Methods for Improving the Quality and Sorting of Intracortical Recordings for Brain-Machine Interfacing

Methods for Improving the Quality and Sorting of Intracortical Recordings for Brain-Machine Interfacing

PhD Thesis by

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Table of Contents

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List of articles

The PhD thesis is based on the following articles referred to by their Roman number in the text.

Study I: Shalchyan, V., Jensen, W., & Farina, D. (2012). Spike detection and clustering with unsupervised wavelet optimization in extracellular neural recordings. *IEEE Transactions on Biomedical Engineering*, 59(9), 2576-2585, doi: 10.1109/TBME.2012.2204991

Study II: Carotti, E. S., Shalchyan, V., Jensen, W., & Farina, D. Denoising and compression of intracortical signals with a modified MDL criterion. *Journal of Medical & Biological Engineering & Computing. (Submitted)*

Study III: A nonparametric Bayesian approach to sorting and tracking non-stationarities of the neural spikes. (Under preparation)

Study IV: Shalchyan, V., Hammad, S., Jensen, W., & Farina, D. Enhancing event-related neural response by using optimized wavelets for spike detection. *IEEE Transactions on Neural Systems and Rehabilitation Engineering, (Submitted)*

Abstract

Recent advances in the development of implantable microelectrode arrays for neural recording has provided the possibility to directly record simultaneous activity of many neurons in the brain. Such information has been used in brain-machine interfaces (BMIs) for helping patients with severe motor disabilities to restore some communication or control functions by using their intent. However, signal degradation factors such as background noise that are normally present in the intracortical recordings can reduce the accuracy of neural information extraction and thereby reduce the efficiency of BMIs. This PhD thesis focuses on proposing signal processing methods to enhance the accuracy and performance of extracting neural information from intracortical signals for BMI applications. The first study (STUDY I) proposed methods to improve spike detection and clustering in low signal-to-noise ratio intracortical signals by conditioning signals in parameterized wavelet bases where signal-dependent criteria were employed to optimize the mother wavelet selection. The work demonstrated that the proposed wavelet optimization could effectively improve the performance of spike detection and clustering to an extent which substantially surpassed several previously proposed methods based on simulation and experimental data test. The second study (STUDY II) investigated the possibility of employing minimum description length principle for optimal wavelet packet basis selection and denoising and proposed an embedded zero-tree wavelet packet coding for compression of intracortical signals. The results demonstrated that the proposed method could better capture the most regularity in the data with respect to the entropy-based optimization and provided better compression and denoising performances with respect to the previous techniques based on synthesized and real data test. Regarding the problem of electrode/tissue drift in the spike sorting, the third study (STUDY III) investigated the preference of nonparametric versus parametric (Gaussian) estimation of cluster densities in Bayesian tracking of nonstationarities of the clusters over long-term recordings. The results from simulated data test showed that the proposed nonparametric method could better estimate cluster dynamics and outperformed parametric model fitting approach. The fourth study (STUDY IV) proposed an automatic signal matching wavelet for detection of multi-unit neural spikes in noisy recordings. The detection performance of the proposed method outperformed previous methods in simulation tests. Further, the experimental results showed that the proposed method effectively enhanced the event-related neural response based on the peri-event time histograms in repetitions of a specific forelimb movement. In conclusion, this PhD project investigated some limitations of current intracortical signal processing algorithms in spike detection, spike sorting, signal denoising and compression which can reduce the performance of BMIs and developed alternative methods to overcome these limitations. The proposed methods outperformed previous approaches in both simulation and experimental data test, and can be used to enhance the efficiency of intracortical BMIs.

Danish Abstract

De seneste fremskridt indenfor udviklingen af implanterbare mikroeletrode matricer har gjort det muligt at foretage optagelser af et større antal nerveceller i hjernen på samme tid. Denne information kan danne grundlag for *Brain-Machine Interfaces* (BMI) der kan hjælpe patienter med svære motoriske handikaps til at genvinde en vis grad af kommunikation eller kontrol funktioner, udelukkende ved brug af personens hensigt. Præcisionen af den neurale information, og dermed effektiviteten af BMI, kan dog reduceres af faktorer såsom baggrundstøj, som ofte er til stede i intrakortikale målinger. Denne PhD tese fokuserer på udviklingen af nye signalbehandlingsmetoder til at forøge præcisionen af den neurale information fra intrakortikale signaler til brug indenfor BMI.

Det første studie (Studie I) præsenterede metoder til at forbedre detektionen af *spikes* samt *clustering* af disse *spikes* fra kortikale signaler med lav signal-til-støj ratio ved at konditionere signaler i parametriserede wavelet-baser hvor signal-afhængige kriterier blev anvendt til at optimere udvælgelsen af *mother wavelets*. Dette studie demonstrerede at denne wavelet-optimering kan forbedre spike-detektion og clustering i et omfang som overgik adskillige metoder der tidligere er foreslået baseret på simuleringer og eksperimentielle forsøg.

I det andet studie (Studie II) blev muligheden for at anvende *minimum description length* princippet til optimal udvælgelse og *denoising* af wavelet basis pakker undersøgt og en indlejret *zero-tree* wavelet pakke kodning til kompression af intrakortikale signaler. Resultaterne demonstrerede at denne metode var bedre til at beskrive hovedparten af dataens irregulariteter i forhold til den entropi-baserede optimering og gav en bedre compression og *denoising* i forhold til tidligere foreslåede teknikker baseret på syntetisk og eksperimentielt data.

I forhold til problemet vedr. variationer i placering af elektrode/væv for *spike sorting*, undersøgte et tredie studie (Studie III) fordelene ved nonparametrisk versus parametrisk (Gaussiansk) estimation af densiteten af *clusters* i Bayesiansk tracking af clusternes non-stationaritet i længerevarende optagelser. Resultaterne fra simuleret data viste at den foreslåede non-parametriske metode var bedre til at estimere clusternes dynamic end parametriske modelerings metoder.

Det fjerde studie (Studie IV) præsenterede en automatisk *signal matching wavelet* til detektion af neurale spikes fra multiple enheder i støjfyldte optagelser. Den foreslåede metode var bedre end hidtillige metoder for tests med simuleret data. Derudover viste tests på eksperimentielt data at metoden forbedrede det event-relaterede neurale respons baseret på peri-event histogrammer under repetitive bevægelser af forbenene.

I dette PhD projekt blev visse begrænsninger ved nuværende signalbehandlingsmetoder til detektion af spikes, signal *denoising* and kompression, som kan reducere BMIs ydeevne undersøgt, og alternative metoder til at overkomme disse begrængsninger blev udviklet. De udviklede metoder var bedre end hidtillige metoder, i tests både med simuleret og eksperimentielt data, og kan bruges til at forbedre effektiviteten af intrakortikale BMI.

Chapter 1: Introduction

A brain-machine interface (BMI) also referred to as brain-computer interface (BCI) is a system that translates neural activity of the brain into commands which drive an external device for communication and/or control purposes. A BMI consists of three main parts (Fig. 1): 1) A sensor device to record neural activity of the brain. The recording can be invasive or non-invasive and regarding to the recording position and electrode type, different types of neural signals can be measured; 2) A signal processor that analyses and translates recorded neural activity into commands for the desired output; 3) An effector device which is controlled by translated neural commands. The effector can be a cursor on a computer screen, a robotic system or an artificial limb (Wolpaw et al. 2002, Waldert et al. 2009). While there are many types of BMIs, I focus in this thesis on BMIs that are directly linked to neural cells within cortex (i.e. intracortical BMIs). An important issue in BMI as a system which translates neural activities into driving commands is the performance. Despite impressive advances in the design and development of BMI systems, the speed and accuracy of current BMIs is still far lower than that of a healthy subject's own translation pathways (Santhanam et al. 2006, Lu et al. 2012, Willett et al. 2013). Improving BMI performance can be studied at any parts of the system as described above (i.e., sensor, processor, or effector). My focus in this thesis is on the signal processing part which extracts neural information (e.g., neural discharge patterns) from raw intracortical recordings. The aim of the PhD thesis is proposing signal processing methods to improve the performance of extracting neural information from intracortical signals for BMI applications.

The Thesis is organized into chapters. Chapter 2 provides required background for the research presented in this thesis. It begins with an overview of clinical applications of BMIs. Different types of BMIs, their capabilities, applications and recent advances are reviewed and potential advantages of intracortical BMIs over other type of BMIs are described. The intracortical signal as the subject of the study is explained in more details. Background information for required signal processing steps for extraction of spiking activities from intracortical signals is described and the limitations and open issues in the current algorithms are highlighted. The chapter also includes a short introduction to wavelet transform. Chapter 3 specifies the aim of the thesis and formulates different studies in the PhD project. Chapters 4-7 illustrate the methods that were developed for each PhD study. Chapter 8 concludes the thesis.

