A Responsive Variable Frequency Stimulator for Seizure Control in a Computational Model

by

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A thesis submitted in conformity with the requirements for the degree of Masters of Applied Science
Graduate Department of Department of Electrical and Computer Engineering
University of Toronto

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Abstract

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2010

Epilepsy, which manifests itself as spontaneous bouts of abnormal low complexity brain activity, is the second most common neurological disorder after stroke. This thesis explores the effect of variable frequency stimulation on seizure control. A responsive variable frequency electrical stimulation system is proposed and validated using a computational model capable of generating spontaneous seizure like events. The proposed stimulation system is demonstrated to outperform open-loop fixed frequency stimulation and responsive fixed frequency stimulation using seizure time based measures and a control energy measure.
Acknowledgements

Firstly, I would like to thank my supervisor, Berj Bardakjian, for his support, guidance and abundant optimism throughout the preparation of this thesis. I would also like to thank the members (and an alumnus) of the Cellular Bioelectricity Lab: Marija Cotic, Eunji Kang, Osbert Zalay, Demitre Serletis, Angela Lee, Dave Stanley and Sam Talasila for all their ideas, suggestions and discussions. In particular, I would like to thank Osbert for developing and providing the CRG SLE model used in this thesis. Finally I would like acknowledge my parents who have supported me throughout my myriad of academic and extracurricular endeavours.
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<th>Acronym</th>
<th>Description</th>
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<tbody>
<tr>
<td>MCO</td>
<td>Mapped Clock Oscillator</td>
</tr>
<tr>
<td>CRG</td>
<td>Cognitive Rhythm Generator</td>
</tr>
<tr>
<td>SLE</td>
<td>Seizure like event</td>
</tr>
<tr>
<td>AED</td>
<td>Anti-Epileptic drug</td>
</tr>
<tr>
<td>FPGA</td>
<td>Field programmable gate array</td>
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<tr>
<td>GPU</td>
<td>Graphics processing unit</td>
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<tr>
<td>EEG</td>
<td>Electroencephalogram</td>
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<tr>
<td>VNS</td>
<td>Vagus nerve stimulation</td>
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<tr>
<td>TMS</td>
<td>Transcranial magnetic stimulation</td>
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<td>DBS</td>
<td>Deep brain stimulation</td>
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<tr>
<td>STFT</td>
<td>Short time fourier transform</td>
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# Table of Symbols

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<th>Symbol</th>
<th>Description</th>
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<td>Proportional, Integrating, Differentiating modes</td>
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<td>$\alpha$</td>
<td>Amplitude state variable in MCO and CRG models</td>
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<tr>
<td>$\phi$</td>
<td>Phase state variable in MCO and CRG models</td>
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<tr>
<td>$S_\alpha$</td>
<td>$\alpha$ portal input</td>
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<tr>
<td>$S_\phi$</td>
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<tr>
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<tr>
<td>$a_k, b_k, c_k$</td>
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<td>$f_s$</td>
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Chapter 1

Introduction

1.1 Epilepsy - A dynamical disease

Epilepsy affects approximately 0.5–1.0% of the population [15]. The incidence of epilepsy is relatively constant among a variety of subpopulations; however, the etiology assigned to each cases is a strong function of patient age [15]. Approximately 24-53 new cases are cases of epilepsy are discovered per 100 000 people on an annual basis. Epilepsy is among the most common neurological disorders and in terms of number of cases is statistically second only to stroke[18]. The high incidence is partially explained by the numerous causes including genetic abnormalities, developmental abnormalities, febrile convulsions, craniofacial trauma, central nervous system infections, hypoxia, ischemia and tumors [18].

Epilepsy is a complex family of conditions which generally manifest themselves as recurrent periods of abnormal brain activity termed seizures. The term “The Epilepsies” was coined to take this into account and more accurately account for the diverse nature of epilepsy. Epilepsy is pragmatically defined in terms of recurrent seizures; however, the underlying condition causing these seizures may be very diverse. Seizures that arise from an acute illness or metabolic disorder are generally not considered epilepsy [36].
Traditionally the prognosis for epilepsy has been poor with a very strong tendency for relapse. More recent studies have shown that the traditional pessimism is not indicative of all treatment options. Pharmacological treatments are effective in up to 70% of people; however, as many as 30% of all patients receive little to no benefit from pharmacological intervention [36, 23]. In a minority of these patients surgical resection is possible where the epilepsy is confined to a surgically accessible region of brain tissue. Patients with multifocal seizures, bilateral or generalized seizures who are non pharmacologically responsive are prime candidates for new types of treatment as they presently have very few effective options [35].

1.1.1 Epilepsy treatment algorithm and intractability

The treatment for epilepsy can be arranged as a systematic process which progresses through diagnostic options and corresponding treatments until a seizure free outcome is produced or the patient is deemed intractable. Intractability has multiple definitions; however, it is commonly defined as treatment failure with 2 anti-epileptic drugs (AEDs) or one seizure per month for 18 months.

The treatment algorithm can be split up into a couple of distinct stages. First, the patients are evaluated to confirm the diagnosis of epilepsy. Neural electrical activity is recorded to determine the type of seizures which allows selection of drugs. This process requires collection of EEG data and can be complicated by very infrequent seizures in some patients. AEDs are administered at progressively higher dosages until seizure are abolished or the patients experience unacceptable side effects.

In the case where no drug/dosage combination can be found, the patient’s epilepsy is deemed intractable and may be a candidate for surgical intervention.
1.2 Surgical Epilepsy Treatment

1.2.1 Vagus Nerve Stimulation

The simplest and least invasive surgical epilepsy treatment involves stimulation of the Vagus or other peripheral nerve. This procedure requires the placement of coiled stimulation leads around a nerve and the implantation of a small embedded stimulator [1]. The procedure as compared to other surgical alternatives is relatively reversible and side effect free and has been used to treat motion disorders for many years. An early blind controlled study of VNS stimulation showed that when VNS was added in addition to constant AED therapy patients with the high level of stimulation had 24.5% reduction in seizure frequency whereas patients with low level stimulation received only a 6.1% decrease [14]. The study used continuous stimulation with an increased duty cycle and frequency in the high level group. Side effects were relatively few in number; however, they were correlated with increased stimulation intensity. In one instance a failure in the electrical stimulator caused permanent damage to the patient.

The surgical procedure in itself does not address epilepsy, rather electrical stimulus administered to the nerve has some effect. Electrical simulation will be described in detail in section 1.3. Vagus nerve stimulation is generally not considered curative and is described by Handforth et al as a “safe adjunctive treatment” with maximum seizure reduction rates of 28% generally in agreement with previous findings. A recent study surveying results five years after FDA approval of the treatment shows that VNS has minimal side effects but is not consistently effective and is almost never curative [37].

1.2.2 Surgery

Surgical treatment of epilepsy is a complex irreversible process that is prone to patient complications and is frequently impossible because of poorly localized seizure foci. Surgical intervention is an irreversible process, unlike the algorithm used in AED drug and
dosage selection. Many different procedures are commonly performed and are discussed in detail in the literature. These include resections (removal of tissue) and disconnection procedures [33].

Surgical procedures require a localized seizure focus, which in the case of lesions or malformations can be ascertained using non-invasive imaging techniques such as MRI [33]. When seizure are not localized through non-invasive imaging, implantation of subdural grid and depth electrodes is required which significantly raises the cost and complexity of treatment. The invasive monitoring family of procedures is complex in itself and can have complication rates as high as 23% [33]. In up to 40% of cases with invasive monitoring, surgeons are unable to progress to surgery because localization of the seizures is not possible [33].

In the case of temporal lobe epilepsy, surgical resection is frequently effective in removing seizures and produces better quality of life than prolonged AED usage [44]. The outcomes from surgical procedures vary significantly but some general trends emerge. In cases were lessioning is detected the outcomes and seizure-free status are superior to extra-temporal cases of resection with no lessioning [33].

