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Hardware, Software, and Statistical Tools for Cognitive Neuroscience

A Thesis submitted in partial satisfaction of the requirements
for the degree Master of Science

in

Bioengineering

by

Teryn Dakota Johnson

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Professor Lara Rangel, Co-Chair
Professor Pedro Cabrales
Professor Andrea Chiba

2017

The Thesis of Teryn Dakota Johnson is approved, and it is acceptable in quality and form for publication on microfilm and electronically:

Co-Chair

Chair

University of California, San Diego

2017

EPIGRAPH

“Whenever you think or you believe or you know, you're a lot of other people: but the moment you feel, you're nobody-but-yourself.”

e.e. cummings

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Chapter 1, in part is currently being prepared for submission for publication of the material. Marcelo Aguilar-Rivera and Teryn D. Johnson, Erik Gonzalez-Leon, Luisa Schuster, Nicole Butler, Todd Coleman, Laleh Quinn and Andrea Chiba. The thesis author was the co-investigator and co-author of this material.

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ABSTRACT OF THE THESIS

Hardware, Software, and Statistical Tools for Cognitive Neuroscience

by

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Master of Science in Bioengineering

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Prosocial behavior is a complex phenomenon that is poorly understood neurobiologically. While it is known that social interactions engage the amygdala, the insular cortex, and the autonomic nervous system, the manner in which these systems interact to cooperatively support prosocial behavior is not known. To investigate the neurobiological underpinnings of prosociality, it is critical to develop a tightly controlled paradigm that is capable of isolating the elements that give rise to prosocial actions. Chapter One describes the design of an effective, low-cost paradigm for investigating

prosociality in rats in which one rat has the ability to stop an aggravating air stimulus from affecting another rat. Researchers are provided with a graphical user interface to control, view, and record behavioral epochs in real time. This paradigm has the potential to become a widely-used standard in the field of social neuroscience.

The temporal coordination of neural activity in rhythms has been hypothesized to be critical for communication between interacting brain regions. Chapter Two proposes a novel pipeline for investigating the manner in which the rhythmic activity in one brain region constrains its ability to influence the activity of another structure. The proposed method uses a generalized linear model with Von Mises distributions as phase regressors to assess the extent to which the phase of neural oscillations in one brain region predicts the neural spiking activity in a downstream region. The pipeline described in this chapter is a novel approach to characterizing the relationship between continuous neural oscillations and discrete spiking activity.

Chapter 1: A Novel Paradigm for Social Neuroscience Research

1.1 Background

Prosocial behavior is an unexplained phenomenon marked by a willingness to act toward the benefit of another individual or group of individuals. While prosociality has been studied genetically, biochemically, psychologically, behaviorally, and anthropologically [1-7], its neurobiological underpinnings remain relatively unexplored. As prosocial actions are often instantiated in response to the perceived needs of others, they necessarily require the ability to assess internal state. The insular cortex, amygdala, and the autonomic nervous system have been tied to social interactions and interoception (the ability to assess internal state) [8-14], but the mechanisms through which these systems interact to promote prosocial behavior remain unknown. Attempts to elucidate the neural mechanisms of prosociality have been hindered by the challenges inherent to temporally isolating relevant behavioral epochs embedded within complex and variable social interactions. To address this need, a robust protocol must be developed which tightly controls and segments the prosocial behaviors into repeated action sequences.

While prosocial behavior is most often associated with humans, it has been reported that other species exhibit varying levels of prosociality, including primates, dogs, and rodents [15-26]. These studies have provided insight into a number of critical behavioral conditions that motivate prosocial interactions in each species. For example, first-hand experience with a stressor was often observed to be a pre-requisite for initiating actions to alleviate the stress of a conspecific in distress [27]. This suggests that internalizing a stressor is an important step in recognizing the distress of another. In addition, regular,

repeated interactions with conspecifics promoted prosocial actions. In both rodents and dogs, prosocial interactions were much more likely among familiar conspecifics [15, 21]. This suggests that prosocial actions require an ongoing relationship between participants. Taken together, these studies provide insight into conditions that should be standardized in future investigations of prosocial behaviors. This study attempts to develop a novel paradigm that not only incorporates critical variables leading to prosocial behaviors, but also temporally isolates them in order to identify the neurobiological underpinnings that support prosocial actions.

The rat is an ideal model organism for linking prosocial behaviors with neural activity. Rats have quick reproductive rates and low cost of care. In addition to these benefits, rodents are ideal for this study because their relatively small size decreases the cost of materials, enables the use of readily available commercial products, and improves reproducibility. The anatomy of the rodent is well-characterized, and a large number of studies have utilized this species for acquiring large-scale, high-density neural recordings in multiple brain regions [28]. Because social interactions engage multiple brain regions alongside the autonomic system, the ability to perform recordings on this scale makes rats ideal for recording local circuits in multiple regions. Initial steps in understanding how both brain and body are recruited during internal state assessment revolves around first understanding how the body's signals process information, both temporally and across neural architecture, with relation to specific social behaviors.

To be able to analyze information flow between multiple neural systems, it is critical that the behavior of interest and the corresponding electrophysiological signals be tightly and precisely synchronized. If this synchronization is not maintained consistently

throughout the study, any results can be easily washed out by neural activity that does not have ties to prosocial activity. To stimulate prosocial interactions, it is necessary to have an adverse stimulus that one rodent is being subjected to which another rodent can alleviate. Types of aggravating stimuli that have been used on rodents previously have included: water submersion [26], tail flicks [29], electric shocks [30], nerve constriction [31], and drug-induced peripheral neuropathy [32]. Because electrophysiology demands quick and repeated measurements, it is necessary that the chosen stimulus be noninvasive, non-debilitating, and quickly actionable. The action that the rodent takes to alleviate the other rodent from the aggravating stimulus must both be distinctive and natural; distinctive in the sense that it should not be confused with other normal behavior that may be demonstrated throughout the course of the experiment, and natural in the sense that it should not be overly difficult for the rodent to perform. Making the action more natural has the secondary benefit of decreasing the training time of the task, thereby making the behavior more reproducible across experimental trials.

The experimental paradigm proposed in this study engages two rodents in social interaction via the use of a three-chambered box, hereafter referred to as the Interoceptive Box, with air-flow as an aggravating stimulus (to which rats are naturally averse). Both rats were put in separate chambers with air flow alternating between chambers. One rat is given access to nose ports that stop air flowing into all three chambers. The rat with control over the airflow is hereafter named the active rat while the rat without control is named the passive rat. By giving the active rat control over the air stimulus, that rat can be recorded and observed under three scenarios: 1) the active rat is subject to the aggravating stimulus, 2) the passive rat is subject to the aggravating stimulus, and 3) the empty chamber is subject

to the aggravating stimulus. This design manages to meet all previously mentioned requirements for studying prosocial behavior electrophysiologically and thereby promises to be a foundational paradigm in elucidating the specific neurobiological mechanisms of prosociality.

