Vulnerability to sleep deprivation : a drift diffusion model perspective

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VULNERABILITY TO SLEEP DEPRIVATION: A DRIFT DIFFUSION MODEL PERSPECTIVE

by

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Dedicated to my mother.

“The ultimate arbiter of truth is experiment, not the comfort one derives from one’s a priori beliefs, nor the beauty or elegance one ascribes to one’s theoretical models.”

Lawrence M. Krauss

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List of Abbreviation

BA	Brodmann Area
BOLD	Blood Oxygenation Level Dependant
CV	Cross Validation
CRLB	CramrRao Lower Bound
DV	Decision Value
DDM	Drift Diffusion Model
DMN	Default Mode Network
EEG	ElectroEncephaloGram
ESD	Evening before Sleep Deprivation
fMRI	functional Magnetic Resonance Imaging
GLM	General Linear Model
sICA	spatial-Independent Component Analysis
IID	Independent and Identically Distributed
ISI	Inter-Stimulus Intervals
KSS	Karolinska Sleepiness Scale
MCMC	Markov Chain Monte Carlo
MGF	Moment Generating Function
MLE	Maximum Likelihood Estimate
MNI	Montreal Neurological Institute
NREM	Non-Rapid Eye Movement
PDF	Probability Density Function
PVT	Psychomotor Vigilance Task
RBF	Radial Basis Function
RSN	Resting State Network
RT	Reaction Time
RW	Rested Wakefulness
SD	Sleep Deprivation
SDT	Signal Detection Theory
SPM	Statistical Parametric Maps
SWA	Slow-Wave Activity
SNR	Signal to Noise Ratio
SVM	Support Vector Machine
TCFE	Threshold Free Cluster Enhancements
VBLANK	Vertical Blanking Interval

List of Notation

$*$	Convolution
$[\cdot]^T$	Transpose
$\sim$	Distributed as
$E(X)$	Expectation with respect to X
$var(X)$	Variance of X
$\lceil(\cdot)\rceil$	Ceil function
$\approx$	converge in probability

Abstract

Most of us have experienced sleep deprivation (SD) every now and then, and know from experience that lack of sleep can adversely affect cognitive function and vigilance. The neurophysiology of sleep and lack thereof, its association with diseases and general well being has been studied extensively for over a century. The lack of sleep has enormous economic, health and life cost. The loss of performance and attention after SD can lead to industrial and transportation accidents, medical errors and lapses in security. While the decline in performance with SD is well established, it was recently (2004) observed that this decline in performance varies significantly between subjects, with some subjects remaining relatively unaffected while others show considerable decline in performance. This subject specific vulnerability towards SD remains stable in time and shows trait like features, i.e., the relative ranking of individuals according to subject specific performance (on some behavioral task) is maintained over time irrespective of sleep history. This suggests a stable neuro-cognitive basis for between-subjects differences in performance. Being able to predict an individual's vulnerability to performance decline when sleep deprived is therefore of considerable interest.

The Psychomotor Vigilance Task (PVT) is a sustained-attention, simple one-choice reaction time (RT) task that measures the speed with which subjects respond to a visual stimulus. It is a proven assay for evaluating vigilance. We use the PVT to evaluate and quantify the degradation of performance with SD on three large independent data sets collected from two different labs over an extended period of time. Instead of looking at the RTs using summary statistics as it is traditionally done, we used the drift diffusion model (DDM) which is a powerful model of perceptual decision making with strong neuro-behavioral underpinnings. Using DDM we tried to address three fundamental questions: (1) How are subjects vulnerable to SD differentially affected compared to resistant subjects. (2) Can these differences measured prior to SD predict performance

following SD? (3) If there are measurable differences in DDM parameters between vulnerable and resistant subjects, can these differences be supported and substantiated by neuro-imaging experiments? In addressing these questions, we intended to gain new insights into the neuro-behavioural underpinnings of differential vulnerability to SD and to construct a classification system that can use easily measurable behavioural data collected prior to SD to predict an individual's vulnerability to performance decline when sleep deprived.

To be able to reliably and efficiently use the DDM to address our research objectives, considerable improvements had to be made to the DDM which was only recently (Ratcliff, 2011) adapted to the one choice RT task like PVT. The statistical properties of the model were poorly understood. The model further lacked efficient ways to simulate and estimate the model parameters. Furthermore, even if we assume that there are measurable differences between the vulnerable and resistant subjects, it remains to be seen as to how these differences are influenced by experimental conditions. Given the importance of wearable devices and smartphones, the behavioural data may soon come from these portable devices instead of controlled laboratory environments. Therefore, the performance of our model must be ascertained across varying experimental conditions.

In this thesis, we made significant improvements in simulation and estimation of the model and understood the statistical limitations of the model. Using the DDM, we showed that the vulnerable subjects had a significantly slower rate of information uptake compared to resistant ones even prior to any SD. This was not anticipated by merely observing PVT performance. We tied these observations to actual brain functions using functional magnetic resonance imaging (fMRI) obtained from subjects in rested wakefulness prior to SD. Finally, we showed the DDM parameters are the most important metrics when it comes to characterizing vulnerability amongst the behavioral metrics. We constructed a classifier that was capable of predicting vulnerability using only behavioral data, taken prior to SD, accurately across data sets taken under varying experimental conditions. We showed that the classification rates were reliable, reproducible and promising. Our results will help clinicians gain a better understanding of differential vulnerability to SD and the classification model has the potential to be used in many practical settings.

Chapter 1

Introduction

We begin this chapter by providing a brief background on vulnerability to SD. We discuss the driving force behind this research as well as the objectives and scope of our work.

1.1 Motivation

The negative consequences of sleep deprivation (SD) are multifaceted and well document in literature (Pilcher & Huffcutt, 1996; Durmer & Dinges, 2005; Knutson et al., 2007; Grandner et al., 2010). Neurobehavioral effects include failure of sustained attention (Lim & Dinges, 2008), reduced information processing capacity (Kong et al., 2011, 2012), impaired memory consolidation (Diekelmann & Born, 2010), emotional dysregulation (Walker & van Der Helm, 2009), and altered decision-making (Walker & van Der Helm, 2009; Vandekerckhove & Cluydts, 2010). The loss of performance due to SD has significant economic, health and life cost (Colten et al., 2006). In many critical scenarios such as the military, hospitals, transportation and security the ability to perform when sleep deprived is a major part of work environment. Even minor differences in performance can have major ramifications in such scenarios. As per the American Academy of Sleep Medicine (AASM) an estimated 250,000 accidents every year (in the US) are related to lack of sleep. The annual economic impact of accidents related to SD is estimated to be between \$43 to \$56 billion (Leger, 1994). Williamson & Feyer (2000), showed that even moderate levels of SD produces impairments in cognitive and motor performance that is equivalent to legally prescribed levels of alcohol intoxication. Work related sleep loss and fatigue in medical training has become a source of increasing concern (Baldwin Jr & Daugherty, 2004). In

