Model Based Detection of a Stimulus Presence from Neurophysiological Signals

by

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Abstract

I address the problem of designing an automated artificial detector that must identify the presence of an external stimulus from observing high pass filtered electrical signals emitted by the neural tissue. The focus is given to experimental settings, in which an electrode is inserted into the tissue and fixed outside the cells (extracellular recording) in an anatomical region, which is densely populated with stimulus reactive neurons. Such signals are considered to reflect the activity of many neurons, and for this reason it is sometimes referred to as “multi-unit activity” (MUA). This detection problem is an interesting intersection of control engineering and brain research, as the brain itself executes stimulus detection tasks and also relies on neural signaling.

The practical commonly used method for identifying a stimulus presence from MUA is the "energy detector" in which the acquired signal is first squared, integrated and thresholded to yield a clear cut decision. The energy detector is supported by years of experience, not only in physiological studies, but also in many other fields, such as radar detection systems, communication system, seismic activity detectors, and other disciplines. Nevertheless, the energy detection scheme is essentially heuristic, and as such, it does not guarantee optimality. Thus, it is possible that a detection scheme that is based on analytic considerations would give a better performance. It is also possible that the biological neural detection scheme, which is naturally employed by the experimentalist conducting the electrophysiological recording, outperforms the energy detector. The objectives of this work were to find the optimal detection scheme for identifying the presence of an external stimulus from observing multi neuron (“multi-unit”) activity alone, and also to better understand the detection scheme employed by neural tissue itself. The thread connecting these two objectives is the use of an analytic probabilistic model for describing the acquired data. The model allows, on the one hand, to analytically derive an
optimal detection scheme by means of mathematical optimization, and on the other hand, it constitutes a quantitative explanation for the processes taking place in the neural tissue.

The contributions of this work include an innovative neuron model, a model for the MUA measurement process, and an optimal detector for stimulus presence which is based on these models. It is shown that the optimal detector outperforms the energy detector, both in simulations and when using real electrophysiological data. It is also shown that the performance gap, in favor of the optimal detector, is substantial mainly in very low probabilities of false alarm errors. Thus, the energy detector is shown to be close to optimum in moderate and high probabilities of a false alarm error. Furthermore, the real data tests show that the energy detector is more robust to isolated and short, yet intense disturbances, and also more robust to noise fluctuations outside stimuli intervals. I discuss a conjecture, inspired by the above model and by the empirical results, that the biological neural tissue itself executes a modified energy detection scheme, and I review experimental results from the literature that allegedly support this conjecture.
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Chapter 1

Introduction

1.1 Research Question

Automated artificial detection of an external stimulus from observing the activity of multiple neurons is of dual interest to control and biomedical engineers, as well as to other researchers of the nervous system: On the one hand, automatic artificial detectors of neural activity are a key element of prosthetic devices that can replace or bypass dysfunctional neural structures in paralyzed patients, or automatically intervene in neurological disorders that are characterized by an exaggerated response to a weak or an absent stimulus. On the other hand, automatic artificial detectors can be greatly improved by understanding the way the healthy nervous system executes detection tasks. Thus, the dual interest in detecting neural activity stems from the fact that the neurons themselves are part of a circuit whose main purpose is to detect and respond to various stimuli. Automatic artificial detection of a stimulus presence, through observation of neuron activity, is therefore a special intersection of control engineering and brain research, and is the main concern of this work.

The techniques of measuring neural activity are diverse, each reflecting different aspects of the processes occurring in the neural tissue. In this work we rely predominantly on our own electrophysiological multi-unit recordings from the pontine nucleus and the inferior colliculus of rats, and also on similar reports by other researchers who recorded multi-unit activity in different locations (e.g. Holstein et al. (1969a) and Holstein et al. (1969b), Tommerdahl et al.
(1999) and in Radner et al. (2001)). In multi-unit recordings, an electrode is inserted in the neural tissue and located outside of the cells (extra-cellular recording as opposed to intracellular recording). In our multi-unit recordings, as well as in the other recordings mentioned above, the electrode was located in a region that is densely populated with neurons that respond to a specific type of stimulus, and it captured the electrical activity of many stimulus responsive cells, rather than the possibly unrelated activity of a single cell. Such densely populated regions are quite common, as the nervous system itself relies on a bundle of neurons (nerves, ganglia, tracts and nuclei and certain cortical regions) for stimuli propagation. Other than the activity of the stimulus responsive neurons, the electrode also captures the electrical activity of many more active cells in the background. However, it is empirically established that this background activity is greatly reduced by high pass filtering above 300 Hertz. The resulting filtered signal is often referred to as ”multi-unit activity” (MUA) and consists of noisy fluctuations, that are somewhat more intense during the stimulus. Interestingly enough, the averaged intensity profile of multi-unit-activity in response to a stimulus with a rectangular intensity has a consistent general form, which was revealed in our tests as well as in research reports of others. Figure 1.1 shows examples of raw multi-unit activity (in the left column) and its corresponding averaged intensity profile (in the right column).
Figure 1.1: Multi-unit response to a stimulus pulse. The left column shows examples of raw data of multi-unit activity in response to the stimulus, and the right column is the corresponding multi-unit peristimulus histogram (PSTH): (a-b) Inferior colliculus response to auditory stimulus which was measured in our experiments. (c-d) Cochlear nucleus response to auditory stimulus as reported by Holstein et al. (1969a) and Holstein et al. (1969b). (e-f) Anterior parietal cortex response to somatosensory stimulus (vibrations), as reported by Tommerdahl et al. (1999). (g-h) Retina response to pulse of light as reported by Radner et al. (2001).
The purpose of this research was twofold. The first purpose was to derive the optimal procedure for detecting the presence of an external stimulus from observing MUA recordings alone, as shown in Figure 1.2. Namely, the detector monitors the electrophysiological response alone (second signal from the top of Figure 1.2) and must raise its detection flag within some predefined delay from the stimulus start. Ideally, the detector would raise its flag throughout the whole delayed version of the stimulus presence (third signal from the top of Figure 1.2), and would set its flag off otherwise. However, real life detectors sometimes raise their detection flag in the absence of a stimulus ("false alarm" error), or set off their detection flag even though a stimulus is present ("mis-detection" error), as shown by the signal at the bottom of Figure 1.2. Thus, the first objective of this work was to design a detector that minimizes these types of errors.

Figure 1.2: Detection of a Stimulus from Electrophysiological measurements inside the brain.

The second goal of this work was to achieve a better understanding of the way the neural tissue itself executes stimulus detection tasks in terms of control theory. The thread connecting these two purposes is the use of mathematical modeling for describing the observed experimental phenomena. For this reason, this work is entitled as "Model Based Detection of Stimulus Presence from Neurophysiological Signals". As shown in Figure 1.3, the model allows to derive an optimal decision regarding the stimulus presence by means of mathematical optimization, and at the same time, is constitutes a quantitative explanation for the processes
underlying the neural response to the stimulus. Figure 1.3 also illustrates the tight relation of the research question of this work to the essence of brain research, as both the artificial detector and the brain itself are fed by neural signals, and both make decisions regarding the stimulus presence.

Figure 1.3: Model based detection of a stimulus from electrophysiological measurements inside the brain.
1.2 Literature Review

In this section I review previous studies on detection schemes for identifying stimulus presence from electrical neural activity, and I separately review past works on neuron modeling and relevant conjectures regarding the detection scheme executed by the nervous system. The literature review is separated into three subsections, since the question of neural modeling is not always coupled with the question of detection of stimuli using neural activity.

1.2.1 Background on Stimuli Detection From Electrophysiological Recordings

Due to its importance to both brain research and biomedical applications, the question of stimulus detection from observing electrophysiological recordings has been previously addressed.

A substantial part of past works on stimulus detection from electrophysiological recordings consider the so-called spike-sorting problem (see review by Lewicki, 1998). In these works, the spike times of a small number of stimulus responsive spiking sources must be identified from data that also includes a small number of unrelated spiking sources. The underlying assumption of the detection schemes based on spike-sorting is that the stimulus related spiking source and the unrelated sources produce different spike shapes, making it possible to distinguish one type of source from the other. However, in the conditions discussed in this work, it is impossible to isolate and identify single spikes with reasonable probability because of the ambiguity of observations that result from cumulative action of a large number of spiking sources embedded in thermal noise. Thus, the detectors based on spike sorting are not suited for the ”multi-unit” activity (MUA) setting considered in this work.

The common practical method for identifying responses to stimuli from multi-unit activity in densely populated regions, is the square and integrate method originally proposed by Weber and Buchwald (1965). In this method, the signal is squared, integrated and finally thresholded to yield a clear cut decision. The method proposed by Weber and Buchwald is essentially heuristic, and as such, it does not guarantee optimality. Nevertheless, this method is supported by years of experience in neuroscience and in other fields, such as radar (Marcum, 1960),
and communications (Urkowitz, 1967; Digham et al., 2007), where the latter two works also suggest analytic explanations for the effectiveness of this method in communications. However, it is possible though that further testing of an endless number of other detection schemes, using a trial and error approach, would yield a better detection scheme.

A different engineering approach for constructing a detection scheme is first to assume a probabilistic model which connects between the event to be detected (auditory stimulus in our case), and the observations (electrode voltage in our case), and then to analytically derive a detection rule which minimizes the risk of an error. A particularly important class of probabilistic models that describe natural phenomena in general, and neural phenomena in particular, are the Gaussian models (see e.g. Roweis and Ghahramani (1999)). These models are so ubiquitous in science due to the central limit theorem, which loosely states that under reasonable conditions, (mainly the existence of a finite third moment) the sum of random variables will converge to a random variable having a Gaussian distribution, where the convergence of the central limit theorem is with respect to the number of random variables in the sum. The general methodology for deducing an optimal detection rule from non-stationary Gaussian observations was stated in the pioneering work of Schweppe (1965) who associated the technique of ”state space” formulation for solving detection problems. The general applicability of a state space formulation (Kalman, 1960; Schweppe, 1965) for analyzing the activity of many neurons ("population decoding") was also discussed recently (Roweis and Ghahramani, 1999; Barbieri et al., 2004; Paninski et al., 2007; Pillow et al., 2011). However, these recent works do not specify a detailed detection scheme, and they do not specify a detailed probabilistic model that specifies stimuli timing and the characteristics of the response (recall that we review model based detection schemes). More specifically, they do not specify the a-priori stimuli timing conditions that the detection is optimized for, and they do not characterize the exact probabilistic law that governs the response of multi-unit activity to a stimulus.

In this work I adopt the multi-unit activity problem setting (or "population decoding” setting), and derive an optimal detection scheme based on analytic considerations. I define the exact detection quality criteria of the problem, the exact probability law governing the problem, and describe in detail the implementation of the detector. The implementation described
in this work makes use of the enormous progress in technology capabilities, which allows to implement and test ideas that were considered only theoretical at the time the ideas of state space based detection were first published (Kalman, 1960; Schweppe, 1965).

### 1.2.2 Background on Neuron Modeling

This research work also yielded an innovative neuron model (Nossenson and Messer (2010), Nossenson and Messer (2011)) which is described in detail in Section 3.1.2.

Due to the understanding that neuron modeling is a key step for understanding how the brain works, the question of neuron modeling has been addressed many times, and there are over a hundred models in the literature (see e.g. Fienberg (1974), Johnson (1996), Burkitt (2006) and Herz et al. (2006), Paninski et al. (2009)). The large number of neuron models is a result of the wide variety of data obtained in different anatomical locations using different experimental setups (see e.g. Fienberg (1974)). Thus, much of the difficulty in modeling a neuron results from the difficulty to separate between the intrinsic functional properties of the neuron from the effects of the measurement setup, and the effect of brain circuitry (that is, effects that are due to a circuit of more than one cell).

Roughly, neuron models can be divided into two categories: 1. Membrane voltage models that follow the pioneering work of Hodgkin and Huxley (1952), and produce an analog prediction for the neuron membrane voltage as a function of the stimulus; 2. System level models that pursue a simplified input to output functional relation for describing the neuron, typically distinguishing only between two measured voltage levels: the presence of a spike (also known as "action potential") or a quiescent state. The system level models could be further divided into deterministic and probabilistic models. While the deterministic models output a single possible outcome to a given stimulus, the probabilistic models return several possible outcomes, each assigned with a probability measure. Typically, this output probability is normalized by a time constant, and the resulting normalized probability is called the *Firing Rate* and has units of Hertz.

The most noticeable difference between these two categories of models is the different abstraction levels (cf. Herz et al. (2006) and also Brette and Gerstner (2005)), however, another
major difference exists. The membrane voltage models were inspired from experiments involving electrical intra-cellular stimulation of nerve cells, whereas the probabilistic models were derived from experiments involving natural external stimulation or artificial pharmacological stimulation which exhibit a clear stochastic behavior (see e.g. Johnson and Swami (1983) and Camproux et al. (1996) for natural and pharmacological stimuli, respectively).

From a strict mathematical point of view, the variety of probabilistic neuron models differ one from another in the exact probabilistic law that connects between the stimulus to the observations. The models also differ in the physical units attributed to the stimulus which is the input of the model. As will be explained next, the model presented in this work is the simplest model in terms of computational complexity and number of free parameters that is useful for solving the binary detection problem from multi neuron activity, and thus it is better from an engineering perspective.

The probabilistic neuron model presented in this work is a Markov point process model. Notable other probabilistic Markov neuron models include the models of Siebert (1965, 1970), the models of Nakahama et al. (1974) and Camproux et al. (1996), and the recent models of Herbst et al. (2008) and Toyoizumi et al. (2009). The model is also closely related to the non Markovian model by Johnson and Swami (1983) which was more recently highlighted by Berry and Meister (1998), Kass and Ventura (2001), and Paninski et al. (2009). Some of the elements of the model by Johnson and Swami (1983) also appear in the many state Markovian model by Gaumond et al. (1982). A common property for these models is that they were proposed following experiments involving natural or pharmacological stimulation. I review next in more detail the similarities and differences of these models with respect to the model presented in this work.

Siebert (1965, 1970) suggested to model the function of the auditory nerve in response to auditory stimulation using a non-homogenous Poisson process. The model of Siebert includes the signal intensity (the square of the pressure) as the input variable and yields tractable results. However, Siebet’s non-homogenous Poisson process fails to predict the known sensitivity of

---

1 Some modern views of science suggest that usefulness and simplicity of models are also pure scientific goals (Box and Draper, 1987; Gribbin, 2009; Paninski et al., 2009). This notion is perhaps best summarized by the saying of George E. P. Box: "All models are wrong but some are useful" (Box and Draper, 1987).
neurons to the stimulus edges and it does not predict correctly the histogram of time intervals between two adjacent spikes (ISI histogram).

Nakahama et al. (1972, 1974) proposed a general K-state Markov chain to model spontaneous activity measured in the brain stem and the thalamus. Such a model was also suggested by Camroux et al. (1996) to model activity following pharmacological stimulation. The models of Nakahama et al. (1974), Camroux et al. (1996), and the recent similar model of Herbst et al. (2008) do predict the shape of the inter-spike-interval histogram (the probability of the time intervals between two adjacent spikes), but they do not yield a close form expression for the spiking probability as a function of the innervating stimulus. Furthermore, the stimulus in the work by Camroux et al. (1996) was pharmacological, and therefore the square of a signal (signal intensity) would not have been adequate for that experiment.

A non-Markovian model which exhibits very similar properties to the model of this work was suggested by Johnson and Swami (1983), and is sometimes referred to in recent literature as the "Inhomogeneous Markov Interval (IMI) process", or the IMI neuron model (Kass and Ventura, 2001; Paninski et al., 2009). In this model, the derivative of the spiking probability is assumed to have a multiplicative form, where one of the terms is due to the stimulus intensity, and the other term is a function which represents the refractory effect. The Johnson and Swami (1983) model predicts the positive edge emphasizing and the decay of the response, but not the negative edge emphasizing and the spontaneous activity. As opposed to the model presented in this work, the Johnson and Swami (1983) model does not yield close form expressions for the firing rate, and it demands complex computations (Johnson and Swami, 1983; Johnson, 1996). The neuron model presented in this work allows to compute any response to stimulus in a recursive manner, and the number of calculations is linear in stimuli duration. Furthermore, in the important case of a rectangular stimulus, the model of this work yields closed form analytic expressions. Another technical advantage of the model presented in this work, with respect to Johnson and Swami (1983), is the number of free parameters. The effect of the refractory period is encapsulated in this work in a single parameter, whereas the model by Johnson and Swami (1983) requires to estimate a function\(^2\). Despite the small number of free parameters

\(^2\)This is equivalent to estimating many parameters of many Markov states, as suggested by Gaumond et al. (1982).
and the low computational complexity, the model presented in this work adequately generates
a firing rate function that emphasizes stimulus edges in a manner which is accurate enough
for the purpose of this work (detection of stimuli from neural activity). The model of Johnson
and Swami (1983) was not developed in the context of stimuli detection, and therefore signal
detection was not used as figure of merit for that model. Interestingly, Berry and Meister (1998)
who used the work of Johnson and Swami (1983) to model responses of retinal Ganglion cells,
do not mention that refractoriness may have some functional purpose, but they do not mention
explicitly the edge emphasizing property and the purpose of detection.

Shortly before submitting the first publication of this work, Toyoizumi et al. (2009) pre-
sented a three state Markovian model that includes a functional dependence on an input vari-
able. From a strict mathematical point of view, the model presented in this work differs from
the work of Toyoizumi et al. (2009) in the order of the Markov chain model, and also in the
functional relation on the input. Toyoizumi et al. (2009) considers exponential dependence on
an input which is assumed to be a (non-continuous) vector of spike trains, whereas I consider
a two state Markov chain which has a square law dependence in a continuous variable (not a
train of delta functions) and this variable is identified as the external stimulus pressure.

This difference results from a different physical interpretation of models, which conse-
quently leads to further differences in the statistics extracted from the model (e.g. mean and
variance). Similar to previous works authored by Paninski (Paninski, 2004; Paninski et al.,
2007), the input of the model by Toyoizumi et al. (2009) is interpreted as an electrical mem-
brane current and the output (the firing rate) is interpreted as probability of an electrical current.

In contrast to the interpretation by Paninski (2004) and Toyoizumi et al. (2009), the input
of the model presented in this work is the local concentration of excitatory neurotransmitters
surrounding the neuron. Namely, the input is a smoothed (integrated) version of the spatial av-
erage of the incoming current of neurotransmitters. The input of the neuron model of this work
is non negative because concentrations of substances are non negative by nature. The output
of the model (the firing rate) is interpreted as a quantity which is proportional to the stream
of neurotransmitters going out of the neuron. The square law dependence is identified as a
property of the biological receptor that converts the energy of the stimulus to a neurotransmitter current. That is, the squaring operation in the model of this work is attributed to cells that are not spiking neurons. This interpretation is different from that of Paninski (2004); Paninski et al. (2007); Toyoizumi et al. (2009) in which each neuron includes an exponential function that transforms the input to have positive values. Finally, the analysis in this work focuses on the case where a bundle of similar neurons are stimulated by a similar average concentration of neurotransmitters, and the firing rate is interpreted as the average current of neurotransmitters generated by this bundle of cells. The underlying assumption of the analysis taken in this work is that due to the unreliable nature of a single neuron, it is important to analyze the case of multi neuron (”Multi-Unit”) signal transduction. As a result of these conceptual differences, the model presented in this work results in a closed form scalar expression for the firing rate as a function of local neurotransmitter concentration with only four unknown parameters.

In summary, the model presented in this work is the simplest neuron model that predicts the natural spread of the inter-spike-interval statistics and that generates a closed-form expression for the firing rate as a function of the innervating stimulus. In particular, it correctly predicts neuron sensitivity to stimuli edges. The physical interpretation of the model is also innovative, as the neurotransmitter concentration is identified as the input variable, and the firing rate is associated with the output current of neurotransmitters. The observed electrical spike is referred to as a side effect of the chemical processes. Finally, I also see an added value in the emphasis given in this work to stress the universality of the phenomena explained by the model using references to real laboratory experiments.

1.2.3 Background on Related Conjectures Regrading the Brain Principle of Operation

As previously stated, detection of stimuli from neural activity is tightly coupled with understanding the operation of the brain itself. The reason is that many of the roles that are attributed to the brain, such as ”decision making”, ”perception” and ”identification”, are all synonymous with the word ”detection” in the sense that they describe the same procedure. Each of these verbs describe a procedure in which the observer (either man or machine) receives input data
(called a "stimulus" in our case) and selects a single action from a finite set of mutually exclusive possible actions (Wiener, 1948; Tanner Jr and Swets, 1954; Swets et al., 1961; Gallager, 2006). The binary detection problem considered in this work is particularly close to the detection tasks associated with the brain, since in both cases the observations available to the decision making system originate from the same building blocks - neurons. Because of this tight connection, in the discussion part of this work, a conjecture regarding the biological detection scheme (decision making scheme) is raised and expressed in terms of control theory, and evidence that allegedly support this conjecture is listed.

Briefly, the conjecture raised in this work suggests that the neural detection scheme is a modified form of the square and integrate detector, (or "energy detector") which is similar to the artificial detection schemes employed in radar systems (see e.g. Marcum, 1960), in traditional electrophysiology (Weber and Buchwald, 1965), in communication systems (Urkowitz, 1967), and in seismic and quality control detectors (Basseville and Nikiforov, 1993). The conjecture raised in this work is complementary to similar earlier conjectures regarding the neural detection (decision making) scheme that have been suggested by Tanner Jr and Swets (1954), and more recently by Cook and Maunsell (2002). Specifically, Tanner Jr and Swets (1954) showed that human psychophysical tests involving several intensities of a stimulus are consistent with a model which assumes a radar-like detection scheme. They also drew a functional block diagram, in which receptor cells, bipolar cells and neurons are represented by different functional blocks which cascade one after the other. However, they did not express the roles of these blocks mathematically. Cook and Maunsell (2002) suggested a neural decision scheme which consists of a leaky integrator of neural activity and a cascaded threshold mechanism. They showed that this model is consistent with the decision to start a motor motion, and that this model outperforms predictions that are based on single neuron responses (spikes). However, Cook and Maunsell (2002) did not explain the physiological basis of their algorithm. Recently, Cain et al. (2011, 2013) suggested to use neural loops models originally developed by Koulakov et al. (2002), in the context of fish eye motor control as a realistic mathematical model for temporal integration in decision making. However, the physiological basis of the neural loop integrator model (Koulakov et al., 2002), and the very existence of neural loops in the fish eye motor control has been questioned (Loewenstein and Sompolinsky, 2003). More
importantly, Cain et al. (2011, 2013) did not explain the physiological origin of the unavoidable threshold in decision making.

A similar difficulty in explaining the threshold mechanism exists not only in models for a voluntary subtle decisions (e.g. Cook and Maunsell (2002)), but also in physiological schemes of simple reflexes which clearly exhibit all-or-none behaviour. The basic physiological reflex scheme involves as little as two nerves: one sensory nerve entering the central nervous system, and another motor nerve controlling the muscle (Burke, 2008). This scheme mainly consider the wiring of the neurons that comprise the nerves. However, it is difficult to explain using this scheme, how neurons which have a continuous range of firing rates (see e.g. the model by Siebert (1965)), produce a full-power-all-or-none response above a certain intensity threshold (Sherrington, 1925; Ebert and Koch, 1997). A deterministic approach in which a single neural spike is associated with a decision threshold crossing event (instead of referring to the firing rates) introduces time scale difficulties, because spikes last for only one millisecond, whereas even primitive decisions such as reflexes last for several hundred of milliseconds (Skljarevski and Ramadan, 2002; Liu et al., 2011). Furthermore, electrophysiological measurements during reflex taken in the spinal cord (Koketsu, 1956; Eccles et al., 1963; Willis Jr, 1999) and in the brain (Ebert and Koch, 1997), often reveal the existence of a negative potential associated with reflexes, as opposed to an expected rise in membrane potential predicted by membrane-voltage neuron models (Burkitt, 2006; Herz et al., 2006; Paninski et al., 2009). Interestingly, these negative potentials occur when increasing the stimulus intensity, and simultaneously with their appearance, a neural segment which was unrelated to the stimulus at lower stimuli intensities, starts to respond to the stimulus (Koketsu, 1956; Ebert and Koch, 1997).

The main innovative elements in my conjecture for the detection scheme of the neural tissue (apart from the previously discussed neuron model) seems to be is the histological association of the receptor cells as the squaring unit, and the association of glia cells as leaky integrators of neurotransmitters having a threshold level after which the integration leak rate changes. I

3Due to the definition of detection (“a procedure of selecting one distinct output out of a finite number of distinct choices”) every decision system must have a threshold at its final stage (Gallager, 2012). The mathematical necessity results from the mapping of the continuous observations into a discrete set of possible outputs.
associate this change in glia leak rate to the logical threshold that characterizes primitive decisions such as reflexes (Koketsu, 1956; Ebert and Koch, 1997), as well as the threshold for more subtle voluntary decisions, which are investigated by the psychological decision making community (e.g. Ma, 2012; Cain et al., 2013). I review published experimental data that supports the existence of a temporal integration mechanism in glia, as well as evidence for the existence of a threshold mechanism in these cells. Finally, I associate the sharp negative electrophysiological waves observed in many examples of neural decision making (voluntary and involuntary) as a side effect of the glia break point.

The exact computational role that is attributed to glia in this work seems to be innovative, although the general link between of glia cells, memory and decision making (switching) has been recently highlighted in the literature (Magistretti, 2006; Haydon and Carmignoto, 2006; Perea and Araque, 2010). Glia cells constitute at least 50% of the brain cells (Azevedo et al., 2009) and they appear in large numbers and in various forms, also in the spinal cord and the peripheral nervous system (Shibata et al., 1997; Kawai et al., 2001; Kiernan and Barr, 2009). These cells had been largely ignored because they do not exhibit electrical spiking activity like neurons (Haydon and Carmignoto, 2006; Perea and Araque, 2010). Instead, these cells were considered as supporting cells, whose main role is to maintain the chemical environment for the neurons which were thought to carry all the computational aspects in the neural tissue (Perea and Araque, 2010). Perhaps due to this conception, the findings of Hertz et al. (1978) and others (see Drejer and Larsson, 1982; Danbolt, 2001), who indicated that glia execute a leaky accumulation of glutamate, were not associated with a significant computational role. The recent high interest in glia cells is largely due to the findings of Cornell-Bell et al. (1990) who demonstrated using a new calcium imaging technique that glia cells have a threshold behaviour which was missed in electrical measurements. These findings triggered studies concerning the computational aspects of glia cells (Haydon and Carmignoto, 2006; Perea and Araque, 2010; De Pittà et al., 2012). Recent advances in magnetic resonance techniques (Sibson et al., 1998; Gruetter et al., 2001; Sibson et al., 1998; Hyder et al., 2006; Haydon and Carmignoto, 2006; Iadecola and Nedergaard, 2007) further stressed the tight chemical interactions between glia and neurons, and strengthen the evidence for temporal accumulation of glutamate by glia, as quantified by Hertz et al. (1978). However, non of the above articles suggested a simple model
which connects between the wealth of experimental data concerning the chemical interactions in the neural tissue to its functional purpose: detection of stimuli.

The conjecture raised in this work explains that the signal squaring by the receptor cells, the edge emphasizing by neurons, and the glia lossy temporal accumulation and logical threshold mechanism, yield a near optimal stimuli detection method. Hence, this work bridges between the psychological decision making community that foster to reason human decisions in terms of probability theory (e.g. Gold and Shadlen, 2007; Zacksenhouse et al., 2010; Ma, 2012, and others), to the works in the biochemical abstraction level (Hertz et al. (1978); Danbolt (2001); Gruetter et al. (2001)).
Chapter 2

Formulation of the Detection Problem and Preliminaries

2.1 Problem Formulation

In this section the stimulus detection problem is formulated using a Bayesian approach. We consider a scenario in which an electrode is implanted in a brain region which is densely populated by neurons that respond to an auditory warning stimulus by changing their activity level after a small delay which is designated as $t_{offset}$. The detector monitors the filtered electrode voltage (the multi-unit activity) and must decide within a very small delay, $T_d$, whether the auditory warning signal is present or not. If the detection is too late, an aversive event would hurt the subject.

The duration of the intervals between the onsets of two consecutive warning signals are independent, identically distributed (IID) random variables. The $l^{th}$ inter-test-interval is designated as $T_{ITI}(l)$ and obeys the following probability distribution:

$$
Pr\{T_{ITI}(l)\} = \begin{cases} 
0 & T_{ITI}(l) < T_{min} \\
\frac{1}{[T_{avg} - T_{min}]^{-1} \cdot \exp\left(-\frac{T_{ITI}(l) - T_{min}}{T_{avg} - T_{min}}\right)} & T_{ITI}(l) \geq T_{min}
\end{cases} \quad (2.1)
$$

where $T_{min}$ is the shortest possible interval between adjacent stimuli, and $T_{avg}$ is the average interval between stimuli. Both parameters are assumed to be known.
The neural activity responding to the warning signal continues until the offset of the aversive event. The total duration of the warning signal, $T_s$, is fixed and it is known a-priori, but the stimuli start times are unknown. Note that if the brain region is responsive to the aversive event rather than to the warning signal, then our formulation holds, with $T_d$ which equals zero.