Chapter 2: Background

Restoring lost abilities in communication and control functions for patients who suffer from neurological disorders has been the main motivation for BMI research. Currently a large population of patients with disabilities effectively uses rehabilitation and assistive technologies and these devices have a serious role in improving the quality of life for these patients. A recent study showed that in United States there are nearly 1 in 50 people living with paralysis (almost 6 million) (Cahill et al. 2009). Paralysis is a major disability which is caused by several disease and injuries. Stroke, spinal cord injury, cerebral palsy, and amyotrophic lateral sclerosis (ALS) are the major reasons for paralysis. Stroke is one of the leading causes of death and disability in the world. According to the World Health Organization report (McKay et al. 2004), annually 15 million people worldwide suffer a stroke, of those 5 million die and 5 million are permanently disabled. Permanent disabilities after stoke are caused by irreversible damages to the neural circuits in central nervous system (Goldstein and Davis 1990). Considering the hierarchical organization of the motor control in the brain, if e.g., the motor cortex area is damaged after stroke, the command for movement intention and planning can be recorded from higher cortical areas (e.g., posterior parietal cortex (Andersen and Cui 2009)) and used for BMI control. Spinal cord injury is another cause of paralysis. It is estimated that three million people worldwide suffer from spinal cord injury (Wyndaele and Wyndaele 2006). Regaining partial function of paralyzed limbs may lead to greater independence is rated as a high priority by patients with paraplegia or tetraplegia (Anderson 2004). One ideal application of BMI for this group of patients would be to read neural commands from the brain and translating them into control of the paralyzed limb by functional electrical stimulation (FES) (Pfurtscheller et al. 2003, Jackson and Zimmermann 2012). ALS is a term used to cover a group of patients who suffer from progressive degeneration of motor neurons. ALS patients gradually lose the ability to move the muscles (Wijesekera and Leigh 2009). The complete paralysis of nearly all voluntary muscles in the body is called locked-in syndrome in which the patient is not able to interact or communicate to external world. Since

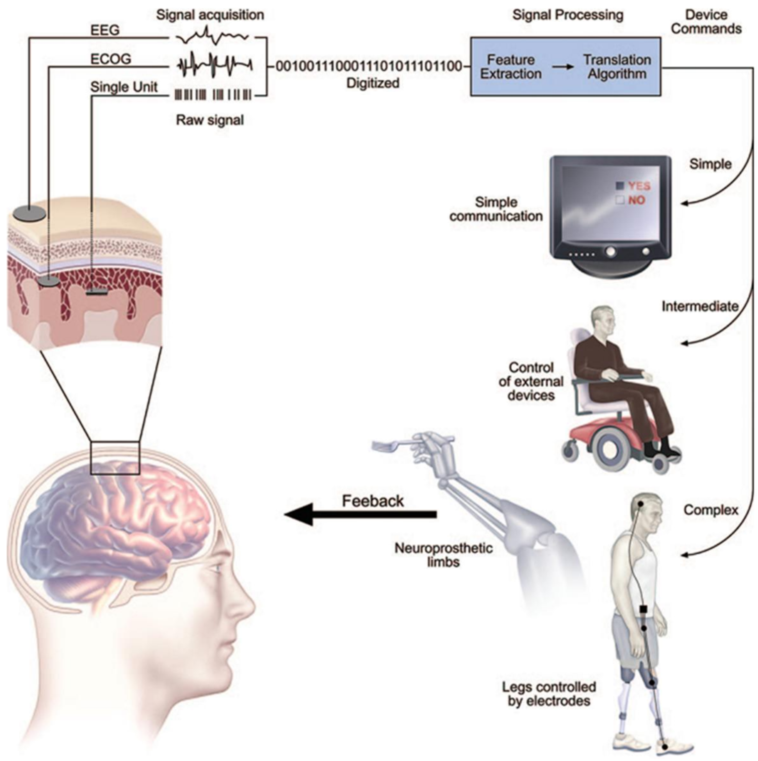

Fig. 1. Essential components and operation of a BMI system (Adapted from (Leuthardt et al. 2006)).

the cortical function in these patients is remained intact, it is possible to use a BMI to control a computer curser for communication or to control a wheelchair with simple commands (Kübler et al. 2005, Hochberg et al. 2006b).

Different Types of BMIs

Various methods for recording brain activity can be used for BMI application. Depending on the position and proximity of the recording electrode from neural cells, different types of neural signals are recorded (Fig. 1). If the electrodes placed outside the head, on the scalp, the recorded electrical activity is referred to as the electroencephalogram (EEG). The electrocorticogram (ECoG) is the recorded electrical activity from electrodes placed on the cortical surface. Neural cell action potentials (APs) and local field potentials (LFPs) can be recorded by using electrodes inserted within the cortex (i.e., intracortical recording). These three types of neural signals are the most common forms of electrical signals used in current BMIs (Lebedev and Nicolelis 2006). In this section we briefly review achievements and capabilities of these BMIs types.

EEG-based BMIs

Employing EEG as a non-invasive signal for BMI was reported from 1970s where the first attempts were made to enable human subjects to attain voluntary control over their brain signals (Nowlis and Kamiya 1970, Plotkin 1976, Vidal 1973). From that time to the present, major approaches for using EEG components in BMI applications can be divided into four categories: slow cortical potentials (SCPs), sensory-motor rhythms (SMRs), P300 evoked potentials, and steady state visual evoked potentials (SSVEPs).

SCPs are slow voltage changes occur over 0.5-10 s time windows in the cortex. Negative shift in the SCPs usually indicate cortical activation associated with movement or other functions whereas positive SCP shifts represent reduced cortical activation (Birbaumer 1999). It has been shown that the human subjects can learn how to control these SCP shifts and thereby gain control over a computer cursor (e.g. perform a binary selection) for communication (Birbaumer et al. 1999). However the communication rate in the SCP-based BMIs is very slow and requires extensive training (e.g., one letter/minute (Birbaumer 2006).

SMRs are recorded over sensory-motor cortical areas and their useful band-limited components for BMIs are the μ rhythm (8-12 Hz) and the β rhythm (18-30 Hz). Typically, performing a movement, preparation for a movement or even imagining a movement is accompanied by an amplitude decrease in μ and β rhythms which is called event-related desynchronization (Pfurtscheller and Lopes da Silva 1999). Using SMRs rhythms for controlling BMIs have received more attention in recent years because they seem to have a faster communication rate and require less training for subject to learn BMI control with respect to SCPs. SMRs have been used in several BMI studies for communication in word processors or binary selections (Wolpaw et al. 1991, Wolpaw and McFarland 1994, Pfurtscheller et al. 2000, Pfurtscheller et al. 2003, Christa Neuper et al. 2006). Researchers have shown that human subjects can learn how to use movement imagination for different limb areas simultaneously to modulate SMR rhythms and to control a computer cursor in multiple dimensions (Wolpaw and McFarland 2004, McFarland et al. 2010). However due to the fact that movement imagination of different limb generate similar desynchronization pattern over a wide area of cortex, independent control of movements in multiple dimensions requires the subject to learn non-natural combination of multiple limb movement imagination (Jackson and Zimmermann 2012).

The P300 event-related potential is another possible BMI control signal. The P300 is a positive deflection in the EEG over parietal cortex about 300 ms after stimulus presentation (see (Walter et al. 1964, Donchin and Smith 1970)). The P300 response can be used as a BMI to indicate the subject's choices evoked by attention of the subject to the preferred versus non-preferred stimuli (Donchin et al. 2000, Sellers and Donchin 2006, Piccione et al. 2006).

The SSVEP is an oscillatory wave appearing over the visual cortical area in response to a visual stimulus modulated at a certain frequency rate. The oscillation frequency of the SSVEP matches that of the stimulus or its harmonics. In an SSVEP BCIs, several flickering lights with different frequencies are presented to the user. When the user gazes at a certain flickering light, the corresponding frequency appears in the SSVEP response and the user preferences can be translated into communication or control commands. Comparing to the other types of EEG-based BMIs, the SSVEPs can provide higher communication rates with less user training time (Middendorf et al. 2000, Cheng et al. 2002, Kelly et al. 2005, Wang et al. 2006b).

In general the EEG-based BMIs attempt to recognize and detect the subject's voluntary intentions by measuring the activity of a large population of neurons. However the spatial and temporal resolution of the EEG signal is highly limited due to the overlapping activities generated from different cortical areas and the low-pass filtering effect of the brain tissue, bone and skin (Lebedev and Nicolelis 2006). Regarding to the literature, it has been shown that the EEG-based BMI approaches can help severely or partially paralyzed patients to gain some basic forms of communication and control (Wolpaw et al. 2002, Birbaumer et al. 1999, Kübler et al. 2001, Sheikh et al. 2003)Although the EEG-based BMIs do not impose the surgery risk for entering the electrodes in the brain, these techniques provide communication channels with a limited capacity. Their typical transfer rate is currently 5-25 bits/s (Wolpaw et al. 2002, Birbaumer 2006) which is not sufficient for controlling a prosthetic limb with multiple degrees of freedom.