an intervention study, Landrigan et al. (2004); Lockley et al. (2004) showed that medical interns who obtained 5 hours of less sleep, had 50% more attentional failures, and committed 22% more serious errors on critical care units and made 5.6 times as many serious diagnostic errors while working a traditional schedule compared with a schedule of reduced work hours. Similar results have been obtained in studies of shift workers (Colquhoun, 1976; Folkard & Monk, 1979; Richardson et al., 1989), truck drivers (Stoohs et al., 1994; McCartt et al., 2000; Lyznicki et al., 1998), medical residents (Marcus & Loughlin, 1996; Steele et al., 1999; Geer et al., 1997), and airline pilots (Neri et al., 2002; Price & Holley, 1989; Bourgeois-Bougrine et al., 2003). Apart from direct consequence of loss of vigilance, SD also plays an important role in incidence of many diseases. SD has been associated with increased all-cause mortality, adverse cardiovascular outcomes, metabolic disorders, obesity and type 2 diabetes (Taheri et al., 2004; Spiegel et al., 2005; Knutson et al., 2007). Gangwisch et al. (2006) showed that SD is a significant risk factor for hypertension and it continued to be significant even after controlling for obesity and diabetes. The progressive decline in sleep duration over the decades as suggested by various polls across different countries (National Sleep Foundation, US; Gallup, US; Great British Sleep Survey, UK; Singapore Sleep Society, Singapore), adds to the importance of this study.

Sleep deprivation is thought to impair neurobehavioral functioning by destabilizing performance, as evidenced by the capacity to perform well for short periods of time, interrupted by occasional attention failures (Doran et al., 2001). The extent to which sleep loss affects performance varies widely across individuals, with some subjects remaining relatively unaffected while others show severe cognitive impairment (Doran et al., 2001). Notably, between-subject differences in performance are trait-like and stable across repeated exposures to sleep deprivation, irrespective of sleep history (H. Van Dongen, Baynard, et al., 2004; H. Van Dongen, Maislin, & Dinges, 2004; Lim et al., 2007). These findings lead to the concept of *SD vulnerability*, and suggest that there is a stable neuro-cognitive basis for individual differences in cognitive vulnerability to sleep loss.

Despite over a century of sleep research, vulnerability remains a relatively new and poorly understood concept. In this thesis, we combine medical imaging, statistical modeling and machine learning to gain insights into the science of differential vulnerability to SD. Pharmaceutical companies, clinicians and neuroscientists

are keen to gain a better understanding of the mechanisms underlying vulnerability, as it may shed new light into the understanding of sleep in general and the plethora of diseases that associate with it. Being able to predict an individual's relative performance decline when sleep deprived has important implications for occupations that require long work hours and night shift work.

1.1.1 Wearable devices, Smartphones and Sleep

Slowly but surely smart phones are becoming ubiquitous. This is further accelerated by rapidly dropping prices of smartphones especially on the AndroidTM(Google Inc., Mountain View - California) platform. As of December of 2013, there are already 1.43 billion smartphone users worldwide which is estimated to reach 2.5 billion in 2017 (Source: eMarketer Research, NY USA, Figure 1.1B). These devices are also becoming portable and distributed data acquisition systems. So much so that an entire industry of wearable devices that work in conjunction with smartphones have come up (Figure 1.1A). This includes devices capable of measuring heart rate, skin temperature, perspiration, calories burned, sleep time and quality across the day. A strong motivation for the current work is to leverage these technologies in the future to predict sleep vulnerability on mass scale and provide unique insights into sleep dynamics above and beyond what is possible currently.

Figure 1.1: A: Most popular wearable biosensor devices as of 2014. Nike, Fitbit and Jawbone combined constitute 97% market share. B: Number of smartphone users across time. The dotted lines are projections.

1.2 Research statement, scope and objectives

The main aim of this research is to develop a framework that provides a unifying picture of vulnerability to SD. We intend to further our understanding of how vulnerable subjects differ from resistant subjects, the underlying neuronal architectures that mediate these differences, and finally, to predict vulnerability reliably and efficiently using only rested data collected prior to any SD. One of the most sensitive measures of performance impairment by sleep deprivation is vigilance (Lim & Dinges, 2010), commonly assessed using the Psychomotor Vigilance Task (PVT) (Dinges & Powell, 1985). During the PVT, participants maintain their fastest possible reaction time (RT) to a simple visual stimulus presented at random inter-stimulus intervals (ISI) ranging from 2 to 10 seconds. Traditionally, the RTs are analysed using summary statistics like mean and median. Unfortunately, due to nature of the RT distribution these summary statistics fail to capture the full distribution. More importantly, these metrics are purely descriptive in nature and lack any real biological basis and provide little insights into the mechanics of the underlying process. To achieve our goals, we move beyond the traditional ways of behavioral and clinical Psychology and apply the latest advances in statistical modeling and machine learning. Specifically, we used the Ratcliff drift diffusion model (Ratcliff & Van Dongen, 2011) (DDM) which is a powerful model of perceptual decision making for single choice RT experiments like the PVT. The DDM allowed us to understand the baseline differences between resistant and vulnerable subjects in terms of the underlying cognitive processes. We conducted functional Magnetic Resonance Imaging (fMRI) studies conducted on the resting brain (i.e. in the absence of any task) to verify if the findings from DDM analysis could be substantiated by independent imaging analysis. Finally, we constructed a classification system incorporating all our prior knowledge to reliably and cheaply predict the subject specific vulnerability to SD using only rested RT data derived prior to SD.

To carry out our investigation, the DDM as proposed by Ratcliff et al., 2011 was substantially improved. The statistical properties, closed form solution and efficient methods for estimating and simulating the model were developed. The resting state fMRI analysis were carried out using model free, data driven methods. Generalized linear models were extensively used to test hypothesis. All studies were conducted within the context of total SD using the PVT as a measure

of vigilance. It should be remembered that while vigilance decrements are an important and robust measure of performance decline in sleep deprived persons, other cognitive domains may not be similarly affected. Therefore our results must be interpreted within this context.

1.3 Issues and Challenges

The strongly multidisciplinary nature of our work presents some unique issues and challenges. The present work can be divided into three rough categories:

- (i) **Model Improvement:** This includes understanding the statistical properties and limitations of the DDM, developing fast and efficient methods to simulate and estimate the parameters of the model.
- (ii) **Design of Experiments:** Clinical trials involving humans are not only costly but also time consuming. Therefore it was of paramount importance that the experiments including the hypothesis we wanted to test were well thought of before hand. We collaborated with multiple laboratories working in the forefront of sleep research to access data and resources that best suited our research goals. Some of the clinical trials were guided by our experimental results and were conducted longitudinally overs months. Ideally, we would like to move away from expensive and time consuming albeit controlled laboratory settings to cheap but unconstrained mobile platforms and wearable devices that can be deployed in field conditions. To be able to do so, the model's predictive capabilities must be tested under widely different experimental conditions. This also necessitates the development of software solutions that would allow inexpensive and cross platform acquisition of PVT data. Currently, such solutions exit, but are very expensive and only available on limited platforms.
- (iii) **Imaging Analysis:** Our investigation involves fMRI scans obtained under rested condition in the absence of any task. Resting state fMRI is a relatively new and powerful method for evaluating regional interactions that occur when a subject is not performing an explicit task. In the absence of explicit task, the 4D space-time data obtained from fMRI is essentially unconstrained making it significantly more difficult to find patters from. Despite these

challenges, the major advantage of resting state fMRI is that if any patterns associated with vulnerability to SD is found, especially before any incidence of SD, then that would imply that these differences are intrinsic properties of the brain mediated possibly by stable functional or structural differences. Combined with the DDM analysis, it provides a powerful framework to understand SD vulnerability.