![Illustrative warning stimulus, aversive stimulus and acquired data waveforms together with false alarm and misdetection costs. In cases where only one stimulus exits, the formulation remains the same, and $T_d$ signifies the allowed delay for asserting the detection flag.](image)

Starting from $T_d$ seconds after the response start time, the subject is at risk of an injury because of the aversive event. It is possible to take an action which eliminates the risk of that specific injury, but at the same time, this action increases the risk from other threats. For example, in the case where the stimulus warns on a forthcoming aversive event, such as an air blow to the eye, shutting the eye-lid can prevent injury. However, whilst the subject’s eyes are shut, there is increased exposure to other threats. This specific example is also illustrated in

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1The a-priori knowledge that stimuli arrive in blocks mean that there is a temporal probabilistic dependence on stimuli presence time. For example, if the stimulus just started, it must continue for another $T_s$ seconds.
As illustrated in Figure 2.2, the goal of the automated decision system (henceforth referred to as the detector) is to keep the subject unharmed for as long as possible by continuously minimizing the risk of injury, $\mathcal{R}_{\text{injury}}(t)$, at any given moment.

$$
\mathcal{R}_{\text{injury}}(t) = E \left\{ C_{MD}(t | r^t_0) \cdot I_{off}(t) + C_{FA}(t | r^t_0) \cdot I_{on}(t) \right\} \\
= C_{MD} \cdot P_{MD}(t | r^t_0) \cdot \bar{I}_{on}(t) + C_{FA} \cdot P_{FA}(t | r^t_0) \cdot I_{on}(t) \\
= \mathcal{R}_{MD}(t | r^t_0) \cdot \bar{I}_{on}(t) + \mathcal{R}_{FA}(t | r^t_0) \cdot I_{on}(t)
$$

(2.2)
The momentary probability for an injury in an infinitesimal time interval, \([t, t + \Delta_t]\), is proportional to the momentary risk times the decision spacing interval:

\[
P_{\text{injury}}(t) = \Delta_t \cdot R_{\text{injury}}(t)
\]  
(2.3)

It follows that the probability of staying uninjured at time \(t = L \cdot \Delta_t\) (i.e.; \(L\) time intervals from time axis origin) is:

\[
P_{\text{uninjured}}(t = N \cdot \Delta_t) = \prod_{n=1}^{L} \left(1 - \Delta_t \cdot R_{\text{injury}}(n\Delta_t)\right)
\]  
(2.4)

Thus, at the limit \(\Delta_t \to 0\), the probability of staying uninjured can be expressed as:

\[
P_{\text{uninjured}}(t) = \exp \left(- \int_{0}^{t} R_{\text{injury}}(t') dt'\right)
\]  
(2.5)

As illustrated in Figure 2.2, the goal of the detector is to decide whether to risk a misdetection \((I_{\text{off}}(t) = 1)\), or to risk a false-alarm \((I_{\text{on}}(t) = 1)\), so that the total risk is minimized and the expected life span of the subject is maximized:

\[
I_{\text{on}}(t) : E\{T_{\text{uninjured}}\} \text{ maximized}
\]  
(2.6)

where, \(E\{T_{\text{uninjured}}\}\) is the expectancy of the first injury time:

\[
E\{T_{\text{uninjured}}\} = \int_{0}^{\infty} t \cdot P_{\text{uninjured}}(t) \cdot P_{\text{injury}}(t) dt
\]

\[
= \int_{0}^{\infty} t \cdot \exp \left(- \int_{0}^{t} R_{\text{injury}}(t') dt'\right) \cdot R_{\text{injury}}(t) dt
\]

\[
= - t \cdot \exp \left(- \int_{0}^{t} R_{\text{injury}}(t') dt'\right) \bigg|_{0}^{\infty} + \int_{0}^{\infty} \exp(- \int_{0}^{t} R_{\text{injury}}(t') dt') dt
\]

\[
= \int_{0}^{\infty} P_{\text{uninjured}}(t) dt
\]  
(2.7)

Note the following subtle points:

1. \(R_{\text{injury}}(t), C_{MD}\) and \(C_{FA}\) are given in units of \([1/sec]\) or \([Hz]\).
2. \(E\{\}\) Stands for ensemble averaging of the costs. The ensemble averaged costs and their corresponding risks, \(\mathcal{R}_{MD}(t)\) and \(\mathcal{R}_{FA}(t)\), are given in units of [Hz].

3. \(I_{on}(t)\) and its complement \(I_{off}(t) = \bar{I}_{on}(t)\) are indicator functions for the decision of the detector. \(I_{on}(t) = 1\) means that at time \(t\) the detector preferred the risk of false alarm and therefore asserts the detection flag.

Table 2.1 summarizes the various quantities that were introduced in this section.

Table 2.1: Random variables, parameters and observables of the problem.

<table>
<thead>
<tr>
<th>Mark</th>
<th>Meaning</th>
<th>unit</th>
</tr>
</thead>
<tbody>
<tr>
<td>(T_{ITI})</td>
<td>Inter-Trial-Interval. A random variable which represents interval duration between consecutive onsets of aversive stimuli.</td>
<td>[sec]</td>
</tr>
<tr>
<td>(T_{min})</td>
<td>Shortest possible interval between consecutive onsets of the aversive stimuli.</td>
<td>[sec]</td>
</tr>
<tr>
<td>(T_s)</td>
<td>Duration of the warning signal.</td>
<td>[sec]</td>
</tr>
<tr>
<td>(t_{offset})</td>
<td>Delay of the neural response to the warning stimulus</td>
<td>[sec]</td>
</tr>
<tr>
<td>(T_d)</td>
<td>The delay from the onset of the neural response to the onset of the aversive event.</td>
<td>[sec]</td>
</tr>
<tr>
<td>(C_{MD})</td>
<td>The momentary cost for mis-detecting the aversive stimulus while it is on.</td>
<td>[Hz]</td>
</tr>
<tr>
<td>(C_{FA})</td>
<td>The momentary cost for falsely alarming on the presence of an aversive stimulus.</td>
<td>[Hz]</td>
</tr>
<tr>
<td>(r_t^0)</td>
<td>Voltage on the multi-unit electrode, (r(t)) from start time until time (t). These are the observables of the problem.</td>
<td>[Volts]</td>
</tr>
<tr>
<td>(\Delta_t)</td>
<td>Sampling interval</td>
<td>[sec]</td>
</tr>
</tbody>
</table>

### 2.2 Practical Performance Evaluation

In the previous section we have defined the quality criteria to be the life span of subjects:

\[
E\{T_{uninjured}\} = \int_{0}^{\infty} \exp \left( - \int_{0}^{t} \mathcal{R}_{injury}(\tau) d\tau \right) dt
\]  

(2.8)
where $E\{\}$ stands for ensemble average, and $\Re_{\text{injury}}(\tau)$ is a weighted sum of the false alarm and misdetection probabilities:

$$
\Re_{\text{injury}}(\tau) = C_{FA} P_{FA}(\tau) + C_{MD} P_{MD}(\tau)
$$

(2.9)

In real laboratory measurements, it is difficult to empirically evaluate the ensemble averaged probabilities $P_{FA}(\tau)$ and $P_{MD}(\tau)$, because it requires experimenting on many subjects. Therefore, in practice, the time averaged probabilities are calculated instead of the ensemble averaged probabilities. We designate the time averaged probabilities as $\langle P_{FA} \rangle$ and $\langle P_{MD} \rangle$, and we define them as follows:

$$
\langle P_{FA} \rangle = \frac{1}{T_{test} - T_{stimuli}} \int_{0}^{T_{test}} I_{FA}(\tau) d\tau
$$

(2.10)

$$
\langle P_{MD} \rangle = \frac{1}{T_{stimuli}} \int_{0}^{T_{test}} I_{MD}(\tau) d\tau
$$

(2.11)

where:

- $T_{test}$ is the duration of the test.
- $T_{stimuli}$ is the total cumulative duration of all the stimuli.
- $I_{FA}(\tau)$ and $I_{MD}(\tau)$ are indicator functions for the false alarm events and misdetection events (of the detector under test), respectively.

Figure 2.3 illustrates the practical method for evaluating and comparing the performances of two different detectors that monitor the same electrophysiological data. The top signal of Figure 2.3 represents the timing of the external stimulus at that experiment, the second signal shows the resulting electrophysiological data, and the two bottom signals represent the two detection flags, one flag from each detector. The third signal from the top represents an ideal detection in which the detection flag is asserted throughout the whole delayed period of the stimulus presence, and de-asserted otherwise. The ideal detection is expected to include some delay relative to stimuli timing, because there exists a delay between the stimulus and the electrophysiological response ($t_{offset}$).
Figure 2.3: Problem Formulation. An auditory stimulus is presented to the rat. The detectors monitor the multi-unit electrophysiological data and must decide whether the stimulus is present or not. A false alarm decision is fined by \( C_{FA} \), whereas a misdetection is fined by \( C_{MD} \). The parameters: \( t_{offset} \), \( T_s \), and \( T_{ITI} \) are explained in Table 2.1.

During the performance evaluation tests, the detectors monitor the electrophysiological data alone and must decide at any given moment whether the external stimulus is present or not. The actual timing of the stimuli is recorded for the purpose of performance evaluation but it is inaccessible to the detectors. When the test is completed, the output of each detection flag is compared to the ideal detection flag (third signal from the top of Figure 2.3). The detection errors that occurred during the delayed version of the stimulus on time are identified as misdetection errors, and the indicator function \( I_{MD}(t) \) marks the times of these errors (these times are marked in red in Figure 2.3). Similarly, the false-alarm error that occurred outside the true detection zone are identified, and the indicator function \( I_{FA}(t) \) marks the times that these errors have happened (FA errors are marked in gray in Figure 2.3). The time averaged false alarm probability \( \langle P_{FA} \rangle \) is obtained by summing the areas marked in red in Figure 2.3,
and then scaling the result by a constant, whereas $\langle P_{MD} \rangle$ is obtained by summing and scaling the areas that are marked in gray.

Note that the time averaged probabilities $\langle P_{FA} \rangle$ and $\langle P_{MD} \rangle$ are random variables that have the following means:

$$E\{\langle P_{FA} \rangle\} = [T_{test} - T_{stimuli}]^{-1} \cdot E\{ \int_0^{T_{test}} I_{FA}(\tau) d\tau \}$$

$$= [T_{test} - T_{stimuli}]^{-1} \int_0^{T_{test}} P_{FA}(\tau) d\tau$$

(2.12)

$$E\{\langle P_{MD} \rangle\} = T_{stimuli}^{-1} \int_0^{T_{test}} P_{MD}(\tau) d\tau$$

(2.13)

Although $\langle P_{FA} \rangle$ and $\langle P_{MD} \rangle$ are random variables, we treat them as if they are equal to their ensemble averages, that is, we assume $\langle P_{FA} \rangle = E\{\langle P_{FA} \rangle\}$ and $\langle P_{FA} \rangle = E\{\langle P_{MD} \rangle\}$.

The underlying assumption of using the time averaged probabilities is that the errors of the detectors under test are ergodic and comply with the following conditions:

$$E[\langle P_{FA} \rangle - E\langle P_{FA} \rangle]^2 \xrightarrow{T_{test} \rightarrow \infty} 0$$

(2.14)

$$E[\langle P_{MD} \rangle - E\langle P_{MD} \rangle]^2 \xrightarrow{T_{test} \rightarrow \infty} 0$$

(2.15)

Observe that when true error probabilities are approximately constants:

$$P_{MD}(\tau) \simeq P_{MD}$$

$$P_{FA}(\tau) \simeq P_{FA}$$

then the true risk is also constant:

$$\Re_{injury} = C_{FA}P_{FA} + C_{MD}P_{MD}$$

(2.16)

and the estimated life span of the subject would be the inverse of the risk:

$$E\{T_{uninjured}\} = \int_0^\infty \exp(-\Re_{injury} \cdot t)$$

(2.17)

$$= [C_{FA}P_{FA} + C_{MD}P_{MD}]^{-1}$$

(2.18)

$$= [R_{injury}]^{-1}$$

(2.19)
In this case, the life span of the subjects could also be expressed using the mean of the empirical time averaged probabilities:

\[
E\{T_{\text{uninjured}}\} = \left[ E\{\frac{T_{\text{test}} - T_{\text{stimuli}}}{C_{FA}} C_{FA}\langle P_{FA}\rangle + \frac{T_{\text{stimuli}}}{C_{MD}} C_{MD}\langle P_{MD}\rangle}\right]^{-1}
\]

(2.20)

\[
= [E\{\tilde{C}_{FA}\langle P_{FA}\rangle + \tilde{C}_{MD}\langle P_{MD}\rangle}\}]^{-1}
\]

(2.21)

Thus, the estimated life span of the subject is also the inverse of a weighted sum of the empirical time averaged probabilities.

Finally, observe that for any given \(\langle P_{FA}\rangle, C_{FA}\) and \(C_{MD}\), the life span of the subject would be maximized if \(\langle P_{MD}\rangle\) would be minimized or if the true detection probability, \(\langle P_D\rangle = 1 - \langle P_{MD}\rangle\) is maximized. For this reason, the quality of the detectors will be evaluated by presenting their probability of true detection \(\langle P_D\rangle\) as function of their false alarm probability \(\langle P_{FA}\rangle\). Such graphs are known as receiver operating characteristic curves or ROC curves.

Figure 2.4 shows a hypothetic example for ROC curves of three hypothetic detectors. The blue solid line represents the ROC curve of detector 'A', the dashed red line represents the ROC of detector 'B', and the dotted black line represents detector 'C'. The curve of detector 'A' passes above the 'B' and 'C' curves which means that the probability of true detection of detector 'A' is higher for every given probability of false alarm. Thus, the performance of detector 'A' is always better than the performances of detectors 'B' and 'C', regardless of the values of \(\langle P_{FA}\rangle, C_{FA}, C_{MD}\). The curves of detectors 'B' and 'C' pass below the curve of detector 'A' and cross each other at the point \(\langle P_{FA}\rangle = P_{FA,x}\). The curve of detector 'B' passes above the curve of detector 'C' until \(\langle P_{FA}\rangle = P_{FA,x}\), and from that point, the curve of detector 'C' is higher. This means that detector 'B' performs better than detector 'C' at probabilities of false alarm lower than \(P_{FA,x}\), and performs worse than detector 'C' at probabilities of false alarm higher than that point. If the cost of a false alarm (\(C_{FA}\)) is very high, compared to the cost of a misdetection (\(C_{MD}\)), then we would choose to work at low probability of false alarms, and therefore detector 'B' would be better than detector 'C'. The opposite is true for low values
of false alarm costs \( (C_{FA}) \) which allow to work at high probabilities of false alarms. Note that in both cases the performance of detector 'A' is still better than those of detectors 'B' and 'C'.

### 2.3 The Commonly Used Detection Scheme

The commonly used scheme for detecting the presence of the stimulus from multi-unit activity is the square and integrate detector, ("energy detector") which was originally proposed in this context by Weber and Buchwald (1965) \(^2\). Here we briefly describe this detector and its digital version. This description is necessary as we later refer to specific blocks and outputs of this detection scheme.

As described in Figure 2.5a, the square and integrate detector consists of three main blocks:

1. A squaring Unit - This unit squares the incoming data.
2. Integrating Unit - This unit sums the incoming squared data. This sum could be generated recursively as in Figure 2.5ab, or explicitly as in Figure 2.5bc. Either way, we refer to the output of the integrating unit as the "Pseudo Likelihood Ratio".

\(^2\)As mentioned in the introduction, this detection scheme is used also in other fields (e.g. Marcum (1960); Basseville and Nikiforov (1993))
3. Threshold Unit - This unit produces a clear cut decision regarding stimuli presence by comparing the Pseudo-Likelihood-Ratio to a fixed threshold.

Note that the original Weber and Buchwald (1965) detector is analog and its output is updated continuously over time (see Figure 2.5a). It requires only one memory unit which is updated recursively; past values are weighted by a decaying exponential, and the rate of the exponential decay is a user defined parameter. For the sake of future discussion, we briefly note that the equation describing the pseudo likelihood ratio of the analog square and integrate detector (here designated as $\Gamma_{LR}$) is as follows:

$$\dot{\Gamma}_{LR} = \alpha_{LR} \cdot \Gamma_{LR}^{\text{lossy integrator}} + \beta_{LR} \cdot r^2(t)$$

The digital version of the square and integrate detector (Figure 2.5b) works in discrete time and requires more memory. The parameter that completely characterizes both versions of the energy detector (excluding the threshold value) is the depth of the integrating window. In the digital version, the integrating window is the number of registers in the register array which is designated as $N_{\text{int}}$. In the case of the recursive analog version, the effective integrating window is defined as follows:

$$N_{\text{int}} = T_{\text{int}} / T_s = (\alpha_{LR} \cdot T_s)^{-1}$$

For each file, several integration lengths were tested and the one that produced the best detection results was selected for the comparison with respect to the optimal detector. These preliminary tests revealed that despite the lower memory requirements, the analog-recursive version of the energy detector with the optimal integration length ($N_{\text{int}}$), had slightly better results compared to the best non-recursive digital energy detector. Figure 2.6 shows a comparison between the detection results of the two forms of the energy detector by presenting the probability of true detection as a function of the probability of a false alarm (see Section 2.2 for more explanation). The blue solid curve with square markers reflects the performance of the analog recursive energy detector with the best integration length. The other three dashed curves reflect the performances of the digital non recursive energy detectors with three different integration lengths.

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3This expression also reflects the first moment ("center of mass").
Figure 2.5: The architecture of square and integrate detectors. (a) Continuous-time-recursive square and integrate detector (Weber and Buchwald, 1965). (b) Digital square and integrate detector with finite integration time (see page 33 in Basseville and Nikiforov, 1993).

integration lengths. The blue solid curve of the recursive energy detector has the best probability of detection compared to the other detectors which are non recursive. The three graphs of the non recursive digital detectors show that the best performance in these SNR conditions is achieved when the integration time is one eighth of the stimulus duration ($N_{int} = Ns/8$). The other two graphs show that prolonging or shortening the integration window does not increase the performance.

Figure 2.6: Performance Comparison between the Recursive form to the non Recursive form of the Energy Detector using MUA data (file #6)
Chapter 3

Signal Model

In this section we describe the statistical nature of the acquired signal \( r^t_0 \). We show that under many realistic measurement conditions, the acquired signal \( r^t_0 \) is a Gaussian process with a specific structure of a covariance function. This property is important for detector construction, because the optimization process of any detector relies on the statistical nature of the received signal. In the first subsection, we list the measurement conditions that this detector is best suited for. In the last subsection, we specify the statistical implications of these experimental conditions. We also show how the mathematical expressions that we obtain relate to experimental quantities that can be measured in the laboratory.

3.1 Model Assumptions

The measurement conditions that are suited for the proposed detector are:

1. The electrode is exposed to many *stimulus responsive* cells (Buchwald and Grover, 1970; Legatt et al., 1980; Gold et al., 2006; Milstein and Koch, 2008).

2. The electrode-neuron medium has a relatively flat amplitude response in frequencies lower than 3000 [Hz] (Logothetis et al. (2007)).

3. The neurons at the brain region of interest are refractory Markov neurons (Nossenson and Messer, 2010).
The following subsections explain the implications of each assumption and the last subsection summarizes the signal model.

### 3.1.1 Presence of Dense Population of the Stimulus Responsive Neurons

(The Central Limit Theorem Assumption)

We require that the electrode is located in a region that is densely populated with neurons that react to the stimulus of interest. Consequently, the multi-unit electrode is exposed to $N_{\text{cells}}$ ($N_{\text{cells}} \gg 1$) stimulus reactive cells, and also to the activity of other cells that are unrelated to the stimulus (Gold et al., 2006; Milstein and Koch, 2008). For example, in the Lateral Geniculate Nucleus (LGN), which is associated with the visual stimulus, cell density is 10K-20K cells per cubic millimeter. Noting that a single nerve cell contributes to electrode voltage of an order of few micro-Volts up to a distance of 200μ (Gold et al., 2006; Milstein and Koch, 2008), so the number of total cells within that radius is of the order of many tens to a few hundreds of stimulus reactive cells\(^1\). Within that radius, part of the cells may be unrelated to the stimulus. However, outside that radius, there are many cells that are unrelated to the stimulus. Though the contribution of each remote cell is small, the cumulative action of a huge number cells is non-negligible. Thus, we can write:

$$r(t) = x(t) + n(t) + v(t) \quad (3.1)$$

where $r(t)$ is the acquired signal, $x(t)$ represents the response to the stimulus and $n(t)$ represents the cells that are unrelated to the stimulus and fire spontaneously. $v(t)$ is a white noise which evolves from the cumulative action of electrical processes that are very weak compared to an action potential (spike).

Due to the large number of cells involved, it is reasonable to assume that the central limit theorem holds and that both the signal and the noise can be approximated as uncorrelated Gaussian processes. i.e.

\(^1\)The number of cells inside a sphere equals the cells density times the sphere volume: $N_{\text{cells}} = \rho_{\text{cells}} \times V_{\text{sphere}}$, where $V_{\text{sphere}} = 4/3\pi r_{\text{radius}}^3$. Using the lower estimations for cell density (10000 cells/mm\(^3\)) and the effective radius ($200μ = 0.2mm$), we find that the number of cells is $N_{\text{cells}} = 4/3\pi(200c - 3)^3 \cdot 10000 = 335$. Note that some of the cells may be unresponsive with regards to the stimulus of interest.
In the Gaussian case, the signal characteristics are completely determined by the mean $\mu(t)$, and the covariance matrix $\Sigma(t_1,t_2)$. The exact values of $\mu(t)$ and $\Sigma(t_1,t_2)$ for both the noise and signal depend on the geometry, the electrical characteristics of the specific brain region, and also on the type of electrode. A practical approach could be to evaluate these functions empirically. We shall show that the covariance matrix of multi-unit measurements has a specific structure which evolves from the nature of the medium and the properties of the point process that is driving each neuron. This property of the multi-unit recordings significantly simplifies both parameter estimation and detector architecture.

3.1.2 The Two State Refractory Markov Neuron Model

We assume that each one of the neurons in the region of interest is the two state refractory Markov neuron (Nossenson and Messer (2010)). We describe this model in detail next (Section 3.1.2.1) and we show evidence that supports the validity of this model in Sections 3.1.2.2 - 3.1.2.3.

3.1.2.1 The Neuron Model

In this section we mathematically describe a neuron model that produces the probability of firing a spike at any given moment, as a function of the innervating stimulus which can be either natural or pharmacological. A high level description of the model is also given in Figure 3.1.

As shown at the left side of Figure 3.1, the raw stimulus is designated as $s(t)$. For the auditory system, $s(t)$ designates air pressure as a function of time. Similarly, for the visual system
Figure 3.1: Probabilistic model for a sensory neuron.

$s(t)$ designates the electromagnetic field. For the skin thermo-receptors, $s(t)$ signifies the temperature and so forth. Each of these sensory sub-systems are typically frequency selective. For example, the light receptors in the retina are sensitive to only part of the electromagnetic spectrum. The cochlea of the hearing system is also frequency selective. For simplicity, it is assumed here that the frequency selectivity of the receptor is known, and that the stimulus is within the appropriate pass band frequencies of the receptor. We designate the filtered stimulus as $s_f(t)$ and assume that it is either equal to $s(t)$ or that the connection between the two is known, so that $s_f(t)$ is known.

In each sensory sub-system, a transducer transforms the stimulus, $s_f(t)$, to a non-negative function $y(t)$. While $s(t)$ represents the raw stimulus, $y(t)$ entails only the aspects of the signal that are relevant for the release of action potential promoting chemicals (excitatory neurotransmitter). For example, in the visual system, $y(t)$ will correspond to the short-term averaged light intensity in the relevant electromagnetic frequencies (see Enroth-Cugell and Lennie (1975)). In the auditory system, $y(t)$ will correspond to the intensity of the acoustical waves at hearing frequencies (see the work of Muller et al. (1991)). Ignoring, for simplicity, the frequency domain selectivity of the light receptors in the retina, or the selectivity of the cochlea in the case of the auditory system, the short term averaged intensity could be expressed as follows:

$$\dot{y} = -ay + bs_f^2(t)$$  \hspace{1cm} (3.5)

where, $y(t)$ corresponds to the momentary concentration of excitatory neurotransmitters, $a$ is

---

2 Mathematically, it is important that $y(t)$ will be non-negative since it corresponds to a probability measure.
the neurotransmitter disposal rate which is given in Hertz, and $b$ is the efficacy of neurotransmitter release in response to the stimulus intensity, $s_f^2(t)$. Note that when the envelope of the stimulus changes slow enough relative to the neurotransmitter disposal rate ($a \gg \dot{y}$) we can set $\dot{y} = 0$ in equation (3.5) and see that the neurotransmitter concentration, $y(t)$, is proportional to stimuli intensity:

$$y(t) = \frac{b}{a} \cdot s_f^2(t) = g_{\text{gain}} \cdot s_f^2(t)$$

(3.6)

where,

$$g_{\text{gain}} = \frac{b}{a}$$

(3.7)

is the stimulus gain.

Next, we model the neuron as a two state Markov chain as illustrated in Figure 3.2. As shown in the figure, the neuron is either in “armed” state, in which it is able to fire, or in the refractory state in which it cannot fire. When the neuron is armed, its’ probability to fire a spike in an infinitesimal time segment $[t, t + \Delta_t)$ is:

$$P_{\text{spike}}(t_{\text{spike}} \in [t, t + \Delta_t) \mid \text{neuron is armed}) = \Delta_t \cdot [y(t) + R_0]$$

(3.8)

where $y(t)$ was defined in (3.5) and $R_0$ is the constant average spontaneous firing rate of the neuron at armed state. Once a spike is fired, the neuron switches to the refractory state. We further assume that the time period that takes the neuron to recover back to the armed state is distributed exponentially with a recovery rate, $R_1$, which is independent with the stimulus intensity. Both $R_0$ and $R_1$ are given in units of [s$^{-1}$] or [Hz]. When recovery is complete, the neuron is back in the “armed state”. Note that if the average recovery time is infinitely small, then our model reduces back to Siebert’s model (Siebert, 1970). The equations describing the probabilities to be in the armed state ($P_0(t)$) and in the refractory state ($P_1(t)$) as a function of time are therefore:

$$\dot{P}_0 = -P_0 \cdot [y(t) + R_0] + R_1 \cdot P_1$$

(3.9)

$$\dot{P}_1 = +P_0 \cdot [y(t) + R_0] - P_1 \cdot R_1$$

(3.10)

By substituting $P_1 = 1 - P_0$ in equation (3.9), we obtain:

$$\dot{P}_0 = -(y + R_0 + R_1) \cdot P_0 + R_1$$

(3.11)
Using the integration factor method, we find that the probability to be in the armed state in any moment as a function of the stimulus intensity through time is:

\[
P_0(t) = \frac{R_1 \int_0^t \exp[\int_0^{t'} (y + R_0 + R_1) dt'] dt + C_0}{\exp[\int_0^t (y + R_0 + R_1) dt]}
\] (3.12)

where \( C_0 \) is determined by the initial conditions:

\[
C_0 = P_0 \mid_{t=0}
\] (3.13)

Finally, the probability of the neuron to fire a spike in the infinitesimal interval \([t, t + \Delta t]\) is the probability of the transition from the armed state to the refractory state:

\[
P_{\text{spike}}(t; \Delta t) = P_0(t) \cdot [y(t) + R_0] \cdot \Delta t
\] (3.14)

The biological interpretation of equation 3.14 is that given a large ensemble consisting of \( N_{\text{cells}} \) refractory Markov neurons, \( N_{\text{cells}} \cdot P_{\text{spike}}(t; \Delta t) \) of these neurons will fire in the interval \([t, t + \Delta t]\).

Another quantity which has a biophysical meaning is the firing rate which is defined as follows:

\[
R_{\text{fire}}(t) \triangleq \frac{P_{\text{spike}}(t; \Delta t)}{\Delta t}
\] (3.15)

The firing rate has units of Hertz ([Hz]) or [s\(^{-1}\)] and it is proportional to the current of neurotransmitters that is released by an ensemble of cells, because each time a neuron fires a spike, a quanta of neurotransmitters is released from its’ synaptic vesicles (Kandel, E.R. and Schwartz, J.H. and Jessell, T.M. (1991); Araque et al. (1999)). Observe that a quanta of neurotransmitters divided by the duration of a small time bin is the definition of a current.
3.1.2.2 Firing Rate Measurements (PSTH) Supporting the Refractory Markov Model

The firing rate statistic is perhaps the most common statistic reported in studies of the nervous system. This statistic is obtained by dividing the time axis to very small time bins and then counting the number of spikes fired by the nerve in each bin. The measurement is usually taken while some stimuli are admitted repeatedly to the subject, and for this reason, it is often referred to as PSTH - peristimulus time histogram. The repetition of the stimulus is made to allow spike count averaging which is performed on all time bins that have the same offset from the nearest stimulus to their left. The PSTH statistics is presented in units of \( \text{spikes/s} \) because the average spike count is divided by the length of the time bin.

In the context of our model, the PSTH is an empirical estimate of the following quantity:

\[
R_{\text{spike}}(t) \triangleq E \{ I_{\text{spike}}(t; \Delta t) \} / \Delta t = P_{\text{spike}}(t) / \Delta t = P_0(t) \cdot [y(t) + R_0] 
\]  

where \( I_{\text{spike}}(t; \Delta t) \) is an indicator which is set to one if a spike was fired in the small time interval \([t, t + \Delta t]\).

