0.93%). These results demonstrate the accuracy of the artifact removal algorithm in removing the unwanted artifacts while securing the bilateral epileptic activity.
2.4 RESULTS

2.4.1 Periodic 4-AP micro-injections generate sustained bilateral status epilepticus like activities within the hippocampi.

Bilateral hourly micro-injections of [25mM] 4-AP solutions, into the rat hippocampal structure, are used to generate spontaneous and sustained hippocampal seizures simulating MTLE status epilepticus. A 100s recording of an exemplary epileptic waveform, resulting from the 4-AP micro-injections, is shown in fig. 2.3. In the figure, the epileptic waveforms, recorded from both sides of the hippocampal structure, are displayed along with three detailed plots of distinct epileptic morphologies observed throughout different regions of the waveforms. While the different morphologies can all be described by high amplitude spiking events, they differ in the timing of the spiking activities. In general, the epileptiform activity, induced by the bilateral 4-AP micro-injections can be classified into two distinct morphologies: (1) high frequency random spiking waveforms (HFRS) and (2) low frequency periodic spiking waveforms (LFPS). In fig.2.3, the epileptic waveform begins with activities that are characteristic of the HFRS morphology (region a) where the spiking events are frequent and lack observable periodicity. These activities continue though out the middle of the waveform (region b) where bursting like patterns are introduced but the spiking frequency is still high, before transitioning to LFPS activities (region c) which are characterized by low-frequency spiking events that are often periodic in nature. The LFPS morphology will then transition back to the HFRS morphology as the cycle repeats itself. These epileptiform activity are sustained throughout the duration (7hrs) of the experiments shown in fig. 2.4.
In the figure, the power of the recorded brain activities for 2s time windows, with 1 s overlap between adjacent windows, are plotted for a control experiment. Upon 4-AP injections, indicated by the arrows, epileptiform activity initiate within both sides of the hippocampal structure shown by the significant increase in the power of the recordings. These power levels are then maintained through out the remainder of the experiment.

2.4.2 5Hz electrical stimulation pulse train, mimicking the LFPS

In order to optimize the stimulation frequency, we studied the natural spiking frequency of the LFPS morphology. Fig. 2.5 plots a segment of bilateral LFPS spiking events. The plot shows correlated bilateral spiking activities that occur periodically with high amplitudes. The inter-spike interval, for this morphology, ranges from approximately 0.1s to 1s across the control group. To determine the frequency of stimulation, power spectrums of 1.6s windowed LFPS data, consisting of 1min bilateral LFPS recordings from each animal of the control group, are computed and averaged together. The mean power spectrum along with the upper and lower standard deviations, across the 15 control animals, is shown in fig. 2.5. The maximum power, during LFPS events, occurs around 5Hz, which is the frequency set for the proposed stimulation protocol. With the stimulation frequency set, the next step is to determine the robustness of the stimulus, i.e. do the evoked potentials stay consistent throughout the length of the experiment. To test this, the same stimulation protocol outlined in the methods section, is applied to three healthy animals for 30 minute sessions during hours 2, 4 and 6. The mean and standard deviation of the bilateral CA3 evoked potentials’ amplitudes, for each session, are plotted in fig. 2.6. The amplitude of an evoked potential is computed by taking the average potential between points a and b and subtracting from it the measured potential at point c. For each animal, the average amplitude for hours 4 and 6 are normalized to the average amplitude of hour
1. Across the three animals, the amplitude of the evoked potentials remains consistent throughout the length of the experiment. A 1-way Anova test did not show significant differences between the average amplitudes of the stimulation sessions for either side (left: $F(2,2) = 0.0791, P = 0.925$ | right: $F(2,2) = 0.203, P = 0.822$) although $N=3$ animals is small.

2.4.3 5Hz electrical stimulation of the VHC significantly reduces the power of epileptiform activity both during and after stimulation and is stimulation intensity dependent.

To determine the effect of the proposed LFS paradigm on the spontaneous epileptiform activity generated within the hippocampal structure, we applied the same 4-AP micro-injection protocol, utilized in the control group, to 15 additional animals labeled as the Stim group. For these animals, 30 minutes of the proposed 5Hz stimulation paradigm is delivered to the VHC fiber tract, at the 15 minute mark of each hour, every other hour, starting from the beginning of hour 2. The signal powers, computed for 2s time windows with 1s overlap, of a Stim animal is plotted in fig.2.7. During the periods of stimulation, delineated by the black bars, the signal power of the epileptiform activity are noticeably reduced when compared to the epileptiform activity of the previous hour and the control group during the same hour, previously shown in fig.2.4. Several observations can be made regarding the suppression effect: it is bilateral, affecting both sides of the hippocampi; it becomes active upon stimulus onset; it persists throughout the entirety of the stimulus train and it terminates at the end of the stimulus train. Fig. 2.8 presents the bilateral mean and standard deviation of the hourly signal power, for both the control group and the stimulation group, along with detailed comparisons of: (a) the signal power, for the hours of stimulation (2, 4, 6), between the control group and the stimulation group; (b) the signal power, for the hours post-stimulation (3, 5, 7), between the control group and the stimulation group; (c) the signal power, between the hours of stimulation, within the
control group and the stimulation group; (d) the signal power, between the hours post-stimulation, within the control group and the stimulation group. All the comparisons are done separately for each side of the hippocampal structure.

For the hours of stimulation, the two left plots in the figure, each hour to hour comparisons between the control group and stimulation group, outlined with the dashed box structures, yields significant reduction in the epileptic signal power (one-tailed $t$-test, df = 28, $P < 0.0001$) for animals that received the proposed stimulation protocol and the effect is consistent in both sides of the hippocampal structure. In total, the average normalized power, during hours 2, 4 and 6, is (LEFT: 134.12%, RIGHT: 136.33%) for the control group and (LEFT: 15.67%, RIGHT: 14.64%) for the stimulation group, resulting in an 88% reduction of epileptic signal power on the left side and 89% on the right side. We now compare the signal power of hours 2, 4 and 6 with each other, within both the control group and the stimulation group. One-way Anova is used to determine whether significant differences exist, if so, post-hoc Tukey-Kramer test is applied to every possible pair-wise comparison. In the control group, neither side of the hippocampal structure exhibited significant difference between the signal power of hours 2, 4 and 6 (Left: $F(2, 42) = 0.490, P = 0.616$ | Right: $F(2, 42) = 1.967, P = 0.153$). Thus while the mean signal power tends to be lower with time, in the control group, they are not significantly different. In the stimulation group, one-way Anova yields significant differences, between the signal power of hours 2, 4 and 6, in both sides (Left: $F(2, 42) = 22.885, P = 1.896 \times 10^{-7}$ | Right: $F(2, 42) = 11.871, P = 8.191 \times 10^{-5}$). Post-hoc Tukey-Kramer tests find significant differences between the signal power of hours 1 and 3, 2 and 3 of the left side and hours 1 and 2, 1 and 3 of the right side. While significant, these differences are small compared to the overall suppression
effect and do not clearly demonstrate any increases in epileptic power reduction with additional episodes of stimulation.

We now study the post-stimulation effect, the two right plots of fig. 2.8. Pair-wise comparisons between the signal power, measured during the hours 3, 5 and 7, of the stimulation group verse the control group yield significant reduction (one-tailed $t$-test, df = 28, $P < 0.0001$) in epileptic signal power, suggesting a continuation of epileptic power suppression even after the stimulation is terminated. Again this effect is seen in both sides of the hippocampal structure. Over all the average normalized power, during hours 3, 5, 7, is (Left: 140.86%, Right: 141.10%) for the control group and (Left: 73.53%, Right: 80.74%) for the stimulation group, an epileptic power suppression effect of 48% for the left side and 43% for the right side. One-way Anova comparisons, between the signal power of hours 3, 5 and 7, within the control group yield (Left: $F(2,42) = 1.638$, $P = 0.207$ | Right: $F(2,42) = 7.022$, $P = 0.0023$), where the only significant difference is between the signal power of hours 1 and 2, measured from the right hippocampal structure (Tukey-Kramer, $P < 0.01$). The same analysis applied to the stimulation group yields (Left: $F(2,42) = 4.288$, $P = 0.02$ | Right: $F(2,42) = 2.438$, $P = 0.0996$), where no significant differences are found between the epileptic signal power of hours 3, 5 and 7, suggesting no increase in the efficacy, of epileptic power suppression, with additional sessions of stimulation.

In order to determine the relationship between the stimulation intensity and the observed bilateral epileptic signal power suppression effect, two groups of animals (N = 10), with half receiving stimulation intensities evoking 50% of the maximum evoked response and half receiving 10%, were compared with the original control and stimulation group in fig. 2.9. In the figure, the bilateral mean and standard deviation of the signal power, for the hours of stimulation (hours 2, 4 and 6), are presented. One-way Anova is used to determine if a significant
difference, in each hourly signal power, exists between the groups, for each side. The results are as follows, for hour 1 (Left: $F(3,36) = 31.335, P = 3.846 \times 10^{-10}$ | Right: $F(3,36) = 15.152, P = 1.542 \times 10^{-6}$) there is significant differences in the mean epileptic signal power between the different groups of stimulation intensity as well as control. However post-hoc test with Tukey-Kramer only found significant differences between the 100% stimulation group and the remaining groups. The animals that received 10% and 50% stimulation, while their mean signal power were lower, did not reach statistical significance when compared to the control group. Similar results were found for hour 2 (Left: $F(3,36) = 45.682, P = 2.333 \times 10^{-12}$ | Right: $F(3,36) = 76.541, P = 1.110 \times 10^{-15}$) where for both sides, only the signal power of the 100% stimulation group yielded significant differences when compared to all other groups, with one exception, animals that received 50% stimulation achieved significant epileptic signal power reduction, in the right hippocampal structure, compared to the control group. For hour 3 the one-way Anova test yield (Left: $F(2,36) = 127.944, P < 10^{-15}$ | Right: $F(2,36) = 73.926, P = 1.887 \times 10^{-15}$). While the 100% stimulation group achieved significant bilateral epileptic power reduction compared to the control group, the 50% stimulation group also yielded significant epileptic power reduction in the right hippocampal structure that is not as effective as the 100% stimulation group. These data show that high intensity stimulation is more effective at suppressing the epileptic events generated in this study and suggests an inverse relationship between epileptic power and the stimulation intensity.

2.4.4 5Hz electrical stimulation of the VHC entrains the hippocampal network into the LFPS morphology.
The continuation of power suppression post stimulation was an unexpected result. Detailed inspection of the epileptiform activity, during the hours following stimulation, reveals that the effect is mainly due to changes in the epileptic seizure morphology from predominately HFRS to LFPS which has lower average power. In table 1, the bilateral mean and standard deviation of the percentage time, occupied by the two epileptic morphologies (HFRS, LFPS), during the middle thirty minutes of each hour, is shown for both the control group and the stimulation group. In the absence of stimulation, the two types of epileptic morphologies transition between each other, thus the sums of their percent duration equal 100%. Also, since the activities recorded from the 2 sides of the hippocampi are very close to synchronous as stated earlier, the percent duration values are equivalent for both sides of the hippocampi. During hour 1, there is no significant difference between the (HFRS, LFPS) percent duration of the control group and the stimulation group, ($t$-test, $P = 0.335$). For the periods of stimulation (hours 2, 4 and 6) LFPS morphology is completely eliminated in the stimulation group while bilateral HFRS duration is significantly reduced ($t$-test, $P < 0.001$), for each hour, when compared to the same time periods in the control group. Overall, for hours (2, 4 and 6), the average HFRS percent durations are (Left: 74.53% | Right: 74.53%) in the control group and (Left: 6.77% | Right: 5.45%) in the stimulation group; the average LFPS percent durations are (Left: 25.47% | Right: 25.47%) in the control group and (Left: 0% | Right: 0%) in the stimulation group. More interestingly, during the periods post stimulation (hours 3, 5 and 7), significant increases in the percent duration of bilateral LFPS morphology are observed in the stimulation group ($t$-test, $P < 0.001$), of each hour, when compared to the control group during the same periods. These increases in the percent duration of bilateral LFPS consequently also lead to decreases in the percent duration of bilateral HFPS morphology during the same time. These data suggest an
entrainment effect by the 5Hz VHC stimulation that promotes LFPS activity while inhibiting HFRS activity. Fig. 2.10 shows visual evidence of this entrainment effect. In the figure, bilateral recordings, surrounding the termination of stimulation, are plotted. Prior to the end of stimulation, the hippocampal network does not exhibit any observable spontaneous spiking activity. However upon the termination of stimulation, spontaneous LFPS waveforms, resembling the stimulation pulse train, appears and continues in the absence of any external stimuli. This pattern is seen throughout the stimulation group. Overall, for hours (3, 5 and 7), the average HFRS percent durations are (Left: 76.24%) | Right: 76.24%) in the control group and (Left: 22.72% | Right: 22.72%) in the stimulation group; the average LFPS percent durations are (Left: 23.76% | Right: 23.76%) in the control group and (Left: 77.28% | Right: 77.28%) in the stimulation group.

2.4.5 5Hz electrical stimulation of the VHC de-correlates the bilateral epileptic events within the hippocampi.