1.4 Outline

Chapter 1 introduces the basic motivation and idea behind this research work along with the scope and objective. Chapter 2 provides literature review of some of related works in this field. This includes two separate sections, one discussing the advances in the understanding of general and differential decline of performance with SD. And the other discussing the advances in the modeling of simple decision process. This includes an introduction to the DDM. In chapter 3, the statistical analysis and improvements in the DDM are discussed. In chapter 4 we lay out the primary questions laid out in our report. We test our hypothesis to see if DDM parameters are capable of discriminating vulnerable subjects from resistant ones in the rested condition. We discuss the possible implications of our results. In chapter 6, we discuss the imaging analysis. A brief introduction of the issues and challenges concerning resting state imaging studies are presented. We interpret the results within the context of DDM. In chapter 5, we construct a classifier capable of predicting the vulnerability to SD from rested RT data. The most important measures derived from baseline PVT performance that can reliably predict vulnerability to SD are reported. In chapter 7, we summarize the work in this thesis and provide a conclusion to the same. We also provide directions for future extensions of the work. In Appendix A, we discuss currently available software and hardware solutions to acquire PVT data. We also discuss the technical challenges in developing a cheap and widely deployable software based PVT acquisition system that can be used in conjunction with the DDM to predict vulnerability on a mass scale. Finally, such a system is developed with the hope that it would be instrumental in taking the current work further. As the chronological ordering of references are important, we have followed American Psychological Association (APA) reference style guidelines in this thesis.

Chapter 2

Review of Literature

The review of literature related to this study has been organized into four sections. In the first section, we discuss the existing literature on performance decline with SD, the neurophysiological models of sleep regulation and vulnerability to SD. One of the most sensitive measures of performance impairment by SD is vigilance (Lim & Dinges, 2010), assessed using mental chronometry (i.e., using RT tasks like PVT). Therefore, in the second section, we discuss the standard way RT distributions are studied. In the third section, we discuss the neurobiological basis of simple decision making and models based on the underlying principles. And in the forth section, we discuss the DDM and its advantages over other models. To maintain a fluid presentation, the literature review for the imaging study, which runs tangential to the current discourse, is discussed in Chapter 6.

2.1 Sleep Deprivation and Vulnerability

2.1.1 Quantifying Performance: The PVT

Degradation of vigilance is probably the most robust alteration of neurobehavioral performance in healthy, sleep-deprived young adults (Lim & Dinges, 2010). The Psychomotor Vigilance Task or PVT proposed by Dinges et al. in 1985, is a proven assay for evaluating vigilance. The PVT is particularly attractive because of ease of scoring, simple metrics and convergent validity (Dinges & Powell, 1985). The test is short, free of learning effects (H. P. Van Dongen et al., 2003) and aptitude difference making it suitable to use on subjects from widely different backgrounds. Its simplicity makes it attractive for mathematically modeling how performance fluctuates according to time-of-day. It is a sustained-attention, RT task that measures the speed with which subjects respond to a visual stimulus. Standard

PVT runs for 10 minutes and the subject is shown a display terminal on which a light appears randomly and a RT counter starts running to which the subject has to respond as soon as possible via a hand held switch. The interval after which a visual stimulus is shown is known as Inter-Stimulus Interval (ISI). In the standard PVT, ISI is distributed uniformly between 2 to 10 seconds. The standard PVT typically results in 95 responses. Figure 2.1 shows a subject taking the PVT using a portable PVT monitor.

There are many variants of the standard PVT. For instance there is a shorter 5 minute variant of PVT which is shown to be viable alternative to the 10 minute test (Loh et al., 2004), there are palm held PVT devices (Thorne et al., 2005), there are instances especially in imaging studies where subjects take the PVT lying down inside a Magnetic Resonance Imaging machine. PVTs longer than 10 minutes are uncommon, this is because longer-duration PVTs are more affected by time-on-task effects (H. Van Dongen et al., 2011). While all variants of PVT are valid it makes comparing results from different set of studies difficult. Therefore, the experimental conditions under which PVTs are taken, play an important role in our investigation.

2.1.2 Performance Degradation with SD

Early investigators studying the effects of SD assumed that exposure to extended periods of SD would successively diminish the ability to perform neurobehavioral tasks. The earliest scientific study of degrading effects of SD could be cited to Patrick & Gilbert (1896). They reported that 90 hours of continuous wakefulness caused both motor and cognitive deficits in three adults, although these findings were not replicated in subsequent experiments (M. Smith, 1916; Robinson & Herrmann, 1922; Robinson & Richardson-Robinson, 1922). Between 1923 to 1934, Kleitman published a series of reports on SD that cleared these discrepancies. His major finding (Kleitman, 1923) was that even after days of sleep deprivation (60 to 114 hours), subjects could often transiently perform at baseline levels on most tasks. There was therefore no evidence to suggest that SD could eliminate specific motor and cognitive function. Instead, during SD most abilities could be maximally utilized by a *new effort*. Further research by Warren & Clark (1937) showed that SD affected neurobehavioral functions by initially destabilizing performance rather than eliminating capacity to perform. Williams et al. (1959)

Figure 2.1: A subject taking the PVT in a reclined position. Inset: A portable PVT monitor, courtesy of artisan-scientific.com.

found that 78 hours of SD caused an 18-fold increase in the number of performance lapses (defined as twice the subjects baseline mean) even though subjects were able to perform fast and accurately throughout the 78 hours of waking. They further observed that lapses were more likely to occur when electroencephalogram (EEG) waveforms showed evidence of transition to sleep.

This observation led to so called *lapse hypothesis* which hypothesized that performance during SD was affected by brief moments of low arousal during which subjects were unable to respond. This meant that SD affected performance variability rather than causing a smooth overall decline. The *wake state instability* hypothesis (Doran et al., 2001) was proposed under similar lines of reasoning. It hypothesizes that two competing forces are in act when sleep deprived the homeostatic drive for sleep and compensatory effort to perform. When homeostatic drive for sleep persists, RT slows down and lapses increase while when compensatory efforts prevail, performance remains relatively unaffected. While appearing very similar to lapse hypothesis there are important differences to be noted. The

lapse hypothesis suggests that performance during SD is essentially normal until it is disrupted by brief periods of low arousal (or lapses). Contrary to this the state instability hypothesis suggests that variability in neurocognitive performance increases as homeostatic sleep-initiating mechanisms become progressively more affected by SD. In other words, wake state instability occurs when sleep initiating mechanisms repeatedly interfere with wakefulness and depending on the severity of SD make cognitive performance increasingly variable and dependant of compensatory mechanisms (see Figure 2.2). From a theoretical standpoint, what the wake state instability suggests is that there are multiple, parallel and distinct mechanisms by which the wake and sleep states interact giving rise to the overall behavioral observations. The wake state instability hypothesis is now well established and is consistent with the established model of sleep regulation (discussed in later section). The interpretation of our results must be made within the context of wake state instability and associated models of sleep regulation.