It is clear from (3.16) that the firing rate depends on the shape of the intensity of the innervating stimulus, \( y(t) \). Though we tested (3.16) on several types of stimuli, here we focus...
only on the response to long rectangular pulses, such as the one depicted in Figure 3.3. The upper drawing in Figure 3 shows the stimulus intensity, $y(t)$, as a function of time, and the lower drawing is the corresponding model based prediction for the firing rate curve which is specified by equation (3.16).

The Figure shows that prior to the stimulus start, the model based firing rate exhibits some constant level of spontaneous activity, designated as $R_{\text{spont}}$. When the stimulus level rises to a new level, $y_p$, the firing rate sharply rises to

a peak level, which is designated as $R_{\text{phasic}}$. Then the response settles down in an exponential manner to a new constant level, $R_{\text{sustained}}$, which is lower than $R_{\text{phasic}}$ but higher than the level of the spontaneous activity. When the stimulus is turned off, the opposite process occurs and the firing rate sharply declines to a level $R_{\text{phasic-off}}$, which is lower than the initial spontaneous level, and then it slowly rises in an exponential manner back to the spontaneous level. Thus, our model predicts that neurons would respond to a sharp rise in the stimulus power with an overshoot in the firing rate, and it predicts an undershot in response to a sharp fall in the stimulus intensity. The model predicts a sustained firing rate in response to the sustained stimulus.

The model also allows obtaining explicit expressions for $R_{\text{spont}}$, $R_{\text{phasic}}$, $R_{\text{sustained}}$ and $R_{\text{phasic-off}}$ which depend on $R_0$, $R_1$, and on the stimulus level, $y(t)$. The general procedure for calculating these firing rates consists of two stages:

1. First, the steady state probability to be in the armed state is calculated by setting $\dot{P}_0 = 0$ in equation 3.11:

$$0 = -(y + R_0 + R_1) \cdot P_0 + R_1 \quad \Rightarrow \quad P_{0,\text{steady-state}} = \frac{R_1}{y_p + R_0 + R_1}$$  (3.17)

2. Then, the firing rate is obtained by multiplying the result of the probability to be in the armed state (3.17) by the present concentration of neurotransmitters:

$$R_{\text{fire}} = P_{0,\text{steady-state}} \cdot [y(t) + R_0]$$  (3.18)

where $y(t)$ represents the neurotransmitter concentration at the time of interest.
Using this method, we find that the following relations hold:

\[
\begin{align*}
    P_{0,\text{spont}} &= \frac{R_1}{R_0 + R_1} \\
    P_{0,\text{phasic}} &= \frac{R_1}{R_0 + R_1} \\
    P_{0,\text{sustained}} &= \frac{R_1}{y_p + R_0 + R_1} \\
    P_{0,\text{phasic-off}} &= \frac{R_1}{y_p + R_0 + R_1}
\end{align*}
\]

\[
\begin{align*}
    R_{\text{spont}} &= \frac{R_0 R_1}{R_0 + R_1} \\
    R_{\text{phasic}} &= \frac{[R_0 + y_p] \cdot R_1}{R_0 + R_1} \\
    R_{\text{sustained}} &= \frac{[y_p + R_0] \cdot R_1}{R_0 + R_1 + y_p} \\
    R_{\text{phasic-off}} &= \frac{R_0 \cdot R_1}{R_0 + R_1 + y_p}
\end{align*}
\]

Note that according to the model, the sharp response on the stimulus rising edge \( R_{\text{phasic}} \) occurs because at the stimulus onset, the probability of the neuron to be armed is high and it still equals \( P_{0,\text{steady-state}} \). Thus, when the stimulus starts abruptly, \( y(t) \) changes abruptly, and the neuron is highly likely to fire because of its high probability to be in the armed state. When the stimulus continues, more and more neurons move to the refractory state, and so the response gradually decays. The sharp response of neurons to the stimulus onset and the following response decay is therefore a result of the refractory period.

The refractory period also explains the undershoot that occurs when the stimulus is first presented and then turned off. In this situation, the neuron initially has a high probability to be in the refractory state due to the initially high level of neurotransmitters. When neuron transmitter concentration abruptly decreases, the firing rate also decreases abruptly below the spontaneous level. This happens because at the time that the stimulus ceases, the probability of the neuron to be in the armed state is lower than its value prior to the appearance of the stimulus (the spontaneous firing).

Moreover, using equation 3.12 one can find out the exponential decay that follows the phasic response which obeys the following equation:

\[
R_{\text{fire, on}} = R_{\text{sustained}} + C_1 \cdot \exp(-[y_p + R_0 + R_1] \cdot t) \tag{3.23}
\]

where,

\[
C_1 = R_{\text{phasic}} - R_{\text{sustained}} \tag{3.24}
\]
Similarly, the exponential recovery from the stimulus turn-off obeys the following structure:

\[
R_{\text{fire,off}} = R_{\text{spontaneous}} - C_2 \cdot \exp(-[R_0 + R_1] \cdot t) \tag{3.25}
\]

where,

\[
C_2 = R_{\text{spontaneous}} - R_{\text{phasic-off}} \tag{3.26}
\]

Figure 3.4 compares the model based firing rate in response to the stimulus pulse, with real laboratory firing rate measurements taken from various locations that are associated with different stimulus modalities. Figure 3.4a is the model based response to the stimulus pulse. Figure 3.4b shows the response of the retina of a cat to a pulse of light, as measured by Enroth-Cugell and Shapley (1973). Figure 3.4c shows the response of the auditory nerve of a mouse to a segment of auditory stimulus, as measured by Gollisch et al. (2002). Figure 3.4d shows the response of olfactory receptor neurons of a fly (Drosophila) to odor, as measured by Nagel and Wilson (2011). Figure 3.4e depicts neural response to salty water placed in the mouth of a rat, as measured by Rosen et al. (2010) from the parabrachial nucleus of the pons (brain stem). Figure 3.4e shows the response of cutaneous temperature sensors of a vampire to increasing steps of heat, as measured by Schäfer, K. and Braun, H.A. and Kürten, L. (1988). Figure 3.4f depicts the neural response to a pulse of pressure in the esophagus, as measured from the sympathetic trunk by Sengupta et al. (1990). The resemblance between the model prediction (Figures 3.3 and 3.4a) and the measured data (Figures 3.4b-g) is evident.

Furthermore, responses similar to those of Figure 3.3 (model prediction) were measured not only in the peripheral nervous system, but also in the central nervous system up to the cortex. Figure 3.5 depicts firing responses which were measured in various locations of the auditory system, and we now list them according to their anatomical order\(^3\). Figure 3.5a shows the response of an Auditory nerve\(^4\) (Taberner and Liberman, 2005). Figure 3.5b Cochlear nucleus response (Koehler et al., 2011). Figure 3.5c shows the response of the Inferior colliculus (Reches and Gutfreund, 2008). Figure 3.5d depicts the response measured from the medial

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\(^3\)Although the examples here cover most of the auditory system, I did not find examples that match the model in recordings from the lateral superior olive (LSO). See Zacksenhouse et al. (1993, 1995, 1998) for examples of responses from the LSO.

\(^4\)This measurement reflects multi-unit activity, and for this reason the intensity of the firing rate is so high.
geniculate body of the thalamus (Hennevin et al., 1995). Finally, Figure 3.5e depicts a response measured from the auditory cortex response (Wang et al., 2005). All five responses shown in Figures 3.5a-e exhibit a sharp response to the stimulus rising edge, and also an exponential decay that follows the initial sharp rise.
Figure 3.4: Sensory Neurons response to pulse.
(a) Model prediction for the firing rate in response to a pulse shaped stimulus (see also Figure 3.3) (b) Response of a retina of a cat to light pulse taken from Enroth-Cugell and Shapley (1973). (c) Response of an auditory nerve of a locust to a modulated auditory pulse, taken from the work of Gollisch et al. (2002)(d) Nagel and Wilson (2011) (e) Neural response to salty water placed in the mouth of a rat (Rosen et al., 2010) (f) Neural response of a vampire to temperature increase, taken from the work of Schäfer, K. and Braun, H.A. and Kürten, L. (1988). (g) Neural response to esophageal pressure (Sengupta et al., 1990).
3.1.2.3 Inter-Spike-Interval (ISI) Histograms Supporting the Refractory Markov Model

Another commonly reported statistic is the empirical probability density function of interval duration between adjacent spikes, or the inter-spike-interval (ISI) statistics. In this section, we compare ISI statistics anticipated by the model with the empirical measurements performed by Johnson and Kiang (Johnson and Kiang, 1976).

Observe that in the model described by equations (3.9)-(3.10), the inter-spike-interval is the time period that takes the neuron to complete a round trip. The round trip starts when the neuron fires a spike and leaves the “armed” state, and ends exactly on the next departure to “the refractory” state. Thus, the total ISI probability is obtained by convolving the probability
to stay in the "refractory" state with the probability to stay in the "armed" state:

\[ P(T_{ISI}) = P_{T_1}(T_1) \ast P_{T_0}(T_0) \]

\[ = R_1 \cdot \exp(-R_1 \cdot T_{ISI}) \cdot \left\{ 
1 - \exp\left(- \int_0^{T_{ISI}} [y(t') + R_0 - R_1]dt' \right) + 
R_1 \int_0^{T_{ISI}} \exp\left(- \int_0^{\tau} [y(t') + R_0 - R_1]dt'\right)d\tau \right\} \]

Figure 3.6 shows a qualitative comparison between model prediction and real laboratory measurements. Figure 5a shows the model prediction for the ISI histogram, as expressed by equation (3.27), and Figure 5b shows the empirical measurement made by Johnson and Kiang Johnson and Kiang (1976). Both the model based ISI probability and the measured statistics have low values at small interval values. Both curves then rise and reach their peak at intermediate values of ISI length and then decline back and reach zero asymptotically. The resemblance between the two graphs is evident. Note, however, that comparing to the empirical ISI histogram (figure 5b), the probability anticipated by the model (figure 5a) for very short ISI is a bit high. This may suggest that our assumption of a single refractory state may be too naive.

![Figure 3.6: Model based ISI probability versus real measurements: (a) The ISI probability density anticipated by the model. (b) ISI histogram of the auditory nerve taken from Johnson and Kiang Johnson and Kiang (1976). The total number of intervals in this measurement was 7,808.](image)
3.1.3 The Electrical Medium Assumption

We assume that the potential at the point of the electrode tip is additive with respect to the spiking sources, and that the medium separating the electrode from each spiking source (neuron) can be modeled as a linear time invariant system. This assumption is widely accepted and has been used in past in the works of de Nó (1947), Clark and Plonsey (1968) and also in the more recent works of Holt (1997), Gold et al. (2006) Milstein and Koch (2008). Thus, the electrical response to the stimulus, \( x(t) \), results from the potential produced by \( N_{\text{cells}} \gg 1 \) stimulus responsive neurons, as shown in Figure 3.7. Each neuron fires at random times, as discussed in section 3.1.2.1. Designating \( I_k(t) \) as the indicator for spike firing at time \( t \) by the \( k \)th neuron, then the signal produced by the total ensemble of neurons is simply the sum of the convolutions of the indicator functions, with the characteristic spike shape coming from each neuron.

\[
x(t) = \sum_{k=1}^{N_{\text{cells}}} g_{x,k}(t) * I_k(t)
\]

(3.28)

Figure 3.7: (a) The additive effect of nearby spiking neurons that respond to the stimulus on electrode voltage, as well as the effect of other unrelated cells on the measured voltage. (b) The linear system from the spiking sources to the analog to digital converter (ADC) consists of cascaded linear time invariant systems, the electrostatic medium and the bandpass filter.

The received spike shape from the \( k \)th neuron, designated as \( g_{x,k}(t) \), is a result of two cascaded time invariant linear (LTI) systems, which are shown in Figure 3.7b: 1) The extra-cellular potential due to the current running through that single neuron; and 2) The electrical circuitry starting from the contact of the electrode with the extracellular fluid, and going through the

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amplifier and the analog bandpass filter until it reaches the analog-to-digital converter. Thus, the acquired spike \( g_{x,k}(t) \) can be represented in the Fourier frequency domain using a transfer function \( H_k(f) \) which has “phase” and “amplitude” responses:

\[
\mathcal{F}\{g_{x,k}(t)\} = G_{x,k}(f) = \underbrace{H_{BP}(f) \cdot H_k(f) \cdot G_x(f)}_{H_k(f)} = \exp\{j\angle H_k(f)\} \cdot |H_k(f)| \cdot G_x(f) \tag{3.29}
\]

where, \( G_x(f) \) is the Fourier transform of the membrane current that generates the spike which is similar in all the stimulus responsive nerves at that region, \( H_k(f) \) is the transfer function of the neuron-electrode medium, and \( H_{BP}(f) \) is the transfer function of the bandpass filter which exists in the signal acquisition system. Figure 3.8a shows an example for a membrane current generating a spike in the time domain (taken from Milstein and Koch (2008), who used a Hodgkin and Huxley (1952) model), and Figure 3.8b shows the same current at the frequency domain. Figure 3.8c and 3.8d show the response in the time and frequency domain, respectively, after going through a band pass filter. Observe that at the frequency domain (Figure 3.8d), the low frequencies are abolished due to the filtering. Also observe that at the time domain (Figure 3.8c), the response is no longer unipolar and it has both negative and positive peaks.

Here, we assume that all nearby neurons have similar nearly flat electrode-nerve channel amplitude responses, \( |\tilde{H}(f)| \), in the frequency range of \( 300[Hz] - 3000[Hz] \) (spike band), and possibly different amplitude attenuations, \( \rho_k \) and different fractional delays, \( \tau_{d,k} \). Thus, the total channel from each neuron can be expressed in the frequency domain using its amplitude response, which is assumed to be flat but may have various attenuations, and by the phase response which is assumed to be linear:

\[
|\tilde{H}_k(f)| \approx \rho_k |\tilde{H}(f)| \quad \forall k \tag{3.30}
\]

\[
\angle H_k(f) = \angle H(f) + 2\pi \cdot \tau_{d,k} \cdot f + \theta_k \quad \tau_{d,k} < 3[ms] \tag{3.31}
\]

Note that neurons that are away from the electrode have lower amplitude (lower \( \rho_k \)), but they outnumber the closer neurons that have larger amplitudes. We assume that these two effects make the contribution of the remote neurons comparable with the contribution of the
nearby neurons. The average intensity gain is defined to be one:

$$E\{\rho_k^2\} = 1 \iff \frac{1}{N_{cell}} \sum_k \rho_k^2 = 1$$  \hspace{1cm} (3.32)

Finally, note that one possible source for phase delay differences ($\tau_{d,k}$) between neurons is the differences in neurotransmitter transmission dynamics ("synaptic dynamics"), described in equation (3.5) of the proposed model.
3.2 The resulting mean and autocorrelation of the signal

Due to the nature of the electrical medium and the nature of the refractory Markov neuron, the acquired signal has a mean and autocorrelation function of a special form.

3.2.1 Response Mean

**Theorem 3.1** The mean response is a convolution of the firing rate with the spatial sum of all spike shapes coming from all responsive neurons. An explicit or implicit presence of a high pass filter (due to a side effect of the electrical medium) in the system, eliminates the mean response.

**Proof:** The expression results from the definition of the mean response:

\[
\mu_x(t) = E\{x(t)\} = \sum_{k=1}^{N_{\text{cells}}} E\{g_{x,k}(t) * I_{\text{fire}}(t)\} \\
= \sum_{k=1}^{N_{\text{cells}}} \sum_{l=0}^{\lfloor t/\Delta_t \rfloor} g_{x,k}(t - l \cdot \Delta_t) p_{\text{fire}}(t_{\text{fire}} \in [l \cdot \Delta_t, (l + 1) \cdot \Delta_t]) R_{\text{fire}}(t) \cdot \Delta t \\
= \left[ \sum_{k=1}^{N_{\text{cells}}} g_{x,k}(t) \right] * R_{\text{fire}}(t) \tag{3.33}
\]

\( \square \)

Three cases can be noted:

**Corollary 3.2** If all the responsive neurons are grouped together and have a similar unipolar response (i.e., the impulse response is all positive or all negative), the response will accumulate and will persist as long as the stimulus is on, as demonstrated in Figure 3.9a.

**Proof:** Because we required the spikes to be unipolar with same polarity, and because the firing rate is a positive quantity, we can replace their spike shape by the their absolute value.

\[
\mu_x(t) = \pm \left[ \sum_{k=1}^{N_{\text{cells}}} |g_{x,k}(t)| \right] * |R_{\text{fire}}(t)| \neq 0 \quad \forall t \tag{3.34}
\]

\( \square \)
Remark 3.3 Unipolar spikes are observed in intercellular recordings and also in extracellular recordings of nerves ensheathed by a non-conducting medium (Holt (1997)). Unipolar response occurs when the spike shape has some power at low Fourier frequencies. The case of unipolar spikes (as in Figure 8a) is not frequently observed in extracellular recording, because the measurement is taken in a conducting medium, and the signal is pre-filtered (before acquisition) by a high pass filter that vanishes the sustained part of the mean response. The high pass filtering is technically required because brain measurements usually suffer from a strong noise at low frequencies (commonly known as local field potentials, or LFP), and without the pre-filtering, most of the dynamic range of the acquisition system would be devoted to that noise. Also note that even in the absence of external high pass filtering, the medium separating the spiking is typically conducting (as opposed to the assumption of a non-conducting medium in the solution, yielding a unipolar spike) that can result in non-unipolar spikes (see e.g. de Nó, 1947; Holt, 1997, that discuss triphasic spikes).

Corollary 3.4 If all responsive neurons have a similar spike shape, but the response of each neuron is not unipolar but wiggles like the response in Figure 3.8c, then the response seems to occur only at stimuli onsets, although spikes are actually fired at an higher rate during the entire period of the stimulus presence. This filtered response is sometimes referred to as “phasic” response. This case is demonstrated in Figure 3.9b. The vanishing of the mean response due to high pass filtering is mathematically explained as follows.

Proof: Let $h_{HF}(t)$ be the impulse response of the high pass filter that exists in the measurement (either explicitly, or as part of the cell-electrode medium), and let $\mu_{x, HF}$ be the mean response after high pass filtering. By taking into account the linear nature of the cascaded filtering operation, and by using the relation expressed in equation 3.33, we find that the resulting high pass filtered mean is:

$$\mu_{x, HF} = h_{HF} \ast \left( \sum_{k=1}^{N_{cells}} g_{x,k}(t) \right) \ast R_{fire}(t) \quad (3.35)$$
Next we apply both the Fourier transform and the inverse Fourier transform to equation 3.35, leaving the expression unchanged:

\[
\mu_{x,HF} = \mathcal{F}^{-1} \mathcal{F} \left\{ h_{HF} \ast R_{\text{fire}}(t) \ast \left[ \sum_{k=1}^{N_{\text{cells}}} g_k(t) \right] \ast R_{\text{fire}}(t) \right\} \\
= \mathcal{F}^{-1} \left\{ H_{HF}(f) \cdot \mathcal{F}\{R_{\text{fire}}\}(f) \cdot \left[ \sum_{k=1}^{N_{\text{cells}}} G_k(f) \right] \right\} \\
\simeq 0
\]  

(3.36)

Note that the firing rate \( R_{\text{fire}}(t) \) tracks the envelope of the stimulus that typically changes at a maximum frequency of several tens of Hertz. Thus, since the support of \( \mathcal{F}\{R_{\text{fire}}\}(f) \) is concentrated mainly in frequencies lower than 300 [Hz], the filtered response will be close to zero. The assumption that \( R_{\text{fire}} \) is confined to frequencies below 300 [Hz] is only slightly violated in cases where the stimulus power envelope includes sharp changes, that are emphasized further by the neurons  \( \square \)

**Corollary 3.5** If a high pass filter exists, and the responsive neurons have different delays one with respect to the other (linear phase offsets), delays that reach two milliseconds, then the residual response at the stimuli edges will be also abolished and the mean response will totally disappear, as illustrated in Figure 3.9c.

**Proof:** We consider the case that each spiking source has a different small delay with respect to the stimulus. In this case we can write

\[
\mu_x = \sum_{k=1}^{N_{\text{cells}}} h_{HF} \ast g_x(t + \tau_{d,k}) \ast R_{\text{fire}}(t), \quad \tau_{d,k} \sim U[0, \tau_{d,\text{max}}] 
\]  

(3.37)

Averaging the delay over the ensemble of \( N_{\text{cells}} \) neurons we find:

\[
\mu_x = N_{\text{cells}} \cdot \mathcal{F}^{-1} \left\{ H_{HF}(f) \cdot \mathcal{F}\{R_{\text{fire}}\}(f) \cdot \int_0^{\tau_{d,\text{max}}} e^{-j2\pi f \cdot \tau_d} \cdot G(f) d\tau_d \right\} \\
= N_{\text{cells}} \cdot \mathcal{F}^{-1} \left\{ e^{j\pi \tau_{d,\text{max}}} \cdot \mathcal{F}\{R_{\text{fire}}\}(f) \cdot H_{HF}(f) \cdot \sin(\pi \tau_{d,\text{max}}) \cdot G_x(f) \right\} \\
= 0 
\]  

(3.38)
If the delay is of the order of a few millisecond say, \( \tau_{d,max} = 2e^{-3}[s] \), then the cut off frequency of the low pass filter will be 250 [Hz]:

\[
\pi f_{max} \tau_{d,max} = \pi/2 \quad \Rightarrow \quad f_{max} = \frac{1}{2\tau_{d,max}} = 250[Hz]
\] (3.39)

However, due the presence of a high pass filter, the mean response at a frequency below 300 [Hz] is totally abolished.

Figure 3.9: Case (a) – A sum of unipolar spikes results in a clear mean response. Case (b) – A sum of aligned (synchronized) wiggling spikes results in a mean response that is seen only at onset and offset. Case (c) – A sum of unaligned spike shapes results in a zero mean response.

In summary, in the presence of a high pass filter, the mean response is abolished.
3.2.2 The covariance of the desired signal

As opposed to the mean response which is sensitive to high-pass filtering and phase shifts, we shall now show that the covariance function is durable to filtering and insensitive to small delays.

**Theorem 3.6** The covariance of the response which results from many neurons ("multi-unit") that are high pass filtered above 300 Hz, obeys the following closed form expression:

$$
\Sigma_x(t_1, t_2) = \sum_{k=1}^{N_{cells}} \int_0^{t_1} g_{x,k}(t_1 - \tau_k) g_{x,k}(t_2 - \tau_k) \cdot R_{fire}(\tau_k) d\tau_k
$$

(3.40)

where \(g_{x,k}\) is the spike shape coming from the \(k^{th}\) neuron.

Furthermore, if spike shapes \(g_{x,k}\) are distributed such that their delays are distributed uniformly and independently of their amplitude distribution, then the covariance has the following expression:

$$
\Sigma_x(t_1, t_2) = \int_0^{t_1} g_x(t_1 - \tau) \cdot g_x(t_2 - \tau) \cdot R_{fire}(\tau) \cdot d\tau
$$

(3.41)

where \(g_x(t)\) has an amplitude frequency response of a high pass filtered spike.

We prove the equation (3.40) and (3.41) in two steps.

**Proof:** Derivation of the covariance expression (proof of equation 3.40).

To obtain the covariance function, \(\Sigma_x(t_1, t_2)\), we first calculate the autocorrelation function, \(R_x(t_1, t_2)\), and then use the general relation:

$$
R_x(t_1, t_2) = \Sigma_x(t_1, t_2) + \mu_x(t_1) \cdot \mu_x(t_2)
$$

(3.42)

where \(\mu_x(t)\) is the signal mean at time \(t\). Thus, the covariance is obtained by subtracting \(\mu_x(t_1) \cdot \mu_x(t_2)\) from the autocorrelation function. The autocorrelation is calculated as follows:
\[ R_x(t_1, t_2) = E \left\{ \sum_{k=1}^{N_{\text{cells}}} \sum_{l=1}^{N_{\text{cells}}} g_{x,k}(t_1) \cdot I_k(t_1) \cdot g_{x,l}(t_2) \cdot I_l(t_2) \right\} \]
\[ = \sum_{k=1}^{N_{\text{cells}}} \int_0^{t_1} \int_0^{t_2} E\{g_{x,k}(t_1 - \tau_{k,1})g_{x,k}(t_2 - \tau_{k,2})\} p_{\text{fire}}(\tau_{k,1}, \tau_{k,2}) d\tau_{k,1} d\tau_{k,2} \]
\[ + \sum_{k=1}^{N_{\text{cells}}} \sum_{l=1}^{N_{\text{cells}}} \int_0^{t_1} \int_0^{t_2} g_k(t_1 - \tau_{k,1}) g_l(t_2 - \tau_{k,2}) p_{\text{fire}}(\tau_{k,1}) p_{\text{fire}}(\tau_{l,2}) \frac{d\tau_{k,1} d\tau_{k,2}}{\mu_{x,k}(t_1) \mu_{x,l}(t_2)} \]
\[ - \sum_{k=1}^{N_{\text{cells}}} \int_0^{t_1} \int_0^{t_2} g_{x,k}(t_1 - \tau_{k,1}) g_{x,k}(t_2 - \tau_{k,2}) p_{\text{fire}}(\tau_{k,1}) p_{\text{fire}}(\tau_{k,2}) \frac{d\tau_{k,1} d\tau_{k,2}}{\mu_{x,k}(t_1) \mu_{x,k}(t_2)} \]

(3.43)

The first line in equation (3.43) is the definition of the autocorrelation, the second line is the autocorrelation due to all cells with themselves, and the third and fourth line comprise the autocorrelation between two different cells (the fourth line removes the autocorrelation due to same neuron, that is, the case of \( k = l \)). Starting from the second line, we incorporate the fact that the averaging indicator functions yields the spike timing joint density function. For the two last terms (lines three and four), we assume that two different neurons are statistically independent, a claim supported by experiments (e.g. Johnson and Kiang, 1976).

Next, we explicitly express the joint timing density function, \( p_{\text{fire}}(\tau_{k,1}, \tau_{k,2}) \), which represents the probability that the \( k^{th} \) neuron will fire at time \( \tau_{k,1} \) and then again at time \( \tau_{k,2} \):

\[ p_{\text{fire}}(\tau_{k,1}, \tau_{k,2}) = p_{\text{fire}}(\tau_{k,1}) \cdot p_{\text{fire}}(\tau_{k,2} | \tau_{k,1}) \]
\[ = \begin{cases} 
  P_0(\tau_{k,1}) \cdot [y(\tau_{k,1}) + R_0] d\tau_{k,1} & \tau_{k,2} = \tau_{k,1} \\
  P_0(\tau_{k,1}) [y(\tau_{k,1}) + R_0] \cdot P_0(\tau_{k,2} | \tau_{k,1}) [y(\tau_{k,2}) + R_0] d\tau_{k,1} d\tau_{k,2} & \tau_{k,2} > \tau_{k,1} 
\end{cases} \]

(3.44)

The first case accounts for the scenario that neuron number \( k \) fired a spike at time \( \tau_{k,1} \). The second case accounts for the case where neuron number \( k \) fired a spike at time \( \tau_{k,1} \) and then fired again at time \( \tau_{k,2} \).
\[ R_x(t_1,t_2) = \sum_{k=1}^{N_{\text{cells}}} \int_0^{t_1} g_{x,k}(t_1 - \tau_{k,1}) g_{x,k}(t_2 - \tau_{k,1}) P_0(\tau_{k,1}) \cdot \left[ y(\tau_{k,1}) + R_0 \right] d\tau_{k,1} + \]

\[ \sum_{k=1}^{N_{\text{cells}}} \left\{ \int_0^{t_1} \int_0^{t_2} g_{x,k}(t_1 - \tau_{k,1}) g_{x,k}(t_2 - \tau_{k,1}) P_0(\tau_{k,1}) \cdot P_0(\tau_{k,2}|\tau_{k,1}) \cdot \right\} \cdot \]

\[ \left[ y(\tau_{k,1}) + R_0 \right] [y(\tau_{k,2}) + R_0] d\tau_{k,2} d\tau_{k,1} \]

\[ + u_x(t_1) u_x(t_2) - \sum_{k=1}^{N_{\text{cells}}} \mu_{x,k}(t_1) \cdot \mu_{x,k}(t_2) \]

\[ I_s - \text{these terms zero out when the mean is zero} \]

Observe that the terms that are related to the mean response (marked with "**"), zero out when the mean, \( u_x(t) \) zeros out (recall from Section 3.2.1 that the mean zeros out when the signal is high pass filtered). It remains to show that the term marked with "*" zeros out due to the refractory period.

Recall from equation 3.12 that the probability to be in the armed state \( P_0(t) \) obeys the following equation.

\[ P_0(t) = \frac{R_1 \int_0^t \exp\left[ \int_0^{t'} (y + R_0 + R_1) dt' \right] dt + C_0 \exp\left[ \int_0^t (y + R_0 + R_1) dt \right]}{\exp\left[ \int_0^t (y + R_0 + R_1) dt \right]} \]  \text{(3.46)}

where \( C_0 \) is determined by the initial conditions:

\[ C_0 = P_0 \bigg|_{t=0} \]  \text{(3.47)}

So the probability that the neuron will fire again at time \( \tau_{k,2} \), given that it fired at time \( \tau_{k,1} \) \( P_0(\tau_{k,2}|\tau_{k,1}) \), is obtained by setting \( C_0 \) to be zero (because we know for sure that the neuron fired at time \( \tau_{k,1} \) and left the armed state). Thus, the expression for \( P_0(\tau_{k,2}|\tau_{k,1}) \) is:

\[ P_0(\tau_{k,2}|\tau_{k,1}) = \frac{R_1 \int_{\tau_{k,1}}^{\tau_{k,2}} \exp\left[ \int_{\tau_{k,1}}^{t'} (y + R_0 + R_1) dt' \right] dt}{\exp\left[ \int_{\tau_{k,1}}^{\tau_{k,2}} (y + R_0 + R_1) dt \right]} \]  \text{(3.48)}
Note that $P_0(\tau_{k,2} | \tau_{k,1})$ is zero for $\tau_{k,2} = \tau_{k,1}$, and close to zero when the difference $\Delta_\tau = \tau_{k,2} - \tau_{k,1}$ is small.

