

**PREDICTION OF PSYCHOPHYSICAL RESPONSES FROM
SPIKE RECORDINGS IN RAT SENSORIMOTOR CORTEX
BY USING BAYESIAN MODELS**

by

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ACADEMIC ETHICS AND INTEGRITY STATEMENT

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ABSTRACT

PREDICTION OF PSYCHOPHYSICAL RESPONSES FROM SPIKE RECORDINGS IN RAT SENSORIMOTOR CORTEX BY USING BAYESIAN MODELS

In this thesis, we studied the fundamental question in neuroscience: how perception is built based on the sensory stimuli from the physical world and turned into motor actions in the face of uncertain neural representations. The vast body of literature contains models using neural activity to decode stimulus parameters, motor responses, and behavioral patterns. In particular, this line of research became more important as sensorimotor neuroprostheses and brain-computer interfaces (BCI) were made possible by recent technology. The main goal of the thesis is to use Bayesian models to understand sensorimotor processing and develop a novel approach for future BCIs. Specifically, spike data were collected from behaving rats during a yes/no detection task. Within a Bayesian framework, priors and posterior beliefs are calculated to match the observed choice of the animal. The random variables for stimulus presentation, neural activity, and motor responses were combined in a probabilistic graph network. First, a somatosensory neuroprosthesis application is demonstrated. Next, the Bayesian model was used to predict trial-by-trial responses offline. It was found that psychophysically low-performing rats could be modelled better with the Bayesian approach. These results were compared to predictions of other supervised learning algorithms. The Bayesian prediction was among the best performing algorithms for low-performing rats. Finally, to reveal the effect of choice history on the current trial's response prediction, previous responses were also included into various Bayesian models incrementally. The results showed that the mean firing rates in a population of neurons are mostly adequate to predict lever presses with high sensitivity and low bias. This thesis provides new insights into computational modeling to understand sensorimotor processing and development of future BCIs. Bayesian modeling can be particularly useful in rehabilitation and during the training period of neuroprostheses.

Keywords: Bayesian, sensorimotor, somatosensory, vibrotactile, touch, rat.

ÖZET

SIÇAN DUYU-MOTOR KORTEKSİNDE KAYDEDİLEN AKSİYON POTANSİYELLERİYLE PSİKOFİZİKSEL YANITLARIN BAYESÇİ KESTİRİMİ

Bu tezde, sinirbilimindeki temel bir soru üzerinde çalışılmıştır. Fiziksel çevremizden kaynaklanan duyuusal uyaranların algıyı nasıl oluşturduğu ve değişken nöral temsillerin nasıl motor davranışa dönüştürüldüğü incelenmiştir. Bu konudaki geniş literatürde, nöral aktiviteyi kullanarak uyaran parametrelerini, motor yanıtları ve davranış örüntülerini kestiren modeller yer almaktadır. Özellikle son yıllarda bu araştırma konusu duyu-motor protezlerinin ve beyin-bilgisayar arayüzlerinin (BBA) gelişmesiyle daha da önem kazanmıştır. Tezin ana amacı, beyinde duyu-motor bilgi işlemeyi daha iyi anlayabilmek ve gelecekteki BBA' lar için yeni bir yöntem kazandırmak adına Bayesçi modeller geliştirmektir. Özel olarak, evet/hayır algılama görevi sırasında davranış halindeki sıçanların duyu-motor korteksinden aksiyon potansiyeli verileri toplanmıştır. Bayesçi yaklaşımla, önsel dağılımlar, kanıya ait sonsal dağılımlar ve hayvanın seçimi tahminlendi. Uyaran varlığı, nöral aktivite ve motor yanıtları için oluşturulan rastlantı değişkenleri olasılıksal bir grafik ağında birleştirildi. Tezde ilk olarak bir beden duyusu nöroprotezi uygulaması sunulmuştur. Daha sonra, psikofiziksel görevdeki her bir deneme cevaplarını çevrimdışı tahminlemek için Bayesçi bir model kullanıldı. Elde edilen sonuçlar, psikofiziksel olarak düşük performanslı sıçanların Bayesçi yaklaşımla daha iyi modellenebileceğini göstermiştir. Sonuçlar diğer güdümlü öğrenme algoritmalarının tahminleriyle karşılaştırmıştır. Bayesçi tahmin, düşük performanslı sıçanlar için bu algoritmalar arasında en iyilerden biri olarak bulunmuştur. Son olarak, geçmiş motor cevaplar da kademeli olarak Bayesçi modele dahil edilmiştir. Bu sonuçlar ise, nöron popülasyondaki ortalama ateşleme oranlarının motor cevabı yüksek hassasiyet ve düşük yanlılık ile tahmin edebildiğini göstermiştir. Tezdeki yöntemlerin ve sonuçların, BBA kullanan rehabilitasyon uygulamalarında ve nöroprotezlere alışma sürecinde faydalı olması beklenmektedir.

Anahtar Sözcükler: Bayesçi, duyu-motor, beden duyu, titreşimsel, dokunma.

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LIST OF SYMBOLS

p	Probability
$p(H)$	Probability of hit rate
$p(h)$	Probability of hit rate
$p(F)$	Probability of false alarm rate
$p(f)$	Probability of false alarm rate
μs	Microsecond
μm	Micrometer
μL	Microliter
mm	Milimeter
μ	Mean (average) value
σ	Standart deviation (std)
S	Stimulus parameter in the Bayesian network model
X	Average firing rate parameter in the Bayesian network model
Y	Behavioral response parameter in the Bayesian network model
$P(Y X)$	Probability of Y parameter given X parameter
$P(X S = s)$	Probability of X parameter given that S parameter has value s
$\pi(x)$	Sigmoid function
$\sum_{j=1}^n$	Summation of all values where j equals from 1 to n
$\mathcal{N}(0, 10)$	Normal distribution with mean is zero and std is ten

LIST OF ABBREVIATIONS

A'	A prime - A non-parametric sensitivity index
A α	Myelinated axons with large diameter
A β	Myelinated axons with medium diameter
Acc	Accuracy performance score for the model
AD	Alzheimer's disease
AFR	Average firing rate
AHP	After-hyperpolarization
ANN	Artificial neural network
AP	Anteroposterior
BBH	Bayesian Brain Hypothesis
BN	Bayesian Network
BCI	Brain-Computer interface or Brain-controlled Interface
BMI	Brain-Machine interface
C/IC	Correct/Incorrect Model
CNS	Central nervous system
CR	Correct rejection
DAQ	Data acquisition
DRG	Dorsal root ganglion
DSP	Digital signal processing
DV	Dorsoventral
E	Excitation
ECOG	Electrocorticograms
EEG	Electroencephalogram
EPSP	Excitatory postsynaptic potential
F1	A harmonic mean of the precision and sensitivity performance score for the model
FA	False alarm
FA	Fast adapting

FES	Functional electrical stimulation
FN	False negative
FP	False positive
FS	Fast spiking
HP	Hind paw area in the somatosensory cortex
I	Inhibition
IB	Intrinsically bursting
ICMS	Intracortical microstimulation
IP	Intraperitoneally
IPSP	Inhibitory postsynaptic potential
ISI	Inter-spike interval
ITI	Inter-trial interval
KNN	K-nearest neighbour
LFP	Local field potentials
LTMR	Low-threshold mechanoreceptor
MEG	Magnetoencephalograms
MI	Primary motor cortex
ML	Mediolateral
PC	Pacinian Corpuscle
PCB	printed circuit board
PD	Parkinson's disease
PDMS	Polydimethylsiloxane
PEF	Psychometric equivalence function
PI	Polyimide
PLA	Polylactic acid
Prec	Precision performance score for the model
PSTH	Peristimulus time histogram
QA	Quickly adapting
R/L	Right/Left Model
RA	Rapidly adapting
RA1	Rapidly-Adapting type 1

RA2	Rapidly-Adapting type 2
RF	Receptive field
ROC	Receiver operating characteristic
RS	Regular spiking
SA	Slowly adapting
SA1	Slowly Adapting type 1
SA2	Slowly Adapting type 2
Sens	Sensitivity performance score for the model
SI	Primary somatosensory cortex
SII	Secondary somatosensory cortex
Spec	Specificity performance score for the model
SVM	Support vector machine
TN	True negative
TP	True positive
VF	Von Frey
WHO	World Health Organization

1. INTRODUCTION

1.1 Motivation

The nature of internal stochastic processes determine how organisms make planning and decision-making. Understanding mechanistic underpinnings of the neural code will provide the next step towards the direction of improvement of everyday tasks of paralyzed or tetra/paraplegic patients using neuroprostheses and relieving them from the constant assistance of caregivers. The excitement in this field stems not only from helping people with neural disorders but also gaining scientific insight into the adaptive mechanisms and plasticity of neurons that generate behavior. Since neural plasticity should always have to be taken into consideration whenever brain-computer interfaces (BCIs) are utilized for cortical implants, it will be a tremendous advantage to have adaptive, intelligent algorithms to communicate with the brain running on the neural interfaces.

A crucial component for the BCI is the decoder, which is a computer algorithm to infer the intention of the subject by utilizing the neuronal activity. The last decades have recorded tremendous projects for direct communication with the nervous system [1–6]. However, practical and technical challenges, such as extensive duration of the training and adaptation periods in the lab to operate these devices, delays the clinical implementation on human subjects and thus human BCIs are not still on the level of non-human primate BCIs. In this manner, Bayesian machine learning algorithms, whose principles are based on probabilistic inference, seem promising to better communicate with the brain in neural language. Targeted communication for the neural interfaces will bring shorter training and rehabilitation periods and quicker adaptation for the patients to utilize these robotic assistive devices in their daily routines.

1.2 Hypotheses and novelty

The aim of this Ph.D. study is to provide crucial insights into the neural coding by predicting the behavioral choice of the animal from their sensorimotor neural activity recordings during a yes/no detection task. During sensory processing, the brain would benefit from probabilistic inference while extracting the statistical features, states of ambiguous and variable sensory stimuli and then reach decisions. In the frequentist approach, it is crucial to state the objective to reject the null hypothesis. However, Bayesian modeling allows more flexibility by predicting the posterior distributions of the model parameters without the need for the null hypothesis. We hypothesize that behavioral responses can be predicted using a Bayesian Network model recruiting the probabilistic distributions of stimulus and neural activity of units.

The second objective is to include neural activity and task-related sequential variables interchangeably into the incremental Bayesian model to interpret their effect on the animal's choice that has been made during the perceptual decision-making task. The difference in this model is to include previous trials' history-dependent variables (i.e.; previous choices, stimulus presence) to observe their effect on the current trial's choice. Further study will be conducted to include short-term and long-term history variables as well as subjective features of the animal (i.e.; reward expectation, bias).

1.3 General Background

1.3.1 Sensory Perception and Neural Encoding

Perception is a vital process for living beings to build internal representations of the physical world via stimulus-evoked sensory data emanating from the surroundings. The sensory stimulus causes to start the electrical transduction process via receptors. Neural encoding emerges with progressive loss of information while sensory signals are transmitted throughout the neuroaxis. Despite this filtered and encoded neural signal, it is the brain's ability to decipher the relevant sensory stimulus information

by decoding it. Since we mainly focused on tactile perception in this study, neural encoding mechanisms will be elaborated in terms of tactile sensation and decoding mechanisms will be the focus of the next section.

1.3.1.1 Peripheral Coding

Somatosensory perception is mediated by cutaneous mechanoreceptors, which are activated by mechanical stimuli; thermoreceptors, which relay temperature information; nociceptors, which are responsible for painful stimuli; purinoceptors, which relay itch. Tactile sensation in the hairy and hairless (glabrous) skin is generated by four types of mechanoreceptors [7–14] lying in the superficial or deeper layers of the dermis. Because of their responsiveness in low-threshold mechanical deformations, these receptors are called low-threshold mechanoreceptors (LTMR). Four types of mechanoreceptors and their afferents have been mainly foci of studies trying to understand the initiation of sensory coding from the physical world into the neural system. All four types of mechanoreceptors (Figure 1.1) and peculiar types of hair follicles are innervated by myelinated axons with large ($A\alpha$) and medium diameter ($A\beta$), all of which fall into two general categories as slowly or rapidly adapting (SA or RA) [15–17].

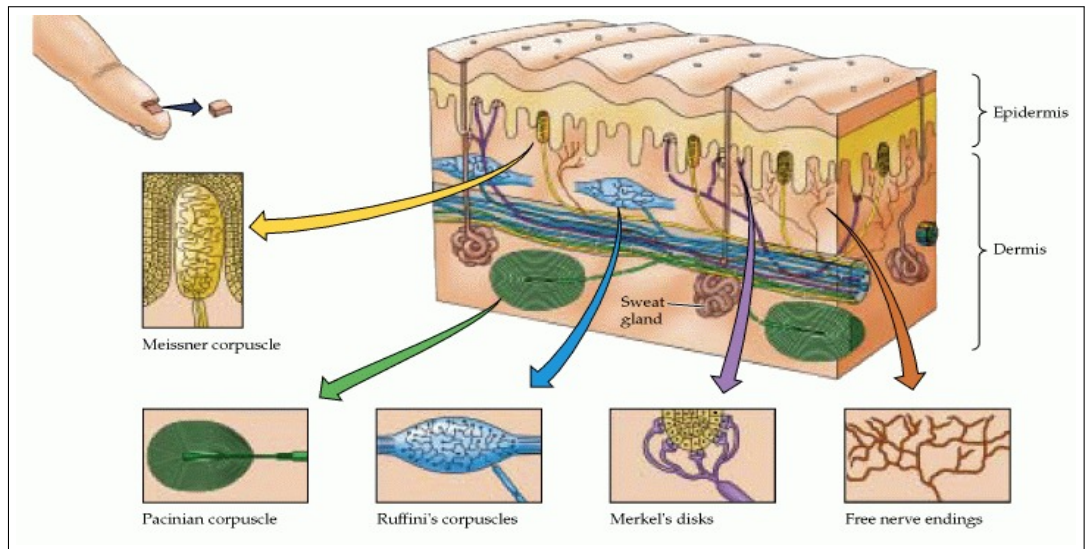


Figure 1.1 Four types of mechanoreceptors in the hairless (glabrous) skin. Adapted from Figure 8.3 in [18].

Merkel cells encode discriminative touch with fine spatial resolution, like edges, corners, and are innervated by slowly adapting (SAI) afferents (Figure 1.2) [19, 20], which has the best tuning frequency lower than 100 Hz. *Meissner corpuscles* also respond to discriminative touch but with lower spatial acuity. Since Meissner's are innervated by rapidly adapting fibers (RAI, also called RA, QA, or FAI), these receptors are sensitive to initial contact of the objects, slippage of them in the hand [16, 21]. Meissner's are in charge of the sense of flutter elicited by low frequency (10-60 Hz) vibrotactile stimulation of glabrous skin [10, 22–24]. These two mechanoreceptors lie in the superficial layers of the dermis, thus having smaller receptive fields (RFs) (2-3 mm in diameter for SAI, 3-5 mm in diameter for RAI [25]) and higher innervation densities. On the other hand, *Pacinian corpuscles* and *Ruffini endings* remain in the deeper portions of the dermis, whose neurophysiological design allows having larger receptive fields and lower innervation densities than those receptors on the superficial layers. Pacinian corpuscles are innervated with rapidly adapting (FAII in human, RAIL, or PC in other mammals) fibers that have peak sensitivity to vibrations around 250 Hz within the 5-1000 Hz range [16, 26, 27], which causes only onset and offset response properties for a ramp-and-hold stimulus [26]. This receptor type responds to high-frequency vibration and to a submicrometer-range motion. At last, Ruffini endings can respond to stretch and movement and it is sensitive to the shape of large objects.

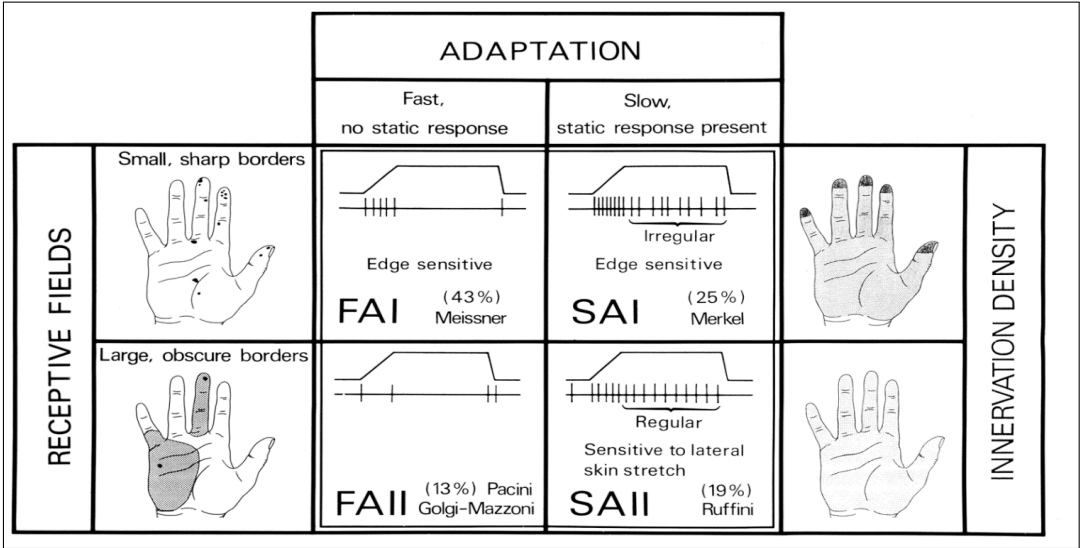


Figure 1.2 Four types of mechanoreceptors and the response characteristics of their innervating fibers. Adapted from Figure 1 in [15].

Although the glabrous skin is the main concern in this study, it is good to know the properties of hairy skin as well for compatibility purposes of the output of the study. Mammalian skin has three types of hair follicles (Figure 1.3); guard hairs (the longest, thickest, and least abundant hairs; they are also called monotrich), down hairs (zigzag hairs or D-hairs, which are named after the down hair of the cat's fur coat; they are the most abundant ones) and awl/auchene hairs [28, 29]. Thickly myelinated fibers ($A\beta$) innervate guard hairs. Hair follicles with $A\beta$ fibers are recruited for the sense of flutter in the human hairy skin [30] and are tuned to a similar frequency (10-50 Hz) similar to Meissner corpuscles [31, 32]. $A\beta$ -hair follicles together with the Meissner corpuscles act for appropriate velocity coding and frequency tuning. Furthermore, $A\beta$ fibers function as movement detectors and adapt rapidly. Their discharges are generated only during the movement of hairs and not during the sustained displacement [30, 33]. The movement velocity is encoded by the spike rate, which increases by increasing velocity [30]. Thinly myelinated ($A\delta$) and unmyelinated fibers (C) are activated by movement of the D-hairs and awl/auchene hairs [34, 35]. Although the conduction velocity for $A\delta$ fibers is half of the conduction velocities of $A\beta$ fibers, D-hair receptors are the most sensitive mechanoreceptors of the hairy skin that need one-tenth of the threshold force of $A\beta$ receptors to be activated [36]. They have larger receptive fields and are activated by the movement of every hair whereas $A\beta$ receptors are only activated by a few hair follicles inside the receptive field area.

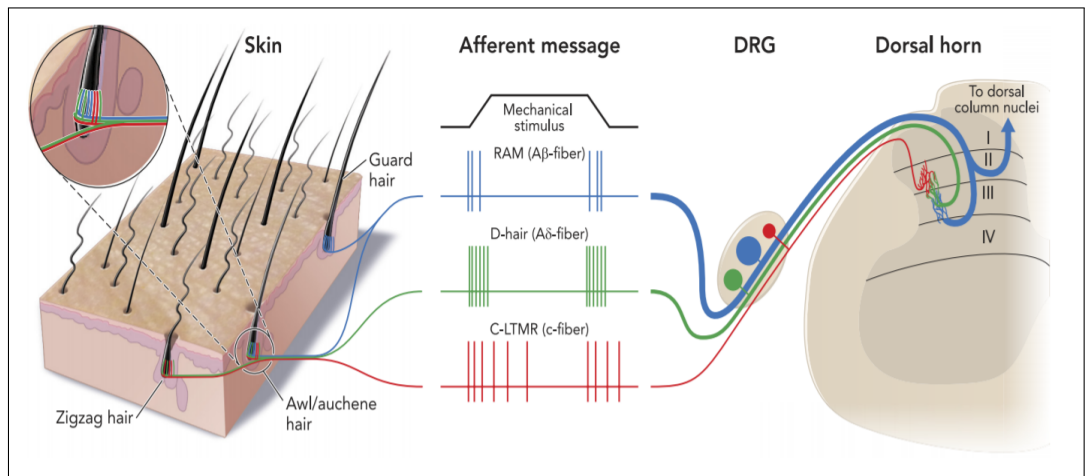


Figure 1.3 Three types of hairs in the hairy skin. Guard hairs are innervated by $A\beta$ fibers while awl/auchene and zigzag hairs are innervated by all types of fibers. Adapted from Figure 1 [30].

Rodents palpate objects specifically with their whiskers (or mystacial vibrissae), which are sinus hairs found around their snout (Figure 1.4). Similar to other types of hairs, these sinuses have slowly and rapidly adapting fibers around their follicles that drive the trigeminal nerve. Tactile sensation and active vibrissal exploration are incorporated by the musculature of the mystacial pad with protraction and retraction movements of whiskers thus, in turn, they have wide range of behavioral repertoire [37]. The entire mystacial pad has 5 rows (A-E) each of which has 5-9 whiskers (Figure 1.4) that their controlling vibrissal muscle tone is amplified via trigeminal loop during active touch [38–40]. The sensorimotor loop is initiated by the movement of the musculature. Thus, it discharges mechanoreceptive afferents of the sinus hairs and provides encoding of different features of the stimulus like curvature, size, and texture as well as direction and frequency of the whisker movement [41–44]. Each whisker has its own corresponding densely-packed columnar organization in the cortex that is called the barrel cortex. Rats encode the texture by neuronal firing rate. Rough surfaces elicit higher spikes and this rate is correlated with the animal's judgement of the surface [43].

Four types of mechanoreceptors and their corresponding afferents are scrutinized for their neurophysiological properties and response characteristics. However, the main question is how the physical world properties, like stimulus features, are represented in the neural code that draws much of our attention. Studies focusing on cutaneous mechanoreceptors [47, 48] examined receptive fields, innervation densities, psychophysical and neural thresholds of slowly adapting (SAI, SAII) and rapidly adapting (RAI, RAI) afferent units with ramp-hold and triangular stimuli. The response properties of these receptors under the mechanical sinusoidal stimulus were assessed concerning stimulus frequency and amplitude [49]. The impulse response characteristics of afferent fibers were also studied and found to having demultiplication and tuning zones for specified frequencies and increasing magnitudes which is defined as entrainment; encoding the stimulus feature as beat by beat fashion [23, 50, 51]. In this manner, rate coding and latency coding are found to be effective in the discrimination of tactile events [52].

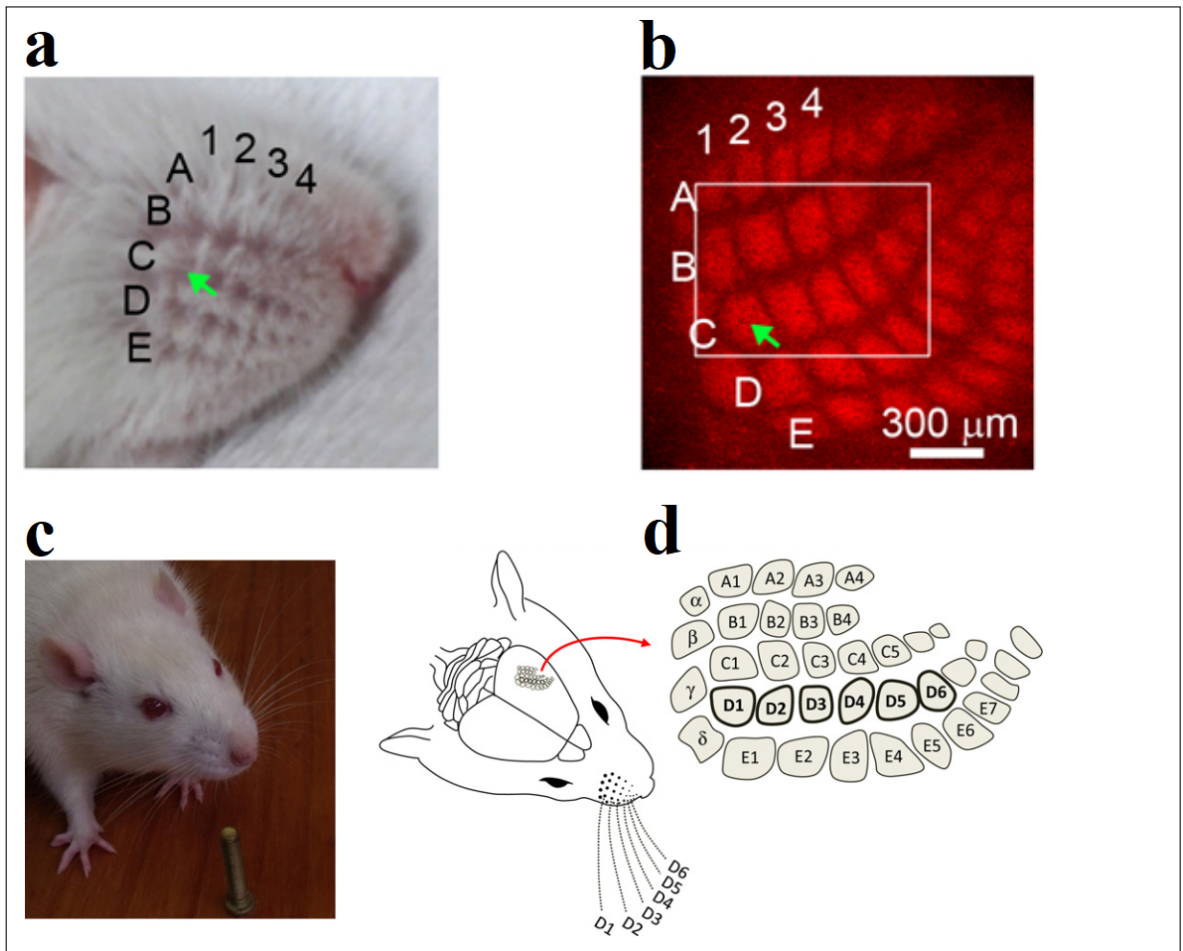


Figure 1.4 Whiskers and somatosensory barrel cortex. a) Five rows (A-E) of mice whiskers on the snout. b) There is one-to-one correspondence in the barrel cortex for each whisker. Layer 4 (L4) of barrel cortex is labeled with red fluorescent protein. For instance, C1 whisker with green arrow in part a) projects tactile information into the C1 barrel in part b). c) A Wistar rat is exploring the objects with its whiskers. d) Right whiskers from D1 to D6 and their highlighted corresponding barrels in the somatosensory barrel cortex. Part a) and b) adapted from [45], part c) and d) adapted from [46].

1.3.1.2 Central Processing and Cortical Coding

Somatosensory information is transmitted through dorsal root ganglion (DRG) cells based on two pathways to the higher-order regions in central processing. The dorsal column-medial lemniscal pathway relays tactile and proprioceptive information to the brainstem, thalamus, and the neocortex while its dorsolateral tract transfers somatosensory information from the lower part of the body (Figure 1.5). The anterolateral tract is responsible for conveying pain and thermal sensory information. DRG cells have two branches of their single axon along the neuraxis; one branch descends to the periphery while the other branch joins the spinal nerve from the dorsal root and

ascends to relay the sensory signal to the brainstem [53, 54] (Figure 1.6).

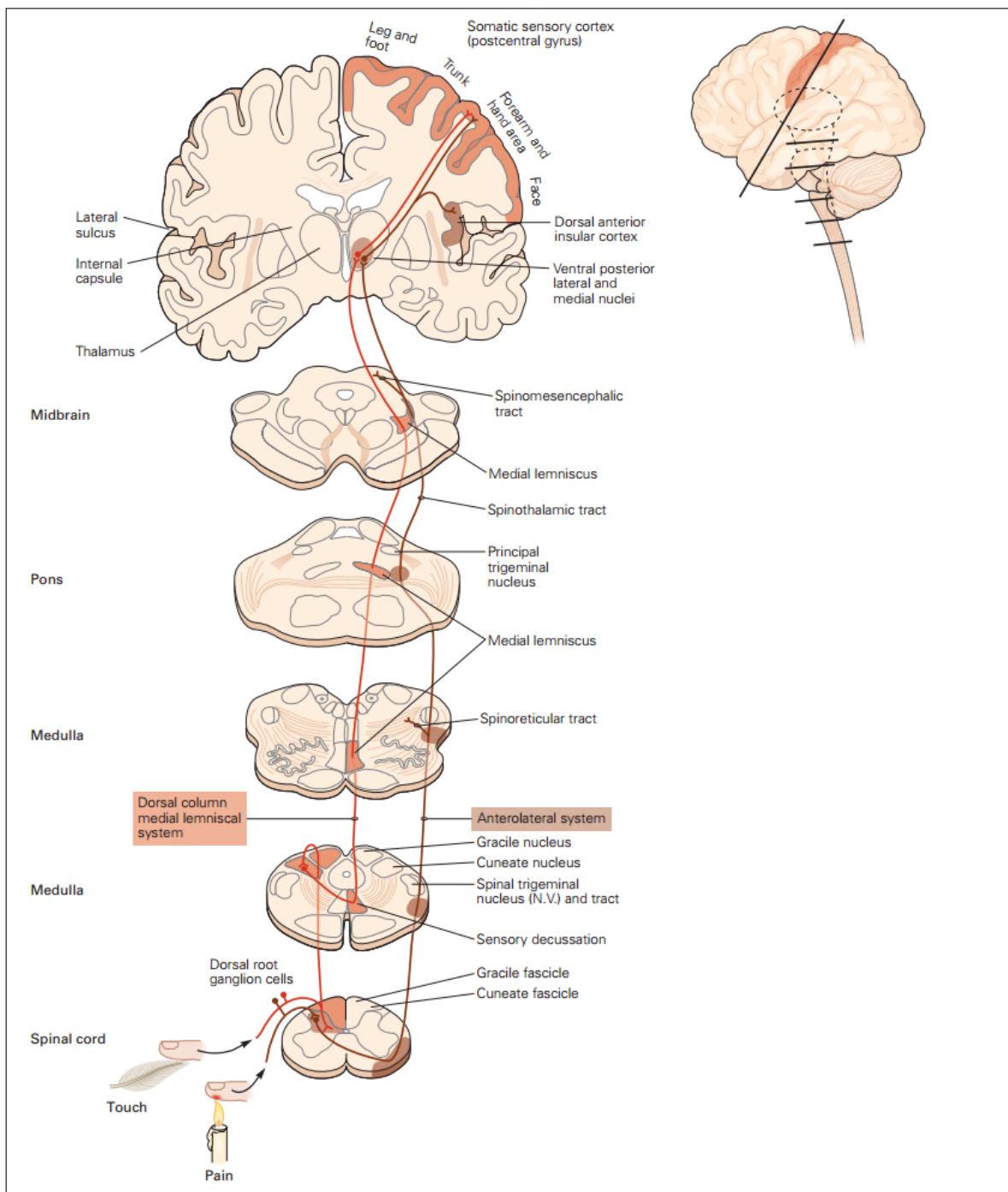


Figure 1.5 Somatosensory information is conveyed from medial lemniscus and anterolateral pathways. Adapted from Figure 22.11 in [16].

This single axon form from the periphery to the medulla constitutes first-order afferents [56]. Each dorsal column has a million fibers of which 90% are DRG cells [16]. The second-order fibers ascend from the medulla to the thalamus and terminate in

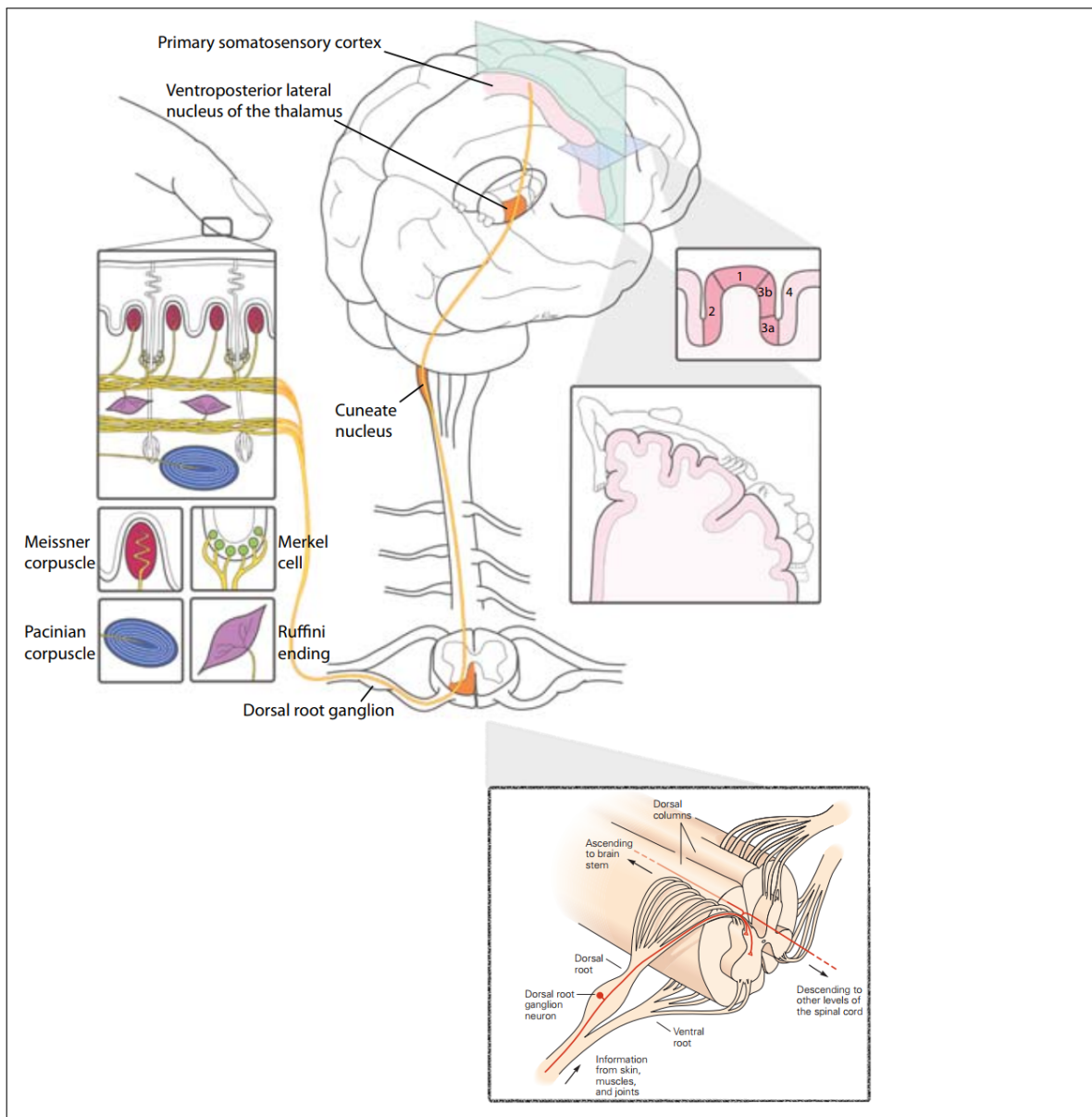


Figure 1.6 Neuroanatomy of touch from mechanoreceptors to the somatosensory cortex. Afferents transmit the sensory signals initiated from four types of mechanoreceptors (left insets) to the synapse in the cuneate nucleus of the brainstem by ascending through the spinal cord. Signals travel from brainstem to the ventroposterior nucleus of the thalamus and somatosensory cortex. Figure adapted from [16, 55].

the ventral posterior nuclei of the thalamus. The third-order fibers make synapses to the primary somatosensory cortex (SI) in cytoarchitectural divisions, like Brodmann's area 3a, 3b, 1, and 2, to process the tactile and proprioceptive information specifically (Figure 1.6). Up to here, from the mechanoreceptors to the SI cortex, sensory neuron carries encoded signal together with processed information at three specific synapse

points, which are dorsal column nuclei, the thalamus, and the cortex.

Regions 3a and 3b project their axons to the regions 1 and 2 while all these

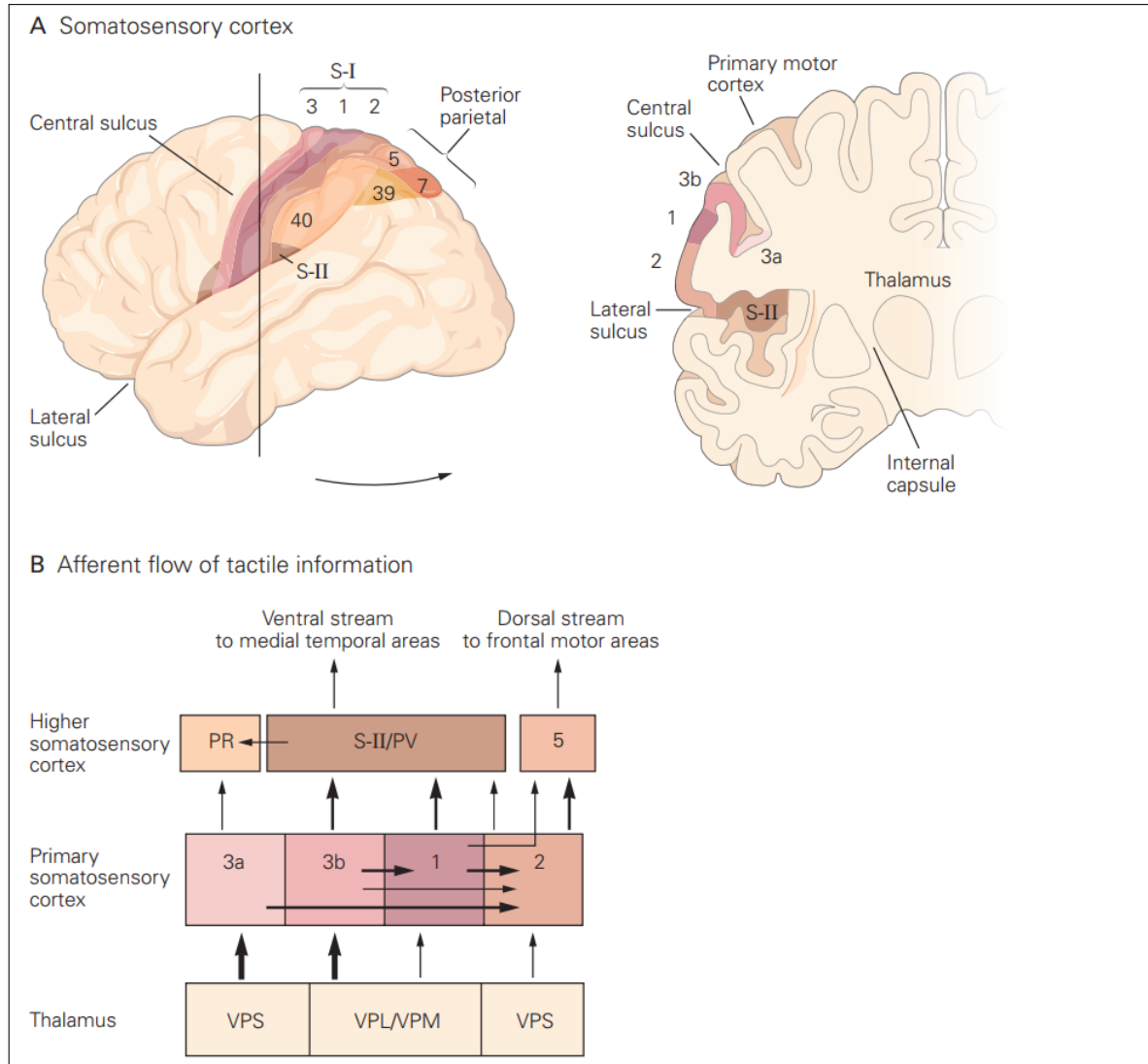


Figure 1.7 Somatosensory areas. A) Parietal lobe has three distinct divisions: primary somatosensory cortex (SI) with Brodmann's areas 3a, 3b, 1, and 2, secondary somatosensory cortex (SII) with Brodmann's area 43, and posterior parietal cortex. B) Hierarchical connections of SI with other cortical and subcortical structures. Adapted from Figure 23.10 in [16].

regions have projections from the thalamus. Thalamocortical inputs first join to the cortex through layer IV from where they are connected to the superficial layers (layer II/III) [57–60]. Later, these connections are directed to the layer V and VI where the somatosensory cortex orchestrates other regions of the neocortex, like the primary motor cortex or thalamus. Regions 3b and 1 have direct tactile sensory information from skin receptors while regions 3a and 2 have proprioceptive signals from joints, muscles,

and skin. The parallel and serial processing between these regions is depicted in Figure 1.7b. After the processing between these regions and layers, the sensory signal is transmitted to the higher cortical areas, as the secondary somatosensory cortex (SII), posterior parietal cortex, and motor cortex, where the signal has more abstract features now to leverage processes during perception and motor control. Besides having specific cytoarchitectural areas, the neocortex has columnar organization (Figure 1.8b) where all the neurons get inputs from the same area, generally, process only one submodality (i.e.; vibration or pressure) and output to the same local area [16]. However, rodents do not usually have that level of segregation in their somatotopic map as primates do. Our study was conducted in an area that has overlapping incoming sensory and outgoing motor control neural activity for the hind limb of the rat (see HP in Figure 1.9).