1.2 Materials and Methods

The methods for the design of this experiment can be broken into two sections: hardware and software. A 3D representation of the Interoceptive Box is shown in Figure 1. One of the most important design goals that was considered in the construction of this paradigm was to ensure that the paradigm was reproducible, not only for subsequent studies but also in studies by other groups. To achieve this, the design of the hardware focused on being easy to construct, easy to maintain, and cheap to produce. Most of the materials of the Interoceptive Box were custom designed to be cost efficient and easy to clean. Rodents, when anxious or in distress, release alarm pheromones into their environment as a mechanism for warning other rodents about stressors [33]. These pheromones drastically increase the stress rodents have when enclosed in a chamber, which, if not accounted for, leads to different levels of stress being placed on the rodents as the experiment is repeated throughout the day. Therefore, each part of the Interoceptive Box was designed modular for ease of disassembly, cleaning, and reassembly between experiments.

All custom hardware components for the Interoceptive Box were designed in Autodesk Inventor and then cut from clear plexiglass acrylic sheets using a commercial laser cutter at the University of California, San Diego. Clear plexiglass was chosen so that the rodents' vision of each or their environment was not limited. Prosociality in rodents has been shown to be dependent on sensory input [34], thereby making it critical that both

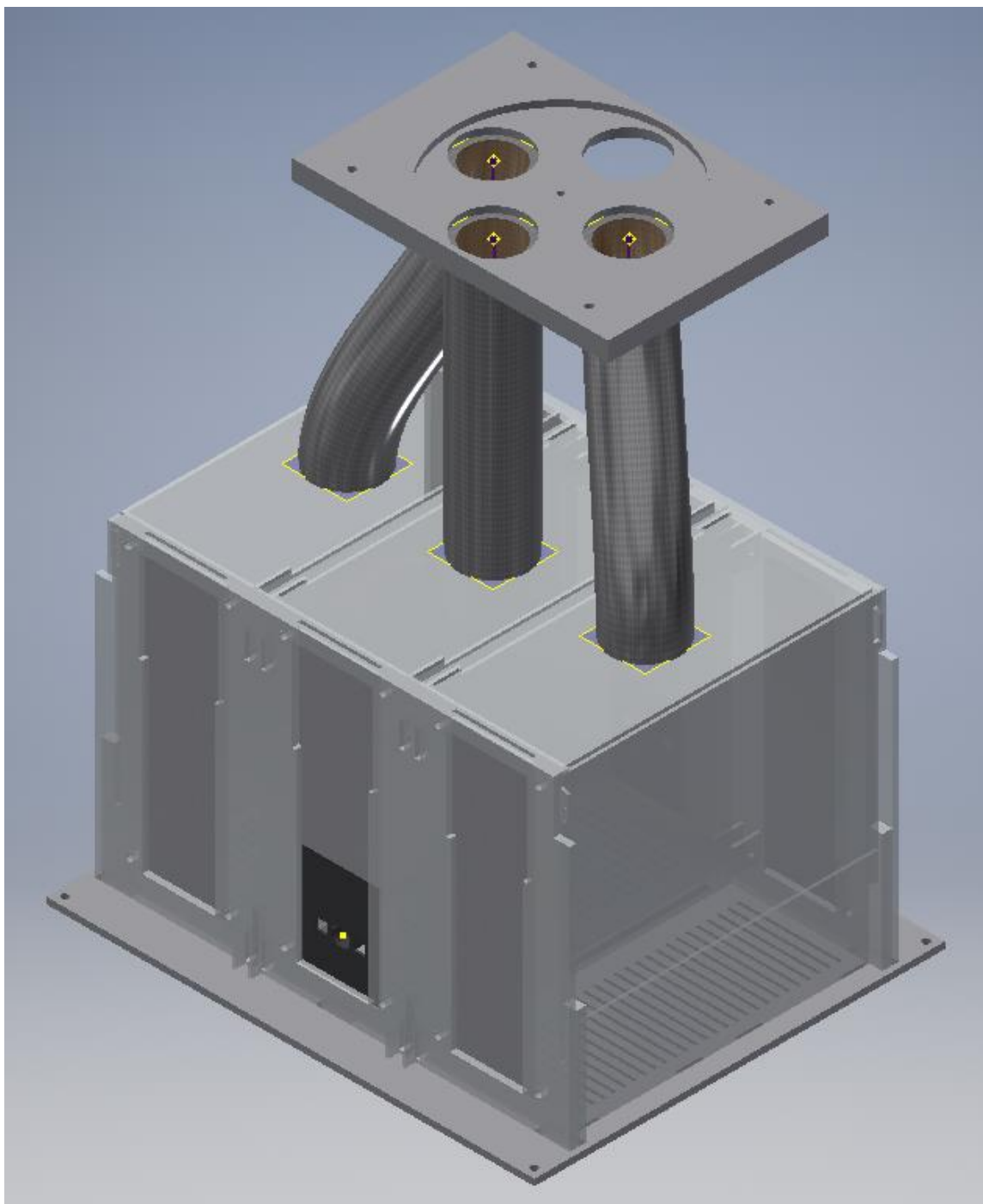


Figure 1. Shows the 3D representation of the Interceptive box. Air is pumped into the three chambers through the roof of the Interceptive Box with flexible hose funneling air into each chamber. Nose pokes are shown attached to the middle chamber.

rodents were made as aware of the other's status as possible. Similarly, the rest of the box is made of clear acrylic to make the rodents as aware of their environment as possible to

decrease the chance that this may cause additional stress. The nose ports were 3D printed with PLA material to which off-the-shelf infrared sensors were attached. All custom files were made publicly available so that anyone with access to a laser cutter and a 3D printer interested in building their own Interoceptive Box may do so, making the Interoceptive Box easily reproducible.

An insulating chamber was then built to encompass the Interoceptive Box to insulate the experiment from outside stimuli. While not strictly necessary for the experiment, the insulating chamber's primary function is to isolate the rodents from the experimenters and any cues that the experimenters may be inadvertently giving to the rodent during experimentation. This paradigm is strictly designed to test prosocial interactions between rodents to which the insulating chamber ensures that interactions are not occurring between experimenter and rodent. The insulating chamber was built using wooden 1'x1' beams with insulating foam blanketing the surface of each face. A door was built using the same material for ease of access to the Interoceptive Box.

A commercial portable air conditioning unit was used to generate the air stimulus. An off-the-shelf stepper motor was used to control the direction of the air generated by the air conditioning unit. An Arduino Uno microprocessor was used to send and receive signals from the infrared sensors, temperature sensor, and the stepper motor. An EasyDriver stepper motor driver was used to handle the circuitry necessary for operation of the stepper motor via the Arduino Uno board. A circuit schematic for the wiring of most of the hardware components is shown in Figure 2. A Logitech HD Pro Webcam C920 was used to record and stream the experiment taking place within the insulating chamber.