Next, we rewrite the integral associated with $P_0(\tau_{k,2} | \tau_{k,1})$ after incorporating the following change of integration variables:

$$\tau_{k,1} = \tau_{k,1} \tag{3.49}$$

$$\Delta_\tau = \tau_{k,2} - \tau_{k,1}; \tag{3.50}$$

The resulting integral is therefore:

$$I_* = \int_{t_1}^{t_2} \int_{t_1^-}^{t_2^-} g_{x,k}(t_1 - \tau_{k,1}) g_{k}(t_2 - \tau_{k,2}) P_0(\tau_{k,1}) \cdot P_0(\tau_{k,2} | \tau_{k,1}) \cdot$$

$$[y(\tau_{k,1}) + R_0][y(\tau_{k,2}) + R_0]d\tau_{k,2}d\tau_{k,1}$$

$$= \int_{t_1}^{t_2} \int_{t_1^-}^{t_2^-} g_{x,k}(t_1 - \tau_{k,1}) g_{x,k}(t_2 - \tau_{k,1} - \Delta_\tau) \cdot P_0(\tau_{k,1} + \Delta_\tau | \tau_{k,1}) P_0(\tau_{k,1}) \cdot$$

$$[y(\tau_{k,1}) + R_0][y(\tau_{k,2}) + R_0] \Delta_\tau d\tau_{k,1} \tag{3.51}$$

Mathematically, we see that two spikes cannot overlap due to the refractory period because $g_{x,k}(t_1 - \tau_{k,1}) g_{x,k}(t_2 - \tau_{k,1} + \Delta_\tau)$ is zero when $\Delta_\tau$ is greater than $\sim 3$ milliseconds, whereas $P_0(\tau_{k,1} + \Delta_\tau | \tau_{k,1})$ is close to zero when $\Delta_\tau < 3e^{-3}$. Figure 3.10 illustrates this point geometrically. The horizontal axis of Figure 3.10 represents the distance between two spikes, and the vertical axis represents the firing time of the first spike. The small box on the top left of the figure (close to the coordinates $[0, t_1]$) represents the support of the multiplication between the two nearby spikes. Because spikes are so narrow, the box starts and ends close to $t_1$ on the vertical axes, and close to zero on the horizontal axes. On the other hand, the probability of a second spike to occur (the big box on the right) starts away from zero. Thus, we have shown that the second and third lines of the autocorrelation function are virtually zero.

We find that the resulting expression for the covariance function equals to equation (3.40):
The effect of the refractory period on equation (3.51). The supports of the two multiplicative terms in the equation are disjoint, so the multiplication is zero for all values of $\Delta t$ and $t_1$. As a result, the integral of this multiplication is also zero.

$$\Sigma_{x,k}(t_1, t_2) = \sum_{k=1}^{N_{cells}}\int_0^{t_1} g_{x,k}(t_1 - \tau_k) g_{x,k}(t_2 - \tau_k) \cdot P_0(\tau_k) \cdot [y(\tau_k) + R_0]d\tau_k$$

$$= \sum_{k=1}^{N_{cells}}\int_0^{t_1} g_{x,k}(t_1 - \tau_k) g_{x,k}(t_2 - \tau_k) \cdot R_{fire}(\tau_k)d\tau_k$$

(3.52)

We next prove equation (3.41) using the following two corollaries.

**Corollary 3.7**: The covariance function, $\Sigma_x(t_1, t_2)$ is durable to filtering.

**Proof**: The durability to filtering is proved in the frequency domain. The standard one-dimensional Fourier transform of a function is used:

$$\mathcal{F}\{g_x(t)\} = G_x(w) = \int_{-\infty}^{\infty} e^{-jwt} \cdot g_x(t)dt$$

(3.53)

and the following definition for the two dimensional Fourier transform (Gardner, 1972):

$$\mathcal{F}_2\{f(t_1, t_2)\} \triangleq \int_{-\infty}^{\infty} f(t_1, t_2) \cdot e^{-jw_1 t_1 + jw_2 t_2}dt_1 dt_2$$

(3.54)

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Using these definitions we can express the covariance function of the resulting from the $k^{th}$ neuron as follows:

$$\Sigma_{x,k}(t_1, t_2) = \mathcal{F}^{-1}_2 \left\{ \int_0^{t_1} g_{x,k}(t_1 - \tau_k) g_{x,k}(t_2 - \tau_k) \cdot R_{\text{fire}}(\tau_k) d\tau_k \right\}$$

$$= \mathcal{F}^{-1}_2 \int_{-\infty}^{\infty} \int_{-\infty}^{\infty} e^{-j\omega_1 t_1} e^{j\omega_2 t_2} \cdot \int_0^{t_1} g_{x,k}(t_1 - \tau_k) g_{x,k}(t_2 - \tau_k) \cdot R_{\text{fire}}(\tau_k) d\tau_k dt_1 dt_2$$

$$= \mathcal{F}^{-1}_2 \int_{t_1 = t_1 - \tau_k}^{t_1} \int_{0}^{t_1} \int_{-\infty}^{\infty} \int_{-\infty}^{\infty} e^{-j\omega_1(t_1 + \tau_k)} \cdot g_{x,k}(t_1) \cdot e^{+j\omega_2(t_2 + \tau_k)} g_{x,k}(t_2) \cdot R_{\text{fire}}(\tau_k) d\tau_k dt_1 dt_2$$

$$\overset{\sim}{= } \mathcal{F}^{-1}_2 \left\{ G_{x,k}(w_1) G^*_{x,k}(w_2) \mathcal{F}\{R_{\text{fire}}\}(w_1 - w_2) \right\}$$

(3.55)

Figure 3.11: The expression for the covariance function of the frequency domain.

Figure 3.11 illustrates the resulting expression for the covariance in the frequency domain (equation 3.55). Note that due to the bandpass nature of $G_{x,k}(w_1)$ and $G^*_{x,k}(w_2)$, the covariance support is confined to a rectangular region between the frequencies $[300, 3000] \times [300, 3000]$. The covariance support is concentrated in a narrow two-dimensional strip in the vicinity of the diagonal of the rectangular region. Although the frequencies below 300 are filtered out, a substantial part of the covariance remains. Thus, the covariance is durable to filtering.

**Corollary 3.8**: The covariance function, $\Sigma_x(t_1, t_2)$, is durable to small delay differences ("linear phase shifts") that are distributed uniformly and are independent of spike amplitude distribution.

55
**Proof:** We assume the spikes shapes from all sources are similar up to amplitude scaling, but have small delays, one with respect to the other. The delays are assumed to be uniformly distributed and independent of the amplitude distribution. That is, we assume

\[ g_{x,k}(t) = \rho_k \cdot g_x(t + \tau_{d,k}) \]  

(3.56)

\[ \tau_{d,k} \sim U[0, \tau_{d,max}] \]  

(3.57)

\[ E\{\rho_k^2\} = 1 \]  

(3.58)

\[ p(\rho_k, \tau_{d,k}) = p(\rho_k)p(\tau_{d,k}) \]  

(3.59)

\[ \Sigma_x(t_1,t_2) = \mathcal{F}^{-1}_2 \left\{ \sum_{k=1}^{N_{cell}} \rho_k^2 G_{x,k}(w_1) G^*_{x,k}(w_2) \mathcal{F}\{R_{fire}\}(w_1 - w_2) \right\} \]  

(3.60)

\[ = \mathcal{F}^{-1}_2 \left\{ \int_0^{\tau_{d,max}} G_x(w_1) G^*_x(w_2) \mathcal{F}\{R_{fire}\}(w_1 - w_2) e^{-j(w_1-w_2)\tau_{d,k}} \cdot d\tau_{d,k} \right\} \]  

(3.61)

\[ = \mathcal{F}^{-1}_2 \left\{ e^{-j|w_1-w_2|\tau_{d,max}/2} \cdot \frac{G_x(w_1) G^*_x(w_2) \sin \left( \frac{1}{2} |w_1-w_2| \tau_{d,max} \right)}{w_1-w_2} \mathcal{F}\{R_{fire}\}(w_1 - w_2) \right\} \]  

(3.62)

\[ = \int_0^{t_1} g_x(t_1 - \tau) \cdot g_x(t_2 - \tau) \cdot R_{fire}(\tau - \tau_{d,max}/2) \cdot d\tau \]  

(3.63)

Note that the small delays act as a low pass filter on the firing rate. However, since the firing rate is typically a slowly varying signal with a typical bandwidth, that is lower than \(300/2[H z]\), the low pass filtering does not affect it significantly \(\square\)

### 3.2.3 The covariance of the background signal

The background noise, \(n(t)\), is the result of the huge number of cells that are electrically active, regardless of the stimulus presence. It is empirically known (e.g. Martinez et al., 2009; Novak et al., 2009) that when this background noise is high-pass filtered above \(300[H z]\), the resulting noise is Gaussian, stationary, and has a characteristic and reproducible spectral shape. Thus, the expression for the covariance remains the same, only the stimulus intensity is set to zero.
and we are left with the spontaneous firing rate of the irrelevant neurons:

\[ \Sigma_n(t_1, t_2) = \int_0^{t_1} g_n(t_1 - \tau)g_n(t_2 - \tau)d\tau \]

\[ = \int_0^{t_1} g_n(\tau)g_n(t_2 - t_1 + \tau)d\tau \]

(3.64)

Note that due to the stationarity property, the exact spectral shape can also be measured empirically by calculating the periodogram.

In addition, the covariance function contains a weak white noise component caused by the electrical equipment and the residuals of the filtering.

\[ \Sigma_v(t_1, t_2) = \sigma_v^2 \delta(t_1 - t_2) \]

(3.65)

3.2.4 Summary of the model

The multi-unit electrode is exposed to many neurons. Some of the neurons react to the stimulus and are considered as the “signal”. Other neurons are unrelated to the stimulus and fire spontaneously. We refer to these neurons as “noise”. Due to the large number of cells involved, both “noise” and “signal” obey the central limit theorem and have Gaussian distributions. Moreover, these Gaussian distributions have a specific structure of covariance function that is described by equations (3.40), (3.64), and (3.65). The covariance intensity depends on the stimuli intensity through the firing rate, which is given by equations (3.11)-(3.15). The signal mean also depends on the firing rate and on the electrode-neuron channel, but unlike the covariance function, it is sensitive to high pass filtering and it is expected to be close to zero most of the time, with possible exceptions regarding the stimulus onset and offset times. Table (3.1) summarizes the model.

3.2.5 State Space Representation of Signal Model

In this section, we show that the signal model, summarized in Table 3.1, has an equivalent “state space” representation. The equivalence is in the sense that both the state space model
Table 3.1: Summary of model

<table>
<thead>
<tr>
<th>Equation</th>
</tr>
</thead>
<tbody>
<tr>
<td>( r(t) = x(t) + n(t) + v(t) )</td>
</tr>
<tr>
<td>( x(t) \sim N(\mu_x(t), \Sigma_x(t_1, t_2)) )</td>
</tr>
<tr>
<td>( n(t) \sim N(0, \Sigma_n(t_1, t_2)) )</td>
</tr>
<tr>
<td>( v(t) \sim N(0, \Sigma_v(t_1, t_2)) )</td>
</tr>
<tr>
<td>( \Sigma_x(t_1, t_2) = \int_0^{t_1} g_x(t_1 - \tau) g_x(t_2 - \tau) \cdot R_{fire}(\tau) d\tau )</td>
</tr>
<tr>
<td>( \Sigma_n(t_1, t_2) = \int_0^{t_1} g_n(t_1 - \tau) g_n(t_2) \cdot \delta(t_2 - t_1) d\tau )</td>
</tr>
<tr>
<td>( \Sigma_v(t_1, t_2) = \sigma_v^2 \delta(t_2 - t_1) )</td>
</tr>
</tbody>
</table>

The mean \( \mu_x(t) \simeq 0 \) with possible exceptions near the stimulus rising and falling edges.

\( R_{fire}(t) \) is calculated using equations (3.11)-(3.15)

\( g_x(t) \) is a function that has the same magnitude of the Fourier transform of a high pass filtered spike produced by the stimulus responsive cells. An example of such a function is given in Figure 3.8, and a possible digital implementation of this function is described in Table A.1.

\( g_n(t) \) is a function whose Fourier transform has the same magnitude of the power spectral density of the background noise.

and the model depicted in Table 2 have the same mean and covariance functions, and since both models are Gaussian, they will have identical statistical properties. We present the state space model, because this formulation is necessary to construct a sequential online detector.

We start the construction of the state space model by repeating equation (3.41):

\[
\begin{align*}
\Sigma_x(t_1, t_2) &= \mathbb{E}\{[x(t_1) - u_x(t_1)] [x(t_2) - u_x(t_2)]\} \\
&= \int_0^{t_1} g_x(t_1 - \tau_k, 1) g_x(t_2 - \tau_k, 1) \cdot R_{fire}(\tau_k, 1) d\tau_k, 1
\end{align*}
\]

(3.66)

Now, ignore for a moment (3.66), and consider the following linear system which is driven by a varying amplitude white Gaussian noise:

\[
x(t) = g_x(t) \ast [f(t) \circ dw_t]
\]

(3.67)

5The notation \( \circ dw(\tau) \) stands for a Stratonivich type (Stratonovich, 1966) white Gaussian noise, which actually results from accumulation of responses over a finite small time interval.
The covariance of $x(t)$ is:

$$
\Sigma_x(t_1, t_2) = E\{g_x(t_1) \ast f(t_1) \circ dw_{t_1} \cdot g_x(t_2) \ast f(t_2) \circ dw_{t_2}\}
$$

$$
= E\left\{\int_0^{t_1} f(\tau_1) \cdot f(\tau_2) \circ dw(\tau_1) \cdot g_x(t_1 - \tau_1)g_x(t_2 - \tau_2)d\tau_1d\tau_2\right\}
$$

$$
= \int_0^{t_1} f^2(\tau)g_x(t_1 - \tau)g_x(t_2 - \tau)d\tau
$$

(3.68)

Observe that (3.66) and (3.68) would be identical if we set $f(t)$ as the square root of the firing rate of a refractory Markov neuron:

$$
f(t) = \sqrt{R_{fire}(t)}
$$

(3.69)

Next, we present the spike response, $g_x(t)$, using a recursive infinite impulse response (IIR) filter:

$$
|\mathcal{F}\{g_x(t)\}|^2 = |G_x(s)|^2 = \left|\sum_{m=0}^{Q_x-1} b_{x,m}s^{Q_x-b-m} \mu_x\right|^2
$$

(3.70)

Figure (3.12) compares the impulse response of an IIR filter with $Q_{x,a} = 6$, $Q_{x,b} = 4$ to an unfiltered Hodgkin & Huxley spike (H&H) taken from Gold et al. (2006). This comparison is for illustration alone, as here we only discuss the case of a filtered spike. Table A.1 in Appendix A lists the coefficients of a filtered version of this spike, which is shown in Figure 3.8.

Recall from 3.8 that expression for the covariance is not sensitive to linear phase shifts, so there exists some degree of freedom for choosing the coefficients $b_{x,m}$.

So far we have shown that the following autoregressive moving average (ARMA) equation yields the same covariance matrix of the process $x(j\Delta_t)$:

$$
x(j\Delta_t) = \sum_{m=1}^{Q_{x,a}} -a_{x,m} \{x([j - m]\Delta_t) - \mu_x([j - m]\Delta_t)\}
$$

$$
+ \sum_{l=0}^{Q_{x,b}} b_{x,l} \cdot \sqrt{R([j - l]\Delta_t)} \circ dw_{[j - l]} + \mu_x(j\Delta_t)
$$

(3.71)
Figure 3.12: Comparison of spike shape versus state space approximation with $Q_{x,a} = 6$ and $Q_{x,b} = 4$, in the time domain (Fig. 3.12a), and in the Fourier frequency domain Fig. 3.12b. The spike shape was taken from Milstein and Koch (2008).

Note that by adding the non-zero mean, $\mu_x(t)$, the ARMA equivalent of $x(t)$ also has the same mean. However, since in the measurement conditions considered in this work, the mean is expected to be zero, it can be ignored.

Similarly, the covariance $\Sigma_n(t_1, t_2)$ associated with the background spontaneous spikes is obtained if $n(t)$ obeys the following stochastic difference equation:

$$n(j \Delta_t) = \sum_{m=1}^{Q_{n,a}} -a_{n,m} n([j - m] \Delta_t) + \sum_{l=0}^{Q_{n,b}} b_{n,l} \circ d\zeta_{[j-l]}$$

(3.72)

Thus, $r(k \Delta_t)$, which is the sum of the uncorrelated random processes $x(j \Delta_t)$, $n(j \Delta_t)$ and $v(j \Delta_t)$, can be expressed using a sum of two ARMA processes that rely on data from the past
and additional white noise components from the most recent observation ("innovations"):

\[
\begin{align*}
\mathsf{r}(j\Delta_t) - \mu_r(j\Delta_t) &= x(j\Delta_t) + n(j\Delta_t) + v(j\Delta_t) - \mu_r(j\Delta_t) \\
&= \sum_{m=1}^{Q_{x,a}} -a_{x,m} \{x((j-m)\Delta_t) - \mu_r(j-m)\} + \\
&\quad \sum_{l=1}^{Q_{x,b}} b_{x,l} \sqrt{R_{\text{fire}}([j-l]\Delta_t)} \circ dw_{[j-l]} + \\
&\quad \sum_{m=1}^{Q_{n,a}} -a_{n,m} n((j-m)\Delta_t) + \sum_{l=1}^{Q_{n,b}} b_{n,l} \circ d\zeta_{[j-l]} + \\
&\quad b_{x,0} \cdot \sqrt{R_{\text{fire}}(j)} \circ dw_j + b_{n,0} \circ d\zeta_j + \sigma_v \circ d\xi_j
\end{align*}
\]

where \( u_r[j\Delta_t] \) is the process mean, and, \( dw_{[j-l]}, d\zeta_{[j-l]} \), and \( d\xi_j \) are independent standard white noise processes.

The final step in the construction of the state space is to convert the two difference equations for \( x[j] \) and \( n[j] \), that are of the order of \( \{Q_{x,a}, Q_{x,b}\} \) and \( \{Q_{n,a}, Q_{n,b}\} \) respectively, to a set of \((Q_{x,max} + Q_{n,max})\) first order difference equations, where:

\[
\begin{align*}
Q_{x,max} &= \max\{Q_{x,a}, Q_{x,b}\} \\
Q_{n,max} &= \max\{Q_{n,a}, Q_{n,b}\}
\end{align*}
\]

This type of representation is known as a state space representation. Note that there are many possible state space representations and they are all acceptable as long as the equation for the observations (3.73) either stays the same or has the same covariance function. We chose the following common set of equations:

\[
\begin{align*}
\mathbf{z}_{k+1} &= A \cdot \mathbf{z}_k + B_k \circ \left[ dw_k \quad d\zeta_k \right]^T \\
\mathsf{r}_k &= C \cdot \mathbf{z}_k + D_k \circ \left[ dw_k \quad d\zeta_k \right]^T
\end{align*}
\]

where:

1. \( \mathbf{z}_k \) is a vector of internal state variables of size \((Q_{x,max} + Q_{n,max}) \times 1\). The first entry of this vector, \( \{\mathbf{z}_k\}_1 \), corresponds to \( x(k\Delta_t) \) minus the latest innovation of \( x(k\Delta_t) \). The
following \((Q_{x,a} - 1)\) entries are used for the construction of \(\{z_k\}_1\). Entry number \(Q_{x,a} + 1\) of this vector, i.e. \(\{z_k\}_{Q_{x,a}+1}\), corresponds to \(n(k\Delta t)\) minus the latest innovation of \(n(k\Delta t)\). The following \((Q_{n,a} - 1)\) entries are used for the construction of \(\{z_k\}_{Q_{x,a}+1}\).

2. The matrices \(A\) and \(B_k\) are given in Appendix A. They generate \(\{z_k\}_1\) and \(\{z_k\}_{Q_{x,a}+1}\).

3. The vector \(C\) sums the state variables \(\{z_k\}_1\) and \(\{z_k\}_{Q_{x,a}+1}\) and the vector \(D_k\) adds the latest innovations that were missing (see step 1). The values of \(C\) and \(D_k\) are also given in Appendix A.
Chapter 4

Optimal Detection of the Stimulus Presence

4.1 The Mathematical Principle of the Optimal Detector

In this section we develop the optimal detector for the problem formulated in Section 2.1.

Recall that the role of the detector is to minimize the risk of an injury given the observations:

\[ R_{injury}(t|r_0^t) = R_{MD}(t|r_0^t) \cdot I_{on}(t) + R_{FA}(t|r_0^t) \cdot I_{on}(t) \]  \hspace{1cm} (4.1)

The risk, \( R_{injury}(t) \), is the average cost of associating the current moment with the wrong group; i.e., declaring on the current moment as a moment where the stimulus is present in a case where there is no stimulus or vice versa. Since our cost functions are piecewise constants, the average risk can be expressed as follows:

\[ R_{injury}(t|r_0^t) = C_{FA} \cdot P_{FA}(t \in T_{FA} | r_0^t) \cdot I_{on}(t) + C_{MD} \cdot P_{MD}(t \in T_{MD} | r_0^t) \cdot I_{on}(t) \]  \hspace{1cm} (4.2)

where \( P_{FA}(t \in T_{FA} | r_0^t) \) is the probability that the current time falls inside the false alarm zone, and \( P_{MD}(t \in T_{MD} | r_0^t) \) is the probability that the current time is within the detection window.

\footnote{The parameters \( T_d, T_s \) and \( T_{\text{min}} \) that are referred to in this section are the allowed response delay, the stimulus duration, and the minimum spacing between adjacent stimuli, respectively. Refer to Section 2.1 for more detailed definitions.}
From equation (4.2), it is evident that in order to minimize the risk of an injury, \( R_{injury}(t) \), the following decision rule should be applied:

\[
I_{on}(t) = \begin{cases} 
1 & C_{FA} \cdot P_{FA}(t \in T_{FA} | r_0^t) < C_{MD} \cdot P_{MD}(t \in T_{MD} | r_0^t) \\
0 & \text{otherwise}
\end{cases}
\]  

(4.3)

Thus, we raise the detection flag if the risk of misdetection is larger than the risk of false alarm. To reach a decision, the detector must calculate the conditional probabilities \( P_{FA}(t \in T_{FA} | r_0^t) \) and \( P_{MD}(t \in T_{MD} | r_0^t) \) and set the output of the detector according to (4.9). Since the duration of the stimulus is a-priori known, asking whether the stimulus is active more than \( T_d \) seconds (this is the legal delay from onset), is equivalent to asking whether the elapsed time from the most recent stimulus onset is greater than \( T_d \), and smaller than \( T_s \) (stimulus duration). Phrasing the detection problem this way is more convenient because two different hypotheses regarding the location of the stimulus onset are mutually exclusive events. This makes it possible to calculate the total probability of an onset presence in one of several possible locations by simply summing the corresponding probabilities of these different onset locations. Defining:

\[
P_{onset}(t - t_{last onset} = k\Delta t | r_0^t) \equiv \text{The probability that the stimulus onset occurred } k\Delta t \text{ seconds ago, given the observations from start time until now (time } t) \]  

(4.4)

Then, the probabilities \( P_{MD}(t \in T_{MD} | r_0^t) \) and \( P_{FA}(t \in T_{FA} | r_0^t) \) can be expressed as the sum of the onset locations probabilities:

\[
P_{MD}(t \in T_{MD} | r_0^t) = \sum_{k=T_d/\Delta t}^{T_s/\Delta t} P_{onset}(t - t_{last onset} = k\Delta t | r_0^t) \]  

(4.5)

\[
P_{FA}(t \in T_{FA} | r_0^t) = \sum_{k=T_s/\Delta t+1}^{\infty} P_{onset}(t - t_{last onset} = k\Delta t | r_0^t) \]  

(4.6)

where \( t \) is the current time, and \( t_{last onset} \) is the moment of last onset.

To avoid using an infinite sum of onset locations, we define:

\[
P_{onset}(t - t_{last onset} \geq T_{min} | r_0^t) = \sum_{k=T_{min}/\Delta t}^{\infty} P_{onset}(t - t_{last onset} = k\Delta t | r_0^t) \]  

(4.7)
Using this definition, equation (4.6) can be written as follows:

$$P_{FA}(t \in T_{FA} \mid r_0^t) = \frac{T_{min}}{\Delta t} \sum_{k=T_{d}/\Delta t+1}^{T_{s}/\Delta t+1} P_{onset}(t - t_{last onset} = k\Delta t \mid r_0^t) + P_{onset}(t - t_{last onset} \geq T_{min} \mid r_0^t)$$ (4.8)

Furthermore, based on principles from the pioneering work of Schweppe (1965)\(^2\), we show in Appendix B that the posterior probabilities, \(P_{onset}(t - t_{last onset} = k\Delta t \mid r_0^t)\) and \(P_{onset}(t - t_{last onset} \geq T_{min} \mid r_0^t)\), of the specific problem that was phrased in Section 2.1, can be calculated in a recursive manner; i.e., the values of these probabilities at time \(t\) are an update of their previous set of values at time \(t - \Delta t\) using the most recent observation.

In the next subsection, we describe the implementation of the detector that sequentially calculates the probabilities for each possible delay from the most recent onset. The detector raises the detection flag if the sum of the probabilities corresponding to onset delays greater than \(T_{d}\), and smaller than \(T_s\) is larger than the sum of probabilities of the remaining alternatives.

### 4.2 Detector Structure

In this section we describe in detail the implementation of the detector. The design is a customization of the work of Schweppe (1965) for sequential detection of multi-unit neural signals. The applicability of the general ideas of Schweppe (1965) for processing neural signals has been discussed in Roweis and Ghahramani (1999); Barbieri et al. (2004); Paninski et al. (2007), but the exact equations here are different.

The basic idea of the detector is to sequentially calculate normalized versions of the posterior probabilities, \(P_{onset}(t - t_{last onset} = k\Delta t \mid r_0^t)\) and \(P_{onset}(t - t_{last onset} \geq T_{min} \mid r_0^t)\), and set the detection flag according to the following equivalent version of the decision rule (4.3):

\(^2\)We chose the work of Schweppe (1965) over later works by Duncan (1968) and Kailath (1969) since it fits the Stratonovich formulation, whereas the other two works fit the Ito formulation.
\[ I_{on}(t) = \begin{cases} 
1 & \left[ \frac{P_{FA}(t \in T_{FA} \mid r^t_0)}{P_{onset}(t - t_{last on} \geq T_{min} \mid r^t_0)} \right] < \left[ \frac{C_{MD}}{C_{FA}} \right] \\
0 & \text{otherwise} 
\end{cases} \] (4.9)

The detector is implemented digitally, and thus the time scale is discrete:

\[ t = j \Delta_t, j \text{ is an integer} \] (4.10)

where \( \Delta_t \) is the duration of the clock cycle:

\[ \Delta_t \equiv \text{sampling interval} \] (4.11)

The possible interval lengths from the last onset are also discretized, and thus the detector tests only the following discrete and finite set of events:

\[ t - t_{last on} = k \Delta_t, k = 1, 2, \ldots, (M_{min} - 1) \] (4.12)

and also the event:

\[ t - t_{last on} \geq T_{min} = M_{min} \Delta_t \] (4.13)

Thus, \( M_{min} \) is set as:

\[ M_{min} \equiv \lceil T_{min} / \Delta_t \rceil \] (4.14)

Note that according to the problem formulation, the event \( t - t_{last on} = 0^- \) (onset is imminent), is contained in the event \( t - t_{last on} \geq T_{min} \).

As shown in Figure 4.1, the detector consists of three main substructures:

1. The register array which stores the normalized posterior probabilities.
2. The Kalman (Kalman, 1960) estimators array.
3. The detection flag assertion unit.