The main problem in computational neuroscience is what are the computational units and how the structures or features of stimulus are encoded in the neuronal activity. There are mainly four types of neural coding strategies to decipher the cortical level coding: rate, temporal, spatial, and latency coding. *Rate coding* [62, 63] is relating the mean firing rate of a neuron to a stimulus, and modulation in firing rate refers to the change in the stimulus feature that the neuron is responsive to. *Time-dependent firing rate* $r(t)$ (also called instantaneous firing rate) is the function for the spike rate versus time when we divide the peri-stimulus window into small discrete time bins. Thus, it is just another type of rate code with smaller chunks. Amplitude and frequency of periodic vibrations are thought to be represented in the *rate code* [63–67]. There are studies claiming that the periodicity of spikes is phase-locked to the stimulus and neurons encode the frequency of vibrotactile stimulus [24, 68]. Here, we will employ the *rate code* for prediction purposes in the Bayesian model, to assess the power of prediction with a simplistic feature (see Chapter 3). Two different stimuli may elicit the same average firing rate for a selected neuron. If there are fluctuations in the spike rate during the stimulus window more rapidly than the stimulus itself, then it is a *temporal code*. Those variations of high-frequency precise spike timing with a shorter scale than the stimulus frequency will carry information on the Fourier components of $r(t)$ at frequencies higher than the stimulus frequency [69–71]. In case of any increment in a stimulus feature is represented by modulation of responses, thus the relative

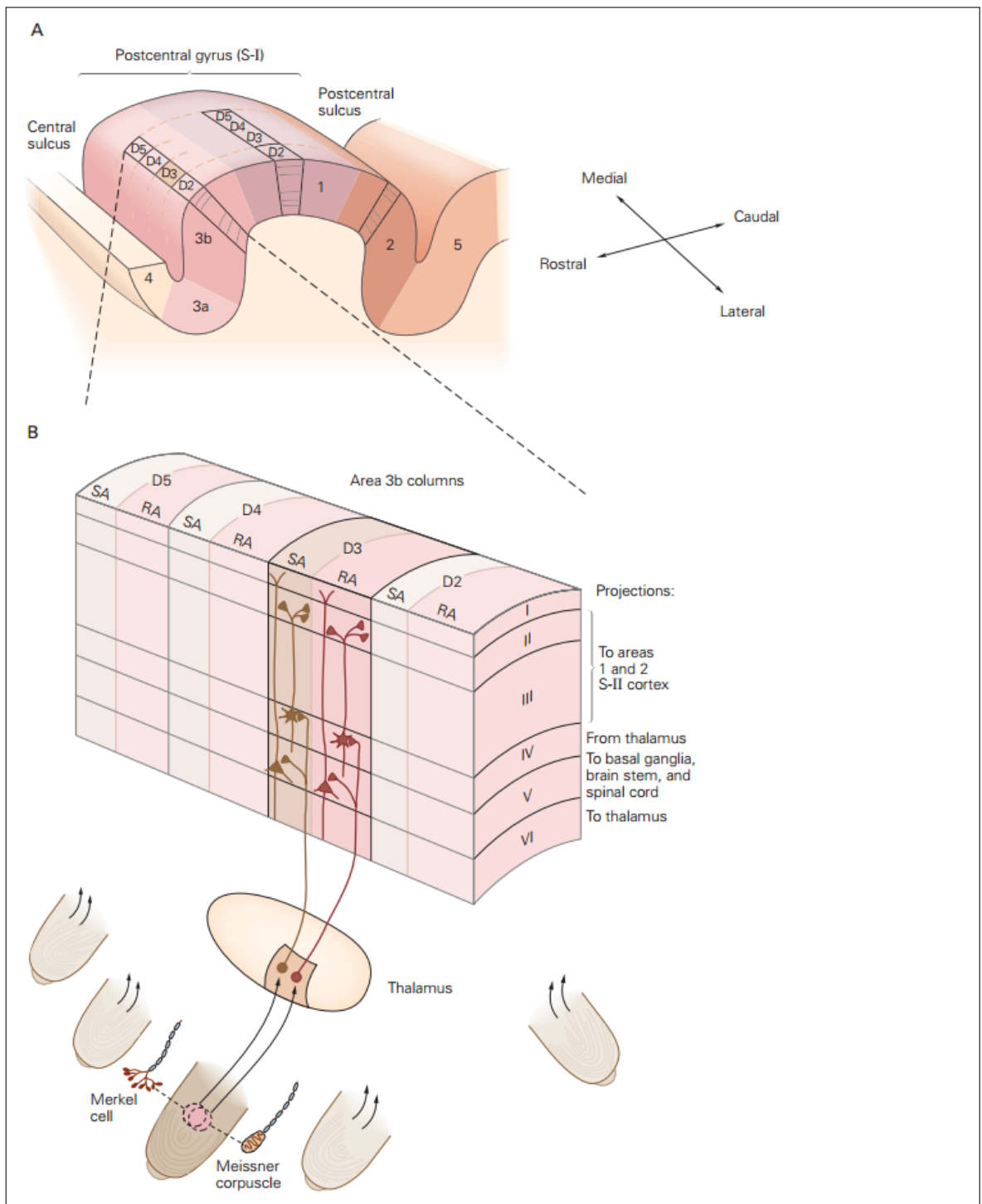


Figure 1.8 Columnar organization of the somatosensory cortex. Adapted from Figure 23.13 in [16].

activation/deactivation of neurons in the population can be decoded as presence or absence of that feature, which is named as *spatial coding* [72]. For the last type, *latency coding*, one can assess latencies in the first spikes in a population of neurons to decode

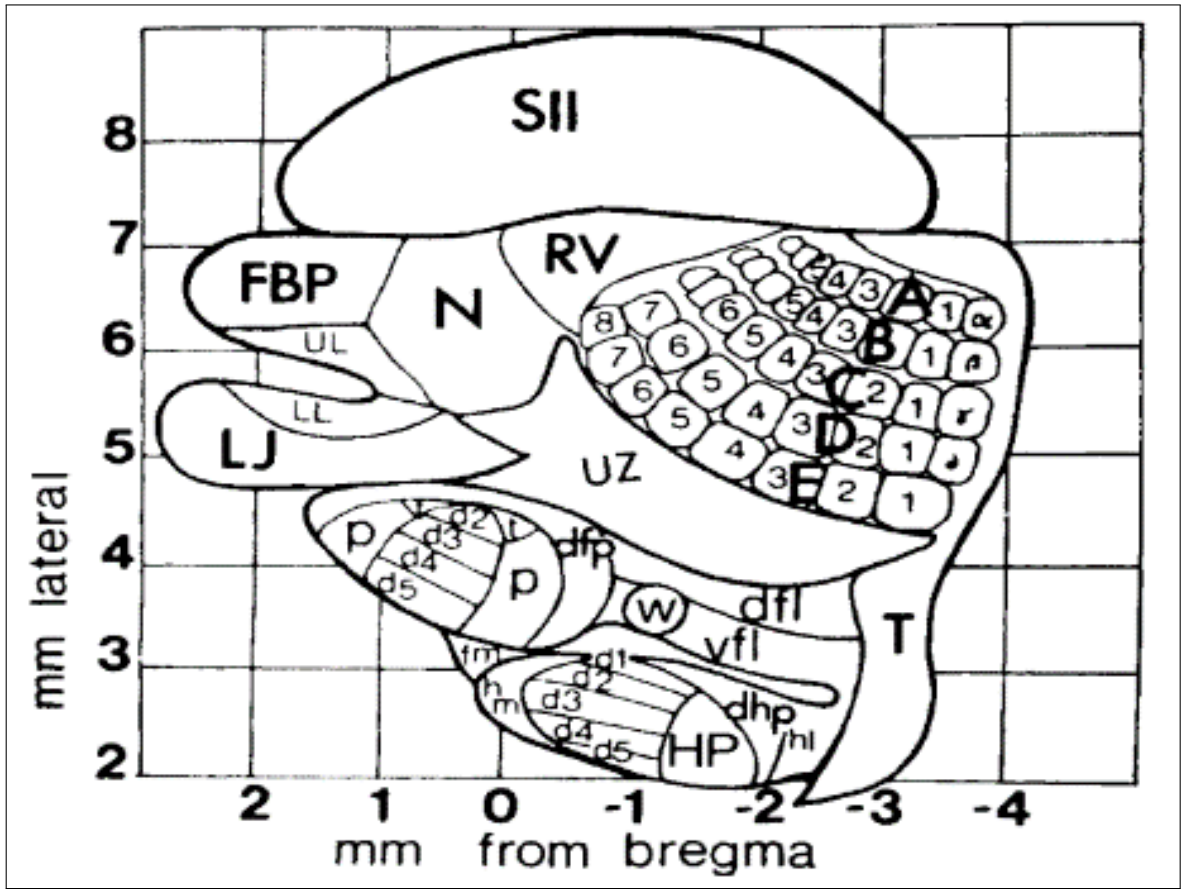


Figure 1.9 Somatotopic representation of rat SI cortex. SII: secondary somatosensory cortex, A-E: rows of barrels (barrel cortex), d1-d5: digits of hindpaw, HP: hindpaw, dhp: dorsal hindpaw, hl: hindlimb. Adapted from [61].

specific features of the stimulus, i.e.; shape or direction of contact force in a grasping task [73,74]. The precise spike timing [75], first post-stimulus spikes, is increased by the transferred information more than that spike rate or count do [76–78]. Other frequently used coding techniques comprise employing information theory [79,80], instantaneous firing rate [81], cumulative-summed spike counts [82], and synchronicity among firing rates [83] to exploit the alphabets of neurons.

Studies about neural coding mostly focused on the barrel cortex, rather than the hindpaw area of SI, because of its densely packaged columnar organization. They found notable cortical state differences before and during the whisker stimulus in the whole-cell patch-clamp recordings of layer II/III of mice barrel cortices [84]. Slow frequency and large amplitude membrane potentials changed into a higher frequency and smaller amplitudes when the stimulus was introduced. Rate coding is found to be more

effective than periodicity coding in terms of an internal representation of the stimulus in SI recordings [64]. In a discrimination task, recorded spike counts for the first 250 ms of the stimulus have more prominent representation than periodicity coding, rate, or count coding of bursts. On the other hand, there are nice entrainment examples for 5 Hz [85] and well-documented cortical patterning of spike or burst firing as a function of frequency or amplitude of the stimulus [24,65,86,87]. The phase-locked population responses in SI of macaques (Figure 1.10) are well in line with the phase-locking in the barrel cortex [88].

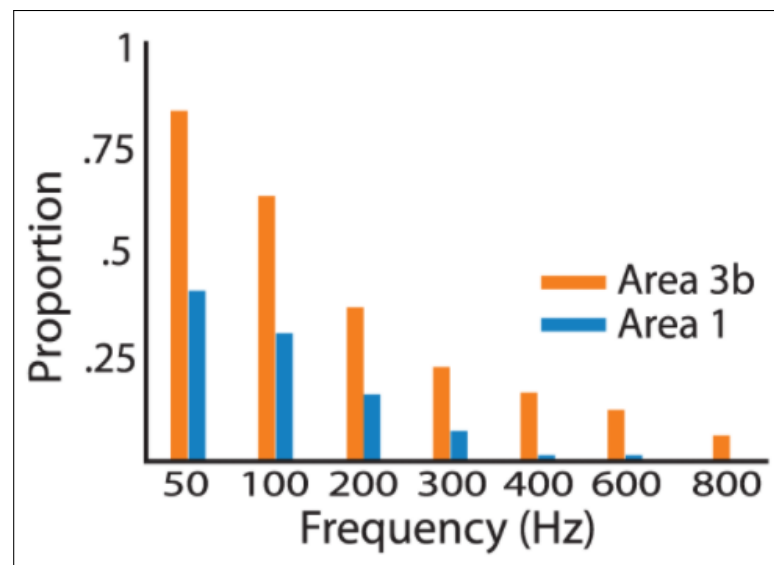


Figure 1.10 Phase-locked population responses of macaques in SI for each tested frequency. Adapted from Figure 2E [86].

The details of the transduction process from the skin to the neocortex are to be solved by relating firing rates of neurons to a peculiar stimulus feature or submodality (i.e.; intensity, shape, texture, vibration). However, there is now a common consensus that cortical neurons are not segregated in terms of submodalities. Instead, they receive convergent inputs from SAI, RA, PC fibers in the form of their spiking response, from which upstream neurons are capable of interpreting the physical properties of stimulus, may intrinsically comprise many features [87,89]. Despite the supporting evidence of the traditional view from previous literature including classification of cortical neurons as SA-like and RA-like [90–94], more recent studies showed the convergence of submodalities has its mass consistency over the segregation hypothesis [95–97]. In Figure 1.11, part a) represents the traditional approach while part b) depicts the convergence

hypothesis from all channels that emphasizes the fact that most of the S1 neurons exhibit both SA-like and RA-like responses (Figure 1.11e). In turn, S1 neurons had to be grouped by functional characteristics, not by sensory submodalities.

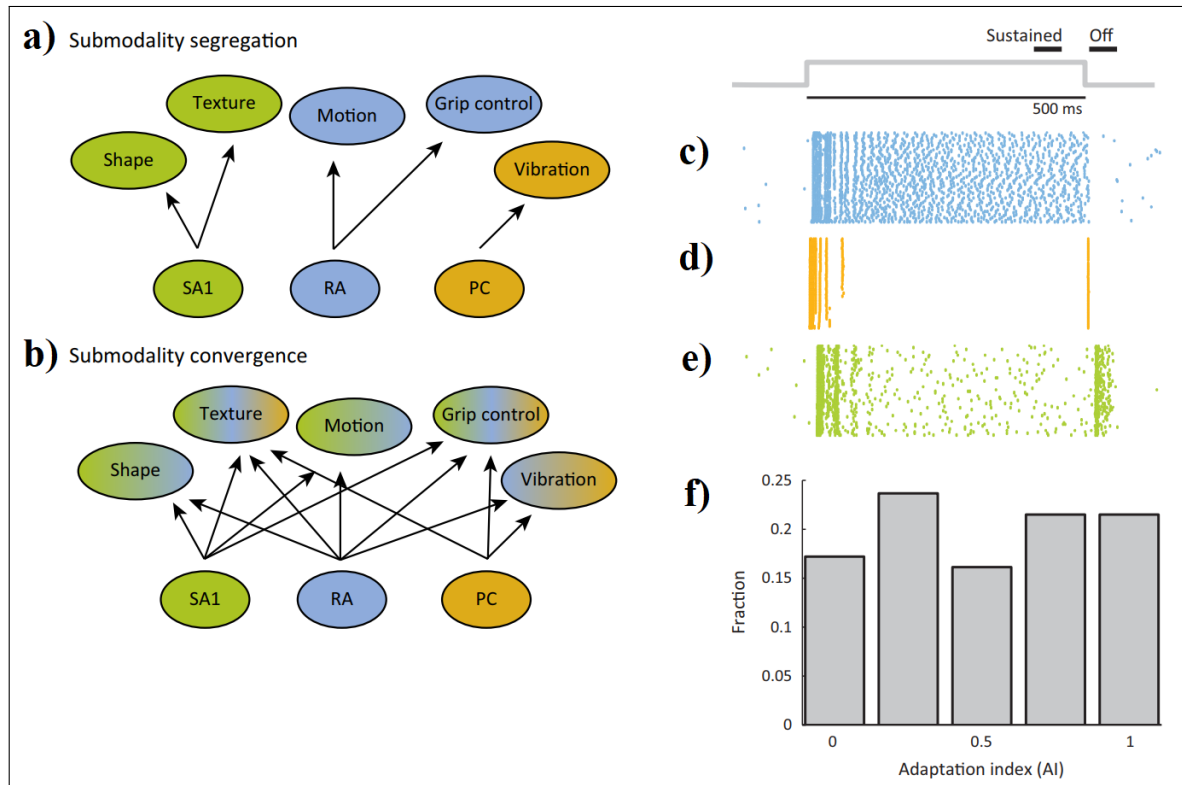


Figure 1.11 Cortical neurons respond both SA-like and RA-like. a) Traditional view of segregation of modalities b) recent approach of convergence of modalities states that most of the afferents, therefore cortical neurons, receive input from multiple submodalities c) Typical SAI afferent response to a 500 ms sustained mechanical stimulus d) Typical RAI afferent response to the same stimulus e) Response of a neuron in area 3b, which is a mixture of RA and SA responses f) Distribution of adaptation index (normalized ratio of OFF responses to the sustained stimuli) shows uniform characteristic. Adapted from Figure 1 and Figure 2 in [89].

When the neural code is scrutinized related to behavior, one should bear in mind that behavioral training stages affect cortical states [98]. Naïve mice had significantly larger membrane potential oscillations (1-5 Hz) than trained mice. In the course of behavioral training, mice had also smaller depolarizing responses day by day. Behaving animals are found to have longer response durations, pre-stimulus response modulations, and more inhibitory fluctuations during the course of training [82]. Figure 1.12 depicts how the neural response for a window aperture stimulus is clear under anes-

thetia (black curve), while the activity turns out to be flattened and inhibited during the three phases of behavioral training (green, blue, red curves) that finding in in line with our results. In accord with the free energy principle [99], smaller evoked responses are observed for the predictable stimuli when compared to incoherent, unpredictable stimuli in the visual cortex. Broad-spiking units in the visual cortex showed a dramatic increase in visual responsiveness during locomotion [100] although narrow-spiking units showed dramatic suppression when a visual stimulus was presented. These results should be kept in mind during that kind of research with cortical recording including behavioral training of rodents. It seems that behavioral prediction from the recordings of awake behaving animals would be an arduous task to accomplish for the Bayesian model under these circumstances of inhibited response and flattened dynamics.

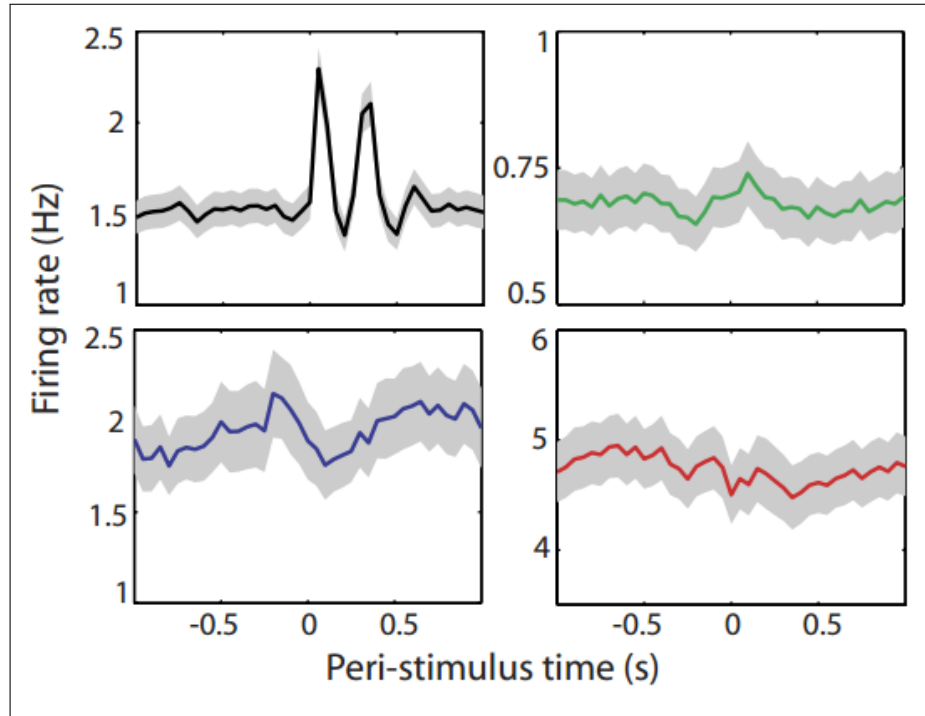


Figure 1.12 Typical single-unit SI responses of rat under anesthesia (black curve), awake (green curve), before training (blue curve) and during training (red curve) reflects the response diversity depending on the cortical states. Adapted from Figure 2E [82].

1.3.2 Neural Decoding and Decision-Making for Motor Control

From the mechanical displacement on a receptor in the skin to the elevation of the cup towards your lips to sip the coffee, sensory information is processed along the way from dorsal root ganglia, somatosensory cortex, multimodal association areas, subcortical regions, motor cortex, and the way back to muscle spindles through the descending lateral corticospinal pathway (Figure 1.13). Although the sensory perception and decision-making processes mediated by numerous brain structures form a series of nested loops, it is a known fact that the somatosensory cortex directly modulates the primary motor cortex with corticocortical pathways [101–103]. The connection between barrel cortex and motor cortex for mice and rats was quantified in layer detail that layer II/III of the vibrissal motor cortex (vM1) has strong input from the vibrissal somatosensory cortex (vS1) and also back project to vS1 (Figure 1.14). Furthermore, this close linkage between somatosensory and motor cortex is crucial for haptic perception [43, 104, 105] and motor coordination tasks [106–112]. The vibrissal system also controls whisker movements regarding the sensorimotor loop [41–43]. An indirect path from the SI barrel cortex to extrinsic muscles is uncovered that it causes whisker retraction even under the pharmacological blockage of the primary motor cortex (M1) [113].

There are millions of patients who suffer from neurological disorders with disrupted signaling pathways between the brain and muscles. Neuroprostheses are recruited to restore lost function by decoding the disconnected signal and bypassing the reconstructed version between intact body parts or directly to the robotic actuators. Besides, motor cortex recordings are such an invaluable resource for neural decoding studies since it has direct observable output to validate the models. Recording techniques vary from macroscale (EEG), mesoscale (local field potentials, single/multi units) to microscale (intracellular) (Figure 1.15). Since EEG runs for low spatial frequencies and patients have to learn to modulate the activity of at least 100 million neurons, it is impractical to use EEG for elaborated limb activity in neuroprosthetics [116]. The spatially-summed activity (electroencephalograms (EEG) and magnetoencephalograms (MEG) recorded on the scalp, electrocorticograms (ECoG) recorded on the dura, and local field potentials (LFP)) and the intended motor action is still poorly matched [117–121].

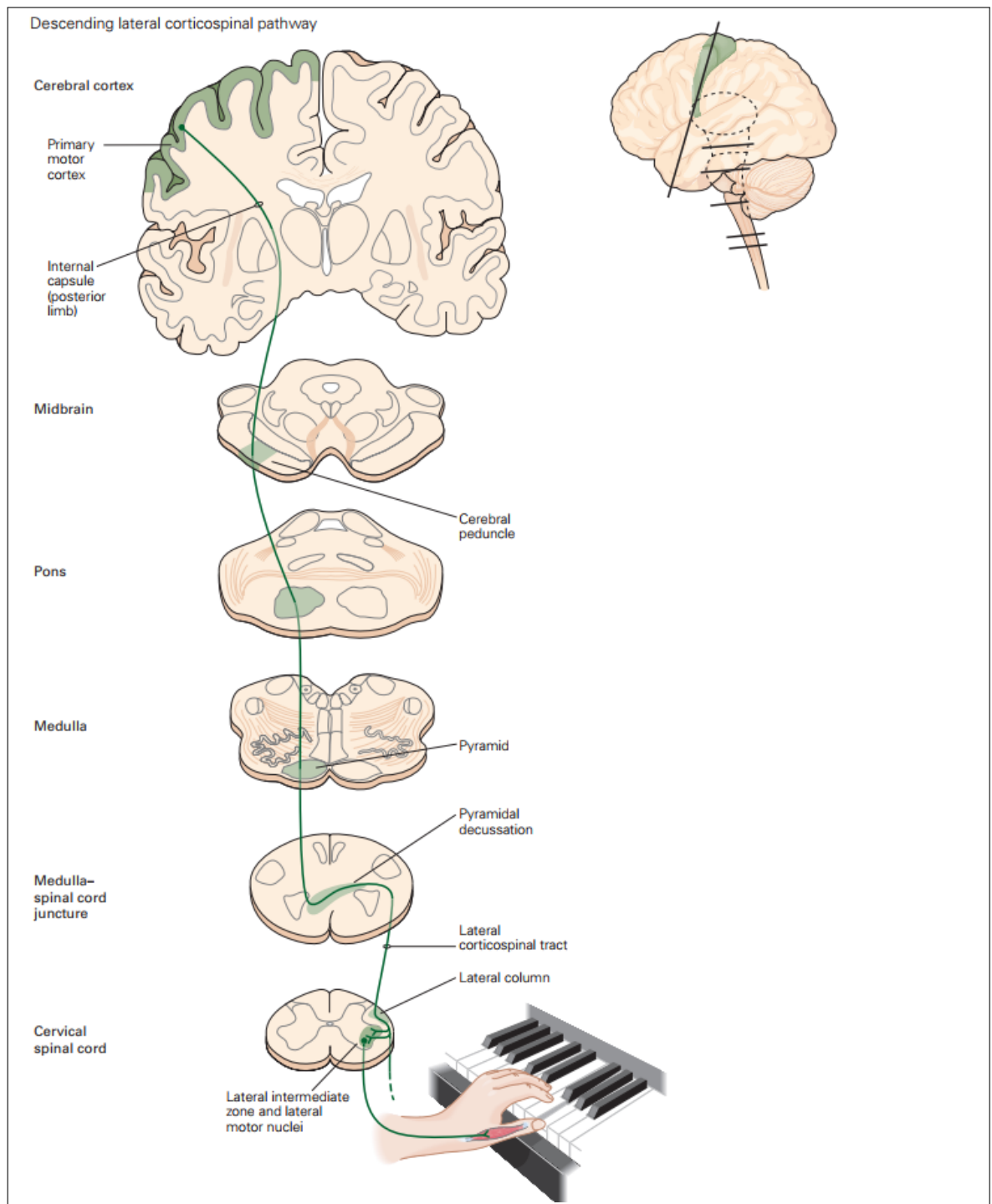


Figure 1.13 Corticospinal tract originates from primary motor cortex and excites the muscle spindles through the ventral horn in the spinal cord. Adapted from Figure 16.8 in [114].

Spiking activity is better characterized for motor output [122–126] given the well-known ability to modulate the activity of single neurons [127] for the last decades. The spiking activity from single units and populations in M1 has already proof-of-

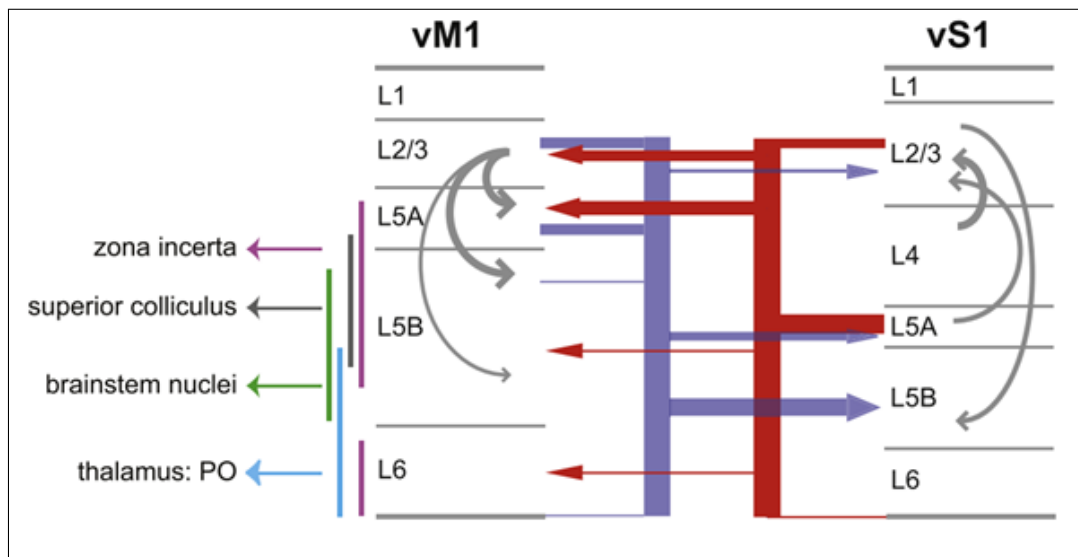


Figure 1.14 Corticocortical network between vSI and vMI. Adapted from Figure 8 in [115].

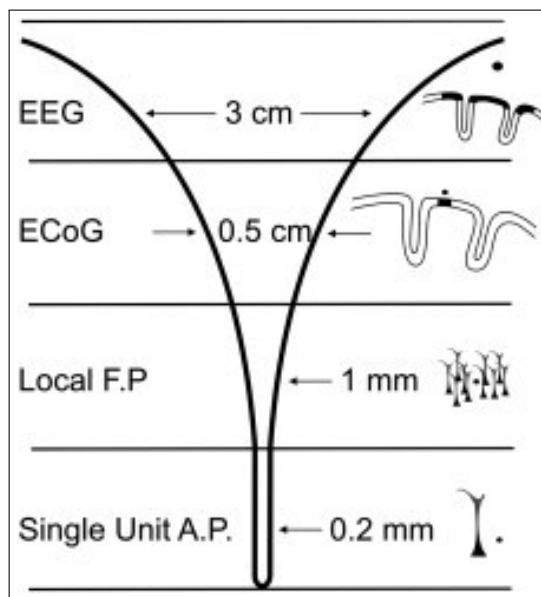


Figure 1.15 Spatial resolution comparisons between recording techniques. EEG electrode (black circle) lying 2 cm above the cortex records across 3 cm (black filled cortical layers). ECoG electrode records from 0.5 cm range. Local Field Potentials (LFPs) and single/multi units are recorded with much higher resolutions. Adapted from Figure 2 in [116].

concept demonstrations to decode two-dimensional (2D) or three-dimensional (3D) hand movements [128–134] during the 1990s. They observed a strong discharge response in M1 neurons before movement and found the preferred direction of movement appears to be strongly presented in M1. Rats were able to get water rewards in real-time for only motor neuronal discharges according to the planned direction even with-

out performing the motor action exactly, which inspired the locomotion restoration for paralyzed patients. Brain-Machine interfaces (or sometimes called Brain-controlled Interfaces or Brain-Computer Interfaces) (BMI or BCI) is focused not only on the prospect of restoring the movement ability of the patients with neural disorders but also on the aspiration of gaining scientific insight into the population activities that generate motor outcome [135–137]. The implementation of this technology in real-time is faced with a suspension period until multiple single-unit are recorded simultaneously. In the late 1990s, chronic recording from the vast amount of single-units with improving microelectrode technology leveraged the studies towards real-time applications of multidimensional BCIs [2, 4, 5, 138–140]. Non-human primates were excellent to learn how to operate external robotic arms [133, 141–143]. Human studies showed that the ideas developed for non-human primates were also transferrable [3, 4, 6, 144–149]. A clinical study [4] is depicted in Figure 1.16, in which a 52-year old tetraplegic patient performs a range of daily activities using a BMI-controlled robotic actuator that registers for the first time a human subject performed better than non-human primates. Another type of BCI application is fused with Functional Electrical Stimulation (FES) to regain the upper limb functionality of a patient with high cervical spinal cord injury [150] (see Figure 1.17). Furthermore, recent developments in BCIs also contained sensory feedback by intracortical microstimulation (ICMS) for the patients to adjust the movements precisely and master tool manipulation [55, 151–155].

A vast body of literature for behavioral modeling utilizing these neuronal features of M1 is effective for the prediction of direction, speed, or velocity [3, 116, 129, 143, 157–160]. In this diverse set of neuroprosthetic application studies, decoder algorithms classified the subject’s hand state by running linear discriminant analysis and then recruited Kalman filter to predict the intended velocity of the hand. However, this candidate algorithm with a very fast converging learning rate during the offline execution will not be able to promise to generalize well in online execution, since the Kalman filter -even it is also based on Bayes’ theorem- has assumptions of linearity on state dynamics and Gaussian noise. In a real-time operation, the adaptation of the algorithm to the modulated, plastic, and ever-changing population activity -as monkeys learn how to do [161–163]- without any assumptions would be crucial. There are also other

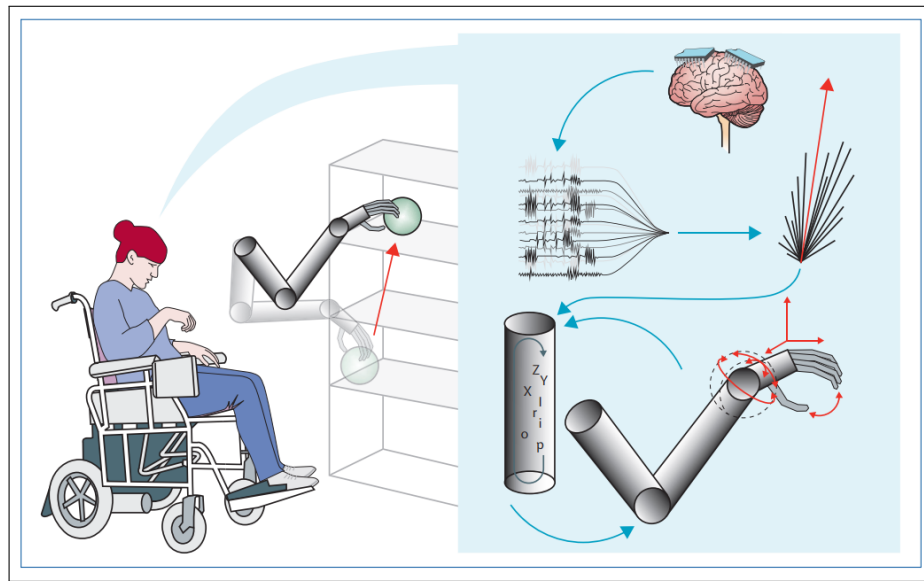


Figure 1.16 A tetraplegic subject with motor cortex implant manipulates objects with bioinspired brain-machine interface (BMI). Adapted from [156].

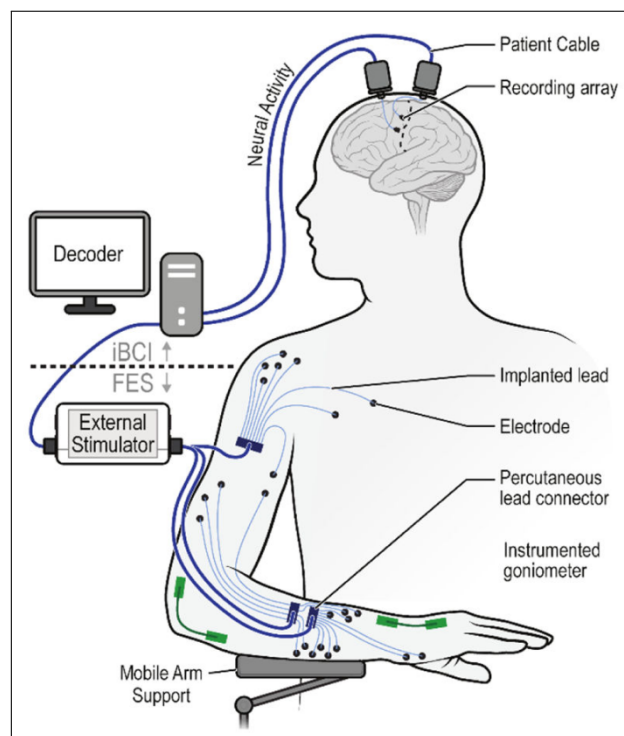


Figure 1.17 A typical FES+iBCI System. Recorded motor cortex activity decoded into command signals for stimulation purposes to muscles and to actuate a mobile arm support. Adapted from Figure 1 in [150].

elegant studies that utilized diverse decoding techniques, such as information theory, to explain the leading neural activity before movement and mutual information explained

well the strength of the relationship between parameters [80, 157, 158, 164, 165].

1.3.3 Bayesian Inference to Explain Behavioral Outcome from Neural Activity

Perception of the physical world is built based on continuously flowing stimulus-evoked sensorineural data and our previous experience about the surroundings. Sensory experience is shaped by the statistical regularities of objects around us. However, elicited sensory responses are always prone to uncertainty stemming from the stochastic nature of the encoding processes. In frequentist approach, as we will see some non-Bayesian approaches within seven commonly used classifying algorithms in Chapter 4, specific values for the parameters are chosen at the end of the optimization process that minimizes the loss function [166]. However, in the Bayesian approach, instead of specific constant values, prior distributions are chosen for those statistical regularities of objects and Bayes' theorem is used to generate posterior distribution for the value to be predicted. Prior information (prior distribution) of the statistical properties of objects allows us to weigh the incoming sea of stimuli (likelihood distribution) accordingly that in turn results in robust estimates of the final decision of belief (posterior conditional probability distribution). Bayesian probability theory [167–170] establishes a normative framework to explain how perceptual inferences of an ideal observer are shaped by joining the multiple cues from sensorineural data and preceding experiences. The free energy principle [99] presents a compelling explanation for the processes at the level of biological agents. Free energy is formulated by the divergence between the probability distribution of environmental stimuli and the elicited neurophysiological distribution encoded by its internal configuration that can be simplified as the amount of prediction error. Biological agents always have a resistance to a disorder tendency that brings minimization of surprise [171, 172]. This corresponds to Bayesian inference in terms of updating posterior belief by minimizing the free energy and suppressing the prediction error to better predict the causes of incoming sensory data.

The Bayesian approach distinguishes itself with this peculiar contribution of prior and observed data from the other statistical inference methods in psychophys-

ical or neurophysiological experiments. The perceptual mechanisms compared with human 'ideal observer' in psychophysical experiments [173–177] are presented in detail that human subjects combine neural distributions from multiple sensory modalities in a Bayes-optimal way. Building accurate Bayesian models requires to approach the problem in the level of 'representation and algorithmic' level of the [178] Marr's three levels (computational, representation (or algorithmic), and implementation) of analysis framework while we claim to remain agnostic about the level of implementation for the perceptual processes in the brain. This view supports Bayesian models to have an instrumentalist approach, in which models only predict the performance of the system, do not summarize, systemize or describe the whole system [179]. The instrumentalist point of view eventually ensures the explanations of stochasticity in neurophysiological events using Bayesian models.

There is a growing body of evidence in literature elucidating behavioral perception is working like a Bayesian machine [176, 180–184]. They propose human subjects behave like an 'optimal' Bayesian observer since the brain represents information probabilistically and updates the probability distribution of hypothesis (H) whenever new data (D) are introduced into the system, as the Bayes' Rule states:

$$P(H|D) = \frac{P(D|H)P(H)}{P(D)} \quad (1.1)$$

If multiple modalities are observed in the experiments [179, 182] Bayes' rule can be extended like:

$$P(S|T, V) = \frac{P(T, V|S)P(S)}{P(T, V)} = \frac{P(T|S)P(V|S)P(S)}{P(T, V)} \propto P(T|S)P(V|S)P(S) \quad (1.2)$$

where S for stimulus, T for tactile, and V for visual individual measurements. The Bayesian decoding approach is utilized to describe spike trains [185], posterior distribution over stimuli [186–189].

In this study, the neural representations leading to perceptual decisions were decoded using Bayesian Decision Theory [190], by specifying a loss function, to min-

imize the deviations of perceptual estimates from animal behavior. Plenty amount of experimental and computational studies explain how computations in the brain are performed to explain population coding [191, 192], preferred orientation, direction tuning [79], hand kinematics [193–195], velocity, and timing of contacts under anesthesia [196]. To our knowledge, there is no study utilizing Bayesian inference to perform choice prediction from neuronal spiking activity with the adaptive input of stimulus distribution during the behavioral yes/no detection task. This study attempts to reconstruct the decision in spite of the stochasticity within the nervous system and provides a novel Bayesian Network algorithm for the future BCI studies.

1.4 Outline

This chapter introduces our motivation, objectives, and general introduction with the background information of the topic. There is a circular pathway throughout the rest of the chapters of this thesis (Figure 1.18). Neural encoding concept is introduced in Chapter 2. A neuroprosthetics application is demonstrated to explain how neural encoding mechanisms bypassed and artificial sensation is elicited by electrically stimulating the sensorimotor cortex of behaving rats during a yes/no detection task. The rest of the chapters (Chapter 3-5) are devoted to neural decoding to better infer the intention of the animals for motor output. Chapter 3 introduces a novel Bayesian Network Model, which is implemented to decipher the decision from neural representations of rats during a perceptual decision-making task. Chapter 4 compares the Bayesian Network algorithm with the other commonly used supervised machine learning algorithms. Chapter 5 introduces an incremental Bayesian model to reveal the history effects on the decision of the behaving animal. Chapter 6 closes this thesis with the conclusion and future directions.