Figure 2.2: PVT RT in milli-seconds for a representative subject. Even after 12 and 84 hours of SD, the subject was able to perform at baseline levels albeit, with a clear increase in the variability in performance. Courtesy of Doran et al. (2001).

2.1.3 Vulnerability to Sleep Deprivation

The decline of performance with SD is well established with over a century of research backing it up. H. Van Dongen, Baynard, et al. (2004); H. Van Dongen, Maislin, & Dinges (2004), showed that not only does the performance vary significantly between subjects, but also that this subject specific difference is stable in time

showing a trait like feature. In simple terms, if a group of subjects are ranked according to their performance on a specific behavioural task after SD and this experiment is repeated in time, then the ranking will remain more or less same. Furthermore, while the inter-individual differences are both significant and stable across time, poor performance in one particular type of task does not imply poor performance in another. Specifically, these trait like inter-individual differences tend to cluster along three independent dimensions (see Figure 2.3): subjective measures, objective measures of sustained attention and cognitive processing ability (H. Van Dongen, Baynard, et al., 2004). In this investigation we are specifically interested in the objective measures of SD, as they are of most practical value. Therefore, care must be taken when extending the implications of our findings to more general scenarios.

Mu et al. (2005); Lim et al. (2007), using imaging studies, showed that these stable performance after SD are possibly mediated by stable neuronal architectures. More importantly due to the intrinsic nature of these architectures, these behavioural performance (E. Chua et al., 2014) as well as brain activation (Caldwell et al., 2005; Y. L. Chuah et al., 2006; Chee et al., 2006) differences are observable even prior to SD. Such findings raise the possibility that baseline measures can be used to predict how well a person will perform when he/she is deprived of sleep. It has been hypothesized, for example, that genetically-determined differences in buildup and dissipation of sleep pressure, as assessed by the amount of electroencephalogram slow wave activity in non-rapid eye movement (NREM) sleep, can influence cognitive responses to sleep deprivation (Viola et al., 2007; Goel et al., 2010; Bachmann et al., 2012; Bodenmann et al., 2012). It has yet to be established, however, whether heritable differences in sleep structure contribute to differences in performance during sleep loss. Nonetheless, it provides strong case to construct a classifier to predict vulnerability using rested data. In the next section, we will discuss about established model of sleep regulation, which is important to understand the mechanics of sleep.

2.1.4 Model of Sleep Regulation

The two process model of sleep regulation proposed by Borbély (1982), posits that sleep is regulated by the interaction of two processes: the homeostatic process S and the circadian process C . The homeostatic process is responsible for the rise

Each of these processes are mediated via separate neuronal architectures and to a large extent can be assumed to be independent of each other. In the most simplest form, the interaction between the processes are assumed to be linear. The time course of Process S is derived from the changes of EEG slow-wave activity (SWA, EEG power in the 0.75-4.5 Hz range). The process C, is independent of sleep and waking, modulates the thresholds which determine the onset and termination of a sleep episode, respectively (see Figure 2.4). The exact model equations have been derived from experiments and a compilation can be found in Achermann & Borbély (2003). Based on refinements of the two process model, many variations have been proposed (see Achermann & Borbély (2003) for an overview). Within the context of our investigation, the two process model in its simplest form provides a powerful conceptual framework for the analysis of experimental data and results without overcomplicating the analysis with irrelevant technicalities.

Figure 2.4: Two-process model of sleep regulation. Process S indicates the homeostatic built-up of sleep pressure and Process C represents the circadian rhythm. The difference between the two processes quantify the sleep pressure.

2.2 Mental Chronometry

Mental chronometry is the use of RTs in perceptual-motor tasks to infer the content, duration, and temporal sequencing of cognitive operations and it is the

core paradigm of experimental and cognitive psychology. For our investigation, PVTs are the primary behavioural task to quantify vigilance. The end result of such an experiment is a set of RTs, which must be analyzed further. In the next section, we will discuss the standard ways RTs are processed, their shortcomings and possible solutions.

2.2.1 Standard RT Analysis

RTs have been used for a long time in cognitive psychology to measure behavioral performance (Luce, 1986). To draw inferences about mental processes researchers initially relied upon summary statistics like mean, median and standard deviation of RT. It was soon realized that these measures fail to capture the complete RT distribution. RT distributions are notoriously skewed (Figure 2.5) and more often than not censored (due to limitation of time). Ignoring the RT distribution shape can have detrimental effect on the analysis. To address these issues, early researchers tried trimming the data or apply non-linear transformations (like reciprocal transformation) to normalize the RT distribution. While this makes the data more symmetrical but this is at the cost of throwing away or ignoring important aspects of the tail. Using higher order moments like skewness and kurtosis to capture full information contained in the RT distribution has severe drawbacks (Ratcliff, 1979). Sampling variances associated with higher order moments is large, making it difficult to get good estimates with practical size of RT samples. Furthermore, higher order moments are extremely sensitive to outliers. An alternative approach is to explicitly assume a model for the shape of RT distribution. Soon focus shifted to parameterized statistical models to describe the distribution. In the next section we will discuss some of the popular models.

2.2.2 Statistical Model of RT distribution

The advantage of parameterized statistical models is that they capture the full RT distribution. Many statistical models were proposed like gamma (McGill & Gibbon, 1965) and log-normal distributions (Luce, 1986) but they are not popular and do not provide good enough fit. Hohle (1965), proposed a decomposition of RT into decision and residual component. He assumed that the decision component has exponential distribution and the residual has normal distribution and both the components are independent. This results in an ex-Gaussian distribution which

Figure 2.5: A sample reaction time (RT) distribution. RT distributions tend to be strongly skewed towards right.

is convolution of exponential and normal distribution. It has three parameters μ, σ and τ , where μ and σ are the mean and standard deviation of normal component and τ parameterizes the exponential component. The expression for the ex-Gaussian is:

$$f(t) = \frac{(e^{\frac{-(t-\mu)}{\tau} + \frac{\sigma^2}{2\tau^2}})}{(\tau\sqrt{2\pi})} \int_{-\infty}^{\frac{(t-\mu)}{\sigma} - \frac{\sigma}{\tau}} e^{-y^2/2} dy \quad (2.1)$$

The assumption made by Hohle remains unproven, although, it was very successful as a convenient summary of empirical RT distribution (Heathcote et al., 1991; Ratcliff, 1988).

While these models provide a good summary of the RT distribution and are certainly better than using simple central tendencies or summary statistics they still have a major downside; these models are purely descriptive, they lack any neurobiological basis. In the absence of a theoretical description behind the model, it is not possible to tie the parameters of the model to the underlying cognitive process and the parameters of the model are in some sense, *arbitrary*. Therefore models inspired by neurobiology of decision process are desirable. In the next section, we will discuss mathematical models of perceptual decision making which are based on the neural basis of decision making as observed with experimentations.