We describe these three sub-units in more detail in the following subsections.
4.2.1 The Register Array

The register array stores logarithmic versions of \( M_{\text{min}} \) normalized posterior probabilities. Each one of the posterior probabilities \( P_{\text{onset}}(t - t_{\text{last onset}} = k\Delta_t | r_{0}^{j}) \), \( k = 1, 2, \ldots M_{\text{min}} \) has a corresponding register which is designated as \( d_{k}[j\Delta_t] \):

- The first register, \( d_{1}[j\Delta_t] \), corresponds to the posterior probability:

\[
P_{\text{onset}}(t - t_{\text{last onset}} = \Delta_t | r_{0}^{j})
\]

- The second register, \( d_{2}[n\Delta_t] \), corresponds to the posterior probability:

\[
P_{\text{onset}}(t - t_{\text{last onset}} = 2\Delta_t | r_{0}^{j})
\]

and so on.
The last register, \( d_{\text{M}_{\text{min}}}[j \Delta_t] \), corresponds to the posterior probability:

\[
P_{\text{onset}}(t - t_{\text{last onset}} \geq T_{\text{min}} \mid r_0^{[j \Delta_t]})
\]

Rather than storing the posterior probability itself, the value that is stored in each register at time \( t = j \Delta_t \) is the following function of the posterior probability.

\[
d_k[j \Delta_t] = \log \left( \frac{P_{\text{onset}}(t - t_{\text{last onset}} = k \Delta_t \mid r_0^{[j \Delta_t]})}{P_{\text{onset}}(t - t_{\text{last onset}} \geq T_{\text{min}} \mid r_0^{[0 \Delta_t]})} \right) \quad k = 1, 2, \ldots, (M_{\text{min}} - 1)
\]

As a result of this normalization, register \( #M_{\text{min}} \) is constantly kept at zero:

\[
d_{M_{\text{min}}}[j \Delta_t] = \log \left( \frac{P_{\text{onset}}(t - t_{\text{last onset}} = k \Delta_t \mid r_0^{[0 \Delta_t]})}{P_{\text{onset}}(t - t_{\text{last onset}} \geq T_{\text{min}} \mid r_0^{[0 \Delta_t]})} \right) = 0 \quad \forall j
\]

The registers are updated every clock cycle (every \( \Delta_t \) seconds) following the arrival of new sampled data from the electrode. The update rules of the registers are designed such that the new value of the register will indeed reflect the logarithm of the normalized posterior probability. Here we only summarize the update rules that follow from direct calculation of the posterior probabilities, which is given in Appendix B. To phrase the update rules in a compact manner, we use the following short notations:

\[
\alpha \equiv \frac{\Delta_t}{T_{\text{avg}} - T_{\text{min}}}
\]

and,

\[
\exp\{q_k[j \Delta_t]\} \equiv Pr(r[j \Delta_t] \mid t - t_{\text{last onset}} = k \Delta_t, r_0^{t-\Delta_t})
\]

The parameter \( \alpha \) is the reciprocal of the mean number of clock cycles that are added to the minimal inter trial intervals (\( T_{\text{min}} \)), and it is known a-priori. The value of \( q_k[n \Delta_t] \) is calculated by the Kalman estimators array (see Section 4.2.2) using the method in Schweppe (1965). Here assume that \( q_k[n \Delta_t] \) is known.

Using the above notations, the register update rules can be stated as follows:

**Rule 1** The update rule for the first register, \( d_1[k] \), is:

\[
d_1[j] = \log(\alpha) + q_1[j] + \log\{1\} - L_{\text{min}}[j]
\]

\[
= \log(\alpha) + q_1[j] - q_{M_{\text{min}}}[j] - \log\{1 - \alpha + \exp(d_{M_{\text{min}}-1}[j - 1])\}
\]
Rule 2 The update procedure of the other \((M_{\text{min}} - 2)\) registers, \(\{d_2[j], \ldots, d_{M_{\text{min}}-1}[j]\}\) is:

\[
d_k[j] = d_{k-1}[j - 1] + q_k[j] - L_{\text{min}}[j]
\]  \hspace{1cm} (4.20)

Rule 3 \(L_{\text{min}}[j]\) is defined as follows:

\[
L_{\text{min}}[j] = q_{M_{\text{min}}}[j] + \log\{1 - \alpha + \exp(d_{M_{\text{min}}-1}[j - 1])\}
\]  \hspace{1cm} (4.21)

Proof: See Appendix B.  \(\Box\)

4.2.2 The Kalman Estimators Array

The array of Kalman estimators consists of \(M_{\text{min}}\) identical units. Each unit outputs the quantity \(q_k(j \Delta t)\), which is the logarithm of the probability of the current observation conditioned by past observations, and the hypothesis that the stimulus occurred \(k \Delta t\) seconds ago; i.e.:

\[
q_k(j \Delta t) \equiv \log\left\{Pr(r[j \Delta t] \mid t - t_{\text{last onset}} = k \Delta t, r_0^{t-\Delta t})\right\}
\]  \hspace{1cm} (4.22)

where \(r[j \Delta t]\) is the most recently received electrode sample (current time is \(t = j \Delta t\)).

- The first Kalman estimator, unit #1, is designed under the assumption that the stimulus onset occurred \(\Delta t\) seconds ago; i.e., \(t_{\text{last onset}} = t - \Delta t\).
- The second Kalman estimator, unit #2, is designed under the assumption that the stimulus onset occurred \(2\Delta t\) seconds ago; i.e., \(t_{\text{last onset}} = t - 2\Delta t\).
- The last Kalman estimator, unit \#\(M_{\text{min}}\), is designed under the assumption that no stimulus has occurred in the last \(T_{\text{min}}\) seconds; i.e.,

\[
t - t_{\text{last onset}} \geq M_{\text{min}} \Delta t
\]

- All the Kalman estimators receive a mean free version of the signal under the corresponding hypothesis. In other words, the mean of the corresponding hypothesis, \(\mu_x[k]\), is removed (see Figure 3.9b that shows examples for signal mean).
Figure 4.2: The different hypotheses of the Kalman estimators. Each Kalman estimator performs the Kalman recursion using a different hypothesis regarding the current variance. The first Kalman estimator always assumes that the stimulus onset occurs now and therefore it is designed for increased variance. The second Kalman filter assumes that onset occurred on the previous sample, and so on. The last filter assumes no stimulus.

A schematic description of the different hypotheses associated with each estimator appears in Figure 4.2.

The Kalman estimators are chained (see Figure 4.1). The purpose of the chaining is to transfer the internal state variable of one estimator to the next. This way, the $k^{th}$ Kalman estimator always maintains the same hypothesis regarding offset from the stimulus, although time progresses (similar to a moving assembly line). In addition to the state vector, the filters also pass on the expected estimation error covariance matrix $\Sigma_{2,k|k-1}[j]$. The latter, however, can be computed at the offline parameter estimation stage, and set as a constant (with the
exception of a short initial transient period, the constant values are the optimal values). The recursive procedure for calculating $\Sigma_{z,k|k-1}[j]$ is given by Equations (C.1)-(C.9) of Appendix C.

In every clock cycle (every $\Delta_t$ [sec]), each one of the $M_{\text{min}}$ estimators receives three new inputs and produces three new outputs. The inputs of the $k^{th}$ Kalman filter at time $t = j \Delta_t$ are the mean free versions of the current electrode voltage, $r[j \Delta_t] - u_x[k]$, and two additional inputs that originate from estimator $(k-1)$: $\hat{z}_{k|k-1}[j]$ and $\Sigma_{z,k|k-1}[j]$. Each filter executes once the recursion that appears in equations (C.1)-(C.5) of Appendix C, and passes on new values of the $q_k[j]$ to the register array, and new values of $\{z_{k+1|k}[j], \Sigma_{z,k+1|k}[j]\}$ to the next estimator, which is estimator $(k+1)$. Note that the recursions executed by different estimators are different because they incorporate different values of $B_k$ and $D_k$ (see state space section (A.3)). Estimator $k$ uses $B_k$ and $D_k$ at all times.

The first Kalman estimator (#1) and the last Kalman estimator (#$M_{\text{min}}$) are an exceptions. The first estimator receives the inputs $\{z_{1|0}[j], \Sigma_{z,1|0}[j]\}$ from the Kalman estimator #$M_{\text{min}}$. The last Kalman estimator (#$M_{\text{min}}$) produces two different sets of predictions:

1. $\{z_{1|0}[j], \Sigma_{z,1|0}[j]\}$ - This prediction is sent to the Kalman estimator #1. It corresponds to the hypothesis that the stimulus will occur in the next sample.

2. $\{z_{M_{\text{min}}+1|M_{\text{min}}}[j], \Sigma_{z,M_{\text{min}}+1|M_{\text{min}}}[j]\}$ - This prediction is sent back to the Kalman estimator #$M_{\text{min}}$. It corresponds to the hypothesis that no stimulus will occur in the next sample.

At the initialization of online stage ($t = 0$), the values of $\{z_{k+1|k}[0]\}$ are set to zero.

$$z_{k+1|k}[0] = 0, \forall k$$ (4.23)
4.2.3 Assertion of the Detection Flag

Recall from Section 4.1 that the detection flag is asserted according to the following decision rule:

\[
I_{on}(t) = \begin{cases} 
1 & \left[ \frac{P_{FA}(t \in T_{FA} | r^t_0)}{P_{onset}(t - t_{last \_onset} \geq T_{min} | r^t_0)} / \frac{P_{MD}(t \in T_{MD} | r^t_0)}{P_{onset}(t - t_{last \_onset} \geq T_{min} | r^t_0)} \right] < \left[ \frac{C_{MD}}{C_{FA}} \right] \\
0 & \text{otherwise}
\end{cases}
\] (4.24)

Using equation (4.8), we express the numerator of (4.24) as follows:

\[
P_{FA}(t \in T_{FA} | r^t_0) / P_{onset}(t - t_{last \_onset} \geq T_{min} | r^t_0) = 1 + \sum_{k = T_s / \Delta t + 1}^{[T_{min} - \Delta t] / \Delta t} \frac{P_{onset}(t - t_{last \_onset} = k \Delta t | r^t_0)}{\sum_{j = T_s / \Delta t + 1}^{M_d} \exp(d_k[j])} \exp(d_k[j]) \] (4.25)

Using equation (4.5), we express the denominator of (4.24) as follows:

\[
P_{MD}(t \in T_{MD} | r^t_0) / P_{onset}(t - t_{last \_onset} \geq T_{min} | r^t_0) = \sum_{k = T_d / \Delta t}^{T_s / \Delta t} \frac{P_{onset}(t - t_{last \_onset} = k \Delta t | r^t_0)}{\sum_{j = T_s / \Delta t + 1}^{M_d} \exp(d_k[j])} \exp(d_k[j]) \] (4.26)

that yields the following decision rule:

**Rule 4** The decision flag is raised according to the following condition:

\[
I_{on}[j] = \begin{cases} 
1 & LR[j] > \frac{C_{MD}}{C_{FA}} \\
0 & \text{otherwise}
\end{cases}
\] (4.27)

where, \( LR[j] \) is the likelihood ratio:

\[
LR[j] = \frac{\sum_{j = M_d}^{M_s} \exp(d_k[j])}{1 + \sum_{k = M_s + 1}^{M_min} \exp(d_k[j])} \] (4.28)

The integer \( M_d \) is the legal delay from the onset of the warning signal expressed as a number of clock cycles:

\[
M_d = T_d / \Delta t \] (4.29)

and integer \( M_s \) is the number of clock cycles in which the warning signal persists:

\[
M_s = T_s / \Delta t \] (4.30)
Chapter 5

Detection Results

5.1 Simulation Study

In this section we study the operation of the detector by means of simulations. Primarily, the goal of the simulations was to quantify the performances of the detectors under ideal model conditions. The simulations were also useful as a qualitative indication for the usefulness of the model, and for verifying the mathematical relations obtained in Section 3.2.

In our simulations, we artificially generated a Multi-Unit response to the stimuli by filtering ideal white Gaussian samples with a time varying amplitude multiplier, (the square root of the firing rate) through a high passed spike shaped filter, as described in Section 3.2.5.

Figure 5.1 shows the specific stimulus and the resulting firing rate curve which were used for the construction of the simulated multi-unit data. The lower drawing in Figure 5.1 shows that the stimulus in our simulations was 400 [ms] long and it included 10 ms rise time and fall time. The near rectangular simulated stimulus had a maximum intensity level of 1 Watt. The upper drawing in Figure 5.1 shows the firing rate curve, which resulted from feeding in that stimulus, to the neuron model presented in Section 3.1.2. The other parameters that define this curve, $R_0$, $R_1$ and $g_{gain}$, are listed in Table 5.1. The square root of this firing curve served as the amplitude multiplier for the white noise samples, which were later filtered by a filter having a spike-like impulse response.
Table 5.1: *Simulation Parameters*

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\Delta t$</td>
<td>$[1/6100]$ [s]</td>
<td>Simulation time step.</td>
</tr>
<tr>
<td>$R_0$</td>
<td>3 [Hz]</td>
<td>Spontaneous firing rate of a neuron in the armed state.</td>
</tr>
<tr>
<td>$R_1$</td>
<td>12 [Hz]</td>
<td>Recovery rate of a neuron.</td>
</tr>
<tr>
<td>$g_{\text{gain}}$</td>
<td>36 [Hz]</td>
<td>Stimulus.</td>
</tr>
<tr>
<td>$R_{ss}$</td>
<td>9.1765 [Hz]</td>
<td>$R_{ss} = (R_0 + g_{\text{gain}})R_1/(g_{\text{gain}} + R_0 + R_1)$</td>
</tr>
<tr>
<td>$|g(t)^2(t)|/R_{ss}$ (Three values: very low, low, and medium-high SNR)</td>
<td>$|g(t)^2|/4, |g(t)|^2/4, |g(t)^2|/4[V^2/\Delta t]$</td>
<td>Signal power due to spontaneous activity of unrelated cells.</td>
</tr>
<tr>
<td>$|g_n(t)^2|$</td>
<td>400 $[(\mu V)^2/\Delta t]$</td>
<td>Signal power due to spontaneous activity of unrelated cells.</td>
</tr>
<tr>
<td>$\sigma_v^2$</td>
<td>$|g_n(t)^2|^2/400 [V^2/\Delta t]$</td>
<td>Power of additive white noise.</td>
</tr>
<tr>
<td>$M_{\text{min}}$</td>
<td>$3630 = 1.5N_s$</td>
<td>Minimal allowed number of simulation steps between adjacent stimuli.</td>
</tr>
<tr>
<td>$M_s$</td>
<td>2420</td>
<td>Stimulus duration.</td>
</tr>
<tr>
<td>$M_d$</td>
<td>1</td>
<td>Allowed detection delay.</td>
</tr>
<tr>
<td>$\alpha$</td>
<td>$1.3327e-08$</td>
<td>Probability of the stimulus onset to occur after minimal duration is over.</td>
</tr>
<tr>
<td>$C_{FA}/C_{MD}$</td>
<td>$(-4000 - 4000)$</td>
<td>Ratio of cost of false alarm to cost of misdetection. Several values were used.</td>
</tr>
</tbody>
</table>
The simulated multi-unit activity also included an additive background noise, which was generated by passing white noise samples through a [300-3000] Hz bandpass filter, and also a very weak white noise component. Three types of artificial data sets were generated, each having a different level of signal to noise ratio (SNR), which is defined here as the ratio between the power of the stimulus responsive neurons to the power of the background noise at steady state:

\[ SNR = \frac{R_{ss} \cdot \|g_x(t)\|^2}{\|g(t)\|^2} = \{0.25, 1, 4\} \quad (5.1) \]

where, \( R_{ss} \) is the steady state firing rate level:

\[ R_{ss} = \frac{R_1(R_0 + g_{gain})}{g_{gain} + R_0 + R_1} \quad (5.2) \]

The very low SNR conditions \((SNR = 0.25)\) simulate situations where most of the power captured by the electrode is due to the background neurons. The medium-low SNR conditions \((SNR = 1)\) simulate situations where only half of the power is due to the stimulus responsive neurons, whereas, the medium high conditions \((SNR = 4)\) stimulate situations where the majority of the signal is due to the stimulus responsive neurons.

The left column of Figure 5.2 shows examples for data generated by the three types of simulations: Figures 5.2a,c,e show simulated multi-unit response to the stimulus when the SNR was \{0.25, 1, 4\}, respectively. In each of these figures, stimuli start and stop times are marked.
by vertical dashed lines. The simulated multi-unit data was generated using Gaussian noise samples, and indeed it looks like noise both during the stimulus time and outside the stimulus time. In the low SNR conditions, (Figure 5.2a) the noise intensity only slightly increases during the stimulus time, and change can be hardly noticed. The change in noise intensity is more visible in the medium-low SNR conditions (Figure 5.2c), and can be clearly seen the high SNR conditions (Figure 5.2e).

The right column of Figure 5.2 shows the averaged response intensity profile in each of the simulated SNR conditions. The dashed lines in Figures 5.2b,d,f were obtained by averaging ten waveforms of responses to the stimulus such that each averaged sample has the same offset with respect to the proceeding stimulus, and then smoothing further by averaging each sample with thirty of its closest neighbours. The solid lines in Figures 5.2b,d,f is the prediction of the model for the smoothed variance, and it was calculated by using the Lyaponov equation for the variance (see equation C.11 in Appendix C). These figures show that the constructed state space acts as expected.
Figure 5.2: Simulated data in three different synthetic SNR conditions. The left column shows the simulated response to stimuli at three different levels of response power. The right column shows the power profile of the response in each simulation.
During the simulations, the optimal detector and the three square-integrate detectors monitored the artificially generated data and produced a new value for their likelihood ratio and pseudo-likelihood ratios every clock cycle. Figures 5.3a-c show the simulated data along with the true likelihood ratio and the three pseudo likelihood ratios in the three different SNR conditions.

(a) SNR=0.25

(b) SNR=1

(c) SNR=4

Figure 5.3: The raw MUA, the true likelihood ratio, and the three pseudo likelihood ratios in three different SNR conditions.
The top signal in Figures 5.3a-c is the artificially generated data. The second signal from the top is the true likelihood ratio as function of the time. The remaining three signals are the pseudo likelihood ratios of the square and integrate detectors, with integration times $N_s/8$, $N_s/4$, $N_s/2$, where the latter is the bottom signal. The vertical dashed lines signify the stimuli presence times. In all three SNR conditions, the true likelihood and the three pseudo likelihood ratios rise in response to the stimulus presence. In medium and high SNR conditions (Figures 5.3b-c), the true likelihood ratio (second signal from the top) barely fluctuates, whereas the three pseudo likelihood ratio exhibit some fluctuations that are very mild for the detector having the longest integration time, and much more intense for the other two integration times. The likelihood ratio of the detector with the longest integration time responds more slowly to the stimulus onset and offset, compared to the other detectors. In very low SNR conditions (Figure 5.3a), all the detectors, including the optimal detector, exhibit very large fluctuations. The square and integrate detector with the longest integration time seems less noisy, even with respect to the optimal detector, but compared to the latter, its pseudo likelihood ratio rises very slowly during the stimulus presence time, so it is difficult to guess the true performance difference between these two detectors from these graphs. Finally, note that in all the three graphs, the true likelihood ratio declines sharply below base line level following the stimulus offset. This occurs because the true likelihood ratio incorporates more effectively the a-priori knowledge regarding the stimulus duration, whereas this knowledge is only indirectly incorporated in the integration time of the three square and integrate detectors.
Figure 5.4: *The detection flag of the optimal detector and the square and integrate detector with $N_{\text{int}} = Ns/4$.***
The detection flag of each one of the detectors was generated by comparing its likelihood ratio to a threshold level. A different threshold level was used for each detector, but it is possible to tag the threshold levels according to the resulting probability of a false alarm, and compare the output of different detectors at the same probability of a false alarm. Figure 5.4 shows examples for the detection flags of the optimal detector (second signal from the top) and the square and integrate detector (bottom signals) at three SNR levels. In all three figures (5.4a-c), the threshold levels where chosen so that the false alarm probability would be $P_{FA} = 0.0035$. In all figures, the output of the optimal detector is asserted more firmly during the stimulus times, which are marked by vertical dashed lines. The performance difference between the two detectors is clearly seen at medium SNR levels (Figure 5.4b). In poor SNR conditions (Figure 5.4a), and in very good SNR conditions (Figure 5.4c) the difference is more subtle because in the former, both detectors perform badly, whereas in the latter, both detectors perform well.

As explained in more detail in Section 2.2, the performance difference at all threshold levels can be summarized by a receiver operation characteristics (ROC) curve, in which the probabilities of true detection of all detectors are sketched as a function of the probability of true detection. Figures 5.5a-c compare the ROC curves of the tested detectors at the three levels of SNR. All the sub-figures focus on the performance at the region of low probability of a false alarm in which the difference between the detectors is substantial. In all sub-figures, the curve of the optimal detector is represented by a solid black line with rectangular markers. The ROC curves of the energy detectors are represented by dashed lines with a different marker for each integration time ($N_{int}$). Note that in all figures, the performance of the optimal detector is superior compared to the energy detectors, and the performance gap is substantial mainly in very low probabilities of a false alarm. In each different SNR conditions, the temporal integration constant of the best energy detector (marked in green with ’x’ marks) was chosen so it would maximize the performance. To demonstrate the optimality of the chosen integration time of the best energy detector, the figure also includes the performances of energy detectors with a shorter integration time (dashed magenta line with circle markers) and a longer integration time (dashed red line with diamond markers). In the low SNR conditions (Figure 5.5a), the peak performance difference occurs close to $P_{FA} = 1e^{-3}$ where the optimal detector reaches a true detection probability of about $P_D \simeq 0.4$, whereas the other detectors have $P_D < 0.1$. The
second best detector (in terms of shear performance) at low SNR conditions is the energy detector with the integration time \( N_{int} = N/8 \). The gap between the performances of the optimal detector to that of the best energy detector closes at about \( P_{FA} = 0.02 \), where \( P_D \approx 0.7 \) for all detectors. In medium SNR conditions (Figures 5.5b), the optimal detector reaches true detection probability of 0.9 (\( P_D = 0.9 \)) at ultra-low probabilities of false alarm (\( P_{FA} < 1e - 6 \)). The second best detector in medium SNR conditions is the energy detector with integration time \( N_{int} = Ns/16 \), and it reaches the true detection probability of the optimal detector only at a false alarm of \( P_{FA} \approx 0.002 \). That is, the best energy detector reaches 90% detection at false alarm probabilities that are three orders higher than those of the optimal detector. At high SNR conditions (Figure 5.5c), the detection probability gap in favor of the optimal detector is as low as 0.07 at very-low probabilities of false alarm of 1e - 6 (that is, \( P_{FA} = 1e - 6 \)), and this gap almost completely disappears at \( P_{FA} = 0.0002 \). The best energy detector in high SNR conditions has an effective integration length of \( N_{int} = 1/128 \cdot Ns \). Note that the duration of integration length of the best energy detector shortens as the SNR increases.
Figure 5.5: ROC curves - The time averaged probability of true detection as a function of the time averaged probability of a false alarm.
5.2 Detection using Real Electrophysiological Data

In this section I report on the detection results obtained using real MUA data acquired in the inferior colliculus and the pontine nucleus of rats. The list of files used, as well as additional data about the stimuli and the anatomical location of the electrode, appear in Appendix D.6. Further details on the surgical procedures for obtaining such MUA recordings are described by Ari Magal in Nossenson et al. (2013).

5.2.1 The Raw Data

In this section we briefly describe the acquired raw multi-unit data. The full data is shown in the supplementary material (Appendix B.1) but here we focus on three representative examples that are shown in Figure 5.6.

The left column of Figure 5.6 shows the full electrode voltage waveform as a function of time, and the right column focuses only on one response to the stimulus from the full session shown to its left. Figure 5.6a shows an example where the raw data maintains an approximately constant envelope with no outliers. This figure is a representative example to a total of seven files out of the twenty files checked. Figure 5.6c shows data which most of the time maintains a constant envelope but contains one intense outlier. Similar outliers existed in twelve out of the twenty files tested. Figure 5.6e shows data which includes a change in magnitude of the envelope, and also an outlier. Such changes in envelope properties occurred in two files only.

The figures in the right column (Figures 5.6b,d,f) show close-ups on the response to the stimulus in each of these representative examples. All of the three waveforms in the right column exhibit fast fluctuations that are similar to densely packed spikes. In all three figures, the amplitude of the fluctuations during the stimulus time is somewhat higher. The three sessions differ from one another in the change in intensity during the stimulus time. The change in intensity is easily noticed in test #10 (second row), and is more subtle in the other two tests.
Figure 5.6: The raw filtered electrode voltage. The right column shows close-ups of raw data of three different tests during the stimulus time, marked by vertical dashed lines. The left column shows the complete waveform.
5.2.2 Raw Data Histogram

The voltage level histograms of the multi-unit data were calculated during the response to the stimulus, and also outside the response to the stimulus using data from twenty stimulus repetitions. All the calculated histograms are shown in Appendix D.2 and two representative examples are shown in Figure 5.7. The x-axis in Figure 5.7 represents voltage level, and the y-axis of the figure represents the empirical probability for the occurrence of that voltage level. Each figure includes a solid line curve and a dashed line curve which represents the histogram during stimulus presence and absence, respectively. The histograms clearly have a near Gaussian shape but not a perfect one. Observe that the variance in the absence of stimuli (dashed line) is smaller than the variance during the stimulus presence. Figure 5.8 shows two demonstrations of the good parametric fit of MUA histogram to Gaussian distribution. Figure 5.8a compares the empirical voltage histogram during stimulus presence (blue line) to a Gaussian probability curve. Figure 5.8b plots the empirical cumulative distribution function (CDF) as a function of the Gaussian model CDF (this presentation is known as a quintile-quintile plot\(^1\)). The figure shows that the value of the model based cumulative distribution function almost equals the value of the empirical cumulative distribution for all values of electrode voltage. Since the expected value almost equals the empirical value the Q-Q plot is a near perfect \(45^\circ\) diagonal line. Similar plots where obtained for all data sets and are shown in Appendix D.2.2.

The histograms support the Gaussianity assumption of the model, but they are not a sufficient proof. A strict mathematical proof requires to show that all linear combinations of the samples are normally distributed, which is an unrealistic task. Thus, for our purpose it is better to show that the detection works better with the Gaussianity assumption, rather than to test the strict and unrealistic mathematical definition.

\(^1\)This curve is generated in three stages. First, the empirical cumulative probability for several MUA voltages is calculated. Then, the model based probabilities at these values are calculated. Finally, the empirical values are sketched as a function of the model based values for the same voltage value.
Figure 5.7: Two representative examples of amplitude histograms in two different sessions, each showing both amplitude distribution during the response to the stimulus (solid line) and in the absence of response to the stimulus (dashed line).

Figure 5.8: Parametric fit of histograms of the data from file #12. (a) Voltage histogram during stimulus presence (blue line) versus Gaussian probability (dark solid line). (b) Quantile-Quantile plot using the same data (see body text for an explanation on this graph).
5.2.3 The Mean Response

The mean response in all of our tests was approximately zero with a possible slight exception on the stimulus onset. Figure 5.9 shows the empirical mean obtained by averaging the responses from fifty stimuli of experiment number 6 (file #6). The averaging was done by summing up the measured voltages at all-time points that had the same offset from the proceeding stimulus, and then dividing by a number of trials. The empirical mean is very similar to the raw data but for its amplitude being lower and closer to zero. Observe that the raw data ranges (most of the time) between $\pm 15\mu V$ whereas the mean response is most of the time within $\pm 2\mu V$. This finding is consistent with our model (Nossenson and Messer, 2011, see also Chapter 3 of this work) which predicts that the mean response will be abolished almost completely by the high pass filter, and only in cases where the cells surrounding the electrode have very little phase offsets could there be some non-zero mean response close to the stimulus edges (stimulus onset and offset).

![Figure 5.9: (a) Mean of File #6 versus (b) Raw Data of File #6](image)

5.2.4 Response Variance

Figure 5.10 depicts the variance of the response (given in unit of $\mu$Watt) as a function of the elapsed time from the stimulus onset (given in seconds). The dashed noisy curve is the empirical variance obtained from the ten stimulus repetitions and additional temporal smoothing.
(integration) of twenty adjacent samples. The solid line is a result of parametric fit of the variance to a population of neurons obeying the model described in Nossenson and Messer (2010, 2011, see also Chapter 3). The vertical dashed lines mark the stimulus onset (left line) and the stimulus offset (right line). The figure shows that prior to the stimulus onset, the variance maintains some constant level. Shortly after the stimulus onset, the variance rises sharply to a peak level and then decays in an exponential manner to a new steady state level, which is higher than the level prior to the stimulus onset, but lower than the peak level. Shortly after the stimulus offset, an opposite process starts and the variance sharply declines to a level which is lower than the level prior to the stimulus onset. The variance then rises in an exponential manner back to its initial level. Observe that the response variance is consistent with the prediction of the model (Nossenson and Messer, 2010, 2011). Figure 5.10 is only a representative example as all other files showed similar response, as shown in Appendix D.4.

![Figure 5.10: Characteristic Variance of the Response](image)

### 5.2.5 Evolution of the Likelihood and Pseudo-Likelihood Ratios

In our tests, we have quantified the detection capabilities of the square and integrate detector and the optimal-model-based-detector using 20 files of raw data multi-unit activity.

Since the performance of the square and integrate detector depends on the integration time $N_{int}$, several values were tested to find the optimal value. The values of $N_{int}$ shown in the
graphs were chosen such that the intermediate value of $N_{int}$ has the best performance, and increasing or decreasing this value only decreases the detection results. The optimal detector and the three square and integrate detectors were required to output a clear cut decision every clock cycle, which is based only on past-to-present data.

To accelerate the tests, we first computed the true likelihood ratio of the optimal detector, and the three pseudo likelihood ratios (of the three square and integrate detectors) throughout each file, and only then did we obtain many different clear cut decisions by applying many different threshold levels on the same likelihood ratio signal.

Figure 5.11: The recorded raw multi-unit data of file #19 (top signal) together with the likelihood ratio of the optimal detector (second from top) and the three pseudo likelihood signals that result from integration times of $N_s/32$, $N_s/8$ and $N_s/2$, respectively. The thick vertical lines border stimuli presence intervals.