The presence of 20% of epilepsy patients who are deemed intractable and left with no viable treatment options provides a strong motivation for the development of novel methodologies to control seizures. It is desirable to have minimally invasive methodologies which are able to rapidly adapt to the diverse nature of the underlying abnormal brain activity responsible for seizures. Electrical stimulation has long been used therapeutically to treat a variety of ailments. The usage of electrical stimulation for seizure control is a relatively recent advance which has been enabled by advances in a number of related fields. The history and development of electrical stimulation for medical usage forms the foundation for the controller presented in thesis.
1.3 Electrical stimulation

Electrical stimulation is the application of electrical energy to modulate the behaviour of biological tissue in a desired fashion. Numerous modalities of stimulation exist. Electrical stimulation has been exploited in an experimental environment in numerous fields. A variety of means of electrical stimulation are available including surface electrodes, implanted electrodes and external/implanted coils. The two types of stimuli can be separated into

- Magnetic field based stimulation as established by Barker et al [7]
- Electric field or potential based stimulation

1.3.1 Transcranial magnetic stimulation

A number of studies have been conducted using magnetic field based stimulation, also known as transcranial magnetic stimulation (TMS), as it has a couple of advantages over electrical stimulation. It does not require implantation of electrodes as the field is often generated in coils placed on the surface of the head (or other body part).

Electronics can be used to provide very precise control of currents in the coil and the generated field; however, the coil generally creates non-specific fields which are difficult to target. The time varying fields generated by the coils induce currents in the underlying neurons. If these currents are of sufficient strength, depolarization will be occur producing a tangible effect [21]. The affects of TMS have been systematically investigated using the motor cortex, where single stimulation pulses in the motor cortex induce discernible motor evoked potential at peripheral muscles [21].

Since its inception, attempts have been made to utilize TMS for treatment of clinical disorders. Pertinent to this thesis, we will discuss TMS as applied to seizure suppression. A number of studies have used periodic stimuli applied using TMS and have shown some positive suppressive results [34]. The results of Rotenberg et al are typical, in
that there is improvement in a fraction of patients; however, the sample size and lack of an effective control prevent any real conclusions about efficacy [34]. In addition, the following stimulation parameters were used: frequency, duty cycle, amplitude and duration. These parameters were highly variable on a case by case basis making trends difficult to establish. No serious side effects or adverse events were associated with TMS and it is generally considered safe[34]. This safety advantage is compounded because TMS is non-invasive.

1.3.2 Electrical stimulation: development

Prior to a detailed understanding of electromagnetism, natural electrical energy sources were known for their medicinal properties. Electrical stimulation has long been an area of research but has recently flourished because the development of electronics has allowed precise control of the applied signal.

Electric fish were known to the Romans to cause torpor [38]. The same fish were named narke by the Greeks because of their numbing or narcotizing ability. Electric fish were used into the 18th century as a means of harnessing electrical energy before the nature of their electrical properties was understood. The understanding that the brain is fundamentally an electrical organ was made by Fritsch and Hitzig in a seminal 1870 paper entitled ‘On the Electrical Excitability of the Cerebrum’. The development of the galvanic cell and Faraday’s work on induction lead to basic controllable systems capable of providing electrical stimulation to patients. Fritsch and Hitzig were able to show that electrically stimulated dogs elicited graded responses: from small movements to seizures based upon stimulus intensity [38].

The development of electrical stimulation was coupled with numerous advances in medicine and surgery resulting in superior outcomes. Of particular interest was the development of the stereotaxis allowing repeatable and accurate localization within the brain, which in itself lowered surgical mortality rates from 12% to < 1% [38]. The pop-
ularity of surgery has at times waned due to the introduction of effective drugs to treat a variety of ailments. When contrasted with the irreversibility of surgical intervention, drugs become an attractive alternative. Recent advances in electronics and the existence of many patients not successfully treated pharmacologically has lead to a resurgence in interest in electrical stimulation as treatment option which is less damaging and irreversible than surgical ablation but capable of producing similar results. Electrical stimulation is in contrast to TMS, an invasive procedure requiring the placement of electrodes in the brain of the patient or at some peripheral location.

Electrical stimulation can be divided into semi-distinct fields.

- Peripheral nerve stimulation is most commonly associated with the Vagus nerve. The Vagus-nerve has been used as a stimulation target due to its broad projection into other regions of the brain [17]. Vagus nerve stimulation has been used therapeutically to treat a large variety of conditions including depression, anxiety, Alzheimer’s disease and migraines [3]. The mechanism of action for Vagus nerve stimulation is unresolved; however, evidence from cat studies suggests that VNS of anesthetized cats causes EEG desynchronization [17]. The desynchronization effect may help to abort seizures by preventing the system from attaining spatially diverse synchronization, a postulated process for seizure formation [30].

VNS was initially FDA approved in 1997 following a series of studies of its effectiveness starting in 1988 [37]. Studies conducted post approval have taken advantage of over 16,000 implanted devices allowing for more comprehensive data collection to be conducted on efficacy and safety. Long term efficacy studies demonstrate positive results with seizure reductions of between 34% and 75% at the median. Other studies have produced less favourable results with reduction in seizure frequency of 25 – 30% at high doses and 6 – 15% at low doses [41].

Quality of life appears to significantly increase in patients experiencing larger seizure frequency decreases; however, a number of tolerability and side effect issues
have arisen. These include voice alternation, cough, headache and many others which seem correlated with stimulation intensity [37]. In all of these cases stimulation has been of a continuous square wave nature. Increased seizure control is correlated with elapsed time after surgery and with increased stimulation intensity [16]. A broad variety of stimulation parameters have been used and little correlation between particular parameters and efficacy has been observed.

- Deep brain stimulation involves the insertion of electrodes into inaccessible regions of the brain. Deep brain stimulation (DBS) was initially tested for pain control inspired by the gate control hypothesis published by Melzak and Wall in 1965 [9]. DBS in this case proved unsuccessful; however, it was subsequently proven successful when applied to involuntary movement disorders (IMD) and some psychiatric disorders. DBS lead insertion has been done in a variety of brain regions including the thalamus, caudate nucleus, centromedian nucleus of the thalamus, cerebellum, hippocampus and the subthalamic nucleus [12].

DBS has been successfully applied to IMDs and the success increased interest in its application to other areas [32]. For epileptic patients, qualitative strategies have been developed to guide placement of electrodes based on knowledge of the patient’s type of epilepsy and anatomical information from seizure localization tests. These observations are summarized by

- Placement within structures believed to have gating effects on seizure activity
- Placement within structures at the focal point of the seizure in the hopes of using stimulation to disrupt seizure initiation and/or propagation

An example of successful electrical stimulation in a low Magnesium rat hippocampal model is shown in figure 1.1. After the stimulation is started, as shown in the bottom trace of figure 1.1, the seizure time decreases and the inter-seizure time increases as shown by the black and grey bars respectively.
Figure 1.1: An example of electrical stimulation mediated seizure control is shown in a low magnesium rat hippocampal model. The top trace depicts seizure activity observed in the field. The bottom trace shows the waveform used for stimulation. Black bars indicate times where seizures are occurring while the grey bars depict interictal times.
1.3.3 Electrical stimulation: Current usage

Electrical stimulation uses implanted surface and/or depth electrodes to apply voltages and currents directly to tissues. Stimulation parameters have broadly varied but constant current or voltage square waves are the most common stimuli. Recently a lot of interest has occurred in electrical stimulation for seizure control. The reasons for this include

- DBS and VNS have been shown to be quite safe thus providing a known path for the implantation of stimulation electrodes and stimulation devices

- Success has been observed in the use of DBS to treat motion disorders. Many other conditions have been unintentionally shown to respond to electrical stimulation [32]

- Electrical stimulation allows rapid treatment modification through electrical parameters and unlike pharmacological interventions, the changes are applied instantaneously

- Electrical stimulators are amenable to complex signal processing algorithms allowing closed loop stimulation

In 2004, Kossoff et al used a NeuroPace external responsive stimulator on four patients. They showed that when used with intracranial electrodes the systems appeared somewhat effective at reducing seizures [22]. Numerous studies using implantable stimulators similar to the one described in [31] have produced somewhat inconclusive results in terms of efficacy; however, the devices appear to be both reliable and safe [5, 39]. In a somewhat disconcerting manner the devices are adjusted and output currents increased until patients experience some sort of response.

1.4 Stimulation protocols

The stimulation protocols described in the previous section have been classified based on stimulus type. A second major classification and the major differentiating aspect of this
thesis is the closed loop nature of the stimulator. Stimulation devices and protocols can be classified based upon their principle of operation. There are generally two divisions of operation for controllers: open-loop and closed-loop.