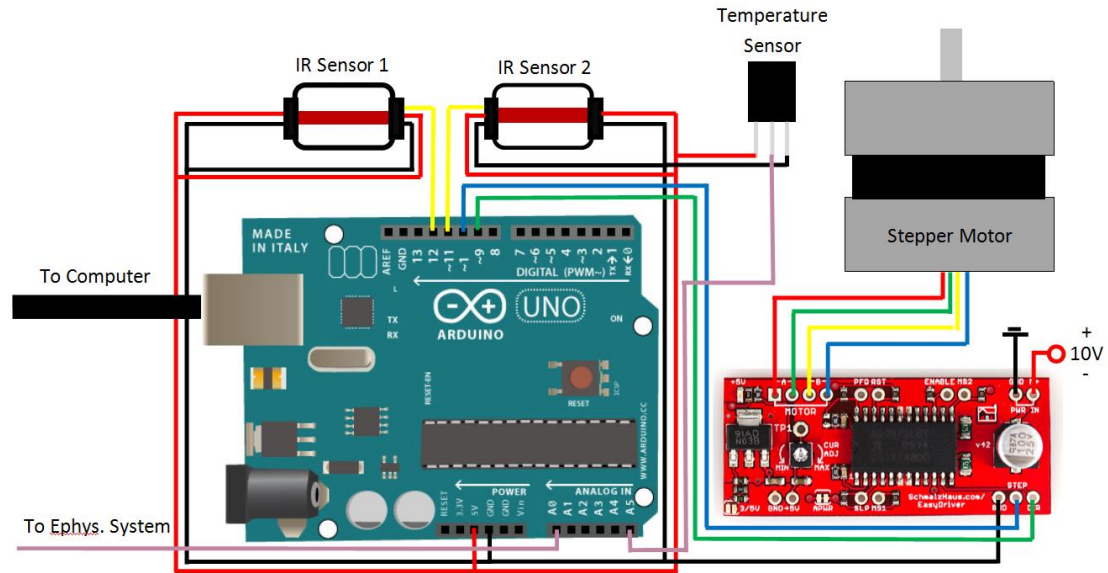


Figure 2. Depicts the wiring schematic that connects the two nose ports, temperature sensor, and stepper motor to the EasyDriver, Arduino board, PC that is running the Python user interface and the electrophysiological system.

The software for the experiment was primarily built in Python programming language so as to be open source and easily introducible to other experimenters. PyQT4 was used to design and build a graphical user interface to display a number of parameters of the experiment: the live stream of the experiment via webcam, the experiment timer, the current trial timer, the temperature of the chamber, the trial counter, a cartoon representation of the active processes of the Interoceptive Box, a section containing input parameters for the experiment, a button that starts the experiment, and a button that stops the current trial. The graphical user interface was designed easy to use and allows the experimenter to closely monitor the experiment occurring within the insulating chamber without biasing the performance of the rodents or the task. The input parameters allow the experiment to control the experiment and includes the experimenter's name, the participating rats' identification number, the stage of the experiment being performed, the



Figure 3. Depicts the graphical user interface used by the paradigm to feed the experimental timing, video live feed, temperature, trial number, and cartoon representation of the three chambers.

number of trials being run, the time between trials, and the name of the files generated by the end of the experiment. An example of the graphical user interface during experimentation is depicted in Figure 3.

In addition to the graphical user interface, Python is responsible for: communicating with the Arduino Uno board, managing the timing of the experiment, saving experiment time stamps to a text file, saving experiment parameters to a header file, saving the temperature data to a text file, and recording, processing, and streaming the video captured by the webcam. All of these different processes are performed behind the scenes and are performed via the use of multithreading and queues to pass information between different threads. The Arduino Uno board, connected to Python via the pySerial package, is responsible for: handling commands sent to it from Python to move the stepper motor to control air flow, gathering and sending temperature data from the Interoceptive Box, and monitoring and sending information when the infrared beam in the nose-poke is

broken. To move the motor, Arduino receives a signal from Python with the number of steps to make. Arduino then signals the stepper motor to make that many steps at a rate of 100 steps per second. The Arduino Uno board samples the temperature in the Interceptive Box ten times per second in Celsius and sends these recordings to Python to be recorded into a text file. The Arduino Uno board similarly samples the signal from the infrared sensor a hundred times per second and sends a signal to Python when the beam between the infrared light and the sensor has been broken. The infrared break beams are sampled at a high frequency to ensure that temporal correlation between the act of turning of the air and the electrophysiological is tightly constrained, making the intervals of behavior less noisy and more easily analyzed. Similarly, temperature is sampled more frequently than strictly necessary to ensure that even minor deflections in temperature can be analyzed alongside electrophysiological recordings.

Python, at the beginning of the experiment, following parameter input, takes the current local time and uses that time as a base point for handling all future timing of the experiment. Simultaneously, Arduino is instructed by Python to send a TTL pulse through a wire to the electrophysiological recording system to time synchronize the electrophysiological recordings with the start of the experiment. This is critical for maintaining a temporal synchronization between the two data sets and necessary for matching prosocial behavior with its corresponding electrophysiological cues. The time difference between this time and any time throughout the duration of the experiment translates directly to the experiment timer displayed on the graphical user interface. For the trial timer, the time when each trial starts is saved and then the difference between the start time and any other time during a trial is displayed. The trial timer is stopped at the

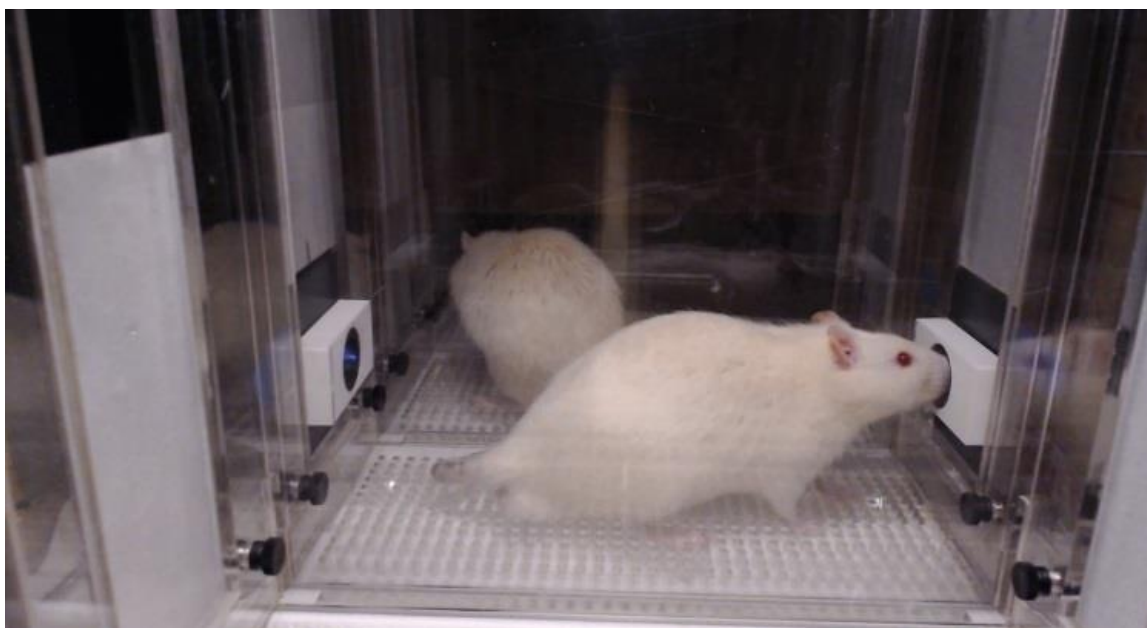


Figure 4. Depicts a snapshot of the recorded 1080p resolution recorded using the Logitech HD Pro Webcam C920.

conclusion of each trial and reset to zero for the next trial. The start of each trial is printed into a text file, along with all the time stamps of each nose poke recorded by Python from Arduino. These time stamps are critical for breaking any repeated prosocial behavior into easily digestible time increments for data analysis against the corresponding electrophysiological signals. In addition to recording the time stamps of trial onsets and nose pokes, at the start of the experiment, Python creates an .hdr file and records all experimental parameters for later recall. This automatically maintains proper documentation for the experiment and ensures that if behavior deviates, these records can be checked to eliminate user error in the data.