The bilateral status epilepticus-like activity, generated within the hippocampal structure, exhibit strong correlations between the two sides. This phenomenon is observed in all the recordings, such as the waveforms plotted in fig.3, 5 and 10, where the activity from one side of the hippocampal structure closely resemble the activity from the contra-lateral side. However, during the periods of stimulation, this mirror-image relationship vanishes. A sample of this disruption in synchrony, between the two sides of the hippocampal structure, is shown in fig.2.11. In the top figures, HFRS activity is seen originating from the left hippocampal structure but is absent from the right hippocampal structure. In the bottom plots, the opposite is true where HFRS activity exists in the right hippocampal structure but not the in the left. To quantify this disruption of synchrony, we compute the time delays that result in the maximum correlation
coefficients between epileptiform activity from both sides of the hippocampal structure. Specifically, for each stimulation animal, following stimulation artifact removal, six 10s segments of HFRS waveform, three from each side of the hippocampal structure, are marked both during stimulation and in the absence of stimulation. This results in 180 segments of HFRS waveform with 90 during stimulation and 90 in the absence of stimulation. It is our hypothesis that, without stimulation, the time delays between the bilateral HFRS activity should be close to zero, due to the observed synchrony between the two sides of the hippocampal structure. With stimulation, this synchrony is disrupted and the measured time delays should be significantly longer. Prior to computation, the data is low-pass filtered at 100Hz and down sampled to 400Hz. For each segment \( x(n), n = 1: N \), the correlation coefficients \( CC(i), i = 1: I \), between \( x \) and the recording from the contra-lateral side of the hippocampal structure \( y(k), k = 1: K \) are computed as

\[
CC(i) = \frac{\sum_{n=1}^{N}(x(n) - \bar{x})(y(i + n) - \bar{y}_i)}{\sqrt{\sum_{n=1}^{N}(x(n) - \bar{x})^2} \sqrt{\sum_{n=1}^{N}(y(i + n) - \bar{y}_i)^2}}
\]  

(1)

where \( i = 1: I, N = 4000, K = 1.44 \times 10^6, I = K - N + 1 \)

and \( \bar{y}_i = \frac{1}{N} \sum_{n=1}^{N} y(i + n) \).

Fig. 2.12 plots the maximum \( CC \) for each segment along with the absolute time delay between the time of maximum correlation and the beginning of segment \( x \). There is a clear difference, in the maximum \( CC \) and their corresponding time delays, between HFRS activity that occur during stimulation and in the absence of stimulation. In the absence of stimulation, 81 out of 90 HFRS segments, exhibit their maximum correlation with the contralateral hippocampus within 2.5ms, which is the limit of the sampling resolution. In contrast, for the 90 HFRS segments that occur
during stimulation, there is not a single instance of the absolute time delay below 2.5ms, instead the minimal delay, during stimulation, is 1.89min. As a whole, the mean absolute time delay is 1.65±6.85min in the absence of stimulation and 19.41±12.28min during stimulation, a significant increase (paired t-test, P < 0.001). The maximum correlation coefficients also demonstrate a similar trend with HFRS waveforms having average coefficients of 0.72±0.11 in the absence of stimulation compared to 0.44±0.09 during stimulation (paired t-test, P < 0.001). The above results suggest that not only can the proposed electrical stimulation protocol suppress the power of epileptiform activity; it also has a disruptive effect on the synchrony between the bilateral HFRS activity in the hippocampal structure.
2.5 DISCUSSION

In this study, we present a novel electrical stimulation paradigm for the suppression of seizures in an acute model of MTLE status epilepticus. The stimulation utilizes an original target, the VHC fiber tract, to simultaneously influence large portions of both sides of the hippocampal structure. The stimulation frequency is determined by approximating the spontaneous periodic spiking frequency observed in the hippocampal structure while the stimulation amplitude is set to induce the maximum evoked response recorded from the CA3 region of the hippocampus. The acute model of MTLE status epilepticus is generated by administering periodic bilateral micro-injections of solution containing 4-AP and shows consistent bilateral spontaneous epileptiform activity, within the hippocampal structure, that persists throughout the length of the experiments. These spontaneous epileptiform activity are characterized by transitions between a HFRS morphology and a LFPS morphology. Using this model, we have demonstrated the ability of the proposed stimulation protocol to significantly reduce the bilateral signal power of the recorded epileptic waveforms during stimulation. Animals that received stimulation show, on average, approximately 88% reduction in the bilateral powers of the epileptic signals when compared to the control animals. We have also shown that the efficacy of the proposed stimulation paradigm depends heavily on the stimulation amplitude where higher stimulation amplitudes resulted in better epileptic power suppression. While the reduction in the bilateral epileptic signal power, due the stimulation paradigm, is significant, the mechanism behind the effect is not understood. One possible explanation is that the stimulation induces increases in the inhibitory pathways throughout large portions of the bilateral hippocampal structure, which reduces the amount of spontaneous epileptiform activity.
Another possible mechanism may be the entrainment effect that was also observed during this study.

One of the observations made during this study is the differential effect of the proposed stimulation paradigm on the two types of epileptic waveform morphologies (HFRS, LFPS) and the resultant changes in the dynamics between them. In the control animals, the HFRS morphology occupies the majority of the time. However in the animals that received stimulation, this trend is reversed. Following the delivery of the stimulus train, there is a significant increase in the duration of the LFPS morphology, where it occupies 77.28% of the time compared to 22.72% in the control group. These results suggest an entrainment effect induced by the stimulation paradigm and may be a possible mechanism for the reduction in the bilateral epileptic power during stimulation. A possible entrainment effect is shown by Sunderam et al. (Sunderam, Chernyy et al. 2009). In the study, low frequency polarizing electric fields were able to entrain the epileptic seizure activities to follow the stimulation frequency. Several studies have also shown that low-frequency low-amplitude (sub threshold) AC electrical stimulations can entrain the hippocampal network to oscillate at the stimulation frequency (Mason, Voss et al. 2010; Reato, Rahman et al. 2010). While these studies have all demonstrated the ability to entrain the hippocampal network using various modes of electrical stimulation, none of them have reported an entrainment following the termination of stimulation. The observation that LFPS morphology is increased in duration, following stimulation, is unique and deserves further study to elucidate the mechanism behind the continuation of the entrainment effect.

In addition to the effects discussed above, the proposed stimulation paradigm also has a disruptive effect on the synchrony of the epileptiform activity between the two sides of the hippocampal structure. In the absence of stimulation, we observed the bilateral epileptiform
activity that consistently mirror each other through out experimentation. In fact, it’s possible to
know the epileptiform activity of one side by simply looking at the epileptiform activity of the
contralateral side. A quantitative study shows that the majority of bilateral HFRS activity are, in
fact, maximally correlated with each other within 2.5ms. It’s also observed that during
stimulation, when HFRS activity do escape, they were confined to only one side of the
hippocampal structure with no visible mirroring activity from the contralateral side and
correlation study yielded the occurrence of maximal correlation at a minimum of 1.89min. One
possible mechanism for this effect may be related to the role of the VHC fiber tract. The VHC is
a significant communication pathway between the two sides of the hippocampal structure. By
applying electrical stimulation directly to the VHC, the communication between the two
hippocampi is disrupted and thus preventing epileptiform activity, originating from one
hippocampus, to invade the contralateral hippocampus. However how does 5Hz electrical
stimulation disrupt the signal conduction, through an axonal fiber tract, is uncertain. While high
frequency stimulation have been shown to block axonal conduction (Jensen and Durand 2009),
there is no evidence suggesting a similar effect with low frequency stimulation. Another
possible mechanism is an increase in the inhibitory factors, within the bilateral hippocampal
network, such as GABA mediated inhibition, due to the stimulation that raises the threshold for
spontaneous epileptiform activity to form or invade. Regardless of the mechanism, this
disruption in synchrony between the bilateral hippocampal structure may be an additional
advantage with the proposed stimulation paradigm. Patients suffering from MTLE can exhibit
bilateral epileptic foci. There are a number of studies that have shown unilateral epileptic focus
induces structural changes, such as neuronal cell death and mossy fiber sprouting, not only in the
ipsilateral hippocampus but also in the contralateral hippocampus (Barr, Ashtari et al. 1997;
Araujo, Santos et al. 2006; Knake, Salat et al. 2009). There are also evidence of an increase in the connectivity between the two sides of the hippocampi as the disease progresses through time (Morgan, Rogers et al. 2011) along with demonstration of unilateral epileptic foci generating an epileptic foci in the healthy contralateral hippocampus (Khalilov, Holmes et al. 2003). Therefore, the ability of the proposed stimulation paradigm to disrupt the connectivity between the bilateral hippocampi could play a significant role in the epileptic suppression witnessed in the animals that received the stimulation.

In summary, we presented a novel electrical stimulation paradigm that can suppress the power of the bilateral status epilepticus like activity in the hippocampal structure, entrain the hippocampal network to mimic the stimulation frequency and disrupt the synchrony of the HFRS epileptiform activity between the two sides of the hippocampal structure. The proposed stimulation paradigm may lead to a possible therapeutic solution not only for adult MTLE patients that experience recurrent seizures, not controlled by current AED treatments, but also for patients suffering from status epilepticus during infancy that could lead to the development of MTLE, later in life. With the implantation of a single electrode within the hippocampal commissural fibers, it is possible for us to deliver epileptic seizure mitigating stimulation to both sides of the hippocampi. While the results presented in this study are promising, we cannot comment about the stimulation’s effect on the physical manifestations during seizures, due to the anesthetized state of the animal. As such, it is not possible to state that the substantial decrease in epileptic powers measured will result in a substantial decrease in the symptoms of the epileptic seizures.
2.6 TABLE CAPTIONS

Table 2.1: A comparison of the HFRS and LFPS %duration between the control group and the stimulation group. In the absence of stimulation, the recorded left and right hippocampal activities mirror each other so only one %duration value is given. During stimulation, the HFRS %duration for the left and right side are given by (left %duration)/(right %duration), while LFPS waveforms are completely suppressed. For hour 1, there is no significant difference between the (HFRS and LFPS) %duration of the control group and stimulation group, $P = 0.335$. In a one to one comparison between the periods of stimulation (hours 2, 4 and 6) for the control group and the stimulation group, there are significant reductions in the %duration of both the HFHAPS and LFPS activities for each hour within both sides of the hippocampi, $P < 0.001$. An hour to hour comparison of the periods following stimulation (hours 3, 5 and 7) yield significant increases in the %duration of LFPS and decreases in HFRS in the stimulation group relative to the control group.
2.7 FIGURE CAPTIONS

**Figure 2.1:** The orientation of: the left and right recording electrodes (LR, RR) in the CA3 cell layer of the hippocampus; the left and right micro-syringes (LmS, RmS) in the CA1 cell layer; the stimulation electrode (Stim) at the VHC; the ground screw; and the reference screw. Samples of the evoked bilateral CA1 potentials recorded from the micro-syringe locations and CA3 potentials from the bilateral recording electrodes, via a single pulse delivered through the stimulation electrode, are shown.

**Figure 2.2:** Example of the stimulus artifact removal method. The top recordings are 2s of the original bilateral epileptic activity signal. This signal is combined with the original stimulation artifact signal (obtained from a healthy animal) to form the test signal. The artifact removal algorithm is then applied to the test signal to yield the artifact templates. Subtraction of the artifact templates, from the test signal, results in the recovered epileptic activity.

**Figure 2.3:** A 100s example of the status epilepticus like waveforms generated by the epileptic model used in the study. The epileptic activities are described by transitions from a HFRS (region a and b) morphology to a LFPS morphology (region c) and vice versa. In the absence of stimulation, these epileptic activities are robust and last throughout the length of the experiment. One notable observation, the bilateral epileptic activities demonstrate significant synchrony between the two sides.
**Figure 2.4:** Average computed epileptic signal power of 2s data windows with 1s overlap between windows, for a control animal, over the duration of the experiment (7hrs). Bilateral micro-injections of 4-AP are marked by the arrows.

**Figure 2.5:** A 3 second sample of the LFPS waveform used to determine the stimulation frequency. The waveform is described by low frequency high amplitude periodic spiking activity. An average of the normalized power spectrum of 1min LFPS waveforms, obtained from each of the 15 control animals, is plotted. The power spectrum shows a peak around 5Hz which is then set as the stimulation frequency.

**Figure 2.6:** Average normalized evoked potential amplitude during the hours of stimulation in three healthy animals. The amplitude is measured as the average potential between a and b subtracting the potential at c. There is no significant difference in the average amplitudes between the different periods of stimulation.

**Figure 2.7:** Average computed epileptic signal power of 2s data windows with 1s overlap between windows, for a stimulation animal, over the duration of the experiment (7hrs). Bilateral micro-injections of 4-AP are marked by the arrows. Periods of stimulation are marked by the bars. During stimulation, the bilateral powers of the epileptic activities are significantly reduced.
**Figure 2.8:** Comparison between the average normalized epileptic power computed for the control group and the stimulation group. During the hours of stimulation (2, 4 and 6) (the left most plots) the stimulation group has significantly lower bilateral epileptic power when compared to the corresponding hours of the control group. For the hours post stimulation (3, 5 and 7)(the right most plots), the bilateral epileptic signal power are also lower in the stimulation group when compared to the corresponding hours of the control group. There is little evidence of an increase in epileptic power suppression, for the 2\textsuperscript{nd} and 3\textsuperscript{rd} stimulation sessions, both during and post stimulation.

**Figure 2.9:** Dose response curve. In five animals the stimulation amplitude is set to evoke 50% of the maximum evoked response, with another five animals receiving stimulation evoking 10% of the maximum evoked response. The bilateral average normalized powers, during the hours of stimulation, are plotted for the above stimulation amplitudes along with the original stimulation group (100%) and the control group. The results show that 100% stimulation intensity is the most effective at suppressing seizures while 10% stimulation did not yield any significant difference in epileptic signal power compared to the control group. During hour 6, 50% stimulation induced, within the right hippocampal structure, epileptic power reduction that is between the control group and the stimulation group, suggesting a possible inverse graded relationship between stimulation intensity and epileptic power reduction.
**Figure 2.10:** A pattern of entrainment by the stimulation protocol. Following the termination of the stimulus train, the bilateral hippocampal network’s spontaneous spiking continues and mimics the applied stimulus train.