1.4.1 Open loop stimulation

Open loop stimulation is the simplest and dominant control topology. In the open-loop system, the output stimulation applied to the patient in not a function of neurological activity. The stimulation is generally periodic on multiple time scales such that the stimulator may stimulate 1 minute on and 5 minutes off with each stimulation period consisting of bipolar square wave pulses of a frequency anywhere from $5 - 300\, \text{Hz}$. The degrees of freedom in stimulus selection include frequency, ON/OFF period, duty cycle of the individual pulses, and current or voltage (intensity).

1.4.2 Closed loop stimulation

Closed loop stimulation encompasses all forms of stimulation in which an input of the stimulator is connected to a measured quantity from the patient or model thus producing a closed feedback path.

Responsive fixed frequency

Responsive fixed frequency stimulation uses feedback from the target system in order to turn ON and OFF the stimulator at appropriate times based upon the nature of the activity occurring in the underlying system. Responsive fixed frequency stimulation has alternatively been called “Semi-Closed loop stimulation” by Li et al and was suggested as answer to the question of “When to stimulate?”[24]. The ON/OFF signals provided to the stimulator are produced using seizure detection or anticipation algorithms [24]. In the progression of stimulation technology, responsive fixed frequency stimulation techniques addresses concerns regarding stimulation permanently altering synaptic networks.
in unpredictable or undesirable ways. Seizure prediction and detection algorithms are often complex and difficult to implement in the computationally and power constrained environment of implantable neurostimulators.

**Responsive variable frequency**

Responsive variable frequency stimulation, a form of which is investigated in this thesis, uses the signals recorded from the system in order to not only gate the stimulator but also modulate the nature of the stimulus such that it is suited to the state of the system. Responsive variable frequency stimulation therefore answers the two stimulation questions [24]:

- When to stimulate?
- How to stimulate?

A number of closed loop stimulation algorithms have been investigated including the use of small pulses, chaos control algorithms and direct negative feedback [31, 10]. Closed loop feedback is the most promising method as it may reduce the burden of tailoring the treatment to the patient’s particular epilepsy. In addition closed loop feedback can naturally adapt to the changing nature of seizures in the system.

All of the above implementations have numerous parameters to control the stimulation and in all cases there is very little insight available to guide parameter selection. Because of the arbitrary tuning process employed with most stimulation devices, even with the responsive fixed frequency Neuropace eRNS system, better strategies are required to adjust the stimulator. These strategies would decrease the amount of intervention and “guess and test” required to optimize a stimulator.
1.5 Hypothesis

A responsive variable frequency stimulator whose frequency is modified by the output of a bank of neuronal modes, receiving their inputs from a Seizure-like event (SLE) model, will improve seizures control as compared to

- open-loop fixed frequency stimulation.
- responsive fixed frequency stimulation.

The modal preprocessing allows customization of the controller in a natural way to suite the system and allow controller efficacy. The proposed closed loop responsive stimulation system presented is both computationally suitable for real-time implementation and suitable for usage in a clinical environment.
Chapter 2

Epilepsy modelling

The study of epilepsy is most easily conducted using models, which can generally be divided into two classes: biological and computational. The distinct advantages and disadvantages of each model type will be discussed below to motivate the choice of model for this thesis.

2.1 Biological models

Animal models provide the most realistic epilepsy models but leave many model parameters uncontrollable. The models can take on numerous levels of complexity related to the quantity of tissue used in the model and consequently the complexity of the intact neuronal network generating the activity.

Biological epilepsy models are primarily generated in two ways, with chemical agents or electrical stimulation. These agents can include pentlenetrazol, kainic acid, bicuculline, picrotoxin and chemical or electrical kindling [12]. Biological models have unique advantages and disadvantages when used in the development of stimulation paradigms. Biological in-vitro or in-vivo models provide access to various levels of intact networks which are significantly more complex than most computational models. They provide a degree of “realism” not attainable in computational models such that success in a bio-
logical model is a good indicator of validity.

In addition there are clear road maps for progressing toward more complex models: from brain slice models, to whole brain regions, to in-vivo animal experiments and ultimately human trials. Despite these advantages biological models, such as the rat hippocampal slice model, frequently used by this and other research groups, exhibit a finite number of seizures with changing dynamics as the seizures evolve.

In addition it is not possible to repeat experiments from the same starting conditions to ensure that the controller is in fact responsible for the observations made of the system. The fundamental problem is that in all biological models we cannot observe the internal states of the system, nor is the system deterministic allowing us to observe the effects of perturbations on the system as compared to a reference, which makes evaluating success difficult.

### 2.2 Computational models

Computational models provide an alternate approach to the study of epilepsy and in particular they provide means to explore the system with varying initial conditions and numerous degrees of freedom. In addition, computational models in general provide access to all the state variables removing many of the challenges presented in biological models at the cost of diminished accuracy.

#### 2.2.1 Cognitive rhythm generators

Cognitive rhythm generators (CRGs) as a modelling tool are a development of the mapped clock oscillator (MCO) explored in a number of publications [6, 46]. Mapped clock oscillators and CRGs are computational blocks that can be coupled together in networks to model the interconnections of the brain.

Mapped clock oscillators exist in two forms: a clock and a labile clock. Each MCO con-
sists of a set of second order differential equations defining the amplitude, $\alpha$, and phase, $\phi$, internal state variables of the MCO and a static non-linearity which maps the internal state variables to an observable output [46].

![Block diagram of a single cognitive rhythm generator unit (CRG).](image)

In polar coordinates, the different types of MCOs are selected by altering the nature of the $\dot{\alpha}$ differential equation while the $\dot{\phi}$ equation remains common among both types. In order to model the complex interconnections of the neuronal world, the MCO model uses a system of portals which allow weighted linear combinations of unit outputs to influence the dynamics of the MCO in question. The general form for the input portal $S_{\rho,n}$ is given below where $c_{\rho,\text{mn}}$ are real valued coupling coefficients between 0 and 1 describing the strength of coupling, $\sigma_n$ are normalization constants, $y_{\text{mn}}$ are the inputs to the portal system. In addition, $S_{\rho,n}^{\text{ex}}$ may optionally be used to represent an extrinsic stimuli applied to the MCO or CRG.

$$S_{\rho,n} = \sum_{m=1}^{M} \left( \frac{c_{\rho,\text{mn}}y_{\text{mn}}}{\sigma_n} \right) + S_{\rho,n}^{\text{ex}}$$ (2.1)

The CRG model is a progression of the MCO model, providing a more biologically rele-
vant coupling systems allowing effective modelling of the sophisticated interconnections of neuronal systems. Figure 2.1 illustrates the internal structure of each CRG unit. The following are the underlying differential equations of each CRG unit in cartesian coordinates where \( \omega_n \) is the intrinsic angular frequency and \( S_{\phi,n}, S_{\alpha,n} \) are phase and amplitude modulation functions.

\[
\dot{u}_{1n} = \omega_n (u_{2n}(1 + S_{\phi,n}) + u_{1n}(1 + S_{\alpha,n} - u_{1n}^2 - u_{2n}^2)) \quad (2.2)
\]

\[
\dot{u}_{2n} = \omega_n (-u_{1n}(1 + S_{\phi,n}) + u_{2n}(1 + S_{\alpha,n} - u_{1n}^2 - u_{2n}^2)) \quad (2.3)
\]

The variables \( u_{1n}, u_{2n}, u_{3n}, u_{4n} \) are the internal state variables of each CRG while \( \beta_n \) controls the tail length of the mode.

\[
\dot{u}_{3n} = u_{4n} \quad (2.4)
\]

\[
\dot{u}_{4n} = \beta_n F_n(y) - 2\beta_n u_{4n} - \beta_n^2 u_{3n} \quad (2.5)
\]

\( F_n(y) \) provides the modal inputs for the CRG, taking directional coupling coefficients, \( c_{mn} \) and the outputs of other CRG units in the network, \( y_m \), as inputs [48]. In addition \( x_n(t) \) can be optionally used to couple external signals into the CRGs. This was an entry point for external stimulation in addition to the \( S_{\phi} \) portal in equations (2.2,2.3).

\[
F_n(y) = \sum_{m=1}^{M} c_{mn} y_m + x_n(t) \quad (2.6)
\]

The output of the system is produced through a non-linear mapping of the internal state variables described in equations (2.2,2.3,2.4,2.5).