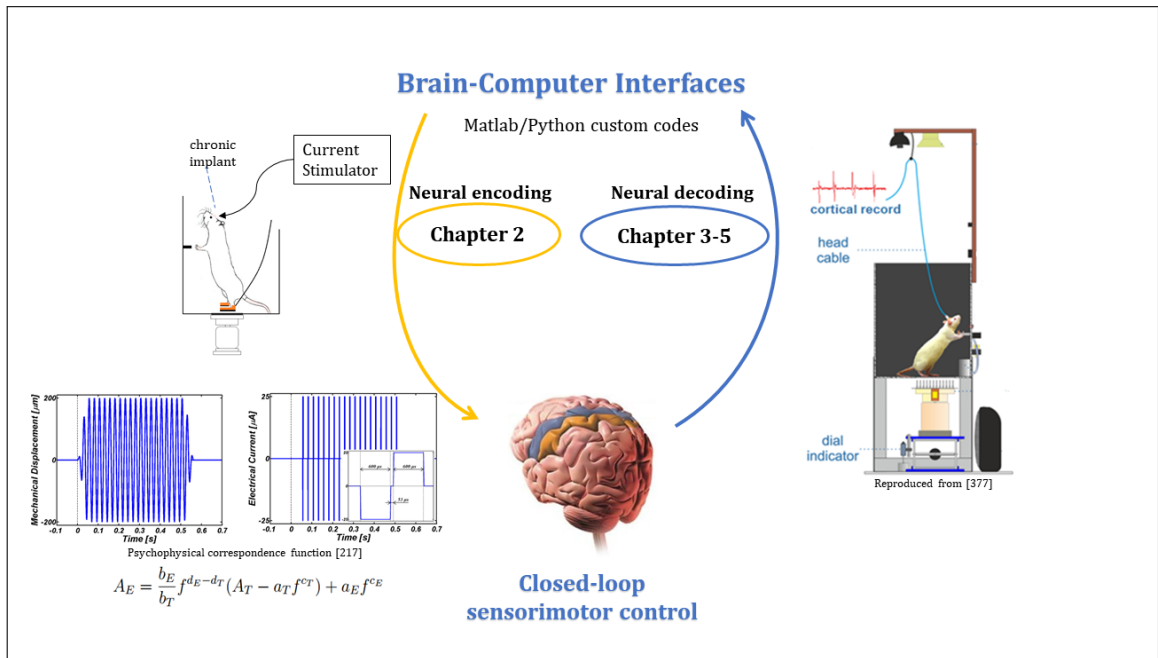


Figure 1.18 A general schematic of the outline of the chapters. Neural encoding concepts will be introduced in Chapter 2. Neural decoding parts will be explained in Chapter 3-5.

2. PERFORMANCE OF AWAKE BEHAVING RATS WEARING ISOLATED NEUROPROSTHETIC BOOTS WITH REAL-TIME INTRACORTICAL MICROSTIMULATION CORRESPONDING TO THE VIBROTACTILE MECHANICAL STIMULATION

This work has been published.¹

2.1 Introduction

Simple prostheses and orthoses go back to the beginnings of human history (e.g. ancient Egypt) and have greatly helped patients suffering from injuries. . Modern electronics technology enabled active prosthetic devices to measure biological signals and provide better control [197]. The last decades have also documented ambitious projects for direct communication with the nervous system (i.e. neuroprostheses), either for supporting sensory [1, 2, 198, 199] or motor function [3, 4, 200], or even both [201–203]. Tapping the neural pathways directly by invasive electrodes increases the amount of biological information tremendously and provides unprecedented methods for diagnostics and neuromodulation therapy (e.g. electroceuticals for metabolic diseases). In some cases, there seems to be no alternative therapeutic method (e.g. in quadriplegia [4]).

One of the major limitations of commercial limb prostheses is the lack or limited use of sensory feedback [204, 205]. It is well known that the sense of touch and proprioception are required for the biological control and the embodiment of the limbs, besides the appreciation of sensory stimuli [206, 207]. For example, in the early versions of the BrainGate system, the patient had to watch the robotic arm continuously while controlling it by cortical spike activity [3]. Sensory feedback is also invaluable

¹Öztürk, S., Devcioglu, I., Beygi, M., Atasoy, A., Mutlu, S., Özkan, M. and Güçlü, B. (2019). Real-Time Performance of a Tactile Neuroprosthesis on Awake Behaving Rats. IEEE transactions on neural systems and rehabilitation engineering: a publication of the IEEE Engineering in Medicine and Biology Society, 27(5), 1053-1062. <https://doi.org/10.1109/TNSRE.2019.2910320>

for the fast adjustment of device hardware or software, as well as for help creating adaptive movement strategies by the user [200, 201]. Inadequate embodiment of the device increases cognitive load and decreases functionality. In the worst scenarios, lack of feedback may cause additional injuries due to slippage of objects or falls. Recently, there have also been increased efforts underway to develop novel electrode interfaces to link devices with the peripheral or central nervous system [208, 209].

Although intracortical microstimulation (ICMS) for artificial sensation was previously used, especially in rats and monkeys, to study fundamentals of sensory processing [210, 211], it has become more important for the application of sensory feedback in neuroprostheses. Electrically stimulating the cortex allows spatial discrimination easily due to the relatively simple layout of the somatotopic organization, but there are many trade-offs between cortical and peripheral stimulation which need to be considered for the desired application based on the patient injury or dysfunction [212]. By manipulating electrical waveform parameters and stimulation sites, it is possible to influence psychophysical measures of sensation such as detection and discrimination probabilities, magnitude scaling, and projection fields [213–215].

In this study, the performance of a microfabricated tactile sensor [216] and the associated tactile neuroprosthetic system was measured by using previously trained rats [215]. The main novelty of the work is the real-time implementation of the signal processing steps and the active use of the sensory neuroprosthesis during a psychophysical task. Although virtual active touch paradigms were tested in monkeys before [217], direct tactile stimulation of a prosthetic-like device was not adopted during active movement. In the current study, however, the rats could process the information obtained from the tactile sensor mounted on their hind paws in real-time via ICMS and use that in a behaviorally relevant manner. Unlike most of the whisker studies in the literature [210], mechanically stimulating the tactile sensor worn on the hind paw, and which mimics the glabrous skin, is more analogous to stimulating the robotic limb of a human amputee (to which we did not have clinical access for the current study). Additionally, the rats were not restrained in the presented work and they behaved freely in the operant chamber during the experiments. This is a more realistic scenario of prosthetic use in practice, and a substantial level of embodiment was observed in rats which actively moved on the chamber floor with the tactile sensor on and sought the

reward by pressing the levers. The presented animal model without amputation is also a promising tool to test various hardware and software components of neuroprosthetic systems.

2.2 Methods

The block diagram of the entire tactile neuroprosthesis and the instrumentation for testing is given in Figure 2.1. The neuroprosthesis system consists of the tactile sensor and the boot worn by the animal, sensor interface and amplifiers, a real-time processor unit, a current stimulator, and a brain implant for providing artificial sensation. The test instrumentation includes an operant chamber and a vibrotactile stimulation system. The details of each component are explained below.

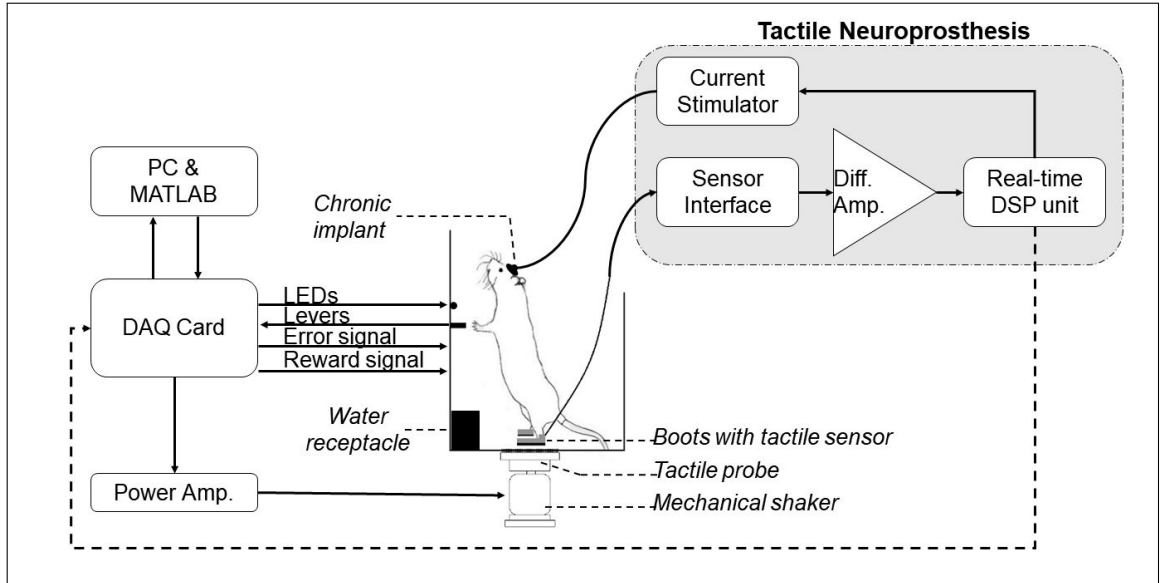


Figure 2.1 Block diagram of the tactile neuroprosthesis and the testing setup. The neuroprosthesis system consisted of the tactile sensor and the boot worn by the animal, sensor interface and amplifiers, a real-time processor unit, a current stimulator, and a brain implant for providing artificial sensation. The test instrumentation included an operant chamber and a vibrotactile stimulation system. The signal flow paths are shown by arrows in the figure. The tactile neuroprosthesis and the testing setup operated independently, except the PC also recorded the intracortical microstimulation pulses (dashed line with arrow) to follow up the errors in the neuroprosthesis. The details of the DSP blocks are shown in Figure 2.4

2.2.1 Animals

Two adult male Wistar albino rats (ages: 18 months) were used in this study (Rat 1 and 2). The animals were already implanted with electrodes and trained to establish psychophysical correspondence between vibrotactile intensity and ICMS (for details, see [215]). Note that the subject identification is different in that previous study). Animals were kept in a reversed daily light cycle (12h dark/12h light). They were deprived of water 36 hours before the experiments; and their weights were maintained within $>80\%$ of their initial values. Food and water were provided ad libitum after the sessions. The experiments were approved by the Boğaziçi University Institutional Ethics Committee for the Local Use of Animals in Experiments.

2.2.2 Tactile Neuroprosthesis

Although somatosensory neuroprostheses are in development for amputees and patients with neural dysfunction, we preferred to perform the experiments on healthy rats. Since amputation or other injury models would be traumatic for the animals, we designed plastic boots which can be worn without hindering behavioral testing. This also allowed switching the neuroprosthesis system and ICMS on and off for comparison without taking off the boots; and hence any particular effect of wearing the boots was mitigated. The boots were made by 3D printing (Zortrax M200; Zortrax S.A., Olsztyn, Poland) using two filaments (Z-Abs and Z-Ultras Z-Filaments; Zortrax S.A., Olsztyn, Poland). A pair of boots was put on the hind paws of rats before each experimental session. Only one boot of the pair, precisely the one contralateral to the brain implant, had the tactile sensor surface. The printed thickness of the boot without the sensor surface was greater than the other one to keep the total thickness the same and prevent mechanical imbalance during behavioral testing.

It was also desired that the boots mechanically isolated the glabrous skin as much as possible from the vibrotactile stimulation applied to the tactile sensor surface. Two design approaches were implemented for this. First, the loosest mesh design pattern was selected for 3D printing (Solid Edge ST9; Siemens PLM Software, Plano,

TX, USA). Second, part of the boots attached to the hind paw was connected to the surface piece only at the backside, similar to a cantilever (Figure 2.2a). The boots did not provide perfect mechanical isolation, but they diminished stimulus detection probability considerably (see Results). The tactile sensor was fixed on the lower surface of the contralateral boot by cyanoacrylate glue (Figure 2.2b). While the boots attenuated the excitation of tactile afferent nerves in the rat skin, the tactile sensor was able to detect the mechanical vibrations applied in the operant chamber well during the psychophysical task.

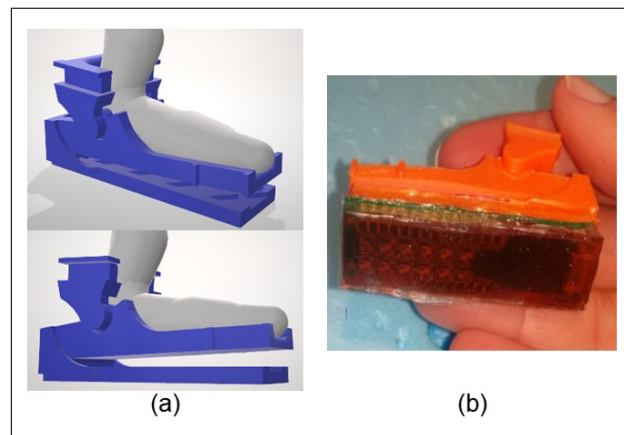


Figure 2.2 (a) Technical drawings of the boots for 3D printing with a dummy foot model. For isolation of the glabrous skin from the vibrotactile stimulation probes, loosest mesh design was used, and a cantilever structure was adopted which further reduced mechanical transmission from the lower surface. (b) Photograph of a boot with the tactile sensor attached to the lower surface.

2.2.2.1 Tactile sensor and preprocessing

The tactile sensor was designed and fabricated for the purpose of the presented study and similar neuroprosthetic applications (for details, see [216]). Polydimethylsiloxane (PDMS) was the lowest layer of the sensor which contacted the chamber floor. It was bonded to a polyimide (PI) sheet. The sheet had a 2x7 cell array and each cell included four serially connected strain gauges made of 50-nm thick aluminum film. Above the PI sheet, a polylactic acid (PLA) substrate was used. A printed circuit board (PCB) was attached to the PLA substrate and connected to the strain gauges via pins through the cavities in the PLA layer.

The resistances of the strain gages changed as mechanical vibrations deformed

the sensor cells of the PI layer. The resistance changes were converted to voltage changes by a custom-made interface circuit (Figure 2.3a). In each channel of the interface circuit, the LM334 integrated circuit was configured as a 1-mA constant current source through each sensor cell. The voltage change across the sensor cell within the interface circuit was amplified at x1000 or x10k gain and band-pass filtered at 10-1000 Hz initially with a custom-made multi-channel amplifier (Figure 2.3b). In most of the experimental sessions, however, some of the sensor cells were previously damaged due to chewing by the rat during the habituation period (neuroprosthesis turned off; rats moved freely with boots on). Since the signal levels were unpredictable in those conditions, the multi-channel output was monitored, but not processed in parallel by the real-time processor. Regardless of the number of functional sensor cells, the cell with the highest signal-to-noise ratio was selected and routed to a single-channel differential amplifier and filter (DAM 50; World Precision Instruments, Sarasota, FL, USA). A single channel is usually adequate for performing the ICMS detection task [215]. The sensitivity range of the tactile sensor is 0.3-0.7 Ω/mm for a maximum 3-4 N force. Before amplification, this corresponds to 0.126 $\mu\text{V}/\mu\text{m}$ for 40 Hz and 0.224 $\mu\text{V}/\mu\text{m}$ for 80 Hz of vibrotactile stimulation.

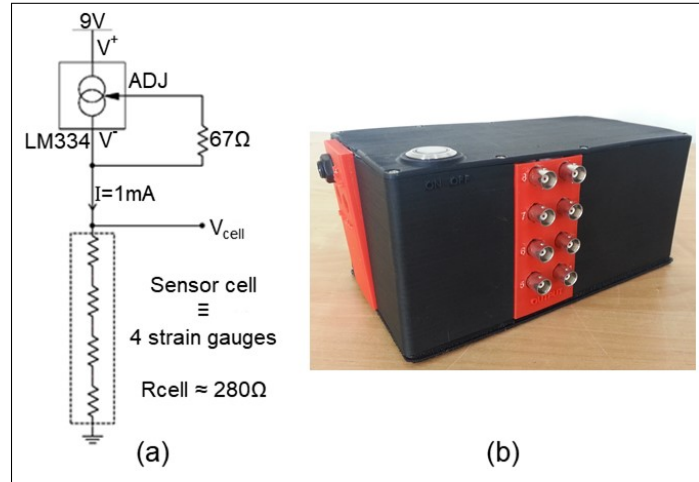


Figure 2.3 (a) Schematic of the sensor interface circuit. Each cell of the tactile sensor contains 4 serially-connected strain gauges (total nominal resistance: $R_{cell} \approx 280\Omega$). The cell is driven by a constant current source (LM334 integrated circuit) and the voltage output (V_{cell}) changes based on the vibrotactile stimulus applied on the sensor surface. (b) The outputs from the interface circuits of the 2x7 cell array were amplified (gain: x1000 or x10k) and band-pass filtered (10-1000 Hz) by a multi-channel amplifier.

2.2.2.2 Real-time processing for artificial tactile sensation

Amplified voltage changes from the tactile sensor were input to a real-time processor (RZ5 Bioamp Processor; Tucker Davis Technologies, Alachua, FL, USA). The vibrotactile information within that signal was processed through successive digital signal processor (DSP) blocks. The blocks are depicted in Figure 2.4, and they were all programmed in Real-time Processor Visual Design Studio (RPvdsEx), a proprietary software by Tucker Davis Technologies. After analog-to-digital conversion (step A in Figure 2.4), the signal was band-pass filtered (step B) according to the vibrotactile frequency ($= f_{center}$) used in the psychophysical experiment (6th order Butterworth, bandwidth: 10 Hz; see Discussion for limitations). The next step (C in Figure 2.4) includes envelope detection (low-pass filter cut-off: 10 Hz), scaling and linear gain adjustment to match the characteristics of preprocessing hardware described above. Therefore, the output of step C is calibrated in micrometers of vibrotactile stimulus amplitude. Afterwards, the signal was processed through the psychometric equivalence function (PEF) for the particular rat subject (step D). This is a computational model derived by the extensive experiments reported in [215]. It establishes a psychophysical correspondence between mechanical vibration amplitude and electrical current amplitude to be used in ICMS². In other words, based on the intensity of the vibrotactile stimulus estimated by the processor, ICMS intensity is adjusted in real-time for artificial tactile sensation. Specifically, the model converts a signal of dB (ref. 1 μm) mechanical intensity to dB (ref. 1 μA) electrical intensity. In step E, an amplitude-modulated pulse train was generated based on the calculated real-time changes in electrical intensity. This pulse train was the digital waveform of the ICMS and had the same frequency as the vibrotactile frequency used in the psychophysical experiments. It was used to generate ICMS with biphasic charge-balanced current pulses (cathodic phase leading, pulse width: 600 μs , inter-phase interval: 53 μs). In the final step (F), the ICMS waveform was converted to an analog signal to control the current stimulator.

²For mechanical intensity, dB values are calculated based on the formula: $\text{dB} = 20\log_{10}[A/1\mu\text{m}]$. A is the zero-to-peak displacement amplitude of the vibrotactile stimulus in micrometers. For electrical intensity, A stands for the zero-to-peak amplitude of the current pulse in microamperes, and in the ratio expression, it is referenced to 1 μA .

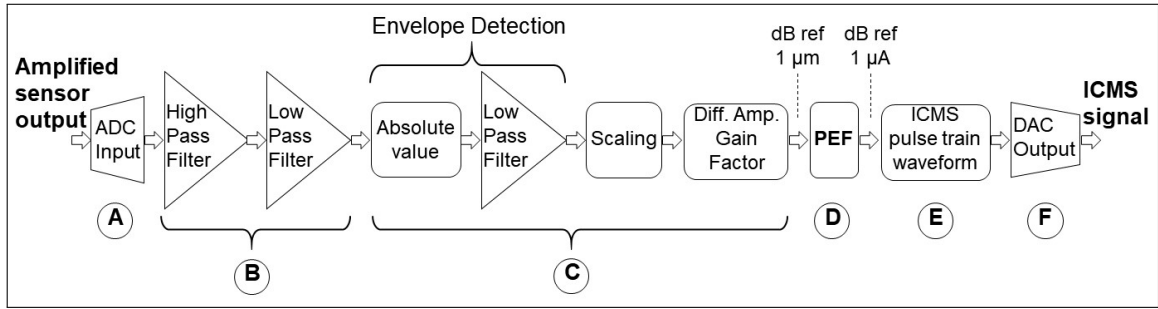


Figure 2.4 Digital signal processor (DSP) blocks. RZ5 real-time processor runs on several DSPs programmed by a proprietary software. See text for the details. A: analog-to-digital conversion; B: band-pass filtering; C: envelope detection, scaling and gain adjustment; D: subject-based psychometric equivalence function; E: pulse train generation and amplitude modulation for intracortical microstimulation (ICMS); F: digital-to-analog conversion.

2.2.2.3 Brain implant and intracortical microstimulation (ICMS)

The animals were already implanted with electrodes (having robust vibrotactile neural activity) in the previous study to establish PEFs [215]. Rat 1 had a microwire array electrode (Teflon coated platinum/iridium (90/10%), 4x4 array, the distance between rows/columns: 0.25 mm, microwire dia. 25 μm ; Plexon Inc., Dallas, TX, USA) in the primary somatosensory cortex (right hem. depth: 0.96 mm, $\sim$ layer V). Only one calibrated channel within the hind limb representation was used for the current experiment. Rat 2 had a single tungsten electrode (parylene coated, dia. 85 μm ; World Precision Instruments) within the same somatosensory area (left hem. depth: 0.88 mm, $\sim$ layer IV/V). The analog signal from the real-time processor was input to an isolated current stimulator (model 2200; A-M Systems, Sequim, WA, USA). This unit has a voltage-to-current converter to generate the same electrical current waveform as the input control voltage. The current output from the device was applied to the brain implant by a Plexon headstage cable and the proper custom-made adapters.

2.2.3 Operant Chamber and Vibrotactile Stimulation

A custom-made operant chamber and vibrotactile stimulation system were used for testing the tactile neuroprosthesis (Figure 2.1; for details, see [218]). The chamber has three LED lights (only middle one is used here), three response levers, a water receptacle, error and reward signal buzzers, and a multi-probe contactor on the floor.

All the probes moved simultaneously through the holes of the floor plate. This allowed stimulation of the hind-paw glabrous skin or the tactile sensor worn by the rat regardless of the animal's location in the chamber. The contactor was attached to an electrodynamic shaker (V201, Ling Dynamic Systems, Royston, Herts, UK) which was driven by a custom-made power amplifier. Mechanical stimulation waveforms were generated by the analog output of a data acquisition card (USB-6259; National Instruments, Austin, TX, USA). Chamber control was also performed by the same card. The psychophysical experiment protocol was run in MATLAB (R2008a; The Math Works, Natick, MA, USA). The chamber was contained in a light- and sound-insulated box, and the rat movements were recorded by an infrared camera. Acoustic white noise (bandwidth: 200 kHz) was played into the box to mask environmental sounds and any auditory cues generated by the instrumentation setup.

2.2.4 Procedure

The animals were already conditioned behaviorally for tactile and ICMS stimuli at the beginning of the current neuroprosthesis study according to a training schedule [218]. Therefore, they could also perform a yes/no psychophysical detection task based on vibrotactile stimuli directly applied on their hind-paw glabrous skin or based on only ICMS applied to the somatosensory cortex. Before the experiments, a habituation period (about ten 1-h sessions) was necessary for the rats to get used to the boots and the sensor cable. The procedure included two main experimental conditions. In Experiment I, the rats wore the boots and the head cable, but the neuroprosthesis was switched off, i.e. no ICMS was applied (boot only). In Experiment II, the tactile neuroprosthesis was operational with ICMS (boot+ICMS). Each experiment was performed at two vibrotactile frequencies (40 and 80 Hz) and at five amplitude levels (range: 8 - 200 μm at 40 Hz and 4 - 40 μm at 80 Hz). The data from the natural condition, i.e. vibrotactile stimulation of the skin, were already available from the previous study for comparison [215]. In that condition, the rats did not wear the boots.

In the psychophysical detection task, the animal started each trial by pressing the middle lever. This caused the middle light to turn on for a duration of 0.6 s, in

which the vibrotactile stimulus was either presented or not. The stimulus on and off trials were random and counter-balanced. The vibrotactile stimuli were sinusoidal mechanical vibrations (duration: 0.5 s, rise/fall time: 50 ms). The rats were trained to press the right lever for detecting the stimulus and the left lever for not detecting it. In both Experiment I and II, the stimuli were applied on the tactile sensor surface of the boots and not directly on the hind-paw skin. Some vibrations were still transmitted to the hind-paw skin via the boot structure (and possibly to the tail touching the floor plate), and therefore, in Experiment I, the rats could perform above the chance level, albeit with low performance. In Experiment II, the performance was much higher due to the artificial sensation generated by ICMS. Based on the mechanical amplitude ranges reported above, ICMS had amplitude ranges of 7 - 120 μA at 40 Hz and 5 - 23 μA at 80 Hz. Hits and correct rejections were rewarded with 7-8 μL of water. An error buzzer was activated for misses, false alarms, and time-outs. Behavioral data (hits, misses, correct rejections and false alarms) were recorded during the experiments (total analysis sessions for 2 rats: 703, average trials in each session: ~ 50).

2.2.5 Neuroprosthesis Errors and Statistical Analyses

In Experiment II, the tactile neuroprosthesis worked in real-time entirely on its own. In other words, it was independent of the psychophysical experiment and the trial conditions. Therefore, it had its own errors, such as generating ICMS pulses when there was no vibrotactile stimulus or not generating ICMS when there was indeed a sensory stimulus. This approach created a realistic scenario for testing the system close to its practical application if adapted for human patients in the future. On the other hand, it also created difficulties for the subject, such as the conflict due to the mismatch between stray vibrations in the boots and nonexistent ICMS pulses. The errors of the tactile prosthesis mainly originated from movement artifacts such as the decoupling of the tactile sensor from the shaker probes and noise in the sensor cables. Since we aimed to demonstrate the proof-of-concept regarding the system and not to develop an ultimate device for rats, the trials with ICMS generation errors (recorded via the dashed-line channel in Figure 2.1) were not included in the statistical analyses.

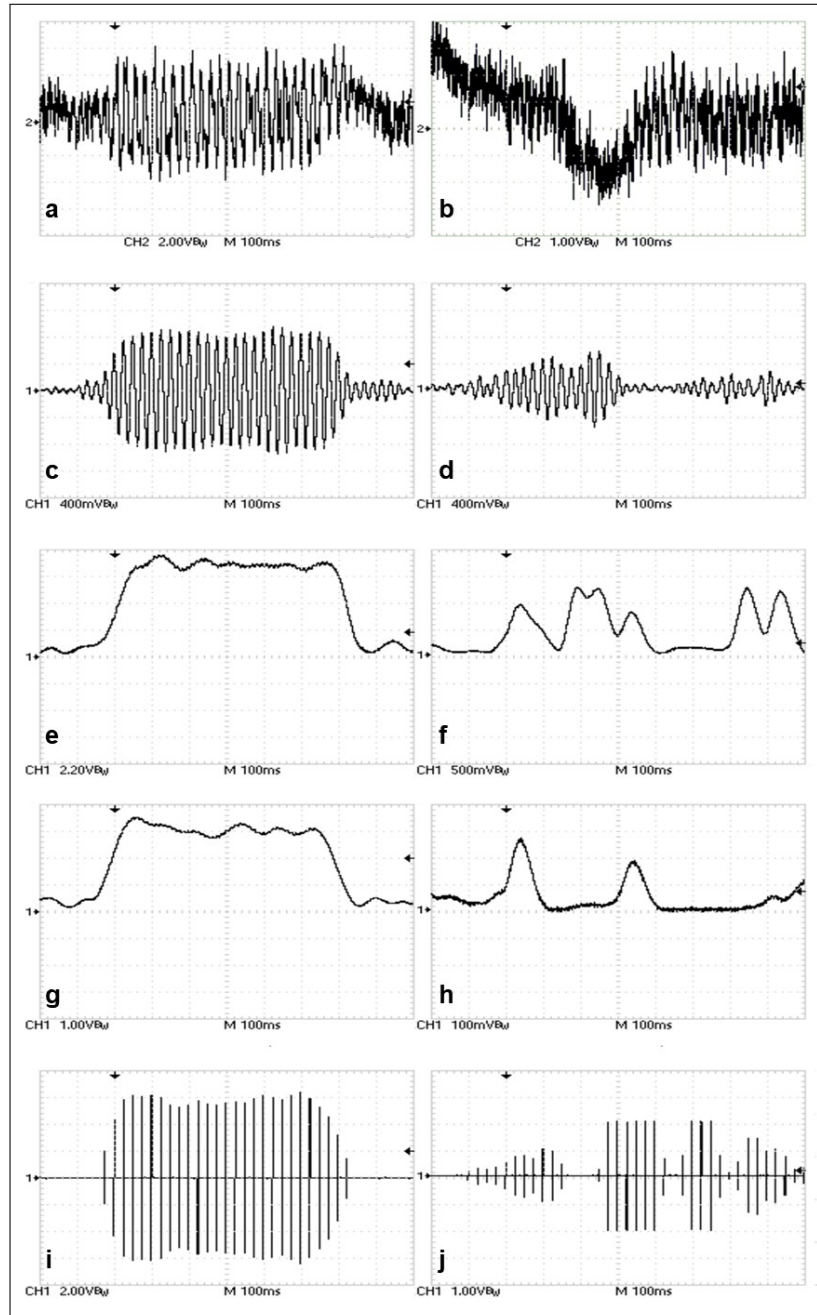


Figure 2.5 Example signals recorded from the tactile neuroprosthesis and the DSP blocks (via auxiliary outputs). The left panels are cases in which the tactile sensor of the boot was stationary. The right panels were recorded while the animals vigorously moved during the psychophysical task; therefore, there are large movement artifacts which sometimes caused neuroprosthesis errors (see text). Note that the oscilloscope displays were not captured simultaneously due to limited availability of acquisition channels. (a, b) Amplified tactile sensor output from the boot (step A in Figure 2.4); (c, d) Sensor signals after band-pass filtering (after step B in Figure 2.4); (e, f) Envelopes of the filtered signals (including scaling and gain adjustment after step C in Figure 2.4); (g, h) Signals calibrated in mechanical intensity are converted to electrical intensity based on the psychometric equivalence function for each rat (step D in Figure 2.4); (i, j) The amplitudes of the intracortical microstimulation pulses (generated in step E in Figure 2.4) are modulated by signals as in (g, h) and output from the digital-to-analog convertor (step F in Figure 2.4) to control an isolated current stimulator.

Specifically, a hit or miss was defined as invalid, if ICMS was not generated for a stimulus-on trial. Similarly, a correct rejection or false alarm was defined as invalid, if ICMS was generated for a stimulus-off trial.

Data from Experiments I and II (artificial tactile sensation) and the previous experiment with natural stimulus were analyzed on receiver-operating-characteristic (ROC) plots and by the nonparametric sensitivity index (A') calculated from hit ($p(h)$) and false alarm ($p(f)$) rate [219]:

$$A' = 0.5 + \frac{(p(h) - p(f))(1 + p(h) - p(f))}{4p(h)(1 - p(f))} \quad (2.1)$$

Analysis of covariance (ANCOVA) was conducted on the dependent variable of A' by using SPSS (Ver. 24; IBM Corp., Armonk, NY, USA). The covariate was the amplitude of the vibrotactile stimulus. The only factor was the experimental condition (natural stimulus, boot only, boot+ICMS). ANCOVA was performed separately at each vibrotactile frequency and for each rat.

2.3 Results

2.3.1 Sensor Output and Signal Processing

Important signals recorded from the tactile neuroprosthesis and the DSP blocks (via auxiliary digital-to-analog converter outputs of RZ5 real-time processor) are given in Figure 2.5 as oscilloscope screen displays. The panels in the left column represent cases in which the tactile sensor of the boot was stationary and directly coupled to the multi-probe contactor. The panels in the right column show cases with large movement artifacts while the animals performed the psychophysical task. Because of the limited availability of acquisition channels, the oscilloscope displays of each column were not captured simultaneously; they may be considered as typical examples of the signal processing steps.

For the measurements of Figure 2.5, the vibrotactile stimulus was at 40 Hz with an intensity of 46 dB (ref. 1 μm) corresponding to $\sim 200 \mu\text{m}$ zero-to-peak amplitude.

The first row of panels (Figure 2.5 a, b) shows the amplified tactile sensor output from the boot (depicted as the signal at step A of the block diagram in Figure 2.4). This level of mechanical stimulation is suprathreshold and would be easily detected if applied on the glabrous skin. If there are no movement artifacts, it can also be measured relatively easily by the tactile sensor (cf. Figure 2.5 a and b). The second row in Figure 2.5 shows the sensor signals after band-pass filtering (after step B in Figure 2.4). The signal without the movement artifacts highly mimics the vibrotactile stimulus waveform. On the other hand, there are interruptions and distortions in the signal with artifacts. It is important to note that Figure 2.5d is not the filtered version of Figure 2.5b, because they were not recorded simultaneously as mentioned above. In the panels of the third row, the envelope of the sensor signal was found and it was calibrated for further processing. For example, the signal in Figure 2.5e represents the amplitude of the vibrotactile stimulus such that the zero-to-peak amplitude (in μm) can be obtained by multiplying it by a calibration factor ($\sim 6.6 \text{ V} \times 30.23 = 199.5 \mu\text{m}$). The calibration factor was embedded in step C of the DSP blocks in Figure 2.4; it accounts for the scaling of the envelope detection and the total gain in the preprocessing hardware (Figure 2.1).

In the fourth row of Figure 2.5, the signals represent the output of the PEF of the particular rat. In other words, these signals are obtained from a model which matches the vibrotactile stimulus with ICMS level for identical psychophysical performance (i.e. hit rate). This model is embedded in step D of Figure 2.4 (see Methods). It basically causes frequency-dependent linear shifts in dB scales. Therefore, the waveform regarding Figure 2.5g would be identical (if measured simultaneously) to that of Figure 2.5e except for a level adjustment for current amplitude values in μA . The intermittent nature of the signals in Figure 2.5f and 2.5h indicates that the ICMS pulses may not last for the full duration of the vibrotactile stimulus. Additionally, movement artifacts may cause spurious waveforms not related to the vibrotactile stimulus (e.g. see double peaks at the ending of the trace in Figure 2.5f). The last row of panels shows the ICMS pulse waveforms generated by modulating the amplitude of a 40-Hz pulse train (see Methods for pulse timing parameters; step E in Figure 2.4) by signals such as those in the fourth row. These were obtained from the digital-to-analog converter of the real-time processor (step F in Figure 2.4). The waveforms in the last row are calibrated to

control an isolated current stimulator which passes current through the electrodes of the brain implant. The calibration factor for Figure 2.5i is 20, which gives $\sim 120 \mu\text{A}$ current amplitude.

2.3.2 Psychophysical Test Results

The tactile neuroprosthesis was tested during a yes/no detection task (see Table A.1 in the Appendix A for trial counts). Since the rats had already known the task, we expected their detection strategies were more or less stable. Nevertheless, the hit and false alarm rates varied from session to session. This variation of psychophysical performance was not only due to neuroprosthesis errors (see Methods), because it also existed in the results for the boot only and, albeit less, in natural stimulus conditions. Figure 2.6 shows sample data from Rat 1 at only one intensity level for each vibrotactile frequency (39 dB ref. $1 \mu\text{m}$ for 40 Hz; 32 dB ref. $1 \mu\text{m}$ for 80 Hz). The diamond symbol shows the hit and false alarm rates in the initial session; and the cross symbol shows them in the final session. The intermediate sessions are depicted by filled circles. In general, the hit rates somewhat increased in successive sessions probably due to a slight learning effect. Additionally, boot+ICMS condition (e.g. Figure 2.6c) mostly yielded higher session-averaged hit rates than the boot only condition (e.g. Figure 2.6a). As expected, the rats performed the best in the natural stimulus condition (e.g. Figure 2.6e,f).

For a given experimental condition (e.g. boot+ICMS at 80 Hz), the data points are located at a particular region above the main diagonal (e.g. Figure 2.6d), which confirms that the detection strategy of a given rat did not change much. However, it is observed that Rat 1 had a left-lever bias (i.e. mostly no-detect responses indicating a conservative criterion) in the boot only (Figure 2.6a) and boot+ICMS (Figure 2.6c) conditions for 40 Hz, because the data points are scattered on the left side of the short diagonal. On the other hand, Rat 2 had some right-lever bias in the boot only condition, and especially for 40 Hz at the boot+ICMS condition (Figure A.1 in Appendix A). Since our focus is on detectability, we did not quantify the bias explicitly. The main conclusions would not change, however, because they measure independent concepts.

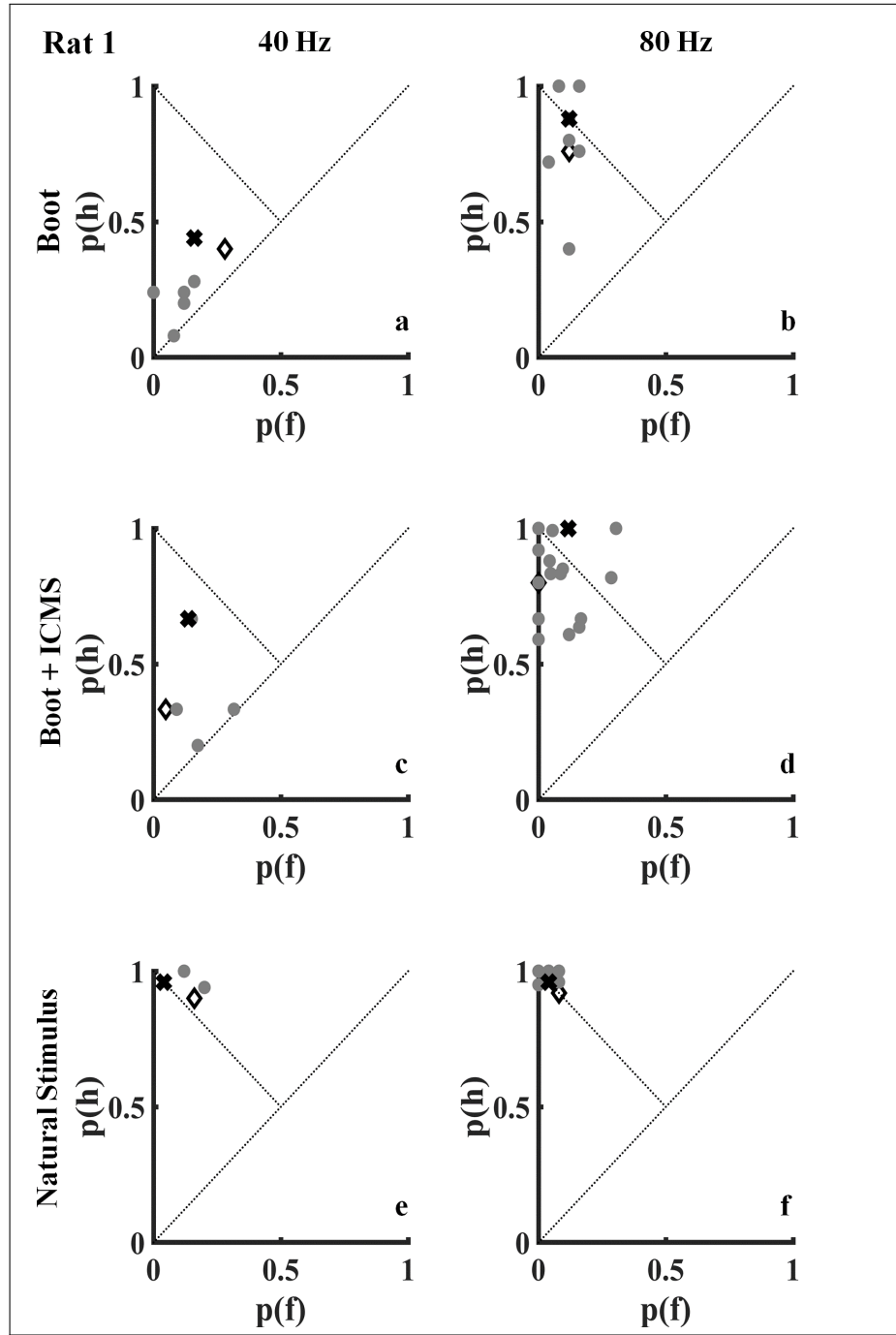


Figure 2.6 Receiver operating characteristic (ROC) plots for Rat 1 in (a, b) boot only (Experiment I) and (c, d) boot+ICMS (Experiment II) conditions at one vibrotactile intensity level for a given frequency (39 dB ref. 1 μ m for 40 Hz; 32 dB ref. 1 μ m for 80 Hz). The remaining data obtained at different vibrotactile intensity levels are similar to ones shown. (e, f) Previous results [215] of a natural stimulus (corresponding intensities, but applied on the skin) are also given for comparison. Diamond and cross symbols refer to the initial and final sessions, respectively. Intermediate sessions are depicted by filled circles.