2.3 Models of Perceptual Decision Making

2.3.1 Signal Detection Theory

Signal detection theory (SDT) is one of the most successful formalisms ever used to study perception (Gold & Shadlen, 2007). SDT provides a framework to convert a single observation of noisy evidence into a categorical choice. Most sensory motor tasks can be thought of as a form of statistical inference (see Parker & Newsome (1998) for a review). Therefore SDT is the natural framework to study them. It starts with the basic assumption that all decision process takes place in the presence of some uncertainty. SDT provides a mathematical structure to this notion. A single observation of noisy sensory evidence e is gathered based on which a particular hypothesis h_1 to $h_n, n \geq 1$ is selected or rejected. The evidence e is derived from the senses and might be the spike count from a single or group of neurons or it might be the difference in spike counts between groups of neurons. It is important to note that e is caused by a stimulus controlled by the experiment and is regarded as a random variable as it is corrupted by noise. The decision process requires the construction of decision value (DV) from the evidence e . SDT provides a flexible framework in that it allows formation of decisions that integrate priors $P(h_i)$, evidence and subjective costs and benefits associated with each of the potential outcomes. Accumulator models which rely on sequential analysis are a natural extension to SDT that accommodates multiple pieces of evidence in time. In these models the noisy evidence is accumulated and the DV is updated with new evidence until it is sufficient to make a decision.

2.3.2 Accumulator Models

Sequential analysis differs from SDT in one important aspect; it assumes that the decision has two parts, the usual one between hypothesis h_1 to h_n and another that decides whether or not it is time to stop the process and commit to a particular hypothesis. Figure 2.6 illustrates the framework. The decision process relies on a sequence of observation in time. After each acquisition, the DV is computed using some function $f_i(e)$ using evidence e_i obtained up to that point, now the process may continue, in which case the accumulated evidence is carried forward or a decision can be made based on the value of DV at that point. In this context e_0 can be thought of as prior probability of the hypothesis. Notice that both

the criteria that stop the process as well as the function f_i which converts the accumulated evidence to a DV could be dynamic and vary with time. Based on different stopping criteria c_i and DV functions f_i we can get different accumulator models. We are interested in a specific kind of accumulator model called the drift diffusion model (DDM) which assumes that the evidence is sampled from a normal distribution in infinitesimal time steps with the process being stopped when the accumulated evidence exceeds a fixed positive or negative number. The model is highly successful in modeling most two choice decision processes and recently adapted to a single choice task like the PVT. Before we discuss the DDM, we will discuss some of the experiments that show the neural basis of perceptual decision making. The accumulator model in general and DDM in particular are derived from such experiments.

Figure 2.6: General framework of sequential analysis model.

2.3.3 Perceptual Decision Making: Neural Basis

The first series of experiments investigating decision making were conducted on primates. Single unit recording studies in monkeys show causal link between behaviour and the activity of neuronal population in sensory regions (Shadlen et al., 1996; Salinas et al., 2000; Gold & Shadlen, 2002; Romo & Salinas, 2003). Similar studies (H. Heekeren et al., 2004; Pleger et al., 2006; Kaiser et al., 2007) have been conducted on humans. These studies not only demonstrate that the representation of evidence in sensory regions is used to make perceptual decisions

but also provide detailed knowledge about the nature of these representations. These experiments strongly support the accumulator model of decision making - sensory evidence is integrated and decision variable is constructed out of it. These studies show that the neural activity (spike count) in areas involved in decision making, increases gradually and saturates until a response is made. More importantly the rate of information is directly proportional to the difficulty of the trial. Particularly, they make way for the DDM (see Figure 2.7). Although, neurophysiological studies show that neural systems not involved in the decision process (like the motor systems) are involved in selecting and planning certain actions which are important from the perspective of decision making. Therefore, the process of decision making is not strictly serial. Notwithstanding the fact that the accumulator model is only an approximation, the DDM still performs very well and is now a well established model of perceptual decision making with multiple experiments supporting it. In the next section we will discuss the DDM in broader detail.

2.4 The Drift Diffusion Model

As discussed in the previous section, the DDM is inspired by experiments on primates and humans and is a good approximation of the underlying neurobiology of decision making. The DDM is based on the diffusion process which is a stochastic process that develops through time. The diffusion process was first used in the context of memory retrieval by Ratcliff in his seminal 1978 paper. A Markov process in which continuous change of state space occurs is called a diffusion process. If the process is characterized by the random variable $X(t); t \geq 0$, denoting the position of the process in state space at time t , then the process can be studied using transition probability densities $p(x_0, t_0; x, t)$ which give the probability density function (pdf) of $X(t)$ as a function of x conditional on $X(t_0) = x_0$. In other words,

$$\text{prob}(a < X(t) < b \mid X(t_0) = x_0) = \int_a^b p(x_0, t_0; x, t) dx \quad (t_0 < t) \quad (2.2)$$

The variable x_0 and t_0 are the backward variables since they refer to earlier time and x and t are called forward variables following similar reasoning. By

Figure 2.7: Top: The accumulator model assumes that the perceptual decision making is a serial process progressing from perception to action. Bottom: Diffusion model is an accumulator model for the neurobiology of decision making inspired by experiments. The figure shows the model for a two choice visual task (house or face?). It assumes that decisions are formed by continuously accumulating sensory information until one of the response criteria are met (a or -b). The rate of information accumulation μ , models the firing rate of the neurons involved in the decision process. The rate is lower (red path) for a difficult task with low sensory evidence and higher (green path) for a easy task (high sensory information). The moment to moment fluctuations in the sample path reflect the noise in the decision process. Figure adapted from H. Heekeren et al. (2004).

virtue of Markov property, $p(x_0, t_0; x, t)$ will satisfy the Chapman-Kolmogorov equation. The Chapman-Kolmogorov equation (Gardiner et al., 1985) is an identity relating the joint probability distributions of different sets of coordinates on a stochastic process. In our case, $p(x_0, t_0; x, t)$ will satisfy the forward and backward Kolmogorov equations 2.3 and 2.4, where $\beta(x, t)$ and $\alpha(x, t)$ are the infinitesimal mean and variance of the process.

$$\frac{1}{2} \frac{\partial^2}{\partial x^2} \{ \alpha(x, t) p \} - \frac{\partial}{\partial x} \{ \beta(x, t) p \} = \frac{\partial p}{\partial t} \quad (2.3)$$

$$\frac{1}{2} \alpha(x_0, t_0) p \frac{\partial^2 p}{\partial x_0^2} - \beta(x_0, t_0) \frac{\partial p}{\partial x_0} = - \frac{\partial p}{\partial t_0} \quad (2.4)$$

Based on the stopping criteria boundary conditions are then imposed on the

stochastic differential equation. For example for a two hypothesis (or two choice) task we can assume that the process starts at some point z and the boundaries are at $y = 0$ and $y = a$ (Figure 2.8, right) then the boundary conditions are:

$$p(z, 0; x, 0) = \delta(x - z); p(z, 0; a, t) = 0; p(z, 0; 0, t) = 0 \quad (2.5)$$

Similarly for a single hypothesis (one choice) task we assume that the process starts at 0 and the boundary is at $y = a$ (Figure 2.8, left). Then the boundary conditions are:

$$p(0, 0; a, t) = 0; p(0, 0; x, 0) = \delta(x) \quad (2.6)$$

The function $\delta(x)$ is the Dirac delta function, a degenerate probability function with all its mass at 0. At the boundary itself density must be equal to 0 so that the terminated process disappears from transition density. When β and α are fixed, which is what we are interested in, Equation 2.4 along with boundary conditions (Equation 2.5 or 2.6) describes a diffusion process with constant drift and constant variance with absorbing boundaries. If $\beta = \mu$ and $\alpha = \sigma^2$ then such a process is equivalent to a Wiener process (or standard Brownian motion) with drift μ and variance σ^2 . The easiest way to theoretically handle such diffusion process is to think of it as a continuous limit of simple random walk. This approach gives considerable insights into the continuous diffusion process and in most cases allows us to find a complete probabilistic description of the continuous process by studying the system under the limiting condition of zero time intervals or $\Delta t \rightarrow 0$. This approximation is very useful when a closed form solution is not available.