As described in detail in Zalay et al [48], an arctan function is used to produce the phase angle while \( W(\phi) \) is an intrinsic output waveform function mapped to the interval \((-\pi, \pi]\).

\[
y_n = c_0 + u_{3n} + \sqrt{u_{1n}^2 + u_{2n}^2} W(\arctan\left(\frac{u_{2n}}{u_{1n}}\right)) \quad (2.7)
\]

In addition, the CRG model employs a bank of modes to process the inputs signals applied to each portal of the dynamic equations. The form of the modes and the equations describing them are presented in more detail in section 3.1.
2.2.2 Cognitive rhythm generator seizure like event model

Both CRGs and MCOs have been used to model a variety of neurological behaviour and are successfully able to capture the complexity of large neuronal assemblies [47]. The seizure model, a development of Zalay et al in a forthcoming publication, employs 4 CRG units coupled through neuronal modes to produce complex and most importantly spontaneous seizure like events. The interconnection of the four CRG units is depicted in figure 2.2. The network consists of two labile CRG units and two clock CRG units coupled through a bank of neuronal modes.

The events are characterized by synchronized rhythmic firing in all subunits producing abnormally large pseudo fields and disrupting normal system behaviour, as is the case in biological seizures. Importantly, only a single excitability parameter needs to be adjusted to move the system from a normal regime into a seizure prone and highly excitable regime. Details of the development of this model and parameters used are available in [47].

Figure 2.3 illustrates the nature of the transition of the internal state variables during system activity as well as a typical field signal illustrating spontaneous ictal events. In addition, figure 2.4 shows the mapper outputs from the individual units comprising the SLE model.

**Pseudo extracellular field computation** The extracellular field, observed in in-vitro and in-vivo experiments arises from electrical activity in the individual neurons of the network. A pseudo field signal is derived using cable theory and the individual outputs of each CRG unit [4].

For a series of isolated current sources in a uniform resistive medium, the potential, \( V_f(t, x) \), at an arbitrary point is given by

\[
V_f(t, x) = \frac{R_e}{4\pi} \sum_{j=1}^{N_{cr}} \frac{I_j(t)}{r_{jx}}
\]  

(2.8)
Figure 2.2: A block diagram illustrating the interconnection of two clock CRG units with two labile CRG units to produce the seizure-like event model.
Cognitive rhythm generator state variables and output

Figure 2.3: a) Phase procession as represented by the $\phi$ variable in the CRG model rapidly increasing during seizure like activity. b) Fluctuations in the $\alpha$ internal state variable during 90 seconds of system evolution c) A typical field signal produced by the SLE exhibiting spontaneous seizures
Figure 2.4: Transmembrane voltage output from each of the 4 CRGs used to generate seizures in the spontaneous SLE model
where $r_{jx}$ is the distance from the recording site to the spatial location of the CRG unit, $R_e$ is the medium resistivity and $I_j(t)$ is the membrane current arising from each CRG unit [45]. The mapper section of each CRG produces an output which is analogous to the transmembrane voltage, $v_m(t)$. Using the core conductor model, equation 2.9 can be derived by relating transmembrane current to $v_m(t)$, where $(r_e, r_i)$ are the external and internal axial resistances respectively.

$$I_m(t) = \frac{1}{r_i + r_e} \frac{\partial^2 v_m(t)}{\partial t^2}$$

Combining equations (2.8, 2.9) we obtain a relation for the field potential based only upon the transmembrane voltage of each CRG and its spatial orientation. Because the CRG model does not confer a specific orientation or geometry for the units, they are chosen to sit in a plane with a centrally placed equidistant recording electrode.

$$V_f(t, x) \propto \sum_{j=1}^{N_{crg}} \frac{\partial^2 v_{m,j}(t)}{\partial t^2}$$

2.3 Seizure Detection and Prediction

2.3.1 Seizure detection and prediction: Introduction

Seizure were long thought to occur due to an underlying random process and thus no prediction was possible; however, the presence of auras (pre-seizure awareness of seizure
onset) in some patients as well as clinical experience suggesting predictability countered this argument. Accurate seizure prediction allows the treatment to only be applied when necessary. Seizure prediction may possibly diminish side effects and improve quality life by decreasing the amount of intervention necessary to suppress seizures. Numerous approaches have been tried including analysis of spike frequency changes, spatial spike distributions, frequency domain characterization, and most successfully the application of nonlinear dynamical measures to the system.

2.3.2 Seizure detection

While the problem of seizure prediction is very complex, seizure detection, is relatively straightforward. Numerous approaches exist many of which are computationally simple and easily implementable, both critical factors for real time implementation. In this thesis no attempt was made to predict seizure onset. As described in the modelling section, all of the state variables of the system are available and thus a simple seizure detection system can be constructed. A simple excitation level based system was used to detect the presence of a seizure. The output of the excitation level when coupled with a simple threshold was a binary signal indicating the presence or absence of seizure like activity.

$$E_{\text{level}} = \frac{1}{N_c} \sum_{i=0}^{N_c} y_i^2$$

(2.11)

The excitation level is given in equation 2.11, where $y_i$ are CRG internal state variables and $N_c$ is the number of crg units. $E_{\text{level}}$ was compared to a threshold and when $E_{\text{level}} > E_{\text{thresh}}$, the system was considered be in seizure and the controller was activated. This condition was reevaluated at each time step and the controller was shut down as soon as the system excitability dropped below $E_{\text{thresh}}$. The proposed detection system requires access to the internal state variables of the system and is therefore not suitable for usage in a real-time biological model. A simple alternate
energy measure is presented in section 4.1 which remedies this problem. In addition the proposed energy measure is computationally efficient and well suited for real-time implementation.
Chapter 3

Controller implementation

The controller used in this thesis was derived from a controller used by Zalay et al in testing of the SLE model. The variable frequency generator, bank of modes and other constituents of the controller are described in the following sections.

3.1 Modes

3.1.1 Neuronal modes

Neuronal modes as used in this thesis are a consequence of a non-linear physiological modelling methodology developed by Marmarelis et al in a series of publications [27, 28, 26]. Marmarelis et al developed a non-parametric modelling approach which allows creation of predictive models for physiological systems for which the underlying structure is unknown. The methodology developed is derived from the discrete time Volterra series shown in equation 3.1 which is capable of modelling non-linear time invariant systems. An alternate equivalent system model can be derived using Wiener series.

\[
y(n) = k_0 + \sum_{m} k_1(m)x(n - m) + \sum_{m_1} \sum_{m_2} k_2(m_1, m_2)x(n - m_1)x(n - m_2) + \ldots \quad (3.1)
\]
Given a set of Volterra kernels \((k_0, k_1, \ldots)\) which describe the dynamics of the system, the output will be given by \(y(n)\) for any input \(x(n)\). A number of computationally efficient methods exist to allow estimation of the Volterra kernels including the Laguerre expansion technique [2]. An alternate and equivalent formulation of the Volterra model is shown in figure 3.1. The block system in figure 3.1 consists of a bank of linear principal dynamic modes (PDMs) which feed into a multi-input static non-linearity. The principal dynamic modes afford a parsimonious representation of the system using only the most significant components as extracted from the Volterra kernels.

For the common case in which only \((k_0, k_1, k_2)\) Volterra kernels are non-zero, a real symmetric matrix, \(C\), can be formed from their coefficients and because of its real symmetric nature it can be eigen-decomposed [2]. In a manner similar to modal analysis of linear systems, the set of the largest eigen-values, \(\lambda_i\), in the spectrum of \(C\) shows the most dominant modes of the system. The corresponding eigenvector, \(v_i\) associated to \(\lambda_i\), is convolved with the input signals to form the inputs \(u_i\). The inputs \(u_i\) in addition to an additive offset are fed into the static non-linearity. A distinct advantage of this model is that a great deal of information regarding the behaviour of the system can be extracted from the nature of the modes: their duration in time, whether they are integrating or

![Figure 3.1: Principal Dynamic Mode implementation of the general Volterra series model for a non-linear system](image.png)
differentiating. In addition, the entire set of parameters may be easily extracted from input/output data obtained from experimental systems.

The model presented above provides the general motivation for the structure of the stimulator. A bank of neuronal modes are used for preprocessing the input and subsequently fed into the static non-linearity described in section 3.2.1.