2.3.3 Detectability

Figure 2.7 includes plots of A' as a function of vibrotactile intensity in three experimental conditions (boot only, boot+ICMS, natural stimulus). A separate graph is presented for each stimulus frequency and each rat. The theoretical range of A' is 0.5 - 1; and therefore, 0.5 corresponds to no detection, and 1 corresponds to perfect detection. The detectability of the natural stimulus (yellow curves in Figure 2.7) was high at the suprathreshold intensity levels tested here, and increased to almost perfect detection as the vibrotactile intensity increased, but with decreasing slope. On the other hand, the boot only condition (blue curves in Figure 2.7) yielded A' values still greater than 0.5, which indicated that the boot isolation was not perfect, and a certain amount of mechanical vibration reached the skin to activate mechanoreceptive afferent nerves. However, there was substantial attenuation in these stray vibrations, because A' values were much smaller than those obtained with the direct stimulation of the skin. The more important results were obtained when the tactile neuroprosthesis was switched on, i.e. boot+ICMS condition (red curves in Figure 2.7). The results show an improvement of A' due to the contribution of the neuroprosthesis compared to the boot only condition. Except only at 28 dB (ref. $1\ \mu\text{m}$) for Rat 2 during 80-Hz tests, average A' values for the boot+ICMS condition were always higher than those of the boot only condition. Additionally, for all three experimental conditions in Rat 1's data (Figure 2.7 a, c), A' values had an increasing trend as a function of the vibrotactile stimulus intensity. Boot+ICMS data were somewhat parallel to boot only data, which strongly supports a constant facilitating effect of the tactile neuroprosthesis. Although a similar effect was observed for Rat 2 (Figure 2.7 b, d), A' values were not modulated by the stimulus intensity as much, except for the natural stimulus condition. This may imply that higher-level vibrations were attenuated more during the mechanical coupling between the boot and the multi-probe contactor for this rat (also see Discussion about the implant electrode).

The trends observed in Figure 2.7 were statistically analyzed by ANCOVA with A' as the dependent variable and vibrotactile intensity as the covariate. The experimental condition (boot only, boot+ICMS, natural stimulus) was the only factor. At both stimulus frequencies, the effect of the experimental condition was statistically sig-

nificant for both rats (Rat 1: 40 Hz, $F(2,11) = 74.8$, $p < 0.001$; 80 Hz, $F(2,11) = 21.1$, $p < 0.001$. Rat 2: 40 Hz, $F(2,11) = 63.6$, $p < 0.001$; 80 Hz, $F(2,11) = 28.5$, $p < 0.001$). The increasing effect of the stimulus intensity (covariate) was also significant in all cases (Rat 1: 40 Hz, $F(1,11) = 37.0$, $p < 0.001$; 80 Hz, $F(1,11) = 87.3$, $p < 0.001$. Rat 2: 80 Hz, $F(1,11) = 16.8$, $p = 0.002$) except for Rat 2 at 40 Hz ($F(1,11) = 1.3$, $p = 0.278$).

We also performed Bonferroni-corrected post-hoc tests for pairwise compar-

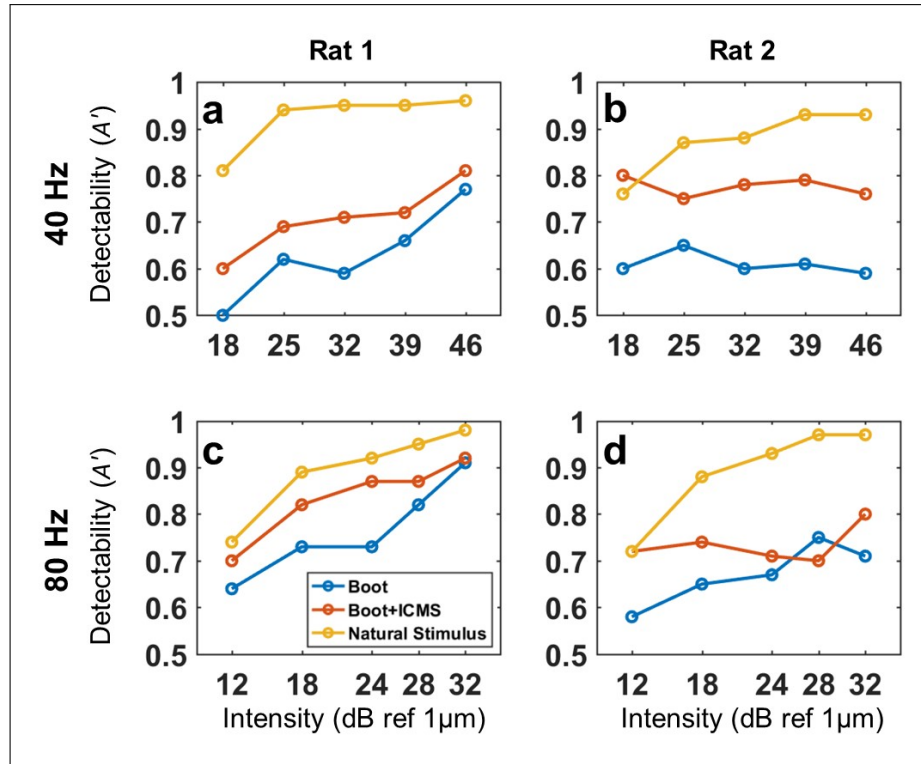


Figure 2.7 Detectability (A') plots for both rats at the tested vibrotactile frequencies (40 and 80 Hz). The data points are from the lower rows of Table A.I in the supplementary document (blue curves: boot only condition, red curves: boot+ICMS condition) and previous data regarding natural stimulation (yellow curves; [215]). The experimental condition had significant effects on detectability (all p 's < 0.001). The effect of the amplitude (covariate) was also significant in all cases ($p < 0.003$) except for Rat 2 at 40 Hz ($p = 0.278$). Bonferroni-corrected post-hoc tests showed that the boot+ICMS condition yielded significantly higher A' values than the boot only condition (Rat 1: 40 Hz, $p = 0.027$; 80 Hz, $p = 0.017$. Rat 2: 40 Hz, $p < 0.001$) except for Rat 2 at 80 Hz due to the measurement obtained for 28 dB ($p = 0.161$). On the other hand, the natural stimulus always caused higher detectability compared to the boot+ICMS condition (all p 's < 0.005). Overall results indicate that the tactile neuroprosthesis improves vibrotactile detection when the boots are on.

isons between the curves in Figure 2.7. The boot+ICMS condition yielded significantly higher A' values than the boot only condition (Rat 1: 40 Hz, $p = 0.027$; 80 Hz, $p = 0.017$. Rat 2: 40 Hz, $p < 0.001$) except for Rat 2 at 80 Hz due to the measurements obtained at 28 dB (ref. 1 μm) ($p = 0.161$).

On the other hand, as expected, boot+ICMS condition gave significantly lower A' values than the natural stimulus in every case (all p 's < 0.005). We also compared the boot condition with the natural stimulus condition; this shows whether the boot could isolate the vibrotactile stimulus from reaching the skin appreciably. The techniques explained in the Section 2.2.2 were found to be effective as observed in the data. Post-hoc comparisons showed that the detectability of the natural stimulus was always much higher than the stray vibrations of the boot only condition (all p 's < 0.001). Overall results indicate that the operation of the tactile neuroprosthesis increases psychophysical detection of the vibrotactile stimulus while wearing the boots.

2.4 Discussion

2.4.1 Previous Studies

Recent studies completed in our laboratory significantly contributed to the current work. Training rats for a psychophysical yes/no detection task requires a rigorous training schedule which may take months of sessions for a given rat [218]. Still, many rats do not learn the intermediate tasks and are eliminated before they are implanted with electrodes. The rats used in the current work were previously trained and their PEFs were derived [215]. This simple computational model establishes a correspondence between the intensities of vibrotactile stimuli and ICMS current pulses and needs to be found for every rat. In the literature, there is also an ongoing effort to generalize such models (e.g. [220]).

Additionally, the microelectromechanical system design of the tactile sensor and the boot were already available and the full calibration data were obtained in our previous work [216]. In that study, we had kept in mind the application of the sensor for the current study and did not optimize it for general use. For robotic hand prostheses, there are much better designs which are promising and may be adopted in tests with human patients (e.g. BioTac from SynTouch, [221]). Most of the state-of-the-art robotic systems are developed with integrated sensors (SmartHand by [222]; Modular Prosthetic Limb from Johns Hopkins University Applied Physics Lab, e.g. see [1]). Our

design for rats is more appropriate for preclinical studies, such as functional testing of electrodes, equipment technology, and ICMS processing algorithms. The tactile sensor can also be used in neuroprosthetic applications with peripheral nerve stimulation.

2.4.2 Limitations

There were certain limitations of working with rats in particular and the instrumentation setup designed for them. We restricted the vibrotactile stimulus frequency below 100 Hz, because the weight of the multi-probe contactor does not allow the electrodynamic shaker to produce appreciable output at high frequencies [218]. This implies that the mechanical vibrations were at lower frequencies than the best frequency range of the Pacinian psychophysical channel, which is the most sensitive channel regarding tactile inputs from the mammalian glabrous skin [223, 224]. Nevertheless, since the stimuli were suprathreshold, the Pacinian channel could still be activated at higher levels during the natural stimulus condition and possibly during the boot only condition. The majority of the activated afferents, however, would be rapidly adapting mechanoreceptive fibers linked to Meissner corpuscles [14, 50, 51, 225] and which mediate the Non-Pacinian I channel [226, 227]. On the other hand, it is not clear which cortical local networks were activated by ICMS here, because there is no well-defined submodality segregation in the rat somatosensory cortex regarding tactile inputs, except the general receptive-field organization [85]. Additionally, it has been reported that there is considerable overlap of somatosensory and motor areas in rats (e.g. see [228]).

During the course of the study several (individually calibrated) copies of the tactile sensor had to be used, because the rats eventually damaged the sensor by chewing on the boots. The multichannel amplifier helped to detect intermittent problems in the sensor cells. Nevertheless, these problems and especially the movement artifacts resulted in invalid trials (Section 2.2.5). Although these neuroprosthesis errors can be minimized in more sophisticated designs, from a biological point of view, similar noisy information also exists in the nervous system. For example, there are stray vibrations during tool use, haptic exploration of objects, and, in general, throughout

our sensorimotor state space. The brain can extract the relevant information among noisy inputs by attentional processes and movement-related sensory gating [229]. We speculate that such neuroprosthesis errors can be accommodated by the complex information processing capability of the brain, which relies on learning and adaptation by experience. However, within the limited scope of the current study and due to the practical difficulties of behavioral experiments with rats, those trials with neuroprosthesis errors could not be corrected online and could have confused the rats.

We further analyzed the invalid trials (Table A.2 in the Appendix A) based on a hypothesized detection strategy, i.e. assuming the rats responded purely according to ICMS (and ignored stray input due to inconsistent mechanical stimulus). The recalculated A' values were mostly higher than the A' values of the boot only condition from the valid trials (Figure A.2 in the Appendix A). However, A' values from the invalid trials were lower or higher than those from the valid boot+ICMS condition depending on the stimulus parameters and the animal. Since we cannot be certain about the animal's strategy, which is probably not constant anyway for every invalid trial, a combination of valid and invalid trials is not appropriate. Nevertheless, the results presented here for valid trials are robust for demonstrating the real-time performance of the tactile neuroprosthesis. It is interesting to note that since the neuroprosthesis system worked continuously during the sessions, the rats received some ICMS pulses while they walked on the chamber floor and activated the tactile sensor, even when the vibrotactile stimulus was not presented. We think that this approach, albeit sometimes resulting in invalid trials, increased the embodiment of the tactile neuroprosthesis because the rats received continuous environmental cues.

2.4.3 Future Improvements

It is important to note that ICMS pulse frequency was already defined a priori in the tactile neuroprosthesis for the related vibrotactile tasks presented here. In practical use, this has to be determined from the tactile sensor signal automatically. For complex signals, it will probably require continuous modulation of pulse frequency based on a multi-band approach as adopted in cochlear implants. It is important to note that there

is no one-to-one correspondence between vibrotactile frequency and ICMS frequency. ICMS pulse parameters, e.g. amplitude and frequency, interact with each other to give a complex artificial sensation which is currently a hot topic of research. At low frequencies, as those used in the current study, successive ICMS pulses may still signal the periodicity in the afferent population response [225]. As soon as periodic tactile information enters the rat cortex, however, strong inhibitory effects limit synchronized spike patterns to frequencies below 20 Hz (e.g. see [85]).

The rats used in this study had different types of electrode implants in the cortex. Rat 2 had a larger-diameter electrode which would affect a larger area, but also lower the current density for a given current. As a matter of fact, at 80 Hz, Rat 2 displayed worse performance than Rat 1 when the tactile neuroprosthesis was switched on. These results are consistent with [215], in which some discrepancy was shown for this rat while matching vibrotactile stimulus and ICMS by statistical analysis. In any case, the PEFs may need routine recalibration in neuroprosthetic applications because of neural plasticity as well as for technical reasons (e.g. electrode degradation, altered tissue interface). Therefore, the algorithms described here, i.e. DSP blocks, should be modified in the future to allow flexible change of PEF parameters. In other words, each experimental session can be preceded by some calibration trials to specify the parameters of a time-adaptive PEF. Recalibration is a significant challenge for all neuroprosthetics in daily life.

A similar adaptive approach may be used to extend the formula for PEFs in order to include different ICMS pulse parameters (e.g. pulse width, inter-phase interval, etc.). Here, PEFs were only defined based on vibrotactile intensity and frequency. Generating biomimetic ICMS pulses would be an ultimate goal for mediating texture information, and that would even require processing kinematic data from other types of artificial sensors such as accelerometers. For both somatosensation and sensorimotor control, limb-movement signals are provided by proprioceptors and the efference copy of motor commands. Sensing movement can be helpful to emulate a movement-related gating effect in the ICMS waveform. It would also be important to investigate the relationship between movement-related signals and the response bias (as opposed to detectability, see Results) in psychophysical tasks.

2.4.4 Other Forms of Tactile Feedback

Cortical neuroprostheses are suitable for neurological conditions such as traumatic and non-traumatic spinal cord injuries, severe neuro-/myopathies, brainstem strokes, and neurodegenerative diseases (e.g. amyotrophic lateral sclerosis) [3, 4, 230]. For these conditions, peripheral neural interfaces are not possible or feasible; therefore, cortical stimulation may be preferred for providing tactile or, in general, somatosensory feedback. Somatotopic organization of the cortex allows a simple planar arrangement of electrodes for high spatial selectivity. Until now, ICMS was demonstrated to be promising in rats, monkeys, and humans, but less invasive epidural stimulation methods are also being investigated. Since higher currents are required for that approach, graphene electrodes are utilized [231]. On the other hand, cortical interfaces bypass many pathways present in somatosensory and motor systems, and encoding of sensory information is more complicated than in peripheral interfaces. The functions of missing pathways may be implemented in the neuroprosthetic device instead [212].

For amputees and neurological conditions less severe than those listed above, peripheral neural interfaces were shown to provide reasonable functionality for somatosensory feedback [199, 201, 203]. The electrode technology is developing very fast for this purpose [208]. In peripheral nerve interfaces, it is more difficult to achieve spatial selectivity, but biomimetic encoding of spike patterns seems less complex. There is also significant know-how on peripheral nerve stimulation, which has enabled highly successful other applications (e.g. cochlear implants, [209]). Instead of tapping the peripheral nerves, non-invasive methods are also sometimes used for providing tactile feedback [205]. These methods either mechanically stimulate the skin by vibrators and indenters, or use percutaneous electrical stimulation to excite afferent nerves. Although non-invasive methods are very easy to apply, they cannot convey much information due to cognitive load limitations. The major problem with non-invasive methods is that the stimulated receptive fields are not the ones related to the missing limb or the neurologically affected area. Targeted reinnervation surgery aims to partially compensate for this issue by redirecting the intact nerves to a close body site, but mechanoreceptive responses still become very different to those used by the nervous system. As a result, the brain has to put a considerable cognitive effort to understand the feedback

signals. Additionally, non-invasive stimulation methods have technical limitations such as poor skin coupling, small number of channels, low spatial selectivity, high energy consumption, large size, and weight.

2.5 Conclusion

The main goal of the presented study was to implement a tactile neuroprosthesis system in real-time and test it in a psychophysical task performed by rats. Although more elaborate designs were previously tested on monkeys and humans, our work is original in the sense that the rats actively engaged in the vibrotactile task. They did not explore the tactile stimulus as in active touch *per se*. The tactile information mediated by ICMS was integrated with proprioception and motor signals to perform the task at a significantly higher performance compared to the condition in which the neuroprosthesis was switched off. In some cases, the performance of the tactile neuroprosthesis approached the natural stimulation (e.g. Rat 1 at 80 Hz). According to our knowledge, this study is the first demonstration of a tactile neuroprosthesis in rats to accommodate sensory information from the glabrous skin. Boots worn on the hind limbs prevented the need for an injury model (e.g. amputation, nerve resection, etc.) and can be used in future animal models to isolate mechanical vibrations.

3. BAYESIAN PREDICTION OF PSYCHOPHYSICAL RESPONSES OF RATS IN A VIBROTACTILE YES/NO DETECTION TASK FROM SPIKING ACTIVITY OF SENSORIMOTOR CORTEX

3.1 Introduction

All living beings are surrounded by an ocean of stimulus waves and tides, which constitute inputs to the internal perceptual world. Mechanoreceptors in the skin transduce tactile stimulus information into neural codes. Peripheral signals are easier to decode because of their prominent rate/intensity characteristics that are called stimulus entrainment [9, 23]. Encoded peripheral signals are continuously recoded along the neuraxis, and thus, in contrast to the periphery, cortical entrainment is barely observable [85]. Sinclair et al. [232] described a rational ground for this phenomenon; the primary somatosensory cortex (SI) filters out this mixture of signals to provide constant and clear perception. This filtering mechanism mainly stems from thalamocortical feed-forward inhibition [233, 234], which affects cortical activity during the stimulus window. When these encrypted cortical signals are decoded better, which is one of the main enthusiasms in neuroscience, brain-computer interfaces (BCIs) will be able to precisely decode movement intentions from the cortical activity and thus encode more naturalistic sensory signals about the external world into the nervous system of amputees or to the cortices of paralyzed patients. In this way, neuroprostheses will have a wider application area in the daily routines of patients with neurological disorders while providing them appreciable freedom of movement.

For a humble first step to neural decoding, rate coding [64, 65, 67, 227] is one of the accepted techniques. It recruits the mean firing rate and helps to estimate sensory stimulus features as well as motor intentions of subjects. For a vast body of background of the coding techniques, you may consult Section 1.3.1.2 in Chapter 1. In the current study, we have chosen the rate code to predict behavioral response because this will

be a baseline study for our future modeling studies. Besides, a more computationally demanding coding technique than the average firing rate may not be suitable to run online on the neural interface of BCIs.

The investigators [128, 130] demonstrated that movement planning is readily available from M1 recordings before it happens. Although this pre-movement information is valuable for decoding, visual feedback [141] improves three-dimensional (3D) brain-controlled movements tremendously. Artificial sensation elicited by intracortical microstimulation (ICMS), as sensory feedback, psychophysically corresponds to naturalistic sensation elicited by mechanical vibrotactile stimulus [215]. The involvement of the somatosensory cortex in motor coordination tasks [106–108] promises to unveil a strongly connected network between S1 and M1, which is elaborated in [109]. This connection has an importance in this study, because the hindpaw area of the rat sensorimotor cortex, in which sensory and motor cortex overlap here, has been the target for recordings. This fact is one of the important aspects of this study to bear in mind while establishing a prediction model for the response of the animal based on the recordings collected from this area.

There are plenty amount of probabilistic prediction models implemented previously. They mostly focused on how stimulus distributions combined. Multimodal responses of behavioral cue combination tasks are well explained with maximum likelihood (ML) estimation [182, 235–237]. The combination of weighted distributions of multisensory modalities from ML explanation paved the way towards the Bayesian prediction models.

Using Bayesian theory [167–169], behavioral studies showed that subjects perform multisensory cue combination tasks [238–242] in a near-optimal way - combining previous knowledge (prior) about the stimulus with the sensory information (likelihood). The posterior probability distribution of stimulus is well represented with the output activity layer of an integrate-and-fire network model [241]. In a neurophysiological study, the neural combination rule of neural response distributions is verified with the congruent and conflicting bimodal stimuli [243], which complies with Bayesian inference. The probability distribution of a stimulus presence is shown to be computed from the activity of neurons in superior colliculus using Bayes' rule [244]. They validated neurophysiological responses [245] not only for the optimal but also for sub-optimal and

minimal Bayesian probabilities. The most prominent multisensory enhancement was observed in the combination of weaker unimodal responses, which property is called ‘inverse effectiveness’ that showed Bayes’ rule works in two directions.

To assess the performance, Bayesian model results were compared with other non-Bayesian approaches [246–249]. The Bayesian framework better explains particular situations [248] while common implicit mechanisms, as prior information, could emerge as the perceptual bias of subjects. Ma et al. [249] compared their Bayesian inference with seven other non-Bayesian alternatives. In another study, they [250] found that Bayesian methods reach the best accuracy to estimate the position of the freely moving rat when the firing rates of hippocampal place cells are used for reconstruction.

The Bayesian decoding is implemented also in motor coordination tasks; the Kalman filter estimates the hand motion of primates from firing rates of the M1 hand area [159]. Integration of distributions was more clearly observed in a human sensorimotor learning task [251] when prior distributions were calibrated experimentally. Sensorimotor tasks proposed that neural activity reflects reward expectation [252], motor planning and decision [253], and probability distributions by the degree of uncertainty [254]. Simulated decision-making neurons encode the posterior probability distributions of perceptual decisions [81]. However, performance decrease for human observers is inevitable in higher-level perceptual tasks [255] when compared to a Bayes’ optimal observer. To excavate optimality in the perceptual inference of neural mechanisms, there is an urgent need for more complex tasks [249]. Here we endeavor to see how the Bayesian model estimates the responses of simpler organisms (i.e., rodents) in a relatively arduous behavioral task. Compared to simpler task paradigms in the literature (e.g., nose poke), this three-lever press (mid lever to self-start, either of side levers to respond) decision-making task demands more cortical involvement regarding tactile stimulus and responds with either of the levers according to the behavioral decision with a novel psychophysical configuration [218].

Besides conducting comparatively plain behavioral tasks, there are many limitations of other studies. In most of the theoretical or experimental Bayesian studies, they mostly focused on estimating the posterior probability of either sensory stimuli or decision outcome when recorded neural activity data were given. However, in the field

of neuroprosthetics, they have already proved that the incorporation of somatic sensory information facilitates BCI manipulation [110, 111, 155]. While inherently having the adaptive distribution of sensory information within the distributions of the model, we here investigated the prediction of the decision task outcome using Bayesian decoding. Furthermore, the Bayesian decoding hypothesis is still not supported with sufficient neurophysiological data [255]. Many studies in this field cover the concept either by computational modeling or experimenting, this twofold study -having both neurophysiological and computational parts- is a candidate to expand the knowledge base about the neural encoding processes that intervene between perception and action. Finally, there are many neural decoding studies for neuroprosthetics. However, they have predominantly recorded from barrel cortex - associated cortical area for whiskers - that has, unfortunately, no analogy with human neural prosthetic usage. Here, to decipher the relevant behavioral decision from single/multi-unit firing rate, the glabrous skin of the hind paw was targeted for mechanical stimulation because of the relevance of the neuroprosthetic device usage in everyday tasks of patients.

In the present study, we recruited a Bayesian Network Model to perform the probabilistic inference for both stimulus distribution and the behavioral decision given the recorded neural activity. We aimed to decode the rat's vibrotactile detection responses from cortical firing rates when the animal was freely behaving and performing a yes/no decision task in an operant chamber that is the closest analogy with the neuroprosthetic applications for humans. Some preliminary data were previously presented as an abstract [256].

3.2 Materials and Methods

3.2.1 Animals

29 adult Wistar rats were used throughout this PhD study. In terms of behavioral task registry, 12 of them were trained for the yes/no detection task. 7 of them learnt the task while 5 of them could not learn and were eliminated from this study. In terms of surgery record, 23 of initial 29 rats were implanted with microelectrodes.

3 of 23 implanted rats had both acute and chronic recordings. 7 of 23 implanted rats provided only acute recordings during the surgery. 4 of 23 implanted rats generated only chronic recordings, which include both awake passive mechanical stimulation condition and active during the tactile detection task in the operant chamber. Only 2 rat (Rat 1, Rat 2) data from those 4 rat data had spike recordings for tactile detection task that is used for the prediction model. 13 of the 23 implanted rats had premature death after the surgery.

Since chronic recordings from 2 rats would not enough to generalize the behavior, we have included previously collected spike data from 8 rats doing same yes/no detection task [215], in which study neural data were not used. Therefore, chronic recordings during a yes/no detection task used in Bayesian network model here comprise data coming from aforementioned 2 rats (Rat 1, Rat 2) and 8 rats (Rat 3 - Rat 10) of the previous study.

10 adult Wistar albino rats (4 female 6 male, 3-8 months old) were used to predict their behavioral responses. Animals were kept in reversed (12h dark/12h light) daily light cycle. They were moderately water-deprived (~ 36 hours) before the experiments. Their weights conformed to $>80\%$ of their initial ad libitum weights during the training and recording sessions. All rats were treated following the guidelines of the Boğaziçi University Institutional Ethics Committee for the Local Use of Animals in Experiments.

3.2.2 Operant Conditioning Chamber

A custom-made conditioning chamber equipped with a vibrotactile stimulation system was used for behavioral training and recording experiments (for training steps in detail, see [218]). Experiment protocol in custom routines (MATLAB R2008a; The Math Works, Natick, MA, USA) generates sinusoidal vibrotactile waveform which is then relayed to the data acquisition (DAQ) card (USB-6259; National Instruments, Austin, TX, USA). An electrodynamic shaker (V201, Ling Dynamic Systems, Royston, Herts, UK) with a custom-made power amplifier vibrates the contactor probes in line with the generated mechanical stimulation waveform. This multi-probe contactor

penetrates through the holes of the chamber floor. Whenever the animal presses the middle lever in the chamber, either stimulus-on or stimulus-off trial is generated in a pseudorandom manner. In the case of stimulus-on trial, generated mechanical vibrotactile stimulus is relayed to the hind-paw glabrous skin of the rat. This system stimulates mechanoreceptors on the skin independent of the position of the feet and gives the animal movement freedom during the detection task. The operant chamber is in an isolated box from sound and light. Any other surrounding sounds and possible auditory cues are masked by acoustic white noise (bandwidth: 20 Hz - 100 kHz) during the detection task.

3.2.3 Psychophysical Detection Task Paradigm

The animals were conditioned on the vibrotactile stimuli applied on their hind-paw glabrous skin and responded to the yes/no psychophysical detection task accordingly. The rat started the task by pressing the middle lever which initiates the middle light turns on during the stimulus window (0-600 ms). Trials were randomly generated and counter-balanced. The mechanical stimulus was either presented or not depending on the current trial was stimulus-on or stimulus-off trial. The vibrotactile waveform had a 500 ms burst of sinusoidal vibrations (200 μm zero-to-peak displacement) with an additional 50 ms rise and fall time. The rats were trained to respond with the right lever in the stimulus-on trial (hit) and with the left lever in the stimulus-off trial (correct rejection) to get the reward ($\sim 7\text{-}8\ \mu\text{l}$ of water). In case of incorrect responses, the error buzzer sound is activated (Figure 3.1).

After each rat learnt the yes/no detection task, their psychophysical performances were tested against the stabilization in the receiver operating characteristics (ROC) plot area. If the probability of hit rate ($p(H)$) vs false alarm rate ($p(F)$) for every session (100 trials) were within the range of 0.2×0.2 unit-squared area in ROC for 5 consecutive sessions, the rat was surgically implanted with microwire arrays.

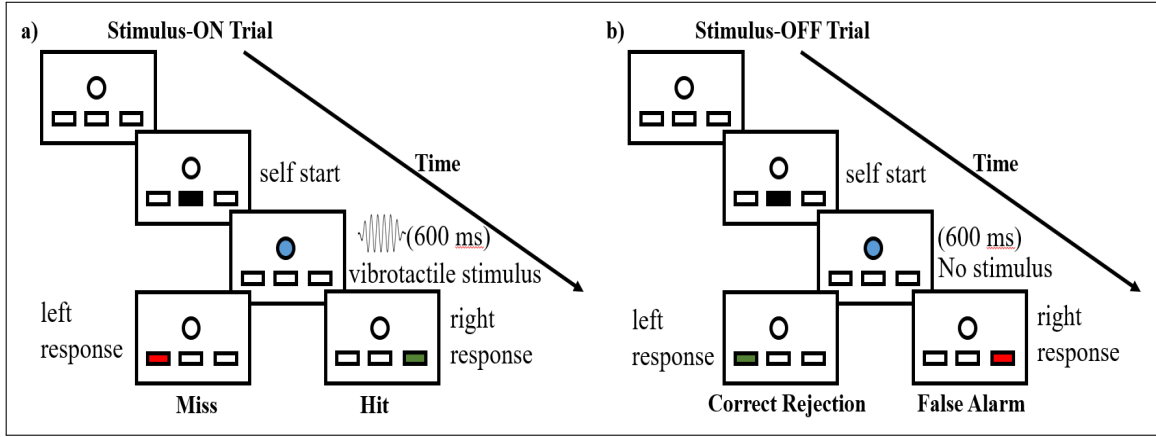


Figure 3.1 Psychophysical Detection Task Diagram. There are one indicator middle LED and three response levels in the operant chamber. a) Task starts when rat presses middle lever. The middle indicator LED is on during the stimulus window. Pseudo-randomly generated trial has mechanical stimulus application in it for this case. Vibrotactile stimulus is applied to hindpaw of the animal. After the mechanical stimulation period is over, rat responds with either right lever (hit) or left lever (miss). a) Task starts when rat presses middle lever. The middle indicator LED is on during the stimulus window. For this case, pseudo-randomly generated trial has no mechanical stimulus application in it for this case. After the mechanical stimulation period is over, rat responds with either right lever (false alarm) or left lever (correct rejection).

3.2.4 Implant Surgery

The rats that had stabilized psychophysical performance metrics were prepared for surgery. Intraperitoneal (IP) ketamine (65 mg/kg) and xylazine (10 mg/kg) injection was used for surgical anesthesia. Supplementary doses, 1/3 of induction dose, were administered whenever palpebral and pedal reflexes were observable. The rectal temperature was kept at 37 °C by a heating pad (TCAT-2LV; Physitemp Instruments, Clifton, NJ, USA). Atropine (0.05 mg/kg) was induced IP before the surgery to prevent bradycardia and diminish bronchial secretions. A digital stereotaxic frame (model 940; David Kopf Instruments, Tujunga, CA, USA) was used to fix the animal's head, and a $\sim 2 \times 3$ mm² craniotomy window was opened for the microwire array penetration to the hindpaw representation of the sensorimotor cortex mapping [61, 228, 257]. Nine of the rats were implanted with platinum/iridium microwire electrodes (Teflon coated platinum/iridium (90/10%), 4x4 array, the distance between rows/columns: 0.25 mm, microwire dia. 25 μ m; Plexon Inc., Dallas, TX, USA). Only Rat 2 was implanted with tungsten microwire array (Teflon coated tungsten, 8x4 array, the distance between rows: 0.50 mm, the distance between columns: 0.25 mm, microwire dia. 33 μ m; Tucker-

Davis Tech., Alachua, FL, USA). The microwires were conformed to similar penetration levels in the sensorimotor cortex (depth: ~ 1 mm, $\sim$ layer V). The ground wire was connected to the cerebrospinal fluid via mounted stainless steel screws on the skull. The microwire array was connected to a unity gain headstage (model E2b; Plexon Inc.) in which isolated neural activity was transmitted to a preamplifier (gain: 1000, 150 Hz-8kHz, model PBX; Plexon Inc.) through the head cable. Spiking activity was monitored during the surgery with an analog oscilloscope and an amplified speaker. Receptive field (RF) mapping for all channels was noted during the mechanical stimulation of the glabrous skin of the hindpaw by using von Frey hairs. Dental acrylic was fixed on the skull and around the screws to stabilize the implantation process. One week of recovery period was given to the rat in its home cage.

3.2.5 Electrophysiological Recording

After one week of recovery, we checked the activity levels of all channels under the light anesthesia (supplementary dose in the surgery) on the same experimental setup used during the surgery. Since awake behaving introduces more activity in the cortex, this step was required to monitor microwire channels clearly before the behavioral psychophysical experiments. The responses of the channels to tapping and von Frey hair stimulation were noted, and silent channels were discounted during the behavioral recording experiments.

The electrophysiological recording sessions were started around two weeks after surgery, depending on the state of the rat's recovery. While the rat was performing the same yes/no detection task, we simultaneously recorded continuous voltage signal from all selected electrode channels through the analog input channels of the DAQ card (sampling rate: 10/50/100 kHz, band-pass filtered: 150 Hz-8kHz). The recording duration was set to match with the stimulus window (0-600 ms), which is initiated by the middle lever press (see Section 3.2.3). The psychophysical task responses of the rat were also saved with the raw voltage data.

3.2.6 Spike Sorting

The decisions of rats are collaborative work of neural populations. To decipher this readout action, we were in need of isolating each unit and extracting how it encoded the response. In the scope of this study, we are interested in the spike rates of each unit, which will be the features of the Bayesian model, thus the recorded raw data was first isolated into single/multi units using Wave_Clus spike sorting algorithm [258]. The outliers were eliminated, and the rest of the spikes were semi-automatically classified into 1 to 3 units using forced clustering. The spike rates of selected units were used for further analysis regardless of being single or multi-unit. When some of the days revealed fewer units than the other days of the same rat, these absent data were marked with a masking value and ignored by the model accordingly. The number of total units ranged from 24 to 44 with $\mu=35.1$ with $\sigma=6.3$ for each rat. All the animals have 16 channel microwire arrays except one has 32-channel electrodes. There are 351 units and 176 microwires in total, which corresponds to 2 units on the average for each channel.

3.2.7 Regular Spiking (RS) / Fast Spiking (FS) Discrimination

In order to find out which type of unit contributed how much to encoded neural signal, we classified neurons as regular-spiking (RS) and fast-spiking (FS) units. According to [259], the duration of the second (after-hyperpolarization (AHP)) phase should be smaller than $350 \mu s$. The mean waveforms of all units were examined and labeled as RS or FS based on the width of the AHP phase. The Bayesian model was then executed separately with three types of inputs: 1) all units, 2) only RS type and 3) only FS type of units.

3.2.8 Bayesian Network Model

A Bayesian network (BN) model ([260]) was recruited for the behavioral task paradigm to have a compact and natural representation of the real world in terms of

conditional dependencies among the parameters, which are stimulus (S), neural firing rate (X), response (Y) (Figure 3.2). These networks, with their nodes for random variables and their edges for direct influence of one parameter over another, are representations of both joint and conditional distributions for the parameters. Since the events started by the initiation of the mechanical vibration generated by the probes in the chamber, stimulus (S) parameter is marginally independent of other parameters. The recorded neural activity (X) was modulated by the S parameter. This causal effect is represented by the edge between nodes S and X . The edges originating from stimulus (S) to firing rate (X) and from firing rate (X) to response (Y) represent direct dependence that is intuitive regarding the behavioral task paradigm. Bayesian networks stand on the intuitions regarding these dependencies between parent and child nodes. In the Bayesian framework, once we know the value of a parent of a child node, the rest of the information flowing from the parents or other ancestors of this parent will be redundant for that specific child node. However, we know that the behavioral response cannot be dependent on only the neural activity recorded from $\sim 2 \times 3 \text{ mm}^2$ craniotomy window. During the behavioral paradigm, there are other factors, such as attentional level, reward mechanisms, subcortical feedbacks or corticocortical connections, that may modulate the engagement of the rat to the task. We assumed that these effects can be represented by the downward arrow originating from the stimulus (S) to the response (Y) (Figure 3.2). These indirect effects may not be caused directly by the stimulus. However, addition of many weak influences with new nodes would convert our BN to a more complex network. Thus, these are only approximations of our true beliefs about the behavioral task, and these assumptions are to be validated by the performance of the model.

In Figure 3.2, the Bayesian Network model consist of these three parameters (S, X, Y), and their corresponding relationships were represented by arrows. Instead of using joint distribution in the figure, we recruited response prediction based on the neural firing rate (Eq. 3.1). In this way, stimulus presence is first predicted based on the neural data. Then, this stimulus distribution is used to predict the behavioral outcome of the animal. This scheme complies well in line with the BCI application for neuroprosthetics when one needs to give a higher priority to elicited neural activity from sensory feedback, instead of using deterministic stimulus presence information.

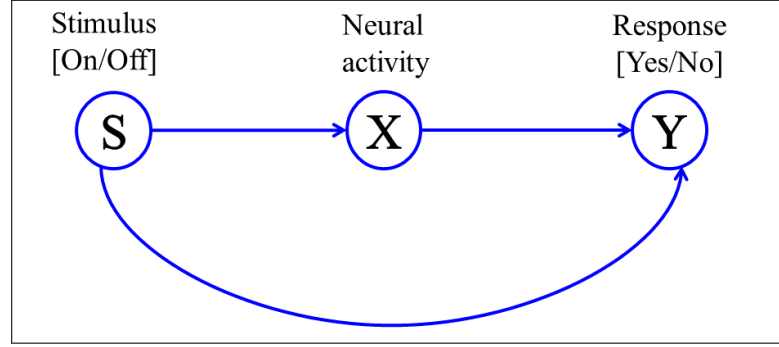


Figure 3.2 Bayesian Network Model: Stimulus (S) creates neural activity (X) in the sensorimotor area, which we record from. Behavioral response type (Y) is influenced from not only the recorded neural activity (X) but also other mechanisms (e.g., subcortical connections, reward mechanisms, attention network, etc.) that are represented by the downward circular arrow. All these effects contribute to shape the decision by the animal during the task.

Thus, mathematical representation of this model can be written as:

$$P(Y|\mathbf{X}) = \sum_{s=0}^1 P(Y|\mathbf{X}, S = s)P(S = s|\mathbf{X}) \quad (3.1)$$

in which, vector forms are highlighted in bold. Inside the summation on the right hand side of the equation, there are two parts: we will call them as **part 1** ($P(Y|\mathbf{X}, S = j)$) and **part 2** ($P(S = j|\mathbf{X})$) for the remaining of the thesis. For each trial, $P(Y|\mathbf{X})$ was calculated from the marginal distribution in Eq. 3.1 which comprises part 1 and part 2. Stimulus (S) and behavioral response (Y) are binary random variables, and their values can be 0/1 which mean stimulus-off/on for S , and left/right lever presses for Y . X represents a augmented column vector of predictors, i.e. mean firing rates for recorded units of this specific trial. Since Y is a binary random variable, which uses X as predictors, it can be implemented as a Bernoulli distribution of parameter π which inherently using Bayesian logistic regression to return probability of a binary decision

(Y). For $Y = y$, **part 1** can be implemented in detail as:

$$\begin{aligned}
 P(Y = y | \mathbf{X} = \mathbf{x}, S = s) &= \pi(\mathbf{x})^y (1 - \pi(\mathbf{x}))^{(1-y)} \\
 \pi(\mathbf{x}) &= \frac{1}{1 + e^{-\boldsymbol{\beta}\mathbf{x}}} \quad y = 0, 1; s = 0, 1; \\
 \mathbf{x} &= [1 \ x_1 \ x_2 \ \dots \ x_i \ \dots \ x_n]^T \quad i = \text{feature index} \\
 \boldsymbol{\beta} &= [\beta_0 \ \beta_1 \ \dots \ \beta_i \ \dots \ \beta_n] \quad n = \# \text{ of features}; \beta_i \sim \mathcal{N}(\mu, \sigma)
 \end{aligned} \tag{3.2}$$

The firing rates for each unit of every trial were given as $\mathbf{X}$ input vector to the Bayesian model shown in Figure 3.2 below. Since there was no closed-form expression of part 1, we applied Gibbs Sampler (*burning=1000, nsamples=1000*) using bayesreg package [261] to extract posterior distributions of the parameters (i.e., $\boldsymbol{\beta}$) of the model, and use these distributions to generate the posterior distributions of Y ($P(Y|\mathbf{X}, S)$) with minimum error.

In part 2, Bayes' formula was used to generate posterior distribution on stimulus (S) given the observed neural activity (X):

$$P(S = s | \mathbf{X}) = \frac{P(\mathbf{X} | S = s) P(S = s)}{P(\mathbf{X})} \tag{3.3}$$

a naïve Bayes assumption is utilized to create $P((X)|S = s)$ distribution. This assumption states that observed features ($X_1, X_2, \dots, X_i, \dots, X_n$) are independent if the class instance, which is stimulus-on/off condition here, is known. A formal representation of this independence assumption would be:

$$(X_i \perp \mathbf{X}_{-i} | S) \quad \text{for all } i \tag{3.4}$$

where $\mathbf{X}_{-i} = \{X_1, \dots, X_n\} - \{X_i\}$. Thus,

$$P(\mathbf{X} | S = s) = P(X_1, X_2, \dots, X_n | S = s) = \prod_{i=1}^n P(X_i | S = s) \tag{3.5}$$

which gives the likelihood distribution to be calculated in Eq. 3.3. Gaussian kernel estimator, which proposes a better fit to real data, was used to calculate the probability distribution of neural firing rate for each unit ($P(X_i|S = s)$):

$$P(X_i = x_i|S = s) = \frac{1}{nh} \sum_{j=1}^n K\left(\frac{x_i - x_j}{h}\right)$$

(3.6)

where i = global feature index

j = local feature index

n = # of features

h = 0.5 spikes/s

where Kernel estimator defined as:

$$K(u) = \frac{1}{\sqrt{2\pi}} e^{-\frac{u^2}{2}}$$

(3.7)

In this way, posterior distributions ($P(S = s|X)$ in Eq. 3.3) were created for stimulus-on or stimulus-off conditions separately. These stimulus distributions (part 2) were used to weigh the Bayesian logistic regression distributions (part 1) accordingly. As a result, Bayesian network model ($P(Y|X)$) predicted the response lever (0, 1) for (left, right) according to a binary decision threshold of 0.5. The model result was registered as left (0) for the values equal or smaller than 0.5 and right (1) for the values bigger than 0.5. The trials were shuffled within each rat's data set. To avoid overfitting, we used ten-fold cross-validation (90/10 % of training/test set) to run the model separately for each rat's individual data. The data set was shuffled before it was divided into 10 batches. The mean performance scores (sensitivity, specificity, f1 score, accuracy) were generated at the end of the ten-fold cross-validation procedure for each rat. These scores were calculated using true positive (TP), true negative (TN), false

positive (FP), false negative (FN) scores for each rat separately.

$$\begin{aligned} Sens &= \frac{TP}{TP + FN} & Spec &= \frac{TN}{TN + FP} & Prec &= \frac{TP}{TP + FP} \end{aligned} \tag{3.8}$$

$$F1 = \frac{2TP}{2TP + FP + FN} \quad Acc = \frac{TP + TN}{TP + FN + FP + TN}$$

3.2.9 Statistical Methods

The spike rates of units were checked against 'non-responsive unit' criteria which eliminate units spiking lower than the average firing rate of overall units for that specific rat. We tested spike rates of hit against miss trials and correct rejection (cr) against false alarm (fa) trials (two-sample t test in Matlab). *Pearson's correlation* analysis was conducted to check if there was any correlation between the spike rates of hit/miss trials versus probability of hit (p(h)) and between the spike rates of cr/fa versus probability of false alarm (p(f)). Two sample *Kolmogorov-Smirnov* test was run to check if the coefficients of the Bayesian Model were drawn from the same population or not. Sensitivity, specificity, accuracy, and f1 score performance metrics (Eq. 3.8) were calculated for the performance measurements of the model.