Figure 2.8: A diffusion process with constant mean β and variance α is equivalent to a Wiener process. Shown here are sample paths for such a diffusion process modeling task with one and two hypothesis respectively.

2.4.1 Diffusion Process Applied to Perceptual Decision Making

Figure 2.9: Components of reaction time.

The diffusion process models only the decision part of the accumulator model. The diffusion process, when applied to behavioral tasks has additional complexities (Ratcliff & Rouder, 1998). The decision process is broken down into three parts. From the onset of stimulus, it takes some time t_1 to encode the stimulus after which the decision process starts which is modeled using diffusion process. Once the boundary is hit decision process stops after which some more time t_2 is required to decode this decision and act. If the total decision time is T_d then the reaction time (RT) is simply the sum of all times spent in encoding, decoding and decision (Figure 2.9). t_1 and t_2 are normally combined and referred to as non-decision time T_{er} .

$$\text{Reaction Time} = t_1 + T_d + t_2 = T_d + T_{er} \quad (2.7)$$

For a two choice (two hypothesis) tasks there are two decision boundaries, without loss of generality one boundary is assumed to be at 0. This gives rise to two parameters, the starting point z_0 and the other boundary a . The starting point z_0 is normally expressed in terms of boundary separation a and encodes the relative value or bias of one hypothesis with respect to other. For instance a z_0 value of $a/2$ suggests an unbiased attempt at the task. The drift rate μ and σ^2 are parameters of diffusion model. It turns out that σ^2 is simply a scaling parameter, in other words, if σ is doubled the other parameters of the model can be doubled to get exactly same model. The choice of σ is arbitrary but we will fix its value at 0.1 in accordance with Ratcliff for ease of comparisons. While for a single trial there

are four parameters μ, z_0, T_{er} and a , when studying subjects some or all of these parameters can be allowed to vary across trial. While variability in drift rates is expected as subjects do not encode stimulus in exactly the same way every time, variability in other parameters may not be so intuitive. A simple diffusion model where parameters do not vary fails to fit experimental RT distributions. Moreover, this affects estimation of parameters adversely by introducing large biases and standard deviation. The RT distributions obtained from experiments can be thought of as contaminated by alternate processes like fast guesses, distractions, changes in motivation and simple RT outliers. The variability introduced in the parameters is simply an implicit way of modeling these contaminants. Variability in boundary a is observed to be of least significance while variability in drift is absolutely necessary to explain experimentally obtained RT distributions. The effects of parameter variability on estimators are discussed at length in (Ratcliff & Tuerlinckx, 2002). Most frequently used two-choice RT task diffusion model has seven parameters:

- (i) Mean drift rate: ξ
- (ii) Across trial variability in drift rate: η
- (iii) Boundary separation: a
- (iv) Mean starting point: z
- (v) Across trial variability in starting point: s_z
- (vi) Mean non-decision time: T_{er}
- (vii) Across trial variability in non-decision time: s_t

Drift is assumed to have a normal distribution $N(\xi, \eta^2)$ while other parameters have a uniform distribution. The model is illustrated in Figure 2.10. These seven parameters constitute the parameter vector $\Theta \in \Re^7$ such that,

$$\Theta = [\xi, \eta, a, z, s_z, T_{er}, s_t]^T \quad (2.8)$$

where $[.]^T$ is the transpose operator.

Figure 2.10: Seven parameter diffusion model for two choice RT task. The non-decision time and the starting point are assumed to be distributed uniform. The drift varies from trial to trial according to a normal distribution.

2.4.2 Extending DDM to The PVT

The PVT, which we will be using extensively in this investigation is a one choice task. The DDM was recently adapted to one choice RT tasks (Ratcliff & Van Dongen, 2011). In the one choice model there is only one boundary. Without loss of generality the process is assumed to start from 0 and the boundary is placed at a . As a result of this the number of parameters reduce to five, $[\xi, \eta, a, T_{er}, s_t]^T$. The model is illustrated in Figure 2.11. With these five parameters the model is not uniquely identifiable. If the value of a is doubled ξ and η can be doubled to give the same distribution of RTs. Due to the difficulty in uniquely identifying model parameters in single boundary tasks (Ratcliff & Van Dongen, 2011), we followed Ratcliff's suggestion to use uniquely identifiable parameter ratios (ξ/a and η/a). This resulted in a model with four parameters $\Theta = [\xi/a, \eta/a, T_{er}, s_t]^T$. In other words, the drift parameters of one subject cannot be compared with another without first normalizing their estimated boundary values. For the sake of simplicity, from this point onwards we will use drift and drift ratio interchangeably. When comparing the drift parameters across group or across subjects, it is implicit

that they were normalized by the estimated boundary parameter. Methods for simulating and estimating parameters of the one choice DDM will be discussed in detail in Chapter 3. As we are using the DDM in the context of PVT, unless specified otherwise, DDM refers to the one-choice DDM.

Figure 2.11: Five parameter diffusion model for one choice RT task. The non-decision time is assumed to be distributed uniform. The drift varies from trial to trial according to a normal distribution.

2.4.3 Experiments Supporting The DDM

An attractive feature of diffusion modeling is that it can predict the response time distribution under different contexts (Ratcliff, 2002) and varying levels of noise (Ratcliff & Tuerlinckx, 2002). The model has been tested by manipulating various facets of the decision process and then observing the corresponding change in diffusion parameters (Voss et al., 2004). They used a color discrimination task to investigate how changing specific aspects of decision process had effects on the corresponding parameters in diffusion model analysis. They found that decision thresholds were higher when subjects were motivated towards higher accuracy, drift rates were lower when stimulus were harder to discriminate. The ability of the diffusion process to separate and identify the different components of the decision

process allowing fine-grained interpretations is what makes it so attractive. For instance Ratcliff et al. (2003) using the diffusion model to study the effect of aging on brightness discrimination task came to the remarkable conclusion that older subjects perform just as good as young subjects in all aspects of performance, except those directly involved in executing the decision (parameterized by T_{er}).

Among the numerous studies using the PVT to characterize performance in sleep-deprived persons, there exists only one (Ratcliff & Van Dongen, 2011) that used diffusion modeling to explain behavior. Diffusion parameters in the SD condition were compared to those obtained in the non-deprived condition. Although SD was found to negatively affect several diffusion model parameters, only the effect on the drift (ξ) parameter was statistically significant. How DDM parameters are differentially affected between subjects based on their vulnerability to SD is not yet known. Figure 2.12, provides a bird's eye view of the time-line of the most important findings pertaining to our research.