ECoG-based BMIs

ECoG signals are recorded by subdural electrode arrays implanted on the cortical surface. ECoGs typically have higher amplitude, higher signal-to-noise ratio (SNR) and offer superior spatial and temporal resolution with respect to EEG recordings. Because the dura–skull–scalp low-pass spatial filtering effect on EEG recordings does not exist in ECoGs (Freeman et al. 2003, Leuthardt et al. 2004). ECoG recording include μ and β rhythms as well as higher frequency gamma rhythms (40-200 Hz) which are not detectable in EEG recordings. Recent studies have shown that ECoG signals associated with movement or motor imagery can provide one or two dimensional BMI control with a few minutes of training (Leuthardt et al. 2004, Schalk et al. 2008). However, so far the possibility of long term clinical studies for ECoG-based BMIs on human subjects has not been provided. The main opportunity for ECoG-based BMI studies have been limited to short-term (one or two weeks) placement of subdural grids in candidates for epilepsy surgery (Leuthardt et al. 2004, Schalk et al. 2008).

Intracortical BMIs

Intracortical BMIs are referring to a group of BMIs that record brain signals from electrodes implanted within cerebral cortex. Fetz and collaborators showed in the late 1960s and early 1970s that monkeys could learn to use the activity of a single neuron to control the movement of a needle on a voltmeter in return for a food reward (Fetz 1969, Fetz and Finocchio 1971). These studies provided initial evidences that intracortical signals from the motor area could potentially be used for controlling BMI systems. Later studies showed that individual neurons in the arm areas of the motor cortex have their own preferred directional tuning (Schwartz et al. 1988). It has been also demonstrated that information about hand movement trajectories can be extracted very accurately from the combined activity of a population (e.g., 50 or more) of neurons in M1 cortical area of monkeys (Schwartz et al. 1988, Georgopoulos et al. 1988, Moran and Schwartz 1999). Chapin et al. presented a closed-loop intracortical BMI in which rats used their cortical spiking activities to control a one-dimensional robot arm for water reward (Chapin et al. 1999). Similar BMI approach was followed by using small populations of neural activity in cortex of primates for real-time closed-loop movement control in two (Serruya et al. 2002) and three (Wessberg et al. 2000, Taylor et al. 2002) dimensions. Carmena et al. reported successful intracortical BMI control of a robotic arm for reaching and grasping in monkeys (Carmena et al. 2003). BMI researches in primates have moved further toward real-time translation of intracortical signals into three-dimensional control of the robot's hand position as well as opening and closing of the hand for grasping and self-feeding (Velliste et al. 2008).

Promising achievements of intracortical BMIs in animal models have inspired studying BMI applications in human subjects. In the late 1990s Kennedy et al. implanted neurotrophic cone electrode in paralyzed human subjects and demonstrated the ability to use intracortical signals to control a computer cursor in one direction (Kennedy and Bakay 1998, Kennedy et al. 2000). The first clinical study of a human intracortical BMI system that used recording from populations of cortical neurons was reported by

Hochberg et al. in 2006 (Hochberg et al. 2006a). The results showed that humans with longstanding tetraplegia could use M1 cortical activity to operate computer software and control a robotic arm without learning or practice (Hochberg et al. 2006a).

Various movement information including limb velocity, position, forces, goals and plans for upcoming limb movement can be extracted from intracortical recordings (Scott 2008, Donoghue 2008, Scherberger and Andersen 2007). Therefore, intracortical recordings from different regions of the cortex are known as a rich source of information for BMI control.

Recent studies have shown that beside spiking activities recorded from intracortical microelectrodes, the LFPs (summation of electrical synaptic currents of all neurons in the vicinity of the electrode) may be used to control BMIs (Mehring et al. 2003, Kennedy et al. 2004, Andersen et al. 2004, Rickert et al. 2005).

Intracortical Recordings

An action potential (AP) is an electrical phenomenon specific to neurons or muscle cells. The difference in concentrations of ions inside and outside these cells makes a natural voltage difference across their cell membrane. When the membrane potential increases to a threshold, specific channels in the cell membrane rapidly begin to open and allow certain ions to pass through the membrane resulting in a transient shift in the potential across the membrane which generate AP. APs are often called spikes as they can be measured in a transient-time typically last for 0.4-3 ms (Nenadic and Burdick 2005). Neurons communicate with each other via synapses. They receive synaptic inputs to their dendrites from many different cells. Synapses can be excitatory or inhibitory and either increase or decrease activity in the target neuron. APs are the basic units of neural activity which pass through the complex network of the nervous systems to form all actions and thoughts (Kandel et al. 2000).

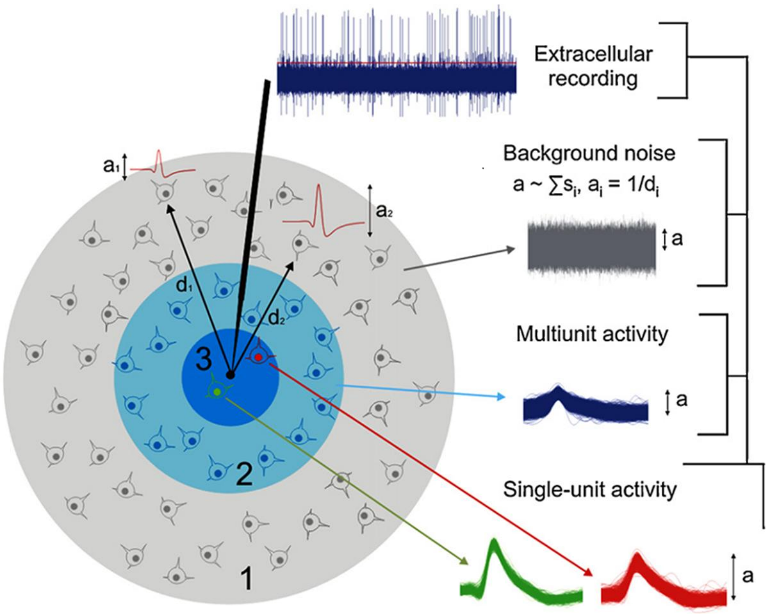

Fig. 2. A simulated schematic of extracellular recording (adapted and modified from (Martinez et al. 2009)). Relative to distance from the recording site (i.e., the center of the sphere), neurons in areas 1, 2, and 3 generate background noise, multi-unit and single-unit activities respectively of the sphere.

Electrophysiological activity of the neurons can be recorded from microelectrodes carefully placed inside neurons (intracellular) or in close proximity outside cells (extracellular). In extracellular recordings, if the electrode tip is small enough, it may allow selective recording of APs from a single neuronal unit. Single-unit APs have lower amplitude with respect to intracellulary recorded APs. Recording of single-unit activity is a particularly important tool for basic neurophysiological studies. It can provide useful information about discharge pattern of single neurons in response to a certain stimulus (neural encoding) (Rieke et al. 1999) or identifying coincident activity among neurons (Averbeck et al. 2006). Using larger electrode in tip size, the selectivity of the recording decreases and the electrode may simultaneously record the activity of several neuronal units which is referred to as multi-unit neural recordings. Separation of the spikes that originate from different neurons based on differences in each neuron's biophysical properties is called spike sorting. Neurons with large cell bodies generate larger spikes in the amplitude than smaller neurons. The spike peak amplitude decreases rapidly with the distance of the neuron from the electrode (Fig. 2). Consequently, microelectrodes record many small overlapping spikes from far away neurons to the recording site which mix together to generate a biological noise on the recording. Other sources of noise include the thermal noise in the recording electrode, the ambient noise of the recording hardware that altogether makes the background noise in extracellular recordings (Lemon and Prochazka 1984).

LFPs are signals that reflect local changes in electrical potentials generated by many nearby dendritic synaptic activity in the recording field (Mitzdorf 1985). In extracellular recordings the LFP has is lower frequency band (<300 Hz) (Pesaran 2009) while the spiking activity is higher frequency band (>300 Hz) (Fee et al. 1996b). Field potentials also can be recorded from electrodes located outside brain tissue. In such a case they only reflect broadly distributed changes in electrical potential over the area of the recording (i.e., EEG and ECoG).

Signal Processing for Intracortical BMIs

In this section, I provide background information in signal processing requirements for extraction of spiking activities from intracortical signals.