3.3 Results

After two weeks of the recovery period, the recording sessions were started for an hour in a day for each rat. We recorded single/multi-unit responses from the sensorimotor cortex of the rat via implanted microwire array. To fix all the conditions for the data, the first two days of recording data were analyzed for all ten rats.

3.3.1 Preliminary Analysis of single/multi-unit responses during stimulus window

3.3.1.1 Neural Activity Due to Vibrotactile Stimulus

The neural activity of two representative units was shown in Figure 3.3. A mechanical vibrotactile stimulus was given between (0-600ms) at 40 Hz 46 dB (ref $1\mu\text{m}$) zero-to-peak amplitude to the hindpaw glabrous skin of behaving rats. In part a, Unit 1 from Rat 4 increases its firing rate with the mechanical stimulus presence. It has 50.3 sp/s firing rate in stimulus-off condition and 70.9 sp/s in stimulus-on condition in which onset response is observable. This unit has 17102 spikes in this cluster. Another unit from Rat 9 decreases its activity with the introduced mechanical stimulus during behavioural task. Spontaneous activity rate was 67.3 sp/s whereas the activity rate decreases to 56.1 sp/s when the vibrotactile stimulus is given to the hind paw of the animal during the task. For the same onset region, where Rat 4 has increased responsiveness, Rat 9 has an observable diminished onset response. Unit 1 of Rat 9 probably gets inhibitory postsynaptic potential (IPSP) inputs while Unit 1 of Rat 4 has excitatory postsynaptic potential (EPSP) inputs during mechanical stimulation. Although these units do not seem to be single units regarding their firing rates, in the scope of this study, we did not need to flag units either being single or multi-unit.

3.3.1.2 Firing Rates With Respect to Psychophysical Responses

The spike rates for each trial are grouped according to behavioral response (Figure 3.4a). Student's t-test results showed that there are significant differences (* for $p < .05$, ** for $p < .01$ in Figure 3.4) between the firing rates of hit versus miss trials during stimulus window for Rat 1, Rat 3, Rat 4, Rat 9, and Rat 10. For correct rejection (CR) versus false alarm (FA) trials, we observed significantly different activity for Rat 1, Rat 3, Rat 4, Rat 7, Rat 9, and Rat 10. In general comparisons, we found a significant difference (t-test $p < .05$) between only CR and FA trials for all trials of all rats (Figure 3.4b).

Similar phenomena were observable here in Figure 3.4 as in the case during stimulus-on conditions in Figure 3.3. There was no significant increase for stimulus-

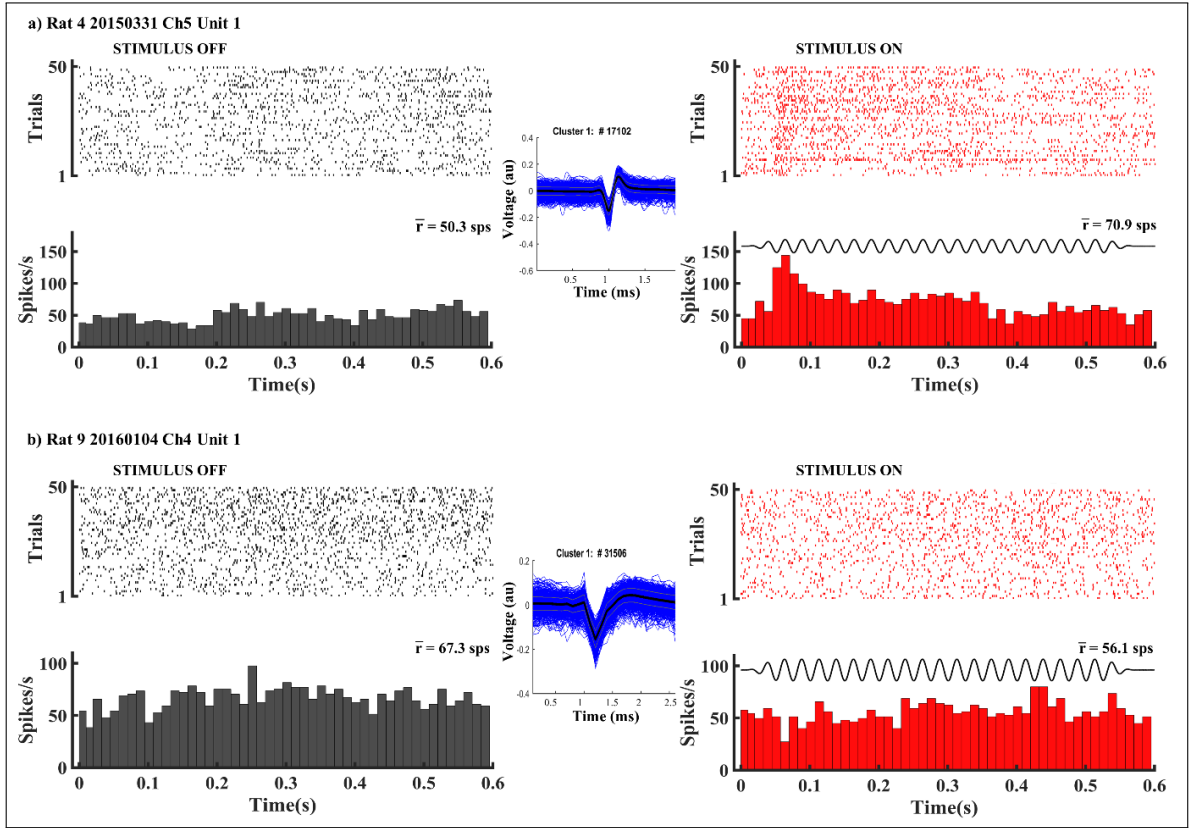


Figure 3.3 A representative raster plot and peri-stimulus time histogram of sensorimotor neural activity for Rat 4 and Rat 9 for stimulus-off and stimulus-on conditions during the yes/no detection task. Mechanical vibrotactile stimulus was between (0-600ms) at 40 Hz 46 dB (ref $1\mu\text{m}$) zero-to-peak amplitude. a) This is a representative unit that increases its firing rate with the mechanical stimulus presence. It has 50.3 sp/s firing rate in stimulus-off condition and 70.9 sp/s in stimulus-on condition in which onset response is observable. There are 17102 spikes in this cluster. b) Another representative unit, which decreases its activity with the introduced mechanical stimulus during behavioural task. Spontaneous activity rate was 67.3 sp/s whereas the activity rate diminishes to 56.1 sp/s when the vibrotactile stimulus is given to the hindpaw of the animal during the task.

on conditions compared to stimulus-off conditions. The variances within subject and between subject were prominent in part a of 3.4 that comprise both increased and decreased responsiveness [82, 100] during the stimulus window. This fact states that the prediction model will not be easily established by only stimulus presence feature since cortical activity of rats has inherent stochasticity and noise.

3.3.1.3 Correlation Between Firing Rates and Response Probabilities

Four types of behavioral response trials (Hit/Miss/CR/FA) were checked against any correlation with their corresponding mean firing rates (R_d) (Figure 3.5). The

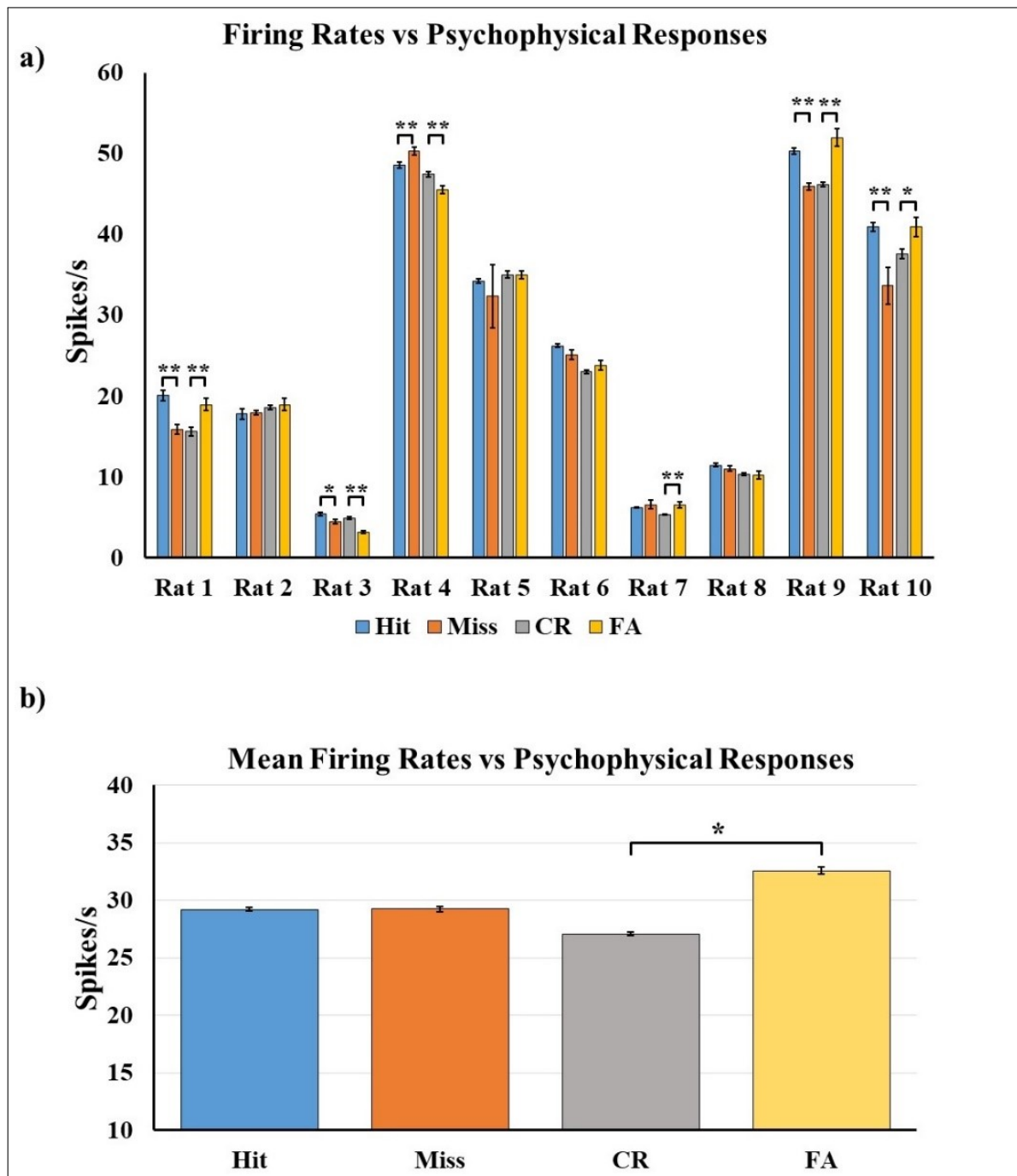


Figure 3.4 Mean firing rates for each type of behavioral response across all trials. Significant differences for hit versus miss, for correct rejection (CR) versus false alarm (FA) trials marked with * for $p < .05$, ** for $p < .01$ a) For ten rats, mean firing rates for Hit/Miss/CR/FA trials. b) Overall firing rates for all rats for Hit/Miss/CR/FA trials.

Pearson's correlation test resulted in no significant pairwise correlation between the probability of hit ($p(h)$) and the mean firing rates (R_d) of hit trials ($r = -.04$, $p = .46$) and between $p(h)$ and R_d of miss trials ($r = -.06$, $p = .43$). Similarly, there was no

significant correlation between the probability of false alarm ($p(f)$) and the mean firing rates (Rd) of correct rejection trials ($r=.20$, $p=.29$) and between $p(h)$ and Rd of false alarm trials ($r=.18$, $p=.31$). There is clear evidence that there are no obvious trends in data between the model predictor (mean firing rate) and the behavioral detection responses. Although there is no correlation, the Bayesian model will be the identifier for the performance while revealing the hidden patterns in data.

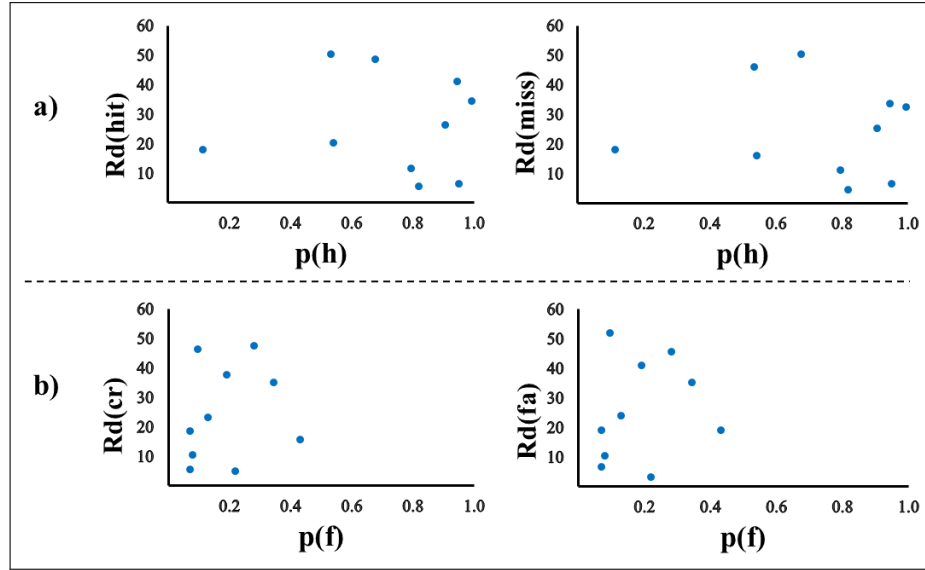


Figure 3.5 The mean firing rates during stimulus window, $Rd(hit)$ for hit trials and $Rd(miss)$ miss trials were plotted against hit rate ($p(h)$). Similarly, $Rd(cr)$ for cr trials and $Rd(fa)$ fa trials were plotted against false alarm rate ($p(f)$). The Pearson's correlation test resulted in no correlation between firing rates of hit/miss trials and $p(h)$, and between firing rates of cr/fa trials and $p(f)$. Each data point represents a different rat.

3.3.2 Response Prediction Based on Bayesian Model

3.3.2.1 Prediction of Right/Left Responses

Bayesian Model was trained to predict right/left responses of the rat. At first, the logistic regression part of the model (part 1 in Eq. 3.1) was trained separately for stimulus-on and stimulus-off trials to respond either 0 (left response) or 1 (right response). Later, the probability values generated were weighted with the probability of having the stimulus in that trial or not (part 2 in Eq. 3.1).

ON/OFF/JOINT Matrices (First part of Bayesian Model Formula): When

the results are assessed independent from the stimulus presence, the MCMC algorithm returns quite stable results from *bayesreg* package for separate response distributions for the stimulus-on, stimulus-off, and 'joint model', which is their resulting model that stimulus-on and stimulus-off distributions ($P(Y|X, S)$ in Eq. 3.1) were weighted regarding to their corresponding stimulus distributions ($P(S|X)$ in Eq. 3.1). Sensitivity and specificity scores of these models are depicted in the performance matrices of Figure 3.6.

In Table 3.1, several performance metrics were summarized the performance

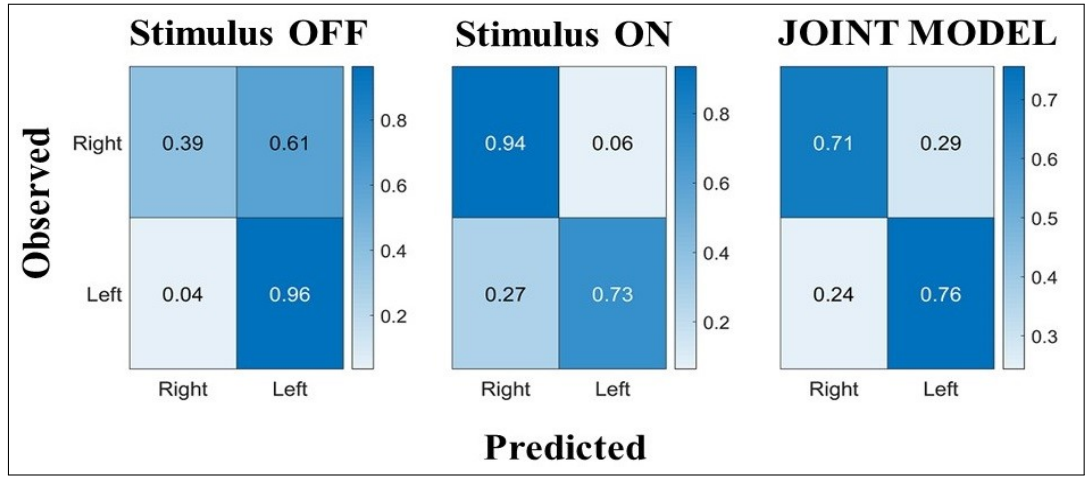


Figure 3.6 Sensitivity (top-left) and specificity (bottom-right) scores of Stimulus OFF/ON and Joint Model are shown in these three performance matrices for Right/Left Bayesian model for all rats. To evaluate Joint Model, Stimulus OFF and Stimulus ON distributions ($P(Y|X, S)$ in Eq. 3.1) were weighted according to their corresponding stimulus distributions ($P(S|X)$ in Eq. 3.1).

metrics of the stimulus-on, stimulus-off, and joint models with different aspects. The mean value of the scores shows that the stimulus-off model predicted the left responses quite well (specificity: 0.96) while the stimulus-on model was better to tell the right responses of the rats (sensitivity: 0.94). Because of the experiment design, rats were expected to perform ideally according to conditioning protocol (left response for stimulus-off trial, right response for stimulus-on trial). Although this is not always the case in practice, mostly having left response firing rates in stimulus-off distribution (specificity: 0.96) and having right response firing rates in stimulus-on distribution (sensitivity: 0.94) explain these high prediction scores correspondingly. In general, the joint model performed with >0.70 scores for sensitivity, specificity, and f1.

Table 3.1

The right/left Bayesian model performance scores for all rats. Stim On/Off/Joint Model
Sensitivity/Specificity/Accuracy/F1 scores for all rats.

	Stimulus-OFF Model					Stimulus-ON Model					Joint Model				
	Sens	Prec	Spec	F1	Acc	Sens	Prec	Spec	F1	Acc	Sens	Prec	Spec	F1	Acc
R1	0.46	0.68	0.84	0.55	0.68	0.79	0.71	0.63	0.75	0.71	0.67	0.75	0.79	0.71	0.73
R2	0.00	0.00	1.00	0.00	0.93	0.07	0.33	0.98	0.11	0.88	0.04	0.50	1.00	0.08	0.91
R3	0.00	-	1.00	0.00	0.78	1.00	0.85	0.17	0.92	0.85	0.72	0.66	0.60	0.69	0.67
R4	0.59	0.73	0.91	0.65	0.82	0.91	0.81	0.57	0.86	0.80	0.81	0.75	0.75	0.78	0.78
R5	0.54	0.67	0.86	0.60	0.75	1.00	0.99	0.00	1.00	0.99	0.96	0.72	0.24	0.82	0.72
R6	0.03	0.50	1.00	0.06	0.87	0.98	0.92	0.13	0.95	0.90	0.59	0.65	0.66	0.62	0.62
R7	0.00	-	1.00	0.00	0.93	1.00	0.95	0.00	0.97	0.95	0.69	0.61	0.54	0.65	0.62
R8	0.00	-	1.00	0.00	0.92	1.00	0.79	0.00	0.88	0.79	0.16	0.53	0.89	0.25	0.57
R9	0.74	0.83	0.98	0.78	0.96	0.83	0.82	0.79	0.83	0.81	0.65	0.89	0.96	0.75	0.86
R10	0.00	-	1.00	0.00	0.81	1.00	0.95	0.00	0.97	0.95	0.94	0.60	0.12	0.73	0.60
Mean	0.39	0.71	0.96	0.50	0.86	0.94	0.89	0.73	0.91	0.87	0.71	0.69	0.76	0.70	0.74

3.3.2.2 Prediction of Correct/Incorrect Responses

In this case, we have defined the flagged event one or zero as pressing a correct or incorrect lever and tried to predict the correct/incorrect response of the animal for that type of Bayesian model. For stimulus-on distribution, nothing has changed. The right/left Bayesian model has almost the same correct/incorrect confusion matrix in stimulus-on case, except for its inherent stochasticity that converges to the same results up to second digit precision after the decimal point. However, for the stimulus-off case in Figure 3.7, the situation is completely reflected across the middle point of the performance matrix in Figure 3.6 (also see in Figure A.3 in Appendix A, confusion matrices of the stimulus-off models are almost -because it is stochastic model- the reflection of each other across middle point between right/left and correct/incorrect model). We trained the correct/incorrect model separately because its flag values were different for the predicted class. Even it runs stochastically, after a thousand sampling of MCMC, it converges similar to scores with the right/left model. The sensitivity score of stimulus-off performance matrix (or true positive in confusion matrix correspondingly) of the right/left model in Figure 3.6 is now close to the specificity score of stimulus-off performance matrix (or true negative in confusion matrix correspondingly) of correct/incorrect model in Figure 3.7. Similarly, the specificity score of right/left stimulus-off distribution is close to the sensitivity score of the cor-

rect/incorrect stimulus-off model as well.

The joint model in this regime favors correct responses more than the right/left

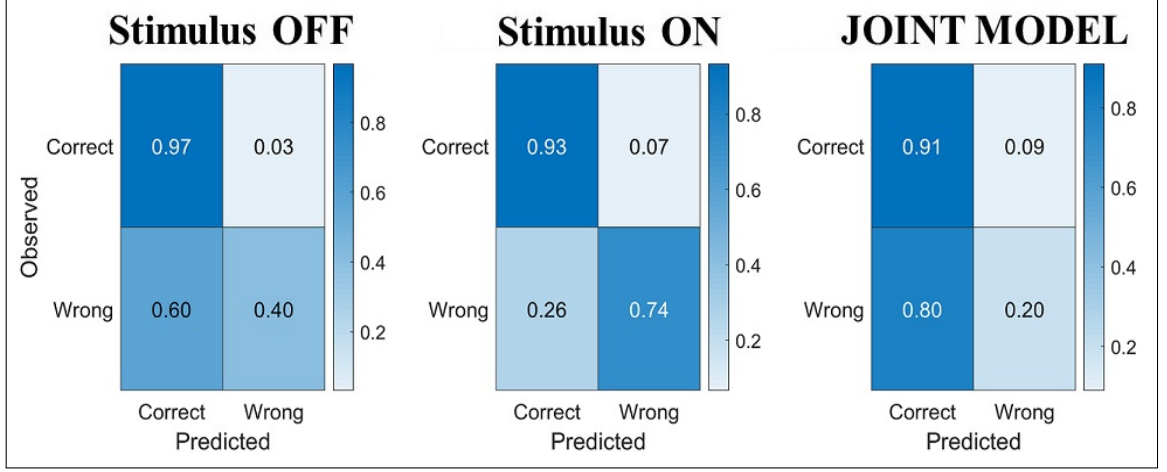


Figure 3.7 Sensitivity (top-left) and specificity (bottom-right) scores of Stimulus OFF/ON and Joint Model are shown in these three performance matrices for Correct/Incorrect Bayesian model for all rats. To evaluate Joint Model, Stimulus OFF and Stimulus ON distributions ($P(Y|X,S)$ in Eq. 3.1) were weighted according to their corresponding stimulus distributions ($P(S|X)$ Eq. 3.1).

model favors right responses (sensitivity for right/left joint model: 0.71, sensitivity for correct/incorrect joint model: 0.91. See Table A.3 in the Appendix A for detailed scores of correct/incorrect model). This makes sense when we bear the fact that the rat seeks the correct lever, and thus the correct/incorrect model reflects this fact with its higher sensitivity score than the right/left model. This correct/incorrect condition is just the change of the way we looked at the problem (see Section 3.4 for more discussion).

3.3.2.3 ROC Statistics (A prime and Bias)

If it were the model behaving in the chamber, meaning that model responses were assessed according to stimulus presence, the behavioral performance scores ($p(h)$ and $p(f)$) would be as in Table 2. Additionally, a non-parametric sensitivity index (A') and bias (B'') scores ([219, 262]) were also calculated.

$$A' = 0.5 + \frac{(p(h) - p(f))(1 + p(h) - p(f))}{4p(h)(1 - p(f))} \quad (3.9)$$

$$B'' = \frac{p(h)(1 - p(h)) - p(f)(1 - p(f))}{p(h)(1 - p(h)) + p(f)(1 - p(f))}$$

The right/left model performed worse than the animal behaving, meaning that this model had lower $p(h)$ and mostly higher $p(f)$ scores than the rats. In contrast, the correct/incorrect model has better behavioral scores than in most of the rats, as shown in Table 3.2 and Figure 3.8. When the summation of $p(h)$ and $p(f)$ values are 1, $p(h)$ and $p(f)$ values lie on the negative diagonal ($p(h)=1-p(f)$) and B'' formula returns zero. B'' values from Rat 6 to Rat 10 were calculated regarding this fact.

Table 3.2
 $p(h)$, $p(f)$, A' and bias (B'') Scores of Rat vs Bayesian Models.

	Rat Behaving				R/L Behaving				C/IC Behaving			
	$p(h)$	$p(f)$	A'	B''	$p(h)$	$p(f)$	A'	B''	$p(h)$	$p(f)$	A'	B''
Rat 1	0.54	0.43	0.60	0.01	0.50	0.37	0.62	0.04	0.71	0.38	0.75	-0.07
Rat 2	0.12	0.07	0.60	0.21	0.01	0.01	0.50	0.00	0.60	0.44	0.64	-0.01
Rat 3	0.82	0.22	0.88	-0.08	0.70	0.43	0.71	-0.08	0.98	0.03	0.99	-0.20
Rat 4	0.68	0.28	0.78	0.04	0.63	0.40	0.68	-0.01	0.81	0.07	0.92	0.39
Rat 5	0.99	0.34	0.91	-0.95	0.97	0.81	0.75	-0.69	0.97	0.04	0.98	-0.11
Rat 6	0.91	0.13	0.94	-0.14	0.53	0.40	0.62	0.02	1.00	0.00	1.00	0.00
Rat 7	0.95	0.07	0.97	-0.17	0.69	0.47	0.68	-0.07	0.99	0.01	1.00	0.00
Rat 8	0.79	0.08	0.92	0.37	0.16	0.10	0.62	0.21	1.00	0.00	1.00	0.00
Rat 9	0.53	0.10	0.83	0.48	0.36	0.10	0.75	0.44	0.91	0.09	0.95	0.00
Rat 10	0.95	0.19	0.93	-0.49	0.95	0.89	0.64	-0.31	1.00	0.00	1.00	0.00

3.3.3 Neuron Type Analysis: RS/FS Classification Result (# of units)

The criteria for a unit to be a fast-spiking neuron is borrowed from [259] that the duration of the second phase of action potential should be smaller than $349 \mu s$. Among 204 units, 35 of them were marked as fast-spiking (FS) and the rest 169 of them were marked as regular-spiking (RS) neurons.

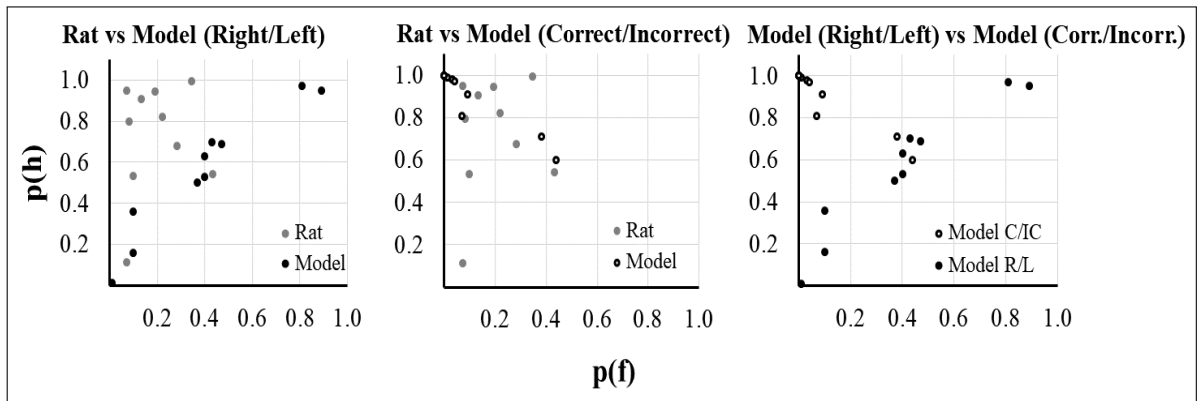


Figure 3.8 Comparative ROC plots for $p(h)$ and $p(f)$ scores for rats, Model C/IC and Model R/L.

3.3.3.1 Performance Matrices (Right/Left Model with RS and FS units)

The right/left Bayesian model was run with only RS unit firing rates as input (RS Model in Figure 3.9) and with only FS firing rates (FS Model in Figure 3.10). The

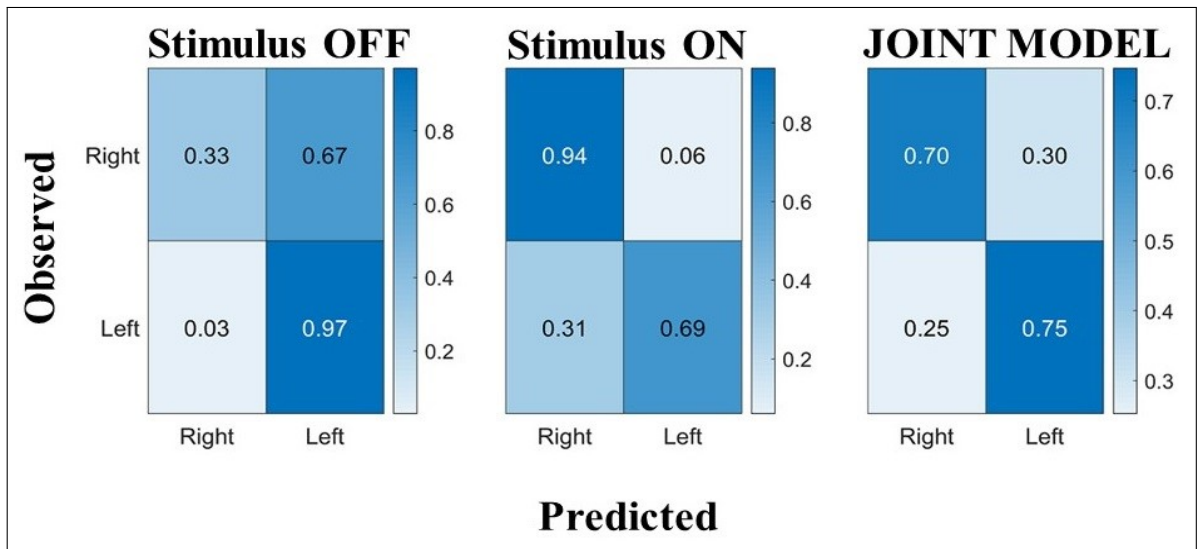


Figure 3.9 Stimulus OFF/ON and Joint performance matrices of Right/Left Model prediction using RS units only of all rats.

RS and FS Model predicted responses with similar scores to the model with all units (Figure 3.6), except that FS Model was better at predicting left responses than right

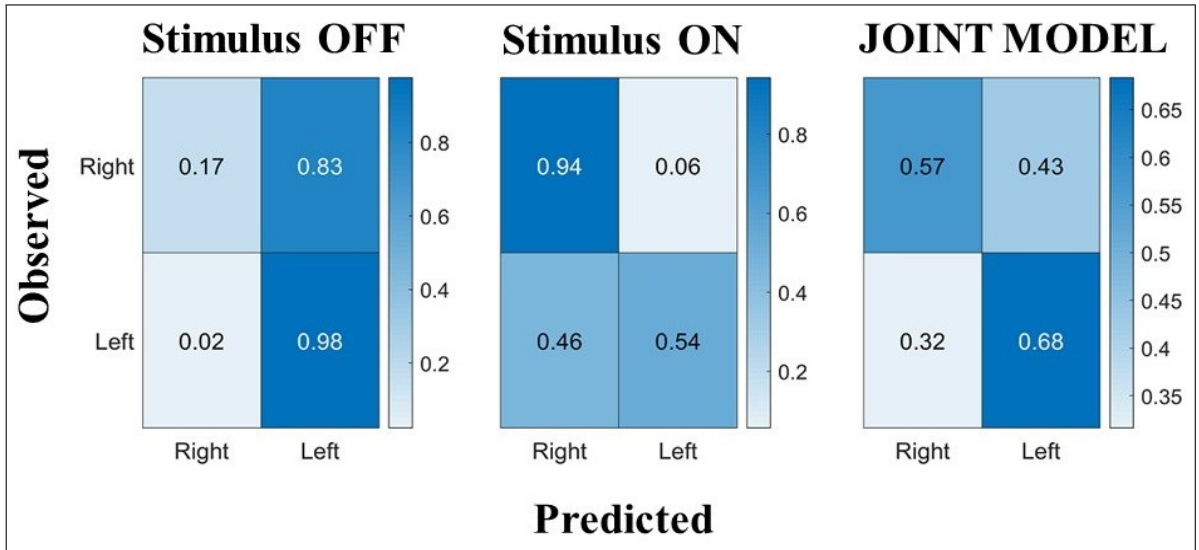


Figure 3.10 Stimulus OFF/ON and Joint performance matrices of Right/Left Model prediction using FS units only of all rats.

responses. This result may be the consequence of the fact that fast-spiking units are inhibitory neurons and may be in charge of stimulus-off trials (see 3.4 for further details).

3.3.3.2 Distribution of Logistic Regression Coefficients

Three different models (All-Unit Model, RS Model, and FS Model) and their performances were examined in detail up to now. These models tried to converge to the best beta coefficients with MCMC to predict the behavior with the highest performance. In Figure 3.11, model results for Rat 4 and Rat 9 are the examples of moderately performing rats and good performing models (see ON/OFF/JOINT Matrices under the Section 3.3.2.1). If the model has balanced confusion matrices from stimulus-on and stimulus-off distributions, it has a wider distribution of coefficients as well. We also observed mixture of Gaussian shapes for beta distributions in good performing models as in the case for Rat 4 and Rat 9. For Rat 2, whose model was left-biased as the rat (Table 3.1), the distributions are sharper. The distributions for Rat 5 are more interesting. The confusion matrix for stimulus-off distribution was balanced, which resembles the distributions of Rat 4 and Rat 9. However, the confusion matrix for stimulus-on was right-biased since the rat performed well. This bias led to

generate the sharpest distributions (see Rat 5 ON Trials in Figure 3.11) among others.

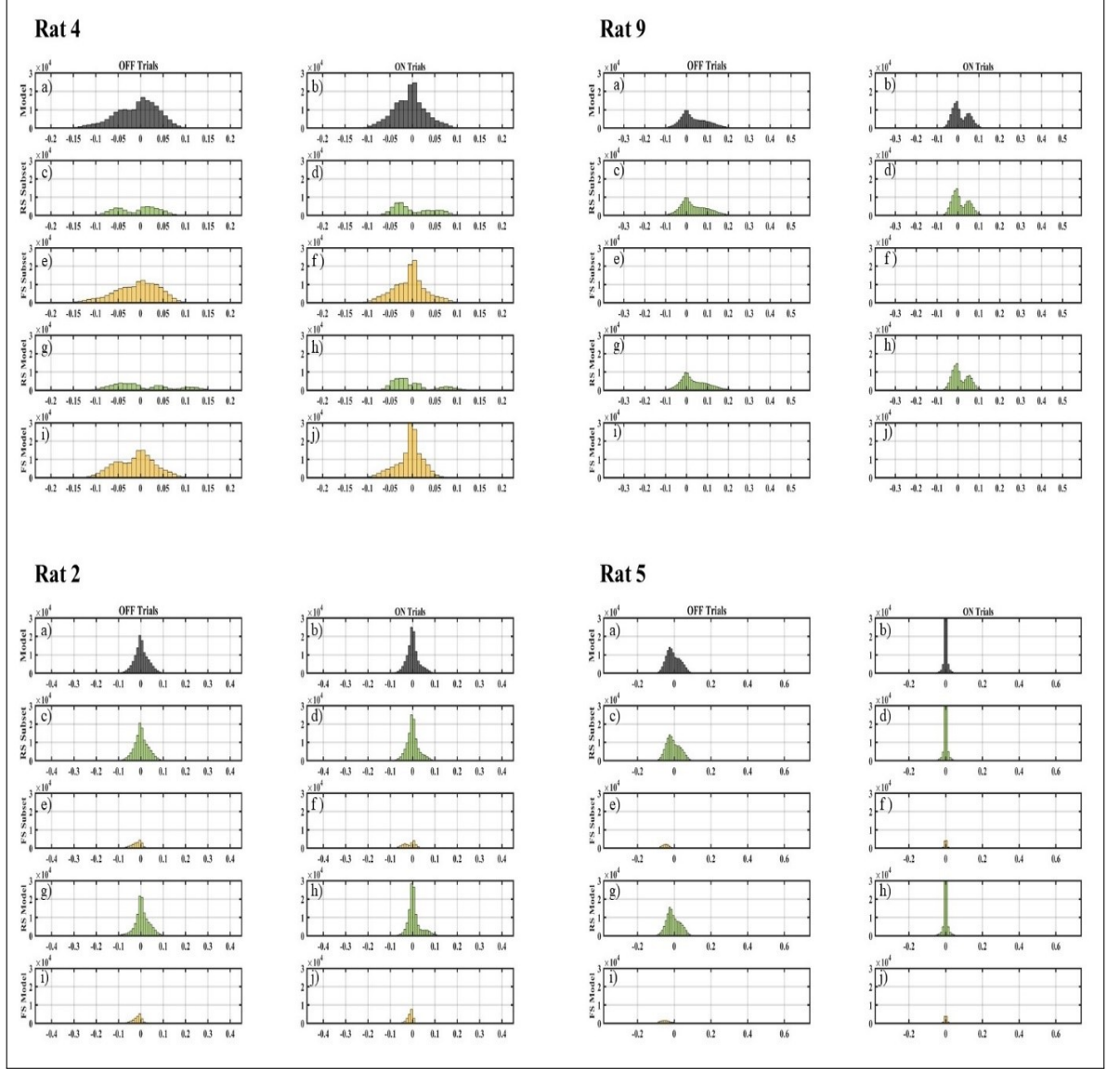


Figure 3.11 Distribution of coefficients for five different models for stimulus-off and stimulus-on trials. For each row; 'Model' refers to the right/left model, 'RS_Subset' refers to the coefficient distributions of RS units in the right/left model, 'FS_Subset' refers to the coefficient distributions of FS units in the right/left model, 'RS_Model' refers to the coefficient distributions of the right/left model that is trained and tested with using only RS units, 'FS_Model' refers to the coefficient distributions of the right/left model that is trained and tested with using only FS units.

3.3.3.3 Kolmogorov-Smirnov Test Results for All Distributions

The coefficient distribution samples were tested with the Kolmogorov-Smirnov

test to check if they were coming from the same population. Besides having the All-Unit model, RS model, and FS model, we analyzed RS/FS subset units of the All-Unit model.

Table 3.3

Kolmogorov-Smirnov Test Results. Tick marks represent the compared distributions are coming from the same distributions. The cross marks mean they are coming from different distributions. The empty cells show there has been no comparison test.