2.5 Summary

In this investigation, we want to improve the understanding of differential vulnerability to SD. This requires integration of different fields including clinical and behavioural psychology, neuroscience, statistics and machine learning. In this chapter, we have reviewed the literature that provides broad context to the work we are doing. We discussed the shortcomings of standard RT measures and earlier models of perceptual decision making compared to the DDM. Some of the literature which are essential in our analysis but do not directly relate to our objectives are discussed in their respective chapters.

Figure 2.12: Timeline shows the major findings in the context of our investigation. While all findings are important, the ones marked in red are heavily relied on in the current work.

Chapter 3

The One Choice DDM: Simulation and Estimation

Despite the popularity of one choice RT tasks (like the PVT) in cognitive psychology, the DDM was only recently adapted (Ratcliff & Van Dongen, 2011) to one choice tasks. The wide spread use of the model is restricted due to complexity involved in estimating the model parameters from data. Furthermore the current method for simulating the model is prohibitively slow. We propose improvements in the simulation process that considerably improves runtime. We also derive a closed form solution for the model and propose a maximum likelihood estimator to determine the parameters. In the next section we will discuss the statistical properties of the model, its limitation, existing methods for simulating and estimating the model and improvements on it. The current analysis is not only important for the current investigation but also essential for the widespread use of one choice DDM in the clinical community.

3.1 Approximate the Diffusion Process

The closed form solution for the DDM has not yet been derived. In the absence of a closed form solution, the easiest way to generate samples from the model is to approximate the diffusion process by a simple random walk. This is done by discretizing the time and evidence axes into small steps. In a simple random walk

The analysis presented in this chapter appears partly in Patanaik, A., Zagorodnov, V. and Kwoh, C. K. "Parameter estimation and simulation for one-choice Ratcliff diffusion model.", Symposium on Applied Computing-Association for Computing Machinery (SAC-ACM) Special Interest Group on Applied Computing (SIGAPP), 24-28 March 2014. doi: 10.1145/2554850.2554872. Used with permission.

successive one step transitions are allowed only to neighboring states only. If the step size is Δ taking place in small time intervals τ , then at the limiting case when $\tau \rightarrow 0$ we will get the diffusion process. Without loss of generality let us consider a particle at the origin, after each time step τ , it takes a step Z where the probability of taking a positive step is p and probability of taking negative step is q , then

$$\text{prob}(Z = +\Delta) = p \quad (3.1)$$

$$\text{prob}(Z = -\Delta) = q, \quad (3.2)$$

Because all steps are assumed to be mutually independent, the moment generating function (mgf) of one step can be easily computed as,

$$E(e^{-\theta Z}) = pe^{-\theta\Delta} + qe^{\theta\Delta} \quad (3.3)$$

After time t there will be t/τ steps resulting into total displacement of $X(t)$, which is the sum of the n independent random steps each with mgf described in 3.3. Therefore, mgf of $X(t)$ is

$$E(e^{-\theta X(t)}) = (pe^{-\theta\Delta} + qe^{\theta\Delta})^{t/\tau} \quad (3.4)$$

The mean and variance of $X(t)$ are

$$E(X(t)) = \left(\frac{t}{\tau}\right)(p - q)\Delta, \quad V(X(t)) = \left(\frac{t}{\tau}\right)(4pq)\Delta^2 \quad (3.5)$$

Under limiting conditions as $\tau \rightarrow 0$ and $\Delta \rightarrow 0$ the mean and variance of the simple random walk should converge to drift and variance parameter of the diffusion process. That is

$$\left(\frac{t}{\tau}\right)(p - q)\Delta \rightarrow \mu * t \quad \text{and} \quad \left(\frac{t}{\tau}\right)(4pq)\Delta^2 \rightarrow t\sigma^2 \quad (3.6)$$

These limits will be satisfied when

$$\Delta = \sigma\sqrt{\tau}, \quad p = \frac{1}{2} \left(1 + \frac{\mu\sqrt{\tau}}{\sigma}\right) \quad (3.7)$$

Note that σ here is the variability in the diffusion process (not the across trial variability in drift η in the DDM) and as discussed in Section 2.4.1 acts as a scaling parameter for the DDM.

3.2 Simulating the DDM

Equation 3.7 ties the diffusion model to random walk. By using small values of τ , the diffusion process can be approximated. The choice of τ parameter trades off with speed; using a very small τ will make the simulation more accurate at the expense of increased computation time. Given a set of parameters $\Theta = [\xi, \eta, a, T_{er}, s_t]^T$, the existing method to simulate the DDM detailed briefly by Ratcliff & Van Dongen (2011) is to sample the drift parameter μ from the appropriate normal distribution $\mu \sim N(\xi, \eta^2)$ and the non-decision time t_{er} from appropriate uniform distribution $t_{er} \sim U(T_{er}, s_t)$. For the particular sampled drift μ the diffusion process is simulated using the random walk approximation. The decision time is then the time taken by the random walk process to hit the boundary a . The sampled RT is simply the sum of sampled non-decision time and the decision time from random walk approximation. On an average case, the complexity of simulation is $\mathcal{O}(\frac{a}{\xi\tau})$. For practical purposes, with $\tau = 0.5ms$, and $a/\xi \approx 250ms$ which represents an average PVT sample, approximately 500 cycles are required to generate a single simulated RT sample. This makes the simulation process extremely slow, especially when a large number of samples are required. The process is illustrated in Figure 3.1.

Figure 3.1: Figure illustrates the standard simulation process for the DDM.

3.2.1 A simplified version of DDM

If we assume that the diffusion parameters do not vary across trials then the model can be considerably simplified. This can help in simplifying and considerably improving the speed of DDM simulation. The analytical solution for RT distribution

can be obtained by solving the first passage time for a Wiener process $X(t)$ with drift μ and standard deviation σ with one absorbing boundary at $x = a$. For simplicity the effect of T_{er} can be considered later, for now we can assume the time axis shifted to T_{er} . The diffusion process will follow the Kolmogorov equations (Equation 2.3 and 2.4) with $\alpha = \sigma^2$ and $\beta = \mu$. Consider the forward equation for now:

$$\frac{1}{2}\sigma^2 \frac{\partial^2 p}{\partial x^2} - \mu \frac{\partial p}{\partial x} = \frac{\partial p}{\partial t} \quad (3.8)$$

Subject to the conditions:

$$p(0, 0; x, 0) = \delta(x), \quad p(0, 0; a, t) = 0 \quad (t > 0) \quad (3.9)$$

These equations arise naturally in heat conduction and diffusion problems. Solving the partial differential equations we obtain (see Cox & Miller (1977), page 221 for details)

$$p(0, 0; x, t) = \frac{1}{\sigma\sqrt{2\pi t}} \left[e^{\left\{-\frac{(x-\mu t)^2}{2\sigma^2 t}\right\}} - e^{\left\{\frac{2\mu a}{\sigma^2} - \frac{(x-2a-\mu t)^2}{2\sigma^2 t}\right\}} \right] \quad (3.10)$$