Signal Conditioning and Spike Detection

Spike detection is the first required signal processing for the BMIs that use spiking activities. Any spike detection method typically involves a signal conditioning step followed by the application of a threshold to separate spikes from the background noise. Various spike detection methods differ in how they perform signal conditioning and/or thresholding techniques. Signal conditioning is performed to emphasize the spike peaks against background noise and the procedure may involve a simple band-pass filtering or more complex techniques such as wavelet transforms. The simplest form of spike detection is application of a voltage threshold which is manually set by the operator and threshold crossings are recorded as spike occurrences. Due to the simplicity and its low computational cost, simple thresholding in time domain has been often used for real-time implementations of advanced cortically controlled BMI systems (Chapin et al. 1999, Hochberg et al. 2006a). A modified version of this method involves a signal rectification before threshold application to include both positive and negative spike peaks (Quiroga et al. 2004). The threshold value may be automatically identified by estimation of the background noise level as a multiple of the noise (i.e., plus signal) standard deviation (Quiroga et al. 2004). Matched filtering is another approach for signal conditioning for spike detection which has optimal detection performance when the spike waveforms are known a priori to the user. However the prior knowledge about the spike shapes is not usually available and therefore the templates must be reconstructed either manually by averaging spikes from a set of test data (Bankman et al. 1993) or by an automatic template reconstruction algorithm (Zhang et al. 2004, Zouridakis and Tam 2000). The detection performance in both cases degrades when the SNR is low (Obeid and Wolf 2004).

The Teager energy operator (TEO) also called as nonlinear energy operator (NEO) has been widely used as a signal conditioner for spike detection (Mukhopadhyay and Ray 1998, Kim and Kim 2000). The TEO generates a waveform proportional to the square of the instantaneous frequency and amplitude is sensitive to higher frequency noise samples (Choi et al. 2006). A modification on the TEO, called the Multi-resolution Teager Energy Operator (MTEO), combines the results of applying the energy operator to the signal with different resolution scales and has shown encouraging results in spike detection (Choi et al. 2006).

A different approach for signal conditioning is using wavelet transform. Using the wavelet transform, the signal is decomposed to different frequency sub-bands in which the spike are better localized whereas the noise is whitened. Therefore application of thresholds in wavelet sub-bands results in better separation of the signal from the background noise (Donoho and Johnstone 1994, Donoho 1995). Based on this rationale, several wavelet-based conditioning and denoising for spike detection have been proposed (Nenadic and Burdick 2005, Diedrich et al. 2003, Kim and Kim 2003b, Brychta et al. 2007, Citi et al. 2008). The optimal spike detection in wavelet-based methods relies on the proper selection of both the mother wavelet function and the frequency sub-band such that the discrimination of the neural spikes from the background noise becomes maximum. In the majority of the existing wavelet-based methods, these selections have been carried out manually using the experimenter's prior knowledge on the shape of the APs in the recordings (Nenadic and Burdick 2005, Diedrich et al. 2003, Kim and Kim 2003b, Brychta et al. 2007, Citi et al. 2008).

Signal Compression

Most of the current studies on intracortical BMIs record data from implanted microelectrodes using electrode wire arrays. Wires travelling through the skin can potentially introduce the risk of infection and/or torque applied to the prosthetic (Harrison et al. 2007). Wires may restrict the movement of the subject in behavioral paradigms. Another potential problem is the external noise and interfering signals, which easily couple to wires to corrupt weak neural signals (Harrison et al. 2007). An alternative is to transmit the neural signals through a wireless communication link to the processing unit. However, intracortical BMIs with high channel count interacting at the single-unit spike activity level of detail would require an ultra-high bandwidth communication link. For example, a typical recording microelectrode array with 100 recording channels sampled at 25 kHz per channel and quantized with 12 bps needs a total bandwidth of 30 Mbps which is currently beyond the capability of common low-power transcutaneous wireless telemetry system. Although using the state-of-the-arts in ultra-wide bandwidth transmitters (Miranda et al. 2010, Gao et al. 2012) this bandwidth may be exceeded in the near future, but only at a great power cost which may cause tissue damage and reduce battery life. Moreover, the number of electrode channels grows very fast with new technologies and in the near future up to hundreds or thousands of implantable nanowire electrodes may become available (Du et al. 2011, Suyatin et al. 2013). Therefore data reduction is a serious demand for the future researches. However there is always a tradeoff between data reduction and the amount of information retained for further signal processing tasks, such as spike sorting. One possibility would be to extract the most critical information onsite and to transmit it to the processing unit outside for translation into neural commands used in BMI control. For instance, one can detect the neural spikes and send the time occurrences to indicate the firing pattern of multi-unit activity (Harrison et al. 2007, Sodagar et al. 2007). However this approach loses single-unit spike identities. Alternatively, one might send only the data samples which pass a threshold level (i.e., as estimation of the noise level) (Perelman and Ginosar 2007, Rizk et al. 2009). Another option is to go further and calculate the discriminative features for each detected spike onsite and send the feature sets through a wireless link (Holleman et al. 2008, Chae et al. 2009). There are also some recent studies suggest to the complete procedure of the spike sorting onsite and send the single-unit firing patterns (Chae et al. 2008, Zhang et al. 2010, Karkare et al. 2011, Chen et al. 2012).

Another approach is to transmit as much information about the signal as possible, under the constraint of low bandwidth. So, rather than using extracted information about spike instants or spike counts, the goal is defined as using a “lossy” compression which reduces transferable bits by identifying unnecessary information (i.e., noise) and removing it. This approach enables reconstruction of the whole intracortical signal at a lower bandwidth that allows more advanced spike detection and sorting signal processing algorithms to be utilized at the back-end. Among those who selected the latter approach, a group of studies have been performed the intracortical signal compression by using vector quantization (VQ) techniques (Paiva et al. 2005, Cho et al. 2007, Rao et al. 2007, Craciun et al. 2011) based on self-organizing maps (SOM) (Kohonen 1990). However these methods involve a computationally extensive learning procedure and also the performances of these techniques have not been tested under low SNR which is not uncommon condition in intracortical recordings.

Wavelet transforms also have been widely used in signal compression (Vetterli and Kovačević 1995). The usefulness of wavelets for data compression and denoising is mainly based on the sparseness capabilities of the transform. It means that a successive projection of the signal on wavelet basis become localized in very few large (i.e., significant) coefficients, while the other coefficient are small enough that can be set to zero (i.e., insignificant). The efficient application of wavelet compression in biomedical signals has been shown in many studies (Hilton 1997, Lu et al. 2000, Brechet et al. 2007, Nielsen et al. 2006). Recently a DWT-based method for compression of multi-channel neural signals has been proposed by Oweiss et al. (Oweiss 2006, Oweiss et al. 2007). More recently the use of compressed sensing (CS) (Donoho 2006) for the compression of continuous neural signals was demonstrated to efficiently work for high SNR neural spike signals (Chen et al. 2010). However another study showed that the CS approach for noisy recorded signals does not work satisfactorily (Bulach et al. 2012).

Spike Sorting

Spike sorting is a processing algorithm to separate single-unit activities related to individual neuronal units from a mixed activity of multiple neurons recorded on an extracellular electrode. To differentiate between measured activities of different cells on the recording signal, the difference between projected spike shapes can be used (Wheeler and Heetderks 1982, Lewicki 1998). A common general assumption in all the spike sorting methods is that each individual neuron in close proximity of the recording electrode generates a distinct spike shape which remains constant during a recording session. Of course, this assumption is only valid under the condition that the electrode and tissue remain in the same position and no electrode/tissue drift happens during the recording. The spike sorting often involves sequential processing steps. Having the segmented spike waveforms from the spike detection step, the first step is a temporal alignment of the waveforms which follows with a feature extraction that emphasizes the difference among waveforms. In the specified feature (or its reduced dimension) space, a clustering will separate the spikes and the firing patterns related to each isolated cluster will be identified as a single-unit activity. In the following we briefly describe different processing steps in the spike sorting (i.e., Alignment, feature extraction, and clustering)

Spike Alignment

The segmented spike waveforms after the detection are primarily aligned to their threshold crossing maximums. The effect of the noise on spike shape distortion together with insufficiency of the sampling rate (i.e., temporal jitter) can result in a misalignment in spike waveform. In order to accurately classify the waveforms, their alignment must be corrected by a reasonable criterion so that that they are accurately registered with one another. The waveforms first need to be up-sampled by an interpolation technique (e.g., a cubic spline) to perform the alignment with higher temporal resolution to minimize the effect of the sampling jitter (Wheeler and Smith 1988). After realigning the waveforms with a robust criterion, the data can be down-sampled to retain its original sampling for the feature extraction step (McGill, Dorfman 1984).

Different criteria have been proposed for the spike alignment in the literature. The waveforms can be aligned to their global peaks or the peak principal component energy of the waveforms (Quiroga et al. 2004, Lewicki 1998, Wheeler and Smith 1988). Another criterion for alignment is putting the waveform to the point of maximum correlations (Wheeler and Heetderks 1982, McGill and Dorfman 1984). Others have proposed alignment to the maximum slope (Chandra and Optican 1997), maximum integral alignment (Zviagintsev et al. 2006), and maximum of MTEO detector output (Choi et al. 2006).