**Figure 2.11:** An example of the disruption between the two sides of the hippocampi during stimulation. The upper samples illustrate a HFRS waveform present in the left hippocampus but absent in the right hippocampus, while the lower samples illustrate a HFRS waveform that is present in the right hippocampus but absent in the left hippocampus. In both cases, bilateral synchrony is disrupted.

**Figure 2.12:** Plot of the maximum correlation coefficients between the two sides of the hippocampi, along with the time delays of maximal correlation, for 180 HFRS waveform segments each 5s in duration. 90 of the segments are obtained during stimulation while the remaining 90 segments happen prior to stimulation. In the absence of stimulation, the epileptiform activity between the two sides of the hippocampi exhibit strong synchrony with 81 out of 90 HFRS segments having their maximum correlation within a delay 2.5ms. During stimulation, the bilateral synchrony is disrupted with a significant increase in the time delays. The correlation values are also significantly lower during stimulation when compared to periods of no stimulation.
### 2.8 TABLES

<table>
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<th>Control LFPS (%duration)</th>
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Table 2.1
2.9 FIGURES

Figure 2.1
Figure 2.2

Left
Original epileptic activity

Right

Original stimulation artifacts

Test signal

Amplitude(mV)

Artifact templates

Recovered epileptic activity

Time (s)
Figure 2.3
Figure 2.4
Figure 2.5
Figure 2.6
Figure 2.7
Figure 2.8
Figure 2.9

Stimulation Intensity (% Max Response)

*** P<0.0001
** P<0.001
* P<0.01
Figure 2.10
Figure 2.12

Max Correlation Coefficient vs. Absolute Delay (min)

+ stim
○ no stim
A tunable support vector machine assembly classifier for epileptic seizure detection.
3.1 ABSTRACT

Automating the detection of epileptic seizures could reduce the significant human resources necessary for the care of patients suffering from intractable epilepsy and offer improved solutions for closed-loop therapeutic devices such as implantable electrical stimulation systems. While numerous detection algorithms have been published, an effective detector in the clinical setting remains elusive. There are significant challenges facing seizure detection algorithms. The epilepsy EEG morphology can vary widely among the patient population. EEG recordings from the same patient can change over time. EEG recordings can be contaminated with artifacts that often resemble epileptic seizure activity. In order for an epileptic seizure detector to be successful, it must be able to adapt to these different challenges. In this study, a novel detector is proposed based on a support vector machine assembly classifier (SVMA). The SVMA consists of a group of SVMs each trained with a different set of weights between the seizure and non-seizure data and the user can selectively control the output of the SVMA classifier. The algorithm can improve the detection performance compared to traditional methods by providing an effective tuning strategy for specific patients. The proposed algorithm also demonstrates a clear advantage over threshold tuning. When compared with the detection performances reported by other studies using the publicly available epilepsy dataset hosted by the University of BONN, the proposed SVMA detector achieved the best total accuracy of 98.72%. These results demonstrate the efficacy of the proposed SVMA detector and its potential in the clinical setting.
3.2 INTRODUCTION

Since the first human electroencephalogram (EEG) recording reported by Hans Berger in 1929, the EEG has become a ubiquitous tool in the management and treatment of patients suffering from epilepsy (Vulliemoz, Lemieux et al. 2009). Regardless of its modality, whether it is surface, scalp or intracranial recordings, the EEG offers the clinician the ability to monitor and localize abnormal electrical activity in the human brain. While essential as a diagnostic tool, the clinical utilization of EEGs presents several challenges. (1) Long-term continuous EEG recordings implemented in the clinical setting generate a very large amount of data that can only be analyzed by trained clinical neurophysiologists. The result is an extremely taxing and often impossible task. (2) When reading an EEG recording, equally qualified physicians often disagree on their analysis of the epileptic seizure activities and there is no consistent standard that can be used as the base reference (Friedman, Claassen et al. 2009; Stefan and Hopfengartner 2009). In these cases, a reliable automated detection algorithm can greatly facilitate the care of epilepsy patients and offer a common diagnosis standard for physicians.

Efforts to study seizure detection began as early as the 1970s (S. S. Viglione 1970) and benefiting from the advances made in computing technology, the field has since established a significant number of published algorithms. Many of these detection algorithms are based on support vector machine classifiers (SVM) which often exhibit superior generalization capabilities compared to other classifiers such as neural networks (Gonzalez-Vellon, Sanei et al. 2003; Acir and Guzelis 2004; Shoeb, Edwards et al. 2004; Acir, Oztura et al. 2005; Andrew B. Gardner 2006; Guler and Ubeyli 2007; Suryannarayana Chandaka 2009). The SVM binary classifier was proposed by Vapnik (Vapnik 1995) and is based on the theory of structural risk minimization (SRM). The SRM principle tries to minimize the upper bound of the generalization error by
finding the balance between empirical performance and the Vapnik Chervonenkis (VC) dimension, a measure of the generalization capability of the classifier. This is a departure from traditional neural networks where the decision boundaries are constructed by minimizing empirical risk alone. While the SRM theory does not guarantee superior generalization performance with SVM classifiers, there are numerous empirical evidence to support the high accuracy of SVMs (Burges 1998).

While published detection algorithms for epilepsy are numerous and often exhibit good performance in the research setting, the implementation of seizure detection in the clinical setting has been less successful. This failure can be attributed to several factors that can degrade the performance of the detector. (1) Epileptic seizure morphology can have significant variations between individual patients. As a result, a seizure detection algorithm with good performance across the general patient population can perform poorly for specific patients that do not fit the design criteria. (2) The seizure morphology of a patient can vary with time due to changes in the state of the patient or the recording equipment. (3) The EEG recordings can be contaminated with physiological and non-physiological artifacts that may imitate epileptic seizure activity. With regard to type I challenges, several studies have demonstrated an improvement in seizure detection performance using patient-specific detection algorithms as compared to patient non-specific algorithms (Qu and Gotman 1997; Wilson 2006; Haas, Frei et al. 2007; Shoeb, Bourgeois et al. 2007). However, these strategies may have little effect on reducing type II and III errors and they require a detector to be trained separately for each patient, which is tedious in the clinical setting.

An alternative strategy is to design tuning capabilities into the detection algorithm so that the operator can adapt the detector to fit a given need. In (Saab and Gotman 2005; Haas, Frei et
the ability to tune the detector is realized by allowing the user to adjust the classification threshold. This is a simple strategy but its effectiveness has not been demonstrated. In this study, an alternative strategy is employed to enable tuning of the SVMA seizure detection algorithm. Instead of tuning by uniformly shifting the decision boundary, thresholding, a novel methodology is used to change the decision boundary based on the available training data. This new detection algorithm consists of the following characteristics:

1. A novel feature set composed of the median Teager energy of the signal, the power of the signal, and the Lempel-Ziv entropy of the signal in five physiological frequency sub-bands extracted using a band-pass Gabor filter bank.

2. A SVM assembly classifier. Each member of the assembly is trained with a different weighting ratio between seizure data and non-seizure data. By choosing different SVMs in the assembly, the user can tune the performance of the detector for a given situation that still takes the training data into consideration and is easy to implement.

The objective of this paper is to implement a novel SVMA seizure detection algorithm to improve the performance of detection algorithms by providing the end user with the ability to easily tune the detection algorithm for specific patients. In the following sections, the algorithm of the proposed detector is first presented. Feature vectors are then extracted from the datasets and their abilities to capture seizure morphologies are examined. The detector is then trained and tested on an epileptic seizure dataset that is publicly available online. The results are used to compare the tuning performance of the proposed detector against threshold tuning, as well as other published detection algorithms on the same dataset.
3.3 METHODS

3.3.1 EEG data and pre-processing

In order to substantiate the efficacy of the proposed SVMA detector, its performance should be compared directly to other published algorithms. However a fair evaluation of different detection algorithms is difficult, if not impossible. Published detection studies employ a wide range of datasets which can have a significant impact on the detection performances achieved. For instance, a dataset chosen with strong epileptic seizure morphology and minimal artifacts will offer significant advantages to the quantification of an algorithm’s performance measure versus a dataset with less selection. In this case, the publicly available dataset, provided by the University of Bonn, is the best method for comparison and a number of detection algorithms have been published using this dataset.

The dataset contains 5 subsets (A-E) each with 100 single-channel EEG segments, 23 seconds/segment in duration. These segments were selected and cut out from the continuous multichannel EEG recordings following visual inspection for artifacts, e.g., due to muscle activity or eye movements. Subsets A and B are surface EEG recordings from five healthy volunteers with eyes open and closed respectively. Subsets C, D and E are intracranial recordings from the hippocampal formation of five epileptic patients all of whom experienced complete seizure remission following hippocampal resection. D and C are seizure-free intracranial recordings from the epileptogenic zone and the hippocampal formation of the opposite cerebral hemisphere respectively. Subset E is recorded during the occurrence of epileptic seizures from ictal sites. The depth electrodes are implanted symmetrically into the hippocampal formations and strip electrodes are implanted onto the lateral and basal regions of
the neocortex. The EEG signals are recorded with a 128-channel amplifier system, at 173.61Hz sampling frequency with 12 bit digitization and an average common reference. In this study, only sets A, D and E are used. This dataset selection is made to match previously published studies listed in table 1. The use of the same datasets is necessary for a more accurate performance comparison between those algorithms and the proposed SVMA detector. While it is not ideal to mix scalp EEG data (set A) with intracranial EEG data (set D and E), the feature vectors used as inputs to the SVMA detector exhibits little difference between set A and C.

3.3.2 Feature Extraction

The single channel EEG data segments are divided into 256 points sliding time epochs with 128 point overlap between adjacent epochs. This is equivalent to approximately 1.47 seconds/epoch and 0.735 seconds of overlap between adjacent epochs. Overall, 3100 epochs are constructed from each dataset for a total of 9300 epochs over the three datasets. The median Teager energy of the signal, the power of the signal and the Lempel-Ziv Complexity of the physiological sub-bands are calculated for every epoch and combined to form the feature vector that is the input to the SVM A classifier. The physiological sub-bands are separated through a five-channel Gabor band-pass filter bank. An illustration of the feature vector construction process is shown in figure 3.1.

3.3.2.1 Median Teager Energy. The Teager energy was first introduced by Herbert M. Teager in 1990 in (Herbert M. Teager 1990) and subsequently derived by J. F. Kaiser (Kaiser 1990). The discrete version of the Teager Energy Operator (TEO) is defined by the equation:

\[ \Psi(x(n)) = x^2(n) - x(n-1)x(n+1) \]  

(1)

where \( \Psi \) is the TEO and \( x \) is the signal. Kaiser’s derivation of this equation is based on the energy of a simple mechanical oscillator where the total energy of the oscillator is proportional to the frequency and amplitude squared. Given:
\[ x(n) = A \cos(\Omega n + \phi) \]  
\[ \Psi(x(n)) = A^2 \sin^2(\Omega) \]  
\[ \text{For small values of } \Omega, \text{ equation (3) can be approximated as} \]
\[ \Psi(x(n)) \approx A^2 \Omega^2 \]  

Equation (4) hints at the utility of the Teager energy as a feature for seizure detection. Unlike traditional energy calculations, the Teager energy is square proportional to both the signal amplitude and the signal frequency. Given that epileptic activities often exhibit higher frequencies in their EEG recordings, the Teager energy may be advantageous in distinguishing seizure events. The calculation of the Teager energy is also trivial. In this work, the median Teager energy for each data segment is extracted as a feature.

3.3.2.2 Power. The power is included as a feature with the Teager energy because the juxtaposition of the two features can offer information for the frequency content of the EEG data. The power \( P \) is calculated as

\[ P(x(n)) = \frac{1}{n} \sum_{n=1}^{n} x^2(n) \]  
where \( n = 256 \), the length of each epoch.

3.3.2.3 Gabor Band-pass Filter Bank. For the extraction of the physiological sub-bands, the single channel signals are filtered through a bank of band-pass filters. The band-pass filters are constructed using the Gabor filter. The Gabor filter \( g(t) \) is described in both the time domain and the frequency domain by

\[ g_\sigma(t) = 2h_\sigma(t) \sin(\omega_c t) \]  
where
\begin{equation}
    h_\sigma(t) = (2\pi)^{\frac{1}{4}} \sqrt{\sigma} \exp(-\sigma t^2 / 4)
\end{equation}

and

\begin{equation}
    H(\sigma) = (2\pi)^{\frac{1}{4}} \sqrt{\frac{2}{\sigma}} \exp\left\{ -\left( \frac{\sigma}{\sigma_c} \right)^2 \right\}
\end{equation}

\(\omega_c\) is the center frequency of the band, \(\sigma\) is the width of the filter in Hertz. The discrete version of the filter is implemented by sampling the continuous version. Given the sampling frequency \(F_s = 173.61\) Hz and \(T = 1 / F_s\), the Gabor filter in discrete form is

\begin{equation}
    g_\sigma[n] = 2h_\sigma[n] \sin(\Omega_c nT)
\end{equation}

\begin{equation}
    h_\sigma[n] = (2\pi)^{\frac{1}{4}} \sqrt{\sigma} \exp(-\sigma nT^2 / 4)
\end{equation}

\(\Omega_c\) is the discrete frequency. The filters’ center frequency and bandwidth are designed with wavelet characteristics where the frequency resolution of the filters increases with a decrease in filter center frequency logarithmically.

\begin{align}
    \omega_m &= 3 \cdot 2^{-(m+1)} \Omega_c; \quad m = 1, \ldots, M - 1 \\
    \omega_M &= 0
\end{align}

\begin{align}
    \sigma_m &= \frac{\sigma_m}{3\sqrt{\ln 2}}; \quad m = 1, \ldots, M - 1 \\
    \sigma_M &= 2\sigma_{M-1}
\end{align}

\(\omega_m\) are the center frequencies and \(\sigma_m\) are the corresponding bandwidths. The adjacent filters intersect at half-peak which results in band-pass filters with constant energy across scales. For this study a five band bandpass Gabor filter bank is constructed with center frequencies of (45, 22.5, 11.25, 5.625 and 0 Hz). These band-pass filters are constructed to overlap the physiological frequencies of Gamma (> 30 Hz), Beta (14-30 Hz), Alpha (8-14 Hz), Theta (4-8 Hz) and Delta (< 4 Hz). These frequencies garner the most clinical interests.
3.3.2.4 Lempel-Ziv Complexity ($C_{LZ}$). Lempel-Ziv complexity measures the number of new patterns in a binary sequence. It is closely associated with entropy and is computationally fast. Recently, Lempel-Ziv complexity has been used in biomedical applications to estimate complexity measures in biological signals (Amigo, Szczepanski et al. 2004; Jing, Jianbo et al. 2006). Although there are several ways to calculating the $C_{LZ}$ of a given signal, the following method was used:

1. The numerical sequence, which is the input signal, is transformed into a binary sequence $B$ by setting values above the median of the signal to 1 and the remaining values to 0, $B = b_1b_2b_3 \ldots b_n$.