Figure 5.11 shows a segment from the recorded raw multi-unit data, (top signal) together with the likelihood ratio of the optimal detector, (second from top) and the three pseudo likelihood signals that result from integration times of $N_s/32$, $N_s/8$ and $N_s/2$, respectively. Stimuli onset and offset times (after adding $t_{offset}$) are marked with thick dashed vertical lines. The figure shows that the likelihood ratio and the pseudo likelihood ratios all rise in response to the stimulus. In the absence of the stimulus, the baseline level of the true likelihood ratio (optimal detector) is almost flat with only tiny fluctuations, whereas the pseudo likelihood ratios are
noisier. Among the three pseudo likelihood ratios, the detector with integration time $N s/2$ has the lowest noise level, and the detector with integration time $N s/32$ has the highest noise level.

A closer look at the average likelihood ratio and the three pseudo likelihoods in response to the stimulus is given in the four sub-figures of Figure 5.12. The upper left sub-figure shows the true likelihood ratios and the remaining sub-figures show pseudo likelihood ratios with the three different integration times. The solid line in each figure represents the empirical mean likelihood obtained from averaging the responses to 60 stimuli, and the dashed line represents the empirical standard deviation of the likelihood/pseudo-likelihoods from the empirical mean. The figures indeed show that in the absence of the stimulus, the true likelihood ratio has very little variance as its standard deviation margin is very close to its mean. All four detectors exhibit a sharp initial response to the stimulus, including the detector with the longest integration time (bottom right figure), which exhibits an only slightly milder rise. This happens because of the strong initial neural response to stimuli. After the sharp initial rise, the true likelihood ratio maintains an approximately constant elevated level with some fluctuations. The three pseudo likelihoods are not flat during the stimulus presence: their initial part has a hill-like shape and only afterwards the response flattens. Note that the width of the hill grows as the integration time $N_{int}$ grows. When the stimulus stops, the true likelihood ratio declines sharply below the baseline level, whereas the decline of the pseudo likelihood ratios is generally slower and it becomes less steep as the integration time grows. The good response of the true likelihood ratio to the stimulus shut down occurs because it more effectively incorporates the a-priori knowledge regarding the stimulus structure. Note that by setting different integration times to the square and integrate detector, we also incorporated some prior knowledge regarding the stimulus duration. Finally, note that in the presence of the stimulus, the standard deviation of the true likelihood ratio grows significantly, whereas the standard deviation of the pseudo-likelihoods is about the same order as in the absence of the stimulus. Recall that the level of standard deviation in the absence of stimuli was already very high for the square and integrate detectors, and was very low in the case of the optimal detector. The sharp rise in the standard deviation of the true likelihood ratio brought it to a level which is comparable to the deviation of the pseudo likelihood ratios.
5.2.6 The Detection Flag (the thresholded likelihood)

After computing the true and pseudo likelihood ratios for each file (as those of Figure 5.11), we obtained decisions regarding the stimulus presence by setting for each likelihood ratio a different threshold level above which the detector asserts its detection flag. The threshold levels for each detector are not the same because the dynamic range of each likelihood ratio is different. Figure 5.13 shows clear cut decisions of the optimal detector and the square and integrate detector at three integration lengths ($N_{int} = Ns/32$, $N_{int} = Ns/8$, $N_{int} = Ns/2$).

The level of the threshold used with each detector was chosen such that it yields the same percentage of false alarms (that is, wrong decisions that occur outside the stimulus on time). In the case of Figure 5.13, the required probability of false alarms was 0.0001. The few cases of false alarms that occurred within the time interval shown in Figure 5.13 are circled. The figure also shows that the detection of stimuli by the optimal detector at 0.0001 false alarm probability is good and solid, whereas the detection of the stimuli by the square and integrate detectors is unstable and its detection flag is asserted only in parts of the stimulus presence time.

In total, we compared each likelihood/pseudo-likelihood ratio, from each file, with 1024 threshold levels that covered all its dynamic range. For each threshold level, $\eta$, we computed
Figure 5.13: Example of detection flags taken from file #19. Hard detection decisions were obtained by thresholding the likelihood and pseudo-likelihood such that \( \langle P_{FA}(\eta) \rangle \approx 0.0001 \). Stimuli zones are marked with dashed vertical lines and the false alarm event are circled. Note that the optimal detector (black solid line) has much better detection at the given false alarm probability.

the probability of a false alarm, \( \langle P_{FA}(\eta) \rangle \), and the probability of true detection, \( \langle P_D(\eta) \rangle \). Recall that \( \langle P_{FA}(\eta) \rangle \) stands for the portion of the time the detection flag was asserted, although it should have stayed off, and \( \langle P_D(\eta) \rangle \) stands for the portion of the time the detection flag was rightfully asserted during stimuli time windows. These plots, which are known as receiver operating characteristic (ROC) curves, are discussed in the next section.

5.2.7 Detection Results (ROC curves)

In this section we quantify the probability of true detection as a function of the probability of a false alarm. Such graphs are known as "Receiver Operating Characteristics" or ROC curves. As we explained in Section 2.2, the meaning of a better probability of detection for a given probability of a false alarm is that the injury rate, \( R_{injury} \), will be smaller and consequently the life span of the subject will be longer. The complete detection results are given in the supplementary (Appendix D.5) and they show that the model based detector obtained better results in 19 out of 20 files tested, and mixed results in the remaining one file. Here we review
in more detail three representative cases.

5.2.7.1 Case 1 - Raw data is free of outliers (7 out of 20 files)

Figure 5.14 shows the empirical probability of true detection \( \langle P_D \rangle \) as a function of the empirical probability of a false alarm \( \langle P_{FA} \rangle \) achieved in recording number 19, which is a representative case for the ROC curves obtained on files containing no outliers (see Section 5.2.1 concerning the raw data). Figure 5.14a shows the ROC at low probabilities of a false alarm, probabilities which are lower than one and a half hundredth of the total time that did not include any stimuli. The figure shows that the probability of the model based detector to correctly detect the stimulus presence \( \langle P_D \rangle \) in such low false alarm probabilities \( \langle P_{FA} \rangle \) is much higher than the detection capabilities of the square and integrate detectors. The optimal detector crosses the 90 percent detection probability with less than five out of one million \( P_{FA} < 5E^{-6} \) false alarm probabilities, whereas out of the square and integrate detectors, the first to cross this detection probability is the detector with the integration time, \( N_{int} = N_s/8 \) which reaches 90% detection probability at a false alarm probability of 0.007. That is, the energy detector reaches 90% detection probability at false alarm values that are 1000 times higher. This means that the model based detector is a good choice when the false alarm probabilities must be very low.

Figure 5.14b (right figure) shows the ROC in both low and high probabilities of a false alarm. The figure shows that the detection probability \( \langle P_D \rangle \) of the square and integrate detector with integration time \( N_{int} = N_s/8 \) is very close to the optimal model based detector starting from a false alarm probability of one hundredth. The square and integrate detector with the highest integration time lags behind and joins the other two square and integrate detectors at a false alarm probability of about two tenths.

5.2.7.2 Case 2 - Raw data includes few outliers (11 out of 20 files)

The effect of outliers

Outliers have a strong harmful effect on the optimal detector. The reason for this is that under
an ideal Gaussian model, signals of such a high amplitude are associated with an almost infinite likelihood ratio in favor of the hypothesis that the stimulus is present. The rare outliers, however, are an exception to the Gaussian model, as they are not a result of strong cumulative activity, but rather isolated events with an overly scaled amplitude. Such events could be due to rare yet very close single cell action potentials, or due to electrical disturbances. Figure 5.15 shows an example of outlier occurrences. The top signal of Figure 5.15 shows the raw data which includes outliers, the second signal is the detection flag of the model based detector, the third signal is the output of the square and integrate detector. The bottom signal indicates the presence of the stimulus. The figure shows that the first outlier leads to a full time assertion of the optimal detection flag, whereas the detection flag of the square and integrate detector is asserted only for a short time after the occurrence of the outlier itself.

Moreover, if the outlier occurs tens of milliseconds before the true stimulus, the detection flag of the optimal detector would treat the outlier as the true detection and would refer to most of the true stimulus as the ceased response to the stimulus. This dual effect is shown in 5.16. The figure shows that when the raw data (top signal) includes an outlier just before the stimulus onset (marked with vertical dashed line), the true likelihood ratio (second from the top) of the optimal detector rises sharply in response to the outlier, crosses the detection threshold (the horizontal line) and remains high long after the very short outlier ends. This threshold crossing
leads to a long period of false alarm (bottom signal). When the true stimulus starts (see dashed vertical line), the likelihood is slightly raised above the detection threshold, but as the strong onset response weakens, the likelihood declines and falls below the threshold, even though the stimulus continues. This leads to a long misdetection period (see second signal from bottom).

Solution to the outlier effect

The harmful effect of the outlier can be easily avoided if the optimal detector is instructed to
ignore any incoming voltage which is larger than a certain multiplicative of the standard deviation of the raw signal during the stimulus time. In our tests, the model based detector forced to zero any sample with an amplitude larger than six times the standard deviation. This solved the harmful effect of the outliers in all the twelve files. Figures 5.17a-b show a ROC curve of the optimal detector and energy detectors before and after outlier removal, respectively. Figure 5.17a shows that before outlier removal, the probability of the square and integrate detectors with \( N_{int} = \{N_s/8, N_s/32\} \) outperform the optimal detector at probabilities of a false alarm lower than 3.5e-3. At higher false alarm probabilities, the performance of the optimal detector and the square and integrate detector with \( N_{int} = N_s/8 \) are the same. This occurs because before the outlier removal, the optimal detector cannot ignore the outliers without mis-detecting the stimulus.

Figure 5.17b shows that after outlier removal the probability of true detection of the optimal detector, combined with outlier removal, is higher than the detection probability of the square and integrate detector for all false alarm probabilities. Again, the performance gap in favor of the optimal detector is substantial mainly at very low probabilities of false alarm. For example, at \( P_{FA} = 1 \times 10^{-3} \) the optimal detector reaches 88% detection, whereas the square and integrate detector reaches only 40% of total stimuli time.

5.2.7.3 Case 3 - Raw data exhibits unstable statistical properties (2 out of 20 files)

Out of the twenty files tested, two files #1 and #13 exhibited noticeable changes in the statistical characteristics of the signal, also in the absence of the stimulus. The reason may be the existence of some other unaccounted for stimulus, or perhaps movement of the electrode. Either way, such changes are expected to affect the detection performances of both detectors, but since the optimal detector is designed to suit more specific statistical characteristics, it is expected to be more sensitive to such statistical changes. The results of file #13, however, appeared similar to those reviewed in the previous section (5.2.7.2), with the optimal detector performing substantially better in low probabilities of a false alarm. However, file #1 exhibited some low noise intensity fluctuations outside stimuli intervals, which did affect the model based detector in a way described by Figure 5.18. The top signal of Figure 5.18 shows the raw
Figure 5.17: *The probability of a stimulus detection as a function of the probability of a false alarm, before and after outlier removal (zero forcing of signals with extremely high amplitude).* (a) Before outlier removal (b) After outlier removal.

data, and the pairs of vertical dashed lines mark the start and stop times of the stimuli. One can observe that prior to stimulus delivery, the multi-unit raw data exhibits increased activity. These fluctuations lead to a rise in the likelihood of the optimal detector (second signal from the top) and also to a rise in and pseudo-likelihood ratio of the energy detector (fourth signal from the top). Consequently, the detection flags of both detectors rise (third and fifth signals from the top) and false alarm events occur (see left arrow in the figure). However, in the case of the model based detector, the fluctuations outside the stimulus interval can also lead to increased misdetection, as shown by the arrow inside the stimulus interval (third signal from the top). Observe that prior to stimulus interval, the optimal detector asserts it detection flag due to the unrelated fluctuations. During stimulus presence, the optimal detector de-asserts the detection flag since it assumes the true stimulus just ceased. The energy detector (the bottom signal) continues to assert its detection flag upon stimulus onset and it de-asserts the flag only later. Thus, intensity fluctuations of an additive unrelated noise can cause the model based detector to misdetect the true stimulus, but they do not have this effect on the square and integrate detector.
Figure 5.18: File #1, Detection of model based and square and integrate detector. Threshold is set such that the false alarm probabilities of both detectors is $P_{FA} = 0.6$.

The ROC curve of file #1 is shown in Figure 5.19. The figure shows that the model based detector outperforms the square and integrate detectors up to false alarm probability of $P_{FA} = 0.6$. Above this false alarm probability, the square and integrate detector with $N_{int} = N_s/2$ has a better detection probability. This is a result of the fluctuations outside stimuli intervals that are discussed above.

Figure 5.19: File #1, Detection of model based and square and integrate detectors.
5.2.7.4 Summary of ROC curves

In 19 out of the 20 files tested, the detection probability of the model based detector was better for every probability of a false alarm. In one file, the square and integrate detector with $N_{int} = N_s/2$ had better detection probabilities starting from a false alarm probability of 0.6.
Chapter 6

Summary and Discussion

Summary of Purpose

The purpose of this research was to develop and evaluate the method which best detects the presence of an external stimulus from observation of the electrical activity of multiple neurons. For this purpose, a model for the observations was developed, and a model based optimal detector was constructed. The performance of the optimal detector was compared with that of the commonly used square and integrate detector, using simulations and also 20 electrophysiological recordings obtained from 8 rats. Although the focus was given to the performances of two artificial external detectors, the underlying aim of the electrophysiological recording procedures performed on the rats was to understand the way the brain itself detects and responds to these stimuli.

6.1 Implications of Results I - The model based detector obtained better results when combined with an outlier remover.

The empirical tests presented here showed that in 19 out of 20 recordings, the model based detector obtained better detection results compared with the square and integrate detector for every probability of a false alarm. The model based detector was shown to be very sensitive
to rare and short signals with extremely high amplitude, and therefore these signals had to be detected and forced to zero to obtain these good detection results. The outlier removal procedure, however, is simple and can be executed online. Despite the easy practical solution to the outliers effect, their influence on the optimal detector demonstrates that the intrinsic imperfection of the central limit theorem, and consequently the imperfection of the Gaussian process models is not negligible when solving real life detection problems. Note that outliers are also likely to occur in other physical phenomena that result from a cumulative effect of many sources.

The performance gap in favor of the optimal detector was particularly substantial in very low probabilities of a false alarm. This makes the model based detector a good option in cases where false alarm probabilities must be very low.

6.2 Implications of Results II - The Square and Integrate Detector is Simple, Robust and Obtains Near Optimal Results

The square and integrate detector also revealed virtues that cannot be underestimated.

First of all, the computational complexity of this detection scheme is much lower than the computational complexity of the optimal detector. Computing of pseudo likelihood ratio requires only linear summation of the squared incoming data, and this sum can be calculated recursively using up to two summation operations in both the digital and analog realization of the square and integrate detector. The optimal detector requires summing exponentials of squared whitened data and then calculating the logarithm of the sum in every clock cycle. The whitening process of the optimal detector (the Kalman filters) requires additional summation and subtraction operations whereby their number is linear in the stimulus length.

The second virtue is its inherent robustness to outliers; the square and integrate detector responded only briefly to outliers, and it did not require a dedicated outlier remover as did the optimal detector. Recall that outliers are an intrinsic imperfection of Gaussian models
which are used to model other scientific phenomena such as seismic vibrations, sonar, radar and more. The last (but not least) virtue of the square and integrate detection scheme is its performance, and we have demonstrated its near optimal performance in moderate to high false alarm probabilities. This detector works particularly well in electrophysiological recordings because the sharp edges of the multi-unit recordings lead to a sharp rise of the pseudo likelihood ratio, even when long integration is employed. Consequently, the square and integrate detector can quickly respond to the stimulus, and at the same time filter out outliers and other random fluctuations.

The virtues listed above reinforce the justification of using this particular method as a stimulus detector based on electrophysiological multi-unit activity observations.

6.3 Implication of Results III - The Model is Instrumental in Predicting Experimental Results.

The superior performance of the model based optimal detector, as well as the three other statistics presented here: the mean, the variance and amplitude histogram of the response, all strengthen the validity of the model which the detector is based on (see Nossenson and Messer (2010, 2011)).

6.4 High Level Perspective of the Experiment

At a high level perspective, our experiments consisted of three major blocks, depicted in Figure 6.1. We channeled an auditory stimulus into the subjects’ ear canal using a loud speaker (see the left side of Figure 6.1). The auditory signal had a zero mean, and an approximate rectangular intensity. The auditory stimulus was processed by the brain and was then acquired using an electrophysiological recording. The acquired signal had an approximate zero mean, but non-zero and non-rectangular intensity (see upper balloon in Figure 6.1). We then attempted to decide whether the auditory signals existed or not using two external detectors: an analytic model based detector, and the square and integrate detector.
The signal model which the optimal detector is based on (Nossenson and Messer, 2010, 2011) explained that the formation of the acquired electrophysiological signal $r(t)$ is a result of three cascaded operations (blocks) that are depicted in Figure 6.2:

1. The first block on the left side of Figure 6.2 describes the functionality of the receptors, the cochlear hair cells. They transform the short term averaged intensity of the auditory signal to neurotransmitter concentration (Nossenson and Messer, 2010, 2011, see also Chapter 3) which is designated as $y(t)$.

2. The second block of the model represents neuron functionality (see the neuron icon in Figure 6.2). The neuron firing rate depends on neurotransmitter concentration at the input. Because each spike of the neuron corresponds to the release of quanta of neurotransmitters from its synaptic vesicles, the firing rate of the neurons is proportional to the current of released neurotransmitters. The neuron transforms the rectangular mean neurotransmitter concentration, $y(t)$, to non-rectangular neurotransmitter current $R_{fire}(t)$, which has an emphasized rising edge. Note that at this point both mean and variance are positive and have a similar shape.

3. The last block (right end of Figure 6.2) describes the measurement process. Due to the nature of the medium separating the electrode from the neurons, and also due to the high
pass filter that exists in the measurement device, the overall voltage that is acquired by the electronic measurement system, \( r(t) \), has almost zero mean, whereas the variance of the signal maintains the shape of the firing rate.

We showed in Section 5.2.4 of this thesis ("Response Variance" section, see also Appendix D.4) that it is possible to recover the firing rate back from the distortion introduced by the measurement technique, by employing squaring and short term temporal averaging, as shown in Figure 6.3. The square and integrate detector then used the same recovered firing rate for detection. It generated a clear cut decision by thresholding a smoothed (integrated) version of the recovered firing rate, as shown at the right end of Figure 6.3.
Figure 6.3: Recovery of the Firing Rate using the Square and Integrate Detector.
6.5 Implications of the Results IV: The modified square and integrate detection scheme

Now, suppose that we had a measurement technique that could see the firing rate directly without losing its non-zero mean due to filtering, and without introducing excessive noise in the absence of high pass filtering (see stage 2 in Figure 6.2). In such a case it would be unnecessary to recover the firing rate using squaring. Instead, we could simply integrate the positive firing rate and threshold the result. Such a detector, which we name the "modified square and integrate" detector, is depicted in Figure 6.4. The top figure (Figure 6.4a) shows the combined block diagram of the signal model and the square and integrate model with two sub-blocks stroked-out. The measurement process is removed from the signal model and the squaring is omitted in the "square and integrate" detector model. The resulting detection scheme, after omitting these two blocks, is shown in Figure 6.4b (the lower figure) and it consists of (1) squaring unit (2) edge-emphasizing unit (3) Integrating unit, and finally (4) thresholding unit. We refer to this detection scheme as the "modified square and integrate" scheme.

Given the robustness of the square and integrate detection scheme against outliers, its good performance in moderate false alarm probabilities and its simplicity, it is only natural to ask whether the neural and neuromuscular tissues make use of it too. We devote the next section to review empirical results from the literature that allegedly support this possibility.
Figure 6.4: The Modified Square and Integrate Detection Scheme. (a) A hypothetic measurement which allows direct sensing of the positive neurotransmitter current coming from neurons concatenated with the capacitor of the square and integrate detector. (b) The resulting “Modified Square and Integrate” detection scheme.
6.6 Evidence for the Modified Square and Integrate Detection Scheme in the Neural Tissue

Binary detection, by definition, is an all-or-none operation. The detector is only allowed to choose between two well distinguished choices. This as opposed to estimation problems in which the output can be continuous and smooth. The simplest example for detection performed by the neural and neuromuscular tissue is therefore a reflex. In healthy subjects, a reflex typically occurs only when the stimulus level is strong and/or the stimulus is aversive, so that a fast protective action is necessary. A reflex should not occur too often without a good reason. In other words, we are looking for a detection scheme that has a high detection probability at low probability of a false alarm. In the former sections we have shown that the square-and-integrate detection scheme is simple and has good performance, which is close to the upper bound of probability of detection for a wide range of probabilities of a false alarm. It is therefore a good candidate for serving as the detection scheme executed by the neural and neuromuscular tissues. Indeed, there is numerous evidence that supports this hypothesis. Because the modified square and integrate detection scheme consists of (1) Squaring, (2) Edge-emphasizing (3) Integrating, and finally (4) Thresholding, I review the empirical evidence for each of these sub-steps separately.

6.6.1 Evidence for Stimulus Squaring in the Auditory and Visual systems

The two main pieces of evidence for stimulus squaring come from measurements of "Firing Rate" in response to steady state stimulation. The firing rate measurement represents the number of action potentials fired by a neuron per time bin, divided by the time bin duration. The firing rate therefore has units of \( [sec]^{-1} \) or \( [Hertz] \). Because each action potential leads to a release of a quanta of neurotransmitters, the firing rate is also proportional to the current of neurotransmitters released by that neuron (quanta of injected neurotransmitters divided by a small time bin is the definition of "current" and it also has units of \( [sec^{-1}] \)).

Muller et al. (1991) reported in their article "Rate-versus-level functions of primary auditory nerve fibres: evidence for square law behaviour of all fibre categories in the guinea pig"
that the firing rate increases in proportion to the intensity of the auditory stimulus (intensity is signal square).

Enroth-Cugell and Lennie (1975) tested the retina of cats and reported: "So, in the dark-adapted eye, ganglion cell discharge closely follows changes in the stimulus luminance\(^1\) and a sustained response is elicited by a sustained stimulus (Fig. 3a)."\(^2\)

### 6.6.2 Evidence for Stimulus Conduction and Edge Emphasizing by Neurons

There is a great number of empirical reports describing the strong response of neurons to the stimulus edges. Interestingly, in many of these reports, the neural response to a sudden appearance of a stimulus pulse has a similar shape, regardless of the modality of the stimuli. Furthermore, responses with similar characteristics are acquired in different anatomical hierarchies, despite their different distances from the stimulus origin.

Figure 3.4 (see Section 3.1.2.2) compares the model based firing rate in response to a stimulus pulse, with real laboratory firing rate measurements taken from various locations that are associated with different modalities. Figure 3.4a is the model based neuron response to the stimulus pulse which was used for the model based detection. Figure 3.4b shows the response of the retina of a cat to a pulse of light, as measured by Enroth-Cugell and Shapley (1973). Figure 3.4c shows the response of the auditory nerve of a mouse to a segment of the auditory stimulus, as measured by Gollisch et al. (2002). Figure 3.4d shows the response of olfactory receptor neurons of a fly (Drosophila), as measured by Nagel and Wilson (2011). Figure 3.4e depicts neural response to salty water placed in the mouth of a rat, as measured by Rosen et al. (2010) from the parabrachial nucleus of the pons (brain stem). Figure 3.4e shows the response of cutaneous temperature sensors of a vampire to increasing steps of heat, as measured by

\(^1\)Note that luminance is a measure for localized light intensity (the square of the electrical field per meter square)

\(^2\)In the experiments of Enroth-Cugell and Lennie (1975), the stimuli were light spots with increasing intensities over a constant dark background, and the measurements were taken only in locations where the light caused an increase in the firing rate. Recent studies by Meister and Berry II (1999), who tested also responses to varying background intensities, suggest that the retina also performs spatial edge emphasizing, in addition to the temporal edge emphasizing which is discussed in this work.
Schäfer, K. and Braun, H.A. and Kürten, L. (1988). Figure 3.4f depicts the neural response to a pulse of pressure in the esophagus, as measured from the sympathetic trunk by Sengupta et al. (1990).

In all these studies (Figures 3.4b-g), the neural response exhibits a sharp rise in response to the stimulus onset, which was then followed by exponential decay towards a new steady state level, which is lower than the response to onset but higher than the spontaneous firing level. When the stimulus is removed, the opposite process takes place and the neural response exhibits sharp decline to a level which is lower than the spontaneous firing rate, which is followed by an exponential rise to the steady state level.

Thus, neurons transport the information regarding the presence of the stimulus in a similar manner which is characterized by edge emphasizing.

Furthermore, responses similar to those of Figure 3.4 (see Section 3.1.2.2) were measured not only in the peripheral nervous system, but also in various locations of the central nervous system, up to the cortex. Figure 3.5 depicts firing responses that were measured in various locations of the auditory system. Figure 3.5a shows the response of an auditory nerve (Taberner and Liberman, 2005). Figure 3.5b shows the response of the cochlear nucleus (Koehler et al., 2011). Figure 3.5c shows the response of the Inferior colliculus (Reches and Gutfreund, 2008). Figure 3.5d depicts the response measured from the medial geniculate body of the thalamus (Hennevin et al., 1995). Finally, Figure 3.5e depicts a response measured from the auditory cortex (Wang et al., 2005). All five responses shown in Figures 3.5a-e are similar, although they were taken in different locations along the auditory path.

6.6.3 Evidence for Temporal Integration of Firing Rate by Glia cells

There is increasing evidence that suggests that certain types of neural tissue cells, classified as glia cells\(^3\), perform both spatial integration (Araque et al., 2001) and temporal integration of neural activity (Pape et al., 2004). The spatial integration hypothesis stems from the fact that each glia cell physically touches many neurons (this many-to-one topology is another

\(^3\)Glia are also classified to subtypes. Most evidence regarding integration performed by glia concern astrocytes and schwann cells.
analogy to our multi-unit detection problem). We review the evidence for temporal integration in the next paragraphs. Note that most of the glia related evidence are not based on electrical measurements, since electrical action potentials are attributed solely to neurons (see e.g. Allen and Barres, 2009).

Hertz et al. (1978) quantified glutamate uptake rate of glia cells using in-vitro experiments. Figure 6.5 which is taken from Hertz et al. (1978) depicts glia’s glutamate removal rate as a function of the instantaneous concentration of glutamate. The figure shows that, up to a certain glutamate concentration, the glia glutamate uptake rate is linear with glutamate concentration. Above a certain threshold point of glutamate concentration, the glutamate disposal rate has also close-to-linear relation to glutamate concentration, but the glutamate-concentration-to-rate multiplier is much smaller. This can be stated by the following formula:

\[ \dot{y}(t) = \begin{cases} 
-a_1 \cdot y & y < \text{threshold} \\
-a_2 \cdot y - c_2 & y > \text{threshold}, |a_2| \ll |a_1| 
\end{cases} \] (6.1)

Figure 6.5: Glutamate uptake rate as a function of glutamate concentration as reported by Hertz et al. (1978).

Where \( y(t) \) stands for glutamate concentration.

Note that in the first (top) mode of equation (6.1), the lossy integration performed by the glia cells is exactly the same as the equation of the analog integrator of the Weber and Buchwald

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4More recent studies (see Drejer and Larsson, 1982; Danbolt, 2001, and references therein) support the findings of Hertz that glia are the major glutamate removers.
(1965) detector (see equation (2.23)), whereas the second (bottom) mode is very similar, but the leak rate, $a_2$, is much smaller and there is an additional constant leak term, $c_2$, which is independent of neurotransmitter concentration. The first (the top) linear mode of equation (6.1), which applies when $y$ is below threshold concentration, corresponds to short time integration, i.e. short memory (equivalent to a small $N_{int}$ of the square and integrate detector), whereas the second linear mode (above threshold concentration) corresponds to long time integration, i.e. long memory (equivalent to a large $N_{int}$).

There are also two other pieces of indirect evidence obtained in-vivo supporting the existence of temporal integration that is executed in the neural tissue. Electrical evidence for integration results from the secondary effect of neuron membrane currents (sub threshold and action potentials), which are expected to occur due to increases in concentration of excitatory neurotransmitters. Figure 6.6b, taken from (Bullock, 1997), shows raw EEG recordings from an electrode located at the top of a human scalp (also known as "Cz electrode") taken in response to a series of auditory stimuli (clicks). Each row in Figure 6.6b shows the raw recorded voltage in response to a different number of clicks. It is evident that the raw EEG voltage in response to each click (without high pass filtering and without squaring) is very similar to the pseudo likelihood ratio of the square and integrate detector, which is shown in Figure 6.6a. Note that in the right figure (Figure 6.6b), no high pass filtering was performed and no squaring was made to recover the firing rate. Nevertheless, a clear response which looks very similar to the integrated firing rate appears. Therefore, this result supports the existence of some integration mechanism in the neural tissue, and it also supports the prediction of our model regarding the existence of non-zero mean in unfiltered measurements.