Feature Extraction

Selecting a group of features from spike waveforms which better characterize the difference between single-unit spikes has been discussed in the spike sorting literature for a long time (Lewicki 1998). In earlier studies where the computer processing resources were limited, efforts were focused on extracting a small number of outstanding visual features from the spike such as peak amplitudes, width, spike area and conduction velocity (Wheeler and Heetderks 1982, Lewicki 1998, Schmidt 1984). The idea of automatic selection of distinctive features for the classification started with principal component analysis (PCA)

(Glaser and Marks 1968, Glaser 1971). PCA is a linear transform that convert the data of interest into a set of ordered orthogonal vectors (i.e., principal components) in which the first component captures the largest variation of the data and the last one represents the smallest variation. In such an order, it would be enough just to select a few of the first components out of many which represent the most variation of the data for the classification. The PCAs are shown to provide more accurate classification with respect to the elementary shape features (Wheeler and Heetderks 1982, Rutishauser et al. 2006). However the PCA procedure involves computation of eigenvectors from covariance matrix of the data which leads to a high computational cost that is not affordable in real-time applications (Gibson et al. 2012).

In some cases, different spikes may have a general similarity but have some transient differences in high frequency features (like sharp edges and steep leading or trailing slopes) and/or in low frequency features (like the duration of the repolarization phase). In these cases the studies showed that such features are usually not reflected in the first principal components, therefore the PCA method may fail to correctly classify such spikes, however these localized time-frequency features in the spike profiles can be captured by wavelet transforms (Letelier and Weber 2000, Pavlov et al. 2007). Some forms of wavelet transform such as discrete wavelet transform (DWT) and stationary wavelet transform (SWT) can be implemented by fast algorithm of filter banks which provide another advantage over complex PCA methods (Letelier and Weber 2000, Zouridakis and Tam 1997). Automatic methods for selection of discriminative wavelet coefficients has been also reported that select a subset of features with higher standard deviation (Letelier and Weber 2000) or higher deviation from normality (Quiroga et al. 2004).

A feature extractor that utilizes projection pursuit based on *negentropy* maximization has been reported to achieve separability higher than that of PCA under low SNRs (Kim and Kim 2003a). Some studies have suggested that using spike derivatives as features can provide comparable discrimination with that of PCA but involve substantially lower computational complexity which makes the method suitable for real-time applications and hardware implementations (Karkare et al. 2011, Gibson et al. 2008, Yang et al. 2008, Paraskevopoulou et al. 2013).

Clustering

The main part of all spike sorting methods is an algorithm that separates the spikes into different clusters in the feature space. Supervised clustering methods such as template matching (Bankman et al. 1993, Gozani and Miller 1994), neural network (Kim and Kim 2000, Chandra and Optican 1997), and support vector machine (Vogelstein et al. 2004, Ding and Yuan 2008), have been used. However an ideal spike sorting method should work automatic and unsupervised. To develop an unsupervised spike sorting, an early effort has been performed by using K-means clustering algorithm (Salganicoff et al. 1988). K-means defines a set of boundaries to partition the data into *K* clusters in which each spike belongs to the cluster with the nearest mean. Although being unsupervised, K-means clustering is rather sensitive to outliers resulted from noises and/or overlapping spikes, which may cause problems in spike sorting. A probabilistic alternative to the spike sorting is Bayesian clustering which models the statistical distribution of each cluster as a multivariate Gaussian and the whole data as a mixture of Gaussians (Lewicki 1994, Harris et al. 2000, Pouzat et al. 2002). However this assumption has been argued that may not be reliable in all conditions (Fee et al. 1996b). A study claimed that using multivariate *t*-distributions instead of multivariate Gaussians is better suited to model the observed statistics in the neural spike clusters (Shoham et al. 2003).

Super-paramagnetic clustering (SPC) (Quiroga et al. 2004) is another approach for spike sorting that does not assume any particular statistical distribution of the data and groups the spikes into clusters in a hierarchical clustering regime with increasing number of clusters from low to high as a function of a parameter called as temperature which is optimized in the algorithm (Quiroga et al. 2004). Some other studies have also reported efficient use of hierarchical clustering approach in the spike sorting problem (Fee et al. 1996a, Kaneko et al. 1999, Geng et al. 2010).

Multi-Units versus Single-Units

Although spike sorting is a unique possibility to extract the neural firing patterns in single-unit level from the extracellular recordings, some studies have shown that even without sorting, mixed spiking activities of neural recordings in multi-unit level can be effectively used for BMI control (Carmena et al. 2003, Stark and Abeles 2007, Fraser et al. 2009, Townsend et al. 2011). In fact, removing the spike sorting from intracortical signal processing can be beneficial in two ways. First, it saves time and computational cost, making the whole procedure more appropriate for real-time implementation. Secondly, under low SNRs where usually no spike sorting method can accurately separate the spikes, such mixed information can still be used for BMI control.

Single Channel versus Array Processing

Multiple recordings of the same neuron from closely spaced arrays of electrodes (e.g., stereotrodes, triodes, tetrodes (McNaughton et al. 1983, Gray et al. 1995) can provide more reliable information about the neural activity that potentially improves the accuracy of spike sorting. However, there are also some sources of noise that can generate approximately similar or correlated potentials on closely spaced electrodes. Different sources for such correlated potentials (i.e., noise) include the noise from the reference electrode, electromyogram (EMG) from muscles in the scalp, jaws and neck, electrical artifacts generated in the wiring harness by abrupt movements, and other types of induced electrical artifact as the subject moves and/or touches various portions of the apparatus (Musial et al. 2002). The spatial gradient across an electrode array of these noise potentials can be used in different array processing methods to separate them from the neural spike activities. (Musial et al. 2002, Bierer and Anderson 1999, Rebrik et al. 1999, Oweiss and Anderson 2001, Oweiss and Anderson 2002, Snellings et al. 2006, Aminghafari et al. 2006).

Open Issues in Signal Processing for Intracortical BMIs

In this section I describe current limitations and open problems in signal processing requirements for extraction of spiking activities from intracortical signals.

Open issues in spike detection

1- Low SNR: Performance of all spike detection methods decreases under low SNR conditions [check definition of all acronyms]. In particular, methods that use the representation of the signal in time domain fail when the spike amplitude peaks are close to or lower than the noise level (Obeid and Wolf 2004, Kim and Kim 2000). Matched filtering can perform better detection when the spike templates are properly identified either by a human operator (Bankman et al. 1993) or by an automatic template reconstruction algorithm (Zhang et al. 2004, Zouridakis and Tam 2000). However the detection performance in both cases degrades when the SNR is low (Obeid and Wolf 2004, Kim and Kim 2000).

2- Optimal Conditioning: Transformation-based spike detection methods (e.g., Wavelet transform, TEO, MTEO, etc.) which project the signal into a new domain for better conditioning (i.e., separation of spike from background noise) always confront a trade-off between optimal selection of the transformation parameters and the detection performance. Due to random positioning of the electrode and the morphology of the neuron (Gold et al. 2006), there is a significant variability in the spike waveforms and their time-frequency characteristics in different experimental recordings. Therefore, optimal parameter selection for the transformation that leads to maximum detection performance is signal-dependent. For instance, various choices of mother wavelet have been reported in different studies for spike detection based on *a priori* knowledge on the spike shapes, including Daubechies (Nenadic and Burdick 2005, Oweiss and Anderson 2001), Symlet (Diedrich et al. 2003, Citi et al. 2008), Coiflet (Kim and Kim 2003b), and Biorthogonal (Nenadic and Burdick 2005). Most of the transformation-based detectors either use fixed parameter selections (not optimal) or need parameter setting by the experimenter which means supervision. Selecting the optimal wavelet function and/or scale parameter needs experimenter supervision for current wavelet-base spike detection methods (Nenadic and Burdick 2005, Diedrich et al. 2003, Kim and Kim 2003b, Brychta et al. 2007, Citi et al. 2008).

Open issues in signal compression

1- Low SNR: A group of approaches which use simple thresholding in time domain onsite to extract and transmit the time occurrences or waveforms of unsorted spikes (Harrison et al. 2007, Sodagar et al. 2007, Perelman and Ginosar 2007, Rizk et al. 2009) fail to detect the spike which peaks are close to the noise level (Obeid and Wolf 2004, Kim and Kim 2000). Using NEO method for onsite spike detection (Holleman et al. 2008, Chae et al. 2009, Zhang et al. 2010, Karkare et al. 2011, Chen et al. 2012) may provide better detection performance than time domain thresholding, However it is sensitive to higher frequency noise samples (Choi et al. 2006). The methods which use nonlinear VQ techniques for compression (Paiva et al. 2005, Cho et al. 2007, Rao et al. 2007, Craciun et al. 2011) have not been tested under low SNR conditions.

2- Unsupervised basis selection: Wavelet based methods need to select a wavelet basis for compression. The basis selection procedure is supervised in most of the proposed methods (Oweiss 2006, Oweiss et al. 2007, Kamboh et al. 2007, Yang and Mason 2011). Wavelet packets have been used previously for basis selection in biomedical signal compression (Brechet et al. 2007, Nielsen et al. 2006), where, however, denoising (and its influence on the choice of the wavelet packets tree) had not been considered in those studies.