### 3.1.2 Neuronal modes for control

The modal architecture employed in the controller is similar to that presented in Zalay et al [47]. The modes are implemented as convolutions where each mode, $m_k$, is convolved with the input signal $x(n)$.

$$\phi_k(t) = \int_0^\infty m_k(\tau) \cdot x(t - \tau) d\tau$$  \hspace{1cm} (3.2)

The major defining characteristic of neuronal modes is the number of zero crossings which determines the ratio of integrating to differentiating nature of the modes. Modes with no zero crossings act as pure integrators whereas modes with one or more zero crossing exhibit progressively stronger differentiating character.

The modes were generated using the following formula as used by Zalay et al [47]:

$$m_k(t) = \sin(2\pi a_k t)e^{-b_k t} + c_k$$  \hspace{1cm} (3.3)

The behaviour of the modes when convolved with a square pulse stimulus is illustrated in figure 3.2. Higher order modes with increased numbers of zero crossings produce more complex derivatives of the input, whereas the pure integrating mode does not recognize rapid changes in the input signal.

Figure 3.2 shows the behaviour of the integrating mode and first and second order differentiating modes. There is also a zero order mode which is effectively a delta function which upon convolution passes the input signal. This mode is referred to as the proportional or 'P' mode and its only parameter is the gain applied.
3.1.3 Neuronal modes in physiology

Neuronal modes offer a convenient method of representing the complex dynamics of a neuronal system using a small number of distinct modes. Marmarelis et al demonstrated modelling of systems using mixtures of integrating and differentiating modes such that the system could be weighted toward being more amplitude sensitive or rate sensitive[28]. Vigmond et al demonstrated that field coupling resulted in differentiating of signals [43]. In addition, numerous examples of neurons with amplitude or rate sensitive input exist such as Monkey Vestibular-Only neurons which are alternatively sensitive to velocity in one direction and acceleration in the other [29]. In addition, the whisker-trigeminal system exhibits integrating behaviour while the pericruciate neurons in cats afforded both first and second derivative sensitive regions [8, 19]. The presence of integrating and differentiating behaviour at multiple scales of the physiology demonstrates the relevance of the neuronal mode system.

3.2 Variable frequency stimulation

A narrow pulse variable frequency stimulator was used to provide control stimuli to the CRG SLE model system. The system draws its control signal from the pseudo-field
recording generated during simulation because it is easily accessible in an experimental setting.

### 3.2.1 Narrow pulse generator

The narrow pulse generator, creates a sequence of biphasic pulses of minimum pulse width, which is based on the sampling rate. The pulse are therefore always a single sample wide and because the output is biphasic a single narrow pulse occupies 2 adjacent time steps. The narrow pulse generator was implemented in software and used the system step frequency, $f_s$, and the target output frequency to calculate where to place the pulses within a window. There is a trade off between the responsiveness of the stimulator, in terms of adjusting frequency based on the input signal, and the range of attainable frequencies. In general, the maximum frequency attainable is $f_s/2$, where $f_s$ is the sampling rate or time step, while the minimum frequency is given by the window size, $T_w$. For a controller update period of $T_w = \frac{100}{f_s}$ with $f_s = 1 kHz$, the minimum possible output frequency is 10Hz.

The narrow pulsetrain function was validated in the frequency domain in comparison with a sinusoidal chirp function. $\sin(\theta(t))$ or $\text{pulsetrain}(\theta(t))$ were evaluated where $\theta(t)$ is the instantaneous phase and $\omega = \frac{d\theta}{dt}$ is the frequency in radians. Letting $\omega = 2\pi f(t)$ and using simple functions for $f(t)$, the frequency domain performance of the pulse generator was verified.

\begin{equation}
    y(t) = \sin(2\pi \int_0^t f(\tau)d\tau)
\end{equation}

\begin{equation}
    x(t) = \text{pulsetrain}(2\pi \int_0^t f(\tau)d\tau)
\end{equation}

The function $f(t)$ was chosen to be a constant, a linear ramp or a quadratic function. Verification in the frequency domain was done using a short time fourier transform which was able to capture the time varying frequency of the signal. The pulse generator produced narrow pulses which resulted in harmonic content in the spectrogram. In order to
more clearly illustrate the frequency modulating effects of the pulse generator, all signals outside a band surrounding the fundamental were removed.

Figure 3.3: Verification of the pulse generator with $f(t) = 50$. a) Instantaneous frequency function. b) A spectrogram of constant $f(t)$ applied to the sinusoid, equation 3.4. c) A spectrogram of constant $f(t)$ applied to the pulse generator, equation 3.5.

### 3.2.2 Modal inputs

The bank of modes as described in section 3.1 were applied to the pseudo field signal and the subsequently rectified signal was used to generate the variable frequency stimulus. The stimulation frequency, when coupled to different modes, was able to capture different aspects of the system behaviour.

### 3.2.3 Implementation

The practical implementation of the stimulator described is constrained by two fundamental factors. The sampling rate, $f_s$ of the system, and window period $T_w = n f_s, n \in \mathbb{Z}$. 

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Figure 3.4: Verification of the pulse generator with $f(t) = t$. a) Instantaneous frequency function. b) A spectrogram of $f(t) = t$ applied to the sinusoid, equation 3.4. c) A spectrogram of $f(t) = t$ applied to the pulse generator, equation 3.5.

They combine to provide limits on the maximum stimulation frequency and with the finite window period, the time lag between controller response and stimulator activation, as well as the lower bound on stimulation frequency. For narrow pulses the maximum attainable pulse rate is $\frac{f_s}{2}$ while the minimum frequency is $\frac{1}{T_w}$, where $T_w$ is the window period.

### 3.2.4 Variable frequency stimulation validation

We validated the variable frequency stimulator coupled to the bank modes using a signal consisting of a single square pulse, as used in demonstrating the behaviour of the neuronal modes in figure 3.2. The single square pulse used had a base value of 100 and a peak value of 200. The signal was processed by the bank of modes and subsequently encoded using the pulse generator. Frequency domain validation was performed using a short time fourier transform (spectrogram, STFT).
Figure 3.5: Verification of the pulse generator with \( f(t) = t^2 \). a) Instantaneous frequency function. b) A spectrogram of \( f(t) = t^2 \) applied to the sinusoid, equation 3.4. c) A spectrogram of \( f(t) = t^2 \) applied to the pulse generator, equation 3.5.

**\( M_0 \) - Proportional mode**

The zero-order mode behaves like a delta function, \( \delta(t) \), preserving the input unchanged. Figure 3.6 b) shows the abrupt frequency transition due to the square wave input. This abrupt change is verified in the 100\( \text{Hz} \) and 200\( \text{Hz} \) frequency bands extracted from the spectrogram (STFT). The 100\( \text{Hz} \) band value goes almost to zero during the high region of the square pulse as expected. The 200\( \text{Hz} \) produces opposite behaviour and significantly increases when the narrow pulses shift to 200\( \text{Hz} \).

**\( M_1 \) - Integrating mode**

Figure 3.7, b) shows the smoothing and averaging effects of the first order mode applied to the square pulse function. The integrating mode produced similar output to \( m_0 \) during constant regions; however, the transitions are smoothed and result in continuous frequency transitions. Figure 3.7 c) shows an expanded view of the encoded signal.

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Figure 3.6: Verification of the proportional mode. a) Input square pulse convolved with $\delta(t)$. b) Expanded view of transition region showing step increase in spike rate. c) 100Hz band extracted from spectrogram. e) 200Hz band extracted from spectrogram.

centered around the frequency transition region. Panel d) of Figure 3.7 is a frequency domain representations of the encoded signal using a spectrogram (STFT).

In the frequency domain there is a clear 100Hz step recreating the input signal, in addition to a continuous spike that arises from the transition slope introduced by the integrating mode. On the falling edge of the pulse, the opposite behaviour is present with a negative spike taking it continuously to zero before returning to 100Hz. Due to the nature of the narrow pulse, harmonics are present which produce the horizontal bars in the figures.

$M_2$ - Differentiating mode

$M_2$, a differentiating mode, selects the edges or other rapidly changing regions of the signal. Figure 3.8 a-b) depict a simple biphasic mode which only produces non-zero output at the rising and falling edges of the signal as the differentiating mode is “rate”
Figure 3.7: Verification of the first order, integrating, mode. a) First order mode. b) Mode applied to square pulse input. c) Expanded view of spike rate transition region. e) Spectrogram (STFT) of narrow pulse coded signal.