Other indirect evidence that supports the existence of a temporal integration of the stimulus in the neural tissue are blood-oxygenation-level-dependent (BOLD) fMRI measurements\(^5\). Figure 6.7 shows imaging of blood oxygen levels reported by Logothetis (2003) that seems like a smoothed (i.e. integrated) version of the firing rate. This means that there is some control mechanism in the neural tissue that tracks the integrated firing rate. Since astrocytes (a subtype

\(^5\) fMRI stands for functional magnetic resonance imaging. As implied by their name, BOLD-fMRI reflect oxygen level throughout the tissue. The exact relation between this imaging method and oxygen blood is not 1:1 and depends also on vascular effects (Davis et al., 1998). The rise in the BOLD-fMRI signal in response to a rise in oxygen level was proved and quantified by Davis et al. (1998).
of glia) are known to be physically connected to capillaries (which deliver oxygen) they were suspected to be associated with the temporal integration depicted in the BOLD fMRI measurements (Haydon and Carmignoto, 2006; Magistretti, 2006). Because the BOLD fMRI technique does not allow to separate the contribution of glia from the contributions of neurons and blood vessels (Davis et al., 1998; Kemp, 2000), an additional technique named $^{13}C$ Nuclear Magnetic Resonance (NMR) was used to quantify the contribution of the various factors (Sibson et al., 1998; Gruetter et al., 2001; Hyder et al., 2006; Magistretti, 2009). The findings of the $^{13}C$ NMR measurements were consistent with a chemical model that connects Glutamate uptake rate to oxygen consumption (Sibson et al., 1998; Gruetter et al., 2001; Hyder et al., 2006; Magistretti, 2009). That is, they supported the assumption that glia execute a leaky integration of glutamate (Hertz et al., 1978, see also equation (6.1)), and that this integration is reflected in the oxygen consumption.
Figure 6.7: Blood Oxygen Level Dependent (BOLD) imaging as reported by Logothetis (2003). The upper figure shows that blood oxygen level tracks the envelope of the firing rate. This supports the existence of some integration mechanism. The lower figure is the empirical firing rate.

6.6.4 Evidence for Threshold Mechanism in Glia Cells

Glia cells (mainly the subtypes Astrocytes and Schwann cells) exhibit threshold behaviour in response to large concentrations of neurotransmitters. We already showed evidence for glia threshold behaviour in Figure 6.5 (taken from Hertz et al. (1978)). Observe that equation (6.1) exhibits two mode of behaviours, depending on glutamate concentrations. The threshold for a change in glutamate uptake rate occurs at glutamate concentrations of $200\mu M$.

There is also evidence based on calcium measurements that support the existence of threshold in glia (Cornell-Bell et al., 1990; Jahromi et al., 1992; Verkhratsky et al., 1998).

Figure 6.8 taken from Cornell-Bell et al. (1990) shows the empirical probability of glia cells to produce a calcium wave in response to glutamate concentration. The figure shows clear threshold behaviour of calcium response by glia cells with respect to glutamate concentration. Note that the threshold depicted in this measurement method occurs at glutamate concentrations of about $1\mu M$.

Another evidence for a threshold mechanism in the neural tissue, which is considerably different from a single spike threshold, appears in many in-vivo electrophysiological studies that involved stimuli with increasing intensities. As representative examples, I list here the studies
Figure 6.8: Percentage of cells showing Calcium activity as function of Glutamate concentration taken from Cornell-Bell et al. (1990).

by Ebert and Koch (1997), Frot et al. (2007), and Perlman (2007). These studies demonstrate the electrophysiological response considerably changes after crossing a certain level of stimulus intensity. Interestingly, after crossing the threshold intensity, the electrophysiological response waveform includes a negative potential component that has an opposite polarity comparing to neural spiking response, which suggests that non-neuron cells may be involved.

Figure 6.9a shows the threshold behaviour of the negative wave as measured in retinal studies by Perlman (2007), and Figure 6.9b shows a closer look on the negative electrical wave from the same study. Figures 6.9a-c show similar responses that were obtained by Ebert and Koch (1997) in a study that examined leg reflex movement in rats, in response to a loud auditory stimulus (startle response). The reflex movement appeared only when stimuli intensities were above 110 dB and they were preceded by a sharp negative EEG wave similar to the one reported by Perlman (2007). Similar waveforms appear also in the spinal cord during reflexes (Koketsu, 1956; Willis Jr, 1999). The latencies of the responses is typically several tens of milliseconds, and the total duration of the negative peak followed by the positive peak is a few hundred milliseconds, which match the delay and duration of a reflex.
Figure 6.9: Evidence for a threshold response in the neural tissue by Ebert and Koch (1997) and Perlman (2007). (a,c) A negative wave appears only above a certain intensity of stimulus. (b,d) A closer look on the negative wave.
6.6.5 Evidence for Threshold Behaviour in Muscles

In this section I shortly note that a threshold function, which is a necessary building block for executing a detection task, also exists in muscle cells. The purpose of this section is to show that a prolonged supra-threshold activity, that lasts a few hundreds of milliseconds exists in cells other than neurons, and that this threshold is linked to an intense stimulus and also to a large dosage of neurotransmitters. As opposed to the case of glia cells, which seem to be linked to an internal threshold (a logical threshold), muscle threshold activity (or all-or-none activity) is observed in reflex responses, even without a special instrumentation. Figure 6.10a taken from Light et al. (2010), shows electrophysiological recordings during blinking. The electrophysiological signal is quiescent until the blinking starts, then a very sharp rise in the electrical potential appears. Figure 6.10b from Carelli et al. (2001) shows a similar sharp (threshold like) response to the stimulus acquired in a patient with myoclonus symptoms (involuntary jerking of a muscle). Figure 6.10c shows forced measurement during reflex response (Liu et al. (2011)). The figure has a similar shape to the electrophysiological measurements (Figures 6.10a,b,d), although the measured quantity is mechanical force and not an electrical potential. Finally, Figure 6.10d, taken from Stern and Bicker (2008), shows an electrophysiological signal similar to the one depicted in Figures 6.10a-b, only the stimulus that caused this response was an artificially delivered pharmacological neurotransmitter (ACh). Note that in the previous three examples, the stimulus was natural and not pharmacological, and yet the response is similar.
Figure 6.10: Evidence for Threshold Response in Muscles. (a) Electrical potential measured near the eyes during eye blink ("SEOG") from Light et al. (2010). (b) Electrical activity during myoclonic jerk (Carelli et al., 2001). (c) Normalized muscle torque during reflex response of a post-stroke patient (Liu et al., 2011). (d) Muscle electrical response to application of Acetylcholine from Stern and Bicker (2008).
6.7 Summary of the Hypothesized Neural Detection Scheme

Figure 6.11 summarizes the hypothesized biological components of the modified square and integrate detection scheme. The blocks in the middle row associate block functionality with their histological classification. The signals at the upper row represent only the dynamics of neurotransmitter concentration, which are relevant for the detection task itself. These signals are similar to the signals of the square and integrate detector. The signals at the bottom represent the electrophysiological measurements that are associated with each step. The first functional block, the receptors together with bipolar cells, convert the external stimulus intensity (stimulus square) to neurotransmitter concentration. The next functional block consists of a bundle of neurons (i.e. nerves and neural tracts). They emphasize stimuli edges and propagate the signal to the next compound that consists of intercellular space surrounded by glia cells and membranes of other neurons. The glia-intercellular-space compound (the second block in Figure 6.11) performs lossy integration of neurotransmitters. The neurotransmitter disposal rate of this lossy integrator has a piecewise linear dependence in neurotransmitter concentration. The disposal-rate-concentration-multiplier is high up to a certain neurotransmitter concentration level, and it is much lower above this threshold level. I associate this threshold with a logical decision that physically means switching. The last functional block (the most right block in Figure 6.11) consists of muscle cells. These cells exhibit all or no activity in response to a certain quantity of neurotransmitters (in this paper we reviewed examples concerning acetylcholine). Note that although the electrophysiological signals (the signals at the bottom row of Figure 6.11) are often similar to the functional signal (top signals: signal power/neurotransmitter concentration/muscle force), there are some stages in which the electrical observation is different from the functional purpose of the corresponding step. In particular, we suspect that glia (the capacitor in our scheme) threshold crossing has a completely different functional operation compared to the radiated electrophysiological signal, and that the latter might only be a side effect of the change in neurotransmitter removal rate.
Figure 6.11: The hypothesized neural detection scheme. The middle row associates the modified square and integrate detection scheme with the hypothesized biological counterparts. The top row shows the functional processing made on neurotransmitter concentration. The bottom row shows the electrophysiological measurements associated with each step.
Table 6.1 summarizes the evidence for the modified energy detection mechanism in the neural tissue. The first row lists the evidence for stimulus squaring by receptor cells. The second row lists the evidence for signal transduction and edge emphasizing by neurons. The third row lists the evidence for the presence of temporal integration in the neural tissue, and the evidence that links glia to this operation. The fourth row lists the evidence for logical threshold behaviour which is also attributed to glia cells. The fifth row lists the evidence for physical threshold in muscles.

### Table 6.1: Evidence for the Modified Energy Detection Scheme in the Neural Tissue

<table>
<thead>
<tr>
<th>#</th>
<th>Operation</th>
<th>Ref.</th>
<th>Description of the evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Stimulus Squaring by Sensory Receptors</td>
<td>Muller et al. (1991)</td>
<td>The steady state firing rate of the auditory nerve is proportional to signal intensity (signal square).</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Enroth-Cugell and Lennie (1975)</td>
<td>The steady state firing rate of retinal ganglion cells in a dark environment is proportional to signal intensity (signal square).</td>
</tr>
<tr>
<td>2</td>
<td>Signal Transduction and Edge Emphasizing by Neurons</td>
<td>Taberner and Liberman (2005), Wang et al. (2005) and others⁶</td>
<td>The references show that stimuli with a rectangular intensity profile result in a firing rate curve with emphasized edges (similar to Fig. 5.10).</td>
</tr>
</tbody>
</table>
| 3 | Lossy Temporal Summation of Neurotransmitters by Glia Cells (astrocytes in particular) | Hertz et al. (1978) | Hertz showed that glia culture performs lossy accumulation of glutamate that obey the following equation:  

\[
\dot{y}(t) = \begin{cases} 
-a_1 \cdot y & y < \text{threshold} \\
-a_2 \cdot y - c_2 & y > \text{threshold}, |a_2| \ll |a_1|
\end{cases}
\]  

(6.2)  

Note the resemblance to equation (2.23) describing the dynamics of the energy test statistic. |

---

⁶See e.g. Ingham and McAlpine (2005), Reches and Gutfreund (2008), Creutzfeldt et al. (1980), Di Lorenzo and Schwartzbaum (1982).
<table>
<thead>
<tr>
<th>Logothetis (2003). Davis et al. (1998); Sibson et al. (1998); Grueter et al. (2001); Hayden and Carmignoto (2006); Hyder et al. (2006); Magistretti (2009)</th>
<th>Blood oxygen level measurements in the vicinity of a recording electrode show that oxygen level tracks the temporal summation of the firing rate over some period of time. This suggests the existence of a mechanism that accumulates substances over time. The physiological connection between blood vessels and glia suggest that they are involved in the temporal integration. Metabolic measurements support the relations between glutamate uptake rate (see the begging of third row of this table), oxygen flow, and control blood over the vessel which are all linked by modelers to glia.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bullock (1997)</td>
<td>EEG recording from the top of the scalp (&quot;Cz electrode&quot;) in response to an auditory pulse has the same shape of the energy test statistic of the Weber and Buchwald (1965) detector. Note that the EEG signal appears without squaring because of the non-conducting surrounding and the absence of a high pass filter.</td>
</tr>
<tr>
<td>Threshold Behaviour of Glia</td>
<td>Neurotransmitter removal rate changes abruptly to a much slower rate when reaching a certain level of neurotransmitter concentration.</td>
</tr>
<tr>
<td>Hertz et al. (1978)</td>
<td>Adding neurotransmitters to Glia cultures leads to an all-or-no activity of calcium waves. The calcium activity starts only after crossing a certain threshold level of neurotransmitter concentration.</td>
</tr>
<tr>
<td>Cornell-Bell et al. (1990). Jahromi et al. (1992); Verkhhratsky et al. (1998)</td>
<td></td>
</tr>
</tbody>
</table>
Intense stimuli result in an electrical response in the brain which is not seen in weaker or non-aversive stimuli. This electrical response has an opposite polarity compared to neural response, which suggests that non-neuron cells may be involved.

Muscle show no-activity, or full-power-activity in response to pouring acetylcholine Stern and Bicker (2008). The measured electrical response is identical to the electrical and force measurements during reflex responses with an external, non-pharmacological stimuli (Light et al., 2010; Carelli et al., 2001; Liu et al., 2011).
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Appendices
Appendix A

State Space Matrices

1. \( \mathbf{A} \) is a matrix of size \((Q_{x,max} + Q_{n,max}) \times (Q_{x,max} + Q_{n,max})\) which consists of two sub-matrices:

\[
\mathbf{A} = \begin{bmatrix} \mathbf{A}_x & 0 \\ 0 & \mathbf{A}_n \end{bmatrix}
\]  

(A.1)

\[
\mathbf{A}_x = \begin{bmatrix} -a_{x,1} & 1 & 0 & \cdots & 0 \\ -a_{x,2} & 0 & 1 & \cdots & 0 \\ \vdots & \vdots & \ddots & \ddots & \vdots \\ -a_{[Q_{x,max}-1]} & 0 & 0 & \cdots & 1 \\ -a_{Q_{x,max}} & 0 & 0 & \cdots & 0 \end{bmatrix} \\
\mathbf{A}_n = \begin{bmatrix} -a_{n,1} & 1 & 0 & \cdots & 0 \\ -a_{n,2} & 0 & 1 & \cdots & 0 \\ \vdots & \vdots & \ddots & \ddots & \vdots \\ -a_{[Q_{n,max}-1]} & 0 & 0 & \cdots & 1 \\ -a_{Q_{n,max}} & 0 & 0 & \cdots & 0 \end{bmatrix}
\]  

(A.2)

See Table A.1 for possible values of \( a_k \).

2. \( \mathbf{B}_k \) is a time dependent matrix of size \((Q_{x,max} + Q_{n,max}) \times 2\) which consists of two column vectors:

\[
\mathbf{B}_k = \begin{bmatrix} \mathbf{B}_{x,k} \\ 0_{Q_{x,max} \times 1} \\ 0_{Q_{n,max} \times 1} \end{bmatrix}
\]  

(A.3)

\[
\mathbf{B}_{x,k} = \sqrt{R_{\text{fire}}(k\Delta_t) \cdot [b_{x,1} - a_{x,1}b_{x,0}, b_{x,2} - a_{x,2}b_{x,0}, \cdots, b_{x,Q_{x,max}} - a_{x,Q_{x,max}}b_{x,0}]^T}
\]  

(A.4)

\[
\mathbf{B}_n = [b_{n,1} - a_{n,1}b_{n,0}, b_{n,2} - a_{n,1}b_{n,0}, \cdots, b_{n,Q_{n,max}} - a_{n,Q_{n,max}}b_{n,0}]^T
\]  

(A.5)

See Table A.1 for possible values of \( b_k \).
3. \( C \) is a constant vector of size \( 1 \times (Q_{x,max} + Q_{n,max}) \):

\[
C = \begin{bmatrix}
1 & 0 & \cdots & 0 & 1 & 0 & \cdots & 0 \\
1 \times Q_{x,max} & & & & 1 \times Q_{n,max}
\end{bmatrix}
\]  

(A.6)

4. \( D_k \) is the following \( 3 \times 1 \) vector:

\[
D_k = \begin{bmatrix}
b_{x,0} \sqrt{R[k \Delta t]} & b_{n,0} \sigma_v
\end{bmatrix}
\]  

(A.7)

| Table A.1: Digital implementation of \( g(t) \) |
|---|---|---|---|---|---|---|
| m | 0 | 1 | 2 | 3 | 4 | 5 | 6 |
| a_m | 1.0000 | −4.1519 | 7.2159 | −6.7732 | 3.6776 | −1.1235 | 0.1562 |
| b_m | −0.1329 | 0.3526 | −0.2523 | −0.0530 | 0.1161 | −0.0300 | −0.0006 |

\[
G(z) = \frac{\sum_{m=0}^{Q_a} b_m z^m}{\sum_{m=0}^{Q_b} a_m z^m}, \quad f_s = 12,000[Hz], \quad Q_a = 6, \quad Q_b = 6.
\]

*Magnitude of the Fourier transform of a spike shape taken from Milstein and Koch (2008) and then high pass filtered above 300[Hz].
Appendix B

Calculation of the Posterior Probabilities by the Detector.

In this section we explain the recursive calculation of the probabilities \( P_{\text{onset}}(t - t_{\text{last onset}} = k\Delta_t | r^t_0) \) and \( P_{\text{onset}}(t - t_{\text{last onset}} \geq T_{\text{min}} | r^t_0) \). Throughout the section we use the following short notations:

\[
\alpha \equiv \frac{\Delta_t}{T_{\text{avg}} - T_{\text{min}}} \quad (B.1)
\]
\[
M_{\text{min}} \equiv \frac{T_{\text{min}}}{\Delta_t} \quad (B.2)
\]

and,

\[
\exp\{q_k(t)\} \equiv Pr(r(t) | t - t_{\text{last onset}} = k\Delta_t, r^{t-\Delta_t}_0) \quad (B.3)
\]

The parameter \( \alpha \) is the reciprocal of the mean number of clock cycles that are added to the minimal inter trial intervals \( (T_{\text{min}}) \). The parameter \( M_{\text{min}} \) is the number of clock cycles within the period \( T_{\text{min}} \). The quantity \( q_k(t) \) stands for the logarithm of the probability that the current observation fits the hypothesis that a stimulus occurred \( k\Delta_t \) seconds ago. The method for calculating \( q_k(t) \) was described by (Schweppe, 1965), and is summarized in Appendix C. In this section, assume that \( q_k(t) \) is known.

We now show that the probabilities \( P_{\text{onset}}(t - t_{\text{last onset}} = k\Delta_t | r^t_0) \) and \( P_{\text{onset}}(t - t_{\text{last onset}} \geq T_{\text{min}} | r^t_0) \) can be expressed using their values at the previous sampling moment and using \( q_k(t) \), \( M_{\text{min}} \) and \( \alpha \):
Claim 1  The probability that an onset occurred in the most recent observation is:

\[ P_{\text{onset}}(t - t_{\text{onset}} = \Delta_t | r_0^t) = \frac{Pr(r_0^{t-\Delta})}{Pr(r_0^t)} \cdot \left[ \begin{array}{c}
Pr(t - t_{\text{last onset}} \geq T_{\min} | r_0^{t-\Delta}) \cdot \exp\{q_0(t)\} \cdot \alpha 
\end{array} \right] \]  

(B.4)

\[ P_{\text{onset}}(t - t_{\text{last onset}} \geq T_{\min} | r_0^t) = \Pr(r_t - \Delta t_0) \cdot \Pr(r_t_0) \cdot \exp\{\exp(q_0(t))\} \cdot \alpha \]  

Proof: The update rule for \( Pr(t - t_{\text{onset}} = \Delta_t | r_0^t) \) originates from the fact that an onset can take place now only if the last onset occurred exactly \( T_{\min} \) ago, or more than \( T_{\min} \) ago. Thus, the probability that an onset is currently observed can be written as follows:

\[ P_{\text{onset}}(t_{\text{last onset}} - t = \Delta_t | r_0^t) = \frac{1}{Pr(r_0^t)} \left[ \begin{array}{c}
Pr(r_0^{t-\Delta_t} | t - t_{\text{last onset}} \geq T_{\min}) \cdot P(t - \Delta_t - t_{\text{last onset}} \geq T_{\min}) 
\end{array} \right] \cdot 
\[ P(t = T - \Delta_t, r_0^t) \cdot \alpha \]  

(B.5)

That is:

\[ P_{\text{onset}}(t - t_{\text{last onset}} = 1 \cdot \Delta_t | r_0^t) = \frac{Pr(r_0^{t-\Delta_t})}{Pr(r_0^t)} P(t - t_{\text{last onset}} \geq T_{\min} | r_0^{t-\Delta_t}) \cdot \alpha \cdot \exp\{q_0(t)\} \]  

(B.6)

Claim 2  The probability that an onset occurred more than \( T_{\min} \) ago is:

\[ P_{\text{onset}}(t - t_{\text{last onset}} \geq T_{\min} | r_0^t) = \frac{Pr(r_0^{t-\Delta})}{Pr(r_0^t)} \cdot \left[ \begin{array}{c}
(1 - \alpha) \cdot P_{\text{onset}}(t - t_{\text{last onset}} \geq T_{\min} | r_0^{t-\Delta}) +
\end{array} \right] 
\[ P(t - \Delta_t - t_{\text{last onset}} = T_{\min} - \Delta_t | r_0^{t-\Delta_t}) \]  

\[ \cdot \exp(q_{M_{\min}} [t]) \]  

(B.7)
Proof: The update rule for $Pr(t - t_{last\ onset} \geq T_{min} \mid r_0^t)$ originates from the fact that an onset occurred $T_{min}$ ago, or before, if no new onset is taking place now, and the last onset occurred either exactly $T_{min}$ ago or before (more than $T_{min}$ ago). Thus, the probability $Pr(t - t_{last\ onset} \geq T_{min} \mid r_0^t)$ can be written as the sum of two mutually exclusive events:

\[
P_{onset}(t - t_{last\ onset} \geq T_{min} \mid r_0^t) = \frac{1}{P(r_0^t)} \left[ (1 - \alpha) \cdot Pr(r_0^{t - \Delta t} \mid t - t_{last\ onset} \geq T_{min}) \cdot Pr(t - t_{last\ onset} \geq T_{min}) + (1 - \alpha) \cdot P_{onset}(t - t_{last\ onset} \geq T_{min} \mid r_0^{t - \Delta t}) \cdot Pr(r_0^{t - \Delta t}) \right] \cdot P_{onset}(t - t_{last\ onset} = T_{min} \mid r_0^{t - \Delta t}) \cdot Pr(r_0^{t - \Delta t}) \cdot \exp\{q_{M_{min}}(t)\}.
\]

That is,

\[
P_{onset}(t - t_{last\ onset} \geq T_{min} \mid r_0^t) = \frac{Pr(r_0^{t - \Delta t})}{P(r_0^t)} \left[ (1 - \alpha) \cdot P_{onset}(t - t_{last\ onset} \geq T_{min} \mid r_0^{t - \Delta t}) + P_{onset}(t - t_{last\ onset} = T_{min} \mid r_0^{t - \Delta t}) \right] \cdot \exp\{q_{M_{min}}(t)\}.
\]

Claim 3 The probability that an onset occurred $k\Delta_t$ seconds ago with $\Delta_t < k\Delta_t < T_{min}$ is:

\[
P_{onset}(t - t_{last\ onset} = k\Delta_t \mid r_0^t) = \frac{Pr(r_0^{t - \Delta})}{Pr(r_0^t)} \left[ (k - 1) \cdot \Delta_t \cdot r_0^{t - \Delta t} \cdot \exp\{q_{k}(t)\} \right]
\]

Proof: The probability that an onset occurred $t'$ [sec] ago where $\Delta_t \leq t' \leq T_{min} - \Delta_t$, depends on how well the observations that have been received up to now fit these hypotheses. These
probabilities are calculated as follows:

\[
P(t - t_{last\,onset} = t' \mid r_0^t) = \frac{1}{P(r_0^t)} \\
\frac{Pr(r_0^{t-\Delta t} \mid t_{last\,onset} = t - t') \cdot P(t_{last\,onset} = t - t') \cdot Pr(r_0^{t-\Delta t})}{P(t - \Delta t - t_{last\,onset} = t' - \Delta t \mid r_0^{t-\Delta t}) \cdot Pr(r_0^{t-\Delta t})} \exp\{q_k(t)\} \tag{B.11}
\]

That is,

\[
P(t - t_{last\,onset} = t' \mid r_0^t) = \frac{Pr(r_0^{t-\Delta t})}{Pr(r_0^t)} \cdot P(t - \Delta t - t_{last\,onset} = t' - \Delta t \mid r_0^{t-\Delta t}) \cdot \exp\{q_k(t)\} \tag{B.12}
\]

\[\square\]

**Remark 1** Since all the probabilities above are multiplied by the same factor, \(\frac{Pr(r_0^{t-\Delta t})}{Pr(r_0^t)}\), the latter is immaterial for the decision rule.

**Remark 2** By dividing the expressions in (B.5) and (B.10) by (B.7), which is the expression for \(Pr(t - t_{last\,onset} \geq T_{min} \mid r_0^t)\), and then taking the logarithm on both sides we obtain the register update rules.
Appendix C

Calculation of the Conditional Probabilities, $q_k(t)$.

In this section we summarize the method developed by Schweppe (1965) for calculating the logarithm of the conditional probability:

$$ q_k[j \Delta t] \equiv \log \left\{ Pr(r[j \Delta t] \mid t - t_{\text{last onset}} = k \Delta t, r_0^{t-\Delta t}) \right\} $$

According to Schweppe (1965), the formula for calculating $q_k(t)$ is as follows:

$$ q_k[j \Delta t] = \frac{1}{2} \left[ - \log \{2\pi \left| \Sigma_{r,k|k-1}[j \Delta t] \right| \} ight. $$

$$ \left. - (\hat{r}_{k|k-1}[j \Delta t] - r[j \Delta t])^T \cdot \Sigma_{r,k|k-1}^{-1}[j \Delta t] \cdot (\hat{r}_{k|k-1}[j \Delta t] - r[j \Delta t]) \right] $$

(C.1)

where, $r[j \Delta t]$ is the received electrode voltage at time $t = j \Delta t$, and the quantities $\Sigma_{r,k|k-1}[j \Delta t]$ and $\hat{r}_{k|k-1}[j \Delta t]$ are obtained using the Kalman algorithm:

1. Kalman predict step:

In this step we assume that the estimated state, $\hat{z}_{k|k}[j \Delta t]$ and the covariance of the state estimation error, $\Sigma_{z,k|k}[j \Delta t]$ are known, and we use them to generate a prediction for the next state as follows:

$$ \hat{z}_{k+1|k}[j \Delta t] = A \cdot \hat{z}_{k|k}[j \Delta t] $$

(C.2)

$$ \hat{r}_{k+1|k}[j \Delta t] = C \cdot \hat{z}_{k+1|k}[j \Delta t] $$

(C.3)

$$ \Sigma_{z,k+1|k}[j \Delta t] = A \cdot \Sigma_{z,k|k}[j \Delta t] \cdot A^T + B_k \cdot B_k^T $$

(C.4)

$$ \Sigma_{r,k+1|k}[j \Delta t] = C \cdot \Sigma_{z,k+1|k}[j \Delta t] \cdot C^T + D_{k+1} \cdot D_{k+1}^T $$

(C.5)
2. Kalman correct step: In this step we correct our state prediction using the newly received sample, \( r(t) \). We also update the covariance matrix of the state estimation error:

\[
\dot{\hat{z}}_{k|k}[j\Delta t] = \hat{z}_{k|k-1}[j\Delta t] + K_k \cdot (r[j\Delta t] - \mu_{r,k} - \hat{r}_{k|k-1}[j\Delta t]) \tag{C.6}
\]

\[
\Sigma_{z,k|k}[j\Delta t] = \Sigma_{z,k|k-1}[j\Delta t] - K_k[j\Delta t] \cdot C \cdot \Sigma_{z,k|k-1}[j\Delta t] \tag{C.7}
\]

where \( K_k \) is defined as follows:

\[
K_k[j\Delta t] = \Sigma_{z,k|k-1}[j\Delta t] \cdot C^T \cdot (C \cdot \Sigma_{z,k|k-1}[j\Delta t] \cdot C^T + D_k \cdot D_k^T)^{-1} \tag{C.8}
\]

Note that the matrices \( \Sigma_{z,k|k}[j\Delta t] \) are deterministic quantities that settle to stable values after some transient period. The steady state value of the matrix \( \Sigma_{z,M_{min}|M_{min}-1} \) is found by solving the discrete algebraic Riccati equation:

\[
\Sigma_{z,M_{min}|M_{min}-1} = A \left[ I - \Sigma_{z,M_{min}|M_{min}-1} C^T [C \Sigma_{z,M_{min}|M_{min}-1} C^T + D_{M_{min}}^T D_{M_{min}}]^{-1} \right] \cdot C \Sigma_{z,M_{min}|M_{min}-1} A^T + B_{M_{min}} \cdot B_{M_{min}}^T \tag{C.9}
\]

The other steady state values of the matrices, \( \Sigma_{z,k|k-1} \) with \( k = 1, 2, ..M_{min}-1 \) are calculated in a recursive manner using equation (C.4) where (C.9) is used as the initial value of the recursion.

The state space formulation also allows the discovery of the variance of the acquired signal. The value of \( \Sigma_z[k] \) is determined by solving the following equation:

\[
\Sigma_z[k+1] = A \cdot \Sigma_z[k] \cdot A^T + B_k \cdot B_k \tag{C.10}
\]

This equation results from taking the expectation of the square of equation (3.76).