3- Computational cost: Advanced methods for compression usually involve more computational complexity which may be suitable for implantable neural signal processors. However using power-efficient VLSI technologies, some implementations of wavelet transform for signal compression in high-density intracortical Implants has been reported (Oweiss et al. 2007, Kamboh et al. 2007, Yang and Mason 2011).

Open issues in spike sorting

1- Optimal feature space: To obtain best separation of the spikes especially under low SNR condition, the spikes should be projected in an optimal basis for clustering. As mentioned before, PCA does not reflect transient differences in higher for lower frequency features. The state-of-the-arts in spike feature extraction use wavelet transform for capturing distinctive localizations in time-frequency (Quiroga et al. 2004, Letelier and Weber 2000, Pavlov et al. 2007). However most of the wavelet based methods use a predefined mother wavelet function that might not provide best separation for any group of spikes. For this reason, Hulata et al. (Hulata et al. 2002) proposed a method for optimal basis selection for the wavelet packet decomposition. However, the method involves a supervised procedure and user intervention in preparing the training dataset for the optimization task.

2- Signal nonstationarity: The problem of time-varying (non-stationary) spike waveform shapes arise during the spike sorting procedure, while the algorithm takes a short-time segment of the recording for analysis and assigns each group of clustered spike shapes to the activity of a neuron; Duo to possible drifts in the position of the recording electrode or tissue over some longer periods of time, geometrical properties of the clustering feature space would be in subject to change, It is also possible that some active units disappears or some new units arise in the recording (Snider and Bonds 1998). Bar-Hillel et al. (Bar-Hillel et al. 2006) proposed an offline batch processing a Bayesian framework in the clustering process, with the source neurons modeled as a non-stationary mixture-of-Gaussians; candidate descriptions of the data and transition probabilities between candidate mixtures were computed for each short time-frame separately; a globally optimal clustering solution was found as the maximum a-posteriori solution of the resulting probabilistic model. Recently, Wolf et al. (Wolf and Burdick 2009) presented a solution of the problem in real-time applications with similar approach on using Bayesian clustering algorithm to optimize a Gaussian mixture model via expectation maximization (EM), they also used prior data to determine both the model parameters to seed the clustering algorithm and the select the model order. However the algorithm can be applied only if the distribution of a neuron's spikes in the feature space could be modeled as Gaussian which often is not verified (Harris et al. 2000, Shoham et al. 2003, Fee et al. 1996a, Schmitzer-Torbert et al. 2005, Delescluse and Pouzat 2006).

3- Overlapping spikes: It may happen that two or more neurons fire simultaneously, in a manner that their projected spikes overlap with each other in the recorded signal. In such a situation the generated spike shape is a rare composition of two or more spikes that is not classifiable to any sorted clusters of single-unit spikes. Overlapped waveforms are generally identified as outliers and discarded in most of the conventional spike sorting methods (Gibson et al. 2012). Generally if the frequency of these overlapping events is relatively low with respect to the firing rates of single-units, discarding them does not cause critical error in the spike sorting. However, the ideal choice is to resolve overlapping waveforms into their component parts to have more accurate timing of single-units. Several methods have been developed for resolving this problem (Zhang et al. 2004, Chandra and Optican 1997, Ding and Yuan 2008, Lewicki 1994, Prochazka et al. 1972, Atiya 1992, Takahashi et al. 2003, Wang et al. 2006a, Ge et al. 2011).

4- Spike sorting withdrawal: Some studies have shown that without spike sorting, multi-unit activities can also be used for BMI control (Carmena et al. 2003, Stark and Abeles 2007, Fraser et al. 2009, Townsend et al. 2011). However, due to limited detection performance of the spike detection methods under low SNRs (i.e. in aforementioned studies), the extracted multi-unit spiking information might be contaminated by noise from spike detection error and thus limit the BMI performance.

Introduction to the wavelet Transform

Since the wavelet transform is used in various forms in the thesis, a short introduction to the different forms used in this thesis is described in this section.

A wavelet transform decomposes any signal $f(t) \in L^2(\mathbb{R})$ over scaled and translated wavelets. A wavelet is a normalized (unit energy) and zero mean function $\psi(t) \in L^2(\mathbb{R})$. The function $\psi(t)$ is sometimes called "mother wavelet". A dictionary of wavelet atoms $D = \{\psi_{u,s}(t)\}$ is obtained by scaling $\psi(t)$ by s and translating it by u (Mallat 2009). The corresponding linear time-frequency transformation is defined by:

$$Wf(u,s) = \langle f(t), \psi_{u,s}(t) \rangle = \int_{-\infty}^{+\infty} f(t) \frac{1}{\sqrt{s}} \psi^* \left(\frac{t-u}{s} \right) dt. \qquad (1)$$

As the scaling parameter s changes, the group of dilated atoms $\psi_{0,s}(t) = \frac{1}{\sqrt{s}} \psi\left(\frac{t}{s}\right)$ cover different frequency ranges. Small values of the scaling parameter s correspond to high frequencies or very fine scales $\psi_{0,s}(t)$ and larger values of s correspond to lower frequencies or larger scales $\psi_{0,s}(t)$. The parameter u also allows changing the time localization center. Each $\psi_{u,s}(t)$ is localized around $t = u$. Therefore the transformation (1) provides a complete time-frequency description of $f(t)$.

There exist many different types of wavelet transform that all of them can be described by the basic transformation formula (1).

Continuous Wavelet Transform

In continuous wavelet transform (CWT) the scaling and translation parameters s, u vary continuously over $\mathbb{R}$ (except $s = 0$). The CWT formula follows the equation (1). The CWT was used in study IV of this PhD thesis as a method for spike detection as previously proposed in (Nenadic and Burdick 2005).

Discrete Wavelet Transform

For some very special choices of the mother wavelet function $\psi(t)$ and also special sampling of the scaling and translation parameters s, u , the wavelet atoms $\psi_{u,s}(t)$ constitute an orthonormal basis for $L^2(\mathbb{R})$. In particular, if we sample the scale parameter s with a dyadic growth $\{2^j\}_{j\in\mathbb{Z}}$ and sample the translation parameters $u \in \mathbb{R}$ as $u = n\,\{2^j\}_{j,n\in\mathbb{Z}}$ then we have wavelet atoms $\psi_{n,m}(t) = 2^{-j/2}\psi(2^{-j}t - n)$ with good time-frequency localization properties that constitute an orthonormal basis for $L^2(\mathbb{R})$. The orthonormal wavelet atoms $\psi_{n.m}(t)$ cover the entire time-frequency domain without overlap (Daubechies 1992). This orthonormal wavelet bases provide a non-redundant and efficient representation of the signal, referred to as discrete wavelet transform (DWT), consisting of as many coefficients as present in the input signal and with a bandwidth set to half of the sampling rate. The DWT can be computed with a fast filter bank algorithm if the wavelet is appropriately designed. The signal is transformed into multiple resolution levels by projecting it on a family of scaling and wavelet functions. The approximation and the detail coefficients are computed on each scale of decomposition by applying a low-pass filter h and a high-pass filter g derived from the scaling and the wavelet basis functions (Mallat 2009). The high-pass filter g can be deduced from the low-pass filter h through the relation $g[k] = (-1)^{1-k}h[1-k]$, and thus one filter defines the entire decomposition. The DWT was used in study I of this PhD thesis for extracting features from spikes prior to clustering.

Stationary Wavelet Transform

The Stationary wavelet transform (SWT) is a dyadic discrete wavelet transform algorithm designed to overcome the lack of translation-invariance of the DWT. The SWT is a redundant scheme as the output of each level of SWT contains the same number of samples as the input. Thus a redundancy equal to the number of decomposition levels exists in SWT coefficients (Nason and Silverman 1995). The fast algorithm for computing SWT is known as "algorithme à trous" (Holschneider et al. 1989). Contrary to the DWT, the SWT does not down-sample the output signal after filtering. Conversely, the discrete filter coefficients are up-sampled at each level by inserting zeros in the filters (impulse response). In this PhD thesis, the SWT was used to extract the time-frequency coefficients in study I and IV.

Wavelet Parameterization

In the case of using orthogonal basis for DWT or SWT, the decomposition and, accordingly, the mother wavelet can be completely defined by the scaling filter *h*, and thus the parameterization of *h* provides a way to describe a family of decompositions and mother wavelets. To generate an orthogonal representation of wavelets in the multi-resolution analysis framework, *h* must satisfy certain conditions which leave $L/2 - 1$ free parameters, where L is the filter length (Lawton 1990, Lawton 1991). For $L = 4$, the design parameter vector is reduced to a scalar parameter α :

$$i = 0, 3 \quad h\,[i] = \frac{1 - \cos(\alpha) + (-1)^i \sin(\alpha)}{2\sqrt{2}}$$

$$i = 1, 2 \quad h\,[i] = \frac{1 + \cos(\alpha) - (-1)^i \sin(\alpha)}{2\sqrt{2}}$$

In the studies, we used the filter length $L = 4$, corresponding to only one independent parameter. This choice reduces the computational time with respect to longer filters and thus may allow the method to be implemented in real-time applications. In this thesis, the parameterization scaling filter was used to find the optimal mother wavelet function for spike detection and sorting in study I and IV.