Python records the video captured by the webcam at 1080p full high definition (1920x1080 resolution) at 15 frames per second. This resolution is compressed to 720p high definition (1280x720 resolution) at 15 frames per second for live streaming on the graphical user interface. The video is compressed using a DIVX compressor and saved in

an .avi file format. AVI is one of the most universal video formats and lends itself well to most video analysis tools. An example of the recorded video is shown in Figure 4. The start of the camera recording is synchronized with the start of the experiment, allowing the time stamps of trial onset and nose poke to be synchronized with the video. This ensures that any other behavioral cues analyzed from the video can easily be correlated to the electrophysiological signals.

1.3 Results

The method for which the rat halted the aggravating stimulus was optimized through several iterations. Originally, a large, commercially available mechanical lever was used to turn off the stimulus. It was found, however, that the rodents, when in distress, were unwilling to put enough force onto the mechanical lever to trigger the end of the trial. This led to freezing behavior and learned helplessness. Following this approach, a piezoelectric variant of the lever was tried; which looked for any deflection in the piezoelectric lever as a trigger to end the trial. This worked was easier for the rats as not much pressure was necessary to trigger the effect. The downside, however, was that the rodents chewed on the piezoelectric lever leading to its damage and malfunction. Finally, nose ports coupled with infrared break beams were chosen as the trigger. This worked better than both levers as the behavior was observed to be more natural to the rodents. The size of the nose pokes went through several optimizations. When the nose poke was too large, it led to more difficulty in the infrared beam picking up when the beam was broken, particularly with younger populations. When the nose poke was too small, the behavior of the rodents displayed a decreased tendency in poking their nose deep enough into the nose poke to trigger the break beam. Furthermore, the placement of the break beams on the nose

pokes was the result of several iterations. Too close to the entrance of the nose poke, led to collateral break beam triggers via the rodent's hair when beside the nose poke. Too far, caused the caused several rodents in the pilot behavioral study to not reliably break the beam.

To be as noninvasive and painless as possible for the rodents, an easily triggered on-and-off stimulus was desired. Air was chosen as the aggravating stimulus, similar to air puffs that have been used previously in various experiments with rodents [35]. The air stimulus has gone through an optimization process in order to cause the maximum level of aggravation in the rodents while not being debilitating. Originally, the cooling feature of the air conditioning unit was utilized. It was found that long exposure to cold air, temperatures around and below fifteen degrees Celsius, caused the rodents to freeze and begin to display learned helplessness. A commercial heater was also experimented with. It was found that with warm temperatures of around 37 degrees Celsius and higher, the rodents did not display the same freezing and distressed behavior as they did at the colder temperatures. The commercial heaters used each had built in safety measures designed to turn off the heater when the temperature was too high. This often became a problem as the heater would turn itself off during experimentation. The distress exhibited by the rodents at room temperature was not drastically different to that at higher temperatures. Therefore, only the fan of the air conditioning unit was chosen to elicit distress behavior in the rodents for the pilot data trials.

1.4 Discussion

All components of this paradigm were designed to be modular, where individual aspects of the design can be changed without affecting the greater scope of the

experimentation. The design proposed in this paper, however, is considered to be optimal as a result of long pilot study and process of optimization.

While air stimulus was ultimately chosen in the current pilot study, an alternative approach to using air as an aggravating stimulus could be the application of a low level of electric current to the feet of the rodents. This alternative approach has the most promise, as it is a very distressing stimulus that is easily triggered on and off without lingering effects. Air stimulus was considered a better alternative to electric shock, however, due to air stimulus having no chance of physically harming the rodent during experimentation while having the added benefit of clearing the scent of alarm pheromones and cleaning product from the Interoceptive Box between experimental trials.

In terms of choice of action to end the aggravating stimulus, nose poking as the trigger to stop the aggravating stimulus proved to be far superior than using either a mechanical or piezoelectric lever. Alternative triggers could be gaze fixation points, embedded pressure pads within the floor of the chamber, or dig spots in the floor. The first two methods suffer from being subject to inconsequential triggering because they do not necessitate deliberate action to trigger. The second and third methods suffer from being space prohibitive, requiring much larger areas to ensure that triggering is not performed accidentally and triggering is distinct between active and passive chambers. Therefore, nose ports were considered the most optimal method for triggering the end of the aggravating stimulus.

While the nose pokes and air onset is automatically recorded by the software protocols, the distress behavior of the rodents is not automatically recorded. To this point, this behavior has been qualitatively observed but not quantified. To quantify distress in the

rodents to be used for data analysis further down the road, previously established behavioral coding protocols will be used [36]. These behaviors include grooming, rearing, orbital tightening, and the flattening of ears. The goal of quantifying the specific distress throughout the duration of the experiment is to ensure that these behavioral cues are being properly synced with observed electrophysiological signals. All behavioral coding is planned to be done offline with the full high definition video recorded throughout the experiment.

In rats, as in humans, the insular cortex and amygdala have been tied to social interactions. These areas, therefore, show promise in being crucial to prosocial interactions. Recording will begin in these two areas during the task to elucidate the mechanisms within this region that are responsible for the prosocial behavior previously recorded. Information flow between the two regions will be characterized, and the neurobiological foundations of prosocial interactions will be able to be explored in a tightly controlled environment.

1.5 Conclusion

The hardware and software created for this protocol was the result of a long, iterative process of optimization that resulted in an effective protocol for acquiring behavioral timestamps in an isolated and highly controlled manner. Future directions with the Interoceptive Box will be to collect electrophysiological signals from the rodents and prove the efficacy of the protocol in correlating the electrophysiological signals with the behavioral signals. As it stands, however, the Interoceptive Box and accompany software is an effective set of tools for studying prosocial behavior and interaction.

Chapter 1, in part is currently being prepared for submission for publication of the material. Marcelo Aguilar-Rivera and Teryn D. Johnson, Erik Gonzalez-Leon, Luisa

Schuster, Nicole Butler, Todd Coleman, Laleh Quinn and Andrea Chiba. The thesis author was the co-investigator and co-author of this material.