Comparison by Figure 3.11			Rats									
			1	2	3	4	5	6	7	8	9	10
ON vs OFF coefficients												
a	b	All-Unit Model	×	×	×	×	×	×	×	×	×	×
c	d	RS Subset	×	×	×	×	×	×	×	×	×	×
e	f	FS Subset	×	×		×	×		×	×		
g	h	RS Model	×	×	×	×	×	×	×	×	×	×
i	j	FS Model	×	×		×	×		×	×		
OFF coefficients												
a	c	All-Unit Model vs RS Sub-set	×	✓	✓	×	✓	✓	×	×	✓	✓
a	e	All-Unit Model vs FS Subset	×	×		×	×		×	×		
a	g	All-Unit Model vs RS Model	×	×	×	×	×	×	×	×	×	×
a	i	All-Unit Model vs FS Model	×	×		×	×		×	×		
c	e	RS Subset vs FS Subset	×	×		×	×		×	×		
g	i	RS Model vs FS Model	×	×		×	×		×	×		
c	g	RS Subset vs RS Model	×	×	×	×	×	×	×	×	×	×
e	i	FS Subset vs FS Model	×	×		×	×		×	×		
ON coefficients												
b	d	All-Unit Model vs RS Sub-set	×	✓	✓	×	✓	✓	×	×	✓	✓
b	f	All-Unit Model vs FS Subset	×	×		×	×		×	×		
b	h	All-Unit Model vs RS Model	×	×	×	×	×	✓	×	×	✓	×
b	j	All-Unit Model vs FS Model	×	×		×	×		×	×		
d	f	RS Subset vs FS Subset	×	×		×	×		×	×		
h	j	RS Model vs FS Model	×	×		×	×		×	×		
d	h	RS Subset vs RS Model	×	×	×	×	×	✓	×	×	✓	×
f	j	FS Subset vs FS Model	×	×		×	×		×	×		

The coefficients of stimulus-on and stimulus-off distributions were significantly different for all cases ($p < .05$). The stimulus-on and stimulus-off coefficients of the All-unit model vs RS subset units of the same model were not different for rats 2, 3, 5, 6, 9, and 10 ($p > .05$). The stimulus-on beta's for the All-unit model versus its RS Subset, as well as RS subset of the All-unit model versus the RS model, were coming from the same population for rats 6 and 9 ($p > .05$). The rest of the comparisons yielded different distributions ($p < .05$).

3.3.4 Reaction Time Prediction Performance of Bayesian Linear Regression Model

The Bayesian Model using Linear Regression was built here to predict the reaction time of the animals in the behavioral task. First, the square root transformation [263] was utilized for asymmetric reaction times. Later, outliers greater than 2.5 standard deviation were eliminated from z-transformed reaction times. The Bayesian linear regression model used the remaining data set with the same parameters as Logistic Regression (10-fold cross-validation, training/test set ratio: 90/10). The mean absolute percentage error values were generated as a performance measure for this model.

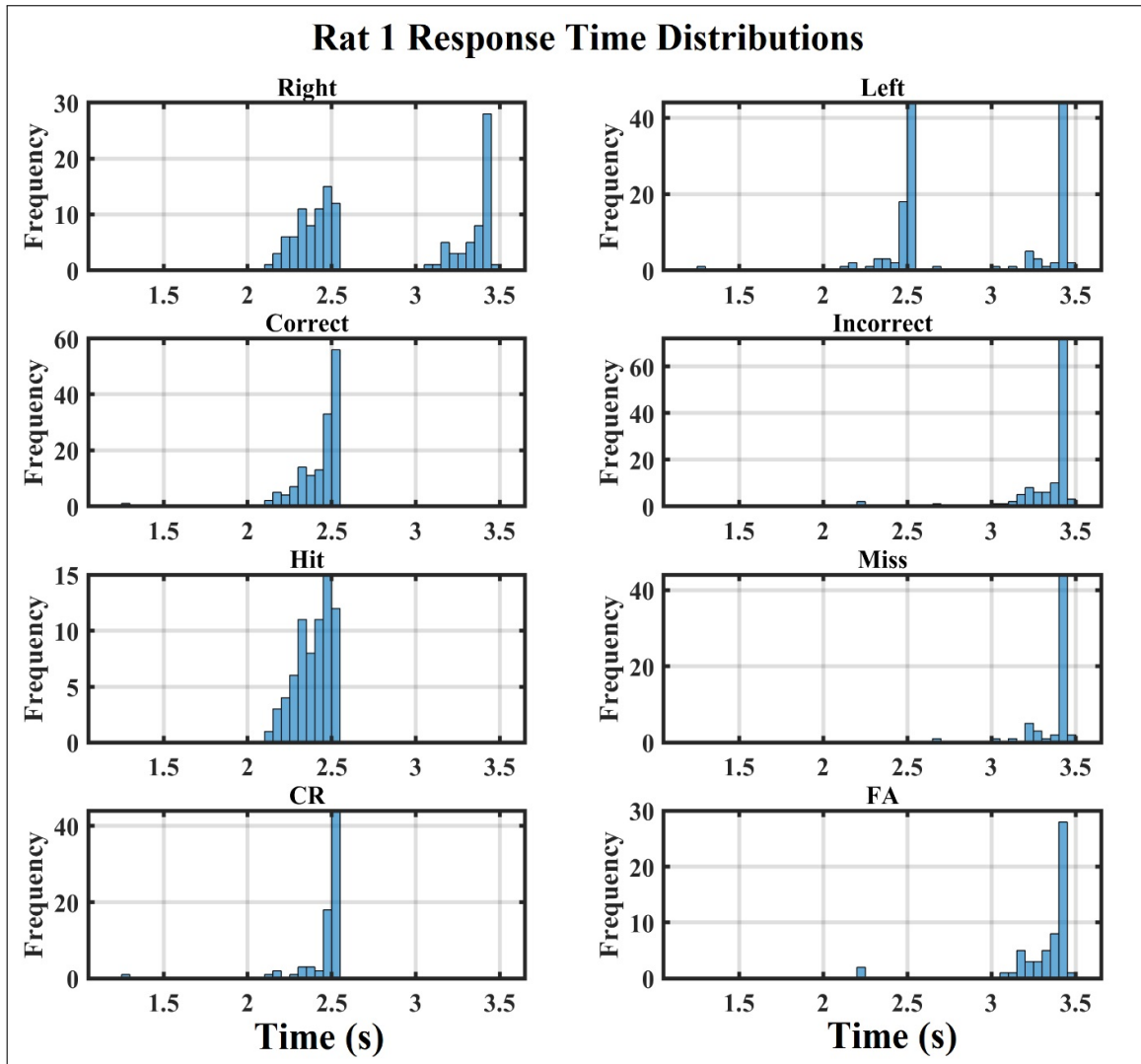


Figure 3.12 A representative reaction time distribution based on behavioral responses.

Table 3.4
Reaction Time prediction MAPE scores for Bayesian linear regression.

	Mean Absolute Percentage Error (MAPE %)		
	Stimulus-OFF Model	Stimulus-ON Model	Joint Model
Rat 1	15	14	12
Rat 2	5	8	4
Rat 3	22	22	22
Rat 4	40	33	35
Rat 5	17	16	15
Rat 6	15	25	15
Rat 7	17	40	18
Rat 8	19	24	16
Rat 9	17	13	14
Rat 10	28	16	20

The linear regression model, which had to predict discrete time values here, was expected to have lower performance scores when compared to the bimodal logistic algorithm. However, the reaction time distributions differed prominently when the rat responded with the true or false lever (Figure 3.12) thus the algorithm might have taken advantage of this phenomenon to predict the response times accurately.

3.4 Discussion

We proposed that the mean firing rate of neural populations, recorded using multi-channel electrodes under the tactile stimulus condition, have enough information to decode the intention of the subject. Previous studies have usually focused on predicting either sensory stimulus [182, 235, 238, 239, 241, 244] or movement planning [253, 264]. However, it is crucial to be precise and accurate on movement directions in everyday usage of neuroprosthetics devices. This is the first demonstration study of which utilizes neural activity together with inherent stimulus distribution in the neurophysiological data during the psychophysical yes/no detection task and returns the estimated decision of detection task using Bayesian estimation.

3.4.1 Bayesian Prediction Using Rate Coding

The compelling machine learning technique we used here is the Bayesian prediction of the decision regarding posterior stimulus distributions. The mean performance metrics in Table 3.1 confirm that this model deciphers required hidden patterns in the neural data to identify the behavioral outcome. Other studies have used temporal code [76, 265] for prediction purposes. However, this technique increases the dimensions of the predictors tremendously. Here, we proposed using a simpler regressor, the mean firing rate during the stimulus window (0-600 ms), which is the predictor of the neural data, that corresponds to the rate code. Instead of using temporal code, we here preferred to see if this simpler coding technique would already be enough to decipher the decision of the animal. If rate coding were not successful, the neural activity would be easily transformed into temporal code as predictors, but with the cost of increasing dimensions of data, which is not needed right now.

3.4.2 Recording From Freely Behaving Animal

In the predecessor study [85], they have recorded single-units from anesthetized rats and were able to observe crystal clear stimulus onset for each stimulus frequency and 5 Hz stimulus entrainment. Here, the animals were awake and unrestrained in the operant chamber for the sake of everyday neuroprosthesis utilization analogy. Even chamber floor was narrowed down towards the probes, we neither knew the exact contact times of probes nor had any claim that the mechanical stimulation always hit the rat's hindpaw skin on the same epoch of each trial. For these reasons, with this type of awake unrestrained rat's neural data (Figure 3.3), we are not always fortunate to see a clear onset or entrainment.

3.4.3 Spike Sorting

To understand how decisions, which are the result of collaborative work from many neurons, are shaped in the brain, the investigators [266] suggest stepping further from single-unit recording with many trial schemes to multi-unit recording with single-trial frameworks. Among many other alternatives (Open Sorter, MountainSort, KiloSort, Klusta, Combinato), Wave Clus [267] was chosen as the spike sorter for its novel algorithm and the benchmark results on real single-channel data. Wave Clus's algorithm uses wavelet transform, which eliminates signal stationarity by regarding both time and frequency domain, and it classifies using superparamagnetic clustering (SPC) [268] of wavelet coefficients instead of principal component analysis (PCA) which is the conventional alternative in spike sorting literature [269, 270]. Among the other sorters, Open Sorter (Tucker-Davis Tech., Alachua, FL, USA) is a commercial alternative and uses principal component analysis (PCA) for clustering. We first tried Open Sorter with Bayesian expectation-maximization option; it generated only one cluster for most of the cases. Using Open Sorter with k-means [271] clustering was another option, but even the older version of Wave Clus had a better clustering performance than PCA. Quiroga et al. [272] have already shown that how SPC with Kolmogorov-Smirnov (KS) test classifies into three clusters whereas PCA with the first three dimensions converged to only one cluster for simulated data. MountainSort was not preferred because of the operating system dependence, it has no Windows version. KlustaKwik is optimized for probe recordings [273, 274], we could not reach any benchmark study about microwire arrays. Combinato algorithm [275] also uses superparamagnetic clustering of wavelet coefficients as in Wave Clus. However, they compared it with the older version of Wave Clus. The new implementation of Wave Clus has been proven to perform better than other alternatives with fruitful comparisons for both simulated and real single-channel recordings [267].

3.4.4 Inter-subject variations of firing rates for behavioral outcomes

Besides having unrestrained animals that introduced movement artifacts, there were also inter-subject differences in cortical activity levels. The expected U-shape for firing rates of hit-miss-cr-fa sequence in Figure 3.4, as in the case of Rat 1, Rat 6, Rat 9, Rat 10, was not common for all rats. Even for Rat 4's significant case, the situation is vice versa. Additionally, we have found significantly changing firing rates among different behavioral responses for half of the animals. Even other parts of the data had no prominent spike rate differences, i.e. Rat 5, 6, and 7, Bayesian model extracted the obscure parameters in the spike data with valuable performances (f1 scores were 0.82 for Rat 5, 0.62 for Rat 6, and 0.65 for Rat 7 in Table 3.1). To this end, Figure 3.4 is important to show the individual differences between animals and the stochasticity of the neural processes. That kind of diverse data provides controversial attributes to the predictor; thus, this provides an opportunity to test the performance of the machine-learning algorithm, which reveals hidden patterns in data. Otherwise, the prediction process would be quite trivial with obvious trends in data.

3.4.5 The Bayesian Prediction (Right/Left Model) Results

These computational techniques create remarkable differences under those kinds of circumstances where the data have no obvious trends in classical neural data analysis. Even if there were no correlations at all between firing rates and behavioral responses (Figure 3.5), the Bayesian model was able to estimate the decision of the rat.

It was tricky to define sensitivity on stimulus-off trials where the goal is now to confirm stimulus nonexistence (stimulus-off matrix in Figure 3.6). One can argue that the definition of the sensitivity should be the ratio of left predictions to the left responses of the rat for the stimulus-off model. However, for the sake of consistent terminology among models, we stick to the definition of sensitivity to be as the ratio of right predictions to the right response observations. If the former would be the case, the sensitivity and F1 scores of the stimulus-off model would have gone higher than those seen in the Subsection 3.3.2.2. In the end, not the metrics for either stimulus

on/off model but the performance of the all-unit model will determine the result. However, Figure 3.6 and Table 3.1 should be examined bearing these facts in mind.

The performance evaluation of the right/left (R/L) Bayesian model for ten rats falls into three categories: good/moderate/biased. If the model generated ≥ 0.65 F1, sensitivity, and specificity scores (Table 3.1), we defined it as 'good' performance. If it has F1, sensitivity, and specificity scores > 0.50 , we marked it as 'moderate' performance. The rest were assessed as either 'left-biased' or 'right-biased' accordingly (see Table A.4 in Appendix A for descriptive purposes), even noticeable sensitivity and F1 scores for right-biased models of Rat 5, Rat 10, and specificity scores of for left-biased models of Rat 2 and Rat 8. To this end, we have three good performing (for Rat 1, 4, and 9), three moderately performing (for Rat 3, 6, and 7), two left-biased (for Rat 2 and 8), and two right-biased (for Rat 5 and 10) models. Fortunately, they are distributed according to all categories that are the indication of diverse sampled neural activity drawn from the whole population.

The confusion matrices were expected to be weighted with more trials on top-left (true positive) for stimulus-on and bottom-right (true negative) for stimulus-off. The 'good' performing models have diagonally weighted joint confusion matrices (see Figure A.3 in Appendix A for confusion matrices of Rat 1, Rat 4, and Rat 9) which leads to 'good' sensitivity, specificity, and f1 scores. However, even if they have top-left weighted stimulus-on and bottom-right weighted stimulus-off confusion matrices, after weighting with the posterior stimulus distribution (part 2 of Bayesian Model formula in Eq. 3.1), the 'moderate' performing models have perturbed balance around the diagonal of the joint matrix. This indicates that the mean firing rate may not be the best predictor of the posterior stimulus distribution for these rats (Rat 3, Rat 6 and Rat 7).

Figure 3.4 illustrates the difference between the firing rates of these rats; these rats -Rat 3, 6, and 7- with 'moderate' performing model have either lower or insignificant firing rates compared to the rats -Rat 1, 4, and 9- with 'good' performing model. A controversy emerges here is that if the rat has lower behavioral scores (see $p(h)$ and $p(f)$ of Rat 1, Rat 4 and Rat 9 in 'Rat Behaving' part of Table 3.2 and also significantly different firing rates (Figure 3.4) then its Bayesian model performs 'good'. This may imply that the decision according to the task has been made with the whole rat brain

but we were able to witness it with the firing rates of a bunch of units recorded from the sensorimotor area. Similarly, if the rat has higher $p(h)$ and $p(f)$ scores (see $p(h)$ and $p(f)$ of Rat 3, Rat 6 and Rat 7 in Table A.4 in Appendix A) and lower or insignificant firing rates, its model performs 'moderate'. In that case, we were not able to observe -as easily as in the former case- the decision made within that small craniotomy window. This finding is in good agreement with the study [82], in which they state that neural responses are getting smaller in duration and magnitude during subsequent days of learning. They also found that more cortical units responded to stimuli compared with the beginning of learning the task. Neural responses of naïve mice have larger fluctuations and depolarizing responses than trained mice for a whisker deflection [98]. Additionally, they have found that more cortical -medial prefrontal cortex and dorsal hippocampus- recruitment during learning might provided top-down control [276]. Although our rats learnt and stabilized in the task before implantation, two weeks of surgery break may cause dissipation of cortical connections between units, which are in charge of the learned task. Yet some of them performed with lower behavioral scores than before the surgery, and thus some rats might not have completely remembered the task. The cortical activity of these rats with lower behavioral scores may have higher depolarized responses or more localized cortical recruitment, and hence is more informative to build the posterior stimulus distribution (part 2 in Eq. 3.1). Whereas the firing rates of the high-performing rats -they remember very well how to perform the task and they may preserve broader cortical recruitment required to perform the task or have smaller responses to stimuli- are not informative anymore for stimulus distribution. Since neural activity during behaving flattens and comprises more inhibitory fluctuations, the high-performing rat cortex may not have enough responsiveness for a decision to be reconstructed for the Bayesian model. In this sense, we speculate that this algorithm may leverage the performance of the human patients during the training period -usually takes a year or so- of neural prosthesis operation after implantation that their performance corresponds to the low-performing rats after surgery.

For the rest of the cases (Rat 8, Rat 10, and Rat 5), the joint model favors either left lever presses (left-biased) or right lever presses (right-biased), even though Rat 5 and Rat 10 have good F1 scores. The stimulus-on confusion matrices had more trials on top-left (true positive) for and the stimulus-off confusion matrices had more

trials on bottom-right (true negative) as expected. However, the joint matrices favored either right or left responses after joining with the posterior stimulus distribution. This consequence shows that predicted stimulus distribution (part 2 in Eq. 3.1) has no effect to balance the on/off distributions properly (part 1 of the same formula). This fact again points to the possibility that these rats, which again have higher behavioral scores, detect stimulus but their tactile responsive neurons are not in the cortical region we have recorded from, suggesting a more collaborative behavior from units across the region.

Exceptionally, Rat 2 did not cooperate for those two days of recording after the surgery. It started to cooperate again but we did not include the rest of the recording data to standardize all conditions for all rats. It had left lever bias that eventually reflected within the model. In summary, if the rat has an average behavioral performance, using rate code as the predictor is enough for the model to have a good performance. However, if the rat has better psychophysical performance-more cortical units involved, the model would switch to temporal neural coding in future to resolve right or left-biased model situations.

3.4.6 The Bayesian Prediction (Correct/Incorrect Model) Results

In the correct/incorrect (C/IC) version of the Bayesian model, we just changed the way we looked at the problem (see Figure 3.7). This time predictor (average firing rate) is tested for reflecting the intention of the animal seeking the correct or incorrect lever instead of the right or left lever. Using *nsamples=1000* parameter for Gibbs Sampling, the sensitivity score of stimulus-off performance matrix (also true positive trial count in confusion matrix) of this model converges to the specificity score of the stimulus-off performance matrix (also true negative trial count in confusion matrix) of right/left model in Figure 3.6. Similarly, the specificity score of stimulus-off performance of this model converges to the sensitivity score of the stimulus-off performance matrix of the right/left model as well. The correct/incorrect joint model favors correct responses more than the right/left model favors right responses (sensitivity for right/left joint model: 0.71, sensitivity for correct/incorrect joint model: 0.91. See Table A.3 in

Appendix A for detailed scores of correct/incorrect model). Because there are more correct trials now, it imbalances the confusion matrices. Even if the correct/incorrect model has higher sensitivity and f1 scores, it has definitely a lower specificity score, which may not be a preferred property for the sake of neuroprosthetic system stability.

3.4.7 Behavioral Performance comparisons for Rats versus Models

A hypothetical scenario would be if these models were in place of the rats and behaving in the operant chamber, the behavioral scores of those in-silico brains would be as illustrated in Table 3.2 and Figure 3.8. Eventhough the C/IC model had some specificity limitations, it performed way better than the R/L model and most of the time better than the rat itself. Because the C/IC model inherently seeks the correct response, it better suits the task paradigm.

3.4.8 The RS/FS Bayesian Prediction (Right/Left Model) Results

Since a vast number of units were classified as regular-spiking, RS Bayesian Model performances are highly resembling the original Bayesian Model run with all units (see Figure 3.9 for a comparison with Figure 3.6). Regular-spiking (RS) units were the majority among all units for all of the rats except Rat 4. These units moderated the model performance for Rat 1 and Rat 7 (see Table A.5 in Appendix A) because of their closer behavioral performance scores to the original model. This is reasonable because of the number of proportions RS/FS units (number of RS/FS units for Rat 1:15/4, for Rat 7: 21/2). For Rat 5, RS and FS units seem that they have collaborated. However, all three models have higher false alarm scores than rat. Our three model subjects were way laxer than the rat. This suggests that the recording electrodes missed some of the units in charge preventing the rat from doing false alarm. In the case of Rat 4, FS units are the majority (number of RS/FS units: 8/25). They had similar scores to the original model and thus may have contributed to the performance more than RS units. Figure 3.10 indicates that FS Model is better at predicting left responses (higher

specificity) than right responses. This result may be the consequence of the fact that fast-spiking units are inhibitory neurons and may be in charge of stimulus-off trials.

3.4.9 Future work and limitations

Our next step will be real-time trial-by-trial decoding of the decision of the animal. For this next step, the spike sorting step should be also online or may be bypassed [277]. The other consideration may be the training the model before the experiment begins. Since the units were not marked as the same unit from the previous day, they may change during the experiment days. Therefore, the previous days' data may not be used instead, we may have to collect a considerable amount of activity data for model training purposes only. There are more complex, sophisticated techniques used for neural decoding. For stimulus location reconstruction, they used an artificial neural network [265, 278]. However, as models are getting more complex, it is harder -mostly impossible- to explain the relationship between inputs and the output of the system. Here, we suggest employing the coefficient distributions as illustrated in Figure 3.11 to relate the incorporation of the features (here units) to the decision of the animal. In this way, human-computer interaction will stick to the common language of mathematics with crystal clear parameters.

3.5 Conclusion

The presented study gave priority to probabilistic inference to extract neural representations of sensory input and motor output distributions. Here, we focused on predicting stimulus presentation and behavioral response in a psychophysical yes/no detection task by using the Bayesian Network Model. Although the models were applied offline here, they can be modified for real-time use to test feasibility in a neuroprosthetic application.

The main results show that Bayesian models perform better in rats with lower psychophysical performance. The Bayesian network model seems better for rats with

degraded behavioral performance, which may include the rats more uncertain about the task and had lower average detectability indices. Since having lower detectability scores may refer to more uncertain cortical state, the mastery of the Bayesian Network model is obvious whenever statistical inference is needed. Lower psychophysical performance refers to the learning and adaptation period of patients for neural prostheses. Therefore, this approach can be particularly useful for the training phase of BCIs or rehabilitation with neuroprostheses. Additionally, this novel implementation can be recruited as a tool to predict motor response for different types of task paradigms adaptively. Some preliminary data were previously presented as an abstract [256].

4. PERFORMANCE COMPARISONS BETWEEN SUPERVISED LEARNING ALGORITHMS AND A BAYESIAN NETWORK MODEL FOR THE PREDICTION OF PSYCHOPHYSICAL RESPONSES BASED ON MULTI-ELECTRODE SPIKE RECORDINGS FROM THE RAT SENSORIMOTOR CORTEX

4.1 Introduction

Fundamental question of machine learning is to search patterns in data to which are offered a rich set of solutions for the last three hundred years. Recognition of hidden patterns with automatic regularity detection is accelerated using computer algorithms. Then, these hidden structures and their interactions are utilized to explain the intrinsic regularities and thus classify the data into different categories. Once these hidden structures are captured by the model, by a process called training or learning phase, extracted features are applied to the test set to assess the generalization performance of the model. These machine learning solutions offer a two-fold advantage. First, these algorithms are inspired by biological processes [279–285] to leverage the generalization capability of the models in possible real-world situations. Secondly, these algorithms equipped with accurate predictive idiosyncrasy on neurophysiological problems uncovered the neuronal level hidden mechanisms by feeding the revealed patterns and rules back to the neuroscience literature.

How the neural activity shapes the motor coordination in tasks is still an intriguing question and deserves attention to reveal its building blocks in the neural code. Classification algorithms are used to predict the most probable state of a given variable, i.e; stimulus presence or intended motor action. These algorithms define a dimensional space depending on the parameter size to predict. This space comprises the hyperplane built with the best parameters that minimize the loss function and attempt to classify the data set. Here, we used seven commonly used supervised machine

learning algorithms (logistic regression, linear discriminant analysis, k-nearest neighbors, decision tree, support vector machine, naïve Bayes, artificial neural network) and compared their readout performances with the Bayesian Network model, which is our implementation introduced in Chapter 3. Those classifiers were expected to decode the intention of the animal during a perceptual decision-making task and report the choice for each trial separately. Classification performance depends on how the algorithm is implemented to build the hyperplane and decision boundaries. There are several studies that compared the neuronal read-out performances of the classifiers [286–293]. However, instead of the comparison within these classifiers, we will compare the novel Bayesian Network algorithm with those seven supervised techniques, which will be described in the Section 4.2, in terms of their read-out performances from sensorimotor spiking activity of behaving rats.

Cortical neuroprostheses are promising for patients with severe neurological disorders, and they require the processing of sensorimotor information for better motor control and somatosensory feedback. This study aims to characterize the performance of the Bayesian network in comparison with standard supervised learning algorithms to predict rats’ lever presses with spike data. This version is only a preliminary attempt to compare supervised machine learning classifiers, comprising probabilistic and empirical types of implementations, with the Bayesian Network Model. Although all classifiers performed with similar scores, the main finding is the performance increment of the Bayesian Network model among the other seven models when the data was coming from the rats with lower behavioral performances. These impaired behavioral scores refer to the neuroprosthetic or robotic arm usage for a patient at the initial stages of adaptation. This finding seems promising to help paralyzed patients or neuroprosthetic device users to substitute the exhausting training and rehabilitation periods with a shorter adaptation time. Some preliminary data were previously presented as an abstract [294].

4.2 Materials and Methods

4.2.1 Animals

Ten adult Wistar albino rats (data from Chapter 3) were already trained to perform a yes/no psychophysical detection task based on vibrotactile stimulation applied on hindpaw glabrous skin (frequency: 40 Hz, duration: 0.5 s, amplitude: 200 μm) (see Chapter 3). The spike recordings from single/multi units during the yes/no detection task were used for choice prediction purposes.

4.2.2 Spike Sorting and Design Matrix

Spikes from 16-channel microwire arrays implanted in the hindlimb representation of the S1 cortex were sorted with the same spike sorting techniques in Chapter 3. Average firing rates of 351 units from 10 rats were used to prepare the design matrix for 7 different algorithms. The design matrices are prepared based on the trial count and the number of units for each rat ($X[\text{trials} \times \text{units}]$).

4.2.3 Software

Seven selected supervised algorithms were run in Python (version 3.8.2) using the SciPy (version 1.5.4), NumPy (version 1.19.4), Pandas (version 1.0.3), Matplotlib (version 3.3.2), Theano (version 1.0.5), and Graphviz (version 0.14.2). All the required software was developed in the PyCharm Professional Integrated Development Environment (IDE) version 2020.2.5.

4.2.4 Supervised Classification Algorithms

Animals' behavioral choices were predicted using supervised machine learning algorithms. Apart from the previous Bayesian Network model, which used both stimulus presence and firing rate as feature set, only average firing rate was used here as an input to the models in the form of a design matrix. Logistic regression, linear discriminant analysis, k-nearest neighbors, decision tree, support vector machine, naïve Bayes, artificial neural network, and the Bayesian network model we implemented in Chapter 3 were executed to predict the behavioral responses for pooled trials of each rat. The canonical implementation details of these algorithms and their runtime parameters can be found in Appendix B. Later, their performances were compared in terms of sensitivity, specificity, precision, F1 score, and accuracy metrics.

4.2.5 Performance Metrics

Cross-validation is executed by creating *KFold* class with (*n_splits=10*, *shuffle=True*) parameters. The data set was shuffled before it was divided into 10 batches. The models were fitted using true positive (TP), true negative (TN), false positive (FP), false negative (FN) scores for each rat separately. These scores are then used to calculate sensitivity (Sens), specificity (Spec), precision (Prec), F1 score (F1), and accuracy (Acc) metrics.

$$Sens = \frac{TP}{TP + FN} \quad Spec = \frac{TN}{TN + FP} \quad Prec = \frac{TP}{TP + FP} \quad (4.1)$$

$$F1 = \frac{2TP}{2TP + FP + FN} \quad Acc = \frac{TP + TN}{TP + FN + FP + TN}$$

The mean values of each 5 metrics returned from 10 batches of the cross-validation process were calculated for each rat. All seven algorithms together with the Bayesian network introduced in Chapter 3 were compared in terms of these per-

formance metrics (sensitivity, specificity, precision, F1 score, accuracy).

4.2.6 Bayesian Network model metrics evaluated based on A' scores of rats

A non-parametric sensitivity index (A') is calculated with the parameters of hit rate (pH) and false alarm (pF) rate given below:

$$A' = 0.5 + \frac{(p(h) - p(f))(1 + p(h) - p(f))}{4p(h)(1 - p(f))} \quad (4.2)$$

The A' scores of the rats are taken into consideration when the Bayesian Network performance was evaluated (see Section 4.3.1).

4.3 Results

4.3.1 Bayesian Network Model Metrics Evaluated Based on A' Scores of Rats

The performance matrices of the Bayesian Network model are evaluated based on the scatter of the A' values of all rats. Figure 4.1 shows the performance contour lines of each rat based on the A' scores. Colored borders define the borders for pre-defined performance levels. A' value of Rat 7 falls into the best region ($>.95$), which refers to very good psychophysical performance for this rat. Rat 6, Rat 10, Rat 8, and Rat 5 fall into $A'>.90$ region, which is again a good performance region. For all these good performing rats, the Bayesian Network model performed moderately (see sensitivity (top-left) and specificity (bottom-right) scores in the performance matrices of Figure 4.2). However, for the rats with lower A' scores (Rat 1, Rat 4, Rat 9), the Bayesian model performed better than the one for the rats with higher A' scores.

This result shows that better sensitivity and specificity metrics (ideally weighted

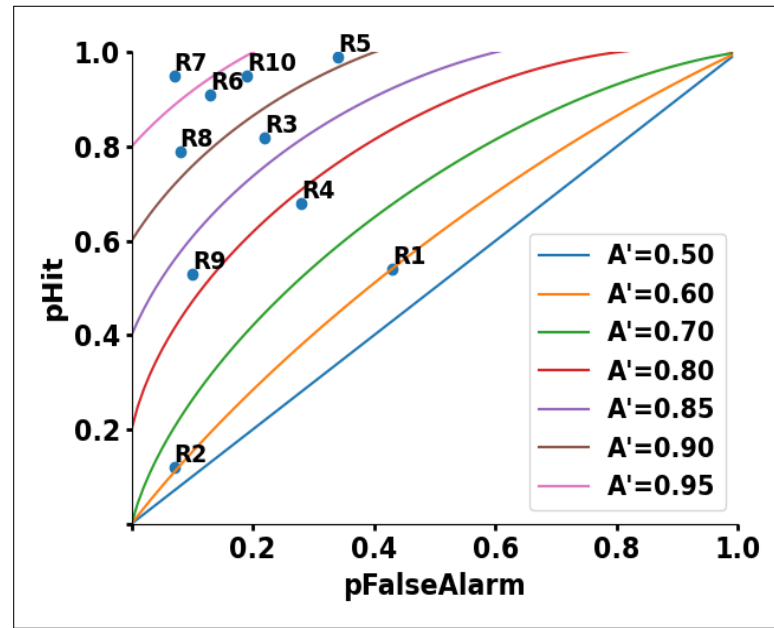


Figure 4.1 Hit rates versus false alarm rates (scattered blue dots) of all 10 rats within the borders of specified A' contours defined in the legend. R7, R6, R10, R8 and R5 have highest A' scores. R9 and R4 are close to 0.8 border. R1 and R2 fall on to the 0.6 A' border, which shows performance decrement in the psychophysical task.

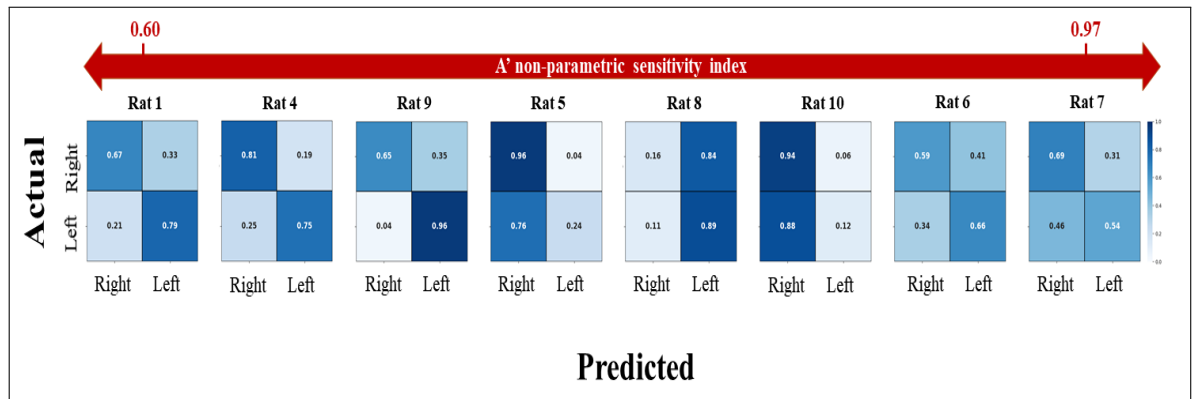


Figure 4.2 The performance matrix has to be weighted more along the left diagonal for an indication of the good performance. The Bayesian model has good prediction scores for Rat 1 and Rat 4, of which matrices were weighted more on top-left (Sensitivity) and bottom-right (Specificity). The Bayesian Network model predicts rat behavior better when the performance of the rat (A') is lower. From left to right, A' scores of rats increase from 0.60 to 0.97. In the same way, the matrices start to be deteriorated by imbalanced or averaged out scores, which is the indication of performance decrease of the Bayesian model for the rats with higher A' values.

along the left diagonal of the decision matrix) for lower A' values (R1, R4, R9) lead to better predictions for Bayesian Network Model. Increasing A' scores (R5, R8, and R10) was the indication of a perturbed decision matrix along any biased direction for the model. Higher A' values (R6 and R7) lead to smoothed-out sensitivity and speci-

ficiency values in these matrices. These results highlight the strength of the Bayesian model on the subjects with lower performance during the usage of neuroprosthetics. Since the rehabilitation and training periods usually take tremendous time during the clinical research, the Bayesian Network Model seems promising to keep the adaptation and rehabilitation durations shorter.

4.3.2 Performance metric comparisons

All 7 supervised algorithms were executed and fitted to the training data set of each rat. The test set performance scores for each rat and 8 algorithms (including Bayesian Network) were compared in Figure 4.3, Figure 4.4, and listed in Table 4.1. The big brown dot in Figure 4.3 and Figure 4.4 shows the Bayesian Network model was among the best performing model. Additionally, the right hand side of the Figure 4.4 compares all models in terms of five different performance metrics. The Bayesian Network Model was among the best three algorithms for those animals having lower psychophysical detectability (with lower A' scores) with respect to five different performance scores (marked with bold at last column of the Table 4.1).

The algorithms gave moderate, but similar performance results with the

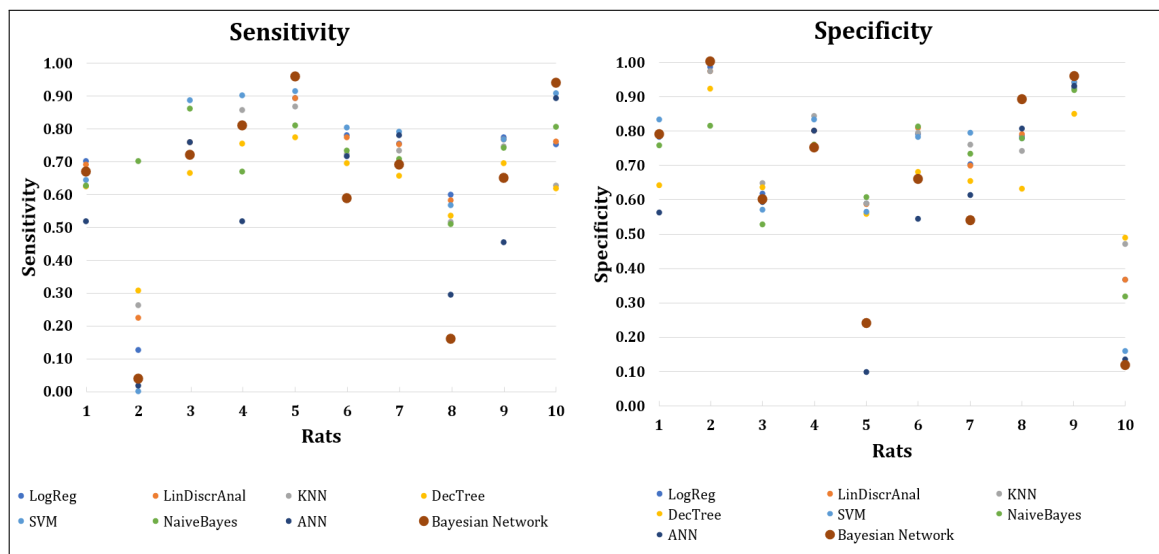


Figure 4.3 Sensitivity and specificity score comparisons of all models for all rats. Bayesian Network model is represented with big brown dot.

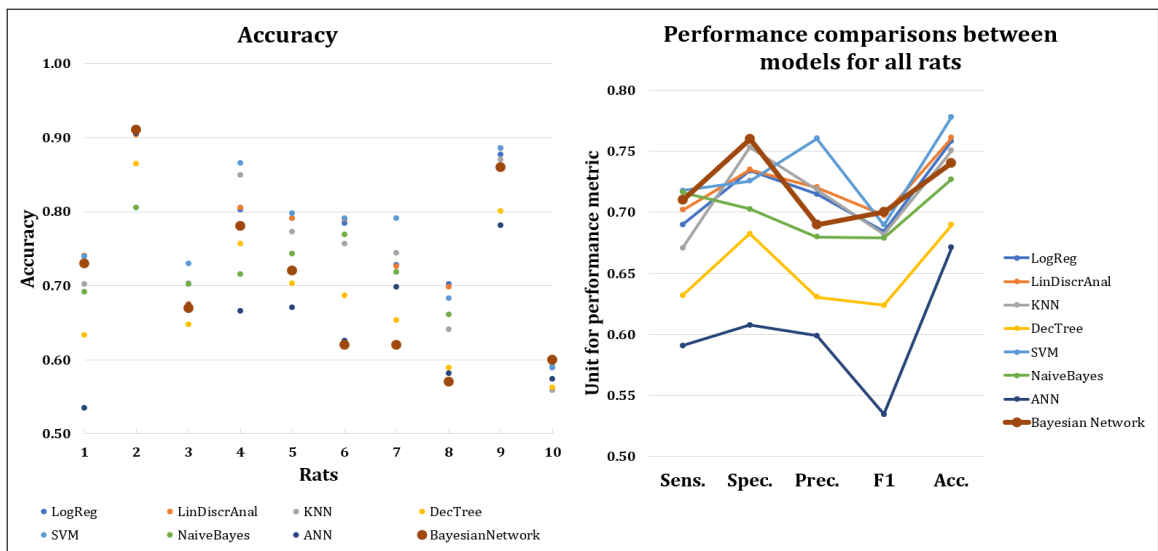


Figure 4.4 Accuracy score comparisons of all models for all rats can be seen on the left. Bayesian Network model is represented with big brown dot. The plot on the right hand side compares all models for the average scores of all rats based on the five selected scores. The Bayesian Network model was among the best performing models.

Table 4.1

Performance metric comparisons among 7 supervised learning algorithms and the Bayesian Network. Results for Bayesian Network algorithm transferred from the results of Chapter 3. Some of the Bayesian model's metrics are marked with bold when this model was one of the top three best performing algorithm in terms of boldfaced metric.

		LogReg					LinDiscrAnal					KNN					DecTree				
	A'	Sens	Spec	Prec	F1	Acc	Sens	Spec	Prec	F1	Acc	Sens	Spec	Prec	F1	Acc	Sens	Spec	Prec	F1	Acc
Rat 1	0.60	0.70	0.78	0.75	0.72	0.74	0.69	0.79	0.76	0.71	0.74	0.62	0.78	0.73	0.66	0.70	0.63	0.64	0.62	0.61	0.63
Rat 2	0.60	0.13	0.98	0.46	0.18	0.90	0.23	0.97	0.47	0.28	0.90	0.26	0.97	0.50	0.32	0.91	0.31	0.92	0.29	0.28	0.86
Rat 3	0.88	0.72	0.62	0.67	0.68	0.67	0.76	0.60	0.67	0.70	0.68	0.76	0.65	0.70	0.72	0.70	0.66	0.63	0.66	0.65	0.65
Rat 4	0.78	0.81	0.80	0.79	0.79	0.80	0.81	0.80	0.79	0.80	0.81	0.86	0.84	0.83	0.84	0.85	0.75	0.76	0.74	0.75	0.76
Rat 5	0.91	0.89	0.59	0.81	0.85	0.79	0.89	0.59	0.81	0.85	0.79	0.87	0.59	0.81	0.83	0.77	0.77	0.56	0.78	0.78	0.70
Rat 6	0.94	0.78	0.79	0.80	0.78	0.78	0.77	0.81	0.81	0.79	0.79	0.72	0.79	0.79	0.75	0.76	0.69	0.68	0.70	0.69	0.69
Rat 7	0.97	0.75	0.70	0.73	0.74	0.73	0.75	0.70	0.73	0.74	0.73	0.73	0.76	0.76	0.74	0.74	0.66	0.65	0.67	0.66	0.65
Rat 8	0.92	0.60	0.78	0.68	0.63	0.70	0.58	0.79	0.68	0.62	0.70	0.51	0.74	0.60	0.55	0.64	0.53	0.63	0.53	0.52	0.59
Rat 9	0.83	0.77	0.93	0.83	0.80	0.88	0.77	0.94	0.85	0.81	0.89	0.74	0.93	0.83	0.78	0.87	0.69	0.85	0.68	0.68	0.80
Rat 10	0.93	0.75	0.37	0.63	0.68	0.59	0.76	0.37	0.63	0.68	0.59	0.63	0.47	0.63	0.62	0.56	0.62	0.49	0.63	0.62	0.56
All Rats	—	0.69	0.73	0.71	0.68	0.76	0.70	0.73	0.72	0.70	0.76	0.67	0.75	0.72	0.68	0.75	0.63	0.68	0.63	0.62	0.69

Table 4.2

Performance metric comparisons among 7 supervised learning algorithms and the Bayesian Network. Results for Bayesian Network algorithm transferred from the results of Chapter 3. Some of the Bayesian model's metrics are marked with bold when this model was one of the top three best performing algorithm in terms of boldfaced metric.