Fine Stationary Wavelet Transform

Considering the basic wavelet transformation formula (1), It is possible to construct a more general translation-invariant dictionary by sampling the scale parameter s with an exponential growth $\{\alpha^j\}_{j\in\mathbb{Z}}$, where $\alpha > 1$, and sampling the translation parameters $u \in \mathbb{R}$ linearly in discrete time (Mallat 2009). A special choice of $\alpha = 2$ in the case of orthogonal and biorthogonal wavelet bases corresponds to the SWT for which fast computer implementation is possible with a filter bank algorithm (Holschneider et al. 1989). In order to increase the resolution of the scaling, one can choose a finer scaling value in the range of $1 < \alpha < 2$. In study IV of this PhD Thesis, a fine scale sampling of $\alpha = 1.25$ was used which is named as fine stationary wavelet transform (FSWT).

Discrete Wavelet Packets Transform

Discrete Wavelet Packets Transform (DWPT) is a generalization of DWT. In DWT, only the low frequency sub-band (the approximation coefficient) is passed through the next level filters (Fig. 3). Whereas in DWPT both low and high frequency sub-bands (the approximation and the detail coefficients) are decomposed in the next level (Coifman and Wickerhauser 1992). The use of a DWPT provides better adaptation to the signal characteristics with respect to the dyadic transform (DWT). This, in turn, implies that a suitable basis has to be chosen among the large number of possible ones induced by different wavelet packet trees. A cost function is usually associated with each possible tree and the best basis is chosen as the result of an optimization process over the costs. . In study II of this PhD Thesis, the DWPT with a customized cost function was used for denoising and compression of intracortical recordings.

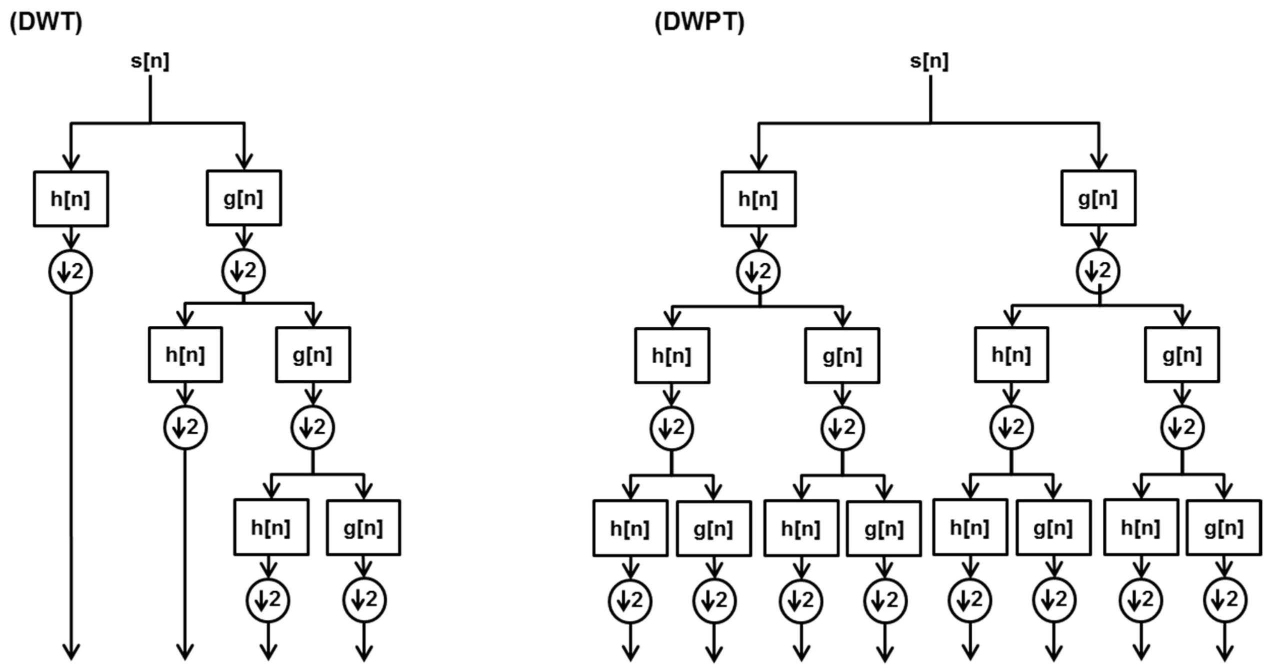

Fig. 3 Decomposition of signal in two types of wavelet transforms (DWT and DWPT) by using filter banks of low-pass *g* and high-pass *h* filters over three levels.

A Note on Definition of SNR

The definitions of SNR in previous works on AP detection and sorting are several, without an accepted common definition (Nenadic and Burdick 2005, Diedrich et al. 2003, Kim and McNames 2007, Kim and Kim 2003). In this PhD thesis, the studies which involve AP detection or sorting (study I, III, IV), the SNR was defined as ratio of the average absolute peak amplitude of APs to three times standard deviation of the background noise as follows.

$$\mathrm{SNR} = \frac{\frac{1}{N}\sum_{i=1}^{N}\mathrm{Max}(|\mathrm{AP}_i|)}{3\sigma_{\mathrm{Noise}}}$$

where $\{\mathrm{AP}_i\}_{i=1:N}$ are the APs waveforms and σ_{Noise} is the standard deviation of the background noise. This definition does not depend on the level of activity (number of spikes) and is intuitively related to the complexity of detection by a threshold. The denominator shows the minimum threshold level can be set to separate the AP peaks from the background noise. For instance, SNR=1 represents the situation in which the spike peaks and the background noise have comparable amplitude levels.

In study II of the thesis, where the purpose is developing a method for joint compression and denoising of the continuous-time intracortical signal, the SNR was defined similar to the general definition in engineering as the ratio of the signal power to the noise power in the recording in decibels:

$$\mathrm{SNR} = 10 \cdot \log_{10}\left(\frac{P_{signal}}{P_{noise}}\right) \mathrm{dB}$$

For example, the SNR in simulated data in study II was defined as

$$\mathrm{SNR} = 10 \cdot \log_{10}\left(\frac{\sum_{i=1}^{n} x_i^2}{\sum_{i=1}^{n}(\hat{x}_i^2 - x_i^2)}\right) \mathrm{dB}$$

where x_i and $\hat{x}_i$ are the i-th sample of the original (noisy) and the reconstructed (denoised) signals, respectively, and n is the length (the number of samples) of the signals.

Chapter 3: Aim of the Thesis

Considering the survey on the current challenges in the field of signal processing for the intracortical BMIs, the aim of the thesis is to propose signal processing methods to enhance the accuracy and performance of extracting neural information from intracortical signals in BMIs. Noise in the recordings, usually holds an important role in degrading the signal quality and limiting the accuracy and performance of information extraction. Therefore, increasing the performance and the accuracy of extracted information in each of the basic processing steps described in the previous section (i.e., spike detection, signal compression, and spike sorting) against noise and disturbance is aimed in this thesis. Methods to increase the accuracy of spike detection in low SNR recordings based on optimal conditioning are proposed in two studies (Study I and Study IV). Another study is dedicated for proposing a method to increase compression rate while reducing noise in a joint compression/denoising scheme for intracortical signals (Study II). To increase the clustering performance for spike sorting step, an optimal feature space selection method is proposed (Study I). Dealing with nonstationarity in intracortical recordings again to increase the spike clustering performance is investigated in a separate study (Study III). Finally, considering the possibility of spike sorting withdrawal, the effect of signal optimal conditioning for accurate detection of multi-unit spiking activity in enhancing event-related neural response is investigated (Study IV). A general description of the proposed methods and the hypothesis for each study is written in detail as following.

Study I: “Spike detection and clustering with unsupervised wavelet optimization in extracellular neural recordings.”

In this study we proposed methods to improve spike detection and clustering in low SNR intracortical signals by employing signal-dependent criteria to optimize the mother wavelet selection. The lattice parameterization was used which provides the opportunity to design scaling filter via unconstrained optimization of a scalar parameter. A signal-dependent criterion for the optimization based on correlation measures on the detected APs was defined. Moreover, another criterion based on a within cluster similarity measure was defined to update the wavelet selection during the clustering task. The hypothesis was that the wavelet which maximizes the criterion would be the optimal choice leading to the best spike detection performance and updating the wavelet selection for feature extraction toward maximum within cluster similarity criterion would further improve the spike clustering performance. Furthermore, it was proposed that the combining significant coefficients (i.e., after thresholding) from multiple scales would provide a robust manifestation for spike detection (i.e., in time-scale domain) without need to transforming back to the time domain. The proposed methods in this study were compared to several previously proposed methods by using a wide range of realistic simulated data as well as selected experimental recordings of intracortical signals from freely moving rats.