Chapter 2: Statistical Pipeline for Assessing Spike-Phase Relationships

2.1 Background

Electrical stimulation of the brain is a widely used method in both research and clinical settings that has yielded varying degrees of success [37-43]. Central to most stimulation studies is the assumption that amplifying the activity of a particular region will enhance that region's function. The variability in success rates across stimulation protocols, however, suggests the need for a modification of the core assumption. Neural networks within a brain region often exhibit a precise temporal coordination to their interactions that may or may not be perfectly replicated in different stimulation studies. As a consequence, successful engagement necessitates that a stimulation paradigm incorporates the natural rhythmic constraints of the network. Stimulation at frequencies outside of a network's natural rhythmic profile for a given computation could result in non-optimal recruitment, and potential suppression of network activity [44]. In order to improve the efficacy of brain stimulation in clinical treatment as well as cognitive enhancement, it is critical that new stimulation methods account for fundamental mechanisms of communication between populations of neurons.

Communication between brain regions is hypothesized to depend upon rhythmic coherence. Periods of depolarization and hyperpolarization create rhythmic windows in which neurons are more or less susceptible to fire, creating a phase dependence to their interactions. Under theories of communication through coherence, optimal temporal windows for communication are defined by a recovery from inhibition or hyperpolarization [45]. If stimulation occurs during periods of hyperpolarization, it would be less effective

in engaging local circuits because the periods of hyperpolarization are effectively inhibiting local neurons from firing. Periods of depolarization would have the opposite effect, essentially priming local populations of neurons to be more susceptible to stimulation [44]. Studies characterizing the relationship between the phase of rhythmic activity in one region and the recruitment of cells in downstream structures often limit their analyses to assessments of spike-phase coherence [46-50]. While spike-phase coherence characterizes single neuron relationships to ongoing rhythmic activity, a tightly constrained model has yet to be developed to generalize the relationship that phase in upstream neural structures can have on spiking activities in downstream neural structures. Understanding this relationship would allow us to develop more principled approaches to engaging neural networks with stimulation.

When developing a model to characterize biological processes, it is critical to follow a careful model design process that ensures that repeatable and generalizable conclusions can be drawn from the model's results. The Box-Tukey Paradigm, developed by George Box and John Tukey, was applied in this thesis as a pipeline for the development of new analytical tools for spike-phase analysis (Figure 5). The Box-Tukey paradigm assesses goodness of fit as a critical part of model development workflow. As a consequence, this workflow enables researchers to minimize both overfitting and underfitting of the data, improving generalizability and repeatability in similar data sets. This is critical when developing a new model for a dataset that has not explored this phenomenon in the past.

The first step to developing a model under the Box-Tukey paradigm is to start with a hypothesis or a question to be addressed. For this study, the question being addressed is

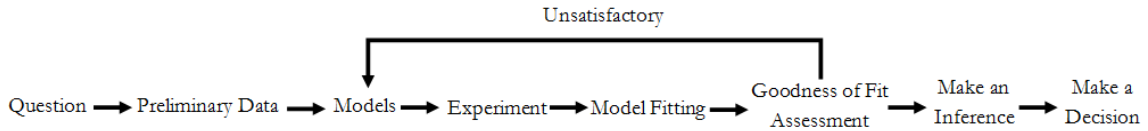


Figure 5. Shows the workflow of the Box-Tukey paradigm for model development.

whether or not the phase of rhythmic population activity in one region is related to downstream spiking in another. This relationship has been observed using spike-phase coherence methods in a number of studies [44, 45, 50]. This, according to the Box-Tukey paradigm, is sufficient evidence and reason for a model to be created to further explore the results of these studies. Because an effective model has not been created around this phenomenon, other models were explored for inspiration. One hurdle with modeling phase is that phase data is circular, thereby precluding many regression methods which typically rely on linear regressors. Linear models are appealing because they generalize easily by the addition or removal of regressor functions based on the shape of the relationship that is attempting to be modeled. A promising pipeline that was created for modeling the effect of extrinsic covariates on spiking behavior relies on the use of linear regressors [51]. As a first step in the development of a new pipeline for modeling the effect of upstream phase to downstream spiking, this pipeline will be used for inspiration.

To use this pipeline for analysis of the effect of phase on a downstream structure, phase must be mapped onto a linear basis function. Methods have been created in order to map any linear distribution function onto a circular space but have struggled with having either computationally efficient or unique solutions [52]. Because of this, the ability to construct circular probability distributions is limited. While computational efficiency is not always something that needs to be considered, considering it in the development of a new model is important in two ways: 1) neural datasets tend to be large, thereby making any

analysis already computationally expensive and 2) computational efficiency makes it easier to diagnose problems with the model while allowing the model to be continuously iterated upon. While most continuous signals can be approximated as the number of basis functions used to construct it approaches infinity, it becomes computationally inefficient and using a basis function that is similar to that which is being modeled is much preferred. Since the underlying relationship is not known, however, a similar basis function to the actual shape can only be assumed until properly verified against the results of the model.

As a first step, an initial starting basis function must be selected. While some studies have looked to map circular data onto linearly increasing or decreasing functions [53], and unit pulses [54], other studies have seen effective results from using Von Mises distributions, essentially a circular version of the normal distribution, to map circular data onto linear space [55, 56]. Without information as to what the underlying basis function should be, using Von Mises distributions as basis functions is a good start due to it being a well characterized circular function with computationally efficient and unique solutions. This chapter proposes to use a previously developed pipeline [51] to determine the effect of phase on predicting the probability of a population of neurons' spiking by mapping phase onto linear space utilizing multiple Von Mises distributions as basis functions. By developing an effective pipeline for exploring the effect that phase can have on the ability of downstream populations to spike, further advancements can be made in developing more effective stimulation studies for clinical treatment and cognitive enhancement.

2.2 Methods

To map the linear representation of phase between $-\pi$ and π onto circular space, a Von Mises distribution was used:

$$f(\theta) = \frac{e^{\kappa \cos(\theta - \mu)}}{2\pi I_0(\kappa)}$$

Where κ is inverse variance, θ is phase, μ is mean, and $I_0(\kappa)$ is the Bessel function of order zero. A regressor matrix, R , was created from these Von Mises distributions. The negative loglikelihood was then calculated:

$$-\log L(\theta_i) = \sum_{i=1}^m -y_i(R_i^T x) + \log(1 + e^{R_i^T x})$$

Where y is the spiking vector and x is a vector containing the weights for each distribution contained within the regressor matrix, calculated as:

$$x = \operatorname{argmin} -\log L(\theta)(x)$$

To calculate x , the Matlab function *fitglm* is used with the linear logit link function and binomial distribution parameters. To ensure that each Von Mises distribution is being best fit to the data at each step, before adding another Von Mises distribution to the regressor matrix, mean and inverse variance is optimized by:

$$\mu, \kappa = \operatorname{argmin} -\log L(\theta)(\mu, \kappa)$$

Following the optimization of each new distribution's mean and inverse variance, the model is evaluated using its minimum description length (MDL) [57] to determine if the data is being overfit:

$$MDL = -\log L(\theta) + \frac{d * \log m}{2m}$$

Where d is the number of distributions being used and m is the length of the dataset. To determine the optimal number of distributions that describe the data without overfitting, the local minimum MDL is found after the addition of each new optimized distribution to the regressor matrix. If the local minimum of the MDL is not found to be the most recently

added distribution, then the model is considered optimized at the previous iteration and that iteration is considered the optimal representation of the data. The conditional probability is then calculated from the optimized regressor matrix:

$$P_i(y_i = 1|\theta_i) = \frac{e^{R_i^T x}}{1 + e^{R_i^T x}}$$

This conditional probability distribution is then used to generate a Kolmogorov-Smirnov plot (K-S plot) using the Time Rescaling Theorem described in [49] to assess goodness of fit. An outline of the pipeline developed for the model and how it fits into the Box-Tukey paradigm is depicted in figure 6.