The initial value at steady state (no stimulus) is found by solving the Lyaponov equation:

\[
\Sigma_z[k] = A \cdot \Sigma_z[k] \cdot A^T + B_k \cdot B_k \tag{C.11}
\]

The other matrices, \( \Sigma_z[k] \) with \( k = 1, 2, ..M_{min}-1 \) are calculated in a recursive manner using equation (C.10). Finally, the variance of the observations \( r(k\Delta t) \) is found using the equation:

\[
\Sigma_r[k] = C \Sigma_z[k] C^T \tag{C.12}
\]
Appendix D

All Data

D.1 Raw Data
Figure D.1: The raw filtered electrode voltage. The right column shows a zoom-in on raw data during the stimulus time which is marked by vertical dash lines. The left column shows the complete waveform.
Figure D.1: The raw filtered electrode voltage (left) and zoom in on a single response stimulus (right).
Figure D.1: *The raw filtered electrode voltage (left) and zoom in on a single response stimulus (right).*
Figure D.2: The raw filtered electrode voltage (left) and zoom in on a single response stimulus (right).
Figure D.2: The raw filtered electrode voltage (left) and zoom in on a single response stimulus (right).
Figure D.2: The raw filtered electrode voltage (left) and zoom in on a single response stimulus (right).
Figure D.2: The raw filtered electrode voltage (left) and zoom in on a single response stimulus (right).
D.2 Histograms

D.2.1 Stimulus On and Stimulus Off Histograms

Figure D.3: Amplitude level histograms during the stimulus presence (dark line) and in the absence of the stimulus (dashed line).
Figure D.4: Amplitude level histograms during the stimulus presence (dark line) and in the absence of the stimulus (dashed line).
Figure D.5: Amplitude level histograms during the stimulus presence (dark line) and in the absence of the stimulus (dashed line).
Figure D.6: Amplitude level histograms during the stimulus presence (dark line) and in the absence of the stimulus (dashed line).
D.2.2 Quantile-Quantile Plots

Figure D.7: Quantile-Quantile plots of data files 1-4.
Figure D.8: Quantile-Quantile plots of data files 5-10.
Figure D.9: Quantile-Quantile plots of data files 11-16.
Figure D.10: Quantile-Quantile plots of data files 17-20.
D.3 Mean responses

Figure D.11: *Empirical mean response using fifty stimuli repetitions*
Figure D.12: *Empirical mean response using fifty stimuli repetitions*
Figure D.13: Empirical mean response using fifty stimuli repetitions
D.4 Response Variances

Figure D.14: The Empirical Variance and its Parametric Estimate.
Figure D.14: The Empirical Variance and its Parametric Estimate.
Figure D.14: *The Empirical Variance and its Parametric Estimate.*
D.5 All ROC curves

Figure D.15: Probability of Detection per Probability of a false alarm (ROC curves) measured in files 1-6.
Figure D.15: Probability of Detection per Probability of a false alarm (ROC curves) measured in files 7-12.
Figure D.15: Probability of Detection per Probability of a false alarm (ROC curves) measured in files 13-18.
Figure D.15: Probability of Detection per Probability of false alarm (ROC curves) measured in files 19-20.
## D.6 Recordings details

### D.6.1 Filenames

Table D.1: *File Names and stimulus duration in each file*

<table>
<thead>
<tr>
<th>File #</th>
<th>File</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Pn tetrode DV5.0.smr</td>
<td>405e-3</td>
</tr>
<tr>
<td>2</td>
<td>Pn tetrode DV7.1.smr</td>
<td>405e-3</td>
</tr>
<tr>
<td>3</td>
<td>Pn tetrode DV8.0 parallel recording with chip.smr</td>
<td>405e-3</td>
</tr>
<tr>
<td>4</td>
<td>Pn tetrode DV8.0.smr</td>
<td>405e-3</td>
</tr>
<tr>
<td>5</td>
<td>Pn tetrode DV8.0RonisDaddy.smr</td>
<td>405e-3</td>
</tr>
<tr>
<td>6</td>
<td>Pn tetrode DV8.0b.smr</td>
<td>405e-3</td>
</tr>
<tr>
<td>7</td>
<td>260711 PN DV7.6.smr</td>
<td>405e-3</td>
</tr>
<tr>
<td>8</td>
<td>260711 PN DV8.0 D.smr</td>
<td>405e-3</td>
</tr>
<tr>
<td>9</td>
<td>270711 PN 7.8.smr</td>
<td>420e-3</td>
</tr>
<tr>
<td>10</td>
<td>rat 1 120209 AP 2.0 ML 2.0 DV 9.4 1st extinction.smr</td>
<td>460e-3</td>
</tr>
<tr>
<td>11</td>
<td>rat 1 120209 AP 2.0 ML 2.0 DV 9.4 2nd baseline before injection.smr 13</td>
<td>460e-3</td>
</tr>
<tr>
<td>12</td>
<td>rat 1 120209 AP 2.0 ML 2.0 DV 9.4 baseline.smr</td>
<td>460e-3</td>
</tr>
<tr>
<td>13</td>
<td>rat 6 implantation PN3.smr</td>
<td>410e-3</td>
</tr>
<tr>
<td>14</td>
<td>PN 2nd recording.smr</td>
<td>420e-3</td>
</tr>
<tr>
<td>15</td>
<td>Si electrode Jan 5 8 chan 5 filtered 300-3000 3 unfiltered 1-10000 location 1 AP 2.0 ML 2.0 DV 9.0.smr</td>
<td>460e-3</td>
</tr>
<tr>
<td>16</td>
<td>Si electrode Jan 5 8 chan 5 filtered 300-3000 3 unfiltered 1-10000 location 2 AP 2.0 ML 2.0 DV 9.2.smr</td>
<td>460e-3</td>
</tr>
<tr>
<td>17</td>
<td>Si electrode Jan 5 8 chan 5 filtered 300-3000 3 unfiltered 1-10000 location 3 AP 2.0 ML 2.0 DV 9.4.smr</td>
<td>460e-3</td>
</tr>
<tr>
<td>18</td>
<td>Si electrode Jan 5 8 chan 5 filtered 300-3000 3 unfiltered 1-10000 location 4 AP 2.0 ML 2.0 DV 9.6.smr</td>
<td>465e-3</td>
</tr>
<tr>
<td>19</td>
<td>Si electrode Jan 5 8 chan 5 filtered 300-3000 3 unfiltered 1-10000 location 7 AP 2.2 ML 2.0 DV 9.0.smr</td>
<td>460e-3</td>
</tr>
<tr>
<td>20</td>
<td>rat 1WN 70 db ap 2.0 ml 2.0 dv 9.65 filter 300-10000 .smr</td>
<td>410e-3</td>
</tr>
</tbody>
</table>
Table D.3: Tested Files Details

<table>
<thead>
<tr>
<th>File #</th>
<th>date (dd/mm/yyyy)</th>
<th>Electrode</th>
<th>Location (DV)</th>
<th>Stimulus Duration</th>
<th>$T_{ITI}$</th>
<th># of Stimuli</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>19/7/2011</td>
<td>tetrode</td>
<td>5.0</td>
<td>405e-3</td>
<td>2.45</td>
<td>56</td>
</tr>
<tr>
<td>2</td>
<td>19/7/2011</td>
<td>tetrode</td>
<td>7.1</td>
<td>405e-3</td>
<td>2.45</td>
<td>43</td>
</tr>
<tr>
<td>3</td>
<td>19/7/2011</td>
<td>tetrode</td>
<td>8.0</td>
<td>405e-3</td>
<td>2.45</td>
<td>60</td>
</tr>
<tr>
<td>4</td>
<td>19/7/2011</td>
<td>tetrode</td>
<td>8.0</td>
<td>405e-3</td>
<td>2.45</td>
<td>60</td>
</tr>
<tr>
<td>5</td>
<td>19/7/2011</td>
<td>tetrode</td>
<td>8.0</td>
<td>405e-3</td>
<td>2.45</td>
<td>60</td>
</tr>
<tr>
<td>6</td>
<td>19/7/2011</td>
<td>tetrode</td>
<td>8.0</td>
<td>405e-3</td>
<td>2.45</td>
<td>60</td>
</tr>
<tr>
<td>7</td>
<td>26/07/2011</td>
<td>tetrode</td>
<td>7.6</td>
<td>405e-3</td>
<td>2.41</td>
<td>60</td>
</tr>
<tr>
<td>8</td>
<td>26/07/2011</td>
<td>tetrode</td>
<td>8.0</td>
<td>405e-3</td>
<td>2.41</td>
<td>60</td>
</tr>
<tr>
<td>9</td>
<td>27/07/2011</td>
<td>tetrode</td>
<td>7.8</td>
<td>420e-3</td>
<td>4.41</td>
<td>47</td>
</tr>
<tr>
<td>10</td>
<td>12/02/2009</td>
<td>tetrode</td>
<td>9.4</td>
<td>460e-3</td>
<td>15.499</td>
<td>60</td>
</tr>
<tr>
<td>11</td>
<td>12/02/2009</td>
<td>tetrode</td>
<td>9.4</td>
<td>460e-3</td>
<td>15.499</td>
<td>60</td>
</tr>
<tr>
<td>12</td>
<td>12/02/2009</td>
<td>tetrode</td>
<td>9.4</td>
<td>460e-3</td>
<td>15.499</td>
<td>60</td>
</tr>
<tr>
<td>13</td>
<td>?</td>
<td>tetrode</td>
<td>x</td>
<td>410e-3</td>
<td>2.45</td>
<td>60</td>
</tr>
<tr>
<td>14</td>
<td>?</td>
<td>?</td>
<td>x</td>
<td>420e-3</td>
<td>2.45</td>
<td>60</td>
</tr>
<tr>
<td>15</td>
<td>5/1/2008</td>
<td>Ti N</td>
<td>9.0</td>
<td>460e-3</td>
<td>2.499</td>
<td>60</td>
</tr>
<tr>
<td>16</td>
<td>5/1/2008</td>
<td>Ti N</td>
<td>9.2</td>
<td>460e-3</td>
<td>2.499</td>
<td>60</td>
</tr>
<tr>
<td>17</td>
<td>5/1/2008</td>
<td>Ti N</td>
<td>9.4</td>
<td>460e-3</td>
<td>2.499</td>
<td>60</td>
</tr>
<tr>
<td>18</td>
<td>5/1/2008</td>
<td>Ti N</td>
<td>9.6</td>
<td>465e-3</td>
<td>2.499</td>
<td>60</td>
</tr>
<tr>
<td>19</td>
<td>5/1/2008</td>
<td>Ti N</td>
<td>9.0</td>
<td>460e-3</td>
<td>2.499</td>
<td>60</td>
</tr>
<tr>
<td>20</td>
<td>?</td>
<td>tetrode</td>
<td>9.65</td>
<td>410e-3</td>
<td>5.2236</td>
<td>144</td>
</tr>
</tbody>
</table>

1In all the recording AP=2.0mm and ML=2.0mm
D.6.2 Auditory Stimulation

The auditory stimulus was used in the laboratory tests consisting of white-noise with intensity of 70 dB. Each recording included 60 identical stimuli. The exact duration of each stimulus varied between recordings and was 400-470 ms, where the first and last 10 ms were the rising/falling phase. The intervals between two stimuli onsets ($T_{ITI}$) varied between recordings and ranged between 2.45-15.5 seconds. For detailed stimuli timing in each experiment, see Table D.6.1 in this appendix.

D.6.3 Digital Preprocessing of Recorded Data

During the detection tests the digital data was preprocessed using only causal operations (to emulate real time processing). These operations included:

1. The recordings that were already band pass filtered between 300-3000 Hz were down sampled by an integer factor to a new sampling rate, $f_{s,new}$, which was chosen such that it was as close as possible to 6000Hz, yet equal or higher than this rate. Unfiltered recordings were bandpass filtered digitally in the range [300Hz, $f_{s,new}/2$ Hz] using a four pole butterworth filter.

2. Power line harmonics at frequencies of 250[Hz] and 450[Hz] were filtered out using a narrow stop band butterworth filter with two poles.

3. A single electrode tip (a single recording channel), which showed the best response to the stimulus, was chosen for the detection tests.
Appendix E

Nomenclature
Table E.1: *Nomenclature, Chapter 2*

<table>
<thead>
<tr>
<th>Mark</th>
<th>Meaning</th>
<th>unit</th>
</tr>
</thead>
<tbody>
<tr>
<td>$T_{ITI}$</td>
<td>Inter-Trial-Interval. A random variable which represents interval duration between consecutive onsets of aversive stimuli.</td>
<td>[sec]</td>
</tr>
<tr>
<td>$T_{min}$</td>
<td>Shortest possible interval between consecutive onsets of the aversive stimuli.</td>
<td>[sec]</td>
</tr>
<tr>
<td>$T_s$</td>
<td>Duration of the warning signal.</td>
<td>[sec]</td>
</tr>
<tr>
<td>$t_{offset}$</td>
<td>Delay of the neural response to the warning stimulus</td>
<td>[sec]</td>
</tr>
<tr>
<td>$T_d$</td>
<td>The delay from the onset of the neural response to the onset of the aversive event.</td>
<td>[sec]</td>
</tr>
<tr>
<td>$C_{MD}$</td>
<td>The momentary cost for mis-detecting the aversive stimulus while it is on.</td>
<td>[Hz]</td>
</tr>
<tr>
<td>$C_{FA}$</td>
<td>The momentary cost for a false alarm in the presence of an aversive stimulus.</td>
<td>[Hz]</td>
</tr>
<tr>
<td>$\mathcal{R}_{FA}(t)$</td>
<td>The risk of a false alarm equals the cost of a false alarm times its probability to happen.</td>
<td>[Hz]</td>
</tr>
<tr>
<td>$\mathcal{R}_{MD}(t)$</td>
<td>The risk of a misdetection equals the cost of a misdetection times its probability to happen.</td>
<td>[Hz]</td>
</tr>
<tr>
<td>$\mathcal{R}_{injury}(t)$</td>
<td>The risk of an injury at time $t$. It equals either $\mathcal{R}<em>{MD}(t)$ or $\mathcal{R}</em>{FA}(t)$ depending on the detector decision.</td>
<td>[Hz]</td>
</tr>
<tr>
<td>$I_{on}(t)$</td>
<td>The output of the detector. $I_{on}(t) = 1$ means that the detector decided that the stimulus is present. The complementary signal $\bar{I}_{on}(t)$ means the opposite.</td>
<td></td>
</tr>
<tr>
<td>$r_0(t)$</td>
<td>Voltage on the multi-unit electrode, $r(t)$ from start time until time $t$. These are the observables of the problem.</td>
<td>[Volts]</td>
</tr>
<tr>
<td>$\Delta t$</td>
<td>Sampling interval</td>
<td>[sec]</td>
</tr>
<tr>
<td>Mark</td>
<td>Meaning</td>
<td>unit</td>
</tr>
<tr>
<td>---------</td>
<td>--------------------------------------------------</td>
<td>-------</td>
</tr>
<tr>
<td>$T_{test}$</td>
<td>Total test duration</td>
<td>[s]</td>
</tr>
<tr>
<td>$T_{stimuli}$</td>
<td>The cumulative duration of all stimuli</td>
<td>[s]</td>
</tr>
<tr>
<td>$I_{MD}(t)$</td>
<td>Indication on a misdetection at time $t$</td>
<td></td>
</tr>
<tr>
<td>$I_{FA}(t)$</td>
<td>Indication on a false alarm at time $t$</td>
<td></td>
</tr>
<tr>
<td>$\langle P_{MD} \rangle$</td>
<td>Time averaged probability of a misdetection</td>
<td></td>
</tr>
<tr>
<td>$\langle P_{FA} \rangle$</td>
<td>Time averaged probability of a false alarm</td>
<td></td>
</tr>
<tr>
<td>$\Gamma_{LR}$</td>
<td>The pseudo likelihood ratio of the square and integrate detector</td>
<td>$[J]$</td>
</tr>
<tr>
<td>$\alpha_{LR}$</td>
<td>The forgetting factor of the square and integrate detector</td>
<td>$[Hz]$</td>
</tr>
<tr>
<td>$\beta_{LR}$</td>
<td>The gain of the square and integrate detector.</td>
<td></td>
</tr>
</tbody>
</table>
Table E.3: *Nomenclature, Chapter 3*

<table>
<thead>
<tr>
<th>Mark</th>
<th>Meaning</th>
<th>unit</th>
</tr>
</thead>
<tbody>
<tr>
<td>$N_{\text{cells}}$</td>
<td>Number of stimulus responsive cells surrounding the electrode.</td>
<td></td>
</tr>
<tr>
<td>$r(t)$</td>
<td>Electrode voltage at time $t$.</td>
<td></td>
</tr>
<tr>
<td>$x(t)$</td>
<td>Voltage due to stimulus reactive neurons.</td>
<td>Volts</td>
</tr>
<tr>
<td>$n(t)$</td>
<td>Voltage due to unrelated cells.</td>
<td>Volts</td>
</tr>
<tr>
<td>$v(t)$</td>
<td>Electronic noise due to measurement equipment.</td>
<td>Volts</td>
</tr>
<tr>
<td>$s(t)$</td>
<td>Raw external stimulus given in normalized units of force (Newtons) per area.</td>
<td>$N/m^2$</td>
</tr>
<tr>
<td>$s_f(t)$</td>
<td>External stimulus force at pass band frequencies of the relevant receptor.</td>
<td>$N/m^2$</td>
</tr>
<tr>
<td>$y(t)$</td>
<td>Neurotransmitter concentration</td>
<td>$\mu M (10^{-3} \text{ mol/m}^3)$</td>
</tr>
<tr>
<td>$a$</td>
<td>Neurotransmitter removal rate</td>
<td>$s^{-1}$</td>
</tr>
<tr>
<td>$b$</td>
<td>Neurotransmitter generation efficiency</td>
<td>$\mu M / \text{Watt}$ or $\mu M / \text{J}$</td>
</tr>
<tr>
<td>$g_{\text{gain}}$</td>
<td>Stimulus gain</td>
<td>$\mu M / \text{Watt}$</td>
</tr>
<tr>
<td>$y_p$</td>
<td>Steady state neurotransmitter concentration during a stimulus pulse.</td>
<td>$\mu M$</td>
</tr>
<tr>
<td>$P_0(t)$</td>
<td>Probability of a neuron to be in an armed state where it can fire spikes</td>
<td></td>
</tr>
<tr>
<td>$P_1(t)$</td>
<td>Probability of a neuron to be in a refractory state where it cannot fire spikes</td>
<td></td>
</tr>
<tr>
<td>$R_{\text{fire}}(t)$</td>
<td>The firing rate</td>
<td>$s^{-1}$</td>
</tr>
<tr>
<td>$T_{\text{ISI}}$</td>
<td>Interval length between two adjacent spikes.</td>
<td>$s$</td>
</tr>
<tr>
<td>$P(T_{\text{ISI}})$</td>
<td>The probability that the interval length between two adjacent spikes equals $T_{\text{ISI}}$.</td>
<td></td>
</tr>
<tr>
<td>Mark</td>
<td>Meaning</td>
<td>unit</td>
</tr>
<tr>
<td>--------------</td>
<td>-------------------------------------------------------------------------</td>
<td>---------------</td>
</tr>
<tr>
<td>$g_{x,k}(t)$</td>
<td>The shape of the spike coming from the $k^{th}$ neuron</td>
<td>$[\text{Volts}]$</td>
</tr>
<tr>
<td>$G_{x,k}(f)$</td>
<td>The shape of the spike coming from the $k^{th}$ neuron at the frequency domain</td>
<td>$[\text{Volts/Hz}]$</td>
</tr>
<tr>
<td>$H_k(f)$</td>
<td>The frequency domain transfer function of the medium separating the $k^{th}$ neuron from the electrode.</td>
<td>$[\text{Volts/Hz}]$</td>
</tr>
<tr>
<td>$H_{HF}(f)$</td>
<td>The frequency domain transfer function of a high pass filter.</td>
<td>$[\text{Volts/Hz}]$</td>
</tr>
<tr>
<td>$\bar{H}_k(f)$</td>
<td>The frequency domain transfer function of the medium separating the $k^{th}$ neuron from the electrode including the concatenated high pass filter.</td>
<td>$[\text{Volts/Hz}]$</td>
</tr>
<tr>
<td>$\tau_{d,k}(f)$</td>
<td>The small timing delay of the $k^{th}$ neuron.</td>
<td>$[\text{s}]$</td>
</tr>
<tr>
<td>$\rho_k(f)$</td>
<td>The amplitude attenuation/gain relative to the averaged spike amplitude.</td>
<td></td>
</tr>
<tr>
<td>$I_k(t)$</td>
<td>Indicator that is set to one when the $k^{th}$ spike fires.</td>
<td></td>
</tr>
<tr>
<td>$\mu_x(t)$</td>
<td>The mean response of the response to the stimulus.</td>
<td>$[\text{Volts}]$</td>
</tr>
<tr>
<td>$p_{fire}(t_1,t_2)$</td>
<td>The probability to fire at time $t_1$ and then again at $t_2$.</td>
<td></td>
</tr>
<tr>
<td>$R_x(t_1,t_2)$</td>
<td>The autocorrelation of the response to the stimulus.</td>
<td>$[\text{Watt}]$</td>
</tr>
<tr>
<td>$g_n(t)$</td>
<td>Background noise equivalent impulse response.</td>
<td>$[\text{Volts}]$</td>
</tr>
<tr>
<td>$\Sigma_x(t_1,t_2)$</td>
<td>The covariance of the response to the stimulus.</td>
<td>$[\text{Watt}]$</td>
</tr>
<tr>
<td>$\Sigma_n(t_1,t_2)$</td>
<td>The covariance of the background noise.</td>
<td>$[\text{Watt}]$</td>
</tr>
<tr>
<td>$\Sigma_v(t_1,t_2)$ or $\sigma_v^2$</td>
<td>The covariance of the additive thermal noise.</td>
<td>$[\text{Watt}]$</td>
</tr>
<tr>
<td>$\Sigma_r(t_1,t_2)$</td>
<td>The total covariance of the acquired signal.</td>
<td>$[\text{Watt}]$</td>
</tr>
</tbody>
</table>
Table E.5: *Nomenclature, Chapter 3 - state space.*

<table>
<thead>
<tr>
<th>Mark</th>
<th>Meaning</th>
<th>unit</th>
</tr>
</thead>
<tbody>
<tr>
<td>$z_k$</td>
<td>A dummy state space vector that generates the signals $x(t)$ and $n(t)$ using a set of autoregressive moving average equations.</td>
<td>Volts</td>
</tr>
<tr>
<td>$a_{x,m}$</td>
<td>The $m^{th}$ autoregressive coefficient generating the spike shape.</td>
<td></td>
</tr>
<tr>
<td>$b_{x,m}$</td>
<td>The $m^{th}$ moving average coefficient generating the spike shape.</td>
<td></td>
</tr>
<tr>
<td>$a_{n,m}$</td>
<td>The $m^{th}$ autoregressive coefficient generating the background noise shape.</td>
<td></td>
</tr>
<tr>
<td>$b_{n,m}$</td>
<td>The $m^{th}$ moving average coefficient generating the background noise shape.</td>
<td></td>
</tr>
<tr>
<td>$Q_{x,max}$</td>
<td>The order of the ARMA equation generating the process $x(t)$</td>
<td></td>
</tr>
<tr>
<td>$Q_{n,max}$</td>
<td>$A \cdot z_k + B_k$ The order of the ARMA equation generating the process $n(t)$</td>
<td></td>
</tr>
<tr>
<td>$A$</td>
<td>A matrix representing the autoregressive part of the state space formulation.</td>
<td></td>
</tr>
<tr>
<td>$B_k$</td>
<td>A matrix representing the moving average part of the state space formulation.</td>
<td></td>
</tr>
<tr>
<td>$C$</td>
<td>A vector which sums two components from the dummy vector $z_k$ that generate the observable $r(t)$.</td>
<td></td>
</tr>
<tr>
<td>$D_k$</td>
<td>The innovations of the latest sample.</td>
<td></td>
</tr>
<tr>
<td>$\Sigma_z$</td>
<td>The Covariance function of the dummy vector $z_k$.</td>
<td></td>
</tr>
</tbody>
</table>
Table E.6: Nomenclature, Chapter 4

<table>
<thead>
<tr>
<th>Mark</th>
<th>Meaning</th>
<th>unit</th>
</tr>
</thead>
<tbody>
<tr>
<td>( P_{onset}(t - t_{last \ onsets} = k\Delta_t</td>
<td>r_0^t) )</td>
<td>The probability that the stimulus onset occurred ( k\Delta_t ) seconds ago, given the observations from start time until now (time ( t )).</td>
</tr>
<tr>
<td>( P_{onset}(t - t_{last \ onsets} \geq T_{min}</td>
<td>r_0^t) )</td>
<td>The probability that the stimulus onset occurred more than ( T_{min} ) seconds ago, given the observations from start time until now (time ( t )).</td>
</tr>
<tr>
<td>( M_{min} )</td>
<td>( T_{min} ) (Shortest possible interval between consecutive onsets of the aversive stimuli) expressed in number of clock cycles.</td>
<td></td>
</tr>
<tr>
<td>( M_d )</td>
<td>( T_d ) (allowed detection delay) expressed in number of clock cycles.</td>
<td></td>
</tr>
<tr>
<td>( M_s )</td>
<td>( T_s ) (the stimulus duration) expressed in number of clock cycles.</td>
<td></td>
</tr>
<tr>
<td>( d_k[j\Delta_t] )</td>
<td>The register that holds a normalized version of the posterior probability ( P_{onset}(t - t_{last \ onsets} = k\Delta_t</td>
<td>r_0^j\Delta_t) ).</td>
</tr>
<tr>
<td>( q_k[j\Delta_t] )</td>
<td>The output of the ( k^{th} ) Kalman filter. It is a logarithmic version of the probability: ( Pr(r(j\Delta_t)</td>
<td>t - t_{last \ onsets} = k\Delta_t, r_0^{t-\Delta_t}) )</td>
</tr>
<tr>
<td>( \alpha )</td>
<td>The a-priori probability of the stimulus to begin in each clock cycle: ( \alpha = \frac{\Delta_t}{T_{avg} - T_{min}} )</td>
<td></td>
</tr>
<tr>
<td>( L_{min}[j] )</td>
<td>The normalization factor of the registers at time ( j\Delta_t ).</td>
<td></td>
</tr>
<tr>
<td>( LR[j] )</td>
<td>The true likelihood ratio of the optimal detector.</td>
<td></td>
</tr>
<tr>
<td>( I_{on}(t) )</td>
<td>The decision of the optimal detector after thresholding the likelihood ratio.</td>
<td></td>
</tr>
</tbody>
</table>
גילוי נוכחות של גורם מותך אזורית
גנורופיזיוולוגיים על סמך מודל

に向ור לשכבה התאור "דוקטור לפילוסופיה"

ג'יר נוסנסון

הוגשgiatan של אוניברסיטת תל-אביב

נישתועיב
גילוי נוכחות של גניון מתוכן אוטות
נירופיזיולוגים על סמך מדד
גיל גנסנוביל

חיבר lem קבלת התואר "דוקטור לפילוסופיה"
והגיש לסנטט של אוניברסיטת תל אביב

אני Geschwind

עבודה ויועשת במכון לרפואת התנ helicoptר
בוחי לרפואתי הרצות-

唐宇 נשיין
עבודה זו נעשתה בהדרכת פרופ' חגי มาיר-ירון

apsulation הבוררת ביחס לפרסים הגלח税务局

עיבודו ו_measurement בהדרכת פרופ' חגי מסר-ירון
5.2.7. Results of the detection (characteristic of the detector)

5.2.7.1 Case 1 - Data is without exceptions (7 out of 20 files).

5.2.7.2 Case 2 - Data contains some exceptions (11 out of 20 files).

5.2.7.3 Case 3 - Data presents statistical instability (2 out of 20 files).

5.2.8 Summary of detection results

6.1 The consequences of the results

- The model, based on the model, achieves an advantage when it is combined with exceptions.

6.2 The consequences of the results

- The energy detector is simple, robust and achieves results close to optimal.

6.3 Significance of the results

- The model is useful for predicting the results of experiments.

6.4 The experiment in perspective

6.5 Consequences of the results

6.6 Evidence of the existence of an energy detector in certain conditions in the nervous system and in the muscular system - skeletal.

6.6.1 Evidence of the square increase of the irritation in the auditory and visual systems.

6.6.2 Evidence of the lengthening of the irritation and emphasis of the endings by the neurons.

6.6.3 Evidence of the accumulation of firing by glial cells.

6.6.4 Evidence of the mechanism of glial cells.

6.6.5 Evidence of the mechanism of glial cells.

6.7 Summary of the hypothesis regarding the mechanism of the nervous system.

6.8 Appendix

138 Appendix A

- Various matrices and spaces.

138 Appendix B

- Calculation of the posterior probabilities by the detector.

138 Appendix C

- Calculation of the probabilities of the variables

138 Appendix D

- All data.

E.2 All data.

138 Shimatzu.

125 List of references
تبعזת

בעבודה זו עסוקת בהכנת גליי אווטומטיים מוספים למדלי המוחה נוכחות של גלי חיטון/category. מתוכ נתון של בחינת היציבות המגנטית במגזר המוחה ואחרי הפעלת סינת אדריכלים ומקסותרה בזה אחריה עליה עוקרת ממקומת מחמק של תאיים גליי חיטון. התוכן המוספים אווטומטיים המתומרים הביא פוטונים של הרבה חיטונים מוספים זו נוחות הוליה ובה מובאים אלו נושאים של פעילות של תאים המוחה במקומות הנוספים הידועים כמאוכלסים בצפיפות בנוירונים המגיבים לגירי חיטון. המשמעות של גליי חיטון היא מAnimationsModule על התקופה של גליי חיטוןuegos Multi Unit Activity או MUA. באירית לפי יום MUA או Activity. בשיטה זו מוחזק במקומת מוחה,List לתחוםгруппת תדרים גבוהים. ליתר דיוק, נדונים ניסיונות בהתקפה בשכבות של תאים הנושאים במקומות הנוספים הידועים כמאוכלסים בצפיפות בנוירונים המגיבים לגירי חיטון. המבקרים בני שיטה זו נושאים את התרשים של גליי חיטון(lists actividades) אותם מוחזק במקומת מוחה. ליתר דיוק, נדונים ניסיונות בהתקפה בשכבות של תאים הנושאים במקומות הנוספים הידועים כמאוכלסים בצפיפות בנוירונים המגיבים לגירי חיטון. המבקרים בני שיטה זו נושאים 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