The output of frequency coding is shown in figure 3.8 c-d) where the edges are coded in changing spike rate. In a manner similar to M1, the coded signal was transformed using a spectrogram (STFT). The frequency domain representation in figure 3.8 e) shows the short period of high frequency activity corresponding to the very abrupt edge in the square pulse.

**M₃ - Multiphasic differentiating mode**

M₃, a multiphasic mode, has a similar differentiating character to M₂. M₃ produces non-zero activity only during rapid changes of the input signal. Figure 3.9 a-b) show the application of the mode to the square pulse input signal. Note that in contrast to figure 3.8 b), M₃ produces a complex multiphasic pulse. In the frequency domain, figure 3.9 e), shows the high frequency pulses corresponding to square pulse edges in figure 3.9 b).
Figure 3.8: Verification of second order, differentiating, mode. a) Differentiating mode. 
b) Mode applied to square pulse input. c) Narrow pulse coded signal in the time domain 
d) Expanded view of spike rate transition region. e) Spectrogram (STFT) of narrow 
pulse coded signal.
These results indicate that the mode coupled to the pulse stimulator captured the rapid changes in the square input signal.

Figure 3.9: Verification of third order, differentiating, mode.  a) Differentiating mode.  b) Mode applied to square pulse input.  c) Output signal produced through narrow pulse coding.  d) Expanded view of spike rate transition region.  e) Spectrogram (STFT) of narrow pulse coded signal.

3.3 Controller overview

The variable frequency stimulator is shown in figure 3.10. The pulse generator implementation contains additional rectification blocks ($\|x\|$) to ensure that the frequency is always positive, a basic requirement. In addition, each signal path contains a limiting block that saturates the frequency command at the lower and upper limit described in section 3.2.1.

Figure 3.10 depicts three modes; however, the architecture is general and a linear combination of any number of modes can be used to feed the pulse generator. These modes
can be designed to trigger the stimulator based upon arbitrarily chosen dynamics present in the system. The architecture presented is very similar to a Wiener-Bose model, as described in [2], in which the signal path from the rectifier through the narrow pulse generator represents the multi-input static non-linearity.

![Block diagram of the variable stimulation system](image)

**Figure 3.10:** Block diagram of the variable stimulation system

The overall controller design is illustrated in figure 3.11. The constituent parts have been described in the previous sections. They are interconnected such that detection mechanism provides a gating signal to the output gains of the system thus turning the controller on and off at appropriate times. The stimulation signal generator block depicted in figure 3.11 is a general block that can take on many forms. In this thesis it resembles the variable frequency stimulator of figure 3.10. In addition, it may be replaced by an input independent generator to mimic a responsive fixed frequency stimulator such as the Neuropace RNS system.

![Summary block diagram of the controller implementation](image)

**Figure 3.11:** Summary block diagram of the controller implementation

For the purpose of comparison in this thesis, a fixed frequency biphasic signal generator was used as a control to evaluate performance. The fixed frequency or “periodic”
stimulator operated in open-loop or coupled to the detection system making it responsive. The open-loop system continuously stimulated the system in a manner similar to that seen in the literature.

### 3.4 Implementational issues

In order to integrate the bank of modes and the variable frequency stimulator a number of issues were addressed primarily related to the nature of the stiff ODE solver used to integrate the differential equations. All simulations and data analysis were performed using Matlab 7.7.0 (The MathWorks, Natick, MA) and a second order Gear’s method based solver [13]. This solver takes partial steps thus evaluating the differential equation right hand side at time-steps of fractional duration in addition to multiple evaluations in order to solve the implicit equations used in the solver. A time counting algorithm was used to separate the dynamics of the solver from the time scales used by the convolution modes. In addition a state machine was developed and used to track the edges of seizures to ensure that the controller rapidly shuts down at the conclusion of seizure like activity.
Chapter 4

Quantifying results

Controller performance was quantified using the percentage seizure time and mean ictal event duration measures which are described in the following sections. An energy measure, Teager energy, is proposed and validated which enables the use of only observable variables when implementing the controller, removing the dependence on internal state variables. In addition, the Teager energy is used to calculate the energy expended by the stimulator in controlling the system.

4.1 Energy measures

Seizure detection can commonly be performed using energy measures. Energy measures are generally simple and computationally efficient making them readily adaptable to real time implementation.

4.1.1 Energy

The simplest energy measure of signal is given by equation 4.1 for a discrete time signal of length N.

\[ E = \sum_{n=0}^{N} x(n)^2 \]  

(4.1)
4.1.2 Teager energy

An alternate measure of energy was presented in [20] and has found strong application in audio and speech processing. Teager energy has been used for seizure detection and evaluation of control efficacy in a number of papers [10, 49]. The Teager energy is given by equation 4.2 for a discrete time signal of length $N$.

$$TE = \sum_{n=1}^{N-1} x(n)^2 - x(n-1) \ast x(n+1)$$  \hspace{1cm} (4.2)

Figure 4.1: Application of the energy measures to test signals. a) Non-zero constant signal. b) $2Hz$ sinusoid. c) Exponential damping applied to sinusoid of b). d) Linearly increasing frequency chirp. e-h) Application of standard energy measure to signals a-d). i-l) Application of Teager energy to the signals in a-d).

Figure 4.1 compares two energy measures when applied to a few common signals: a non-zero constant, a constant frequency sinusoid, an exponentially damped sinusoid and a linear chirp. The Teager energy measure produces superior results in extracting the underlying energy of the signal in all cases. The constant signal is shown to have zero teager energy while the sinusoid is constant. The exponentially damped sinusoid
produces an energy that decays exponentially and more rapidly than the envelope as expected. The linear chirp, produces a quadratic energy function as expected when the Teager energy is applied; however, even for large window sizes the conventional energy is not conclusive. In all cases the Teager energy is able to capture the underlying energy of the signal and remains insensitive to window size variation. The plots in the figure were produced with a window size of 200ms as used by [10]. Details of the derivations of expected energy for various signals are presented in [20].

We used the excitation level described in section 2.3.2, which is dependent on internal state variables of the CRG SLE mode, to gate the seizure stimulation system. In figure 4.2 the energy measure is applied to a typical pseudo-field recording from the CRG SLE model. The energy measure strongly correlates to the excitation level measure of activity without knowledge of the internal state of the system. This correlation is of critical importance for experimental work as it removes the dependence of the controller on internal state variables. In addition the proposed measure is very computationally simple and readily suitable for real-time implementation.

4.1.3 Applied control energy

The Teager energy was also applied to the output of each of the controllers in order to measure the amount of energy applied by each controller in the process of controlling the system. The calculated value was used as an efficacy measuring in evaluating controller performance.

4.2 Performance measures

Performance of the controller was quantified using a number of measures based upon the time the system spent in the ictal (seizing) state. In a manner consistent with the operation of the controller threshold system, the percentage seizure time was calculated
Figure 4.2: Energy measured applied to an unstimulated pseudo-field signal. a) A pseudo-field signal obtained from the CRG SLE model. b) Excitation level signal from CRG model. c) Teager energy applied to field signal captures same seizure activity as excitation level.
based upon a single threshold applied to the excitation level state variable obtained from the CRG model. After suprathreshold regions were identified using the thresholding algorithm, the end points of the seizing intervals were recorded for use in deriving performance measures. The series of points produced provided two sets of data. The series of seizure times describes the length of each seizure while the series of times between seizure events forms another time series describing the inter-seizure times. These two time series can be used to calculate a few measures on each stimulation iteration. Figure 4.3 illustrates a sample of the seizure classification process. The black trace in the lower panel of figure 4.3 shows the individual isolated events that are classified as seizures as well as the inter-seizure times.

4.2.1 Normalization

The thresholding and time series extraction described in section 4.2 were also calculated on the unstimulated system for each unique set of initial conditions. This resulted in a control time series for each experiment. Different initial conditions, because of the nonlinear nature of the system, produced rapidly diverging and consistently unique patterns of activity. This meant that the control time series was required for normalization in order to account for specific initial conditions that were “harder” to control because of the starting location in the state space.

4.2.2 Measures

Using the experimental and control time series obtained in sections (4.2,4.2.1) three measures can be computed.

- Percentage seizure time is the sum of all the regions where the system excitation level is above threshold.