2.3 Simulation

After development of a model, it is critical to analyze how the model performs on data that is well characterized. With this goal, four situations were simulated to evaluate the ability of the model in creating a probability distribution with spikes occurring given a phase: 1) where there is a distinct, unimodal phase dependence on cell spiking, 2) where there is no distinct phase dependence on cell spiking and spikes are randomly distributed, 3) where there are multimodal phase dependencies on cell spiking, and 4) where there is geometry that is not easily characterized by Von Mises distributions as basis functions.

The first two simulations serve to test the boundary cases of the most idealized and the least idealized situations. For a model to be effective, it needs to be able to recover at least these two conditions. If the first simulation does not yield promising results in a controlled setting, then any preference in phase cannot be properly recovered. If the second simulation is not properly recovered, then the model may end up returning preference relationships when they do not really exist. The third condition tests the relationship

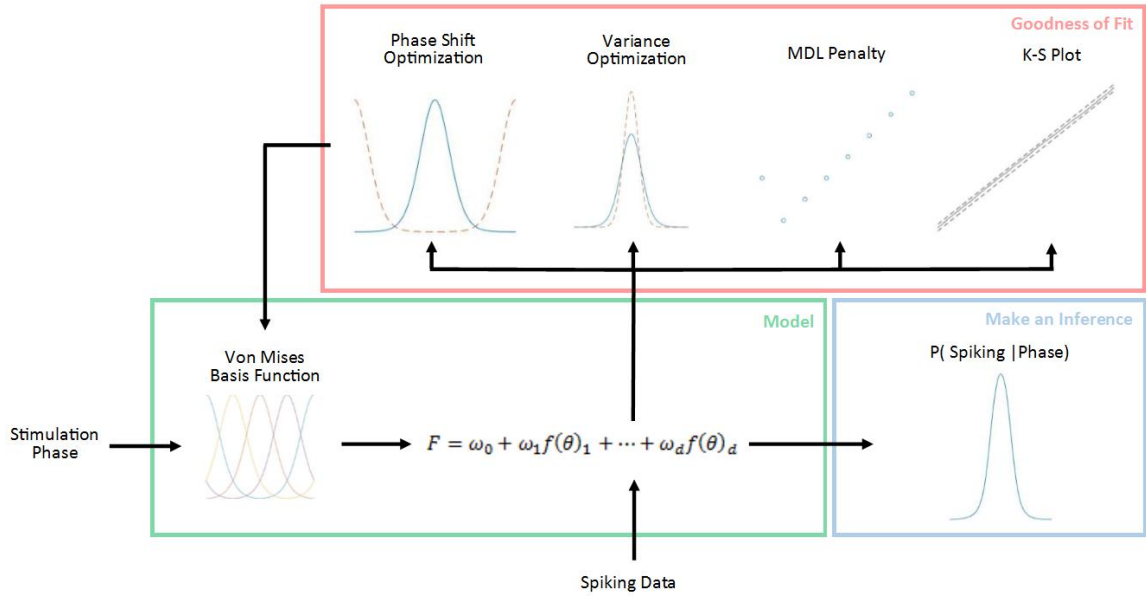


Figure 6. Depicts the work pipeline for the model including the model's inputs. The pipeline starts with stimulation phase that is mapped onto linear space using a Von Mises distribution. That mapped phase is then solved in a GLM for associated weights at various variances and means to determine where the optimal placement of that distribution should be. This process is repeated several times. A minimum description length penalty term is then applied to the negative log likelihood to determine at what point the model is optimally fit. At this point, a K-S plot is generated to test the fit. If the fit is good, the conditional probability function is generated.

between the MDL penalty term and the resolution of the probability distribution output from the model. Essentially, the third simulation checks how detailed the model can be before the penalty term starts to smooth the data even when additional preferences exist. The fourth simulation experiments with how well the Von Mises basis functions do in recreating probability distributions that have difficult geometries for Von Mises distributions to approximate.

All simulations were created to last twenty seconds long with a sampling rate of 1000 Hz. Twenty seconds of data is a moderate amount of data to base conclusions off of and 1000 Hz recording frequency is a standard recording rate for recording local field potential in electrophysiological studies. By using these two conditions, the data the simulations are being created from is similar to what actual electrophysiological data would