	SVM						NaiveBayes					ANN					Bayesian Network				
	A'	Sens	Spec	Prec	F1	Acc	Sens	Spec	Prec	F1	Acc	Sens	Spec	Prec	F1	Acc	Sens	Spec	Prec	F1	Acc
Rat 1	0.60	0.64	0.83	0.79	0.70	0.74	0.63	0.76	0.71	0.66	0.69	0.52	0.56	0.53	0.49	0.53	0.67	0.79	0.75	0.71	0.73
Rat 2	0.60	0.00	1.00	NaN	0.00	0.91	0.70	0.82	0.28	0.39	0.81	0.02	1.00	0.24	0.02	0.91	0.04	1.00	0.50	0.08	0.91
Rat 3	0.88	0.89	0.57	0.69	0.77	0.73	0.86	0.53	0.66	0.74	0.70	0.76	0.59	0.67	0.70	0.67	0.72	0.60	0.66	0.69	0.67
Rat 4	0.78	0.90	0.83	0.83	0.86	0.87	0.67	0.76	0.72	0.69	0.72	0.52	0.80	0.69	0.51	0.67	0.81	0.75	0.75	0.78	0.78
Rat 5	0.91	0.91	0.56	0.81	0.86	0.80	0.81	0.61	0.81	0.81	0.74	0.96	0.10	0.69	0.79	0.67	0.96	0.24	0.72	0.82	0.72
Rat 6	0.94	0.80	0.78	0.79	0.79	0.79	0.73	0.81	0.81	0.76	0.77	0.72	0.54	0.66	0.64	0.63	0.59	0.66	0.65	0.62	0.62
Rat 7	0.97	0.79	0.79	0.80	0.79	0.79	0.71	0.73	0.74	0.72	0.72	0.78	0.61	0.69	0.72	0.70	0.69	0.54	0.61	0.65	0.62
Rat 8	0.92	0.57	0.78	0.66	0.60	0.68	0.51	0.78	0.64	0.56	0.66	0.29	0.81	0.51	0.31	0.58	0.16	0.89	0.53	0.25	0.57
Rat 9	0.83	0.77	0.94	0.86	0.81	0.89	0.74	0.92	0.81	0.77	0.86	0.46	0.93	0.72	0.46	0.78	0.65	0.96	0.89	0.75	0.86
Rat 10	0.93	0.91	0.16	0.60	0.72	0.59	0.81	0.32	0.62	0.70	0.60	0.89	0.13	0.59	0.70	0.57	0.94	0.12	0.60	0.73	0.60
All Rats	—	0.72	0.73	0.76	0.69	0.78	0.72	0.70	0.68	0.68	0.73	0.59	0.61	0.60	0.53	0.67	0.71	0.76	0.69	0.70	0.74

Bayesian Network model (sensitivity=.71, specificity=.76, precision=.69, F1=.70, accuracy=.74). In individual subject comparisons, it was observed that classification performance somewhat depends on the animal's psychophysical performance. The Bayesian network model was more suitable for rats with lower detectability indices ($A' < .92$). Linear Discr. Analysis, Logistic Regression and SVM were better predicting responses of animals with higher A' scores. These algorithms were amongst the top three performing for most of the rats.

4.4 Discussion

Different types of machine learning algorithms confront us with a trade-off between their memory consumption and execution performances within shorter timescales. Regarding the limitations lying on the neural interfaces, the better performing algorithms should be selected based on the shortage of memory and storage as well as the agile classification results from the executing algorithm in real-time. The feature set size together with the whole data set size in design matrix will affect the execution process of each algorithm.

Classification algorithms are built on top of principles of neurophysiological processes and thus computational agents feedback the neuroscientific knowledge background to disclose the hidden mechanisms ongoing on the level of biological agents. There is a vast body of literature using these algorithms to crack the neural code [279–285, 293, 295]. However, the techniques inherently comprising the building blocks of the neurological processes, like stochasticity during the information transfer among neuronal populations, deserve more attention than other empirical solutions. Here, we focused on a probabilistic model, a Bayesian Network model, to explain the animal behavior during a decision-making task, by shaping the model structure according to given task variables.

Although this is a preliminary study, we found that the Bayesian network has prominent read-out performances of neural populations during the yes/no detection task among other supervised techniques. It is among the first three best performing algorithms whenever rats behaving with low behavioral scores. This finding indicates

the strength of the Bayesian Network algorithm, which intrinsically executes and learns the rules based on probabilistic inference with the given task-related information flow. Although the graphical model of the algorithm is built depending on the task structure, which may give an advantageous position to this specific algorithm, this result may uncover the importance of the effectiveness of custom algorithms over the commonly used ones. Neural activity of the animals with lower psychophysical scores may represent a more uncertain feature space with smoothed out distributions, from which more difficult to reach a certain decision. Under these circumstances, the Bayesian Network algorithm is good at representing the cortical states of the animal and thus this model is as powerful as being among the three best-performing models.

4.5 Conclusion

The prediction performances of the eight supervised algorithms (seven commonly used and one novel Bayesian Network implementation) are compared for a perceptual decision-making task of rats using the mean firing rates as the feature set. High inter-subject variance yielded moderate classification performance regardless of the algorithm used. The Bayesian network model have high prediction scores as the first three best performing algorithms for low-performing rats, which have lower average detectability indices. Since having lower detectability scores may refer to more uncertain cortical state, the proficiency of the Bayesian Network model is obvious whenever statistical inference is needed. Lower psychophysical performance refers to the learning and adaptation period of patients for neural prostheses. This method promises future utilization of the neuroprostheses in terms of allowing better performance for patients during the training and rehabilitation periods. These results have also demonstrated the increment in performance for the personalized and task-related model implementations among other commonly used well-known BCI algorithms.

5. PERFORMANCE COMPARISONS BETWEEN RATS AND INCREMENTAL BAYESIAN MODELS BASED ON AVERAGE FIRING RATES OF SENSORIMOTOR CORTICAL NEURONS

5.1 Introduction

Perception of any living being is modulated continuously by bottom-up and top-down mechanisms of attentional processing [296]. External stimuli from the physical world represent a bottom-up mechanism, which corresponds to likelihood distribution in the Bayesian framework. Modulations via cortical cholinergic inputs based on previous experience or knowledge refer to a top-down mechanism, which is -in Bayesian terms- prior distribution. All types of sensory observations together with the outputs of the current step would be the prior information for the posterior distribution of the next step, which describes the Bayes filter. In Chapter 3, the Bayesian framework is discussed broadly and the Bayesian model is scrutinized in terms of how the decision is affected by the momentary neuronal sensory neuronal response. In this chapter, we will not only be focusing on the effect of current sensory response but also many variables that have sensory and nonsensory influences on choice. Thus, the investigations of how the decision-making process is affected by those variables within the prior distribution would be broadened to encapsulate previous features, like sensory input and motor output related parameters.

Skill learning includes interpretation of physical facts and internalization of the procedures needed to perform the skill [297]. After the steps of the procedures are uncovered, consolidation of the skilled memory is guaranteed via generalization, discrimination, and strengthening. History-dependent variables (win-stay/lose-switch or perseverance) are used to generalize the rules of the physical world and develop new adaptive behavioral strategies [298–301]. Not only the current trial’s stimulus but also history terms depending on the outcomes of the previous trials, like reward expectation, confi-

dence level, and choice, have an influence on current trial choice [302–305]. The history-dependent internal bias and prior expectations are also other factors that change the behaviors during a decision-making task [306,307]. These behavioral features are modeled response-by-response to prove the effectiveness of the previous choices on the current choice [297,308–310]. Subjective and objective reward values are also found to be efficacious on visual processing and choice [311].

However, Akrami et al. [312] state that previous sensory history has a stronger effect on behavior than the preceding choice/outcome variables. Prior sensory stimulus information is well represented in the posterior parietal cortex (PPC). They switched off the PPC neurons using optogenetic silencing to observe how prior information is disrupted. PPC neurons had significant information about the stimuli of previous trials and their silencing significantly reduced the regression weights of sensory-history features. Recent or longer history effects are studied to better observe how weights are changing for task-related or irrelevant variables [313,314]. To better understand the task learning effects, Roy et al. [314] modeled a dynamic logistic regression to reveal the evolution of weights for a behavioral feature set during task learning. Besides having the dependencies on the stimulus, choice history, and internal bias in early training, those unbalanced weights disappeared in the course of training, and weights of the binary stimulus were balanced accordingly, which showed learning and evolving psychophysical strategy. The only significant weight was for the stimulus of the previous trial. In agreement with the previous studies, but bringing a new point of view, Jiang et al. [315] tried different stimulus strengths and showed their effect on the current choice together with the trial history variables. They presented that, at a lower contrast level of a visual stimulus, previous choices and task outcomes had more effect on the current choice. Whereas, when the stimulus was higher, trial history variables had less influence on the current choice.

Learning processes are studied in great detail by stochastic [316–318] or linear-nonlinear models to predict animal’s behavior together with the suboptimal choices they made [319–322]. Simpler models explain the action and behavior based on synaptic connectivity, reinforcement effects [323–326], or in terms of melioration principle (i.e., the decision is made towards a higher throughput in each trial) [327–329]. More advanced ones [300,308,317,319,330–333] disclosed that how each specific task-related

and subjective features, like stimulus history, choice, outcome, reward expectation, have observable influences on the instant choice of the animal. Even though outcome-driven decision-making is led by the goal-directed system [334–336], and stimulus-driven choice is directed by the habit-system [337–339], it is still hard to predict what will be the action of the animal and there remains the need to include more features, like neural activity history, into the model.

History-dependent behavioral and subjective variables were examined very well in plenty of studies discussed above. However, few studies included neuronal activity in the feature set to decode the individual’s action selection. The time integration effect on learning and adaptive behavioral strategies on choice would be explained better when we included internal neuronal representations of the task-related and irrelevant parameters. To our knowledge, there is no study encapsulating preceding neuronal activity features together with the related previous choice, outcome, stimulus, to predict the current trial’s outcome over a long period of time in a Bayesian manner.

In this study, we scrutinize different aspects of the task-related variables, which are stimulus presence and the last three previous choices of animal, by jointly combining them with neural activity to accommodate the incremental information to develop new Bayesian network models. These variables are combined in a manner of behaviorally relevant way regarding the decision-making task. In Chapter 3, the proposed Bayesian Network model is built by joining neural activity and stimulus presence in the current trial to predict the instant choice of the animal. Here, the incremental Bayesian model recruits not only neural firing rate and stimulus parameter but also three preceding responses of the animal. Additionally, former Bayesian Network model is fitted to all the data. Now, in this regime, we allow the data to choose the best model, which generalizes well the decision-making process with respect to given parameters. Thus, we aim to decipher the best combination of independent variables with their weights predicted that explains the behavior of the animal. This study investigates how psychophysical sensitivity and bias of the model improves when the neural activity is introduced as a feature. The prominent effects of the average firing rate feature among other features on the behavioral performance of the model are assessed using nonparametric sensitivity indices. Furthermore, we reveal how sensorimotor activity -even it is a coarse representation like average firing rate- intrinsically has the decision-making rules and

will allow us to transfer these rules from the animal brain to the in silico brain in near future. Some preliminary data and results are presented in [340].

5.2 Materials and Methods

5.2.1 Animals

Same spiking activity data from 10 Wistar rats in Section 3.2.1 were used in this study. All rats were treated following the guidelines of the Boğaziçi University Institutional Ethics Committee for the Local Use of Animals in Experiments.

5.2.2 Apparatus

The same workflow described in Section 3.2.2 to Section 3.2.6 is used for this study. After spike sorting was performed, average firing rates for each sorted pseudo-unit of rats and their corresponding behavioral choices for each trial were prepared as the design matrix for the new incremental Bayesian models here.

5.2.3 Data and preprocessing

The number of features is predefined based on the hypothesis that time-dependent task variables influence the current trial's outcome. The average firing rates ($f(t)$) in the form of the 2D vector ($[n \times 1]$) are inherited from the Bayesian model described in Chapter 3. n is the maximum number of units for each rat after spike sorting is executed. If some of the days reveal fewer units, these absent data are marked with a masking value and ignored by the model accordingly. The number of units (n) ranged from 24 to 44 with $\mu=35.1$ with $\sigma=6.3$. All the animals have 16 channel microwire arrays except one which has 32-channel electrodes. For 351 units and 176 microwires,

there were 2 units on the average for each channel. In this manner, design matrix has columns for the maximum number of units ($\mu=35.1$), for the last three responses ($r(t-1)$, $r(t-2)$ and $r(t-3)$) and for the stimulus condition ($s(t)$) that corresponds to 39 features on the average.

5.2.4 Software

The fundamental running gear of this study is the probabilistic programming (PyMC3) library [341], which is a Python package that provides Bayesian statistical inference and probabilistic machine learning. This library has plenty of stochastic model implementations that one needs during the development and implementation of incremental Bayesian models. 12 different types of incremental Bayesian models were implemented in Python (version 3.8.2) using the PyMC3 library (version 3.9.3) and fitted using No-U-turn (NUTS) sampler [342]. The required dependencies are Theano (version 1.0.5), NumPy (version 1.19.4), SciPy (version 1.5.4), Pandas (version 1.0.3), Matplotlib (version 3.3.2) and Graphviz (version 0.14.2). All the required software was developed in the PyCharm Professional Integrated Development Environment (IDE) version 2020.2.5.

5.2.5 Incremental Bayesian Models

Since we predicted the binary response of the animal ($r(t)$), every individual trial represented as a Bernoulli trial:

$$r(t) = \begin{cases} 1 & \text{if } g(x|p) \geq 0.5 \\ 0 & \text{if } g(x|p) < 0.5 \end{cases} \quad \begin{matrix} \text{where } g(x|p) = p^x(1-p)^{1-x} \\ x = [0, 1] \text{ for left/right response} \end{matrix} \quad (5.1)$$

p is the probability of pressing the right lever for a given trial t with a sigmoid function, given that;

$$p(t) = \frac{1}{1 + e^{-z(t)}} \quad z(t) = b_0 + \sum_{i=1}^3 b_i r(t-i) + b_s s(t) + \mathbf{b_F} \mathbf{f(t)} \quad (5.2)$$

where b_0 is the intercept, b_1, b_2, b_3 are the weights for the previous trial outcomes ($r(t-i)$ in $[0,1]$ for left/right correspondingly). b_s is the weight for the stimulus condition ($s(t)$ in $[0,1]$ for stimulus-off and stimulus-on) of the current trial. Vector forms are marked as bold in the formula in which $\mathbf{b_F}$ and $\mathbf{f(t)}$ are vectors in the form of $[1 \times n]$ and $[n \times 1]$. n is the number of units assigned in the preprocessing step that is 35 units in general. In this manner, the incremental Bayesian model has parameters that are normally distributed as priors:

$$\begin{aligned} b_0 &\sim \mathcal{N}(0, 10) && : \textit{intercept} \\ b_1 &\sim \mathcal{N}(0, 10) && : \textit{weight for } r(t-1) \\ b_2 &\sim \mathcal{N}(0, 10) && : \textit{weight for } r(t-2) \\ b_3 &\sim \mathcal{N}(0, 10) && : \textit{weight for } r(t-3) \\ b_s &\sim \mathcal{N}(0, 10) && : \textit{weight for } s(t) \\ \mathbf{b_F} &\sim \mathcal{N}(0, 10)[1 \times n] && : \textit{weight for } \mathbf{f(t)} \end{aligned} \quad (5.3)$$

and 39 features ($\mathbf{f(t)}$, $s(t)$, $r(t-1)$, $r(t-2)$ and $r(t-3)$) in total. Those features and prior distributions are represented in an incremental Bayesian form in Figure 5.1.

For each and every component (A, B, C, X, Y) of this graphical representation, a reasonable combination is run to generate 12 different incremental models with given feature sets below:

These combinations of models are mainly focused on having stimulus (X) and firing rate (Y) parameters. Later, they have also included various combinations of previous responses (A, B, C) accordingly. These combinations of components were relevant with the task variables and suitable for the dynamics of the operant conditioning. These 12 different models were sampled to generate posterior distributions of current response ($r(t)$) using PyMC3 library with predefined parameters ($tune=2000$,

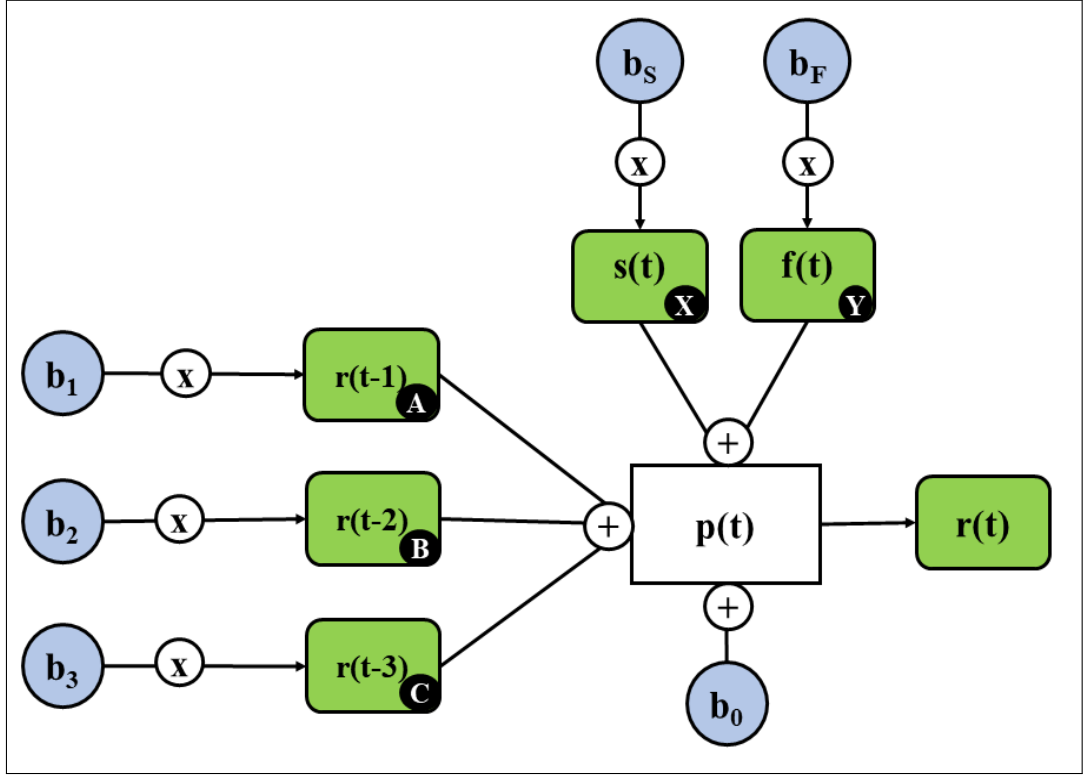


Figure 5.1 Incremental Bayesian Model.

chains=2, target_accept=0.95, cores=1). The data set for each rat was divided into 70% training and 30% test sets. All 12 Bayesian incremental models were run separately for each rat.

A non-parametric sensitivity index (A') and bias index (B'') [219, 262] were used to compare model performances with psychophysical data.

$$A' = 0.5 + \frac{(p(h) - p(f))(1 + p(h) - p(f))}{4p(h)(1 - p(f))} \quad (5.4)$$

$$B'' = \frac{p(h)(1 - p(h)) - p(f)(1 - p(f))}{p(h)(1 - p(h)) + p(f)(1 - p(f))}$$

After all A' and B'' scores for models were calculated, these values were compared with rat scores using paired t-tests.

Table 5.1
12 incremental Bayesian models and their corresponding feature sets.

Model #	Abbreviation	Feature Set
1	X	stimulus condition (stimulus equals 0/1 for stimulus-off/stimulus-on)
2	XA	stimulus condition and 1 previous response (response equals 0/1 for left/right)
3	XAB	stimulus condition and 2 previous responses
4	XABC	stimulus condition and 3 previous responses
5	XY	stimulus condition and mean firing rates of all units
6	Y	mean firing rates of all units
7	YA	mean firing rates of all units and 1 previous response
8	YAB	mean firing rates of all units and 2 previous responses
9	YABC	mean firing rates of all units and 3 previous responses
10	XYA	stimulus condition, mean firing rates and 1 previous response
11	XYAB	stimulus condition, mean firing rates and 2 previous responses
12	XYABC	stimulus condition, mean firing rates and 3 previous responses

5.3 Results

The flexibility PyMC3 provides us to generate 12 different incremental models using a combination of 39 behavioral and neural features together. As mentioned earlier, we will try to reveal the significance of the features on top of each other and expect to observe how neural activity information - even it is a coarse representation like average firing rate- will transfer the decision-making rules from the animal brain to the *in silico* brain.

After all 12 models were performed, their hit rates ($p(h)$) and false alarm rates ($p(f)$) were calculated as if the model was behaving in the chamber to draw an analogy between the biological brain and in silico brain.

The nonparametric performance index (A') and bias (B'') were calculated using these $p(h)$ and $p(f)$. Table 5.2 gives the detailed information to compare A' scores for each rat and each incremental model. Primitive models as X, XA, and XAB (see Table 5.2) had high A' scores but high biases as well.

From model XABC till the model XYABC, there was no significant difference between A' scores of the rats and their corresponding model A' scores (paired t-tests: $p's > 0.1$). The last row of Table 5.2 shows how the bias term started with high values when compared to the rats' biases. To begin with, XA and XAB models was a good

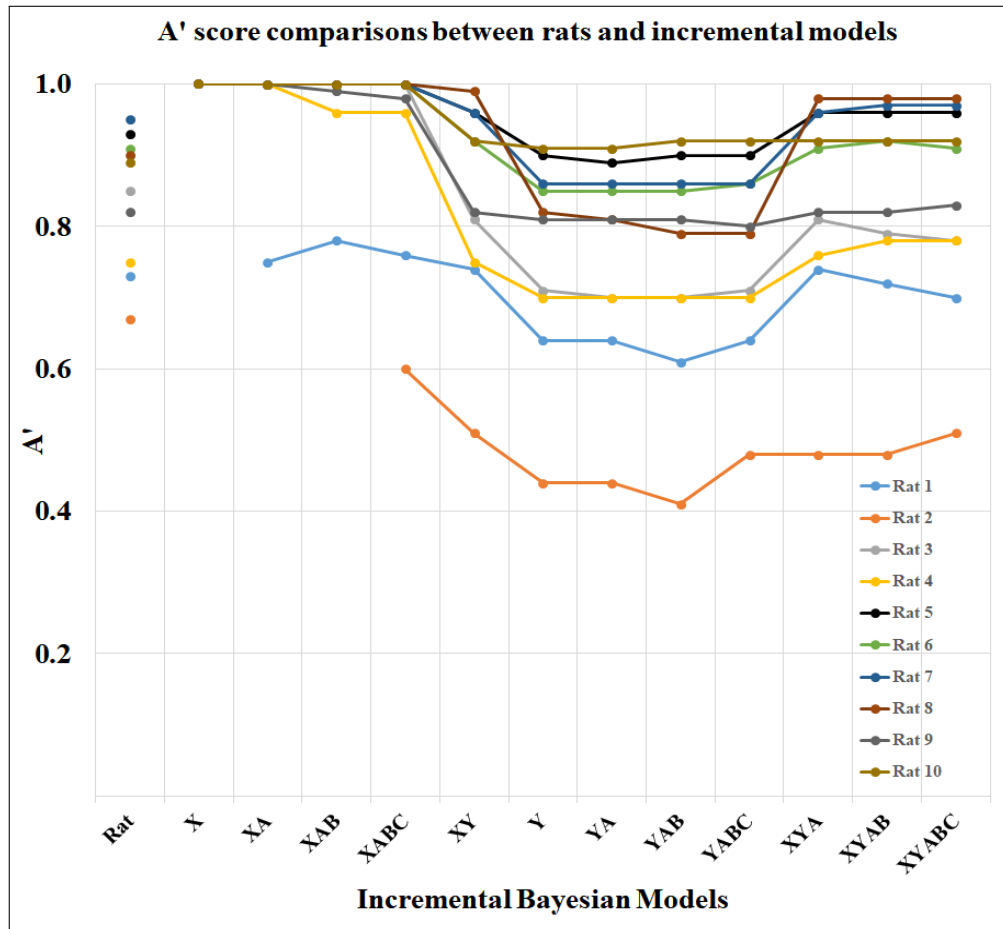


Figure 5.2 A' comparisons for rats and incremental model when these models are trained with the specific rat's data.

step to see how biased these models were in the light of only stimulus condition and previous choice information. It is quite similar to binomial distribution observations starting with a couple of Bernoulli trials (i.e. coin toss). Those Bernoulli trials start with a very high biased state, be dependent on the first couple of observations. Then, it evolves to a more unbiased state in time. When the XABC model was introduced, the bias score also began decreasing, which is expected (see Figure 5.3). This result suggests that the involvement of more previous choices would relieve the models from those biased states even more. There was a substantial decrease in the bias whenever we include the firing rate component (Y). Even if we excluded 3 previous choices from the model, it still performed better (see XABC and XY in Figure 5.3). From model XY to XYABC, there was no significant difference between the bias indices of the rats and the models (paired t-tests: p 's > 0.2). Thus, models started performing better and

closer to rats in this perceptual decision-making task whenever they had a prominent feature set like average firing rates, of which process began with the inclusion of the Y component in the model. It may seem contradictory to say better although A' value starts to decrease in Figure 5.2 or Figure 5.3. However, we take into consideration A' and B'' together for the performance evaluation. There was always the trade-off for having lower bias comes together with lower A' values, which was quite acceptable. A very high A' value always conceals high B'' in itself. In this manner, we qualitatively defined an 'optimum zone' in Figure 5.3 to assess the selected incremental in silico models performed equivalently to the rat models.

To summarize, incremental Bayesian models using feature sets based on av-

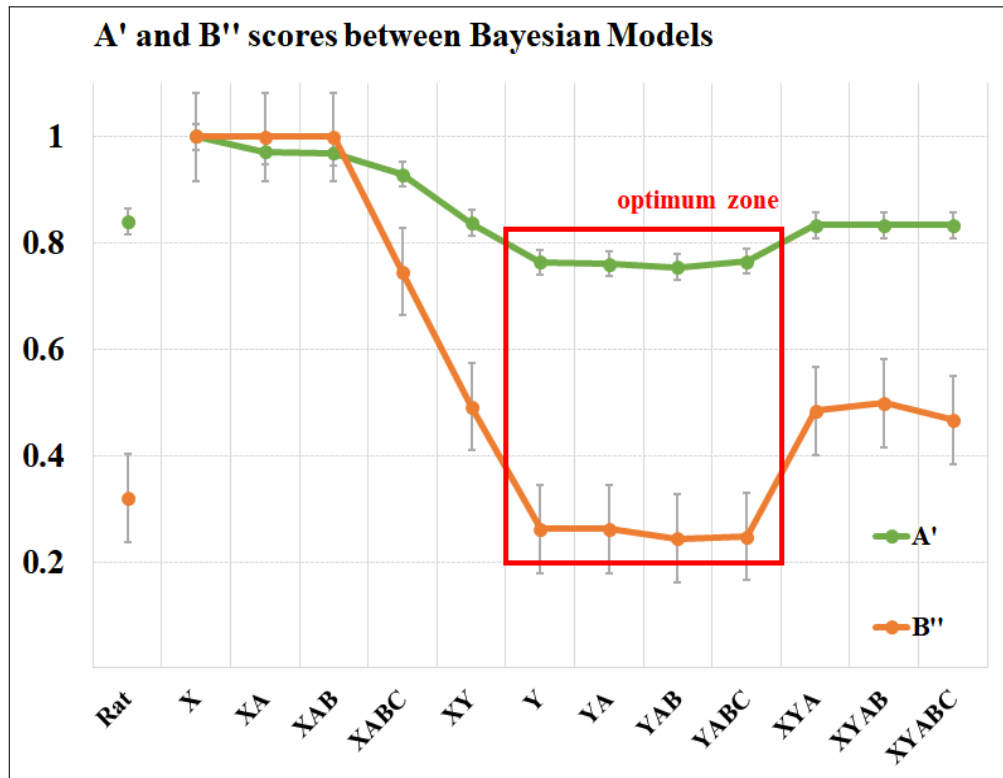


Figure 5.3 Mean A prime and bias comparisons for rats and incremental model when these models are trained with the specific rat's data

erage firing rates from a population of cortical neurons seem to be adequate to yield the psychophysical performance in a yes/no detection task. In addition, whenever the current stimulus condition (X) was again introduced into the models after the optimum zone (XYA, XYAB, XYABC), the bias values were also started to increase with small increments in the A' as well. This means stimulus existence brings bias into the

Table 5.2

Comparison of A' scores (a non-parametric sensitivity index) achieved by rats and Bayesian models. The model A' scores marked with bold are higher than or equal to the A' score of the rat.

Behavioral A' Scores		A' Scores for incremental Bayesian models											
	Rats	X	XA	XAB	XABC	XY	Y	YA	YAB	YABC	XYA	XYAB	XYABC
Rat 1	0.73	NaN	0.75	0.78	0.76	0.74	0.64	0.64	0.61	0.64	0.74	0.72	0.70
Rat 2	0.67	NaN	NaN	NaN	0.60	0.51	0.44	0.44	0.41	0.48	0.48	0.48	0.51
Rat 3	0.85	1.00	1.00	1.00	1.00	0.81	0.71	0.70	0.70	0.71	0.81	0.79	0.78
Rat 4	0.75	1.00	1.00	0.96	0.96	0.75	0.70	0.70	0.70	0.70	0.76	0.78	0.78
Rat 5	0.93	1.00	1.00	1.00	1.00	0.96	0.90	0.89	0.90	0.90	0.96	0.96	0.96
Rat 6	0.91	1.00	1.00	1.00	1.00	0.92	0.85	0.85	0.85	0.86	0.91	0.92	0.91
Rat 7	0.95	1.00	1.00	1.00	1.00	0.96	0.86	0.86	0.86	0.86	0.96	0.97	0.97
Rat 8	0.90	1.00	1.00	1.00	1.00	0.99	0.82	0.81	0.79	0.79	0.98	0.98	0.98
Rat 9	0.82	1.00	1.00	0.99	0.98	0.82	0.81	0.81	0.81	0.80	0.82	0.82	0.83
Rat 10	0.89	1.00	1.00	1.00	1.00	0.92	0.91	0.91	0.92	0.92	0.92	0.92	0.92
Mean A'	0.84	1.00	0.97	0.97	0.93	0.84	0.76	0.76	0.76	0.77	0.83	0.83	0.83
Mean B''	0.32	1.00	1.00	1.00	0.75	0.49	0.26	0.26	0.24	0.25	0.48	0.50	0.47

medium that is quite reasonable since the task itself is a yes/no detection task.

Our results were consistent with the previous literature [314] in terms of behavioral features. The incorporation of the previous choices seemed to be balanced in time with decreasing bias values. However, it is evident from the results that the mean spike rate had the highest influence over other behavioral features. When there was no firing rate component in the model, it was obvious to see the effect of adding a third previous response (from XAB to XABC). However, when the model had already the firing rate component (Y), the addition of the all three behavioral response parameters (A, B, and C) had no significant effect than the previous ones (from Y, YA, YAB to YABC). These results seemed to indicate the mean firing rate is an important part of the feature set for the prediction models. However, this work presents only a preliminary attempt to the inclusion of neuronal activity into the model's feature set blending with behavioral features. The feature set will be extended to include the firing rates from previous trials, of which alternatives will be scrutinized in Section 5.4.

5.4 Discussion

The previous study in Chapter 3 has documented the effectiveness of Bayesian statistics on predicting the instant responses of the animal based on the neural activity and stimulus distribution during the perceptual decision-making task. This was kind of a baseline study. We kept on investigating furthermore about the prediction parameters. There are plenty of studies in the literature that utilize history terms of the behavioral task to predict the future outcomes. From one aspect, they focus on prior choices, confidence level, and reward expectation to predict upcoming choices of the animal [298–304]. From another one, stimulus condition and its strength attract more attention than previous choices and other subjective variables [312–315]. Few studies are focusing on neuronal activity data for prediction. However, history effects of spiking activity and how its low-dimensional components influence future decisions together with the preceding task parameters have not been focused on yet. Here, we built a novel incremental Bayesian models on top of the Bayesian Network model in Chapter 3 that is equivalent to XY model here in terms of feature set despite having

disparities in implementation details.

In this preliminary study, our findings indicate that there is a higher influence of current sensorimotor activity on the decision than other task-related parameters as previous choices or stimuli. Although we have only been able to cover the preliminary steps, to our knowledge, this is the first study that blends the neuronal firing rate with the history-dependent task-related parameters. Since neural coding mechanisms are still under investigation and we still do not know how the details of physical world stimuli are represented in neural activity, it is reasonable to add neural activity as a feature of the model in case of we miss some of the most important components that lead to the decision. However, there are some limitations worth noting. Whenever we accept preceding trials' neural data, the dimensions of the data will also expand. Instead of using all dimensions, the best practice is usually to extract the principle components that explain the variance best and utilize these dimensions as a feature set for that neural data. An alternative solution would be to use time-dependent firing rate. This will bring a more detailed version of the spike rate feature. General practice for time-dependent firing rate is to divide the recording duration into chunks so that it will be more informative than the average firing rate. In this form, models will have better feature sets.

Further study will be conducted to include stimulus conditions of the previous trials as well as spike rates of preceding trials. The short-term and long-term effects of these features will be examined in detail on the prediction performance of the models. Behavioral states (hit/miss/correct rejection/false alarm) will also be considered in terms of the prediction performances.

5.5 Conclusion

In this part of the study, we focus on plenty amount of feature sets of the Bayesian prediction model and scrutinize their effectiveness and influence per se on the decision-making processes in a forced-choice yes/no detection task. These features are compared within each other qualitatively. It is shown that firing rate carries invaluable information about the decision on top of other task-related parameters. The main goal

of this study is to reveal the best combination of personalized and task-specific feature set for brain-machine interfaces running on neuroprosthetic devices, which are expected to run in real-time with agile manipulations and instant decisions of the algorithm to perform as close as the biological agents of the patients. The incremental models, although they still need to be advanced, promise to return the prominent parameters for a decision-making task.

6. GENERAL CONCLUSIONS AND FUTURE WORKS

In this thesis, we introduced neural decoding models based on the sensorimotor neural representations of animals to explain the motor output in a perceptual decision-making task. The main contributions of this study are mainly related with the probabilistic models we developed. The Bayesian Network Model (Chapter 3), which is our implementation in the context of neural activity and task parameters, provided unique perspectives to interpret the motor responds of animals depending on their psychophysical performances. The incremental Bayesian model (Chapter 5) demonstrated how neural activity introduces a new level of knowledge base into the model regarding the psychophysical sensitivity and bias among other task related parameters. In Chapter 2, we recruited a neural encoding model (the psychophysical correspondence function) [215] to elicit similar sensations with the mechanical vibrotactile stimulation by electrically stimulating the rat sensorimotor cortex. A novel tactile neuroprosthesis system comprising a pair of isolated boots and a tactile sensor relayed the tactile information to the sensorimotor cortex during the yes/no detection task. The psychophysical performance of rats were higher than the case when the neuroprosthesis was switched off. The sensitivity scores of the case when the prosthesis was switched on reached to the level of natural stimulation for some cases. To our knowledge, this is the first study for a tactile neuroprosthesis in rats that elicits equivalent natural tactile sensation without the need for an injury model.

Successful demonstration of neural encoding model paved the way towards neural decoding models for us to implement. A novel Bayesian Network model (Chapter 3) provided new insights into neural representations of the perceptual decision-making and predicted the psychophysical performance of rats in a yes/no detection task. This study supports the Bayesian Brain Hypothesis (BBH) at the behavioral and neuronal level (refers to Marr’s computational and representational (or algorithmic) levels; see Section 1.3.3). The first step revealed stimulus distribution given the sensory-elicited neural data using Bayes’ theorem. This adaptive implementation of the stimulus component of the model would be such an invaluable contribution for the future BCI design

since neural activity during behavior was always prone to modulation and this interface will be a better communication port. At the second step, motor output is inferred using logistic regression by sampling and estimating the parameter distributions. Thus, we circumvented a Bayesian Network Model that predicts the behavioral response of the animal in a yes/no detection task based on sensorimotor single/multi-unit recordings. The noisy pattern of the cortical activity of behaving rats inherently comprise echoes of their mental representations of decisions. The results of this model indicated that the behavioral output of the low-performing rats was more predictable than high-performing rats using Bayesian inference. This novel finding was interpreted in terms of training and rehabilitation periods of neuroprosthetic usage and could lead to a better adaptation periods and embodiment for the patients. Besides, task-related implementation of the Bayesian Network offers an understanding of the external and internal representations during the skill work. Our study provides a framework for future studies to develop new intelligent BCI algorithms.

Further studies were conducted to compare the Bayesian Network with commonly used seven different supervised machine learning techniques (Chapter 4). A plenty of probabilistic (Linear Discriminant Analysis, Naive Bayes) and non-probabilistic (KNN, Decision trees, SVM, ANN) models were compared with our new model, which comprised a task-related design. This comparative study proved that the Bayesian model was one of the best three algorithms when the subject was low-performing. Specifically, low-performing rats were better predicted with this novel implementation of Bayesian Network model, which could yield high prediction performance for the model during adaptation periods and rehabilitation phases of patients using BCIs. These results have shown that, personalized BCI algorithms based on the specific task parameters can be developed with as powerful prediction scores as the well-known commonly used other machine learning algorithms.

The Bayesian model implementation has been further improved with additional task-related design using probabilistic programming. This novel incremental design additionally comprises history-dependent previous choices that may affect the current choice of the animal (Chapter 5). The neuronal firing rate feature has been the most effective on the other behavioral task parameters; such as previous responses, stimulus existence. Further development will include different types of history-dependent task-

related and subjective parameters, such as internal bias, the expectation of stimulus, or reward expectation. In this way, we have shown that it is possible to read out the motor intention of rats with adequate and relevant feature set during a behavioral yes/no detection task. Therefore, it is possible to reach the best combination of personalized task-related feature set for brain-computer interfaces running on neuroprosthetic devices to decode the motor intention of patients in the near future.

APPENDIX A. Supplementary Figures and Tables

A.1 Chapter 2 Supplementary Figures and Tables

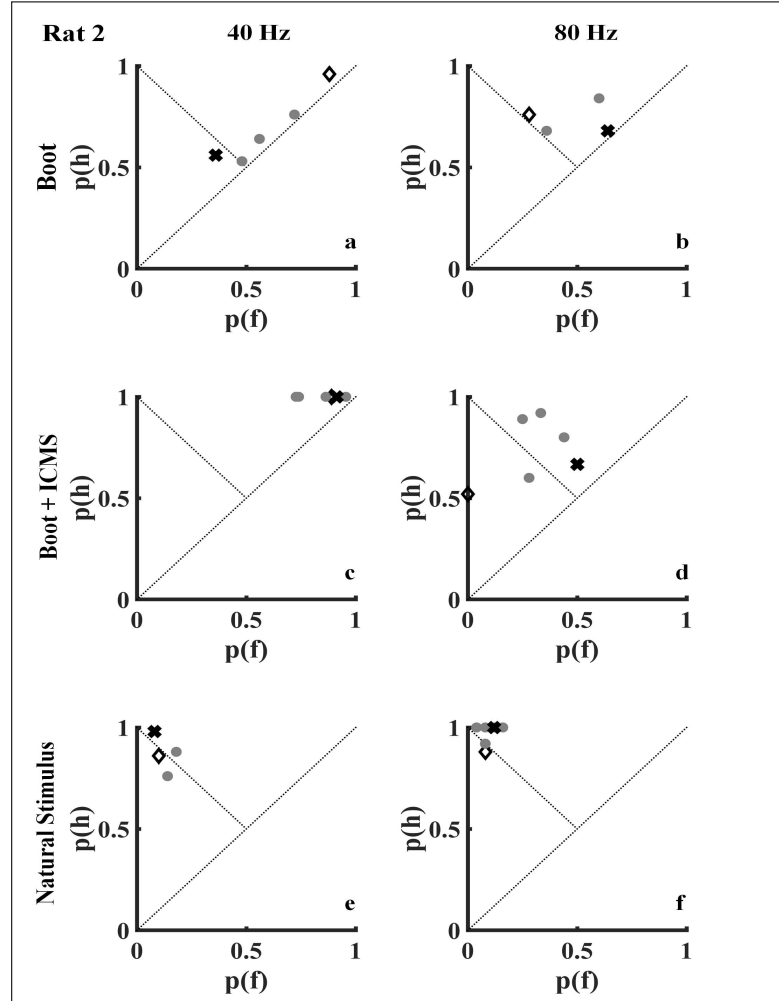


Figure A.1 Receiver operating characteristic (ROC) plots for Rat 2 in (a, b) boot only (Experiment I) and (c, d) boot+ICMS (Experiment II) conditions at one vibrotactile intensity level for a given frequency (39 dB ref. $1 \mu\text{m}$ for 40 Hz; 32 dB ref. $1 \mu\text{m}$ for 80 Hz). The remaining data obtained at different vibrotactile intensity levels are similar to ones shown. (e, f) Previous results [215] of a natural stimulus (corresponding intensities, but applied on the skin) are also given for comparison. Diamond and cross symbols refer to the initial and final sessions, respectively. Intermediate sessions are depicted by filled circles.