2. The binary sequence $B$ is then rewritten as a consecutive series of words $B = w_1w_2 \ldots w_j$, where $w_1 = b_1$ and $w_j$ is a word that has not appeared in the previous $n-1$ words.

3. Let $J$ = the number of words extracted from a given sequence $B$ of length $N$. Then $C_{LZ}$ is defined by

$$C_{LZ} = J\left[\log_2(N)+1\right]/N$$

(13)

For large values of $N$, equation 13 can be rewritten as

$$C_{LZ} = J\log_2(N)/N$$

(14)

For example, the sequence $B = 100101110011$ is parsed into $1\cdot01\cdot10\cdot11\cdot110\cdot011$. Since there are a total of 7 words so $J = 7$, $N = 14$ and $C_{LZ} = 1.9037$. For this study, $C_{LZ}$ is calculated for each physiological sub-band and because the epoch lengths are kept constant at $N=256$, $C_{LZ}$ can be approximated by $J$ alone.

3.3.3 Support Vector Machine Assembly (SVMA)
The SVMA is composed of a group of separately trained SVM classifiers. Figure 3.2(a) illustrates the architecture of a single SVM. Given the data sets, \((x_1, y_1), \ldots, (x_m, y_m)\) \(\mathcal{X} \times \{\pm 1\}\), where \(x\) are patterns of the data and \(y\) are the class labels of each data set \(x\). The SVM tries to construct the optimal hyperplane that yields the maximum margin of separation between the members of the two classes by solving the following quadratic programming optimization problem.

\[
\begin{align*}
\text{minimize} & \quad \frac{1}{2} \|w\|^2 \\
\text{subject to} & \quad y_i \cdot ((w \cdot x_i) + b) \geq 1 \\
& \quad i = 1, \ldots, m \\
& \quad w \in \mathbb{R}^N, b \in \mathbb{R}
\end{align*}
\]

(15)

For non-linearly separable data, a soft margin can be constructed by the introduction of the slack variable \(\xi_i \geq 0\), \(i = 1, \ldots, m\). The new optimization problem becomes

\[
\begin{align*}
\text{minimize} & \quad \frac{1}{2} \|w\|^2 + C \sum_{i=1}^{m} \xi_i \\
\text{subject to} & \quad y_i \cdot ((w \cdot x_i) + b) \geq 1 - \xi_i \\
& \quad \xi_i \geq 0, \quad i = 1, \ldots, m. \\
& \quad w \in \mathbb{R}^N, b \in \mathbb{R}
\end{align*}
\]

(16)

where \(C\) is a user defined constant greater than 0. This problem can be solved with its Lagrangian dual and can be simplified to
\[
\text{maximize } \sum_{i=1}^{m} a_i - \frac{1}{2} \sum_{i,j=1}^{m} a_i a_j y_i y_j (x_i, x_j) \\
\text{subject to } \quad C \geq a_i \geq 0, \\
\sum_{i=1}^{m} a_i y_i = 0.
\]

where \( w = \sum_{i=1}^{m} a_i y_i x_i \)

\[i = 1, \ldots, m.\]

so the decision function becomes

\[ f(x) = \text{sgn} \left( \sum_{i=1}^{m} y_i a_i (x \cdot x_i) + b \right). \]

From this deduction, it is clear that \( w \) only depends on the patterns \( x_i \) where \( a_i \) is not zero; these are the support vectors. These support vectors lay on the margin of the decision boundary and all other data points are irrelevant. Since the feature vector \( x \) only appear in the equations as dot products the decision functions can be converted to the form

\[ f(x) = \text{sgn} \left( \sum_{i=1}^{m} y_i a_i K(x, x_i) + b \right) \]

where \( K(x, x_i) \) is a kernel function that maps the input space into a higher dimensional feature space. In this higher dimension, the hyperplane decision boundary is then constructed that results in nonlinear decision curves in the input space. In the proposed SVMA detector, all implementations of the SVMs are done with the Radial Basis Function kernel (RBF)

\[ K(x, x_i) = \exp \left( \gamma \| x - x_i \|_2^2 \right), \gamma > 0 \]

where \( \gamma \) is the radius of the RBF function set by the user using the \textit{LIBSVM} tool kit. (Chih-Chung Chang 2001)

The architecture of the SVMA detector is shown in figure 3.2(b). The detector consists of an assembly of individual SVMs. Each SVM in the collection is trained with the same data but different weighting ratios between the seizure data and non-seizure data ranging from non-
seizure: seizure of 512:1 to 1:512 in powers of 2. With this strategy, SVMs trained with higher weights for seizure data are correspondingly more sensitive to seizure activity while SVMs trained with higher weights for non-seizure data are less likely to give false detections. The end user can then tune the detector by choosing the output of a particular SVM classifier, in the assembly as the detector’s output.

3.3.4 Detection Performance Evaluation

The performance of the proposed seizure detection algorithm is evaluated with the following parameters:

\[ a) \text{ Sensitivity: } \frac{TP}{TP+FN} \]
\[ b) \text{ Specificity: } \frac{TN}{TN+FP} \]
\[ c) \text{ Total Accuracy: } \frac{TP+TN}{TP+FN+TN+FP} \]

where TP = true positives, FN = false negatives, TN = true negatives, FP = false positives.

d) Mean detection latency: The BONN dataset used in this study does not have continuous data segments consisting of a pre-seizure period, seizure onset and post-seizure period, so it is not possible to determine the traditional detection latency which basically defines the period between the actual seizure onset and the first detection of seizure. However, because the proposed SVM algorithm can affect the true detection latency via tuning, an alternative definition is used for the detection latency. In this study, we measure the detection latency as the time difference between the beginning of a seizure segment and the first epoch within that seizure segment that is classified as seizure. While this quantification of detection latency is not ideal, it does offer insight into how the SVM algorithm can affect the true detection latency.

3.3.5 Training & Testing Strategy
One hundred training and testing dataset pairs are randomly created using the EEG dataset obtained from Department of Epileptology, University of Bonn. Each training set is randomly constructed from the concatenation of 20% of the available seizure data segments (20 out of 100 segments from set E) and 20% of the non-seizure data segments (20 out of 100 segments from set A and 20 out of 100 segments from set D). The remaining 80% of data segments are combined together to form the testing set (80 segments separately from dataset A, D and E). This results in 60 data segments or 1860 epochs per training set and 240 data segments or 7440 epochs per test set. Each train/test dataset pair is dubbed a “virtual patient” or VP and each seizure segment is counted as a single seizure. The proposed SVMA detection algorithm is then trained on the training dataset for each VP and evaluated on the corresponding test dataset.
3.4 RESULTS

3.4.1 Feature Extraction

The features chosen for the SVMA input are first evaluated for their ability to capture seizure activity relative to baseline activity. Seven features are extracted from each epoch of data 256 points in length. They include the median Teager energy, power and the Lempel-Ziv complexity of five physiological sub-bands isolated through a Gabor band-pass filter bank. Figure 3.3(a) shows the frequency response of the five-band Gabor filter bank. The frequencies are normalized to the sampling frequency. Examples of the output of the Gabor filter bank are displayed in figure 3.3(b). In the figure, data segments of 23 seconds in duration, obtained separately from datasets A, D and E are displayed along with their corresponding filtered waveforms. Following the filter stage, the $C_{LZ}$ coefficients are calculated for each filtered sub-band. These $C_{LZ}$ values are then combined with an epoch’s median Teager energy and power to form the input feature vector for the SVMA classifier.

To determine the sensitivity of the chosen features to the presence or absence of a seizure event, the normalized values for each feature during epileptic seizure epochs versus non-seizure epochs were computed and plotted in figure 3.4. In figure 3.4(a), the features calculated for the 9300 data epochs extracted from set A, D and E are concatenated together with the set E features in the middle. In figure 3.4(b), the mean and standard deviation of the features during seizure and non-seizure epochs are plotted. The majority of seizure epochs contain higher power relative to non-seizure epochs, but there are non-seizure epochs that also contain high power and could lead to false seizure detections. In comparison, high median Teager energies are all confined within seizure epochs, an advantage when compared to power. However, during seizure epochs, the Teager energies display larger variations when compared to powers of the same period. The
Lempel-Ziv complexities, from the extracted physiological sub-bands, also demonstrate average amplitude differences between seizure epochs and non-seizure epochs. In the highest frequency band centered at 45Hz, there is a uniform increase in $C_{LZ}$ values during seizure epochs, while the remaining lower frequency bands all exhibit a reduction in the computed $C_{LZ}$ values. Using one-sided two sample t-tests with unequal variances, the features all show significant differences in means between non-seizure and seizure epochs, $P < 0.001$.

### 3.4.2 Detection Performance

The proposed SVMA seizure detection algorithm utilizes an assembly of SVM classifiers each trained with a different weighting ratio between seizure and non-seizure data. By selecting the output of a particular SVM within the assembly as the output of the SVMA classifier, the operator can tune the performance characteristics of the detector and achieve higher classification performances. To evaluate the tuning capability of the SVMA, each member of the assembly is trained and tested over 100 VPs and the resultant mean and standard deviation of the classification sensitivity, specificity and total accuracy are plotted in Figure 3.5(a). From left to right on the x-axis, member SVMs are trained with weighting ratios heavily favoring non-seizure data (512:1) to ratios that heavily favor seizure data (1:512). The weighting ratios increase in powers of 2, which results in a total of 19 SVMA members. In most detection studies, the classifier weighs seizure and non-seizure data equally during training corresponding to a weighting ratio of (1:1). Therefore, the performance of each SVMA member can be compared directly to SVM$_{1:1}$, as comparisons with the traditional SVM classifier. Starting from one extreme where the SVMA members are weighted heavily towards non-seizure data, SVM$_{512:1}$ achieved a detection specificity of $98.77\pm1.24\%$. This is an improved performance compared to the specificity of SVM$_{1:1}$, which is $97.33\pm1.74\%$. However, this improvement comes at the
expense of sensitivity which is reduced from 85.77±6.00% with SVM\(_{1:1}\) to 75.54±6.97% with SVM\(_{512:1}\). Accordingly, by increasing the weighting ratio to favor seizure data, moving along the x-axis, the SVM classifiers are able to achieve higher sensitivities at the expense of specificities. For example, SVM\(_{1:512}\), has an increased sensitivity of 95.47±2.39% relative to 85.77±6.00% with SVM\(_{1:1}\) and a decrease in specificity from 97.33±1.74% with SVM\(_{1:1}\) to 86.79±5.31%. The best mean total accuracy over the 100 VPs is 94.11±0.91%, achieved with SVM\(_{1:2}\) instead of SVM\(_{1:1}\), which achieved a mean total accuracy of 93.48±1.17%. The mean total accuracies then decrease as the detector is tuned away from SVM\(_{1:2}\) along either direction of the x-axis. At the extremities, the mean total accuracies are 91.03±1.50% for SVM\(_{512:1}\) and 89.67±3.31% for SVM\(_{1:512}\). These results first demonstrate the tuning capability of the SVMA algorithm. By simply choosing a specific SVMA member, the user can tune the proposed detector to operate with greater sensitivity or specificity. These results also suggest that higher classification performances can be achieved over the traditional SVM\(_{1:1}\) classifier, by simply weighting the non-seizure and seizure data differently, such as (1:2).

Another important performance parameter in seizure detection is detection latency, particularly for closed-loop DBS control of seizures. Figure 3.5(b) plots the mean seizure detection latency for each SVMA member evaluated over the 100 VPs. The mean detection latency reach a minimum of 1.62±0.86s, when the SVMA is tuned to (1:64). This is a noticeable improvement over a mean detection latency of 2.48±1.36s achieved with the traditional SVM\(_{1:1}\) detector. Further tuning towards weighting ratios favoring seizure data does not result in additional benefits in detection latency. Since each epoch spans a period of 1.47s with a 0.735s overlap between adjacent epochs, the SVMA tuned to SVM\(_{1:64}\) is able to detect almost every seizure segment upon the first epoch of epileptic seizure activity. This may offer a significant
advantage in situations where fast responses are necessary for effective treatment of epileptic seizures. However, when the SVMA is tuned for higher specificity, the detection latency increases and approach a maximum of 4.23±1.91s at a weighting ratio of (64:1). Further weighting towards non-seizure data does not alter the detection latencies significantly.