- Mean ictal event duration is the average length of each individual temporally iso-
Figure 4.3: top: Excitation level calculated from the CRG internal state variables. bottom: the light trace shows the field signal. A high level of the black trace indicates the system was classified as in the ictal state while a low level indicates the system was classified as normal.
lated region where the excitation level is above threshold

- Percentage inter-seizure time follows directly from percentage seizure time and is the sum of the time the system is below threshold for each recording

This thesis focuses on the first two measures, percentage seizure time and mean ictal event duration, as inter-seizure time is directly related to total seizure time. Once the measures were calculated they were normalized using their corresponding control signals.

### 4.2.3 Multi-case averaging

In order to obtain consistent and reliable results the measures used are all average values constructed from a diverse set of initial conditions. The initial conditions describe the starting point of the system in state space and effect the entire evolution the system. For each initial condition the measures were computed as described in section 4.2 and they were subsequently averaged over the set of initial conditions producing a “mean” measure.
Chapter 5

Results

The effect of gain on the performance of the fixed frequency and variable frequency stimulators was explored and it was shown that relatively low gains produced superior performance. In addition, the responsive variable frequency stimulator was shown to perform statistically significantly better than the open-loop and responsive fixed frequency stimulators. Finally, the energy applied by the responsive variable frequency stimulation system was shown to be > 3 times less than the energy used by the open-loop fixed frequency stimulator in controlling the system. The stimulation system presented here does not experience unstable feedback and ringing behaviour as has been seen in experimental systems [10] and in our own experimental work even when relatively large gains were used with direct feedback loops.

As discussed in section 1.4 the stimulation paradigm most frequently used in clinical situations is effectively open-loop. The stimulation waveform is typically a biphasic square wave with a fixed frequency and duty cycle [40, 42, 25]. The open-loop and responsive fixed frequency stimulators form the control used to evaluate the performance of the variable frequency stimulator. The two types of stimulation compared in this thesis are illustrated in figure 5.1.
5.1 Performance comparison of stimulator architectures

The performance of the open-loop and responsive fixed frequency stimulators was compared to that of the responsive variable frequency stimulator. It was shown that the responsive variable frequency stimulator statistically significantly outperformed the responsive and open-loop fixed frequency stimulators.

A comparison of the fixed frequency vs the variable frequency stimulators was conducted by selection of the best performing gain based upon the results from sections 5.2, 5.3. This selection resulted in choosing the cases with gains of 0.1. The efficacy measures are plotted for comparison in figures 5.2, 5.3.

Note that a lower value indicates better performance in both metrics. Lower values in the percentage seizure time indicates that the system spends less time in the ictal state as a fraction of total simulation time. Lower values of the mean ictal event duration
Figure 5.2: Percentage seizure time comparison for a gain of 0.1 for the responsive and open-loop fixed frequency stimulators and the responsive variable frequency stimulator.

indicates that average isolated ictal event is decreased in duration.

Performance difference were quantified using a t-test and the null hypothesis of distributions of equal mean and variance. Probability plots were generated to verify that the data sets used were drawn from close to normal distributions. A typical plot is shown in figure 5.4 showing the data set clustered along the normal distribution line indicating that the data set was likely drawn from a normal distribution and validating the usage of t-testing. The test was applied to each pair of the responsive and open-loop fixed frequency results and a variable frequency result. The p values are summarized in tables (5.1,5.2).

Significance levels of $p < 0.084$ and $p < 0.059$ were obtained for the integrating mode, $M_1$, when evaluated using total seizure time and mean ictal event duration respectively and compared to the responsive fixed frequency stimulator. The responsive variable frequency stimulator also performed better than the open-loop fixed frequency stimulator with p-values of $p < 0.018$ and $p < 0.05$ for percentage seizure time and mean ictal event duration respectively. These results indicate that the best overall performance is obtained
Figure 5.3: Mean ictal event duration comparison for a gain of 0.1 for the responsive and open-loop fixed frequency stimulators and the responsive variable frequency stimulator.

Figure 5.4: Probability plot of a typical data set to illustrate normality of the data.
<table>
<thead>
<tr>
<th>Mode</th>
<th>Percentage seizure time</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proportional</td>
<td>1.00</td>
<td>$p &lt; 0.157$</td>
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<tr>
<td>Integrating</td>
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<td>$p &lt; 0.018$</td>
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<tr>
<td>Differentiating</td>
<td>0.95</td>
<td>$p &lt; 0.105$</td>
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<td>$p &lt; 0.272$</td>
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<tr>
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<td>$p &lt; 0.050$</td>
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<tr>
<td>Differentiating</td>
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</table>

<table>
<thead>
<tr>
<th>Mean ictal event duration</th>
<th>Mode</th>
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</thead>
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<tr>
<td>Differentiating</td>
<td>0.96</td>
<td>$p &lt; 0.346$</td>
</tr>
</tbody>
</table>

Table 5.1: Statistical test for percentage seizure time

Table 5.2: Statistical test for mean ictal event duration
by coupling the variable frequency stimulator to an integrating mode as a pre-processing stage. The results also suggest that the detection system has relatively little effect on the performance of the fixed frequency (periodic) stimulator; however, a significant advantage of using the detection system is discussed in section 5.4.

5.2 Fixed frequency stimulation

The motivation for selection of the gain of 0.1 is provided in the following section which analyzes the effect of gain on the fixed frequency stimulator performance. Improved performance, based on percentage seizure time and mean ictal event duration, in the fixed frequency stimulator was shown to correlate with lower gain. Responsive and open-loop fixed frequency were compared and the detection system was shown to have a weak effect on the performance metrics.

5.2.1 Open loop fixed frequency stimulation

The fixed frequency stimulation parameters chosen as a control are $f_{\text{stim}} = 100\,Hz$ with a stimulation time of $1.5\,ms$. The parameters are typical of those used in clinical stimulation applications with implanted stimulators [40, 42, 25]. The stimulation was performed using a biphasic square wave and the gain was varied to observe its effect on performance as judged by the percentage seizure time and mean ictal event duration. Lower values of these metrics indicate better performance as they respectively imply that the total time the system spends in seizure is decreased and the average duration of each SLE event is decreased. A typical example of control using the periodic stimulator is illustrated in figure 5.5. The sample control traces presented illustrate the strong effect of gain on performance. At low gains the stimulator was effective while at high gains the stimulator seemed to exacerbate seizure like events.

The observations of figure 5.5 were quantified using normalized seizure time and mean
Figure 5.5: Psuedo field recordings from the CRG model. a) The field recording in the absence of stimulation shows frequent spontaneous seizure like activity. b) Low gain (0.1) periodic stimulation decreases the number of seizures and their duration. c) High gain (10) causes increased seizure activity that is almost continuous throughout the recording.
seizure time. In figures (5.6,5.7), the values presented represent averages over a randomly selected set of 16 initial conditions in order to ensure consistency of the results. Both measures indicate decreasing performance with increasing gain. The performance is best at small gain; however, little change is seen between gains of 0.1 and 1.

### 5.2.2 Responsive fixed frequency stimulation

The fixed frequency stimulator was tested when coupled to a detection system and performance was inversely related to gain. The periodic stimulation parameters used with the detection system were the same as those used in section 5.2.1 with a stimulation time of 2s.

Periodic stimulation coupled to the detection system improved performance by lowering the percentage seizure time and the mean ictal event duration. Both measures exhibited maximum improvement at low gains over a set of 16 randomly generated ini-
Figure 5.7: Mean ictal event duration for the periodic stimulator as a function of gain. Open-loop performance is depicted in the first set of bars while responsive fixed frequency results are shown in the second set of bars.

5.3 Responsive variable frequency stimulation

The variable frequency stimulator was demonstrated, using the percentage seizure time and mean ictal event duration, to have a performance peak at low gain and with $M_1$ (the integrating mode) as the preprocessing stage. The variable frequency stimulator was investigated in a similar manner to the fixed frequency stimulator. The performance was compared using percentage seizure time and mean ictal event duration over the controller parameters of gain and mode. The gain was allowed to take on values of $(0.1, 1, 10)$ while the system was coupled through a proportional ($M_0$), integrating ($M_1$) or differentiating ($M_2$) mode. A detailed description of the operation of the variable frequency generator and mode system is provided in section 3.4.
Figure 5.8: Seizure suppression by variable frequency stimulation. a) Pseudo field signal in the uncontrolled system. b) Pseudo field signal with responsive variable frequency control applied. c) Stimulation signal applied to the CRG model

Figure 5.8 shows the effect of the controller in stopping seizure activity. The number of seizures present in figure 5.8 b) is significantly diminished and the “interictal” periods are significantly increased in duration. Despite what mostly appears to be successful control, the controller is unable to completely prevent the system from producing ictal behaviour which is consistent with what is observed in biological stimulation studies.