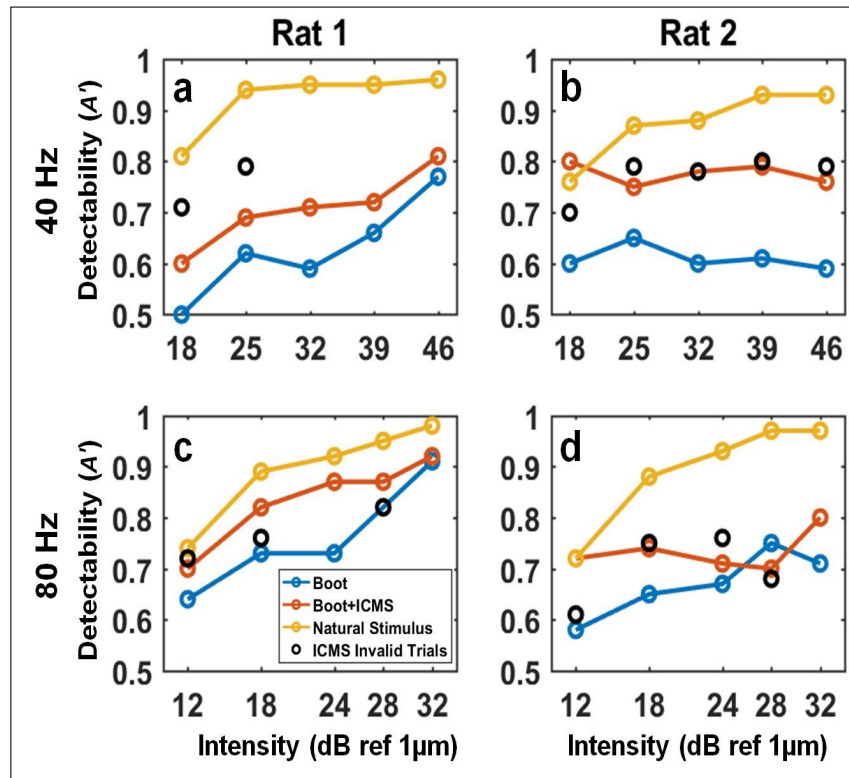


Figure A.2 Detectability (A') plots for both rats at the tested vibrotactile frequencies (40 and 80 Hz). The data points are from the lower rows of Table A.1 (blue curves: boot only condition, red curves: boot+ICMS condition), previous data regarding natural stimulation (yellow curves; [215]), and from the lower rows of Table A.2 regarding invalid trials (black open circles). Invalid trials (see text) were interpreted based on a hypothesized ICMS detection. Overall results indicate that the tactile neuroprosthesis improves vibrotactile detection when the boots are on.

Table A.1

Psychophysical Test Results of the Tactile Neuroprosthesis. Trial counts show pooled sessions for a given intensity. Average A' shows the mean detectability across sessions. Session A' values were calculated according to Eq. 2.1 in the main text. Sessions with only practically meaningful A' values (nonzero denominator and >0.5) were included in the average.

Rat 1																					
40 Hz											80 Hz										
	Boot					Boot+ICMS						Boot					Boot+ICMS				
Intensity (dB ref 1 μ m)	18	25	32	39	46	18	25	32	39	46	12	18	24	28	32	12	18	24	28	32	
Number of Hits	5	68	49	47	61	2	11	11	11	49	125	118	210	502	180	23	55	154	158	234	
Number of Stimulus-On Trials	100	275	225	175	150	7	26	26	31	68	300	300	425	650	225	73	87	212	193	294	
Number of False-Alarms	5	47	36	23	15	8	24	14	19	43	87	67	94	191	26	44	30	43	75	33	
Number of Stimulus-Off Trials	100	275	225	175	150	40	98	76	127	205	300	300	425	650	225	201	208	317	359	383	
Average A'	0.50	0.62	0.59	0.66	0.77	0.60	0.69	0.71	0.72	0.81	0.64	0.73	0.73	0.82	0.91	0.70	0.82	0.87	0.87	0.92	
Rat 2																					
40 Hz											80 Hz										
	Boot					Boot+ICMS						Boot					Boot+ICMS				
Intensity (dB ref 1 μ m)	18	25	32	39	46	18	25	32	39	46	12	18	24	28	32	12	18	24	28	32	
Number of Hits	81	87	106	83	117	27	35	45	35	46	205	138	231	272	74	14	26	32	21	89	
Number of Stimulus-On Trials	100	108	125	119	150	27	40	46	35	47	312	155	286	325	100	17	28	40	27	121	
Number of False-Alarms	72	76	94	73	104	141	122	146	110	144	179	130	179	177	47	55	108	71	76	32	
Number of Stimulus-Off Trials	100	110	125	121	150	175	163	179	130	166	308	157	289	325	100	80	128	119	104	109	
Average A'	0.60	0.65	0.60	0.61	0.59	0.80	0.75	0.78	0.79	0.76	0.58	0.65	0.67	0.75	0.71	0.72	0.74	0.71	0.70	0.80	

Table A.2

PSYCHOPHYSICAL RESPONSES FOR INVALID TRIALS (SEE TEXT) Trial counts show pooled sessions for a given intensity. Average A' (ICMS) shows the mean detectability across sessions for only invalid trials based on a hypothesized ICMS detection. Sessions with only practically meaningful A' values (nonzero denominator and >0.5) in both Table I and II were included in the average. Missing values indicate no such sessions. Session A' values were calculated according to Eq. 2.1 in the main text. Right-lever press is defined as a false alarm during a stimulus-on trial without ICMS, but as a hit in a stimulus-off trial with ICMS.

Rat 1										
Boot+ICMS (Invalid Trials)										
	40 Hz					80 Hz				
Intensity (dB ref 1 μm)	18	25	32	39	46	12	18	24	28	32
Number of right lever presses (false alarms)	9	21	7	57	120	82	62	110	187	117
Number of Stimulus-On Trials without ICMS	43	99	19	119	182	177	163	168	239	128
Number of right lever presses (hits)	5	6	1	1	8	13	6	7	24	9
Number of Stimulus-Off Trials with ICMS	10	27	6	23	45	49	42	67	77	39
Average A' (ICMS)	0.71	0.79	-	-	-	0.72	0.76	-	0.82	-

Rat 2										
Boot+ICMS (Invalid Trials)										
	40 Hz					80 Hz				
Intensity (dB ref 1 μm)	18	25	32	39	46	12	18	24	28	32
Number of right lever presses (false alarms)	139	126	166	100	80	59	100	69	73	15
Number of Stimulus-On Trials without ICMS	173	160	179	115	96	83	122	109	98	17
Number of right lever presses (hits)	18	31	42	19	22	12	20	17	14	20
Number of Stimulus-Off Trials with ICMS	25	37	46	20	23	20	22	27	21	22
Average A' (ICMS)	0.70	0.79	0.78	0.80	0.79	0.61	0.75	0.76	0.68	-

A.2 Chapter 3 Supplementary Figures and Tables

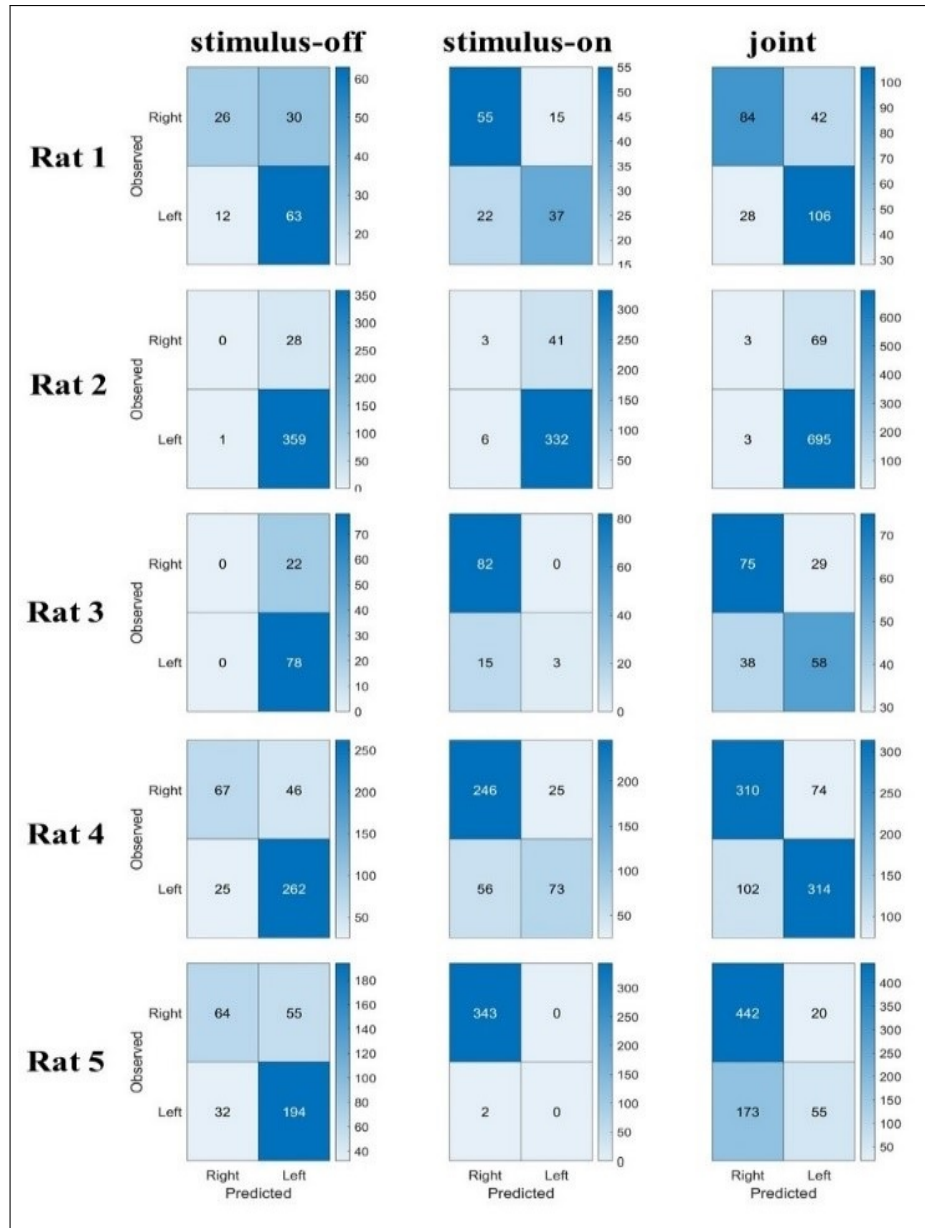


Figure A.3 The confusion matrices of all rats for Right/Left Bayesian Model.

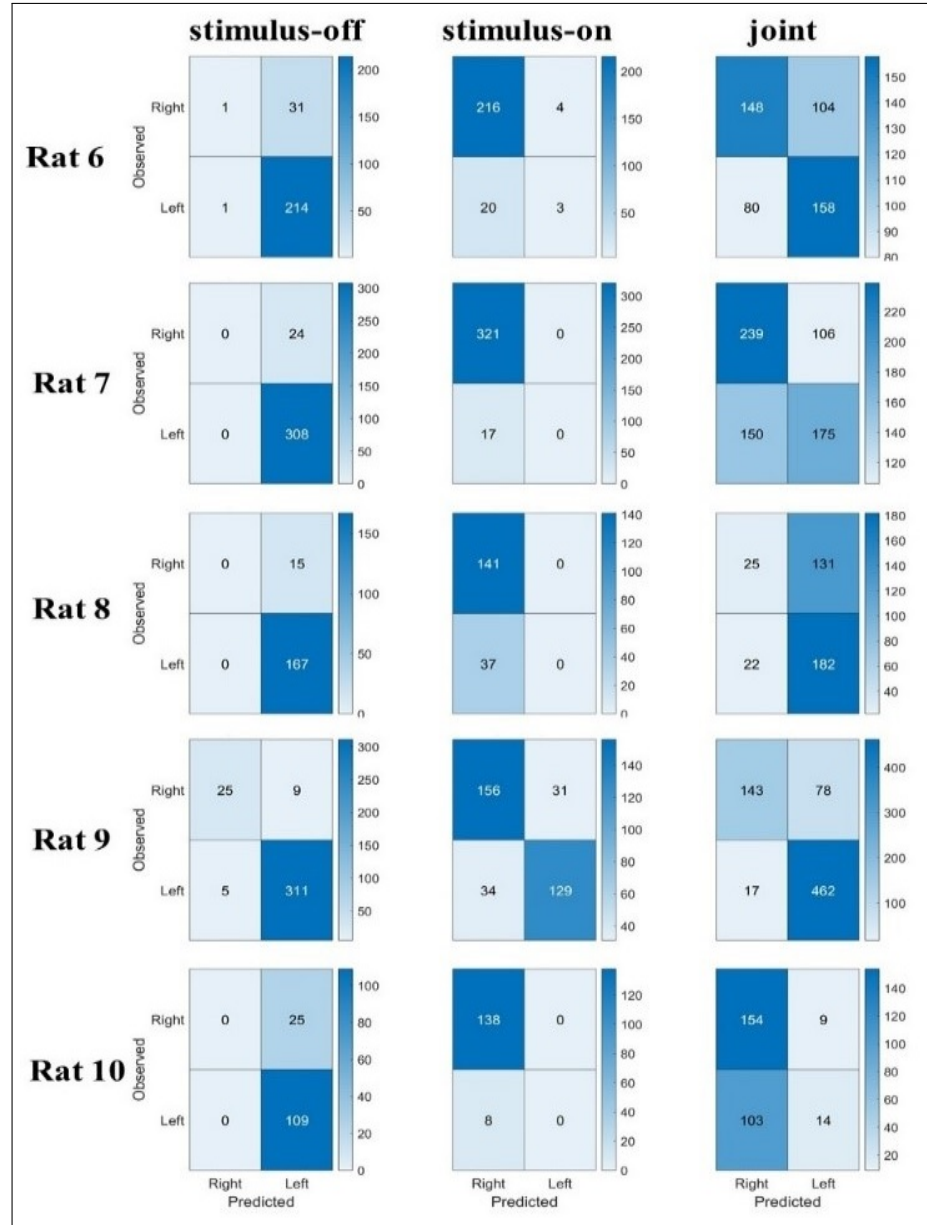


Figure A.4 The confusion matrices continued for Right/Left Bayesian Model.

Table A.3

The Correct/Incorrect performance scores for all rats. Stim On/Off/Joint Model Sensitivity, Specificity, Accuracy and F1 scores for all rats

	Stimulus-OFF Model					Stimulus-ON Model					JOINT Model				
	Sens	Prec	Spec	F1	Acc	Sens	Prec	Spec	F1	Acc	Sens	Prec	Spec	F1	Acc
Rat 1	0.84	0.72	0.55	0.77	0.72	0.80	0.73	0.67	0.76	0.74	0.65	0.54	0.31	0.59	0.50
Rat 2	0.99	0.93	0.00	0.96	0.92	0.02	0.14	0.98	0.04	0.87	0.57	0.52	0.41	0.54	0.50
Rat 3	1.00	0.78	0.00	0.88	0.78	1.00	0.85	0.22	0.92	0.86	0.97	0.79	0.00	0.87	0.78
Rat 4	0.91	0.84	0.58	0.88	0.81	0.91	0.83	0.60	0.87	0.81	0.87	0.71	0.16	0.78	0.66
Rat 5	0.88	0.77	0.50	0.82	0.75	1.00	0.99	0.00	1.00	0.99	0.97	0.83	0.08	0.90	0.81
Rat 6	1.00	0.87	0.03	0.93	0.87	0.99	0.93	0.19	0.96	0.92	1.00	0.89	0.00	0.94	0.89
Rat 7	1.00	0.93	0.00	0.96	0.93	1.00	0.95	0.00	0.97	0.95	0.99	0.94	0.00	0.96	0.93
Rat 8	1.00	0.92	0.00	0.96	0.92	1.00	0.79	0.00	0.88	0.79	1.00	0.86	0.00	0.92	0.86
Rat 9	0.99	0.97	0.71	0.98	0.96	0.85	0.82	0.79	0.83	0.82	0.93	0.74	0.14	0.82	0.71
Rat 10	1.00	0.81	0.00	0.89	0.81	1.00	0.94	0.00	0.97	0.94	1.00	0.88	0.00	0.94	0.88
Mean	0.97	0.88	0.39	0.92	0.86	0.94	0.89	0.74	0.91	0.88	0.91	0.78	0.21	0.84	0.74
$\pm$ std	0.02	0.03	0.10	0.02	0.03	0.10	0.08	0.12	0.09	0.03	0.05	0.05	0.05	0.05	0.05

Table A.4

The assessment of Right/Left Bayesian Model performance for all rats is divided into three groups of good/moderate/biased.

Rat Performance			Confusion Matrices		
	p(H)	p(F)	OFF	ON	JOINT
Rat 1	0.54	0.43	balanced	balanced	good
Rat 2	0.12	0.07	left-biased	left-biased	left-biased
Rat 3	0.82	0.22	left-biased	right-biased	moderate
Rat 4	0.68	0.28	balanced	balanced	good
Rat 5	0.99	0.34	balanced	right-biased	right-biased
Rat 6	0.91	0.13	left-biased	right-biased	moderate
Rat 7	0.95	0.07	left-biased	right-biased	moderate
Rat 8	0.79	0.08	left-biased	right-biased	left-biased
Rat 9	0.53	0.10	balanced	balanced	good
Rat 10	0.95	0.19	left-biased	right-biased	right-biased

Table A.5
The Behavioral performances of the Right/Left Model and its RS/FS versions

	Rat Behaving				R/L Model Behaving				RS Model Behaving				FS Model Behaving			
	p(H)	p(F)	A'	B''	p(H)	p(F)	A'	B''	p(H)	p(F)	A'	B''	p(H)	p(F)	A'	B''
R1	0.54	0.43	0.60	0.01	0.50	0.37	0.62	0.04	0.45	0.35	0.59	0.04	0.21	0.24	0.45	-0.05
R2	0.12	0.07	0.60	0.21	0.01	0.01	0.26	-0.32	0.00	0.01	0.25	-0.33	0.00	0.00	-	-
R3	0.82	0.22	0.88	-0.08	0.70	0.43	0.71	-0.08	0.69	0.45	0.70	-0.07	-	-	-	-
R4	0.68	0.28	0.78	0.04	0.63	0.40	0.68	-0.01	0.52	0.43	0.58	0.01	0.61	0.39	0.68	0.00
R5	0.99	0.34	0.91	-0.95	0.97	0.81	0.75	-0.69	0.97	0.83	0.75	-0.69	0.96	0.93	0.60	-0.23
R6	0.91	0.13	0.94	-0.14	0.53	0.40	0.62	0.02	0.53	0.43	0.59	0.01	-	-	-	-
R7	0.95	0.07	0.97	-0.17	0.69	0.47	0.68	-0.07	0.72	0.48	0.70	-0.11	0.54	0.51	0.52	0.00
R8	0.79	0.08	0.92	0.37	0.16	0.10	0.62	0.21	0.14	0.07	0.66	0.33	0.05	0.08	0.34	-0.22
R9	0.53	0.10	0.83	0.48	0.36	0.10	0.75	0.44	0.36	0.10	0.76	0.45	-	-	-	-
R10	0.95	0.19	0.93	-0.49	0.95	0.89	0.64	-0.31	0.97	0.90	0.68	-0.45	-	-	-	-

APPENDIX B. Supervised Classification Algorithms and their runtime parameters

In Chapter 4, the performance of seven different supervised algorithms were compared with the performance of the Bayesian Network algorithm we implemented in Chapter 3. The canonical implementation principles of those algorithms, which are logistic regression, linear discriminant analysis, k-nearest neighbors, decision tree, support vector machine, naïve Bayes, artificial neural network, are explained in detail below with their corresponding runtime parameters.

B.1 Logistic Regression

This algorithm handles the data set as a two-class classification problem. It generates a nonlinear hyperplane using the sigmoid function acting on the linear function of feature set $\mathbf{x}$. Thus, class probabilities for left press (L) and right press (R) are calculated as such [166]:

$$P(L|\mathbf{x}) = \sigma(\boldsymbol{\beta}\mathbf{x}^T) \quad P(R|\mathbf{x}) = 1 - P(L|\mathbf{x}) \quad (\text{B.1})$$

where $\sigma(\cdot)$ is the logistic sigmoid function in the form of:

$$\sigma(\boldsymbol{\beta}\mathbf{x}^T) = \frac{1}{1 + \exp(-\boldsymbol{\beta}\mathbf{x}^T)} \quad (\text{B.2})$$

where bold-face variables represent the vector form. Within these two probability distributions, $P(L|x)$ and $P(R|x)$, the class returns the higher probability is selected for the given specific feature set. In the case of a given trial for the decision-making task, the feature set is the firing rate vector for all units averaged over the recording dura-

tion. After the optimization of parameters (β), the class with higher probability, either right (R) or left (L) is chosen for the upcoming choice of the animal.

LogisticRegression class is implemented with regularized logistic regression under sklearn library in Python. The algorithm was executed with parameters: Penalization standart (penalty='l2'), dual or primal formulation (dual=False), tolerance for stopping criteria (tol=1e-4), inverse of regularization strength (C=1.0), flag to add intercept to the decision function (fit_intercept=True), flag to scale the intercept (intercept_scaling=1), equal class weights (class_weight=None), flag to shuffle data (random_state=None), optimization algorithm (solver='lbfgs'), maximum number of iterations before the solver converges (max_iter=4000), a binary problem fit using 'auto' since the data (multi_class='auto'), solver stages to declare to console (verbose=0), erase previous solution (warm_start=False), number of CPU cores (n_jobs=None), and no Elastic-Net mixing parameter (l1_ratio=None).

B.2 Linear Discriminant Analysis

Linear Discriminant Analysis (LDA) is just another type of supervised classifier algorithm. It estimates a linear decision boundary (Figure B.1) to cluster the given data set. This model fits a Gaussian density for each class then uses Bayes' rule to generate conditional class densities over data points. LDA is also used to reduce the dimensionality by projecting the data to the most discriminative direction. Linear discriminant function [166, 343] is:

$$y(\mathbf{x}) = \boldsymbol{\beta}\mathbf{x}^T + \beta_0 \quad (\text{B.3})$$

where the first term on the right-hand side is the new projected form of the data point vector ($\mathbf{x}$) on the decision surface together with the second term for bias (β_0). All data points for $y(\mathbf{x}) \geq 0$ are assigned to the right press (R) class of the animal, otherwise left press (L) class.

LinearDiscriminantAnalysis class is created with parameters: singular value

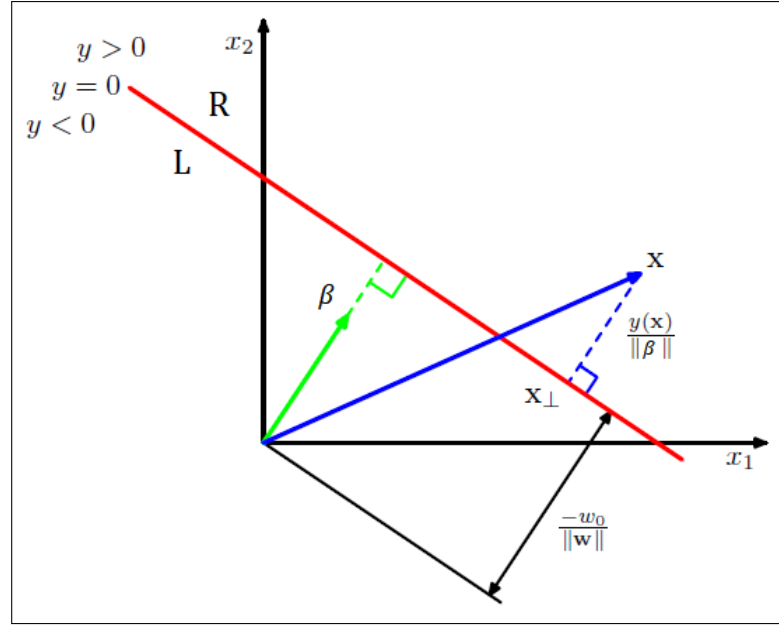


Figure B.1 Two-dimensional linear discriminant. Red line is the decision surface, perpendicular to β . Adapted from Figure 4.1 in [166].

decomposition solver (solver='svd'), no shrinkage (shrinkage = None), prior probabilities of classes (priors = None), number of components to affect transform method and 'None' reveals $n_components = \min(n_classes-1, n_features)$ ($n_components = None$), flag to explicitly compute the weighted within-class covariance matrix (store_covariance = False), and absolute threshold for a singular value of X to be considered significant (tol = 1e-4).

B.3 K-nearest neighbors

The first non-parametric algorithm used for comparison of the supervised techniques in this study is K-nearest neighbors. A hypothetical sphere in d-dimension is drawn with V volume in the hyperplane that centers the given data point x to be classified. Later, the density estimate [166] is given by:

$$p(x|L) = \frac{K_1}{N_1 V} \quad (\text{B.4})$$

where K_1 points lie in the hypersphere coming from the class left press (L), which in total N_1 points exist in class L. Therefore,

$$p(x) = \frac{K}{NV} \quad (\text{B.5})$$

unconditional density is used with the class priors:

$$P(L) = \frac{N_1}{N} \quad (\text{B.6})$$

to estimate the posterior probability of x belonging to class L:

$$P(L|x) = \frac{p(x|L)P(L)}{p(x)} = \frac{K_1}{K} \quad (\text{B.7})$$

in which probability density is shaped that the class having the most examples will have the highest probability.

KNeighborsClassifier class is created with parameters: number of neighbors (`n_neighbors = 5`), weigh all points uniformly (`weights = 'uniform'`), select the best algorithm depending on the fit method parameters (`algorithm = 'auto'`), leaves of the tree (`leaf_size = 30`), power parameter for the Minkovski metric (`p = 2`), the distance metric, which will be Euclidian if it is called with `p = 2` together, for the tree (`metric = 'minkowski'`), additive parameters for the metric function (`metric_params = None`), the number of parallel jobs to execute for the search of neighbors (`n_jobs = None`).

B.4 Decision trees

The second non-parametric classifier we used in this study is Decision Trees [166,343,344]. It is a hierarchical model that divides the input space into local regions and makes sequential binary decisions based on the data set. Figure B.2 below illustrates the traversal process of a binary tree. The first step starts by dividing the input space either $x_1 \leq \Theta_1$ or not. Later, on the second step, or second level on the three, the binary division process continues with $x_2 \leq \Theta_2$ process for the $x_1 \leq \Theta_1$ branch. This binary decision process continues recursively until the class name is found in the leaf node. Any new x will follow the path along the tree to find its cluster. It is worth noting that decision trees are not probabilistic models. The model flexibility depends on the data set.

DecisionTreeClassifier class is created with parameters: measurement crite-

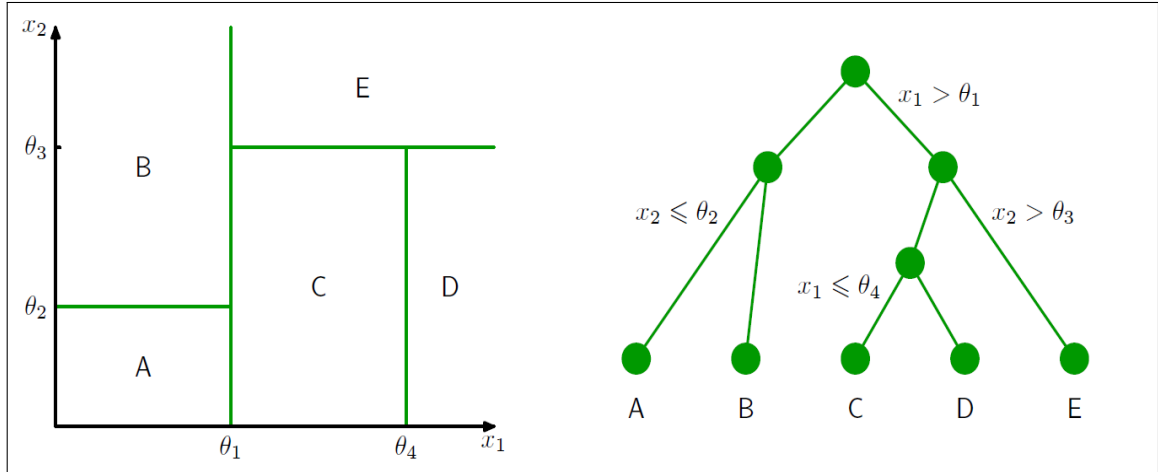


Figure B.2 Five decision regions (A-E) are assigned on the left based on the values of x_1 and x_2 . On the right-hand side, their corresponding binary tree is depicted. Adapted from Figure 14.5 and 14.6 in [166].

riterion for split quality (criterion = 'gini'), choose best split at each node (splitter = 'best'), expand the tree until all leaves are pure or min_samples_split+1 is reached (max_depth = None), required samples to split a node (min_samples_split = 2), minimum number to be a leaf node (min_samples_leaf = 1), minimum fraction of weight within the sum of all weights to be a leaf node (min_weight_fraction_leaf = 0), maximum number of features, in which 'None' returns max_features = n_features (max_features = None), randomness of the estimator (random_state = None), un-

limited number of leaves (`max_leaf_nodes = None`), the impurity decrease criterion to split a node (`min_impurity_decrease = 0`), the impurity criterion to split a node (`min_impurity_split = None`), equal class weights (`class_weight = None`), the criterion to select the subtree with the largest cost complexity and smaller `ccp_alpha` (`ccp_alpha = 0.0`).

B.5 Support vector machine

Support vector machine (SVM) is just another decision machine that does not inherently comprise posterior probabilities. Here, we used the C-Support Vector Classification implementation of SVM in the `libsvm` package [345]. The decision boundary is shaped depending on the subset of the data points, which are support vectors, around the border within the predefined margin. Finding the best parameters requires solving a non-linear convex optimization problem.

SVC class in `sklearn` library is created with parameters: regularization param-

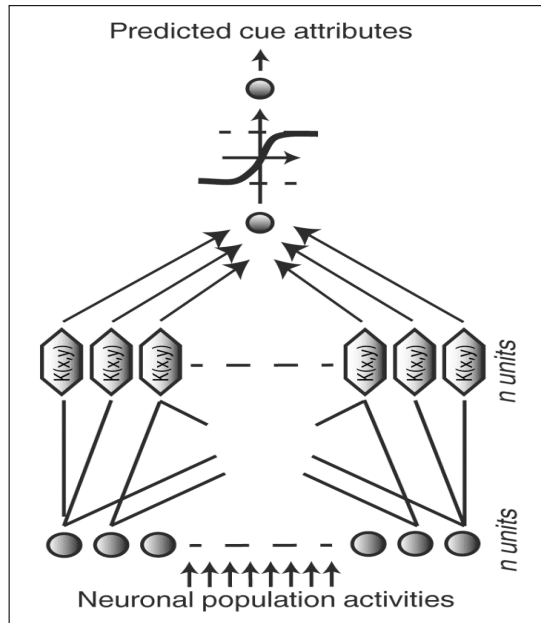


Figure B.3 A representative Support Vector Machine (SVM) model using LIBSVM [345] implementation. Adapted from Figure 2 in [293].

eter (`C=1.0`), kernel type to be used in algorithm (`kernel='rbf'`), the degree of polyno-

mial for the kernel function (degree = 3), kernel coefficient, which uses $1/n_features * X.var()$ for 'scale' (gamma = 'scale'), independent term in the kernel function (coef0 = 0.0), flag to use shrinking heuristic (shrinking = True), flag to enable probability estimates (probability = False), stopping criterion (tol = 1e-3), kernel cache size (cache_size = 200), all classes equal weights (class_weight = None), flag for output to console (verbose = False), no limit for solver iterations (max_iter = -1), one-vs-rest decision function but it is ignored for binary classification (decision_function_shape = 'ovr'), break ties based on the confidence values (break_ties = False), flag to shuffle data (random_state = None).

B.6 Naïve Bayes

Naïve Bayes classification [166, 343] states the assumption of conditional independence among the inputs ($\mathbf{x}$) and reduces a d-dimensional feature space into one-dimensional based on each feature (x_a):

$$p(\mathbf{x}|R) = \prod_{a=1}^d p(x_a|R) \quad (\text{B.8})$$

The posterior probability is then calculated using Bayes' theorem:

$$P(R|\mathbf{x}) = \frac{p(\mathbf{x}|R)P(R)}{p(\mathbf{x})} \quad (\text{B.9})$$

as if the mean firing rates of units are not correlated and independent. The probability of right press (R) in the specific trial of the animal is determined under the assumption of independent spiking units.

GaussianNB class is created with parameters: prior probabilities for the classes (priors = None), the largest variance of all features (var_smoothing = 1e-9).

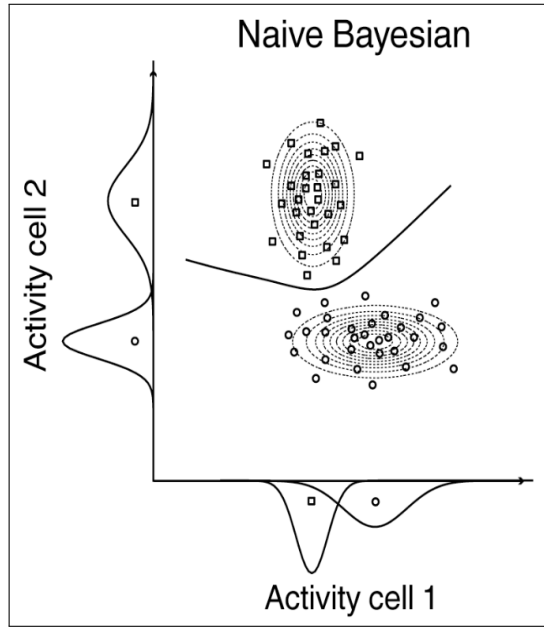


Figure B.4 Naïve Bayesian classifier builds a decision boundary between two distributions of cell activities. Adapted from Figure 3 in [293]

B.7 Artificial Neural Network (Multilayer Perceptron)

The last algorithm that is compared with other supervised classifiers and the Bayesian Network is Multilayer Perceptron. Bishop [166] criticizes the name 'Multilayer Perceptron' being a misnomer. It consists of multiple layers of continuous nonlinear activation functions rather than perceptrons, which refers to discrete nonlinearities. Neural network designs are inspired by neurophysiological processes in the brain [279–285]. This algorithm is another type of nonparametric classifier in terms of allowing the parameters updated during training that are determined based on the maximum likelihood framework. This recalls a nonlinear optimization problem determining parameters by minimizing the log-likelihood using error backpropagation. Updated parameters reveal better estimates in each new epoch. Thus, depending on the computational power, the best estimates for the network parameters are determined to apply to the test set.

MLPClassifier class is created with parameters: number of neurons in a hidden layer (`hidden_layer_sizes = 5`), activation function, which is hyperbolic tangent (`activation = 'tanh'`), the algorithm for the weight optimization, which is stochastic gradient

descent (solver = 'sgd'), penalty term for regularization(L2) (alpha = 0.0001), mini-batch size, which is min(200, n_samples) when set to 'auto' (batch_size = 'auto'), learning rate for weight updates (learning_rate = 'constant'), initial learning rate (learning_rate_init = 0.001), the exponent for inverse scaling learning rate (power_t = 0.5), the maximum number of iterations for the solver (max_iter = 5000), flag for shuffling samples in each iteration (shuffle = True), generation of random numbers for bias and weights initialization (random_state = None), optimization tolerance criterion (tol = 1e-4), not to print steps of progress (verbose = False), flag to use previous solution (warm_start = False), the momentum for gradient descent (momentum = 0.9), flag to use Nesterov's momentum (nesterovs_momentum = True), flag to stop for training if validation score is not improving (early_stopping = False), validation set fraction to use in early stopping (validation_fraction = 0.1), the rate of decay for first moment vector estimates in adam (beta_1 = 0.9), the rate of decay for second moment vector estimates in adam (beta_2 = 0.999), the criterion for numerical stability (epsilon = 1e-8), the maximum number of epochs when no improvement with respect to 'tol' criterion (n_iter_no_change = 10), the maximum number of loss function calls (max_fun = 15000).

All these 7 models are given to the crossvalidate function in the sklearn library with the parameters: instantiated 7 model classes (estimator = model), design matrix for the selected rat ($X[trialsxunits]$), (y = None), (groups = None), (scoring = None), (cv = None), (n_jobs = None), (verbose = 0), (fit_params = None), (pre_dispatch = '2*n_jobs'), (return_train_score = False), (return_estimator = False), (error_score = np.nan)

APPENDIX C. Publications

Articles

- ÖZTÜRK S., DEVECİOĞLU İ., and GÜÇLÜ B. Bayesian prediction of psychophysical detection responses from spike activity in the rat sensorimotor cortex. (Submitted)
- ÖZTÜRK S., DEVECİOĞLU İ., BEYGİ M., ATASOY A., MUTLU Ş., ÖZKAN M., GÜÇLÜ B. Real-Time Performance of a Tactile Neuroprosthesis on Awake Behaving Rats, IEEE Transactions on Neural Systems and Rehabilitation Engineering, vol. 27, pp. 1053-1062, 2019.

Conference Proceedings

International Conference Proceedings

- ÖZTÜRK S., DEVECİOĞLU İ., and GÜÇLÜ B. Relationship between psychophysical sensitivity index and Bayesian prediction accuracy in behaving rats. Oral presentation. Barrels XXXIV, Nov 3-5, 2021.
- ÖZTÜRK S., DEVECİOĞLU İ., and GÜÇLÜ B. Comparison between psychophysical performance of rats and incremental Bayesian models based on average firing rates of SI cortical neurons [Poster Presentation #P176.05]. SfN Global Connectome: A Virtual Event, January 11 - 13, 2021.
- ÖZTÜRK S., DEVECİOĞLU İ., and GÜÇLÜ B. Comparison of a Bayesian network model with supervised learning algorithms for the prediction of behavioral responses based on multi-electrode spike recordings from rat sensorimotor cortex [Poster Presentation #928]. FENS 2020 virtual forum, July 11-15.

- ÖZTÜRK S., GÜÇLÜ B. Predicting psychophysical response from multi-electrode spike recordings in rat SI cortex [Poster Presentation SFN 2019]. Neuroscience 2019, October 19-23, Chicago, IL, USA.
- ÖZTÜRK S., GÜÇLÜ B. Predicting psychophysical response from multi-electrode spike recordings in rat SI cortex [Oral Presentation]. The 4TH Joint Satellite Meeting of Turkey Chapter of Society for Neuroscience (SFN) & Neuroscience Society of Turkey (NST=TÜBAS), 2019 October 18, Chicago, IL, USA.
- ÖZTÜRK S., GÜÇLÜ B. Prediction of Behavioral Responses from Cortical Spike Recordings in Rats [Oral presentation at ENCODS 2019]: European Neuroscience Conference by Doctoral Students (June 2019), London, United Kingdom.
- ÖZTÜRK S., GÜÇLÜ B. Prediction of Behavioral Responses Using Bayesian Model from Multi-Unit Spike Recordings in Sensorimotor Cortex of Rats, Poster presentation at UK Neural Computation (July 2019), Nottingham, United Kingdom.

National Conference Proceedings

- ÖZTÜRK S., VARDAR B. and GÜÇLÜ B. Sorting spikes from S1 cortex for prediction of behavioral events in neuroprostheses [Poster Presentation]. Anatomy: An International Journal of Experimental and Clinical Anatomy, 12 (Suppl 1): P-023, 2018., 16th Turkish Neuroscience Congress (May 20-23, 2018) , Istanbul, TURKEY.
- ÖZTÜRK S., DEVECİOĞLU İ., and GÜÇLÜ B. Demonstration of a sensory neuroprosthesis on behaving rats [Poster Presentation]. 15th Turkish Neuroscience Congress (May 07-10, 2017) , Istanbul, TURKEY.

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