The above studies demonstrate the tuning capability of the SVMA detector to alter its sensitivity, specificity, total accuracy and detection latency performance characteristics. In order to study the effect of patient-specific tuning with the SVMA detector, the detector was tuned to achieve the best classification performance for each individual VP and the resulting classification performance parameters analyzed over the 100 VPs. In figure 3.6(a), the number of VPs receiving the best detection accuracy for a given SVM member is plotted. Out of 100 VPs, the baseline SVM1:1 classifier obtained the best total accuracy for only 12 VPs. The remaining 88 VPs all benefited from tuning the detector ranging from SVM512:1 to SVM1:16. Amongst the SVMA members, SVM1:2 achieved the best detection performance for the largest number of VPs at 39. However, even these are only a fraction of the 100 VPs in the study. These results demonstrate that the traditional SVM detector is only optimal for a small portion of patients. Even when using SVM1:2, which offers the best classification performance on average across the 100 VP, the majority of VPs can still benefit from patient-specific tuning with the SVMA detector.

To quantify the advantage in detection performance with the SVMA detector over the baseline SVM1:1 detector, figure 3.6(b) plots the improvement in total accuracy obtained with the SVMA detector over the baseline SVM1:1 detector for all 100 VPs. The gains in detection performance with the SVMA over SVM1:1 are not uniform across the VP population. Rather, the increases in performance are inversely proportional to the baseline detection performances. To
illustrate this trend, a logistic, quadratic and linear function were fitted to the dataset. Within the domain of 90 to 96% baseline total accuracy, all three models show higher gains in total accuracy with the SVMA detector when lower baseline total accuracies are achieved with the SVM$_{1:1}$ detector. The average total accuracy across the 100 VPs increased from 93.48±1.17% with the SVM$_{1:1}$ detector to 94.46±0.69% with the SVMA detector, $P < 0.001$ using one-sided two sample t-tests with unequal variances. The individual total accuracy gains ranged from 0% to 3.56% while the baseline total accuracies ranged from 90.22% to 95.50%. These results support the ability of the SVMA detector to facilitate patient-specific tuning and improve detection performance over traditional SVM classifiers. In the next section, the SVMA algorithm is compared with the most common tuning strategy, threshold tuning.

Threshold tuning is a common technique used for altering the performance of a given classifier. It is often implemented by changing some classification threshold to tune the classifier. For instance, in the case of the traditional SVM classifier, classification threshold can be changed by simply shifting the signum function in equation 18 along its domain. In order to compare the performances between the traditional SVM detector with threshold tuning and the SVMA algorithm, a baseline SVM detector with a total of nineteen separate classification thresholds is implemented. The classification thresholds are chosen in a logarithmic fashion and threshold level 10 is the baseline SVM detector, it is identical to SVM$_{1:1}$. Lower threshold levels are designed for increased specificity while higher threshold levels achieve increased sensitivity. The two detection schemes are tested over the same 100 VPs data set and the effect of threshold tuning on the baseline SVM detection performance is shown in figure 3.7. Figure 3.7(a) plots the mean and standard deviation of the sensitivity, specificity and total accuracy evaluated over the 100 VPs as the SVM is tuned across the nineteen detection thresholds. The
performance measurements of threshold tuning exhibit similar patterns to the SVMA algorithm shown in figure 3.4(a). The sensitivity and specificity measurements display logistic function-like behaviors and approach limits when the detectors are tuned to the extremities, while the total accuracy measurements achieve their maximum when the detectors are tuned to level 11. Figure 3.7(b) plots the effect of threshold tuning on detection latencies. Again the plot shape is similar to SVMA tuning, but with major differences in the range of the detection latencies. These results support threshold tuning as an effective strategy for changing the behavior of the classifier.

Figure 3.8, similarly to figure 3.6 for the SVMA algorithm, examines the performance effect of patient-specific tuning with threshold tuning. In figure 3.8(a), the number of patients receiving the best detection performance for a given classification threshold is plotted. The baseline detector, threshold level 10, was only optimum for 5 VPs out of the 100 VP population. In contrast, tuning the baseline SVM detector to threshold level 11 achieved the best performance for the most number of VPs at 55. The remaining 40 VPs are distributed between threshold levels 8 to 12. Out of the 100 VPs, 95 benefited from threshold tuning. In figure 3.8(b), these gains in total accuracies are plotted against the baseline total accuracies for each VP. Similarly to figure 3.6(b) for the SVMA detector, VPs with lower initial performances with the baseline SVM detector often benefited more from threshold tuning. This trend is illustrated by fitting the same three functions (logistic, quadratic and linear) to the plot. Comparison with the trends shown in figure 3.6(b) shows the SVMA detector achieves higher gains over threshold tuning across the VP population. Figure 3.9 shows a closer comparison of the performance gains achieved with the SVMA algorithm and threshold tuning. Figure 3.9(a), 9(b) and 9(c) separately compares the fitted logistic, quadratic and linear functions for the two strategies. For all three fitted functions, the SVMA algorithm obtained higher gains in total detection accuracy over
threshold tuning, \( P < 0.001 \) using one-sided two sample t-tests with unequal variances. When patient-specific tuning is performed, the SVMA algorithm is able to improve the mean total accuracy for the 100 VPs to 94.46\( \pm \)0.69\% from the baseline total accuracy of 93.48\( \pm \)1.17\%, while threshold tuning improved the mean total accuracy to 94.11\( \pm \)0.80\%. These results support the SVMA algorithm as a more effective tuning strategy compared to threshold tuning.

The improved total accuracies demonstrated with the SVMA algorithm over the traditional threshold tuning strategy could be attributed to the design of the SVMA. In threshold tuning, the classification threshold is shifted uniformly along the decision curve independent of the training data. In contrast, by constructing each decision curve with pre-defined weightings of the available data, tuning with the SVMA algorithm utilizes the information present in the training data and is less stochastic in nature compared to threshold tuning. Figure 3.10 illustrates this concept. In the figure, the SVMA algorithm and threshold tuning are both implemented on the same dataset. The dataset includes a training set, composed of 20\% of the non-seizure data and 20\% of the seizure data chosen randomly, and a testing set composed of the remaining 80\% seizure and non-seizure data. In order to allow 2-D visualization of the classification boundaries, the feature set is reduced to just the normalized median Teager energy and the power of individual epochs. Figure 3.10(a) plots the training data, the trained baseline SVM classification boundary and the best performing classification boundaries obtained with the SVMA algorithm as well as threshold tuning. Figure 3.10(b) plots the same classification boundaries but over the testing data. In both plots, the boundaries are located in the lower left corners indicated by the arrows. In this trial, the baseline SVM obtained a total accuracy of 87.97\%. With threshold level 11, threshold tuning achieved its best total accuracy of 89.85\%. Using the SVMA detector, a high total accuracy of 95.93\% was achieved with SVM\(_{1.8}\). In figure 3.10(c) and 10(d), closer
examinations of these classification boundaries are displayed by limiting the domain of the feature space to $(0.05 \times 0.05)$. The classification boundary constructed through threshold tuning is parallel to the baseline boundary but shifted to increase its seizure sensitivity. These shifts are independent of the available information in the training data and must remain orthogonal to the baseline classification boundary. In contrast, the SVMA classification boundary is constructed from a different weighting of the training data and is not limited to being parallel to the baseline classification boundary. As such, the SVMA detector is able to utilize the information in the training data and construct a new classification boundary that incorporates additional classification regions with seizure activity and offer a superior classification performance on the test set.
3.5 DISCUSSION

The novel SVMA seizure detection algorithm presented in this study combines effective features to characterize epileptic seizure activity and a unique strategy for patient-specific tuning. When the SVMA detector was tested on the BONN epilepsy dataset, it demonstrated a higher mean classification performance of 94.46±0.69% over the traditional SVM classifier performance of 93.48±1.17% evaluated over 100 VPs, P < 0.001. The SVMA detector also achieved a higher mean classification performance when compared with the threshold tuning classification performance of 94.11±0.80% over the same VP dataset, P > 0.001. These results validate the potential classification performance of the proposed SVMA detector and its patient-specific tuning capability.

To compare the efficacy of the SVMA algorithm against these published algorithms, the SVMA detector is retrained using 50% of the available data and tested over the remaining data, resulting in 4650 epochs for training and 4650 epochs for testing. This training/testing protocol is closer to the protocols used by other published studies and results in a more accurate comparison. Table 1 lists the published algorithms, the datasets that were used, the training/testing protocols and the highest detection performances achieved. In chronological order, Kannathal et al published a seizure detector using an adaptive neuro-fuzzy inference system and entropy measures (Kannathal, Choo et al. 2005). They used the datasets A and E with 57% of the data used for training and the remaining 43% for testing. While the total accuracy was not reported in their publication, it is calculated to be 92.22% from information given in the paper. Guler et al combined Lyapunov exponents with a recurrent neural network to implement their seizure detection algorithm (Nihal Fatma Guler 2005). The algorithm was tested
on the datasets A, D and E with 50% of the data used for training and 50% for testing. In their study, the algorithm was designed to do multi-class classification for each dataset. In order to compare their results to the binary classification results reported in this work, the specificity and total accuracy of their detection algorithm are recalculated using the information given in their confusion matrix. Their detector achieved a binary classification total accuracy of 97.79%. Mousavi et al extracted autoregressive parameters from datasets A, C and E and combined them with a multilayer perceptron classifier for their detection algorithm (Mousavi, Niknazar et al. 2008). While their training/testing protocol was not given, the algorithm is reported to have a total accuracy between 91 to 96%. Most recently, Chandaka et al presented a cross-correlation aided support vector machine detector that achieved a total accuracy of 95.96%, using datasets A and E and training/testing partition of 50%/50% (Suryannarayana Chandaka 2009). Finally, Ubeyli implemented a detector using Lyapunov exponents, wavelet coefficients and the power spectral density with a multilayer perceptron neural network (Derya Ubeyli 2009). The algorithm is studied over the datasets A, D and E with a training/testing partition of 50%/50%. Similarly to (Nihal Fatma Guler 2005), the algorithm is designed for multi-class classification and binary classification results are recalculated using the information in the confusion matrix presented in the paper. The total classification accuracy for binary classification is 97.33%. Finally, by implementing the proposed SVMA seizure detection algorithm with a training/testing partition of 50%/50%, a high total accuracy of 98.72% is achieved. This is the highest total accuracy within the published manuscripts compared and demonstrates the effectiveness of the SVMA seizure detector.

During this study, an interesting observation is made on the $C_{LZ}$ values for the different physiological sub-bands. The four lower frequency sub-bands all show a decrease in $C_{LZ}$ values
during seizure epochs compared to non-seizure epochs, while in the Gamma sub-band, the $C_{LZ}$ values are larger during seizure epochs compared to non-seizure epochs. These increases in complexity in the gamma frequency band are expected and are most certainly due to the high frequency spiking waveforms that appear during seizure activities. However, the reasons for the decreases in complexity or increases in periodicity in the lower frequency sub-bands, are less clear. A plausible explanation may be non-synaptic interactions in the epileptic network. For instance, Feng et al. induced non-synaptic epileptic activities in-vivo using the calcium chelator, EGTA (Feng and Durand 2003). In their work, they recorded periodic slow wave seizure activity measuring $0.69 \pm 0.79$ Hz. These periodic slow waves may be due to fluctuations in the extracellular potassium concentration and can themselves illicit fast epileptic spiking activities (Feng and Durand 2006; Park, Feng et al. 2008).

In conclusion, this research presents a novel SVMA seizure detection algorithm. The SVMA detector not only offers excellent classification performance but is designed to facilitate patient-specific tuning. The SVMA detector demonstrated superior detection performances when compared with traditional SVM classifiers and threshold tuning. It achieved a high detection performance when compared with other published detection strategies using the publicly available BONN dataset. The major disadvantage of the proposed algorithm lies in its increased calculation complexity relative to single SVM classifiers. During the training phase, each member of the SVMA must be trained separately. While this process can be parallelized, the training of SVMs on large problem sets is inherently slow and training multiple SVMs can be taxing even for today’s computers. However, once trained, the SVMA detection algorithm can be applied with little effort. This study supports the proposed SVMA detector as an effective tool in monitoring epileptic EEG activities in the clinical setting and as a potential closed-loop
control device for new treatment paradigms such as electrical stimulation strategies.

Acknowledgements: This work was supported by NIH Grant R01-NS-40894.
3.6 TABLE CAPTIONS

Table 3.1: Comparison of the SVMA detection algorithm with other published algorithms. The table lists the individual datasets used by each study, the partition of the datasets between training/testing and the relevant performance measures.
3.7 FIGURE CAPTIONS

**Figure 3.1:** Feature extraction flow chart. Starting with the input signal $x$, the median Teager energy ($\Psi$) and power ($P$) are calculated for each epoch while the Lempel-Ziv complexities ($C_{LZ}$) are calculated for each filtered sub-band ($G$). The features are then normalized and combined together to form the feature vectors that are the inputs to the SVMA detector.

**Figure 3.2:** (a) Support Vector Machine architecture. The feature vector $x$ is input to the $N$ kernel functions $K$ corresponding to the $N$ support vectors. (b) The Support Vector Machine Assembly architecture. The feature vector $f$ is input to each member of the SVMA. The SVMA consists of an assembly of SVMs each trained on the same dataset but with a different weighting ratio between seizure and non-seizure data, (Non-Seizure:Seizure). Once trained the output of the SVMA can be tuned by the human operator via gating of its members individual outputs.

**Figure 3.3:** (a) Frequency response of the Gabor filter bank. The frequencies are normalized with respect to the sampling frequency. There are a total of five sub-bands each overlapping a different physiological frequency range: 1-Gamma; 2-Beta; 3-Alpha; 4-Theta; 5-Delta. (b) Examples of the Gabor filter bank outputs. Three data segments spanning 23s each are obtained separately from the datasets A, D and E and plotted in row 1. Their corresponding filtered waveforms by the Gabor filter bank are plotted from the highest to the lowest frequency bands, in subsequent rows.
**Figure 3.4:** (a) Extracted features during seizure segments and non-seizure segments. The plots are constructed by concatenating features extracted from set E (highlighted in gray) in between features extracted from set A and D. (b) A comparison of the mean and standard deviation of each feature for both seizure and non-seizure data. The computed Power and median Teager Energy are both much higher during seizure epochs compared to non-seizure epochs. The Lempel-Ziv complexities of the lower frequency sub-bands are lower during seizure activity relative to baseline. However in the Gamma band, the Lempel-Ziv complexity is actually higher during seizure activity versus baseline. P < 0.001 for all features.