Study II: "Denoising and compression of intracortical signals with a modified MDL criterion."

In this study we investigated the possibility of employing *minimum description length (MDL) principle* as a cost function for optimal wavelet packet basis selection for denoising and compression of intracortical signals. Previous studies have shown that the commonly used *entropy* cost function for wavelet packet basis selection does not account for the statistical properties of the noise and the sensitivity of the basis search to noise realization can result in highly variable performance (Krim et al. 1999, Krim and Schick 1999). The hypothesis in this study was that using a modified MDL-base criterion in wavelet packet basis selection and denoising would better capture the most regularity in the data with respect to the entropy-based optimization. Moreover, an embedded zero-tree wavelet packet (EZWP) coding was used for compression of the wavelet packet coefficients after denoising. The method was tested on both simulated and experimental intracortical signals to assess its performance with respect to standard state-of-the art denoising techniques.

Study III: “A nonparametric Bayesian approach to sorting and tracking non-stationarities of the neural spikes.”

In this study we proposed a nonparametric probability density estimation of spike feature clusters for tracking nonstationarities of neural signals over successive time intervals. Kernel based density estimation was used to learn cluster probability distribution functions (PDFs) in two-dimensional feature space. In each new time intervals the spikes were associated to their clusters by using a naïve Bayes classifier with learnt cluster PDFs from past and cluster PDFs were updated according to the new data. The hypothesis was that using the proposed method, smooth changes in spike waveforms could be better tracked during a long period of time with respect to Gaussian model-based approach for cluster tracking. The method was tested by using synthetically generated spike data that simulate a non-stationary scenario.

Study IV: “Enhancing event-related neural response by using optimized wavelets for spike detection.”

The objectives of this study were: 1) to develop a completely unsupervised conditioning method for optimal detection of neural spikes from intracortical signals with low SNR; and 2) to investigate the effect of using the proposed optimal spike detection on representation of event-related neural response in primary motor cortex recordings during a behavioral experiment. For the first objective, a novel algorithm was proposed that convolves the signal with a large dictionary of wavelet functions, each scaled to match several frequency sub-bands. The method blindly estimates the SNR and selects the signal projections that yield maximum SNR. A combination of the selected signal projections is then used for detecting multi-unit spikes. The hypothesis was that using selected signal projections which maximize the blind criterion would provide optimal spike detection in terms of the measured detection performance. The hypothesis for the second objective was that using the proposed optimization method in spike detection task would enhance the representation of event-related neural response relative to other (non-optimal) spike detection methods. The proposed algorithm was first tested with different wavelet dictionaries and compared to previously proposed methods by using simulated data. Further, the algorithm was tested using intra-cortical recordings from rats trained to perform a specific forelimb movement.

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Chapter 8: Conclusions

An overview of applications and recent achievements in intracortical BMI systems was conducted in chapter 2. Based on that, extending the use of intracortical BMIs outside the research environment in clinical applications is expected in the near future. However to move toward clinically viable intracortical BMIs, the system performance should be reliable enough over long-term usage. Signal degradation factors such as background noise that exist in the intracortical recordings can reduce the accuracy of neural information extraction and thereby reduce the efficiency of BMIs. Therefore the aim of this thesis was to develop a set of methods and algorithms to enhance accuracy of neural information extraction from intracortical signals against signal degradation factors to improve the overall performance of BMI systems. For this purpose, a set of limitations in available neural information extraction methods were identified in required steps of processing intracortical signals including spike detection, spike sorting, signal compression and denoising. In each step alternative methods were proposed to overcome current limitations.

The first study (Study) was dedicated to develop methods for enhancing spike detection and sorting accuracy in intracortical recordings. The study showed that neural spikes can be effectively detected by using a combination of denoised wavelet frequency sub-bands. The study also showed that optimal selection of mother wavelet from a parameterized function could significantly improve the spike detection performance by using a signal-based criterion. In the next step, the parameterized wavelet was used for optimal selection of distinctive wavelet features for spike sorting. The results demonstrated that the proposed optimization could improve spike sorting performance.

The results from the Study I demonstrated that using wavelet transform in both spike detection and spike sorting could improve the accuracy of neural information extraction which has been also shown in other studies (Nenadic and Burdick 2005, Diedrich et al. 2003, Kim and Kim 2003b, Brychta et al. 2007, Citi et al. 2008, Letelier and Weber 2000, Pavlov et al. 2007, Quiroga et al. 2004). However the significance of this study lies in demonstrating the sensitivity of spike detection (or sorting) performance to the mother wavelet selection and proposing signal based criteria for unsupervised optimal selection of the wavelet. The computational cost of the optimization process may be considered as a limitation for online implementation. However as proposed in the work, the optimization can be updated occasionally (e.g., every 10 s). Another limitation of this study was the use of dyadic divisions in the frequency domain which is not necessarily an optimal choice for finding the signal energy localization in the frequency band. This issue was addressed in Study IV.

The second study (Study II) proposed methods to improve the performance of denoising and compression of continuous intracortical signals. The study demonstrated that the modified MDL criterion could be effectively employed as a cost function for wavelet packet basis selection and denoising of low SNR intracortical recordings. The study also proposed applying a zero-tree coding on denoised wavelet packet coefficients for compression of the signals. Under low SNR conditions, the result showed that, in combination of zero-tree coding with different algorithms for wavelet packet basis selection and denoising, the best combination in terms of SNR of the reconstructed signal was achieved by using MDL-based wavelet basis selection and the per band soft denoising. The obtained results imply that under low SNRs, MDL criterion could better capture the most regularity in the data with respect to the entropy-based optimization. This can be considered in agreement to what has been shown in previous studies that the entropy cost function for wavelet packet basis selection does not account for the statistical properties of the noise and the sensitivity of the basis search to noise realization can result in highly variable performance (Krim et al. 1999, Krim and Schick 1999).

Study III focused on clustering nonstationarity of spike waveforms caused by electrode/tissue drift. A sequential Bayesian clustering based on nonparametric estimation of cluster PDFs in two-dimensional PCA basis was proposed. By dividing long recording time into short time frames, the cluster PDFs were estimated with kernel-based methods and the PDFs were used as priors for Bayesian classification of data in the subsequent time frame. It was shown that the clustering performances obtained from nonparametric estimation of cluster PDFs were consistently higher than the clustering performances resulted in Gaussian estimation of cluster PDFs for all cases in simulation tests. The results of Study III imply that Gaussian estimation of cluster PDFs might not be able to correctly capture the cluster PDFs even in short time segments which cause in reducing the clustering performance. The assumption of Gaussianity for variability of individual single-unit waveforms has also been challenged by previous studies (Fee et al. 1996, Harris et al. 2000, Shoham et al. 2003, Schmitzer-Torbert et al. 2005, Delescluse and Pouzat 2006). Given the constraints outlined in the Study III, the work did not propose a fully automatic spike sorting algorithm with cluster tracking. Nevertheless, it showed the possibility of Bayesian cluster tracking by using kernel-based estimation of cluster PDFs. There are indeed several issues to be addressed in future works such as identifying number of neurons and recognizing appearing or disappearing neurons during cluster tracking for making this method an unsupervised algorithm for practical online applications.

Study IV proposed a novel method to improve the accuracy of spike detection in multi-unit intracortical recordings. The study suggested convolving the signal with a large dictionary of wavelet functions, each scaled to match several frequency sub-bands. The method blindly estimated the SNR and selected the signal projections that yield maximum SNR. A combination of the selected signal projections (as in Study I) was used for detecting multi-unit spikes. It was shown that the use of dyadic divisions (as in Study I) in the frequency domain was not an optimal choice for finding the signal energy localization in the frequency band. But rather increasing the resolution in sub-band divisions could effectively improve the detection performance with respect to the use of dyadic sub-band divisions. The results also showed that the defined spikiness criterion could better match the nature of the spiky signals as a blind estimator of the SNR with respect to previously proposed kurtosis criterion.

Further, the proposed spike detection algorithm and other spike detectors were applied to intra-cortical recordings from freely moving rats and compared with respect to the resultant event-related modulation of neural response based on the peri-event time histograms. The results demonstrated that using the proposed optimization method in spike detection task could enhance the representation of event-related neural response with respect to other (non-optimal) spike detection methods. This was an important implication of the study which supported the aim of the thesis and showed that improving the accuracy in the spike detection step could be used to extract more reliable information about underlying neural response which implies enhancing the performance in BMI applications.

In conclusion, this PhD project investigated some limitations of current intracortical signal processing algorithms in spike detection, spike sorting, signal denoising and compression which can reduce the performance of BMIs and developed alternative algorithms to overcome these limitations. The proposed methods can be used in future to improve the performance of intracortical BMIs.

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