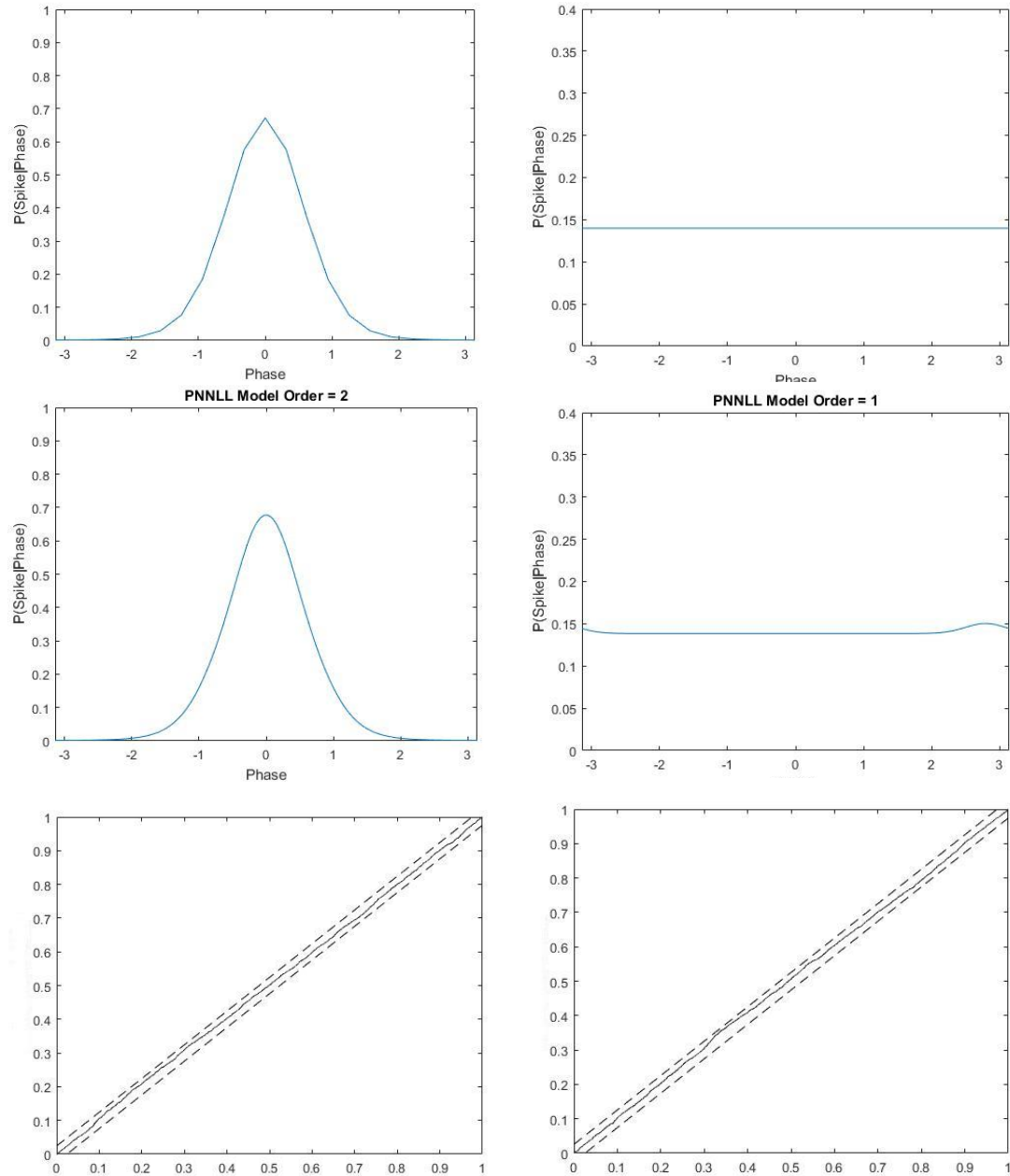


Figure 7. Shows the results of the model generation for simulation one, spikes aligned to a zero phase (left column), and simulation two, spikes randomly distributed (right column). The first row shows the ground truth probability fed into the model. The second row shows the output probability that the model predicts, as well as shows in the title how many Von Mises distributions were used to generate the probability. The third row shows the goodness of fit in a K-S plot with 95% confidence diagonals.

look like. The phase created for the stimulation study is a linearly repeating phase data set from $-\pi$ to π at a 50 Hz frequency.

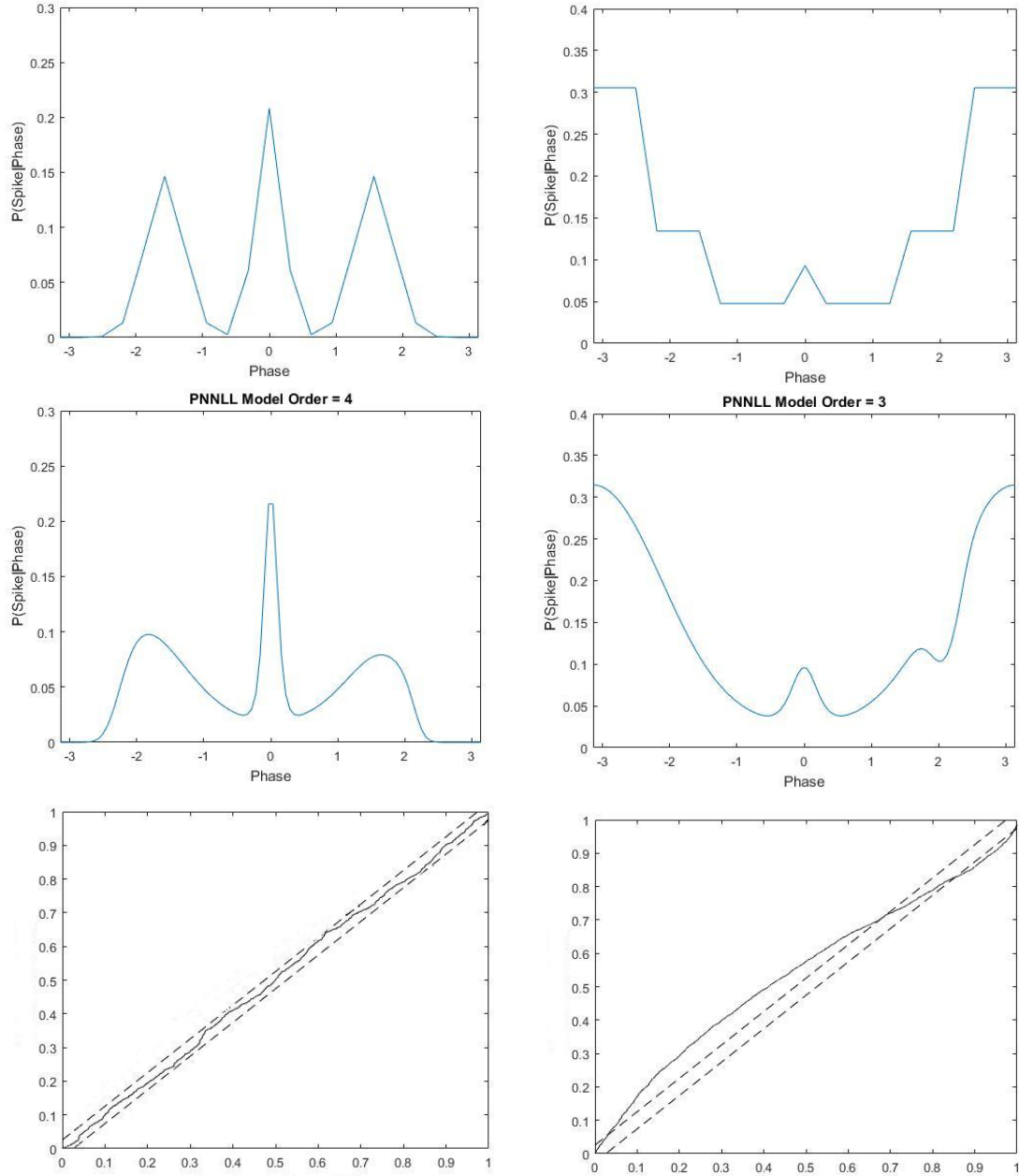


Figure 8. Shows the results of the model generation for simulation three, multimodal preference to phase (left column), and simulation four, phase preference with more difficult geometries (right column). The first row shows the ground truth probability fed into the model. The second row shows the output probability that the model predicts, as well as shows in the title how many Von Mises distributions were used to generate the probability. The third row shows the goodness of fit in a K-S plot with 95% confidence diagonals.

2.4 Results

The results of all four simulations are shown in Figures 7 and 8 along with their respective K-S plots to assess their goodness of fit. As can be seen in the first two

simulation conditions, the model faithfully reproduces the ground truth probability distributions and the model reports a greater than 95% confidence from the K-S plots. The first simulation reported using two Von Mises distributions in recovering the original probability function, while the second simulation reported using one.

The third and fourth simulations yielded mixed results. While the multimodal condition in simulation three recovered that there were three phases that showed preference, the exact probability was not faithfully recovered. This is shown within the K-S plot of simulation three where there is less strict adherence to the 95% confidence than simulation one or two. Simulation four recovers the general shape of ground truth probability function but, because the true shape is not easily reproducible by Von Mises distributions, it leads to smoothing of the probability distribution function that does not exist within the true function. This results in the large deviation from the 95% confidence interval reported in its representative K-S plot.