**Figure 3.5:** SVMA tuning characteristics. (a) The mean and standard deviation of the sensitivity, specificity and total accuracy across 100 VPs as the SVMA is tuned from SVM\(_{512:1}\) to SVM\(_{1:512}\), where the weighting ratio is (non-seizure:seizure). The proposed SVMA detector can be easily tuned to provide a wide range of sensitivity and specificity performance levels, while the best mean total accuracy is achieved with SVM\(_{1:2}\). (B) The mean and standard deviation of the detection latency as the SVMA is tuned from SVM\(_{512:1}\) to SVM\(_{1:512}\).

**Figure 3.6:** Patient specific tuning with the SVMA detector. (a) The number of VPs with the best total accuracy for a given SVM in the SVMA is plotted. The baseline SVM\(_{1:1}\) is the best detector for only 12 out of 100 VPs. The remaining 88 VPs all benefited from tuning with the SVMA. SVM\(_{1:2}\) is the best detector for the largest number of VPs (N= 39). (B) The improvements in total accuracy with the SVMA detector is plotted against the baseline total accuracy obtained with SVM\(_{1:1}\) for each VP. Three separate functions are fitted to the dataset (Logistic, Quadratic,
These trends show an inverse relationship between the gain in detection performance with the SVMA algorithm and the baseline detection performance.

**Figure 3.7:** Threshold tuning characteristics. (a) The mean and standard deviation of the sensitivity, specificity and total accuracy across 100 VPs as the detection threshold is tuned from level 1 to 19. Level 10 is the baseline SVM = SVM_{1:1}. Lower levels are designed for increased specificity while higher levels for increased sensitivity. The best mean total accuracy is achieved with level 11. (b) The mean and standard deviation of the detection latency as the detection threshold is tuned from level 1 to 19.

**Figure 3.8:** Patient specific threshold tuning. (a) The number of patients with the best total accuracy for a given threshold level. Traditional SVM (level 10) is the best detector for only 5 out of 100 VPs. The remaining 95 VPs received better total accuracies when the detection threshold is tuned to other levels with level 11 achieving the best performance for the most number of VPs, N=55. (b) The gains in total accuracy with threshold tuning are plotted against the baseline total accuracy for each VP. Three separate functions (Logistic, Quadratic, Linear) are fitted to the dataset. A similar trend to SVMA is observed where higher gains are achieved with threshold tuning when the baseline detection performances are poor.

**Figure 3.9:** Performance comparison between the SVMA algorithm and threshold tuning. (a) Comparison between the fitted logistic functions of the SVMA total accuracy gains versus the threshold tuning gains. (b) Comparison of the fitted quadratic functions of the SVMA total...
accuracy gains versus the threshold tuning gains. (c) Comparison of the fitted linear functions of the SVMA total accuracy gains versus the thresholds tuning gains. In all three plots, the SVMA detection performance gains are higher than the gains achieved with threshold tuning.

**Figure 3.10:** Comparisons between the classification boundaries constructed with the baseline SVM detector, the SVMA algorithm and threshold tuning. For these plots, the 2-D feature vectors of the VPs are constructed with normalized median Teager energy and Power. (a) The feature vectors extracted from the training dataset along with the trained baseline classification boundary, the best performing SVMA classification boundary and the best threshold tuning classification boundary (the boundaries are indicated by the arrow). (b) The feature vectors extracted from the testing dataset along with the same classification boundaries in (a). (c) A closer look at (a) by limiting the domain to 0 to 0.05 for both the median Teager energy and Power. (d) A closer look at (b) by applying the same limits as in (c). With threshold tuning, the boundaries are constructed independent of the training data and are limited to surfaces parallel with the baseline classification boundary. The SVMA algorithm instead, is able to construct classification boundaries that are dependent on the training data and thus offer better detection performances.
## 3.8 TABLES

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Table 3.1
3.9 FIGURES

Figure 3.1
Figure 3.2a
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CHAPTER 4

Conclusions and Future Work
The culmination of the work presented here is to advance the treatment of patients suffering from Mesial Temporal Lobe Epilepsy. Three objectives are set to accomplish this endeavor. (i) Design and characterize an in vivo model of MTLE status epilepticus in rats. (ii) Design and verify a low frequency electrical stimulation paradigm for the suppression of bilateral MTLE status epilepticus. (iii) Design and implement a robust seizure detection algorithm that offers patient specific tuning. In the following section, the results and conclusions of each objective is summarized along with possible future directions.

4.1 OBJECTIVE I.

Design and characterize an in vivo model of MTLE status epilepticus in rats. In this objective an experimental model of MTLE status epilepticus was implemented and characterized. The experimental model is needed for the study of the proposed low frequency electrical stimulation paradigm to suppress MTLE status epilepticus in objective II. As such, the model must mimic MTLE status epilepticus by generating consistent bilateral hippocampal epileptiform activity that includes both ictal like and interictal like waveforms. It is our hypothesis that continuous bilateral micro-injections of high concentration [20mM] 4 Aminopyridine (4-AP) can induce persistent bilateral epileptic activity in the hippocampal structure. Quantification of the epileptiform activity with the average epileptic signal power and visual inspection of the percent duration demonstrated persistent bilateral epileptiform activity throughout the length of the experiments (7 hrs). These epileptiform activity consisted of a high frequency random spiking morphology (HFRS) similar to ictal waveforms, and a low frequency periodic spiking morphology (LFPS) resembling interictal spiking waveforms with spiking frequency around 5Hz. The bilateral epileptiform recordings, from the CA3 region of the
hippocampal structure, are characterized by continuous transitions between the HFRS and LFPS morphologies, with HFRS occupying the majority of the time. These data support the hypothesis that bilateral micro-injections of 4-AP can induce persistent bilateral hippocampal epileptiform activity mimicking MTLE status epilepticus. Besides accomplishing the objective, an interesting observation is also made during this work. The epileptiform activity, within the two sides of the hippocampal structure, present a near mirror image of each other throughout experimentation showing synchrony between the epileptiform activity of each side.

4.2 OBJECTIVE II.

Design and verify a low frequency electrical stimulation paradigm for the suppression of bilateral MTLE status epilepticus. In this objective, a low frequency electrical stimulation paradigm is designed and tested on the experimental MTLE status epilepticus model obtained in objective I. The stimulation paradigm utilizes a novel target, the ventral hippocampal commissure (VHC), to deliver therapeutic electrical stimulation to large portions of both sides of the hippocampal structure. The frequency of the stimulation is set to 5Hz to mimic the LFPS spiking frequency acquired from objective I. The stimulation intensity is set to the current that elicits the maximum antidromic evoked response, recorded in the CA3 region of the hippocampal structure. It is our hypothesis that 5Hz electrical stimulation of the ventral hippocampal commissure (VHC) can suppress bilateral status epilepticus. An hour to hour comparison between the control group and the stimulation group, during the hours of stimulation, shows a significant reduction in the bilateral epileptic signal power and the percent duration of HFRS activity, and the complete elimination of LFPS activity within the stimulation group. For the hours post stimulation, a significant reduction in the bilateral epileptic signal
power is also observed in the stimulation group when compared to the signal power during the corresponding hours in the control group. During these same periods, a significant increase in the percent duration of bilateral LFPS activity, and a corresponding decrease in the percent duration of HFRS activity is also observed in the stimulation group, when compared to the control group. This result along with the observation of the appearance of LFPS waveforms upon stimulation termination suggests an entrainment effect by the low frequency stimulation paradigm. A comparison between the three sessions of stimulation did not yield significant differences, suggesting that multiple stimulation sessions do not increase the effectiveness of the stimulation paradigm. During stimulation, it was observed that the bilateral epileptiform activity, that escapes suppression, are no longer mirror images of each other and a correlation study between the HFRS activity of the two sides yielded significantly longer time delays between the two sides during stimulation. While there is a post stimulation reduction in the bilateral epileptic signal power, there still exist considerable epileptiform activity in the absence of stimulation and these activity appear upon the removal of stimulation. Thus the proposed low frequency stimulation paradigm, if applied to a subject suffering from MTLE seizures, should be applied continuously based on the evidence from this study. In conclusion, the results presented support the hypothesis that the low frequency electrical stimulation paradigm can suppress bilateral hippocampal seizures.

4.3 OBJECTIVE III.

Design and implement a robust seizure detection algorithm that offers patient specific tuning. In this objective an automated seizure detection algorithm is implemented and its performance characterized. The detector is composed of an assembly of SVM classifiers each
trained with a different emphasis between seizure and non-seizure data. **Hypothesis:** It is our hypothesis that an epileptic seizure detector constructed from an assembly of SVM classifiers, each trained with a different weighting ratio between seizure data and non-seizure data, can offer the end user easy patient specific tuning and achieve superior classification performance. Using the publically available BONN dataset we first established the ability to tune the detector’s sensitivity, specificity, total accuracy and detection delay by simply choosing difference SVM classifiers from the SVM assembly. An investigation of the classification performance over 100 virtual patient demonstrated improvements in total accuracy with the proposed SVM assembly detector vs. traditional SVM classifiers. The algorithm is compared to other published results using the same dataset and achieved the best total accuracy. A comparison between the proposed tuning methodology and threshold tuning also yielded better performance with the SVM assembly tuning strategy. Analysis of the classification boundary constructed via SVM assembly tuning and threshold tuning shows that the proposed tuning strategy is able to construct classification boundaries using information within the training dataset, while thresholding can only construct hyperplanes parallel to the original classification boundary, without taking into account the additional information in the training dataset. This characteristic provides the proposed SVM assembly better tuning performance over traditional thresholding strategies.

### 4.4 Future Directions

In this work, we laid the foundation for new potential therapies for treating epilepsy including an electrical stimulation paradigm for the suppression of bilateral MTLE status epilepticus and an automated seizure detection algorithm that can be used both in clinical settings for the monitoring patients and as the control for close-loop therapeutic devices.
The proposed low frequency stimulation paradigm demonstrated the ability to suppress bilateral hippocampal epileptiform activity in a model of MTLE status epilepticus. However questions still remain that should be investigated.

(1) The effect of the low frequency stimulation paradigm on the kainic acid model of epilepsy (Raedt, Van Dycke et al. 2009). The kainic acid epilepsy model is a chronic experimental model in rats. Initial injections of kainic acid solutions into the rat hippocampal structure generate hippocampal status epilepticus and leads to spontaneous seizures weeks later. The experimental animals often exhibit hippocampal sclerosis similar to human patients suffering from MTLE. This model provides an excellent future test stage for the proposed low frequency stimulation paradigm. In one experimental setup, the stimulation paradigm can be applied immediately following the initial kainic acid injection to suppress the resultant hippocampal status epilepticus. The stimulation should last until the end of the early status epilepticus stage, and then it should be terminated. The amount of seizure reduction during the initial status epilepticus stage, as well as weeks later when spontaneous epileptic seizures occur, should be quantified and compared to control animals that did not receive any stimulation. This experimental design will not only demonstrate the robustness of the proposed low frequency stimulation paradigm to suppress a different experimental model of hippocampal status epilepticus, but also elucidate the ability of the stimulation, through the suppression of early stage status epilepticus, to prevent the formation of spontaneous seizures later in life. In a second experimental setup, the stimulation should be applied to animals, following the development of spontaneous seizures weeks after the initial kainic acid injections.
Again the seizure severity in these animals should be quantified and compared with control animals to establish the ability of the proposed stimulation paradigm to suppress a model of adulthood MTLE. For these studies, bilateral injections of kainic acid can be used to generate bilateral epileptic seizures.

(2) A stimulation frequency study should be done to determine the most effective stimulation frequency. This will give insight into the entrainment theory and the possible mechanism of the epileptic seizure suppression effect.

(3) The mechanism of the observed epileptic seizure suppression effect via electrical stimulation. This is arguably the most important question with the most elusive answer. It has been postulated many times that low frequency stimulation may increase the network inhibition within the hippocampal structure. The most obvious of these inhibition factors is GABA mediated inhibitory pathways. However to study this, in vitro preparation must be utilized so that various physiological and environmental factors can be controlled and manipulated.

The SVM assembly detector presented in this work demonstrated superior performance to other published results using the same dataset as well as the traditional SVM algorithm and threshold tuning. The next step for this algorithm is to implement it in a clinical setting. Additional training data should also be collected and the detector retrained on these data. If positive feedback is obtained from physicians, the algorithm can be embedded into a software package for clinical use. The algorithm can also be combined with the proposed low frequency stimulation paradigm and the necessary hardware to form a close-loop, implantable therapeutic device for the treatment of MTLE seizures.
APPENDIX A

A Multi-Scale Support Vector Machine Ensemble for Binary Classification
A.1 INTRODUCTION

In recent years, support vector machines (SVMs) have received considerable attention because of their superior performance in pattern recognition and function regression (Burges 1998; Scholkopf, Smola et al. 2000; Smola 2004; Ying and Jun 2004). SVMs are developed based on the idea of structural risk minimization (SRM), which shows generalization errors to be bounded by the sum of training errors and a term depending on the Vapnik-Chervonenkis (VC) dimension of the learning systems. By minimizing this upper bound, high generalization performance can be achieved (Cortes and Vapnik 1995; Vapnik 1995). Moreover, unlike other machine learning methods, generalization errors of SVMs are not related to the input dimensionality of the problem, but to the margin with which it separates data. This explains why SVMs can have good performance even in problems with a large number of inputs (Osuna, Freund et al. 1997; Pontil and Verri 1998). The basic principle of SVMs is to find an optimal separating hyperplane so as to separate two classes of patterns with maximal margin (Cortes and Vapnik 1995; Vapnik 1995). Classification and function approximation using SVMs are formulated as quadratic programming (QP) problems which can be solved efficiently by using many well-documented optimization algorithms (Cortes and Vapnik 1995; Vapnik 1995; Mangasarian and Musicant 1999). It is well-known that the major task of the SVM approach lies in the selection of its kernel. Choosing different kernel functions will produce different SVMs and may result in different performances (Aronszajn 1950; Scholkopf 1998; Shawe-Taylor, Bartlett et al. 1998). In the SVM literature, there exist polynomials SVMs, radial basis function (RBF) SVMs, two-layer neural network (NN) SVMs, and so on. They correspond to the kernel functions of polynomial, radial basis function, and two-layer NN, respectively. Once the kernel is fixed, SVM classifiers have only a user-chosen parameter (the error penalty), but the
kernel is a very big rug under which many parameters have to be determined. Some work has been done on limiting kernels using prior knowledge, but the best choice of a kernel for a given problem is still an open research issue (Scholkopf, Kah-Kay et al. 1997; Shawe-Taylor, Bartlett et al. 1998).