Figures (5.9,5.10) show the effect of the gain and the mode on performance, where $M_0$ is the proportional mode, $M_1$ is the integrating mode and $M_2$ is the differentiating mode as described in section 3.1. The integrating mode exhibits strongly gain sensitive performance and follows the general trend present in all of the modes in which lower gain produced better results.

The performance of the integrating mode was further investigated over a range of gains on either side of 0.1. Figure 5.11 illustrates the performance based upon percentage seizure time and mean ictal event duration. Increasing or decreasing the gain causes the
Figure 5.9: Percentage seizure time as a function of gain and the preprocessing mode used in the responsive variable frequency stimulator.

Figure 5.10: Mean ictal event duration as function of gain and the preprocessing mode used in the responsive variable frequency stimulator.
performance of the controller to decrease as expected suggesting that a gain of 0.1 is indeed a best case result and a valid basis for comparison.

Figure 5.11: Fine grained investigation of the role of gain on performance of the responsive variable frequency stimulator coupled to the integrating mode.

The percentage seizure time is lowest in the case of the integrating mode. The same result is also observed when considering mean ictal event duration. It also interesting to note that for large gains the controller may in fact make the system more prone to seizure like activity. In addition we note that very small gains show degraded performance as the control is no longer able to effectively perturb the system. This indicates that selection of stimulation parameters is a complex process in which great care must be taken to avoid worsening conditions.

5.4 Stimulation energy

The energy required to achieve seizure control is demonstrated to be significantly lower in the variable frequency stimulator as compared to the fixed frequency stimulator. Fig-
Figure 5.12 shows the mean energy applied by the controller for the best performing gain from the responsive and open-loop fixed frequency stimulators in addition to the responsive variable frequency stimulator coupled to $M_1$. The mean stimulation energy required by the integrating mode is three times smaller than that required by open-loop fixed frequency stimulation while maintaining a significant performance improvement. Interestingly, the addition of the prediction system to the fixed frequency controller reduced the control energy but did not improve the controller performance as judged using percentage seizure time and mean ictal event duration.

![Figure 5.12: Mean stimulation energy with a gain of 0.1 from the responsive and open-loop fixed frequency stimulators in addition to the responsive stimulator coupled to the integrating mode, $M_1$.](image)

The finding of diminished control energy has a number of important implications relating to the practical design and implantation of stimulators which are discussed in chapter 6.

The results presented indicate that the responsive variable frequency stimulation improves controller performance by lowering the total time spent in the ictal state and lowering the duration of each ictal episode. In addition, the use of the seizure detection
mechanism reduces the applied control energy which may facilitate simplified stimulator design and fewer adverse stimulation effects in patients.
Chapter 6

Discussion

The guiding philosophy in the design of the controller was to produce a system which would naturally interact with the underlying biological system. The findings of this thesis indicate that a fully closed loop stimulator using variable frequency stimulation outperforms a responsive or open-loop fixed frequency stimulator.

The controller, as currently designed, resembles a classical controller in that it includes an error signal which is used to couple and decouple the controller from the system. The controller was modelled on a Wiener-Bose type linear-non-linear cascade which has been successfully employed to model spiking neuronal systems [28]. The controller then resembles a spiking neuron which is selectively coupled into the system in order to push the system away from undesirable regions of the state space. Feedback regulation is present throughout the body for homeostatic maintenance and on a microscopic level within neural systems [11]. This provided the motivation for the stimulation system design and its resemblance to a classical feedback controller.


6.1 Variable frequency stimulation improves performance

The variable frequency stimulator, when coupled to the threshold gating system, significantly improved seizure control as verified using percentage seizure time and mean ictal event duration when compared to the clinical standard of continuous fixed frequency stimulation. Variation in frequency provides a natural way to interact with the neuronal system, where it is well known that information is frequency coded for transmission. Thus, the stimulator is interacting with the system in its own native frequency coded language. The results suggest that tailoring the stimulus to the underlying dynamics of the system through the modes and using a stimulus which operates in a similar fashion to the neurons will provide superior performance.

6.2 Closed loop responsive stimulation

Responsive stimulation: the combination of seizure detection with the responsive stimulator proved more effective than continuous stimulation. This finding validated the premise of responsive stimulation which is at present infrequently used in clinical situations. A current state of the art responsive stimulator undergoing clinical trials, the Neuropace RNS system, contains a seizure detection system coupled to a stimulator delivering “current-controlled, charge-balanced biphasic pulses” [39] through implanted electrodes. Though this system is a leap forward compared to open-loop continuous stimulation, its efficacy is unverified and it still unable to intelligently adapt the stimulation signal. The system proposed in this thesis fully closes the loop and has been demonstrated to be effective. The responsive stimulator, as implemented through the use of the seizure detection block, decreases the energy delivered and therefore the power consumption of the stimulation device, a critical concern in implantable devices where battery
changes are costly and high risk. The simple responsive stimulator presented was dependent on internal state variables; however, an appropriate energy measure was presented and applied to the pseudo-field producing a signal which was strongly correlated to the excitation level. This energy measure effectively removes the controller dependence on internal state variables.

6.3 Implementational advantages of variable frequency stimulation

As demonstrated in section 5.4, the stimulation energy required by the controller is decreased by a factor 3 or more when the seizure gating detection system was used. This is critically important for a number of reasons.

- Decreased stimulation energy consumption lower the total power consumption and allows for increased battery life. This means patients must undergo fewer operations to replace batteries which decreases the risk of surgical complications.

- Stimulator operation dissipates power in the circuitry of the stimulator and results in heat dissipation. Stimulators must be carefully designed to limit temperature rise to avoid surrounding tissue damage. The significantly lower heat dissipation arising from variable frequency stimulation makes this aspect of the design easier.

The above two factors allow for the design of more compact stimulators by decreasing the battery size and the area necessary to dissipate heat generated by the electronics.

The combination of decreased energy consumption and better performance as verified using percentage seizure time and mean ictal event duration indicates that the responsive variable frequency stimulator provides a superior seizure control solution to presently available alternatives.
6.4 Future work

The results suggest that significant improvements in seizure control can be achieved through the use of responsive stimulation and variable frequency stimulation. The implementations of the responsive controller has been presented and is readily amenable to real-time implementation for biological interfacing.

6.4.1 Experimental work

The next step involves applying these techniques to in-vitro brain slice experiments and subsequently in-vivo animal experiments. In-vitro models provide a significantly more accurate environment to test the system and are the next logical step in validating the controller on progressively more complex models. The intrinsic variable frequency generation function is implemented in software and is rapidly computed. In addition the energy measures can be very rapidly computed and evaluated to turn the controller on and off removing the dependency of the controller on internal state variables and resolving one the final major implementation hurdles. The bank of modes is the most computationally intensive section of the controller and bears a strong resemblance to a bank of finite impulse response filters. The problem of FIR filter implementation has been frequently addressed and numerous high speed implementation exist for general purpose processors, GPUs and FPGAs. The variable frequency stimulation technique could ultimately be used in implantable neural stimulators as it is computationally efficient and would not require significant design changes from modern neurostimulators.

6.4.2 Seizure prediction

As an addition enhancement to this system, replacement of the seizure detection block with a suitable prediction system would provide insight into the importance of stimulation timing in aborting ictal activity.
6.4.3 Controller architectures

As discussed previously, the system has the form of linear-non-linear cascade commonly used for neuronal modelling. Expansion of this topology to produce a more comprehensive model or outright use of a neural model as the closed loop stimulator would provide an even more biologically relevant stimulation signal. Using a neuronal model to augment the system would alleviate some of the difficulties in using a classical feedback architecture: in particular defining and implementing an error signal.

6.5 Conclusions

A fully closed loop responsive stimulator has been developed and validated using the CRG SLE model. The variable frequency stimulator was coupled to a bank of preprocessing modes and the integrating mode was shown to provide the best controller performance. In addition the use of a seizure detection mechanism to gate the controller operation was demonstrated to decrease applied control energy. The proposed system decreased the control energy applied leading to the possibility of smaller implantable devices with enhanced longevity. In addition the entire proposed system is readily amenable to real-time implementation and usage in a clinical environment.
Bibliography