2.5 Discussion

As a first step, the model described in this chapter is highly promising. The model was able to faithfully reproduce both simulation one and two, thereby successfully proving itself in the two most basic and extreme conditions that could be encountered in real data. It is additionally encouraging that the K-S plots for both simulations report high confidence. While the results of simulation three and four are not perfect, it is encouraging that the discrepancies are shown in the K-S plot, thereby reporting that there is a problem with the generated fit. This is encouraging because it indicates that when there are discrepancies between the fit and real data, it will be revealed by the K-S plots.

One clear difference between the original conditional probabilities and those calculated from the model is the smoothness that the model imposes. This is a direct consequence of using Von Mises distributions as basis functions. This causes an increased error between the ground truth conditional probability function and the conditional probability function created by the model when the true conditional probability function has a shape that is difficult for Von Mises distributions to approximate to. This is the reason why simulation four suffers more greatly in fit than the other three simulations. While other basis functions, such as a linearly increasing or decreasing or unit pulse, would better represent simulation four, they would be worse at reproducing conditions simulation one, two, and three.

Von Mises distributions were chosen as basis functions for this analysis because the relationship between phase and probability of spiking in a downstream structure has not yet been carefully characterized. As such, using Von Mises distributions as basis functions is a good starting place as they are well studied and have unique solutions. While other distribution functions have been experimented with to make their mapping to circular space [50] have unique solutions, these processes remain computationally expensive. In addition, there is no evidence that other basis functions will perform more optimally when handling real data. With that in mind, once the model has been tested on real data it can be evaluated against other basis functions (such as other circular distributions, linearly increasing or decreasing, and unit pulses) to identify which basis function is the most consistently optimal for reproducing real data with high confidence.

Using the MDL as a penalty method proved to be a decent method for preventing large amounts of overfitting while being computationally efficient. As can be seen in both

the first and the third simulation condition, however, overfitting did occur. Because there was only one phase preference in simulation one, one Von Mises basis function should have been adequate to model it. Instead, the model determined two to be optimal. Similarly in condition three, there were three phase preferences but the model determined four was optimal. While this level of overfitting is not terrible, any amount of overfitting can lead to exponentially longer computation times in larger data sets. Cross validation is a potential alternative method for determining the appropriate number of distributions to describe the data that would likely do better at minimizing overfitting. Cross validation is much more computationally expensive, however, and requires multiple data segments to be cross validated against. Using the MDL penalty method is useful for situations in which data is limited or data is being piloted but can ultimately be replaced with a cross validation method in more comprehensive studies with larger data sets.

2.6 Conclusion

The pipeline outlined in this chapter has demonstrated a method that has shown promise in approximating the conditional probability of a spike occurring at specific phase preferences. While the Von Mises basis functions will not recover the exact shapes of all possible probability distributions, it is an appropriate choice for basis function until more is known about what the shape that the phase-spiking relationship is like. At the time where the relationship is better characterized, new circular basis functions can be utilized in this pipeline. To pilot the exploration of the relationship between phase and spiking time, the proposed pipeline is an effective method at exploring pilot data and can be used for analyzing phase preference in downstream structures in different regions throughout the brain.

Chapter 2, in part is currently being prepared for submission for publication of the material. Johnson, T.D., Rivière, P. D, Coleman, T.P., Rangel, L.M. “Statistical Pipeline for Assessing Spike-Phase Relationships.” The thesis author was the primary investigator and author of this material.

APPENDIX

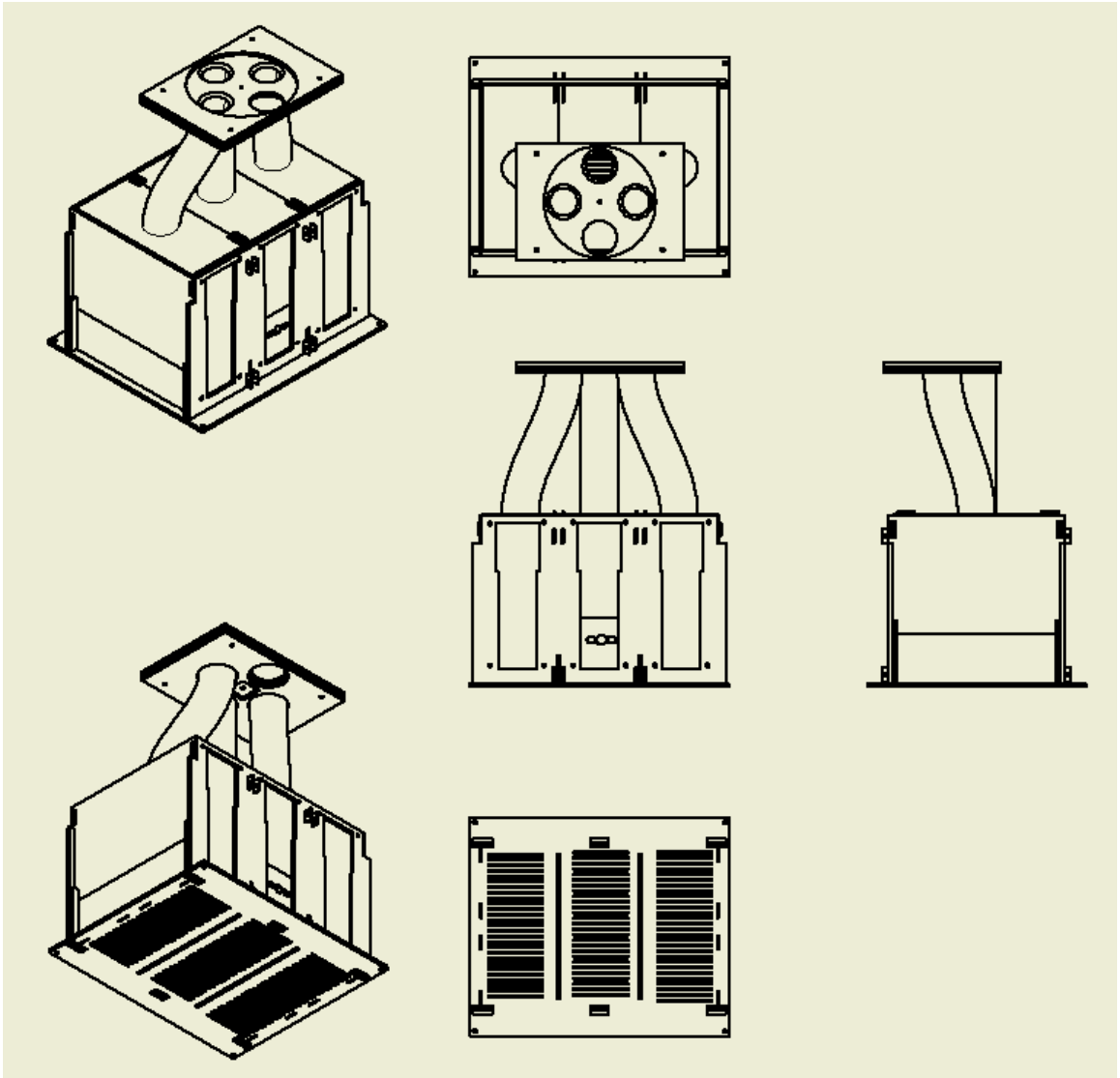


Figure 9. Depicts a full engineering schematic of the interceptive box from multiple angles.

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