In this paper, we present a Multi-Scale SVM (MS-SVM) Ensemble classifier. The approach is motivated by ideas and principles from multi-resolution and wavelet theory (Daubechies 1992; Boashash 2003). The concept of multi-resolution analysis has been first introduced in signal processing. It becomes especially popular after the introduction of wavelets. It has been successfully applied to the analysis of the multi-resolution nature of signals such as: the identification of local features of signals; modeling local features and distinguishing them from false features such as noise and outliers; constructing a compact signal representation. With wavelets, one first obtains a coarse approximation to a signal using a globally smooth basis function. Successive enhancement to the approximation accuracy is then achieved by adding localized basis functions with increasingly finer scale until a desired level of accuracy is achieved. We show how this approach can be used to construct a multi-scale SVM ensemble classifier to learn complicated decision functions which contain both fine detail and large smooth regions. We first give a summary of the traditional SVM classifier.
A.2 METHODS

A.2.1 Support Vector Machines

The support vector machine (SVM) is a linear classifier first proposed by Vapnik. (Cortes and Vapnik 1995; Kecman 2001) SVM is a relatively new approach in seizure detection based on the theory of structural risk minimization. The theory states that the minimization of risk (classification error on unseen data) requires the minimization of both the empirical risk (training error) and the capacity of the class of decision functions. The best known capacity measure is the VC dimension which is defined as the largest number of points that can be separated in all possible ways using functions of the given class. Traditional neural networks, construct decision boundaries by minimizing the classification error of the training set. In SVM training, the criteria to minimize both the empirical risk and the VC dimension results in a linear decision boundary that maximizes the margin between the training data and the boundary. In general, this training strategy gives SVMs higher classification performance on unseen data sets, higher generalization abilities.

Fig.1 illustrates the architecture of the SVM. Given the data sets, \((x_1, y_1), \ldots, (x_m, y_m)\) \(X \times \{±1\}\), where \(x\) are patterns of the data and \(y\) is the class labels of each data set \(x\). To construct the optimal hyperplane that yields the maximum margin of separation between the members of the two classes, the following quadratic programming optimization problem must be solved.

\[
\begin{align*}
\text{minimize}_{w, b} & \quad \frac{1}{2} \|w\|^2 \\
\text{subject to} & \quad y_i \cdot ((w \cdot x_i) + b) \geq 1 \\
& \quad i = 1, \ldots, m. \\
& \quad w \in \mathbb{R}^N, b \in \mathbb{R}
\end{align*}
\]
For non-linearly separable data, a soft margin can be constructed by the introduction of the slack variable $\xi_i \geq 0$, $i = 1, \ldots, m$. The new optimization problem becomes

$$
\text{minimize} \quad \frac{1}{2}||w||^2 + C \sum_{i=1}^{m} \xi_i \\
\text{subject to} \quad y_i \cdot ((w \cdot x_i) + b) \geq 1 - \xi_i \\
\xi_i \geq 0, \quad i = 1, \ldots, m. \\
w \in \mathbb{R}^N, b \in \mathbb{R}
$$

where $C$ is a user defined constant greater than 0. This problem can be solved with its Lagrangian dual and can be simplified to

$$
\text{maximize} \quad \sum_{i=1}^{m} a_i - \frac{1}{2} \sum_{i,j=1}^{m} a_i a_j y_i y_j (x_i \cdot x_j) \\
\text{subject to} \quad C \geq a_i \geq 0, \\
\sum_{i=1}^{m} a_i y_i = 0. \\
\text{where } w = \sum_{i=1}^{m} a_i y_i x_i, \\
i = 1, \ldots, m.
$$

So then the decision function becomes $f(x) = \text{sgn} \left( \sum_{i=1}^{m} y_u a_i (x \cdot x_i) + b \right)$. From this deduction, it is clear that $w$ only depends on the patterns $x_i$ where $a_i$ is not zero, these are the support vectors. These support vectors lay on the margin of the decision boundary and all other data points are irrelevant. Since the feature vector $x$ only appear in the equations as dot products the decision functions can be converted to the form

$$
f(x) = \text{sgn} \left( \sum_{i=1}^{m} y_u a_i k(x \cdot x_i) + b \right)
$$

where $k(x \cdot x_i)$ is a kernel function that maps the input space into a higher dimensional feature space. In this higher dimension, the hyperplane decision boundary is then constructed, resulting
in non-linear data classification in the original input space. In this paper, the SVMs are constructed with the radial basis function kernel (RBF):

$$k(x_1 \cdot x_2) = \exp \left( -\frac{\|x_1 - x_2\|^2}{\sigma^2} \right)$$

The RBF kernel has one parameter $\sigma$ to be set by the user. It determines the effective radius of the particular RBF kernel. When applying a RBF based SVM for classification, the user must first find the optimum $C$ and $\sigma$ pair. This is generally done with an exhaustive grid search through the $C$ and $\sigma$ parameter space using cross-validation. It is straightforward to realize that if a RBF kernel is used and its standard deviation $\sigma$ is large, then the surface $f(x)$ will be a smooth function of $x$. Hence the decision surface, where $f(x) = 0$, will also be smooth. This will be good for generalizing in regions of sparse training data, but it will be poor at fitting any rapidly fluctuating parts of the decision boundary. With a small $\sigma$, will be good at fitting rapid fluctuations (as long as there is enough training data in such regions) but it will be poor at generalizing in regions of sparse training data, since $f(x)$ will tend back to zero in between neighboring points of the same class which are significantly more than $2\sigma$ apart. Hence it is desirable to allow kernel functions of more than one scale to be used to define a given decision surface. Thus intuition suggests a multi-scale SVM classifier may offer superior classification performance for certain problems.

A.2.2 Multi-scale SVM ensemble classifier

It is our aim to design a SVM classifier that can fit given datasets with a multi-scale RBF structure. Given a training set $(x_1, y_1) ... (x_m, y_m)$ where $x_i \in \mathbb{R}^d$ and $y_i \in \{+1, -1\}$, we introduce a hierarchical multi-scale SVM ensemble classifier $H(x) = sgn(\sum_{i=1}^{m} y_i a_i K_\sigma(x \cdot x_i))$ where $K_\sigma \in \{K_{\sigma_{\text{min}}} ... K_{\sigma_{\text{max}}}, \{K_{\sigma_{\text{min}}} ... K_{\sigma_{\text{max}}}}\}$ is an ensemble of radial basis functions with
a different scale parameter $\sigma$ for each RBF member in the ensemble. $\sigma = b^p$ where $b$ is a constant base value and $p \in Z$, where $p_{j+1} = p_j + 1$. Thus the RBF ensemble $\{K_{\sigma_{min}} \ldots K_{\sigma_{max}}\}$ can be rewritten as $\{K_{b^{P_{min}}} \ldots K_{b^{P_{max}}}\}$, where $K_{b^p}(x_1 \cdot x_2) = \exp \left( -\frac{||x_1-x_2||^2}{b^{2p}} \right)$. The architecture of the proposed multi-scale SVM ensemble classifier is illustrated in figure 2. A feature vector is inputted in a parallel manner to an ensemble of RBF based SVM, $K_{\sigma}$. Each $K_{\sigma}$ specializes on a different scale determined by the RBF parameter $\sigma$. The outputs of each $K_{\sigma}$ are then used as inputs to the selector where the feature vectors classification is determined.

In table 1 along with figure 2, the procedure for the multi-scale SVM ensemble classifier is described in detail. The $H(x)$ ensemble classifier begins with a single base classifier, which we will initially set as a linear SVM classifier. $H(x)$ is then trained on a particular dataset. Once trained, two new datasets are generated from the training points that have been falsely classified by $H(x)$. The first dataset is composed of all the miss classified training points belonging to class(+1) and the entirety of the class(-1) training points,(the (+1 Training Set). The second dataset is composed of all the miss classified training points belonging to class(-1) and the entirety of the class(+1) training points, the(-1 Training Set). Two new $K_{\sigma}$ SVM classifiers are trained separately on the two new datasets (+1 Training Set, -1 Training Set). The two $K_{\sigma}$ SVMs classifiers have the scale parameter $\sigma$ larger than the previous stage of classifiers. This is done by incrementing the parameter $p$ by 1, since $\sigma = b^p$. The two new $K_{\sigma}$ SVMs are then added to the $H(x)$ ensemble classifier, and the entire process starts all over again until the $H(x)$ reaches 100% training accuracy or a user defined training accuracy. In summary, the $H(x)$ ensemble classifier starts with a single base classifier. It is then trained on a particular problem. If there are training errors, two new datasets are constructed using the miss classified training points.
The new datasets are then used to train two additional $K_\sigma$ SVMs with a higher $\sigma$ parameter. These two new $K_\sigma$ SVMs are then incorporated into the $H(x)$ ensemble classifier, and the process starts over until a certain training error is reached. In some cases, the miss-classified training points belong to a single class. In this case, only one new $K_\sigma$ SVM is trained and incorporated into the $H(x)$ ensemble.

In order to combine the outputs for each $K_\sigma$ SVM, a Selector is utilized. The Selector consists of a set of rules that determines the final output of the $H(x)$ ensemble classifier. For a given input vector $x$, the vector is simultaneously inputted into each level of the $H(x)$ ensemble. I: The base level consists of one classifier and its output is a possible classification of $x$. II: For the scale levels consisting of two $K_\sigma$ SVMs, the outputs of the two $K_\sigma$ SVMs must agree in order to change the classification of $x$ otherwise the classification of $x$ is set to the output of the base classifier. III: For scale levels with only a single $K_\sigma$ SVM, if the $K_\sigma$ SVM is trained on a (+1 Training Set) then the classification of $x$ is set to +1 if the output of $K_\sigma$ SVM(x) is +1. Similarly, if the $K_\sigma$ SVM is trained on a (-1 Training Set) then the classification of $x$ is set to -1 if the output of $K_\sigma$ SVM(x) is -1. (4) Outputs of $K_\sigma$ SVM with a higher $\sigma$ can override the classification of $x$ of previous scales including the base classifier.

A.2.3 Datasets

For benchmarking the proposed MS-SVM Ensemble classifier, we use 11 binary classification datasets. The datasets include 5 real world problems, acquired from the UCI machine learning database (Newman 2007) and 6 artificial problems generated with the R package mlbench (Friedrich Leisch 2009). Details of the datasets are listed in table 2. During the benchmarking process, the real world problems are randomly partitioned such that 90% of the data are used for training the classifiers and 10% of the data are used for testing, this was
done through 100 trials. For the artificial datasets, we randomly generated 100 training sets of 200 samples each and 100 testing sets of 1000 samples each and 100 trials are conducted through each training set – testing set pair.
A.3 RESULTS

To illustrate the effectiveness of the proposed MS-SVM ensemble classifier $H(x)$, we start $H(x)$ with a simple linear classifier using a linear SVM. It is our hypothesis that by adding additional levels of $K_\sigma$ SVM classifiers to the base linear classifier, we construct a MS-SVM ensemble that exhibits superior classification performance. The datasets used are described in the previous section. The C parameter for the SVM classifiers are set to 1, smaller C values reduce the complexity of the trained SVM classifiers. The RBF standard deviation parameter $\sigma = b^p$ is determined with $b = 1.5$ and $p = \{-10,-9,-8 \ldots$ when training error reaches zero).

To further clarify the proposed MS-SVM algorithm, the evolution in the decision boundary of the MS-SVM trained on the Spiral problem set is displayed in figure 4. Figure 4.A is a plot of the Spiral problem set. The first step in training the MS-SVM is to initialize the base classifier. It’s decision boundary is shown in figure 4.B. By design, the base decision boundary is linear. Once the base classifier is trained, additional SVM classifiers of increase $\sigma$ where $\sigma = b^p$ is added to the MS-SVM ensemble. Figure 4.C is a plot of the MS-SVM decision boundary at $p = 1$. At each scale level, the MS-SVM is re-trained over the training set and any miss-classified training points are then used to create two new training sets (+1,-1) training sets. Each training set is composed of the miss-classified training points of that class respectively and the entirety of the training points belonging to the other class. These training sets for post $p=1$ MS-SVM is shown in figure 4.D and 4.E. The corresponding new SVM classifiers ($p=2$) trained on each training set is displayed in 4.F and 4.G. These new SVM classifiers are then added to the MS-SVM ensemble to create a new decision boundary shown in figure 4.H. This process continues until the training error reaches a preset condition, in this case 0. The final complete
MS-SVM ensemble decision boundary is illustrated in figure 4.1, which correctly classifies the entire spiral training set.

Figure 5 plots the classification accuracy of each problem set over 100 trials. For each dataset, the mean classification accuracy is plotted for each additional level of $K_\sigma$ SVM added to the $H(x)$ ensemble. The values are normalized by the final mean classification accuracy for each problem set respectively, the final classification accuracy is the classification accuracy of $H(x)$ when the last level of the $K_\sigma$ SVMs are added to the ensemble. The final classification accuracy for the different problem sets are detailed on the sides of the problem set names. The figure illustrates the step wise increase in the $H(x)$ ensemble’s classification accuracy as additional levels of $K_\sigma$ SVMs are incorporated into the ensemble at finer resolutions. For most problem sets the additional levels of RBF SVM classifiers increases the effectiveness of the ensemble classifier relative to the baseline classifier, which is a linear SVM classifier. However for the Two Norm problem set, no improvement was achieved because the base linear classifier is able to achieve very high training and testing accuracies.

The acute observer will also notice that the addition of certain scale levels actually negatively impacts the performance of the ensemble classifier. In order to reduce this effect, the training set is split into 2 partitions: a training dataset consisting of 90% of the original training set and a validation dataset consisting of the remaining 10%. The $H(x)$ ensemble is constructed using the 90% training dataset and then evaluated over the 10% validation dataset. This process is iterated through 500 trials and the final result is used to remove any negative impacting $K_\sigma$ SVMs from the $H(x)$ ensemble. The augmented $H(x)$ ensemble classifier is then validated over the unseen test dataset.
Another observation can be made regarding the interpretation of the proposed algorithm. While the algorithm is presented as a MS-SVM ensemble classifier, it can be understood as a strategy for improving the classification performance of an arbitrary base classifier through the addition of RBF SVM classifiers of finer resolution on miss-classified training points. With this understanding, the proposed MS-SVM ensemble can be utilized to improve the classification performance of an already existing classifier. To study this, we repeat the experiments done previously using the 10 datasets. However in this new set of experiments, instead of a linear classifier, we choose an optimized RBF SVM classifier for the base classifier. The RBF SVM base classifier has two parameters \((C, \sigma)\) that must be tuned to optimize its performance. This is done at the beginning of each trial using 10-fold cross-validation on the training set. The MS-SVM ensemble algorithm is then used to construct the final \(H(x)\) ensemble, table 3 lists the results. The classification accuracy of the base RBF SVM classifier is shown in the first column, the accuracy of the \(H(x)\) ensemble is shown in the second column, the difference in performance \((\text{Accuracy}(H(x)) - \text{Accuracy}(\text{base}))\) is shown in column three. Column four is the classification results obtained by (David Meyer 2003) over the same datasets. The same training and testing protocols are used in this study, as compared to the study done by (David Meyer 2003), in order facilitate the comparison of the results.

We first validate the base SVM classification accuracy results with the results published in (David Meyer 2003). For all the datasets, the base SVM classification accuracies are comparable. In fact for all the relevant datasets, the mean classification accuracies for the base SVM classifier are either equivalent or higher except for the Heart dataset. This offers additional confidence in using the base SVM performances achieved in this study as representatives of the general SVM classification accuracies for each dataset.
One hundred trials are conducted for each dataset, with the training set and test set randomized for each trial. Within each trial the base SVM classifier is first trained and evaluated over the unseen test set. Then the proposed MS-SVM Ensemble algorithm is applied to the same training and test set. For all the datasets, the MS-SVM Ensemble algorithm either increased the classification performance relative to the base SVM classifier or did not change the performance. There was no case where the ensemble classifier degraded the mean classification accuracy of a dataset. Table 4 further demonstrates this observation. In the table, the number of trials (number in the parentheses) and their corresponding change in classification accuracy for each dataset are presented. The Liver dataset received the most significant performance boost with the proposed ensemble algorithm, with an increase in mean classification accuracy of 1.77%, over 100 trials, compared with the base SVM classifier. Looking at a per trial basis, 33 trials received an increase in classification performance of 2.94% while 9 trials a 5.89% increase and 3 trials received an 8.82% increase. These are significant gains over the traditional SVM classifier. It demonstrates that the proposed MS-SVM ensemble classifier can greatly enhance the classification performance of the base classifier for given problem sets. The data also shows minimum degradation in the performance of the classifier due to the MS-SVM implementation. Within the 1000 trials ran over the 10 datasets, only 14 trials for the P.I. Diabetes problem set exhibited a decrease in classification accuracy over the base SVM classifier. Within the P.I. Diabetes, there is more than double the number of trials that showed an increase in performance, 31 trials.

There are a number of problem sets where the MS-SVM algorithm did not offer any improvement over the base SVM classifier. We believe this is mainly due to the underlying difficulty of the problem set. For instance, the Spiral dataset used in the study is classified with
99.24% accuracy by the base SVM classifier. There is little room for improvement. A more
difficult problem set will better demonstrate the increase in performance by the MS-SVM
ensemble. The original Spiral problem set consists of 2 spirals entangled over 1 cycle of rotation
and the addition of Gaussian noise with a standard deviation of 0.05. We now construct a second
and more challenging Spiral problem composed of two entangled spirals, 3 cycles of rotation and
a standard deviation of 0.3. This new training dataset is shown in figure 6.A. Once again we
first apply a grid search method and 10 fold cross-validation to find the optimal \((C, \sigma)\) parameter
pair for the base RBF SVM classifier. The results are then used to train a new base SVM. The
base decision curve is shown in figure 6.B. We then apply the MS-SVM algorithm on the same
training set, after selecting the final scale levels to be included into the MS-SVM ensemble the
final ensemble decision curve is shown in figure 6.C. Figure 6.D and E. illustrate both the base
SVM decision curve and the MS-SVM ensemble decision curve superimposed with the spirals in
the absence of Gaussian noise. From the figures, the MS-SVM decision curve clearly resembles
the spiraling structure of the dataset while the same spiraling structure is lost in the base SVM
decision curve. When applied on the same unseen test set, the base SVM achieved 50%
classification accuracy while the MS-SVM ensemble achieved 72% classification accuracy, a
significant improvement.
A.4 Discussion

In this paper, we have introduced a Multi-Scale SVM ensemble classifier that utilizes the standard deviation parameter $\sigma$ of the Radial Basis Function to construct ensemble members that specializes in the classification of different scale levels. The MS-SVM algorithm initializes with a base classifier and then additional classifiers of finer scale are added to boost the overall performance of the ensemble. The proposed algorithm can also be interpreted as a method for enhancing the classification performance of a preexisting base classifier. Using both linear and RBF SVM base classifiers, we illustrated the method and the performance of the MS-SVM algorithm. The results demonstrate the efficacy of the ensemble algorithm to offer superior classification accuracy over traditional SVM methods. However because the selection of the base classifier is not limited to the SVM, the proposed ensemble algorithm can be similarly applied to other classification techniques with the goal of improving their classification performance.

The MS-SVM ensemble algorithm also poses several limits. The algorithm requires much greater training time compared with traditional SVM methods. With large datasets, this could become a significant issue. The algorithm is more effective at increasing the classification performance of under-fitted base classifiers as opposed to over-fitted base classifiers. This is because the algorithm focus on the miss-classified training samples of the base classifier so that a base classifier with minimum training error has little or no data for the MS-SVM algorithm to train on. This effect is well demonstrated with the Spiral datasets. A less challenging spiral problem can be classified almost completely with a traditional SVM classifier and no improvement is gained with the MS-SVM ensemble. However a much more challenging spiral problem shows a 22% increase in classification performance of the MS-SVM ensemble over the
base traditional SVM classifier. Another issue that need further study pretends to the parameter \( \sigma \). In this current study, the \( \sigma \) of the radial basis function is controlled by the equation \( \sigma = b^p \), where \( b=1.5 \) and \( p=\{-10,-9 \ldots \text{ etc}\} \). It is possible that a smaller \( b \) value would allow for a more detailed sampling of the scale parameter space and offer improved classification accuracies.
A.5 TABLE CAPTIONS

Table A.2: MS-SVM algorithm

Table A.2: Binary classification problem set details.

Table A.3: Classification accuracy comparison between the base SVM classifier, the MS-SVM ensemble classifier and published results by other studies.

Table A.4: Classification accuracy change distribution. Accuracy%(# of trials)
A.6 FIGURE CAPTIONS

**Figure A.2**: SVM architecture, x is input, L is input dimension, K is kernel, N is the number of support vectors, a is the weight of the support vectors.

**Figure A.3**: MS-SVM architecture.

**Figure A.4**: MS-SVM algorithm flow chart.

**Figure A.4**: Evolution of MS-SVM decision boundary. A: Spiral problem set. B: Base classifier decision boundary. C: MS-SVM decision boundary (p=1,b=1.5). D: (+1) training set. E: (-1) training set. F: New SVM classifier (p=2,b=1.5) trained on (+1) training set. G: New SVM classifier (p=2,b=1.5) trained on (-1) training set. H: MS-SVM decision boundary (p=2,b=1.5). I: The final MS-SVM decision boundary.

**Figure A.5**: Classification accuracy for MS-SVM ensemble with each additional scale level.

**Figure A.6**: Comparison of MS-SVM decision boundary with base SVM decision boundary. A: Very Noisy Spiral problem set. (sd=0.3) B: Base SVM decision boundary. C: MS-SVM decision boundary D: Base SVM decision boundary superimposed over noiseless spiral dataset. E: MS-SVM decision boundary superimposed over noiseless spiral dataset. Notice the MS-SVM
decision boundary is much closer in structure to the noiseless spirals as compared to the base SVM decision boundary.
1. **INPUT:** \( S = \{(x_1, y_1), \ldots, (x_m, y_m)\} \)

2. **INITIALIZE:** \( H(x) \) with a base classifier. Set SVM parameter \( C=1, \sigma = \sigma_{\text{min}} \)

3. **DO WHILE** (TRAINING ERROR > Predefined Threshold)

   Train ensemble classifier \( H(x) \) with data set \( S \).

   If (TRAINING ERROR > Predefined Threshold)

   Construct two new training sets \( S_{+1}, S_{-1} \).

   \[
   S_{+1} = \{\forall (x_i, y_i): H(x_i) \neq y_i, y_i = +1\} + \{\forall (x_i, y_i): y_i = -1\}
   \]

   \[
   S_{-1} = \{\forall (x_i, y_i): H(x_i) \neq y_i, y_i = -1\} + \{\forall (x_i, y_i): y_i = +1\}
   \]

   Train two new \( K_{\sigma} \) SVMs separately with \( S_{+1} \) or \( S_{-1} \).

   Add the two new \( K_{\sigma} \) SVM classifiers to the \( H(x) \) ensemble.

   Increase scale parameter \( \sigma \).

   (If training errors occur only in one class then only one new training set and one new classifier is trained and added to the ensemble for that scale level.)

   **GOTO STEP 3.**

4. **SELECTOR:** Decides final output of \( H(x) \).

   **A:** \( H(x) = \) output of base classifier if the rules below are not met.

   **B:** Given a \( \sigma \) level if \( K_{\sigma} \) SVMs(+1) = \( K_{\sigma} \) SVMs(-1) for \( x \) then \( H(x) = \) output of that scale level.

   **C:** If a \( \sigma \) level only has one \( K_{\sigma} \) SVM then \( H(x) = +1 \), if \( K_{\sigma} \) SVMs(+1) = +1 or \( K_{\sigma} \) SVMs(-1) = -1.

   **D:** Outputs of higher \( \sigma \) levels override outputs of lower \( \sigma \) levels.

---

**Table A.1**
<table>
<thead>
<tr>
<th>Dataset</th>
<th># Instances</th>
<th># Attributes</th>
<th>Class Distribution (%)</th>
</tr>
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<tbody>
<tr>
<td>Credit</td>
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<td>24</td>
<td>29.89/70.11</td>
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<tr>
<td>Heart</td>
<td>303</td>
<td>13</td>
<td>45.54/54.46</td>
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<tr>
<td>Liver</td>
<td>345</td>
<td>6</td>
<td>42.58/57.42</td>
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<tr>
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<td>768</td>
<td>8</td>
<td>34.90/65.10</td>
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<tr>
<td>Sonar</td>
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<td>60</td>
<td>46.64/53.36</td>
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<tr>
<td>Spirals</td>
<td>200(1000)</td>
<td>2</td>
<td>50.00/50.00</td>
</tr>
<tr>
<td>Circle in Square</td>
<td>200(1000)</td>
<td>2</td>
<td>50.00/50.00</td>
</tr>
<tr>
<td>TwoNorm</td>
<td>200(1000)</td>
<td>20</td>
<td>50.00/50.00</td>
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<td>ThreeNorm</td>
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<td>20</td>
<td>50.00/50.00</td>
</tr>
<tr>
<td>RingNorm</td>
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<td>20</td>
<td>50.00/50.00</td>
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*Table A.2*
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<th>$Accuracy_{SVM_{base}} - Accuracy_{H(x)}$</th>
<th>Meyer et el.</th>
</tr>
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<td>86.03%</td>
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Table A.3
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<td>0.00%(98)</td>
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<tr>
<td>Liver</td>
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<td>5.89%(9)</td>
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<td>2.29%(1)</td>
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<tr>
<td></td>
<td>0.00%(54)</td>
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<tr>
<td>P.I.Diabetes</td>
<td>2.63%(5)</td>
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<tr>
<td></td>
<td>1.32%(26)</td>
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<tr>
<td></td>
<td>0.00%(54)</td>
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<td></td>
<td>-1.32%(14)</td>
</tr>
<tr>
<td></td>
<td>-2.63%(1)</td>
</tr>
<tr>
<td>Sonar</td>
<td>0.00%(100)</td>
</tr>
<tr>
<td>Spirals</td>
<td>0.00%(100)</td>
</tr>
</tbody>
</table>

Table A.4
A.7 FIGURES

Figure A.1
Figure A.2
Figure A.3
Figure A.4
Figure A.6
REFERENCES