If T is the first passage time from 0 to a then the probability density of RT is $f(t)$. For $\mu > 0$, the process is bound to reach the boundary at a and $f(t)$ can then be computed as:

$$\begin{aligned} f(t) &= -\frac{d}{dt} \int_{-\infty}^a p(0, 0; x, t) dx \\ &= -\frac{d}{dt} \left\{ \phi\left(\frac{a-\mu t}{\sigma\sqrt{t}}\right) - e^{\frac{2\mu a}{\sigma^2}} \phi\left(-\frac{a+\mu t}{\sigma\sqrt{t}}\right) \right\} \\ &= \frac{a}{\sigma\sqrt{2\pi t^3}} e^{\left\{-\frac{(a-\mu t)^2}{2\sigma^2 t}\right\}} \end{aligned} \quad (3.11)$$

where ϕ is the standard normal integral. The mgf of T can be computed as:

$$f^*(s) = \int_0^\infty e^{-st} f(t) dt = e^{\left[\frac{a}{\sigma^2}(\mu - (\mu^2 - \sqrt{\mu^2 + 2s\sigma^2}))\right]} \quad (3.12)$$

Differentiating twice with respect to s and setting s to 0 give the first two moments as:

$$E(RT) = \frac{a}{\mu} \quad V(RT) = \frac{a\sigma^2}{\mu^3} \quad (3.13)$$

Subtracting back T_{er} from equation 3.11 we obtain the distribution of RT as:

$$f(RT) = \frac{a}{\sigma\sqrt{2\pi(t-T_{er})^3}} e^{\left\{-\frac{(a-\mu(t-T_{er}))^2}{2\sigma^2(t-T_{er})}\right\}} \quad (3.14)$$

The mean and the variance of the RTs will be:

$$E(RT) = T_{er} + \frac{a}{\mu} \quad V(RT) = \frac{a\sigma^2}{\mu^3} \quad (3.15)$$

It is interesting to notice that the distribution of RT (equation 3.14) is actually a shifted inverse Gaussian distribution. Its statistical properties are well studied (Folks & Chhikara, 1978).

3.2.2 A mixed simulation method

While the equation 3.14 is valid for all values of drift μ , the process is guaranteed to terminate only if the drift is positive. On the other hand if drift is zero or negative ($\mu \leq 0$) then the process may never terminate and the distribution in equation 3.14 becomes defective. In other words for negative or zero drift value, the process has a finite probability of never terminating and the point mass at infinity is:

$$P(T = \infty) = 1 - e^{\frac{2\mu}{\sigma^2}} \quad (3.16)$$

When the drift is positive, samples from equation 3.14 can be generated (Michael et al., 1976) using the algorithm 1.

Algorithm 1 Sampling from shifted inverse Gaussian distribution

Given distribution parameters: drift $\mu > 0$, boundary a and shift t_{er}
 Sample a random variable α from a standard normal distribution:
 $\alpha = N(0, 1)$
 Sample another random variable β from a uniform distribution between 0 and 1:
 $\beta = U(0, 1)$
 Now obtain the value of x as:

$$x = \mu + \frac{\mu^2 \sigma^2 \alpha^2}{2a^2} - \frac{\mu \sigma^2 \alpha}{2a^2} \sqrt{\frac{4\mu a^2}{\sigma^2} + \mu^2 \alpha^2}$$

if $\beta \leq \frac{\mu}{\mu+x}$ **then**
 return $x + t_{er}$
else
 return $\frac{\mu^2}{x} + t_{er}$
end if

Using this algorithm, samples for the DDM can be generated much more efficiently and accurately when drift is positive without relying on random walk approximation. For most experiments the proportion of negative or zero drift is very small. The DDM simulation starts similar to previously described method; given the parameters of the DDM, $\Theta = [\xi, \eta, a, T_{er}, s_t]^T$ the drift parameter μ

is sampled from the appropriate normal distribution $\mu \sim N(\xi, \eta^2)$ and the non-decision time t_{er} from appropriate uniform distribution $t_{er} \sim U(T_{er}, s_t)$. If the sampled drift $\mu \leq 0$, then simulation is carried out as usual using random walk simulation. But if the sampled drift $\mu > 0$, then the appropriate shifted inverse gaussian distribution is sampled using algorithm 1. By relying on the shifted inverse Gaussian distribution for positive drifts and falling back on random walk approximation otherwise can significantly improve simulation speed without compromising accuracy. We refer to this method of simulation as the *mixed simulation method*.

3.2.3 Simulating PVT

Once we can simulate the DDM, simulating PVT is straightforward. A standard PVT runs for 10 minutes with the ISI varying uniformly between 2 and 10 seconds. The maximum time allowed to respond is usually 10 seconds. To simulate the PVT, we first sample uniformly between 2 and 10, this constitutes the simulated ISI. Then a RT is simulated from the DDM. If the sampled $RT > 10$ then the RT is taken to be 10. The sampled RT is added to the sampled ISI and the process is continued till the total time exceeds 10 minutes. The sequence of RTs generated constitutes a simulated sample of the PVT. Notice that as the duration of PVT is fixed, slow responses can strongly affect the number of samples collected within the time-frame of the test.

3.3 DDM parameter estimation

3.3.1 Problem statement

Given a set of N response times generated by a one choice task experiment (RT data), such as PVT experiment, we assume that each response is independent and identically distributed (IID) and is a result of an underlying DDM parameterized by $\Theta = [\xi, \eta, a, T_{er}, s_t]^T$. The goal is to estimate these parameters as accurately and efficiently as possible from the least amount of RT data. To be useful, the estimation process must be fast, unbiased and should have low variance in estimation error. Irrespective of the estimation algorithm, the efficiency (variance in estimation error) cannot be lower than the CramrRao lower bound (CRLB), which states that the variance of an unbiased estimator is at least as high as

the Fisher information (Radhakrishna Rao, 1945). This is important in our investigation because it provides an upper bound on the performance of any estimator for a given size of data.

3.3.2 DDM: identifiability issues

As discussed in Chapter 2, the five parameter DDM is not uniquely identifiable. In the subsequent chapters, while estimating, all parameters are assumed to be free, but when reporting results, invariant parameter ratios ($\xi/a, \eta/a$) are used instead of the original parameters.

3.3.3 Current estimation method

The parameter estimation process briefly described by Ratcliff & Van Dongen (2011), relies on the simulation based on random walk approximation and leaves several free parameters that can be altered depending on the data. To estimate the parameters Θ of the model, RT distribution is simulated and compared with RT data obtained from experiments using a χ^2 goodness of fit. An iterative algorithm based on simplex minimization routine (Nelder & Mead, 1965) is used to successively improve the model fit. For the simulation process 20,000 RTs per distribution are obtained. A step size of 0.5 ms for the random walk approximation is chosen. To fit the model to data, 0.05, 0.1, 0.90, 0.95 quantiles of the RT distribution are obtained. These quantile RTs are used to find the proportion of responses in the RT distribution from the model lying between the data quantiles which are multiplied by the number of observations to get the expected values (E). The observed values (O) are simply 0.05 multiplied by the number of observations. A χ^2 statistic is then computed as $\frac{\sum(O-E)^2}{E}$. The method is very sensitive to initial estimate of the parameters, therefore good starting point for the estimator is essential to avoid local optimas. Ratcliff & Van Dongen (2011) suggested using a Markov chain Monte Carlo (MCMC) based maximum likelihood estimate (MLE). The MCMC-MLE method is discussed in next section. The estimation process is summarized in Figure 3.2.

3.3.4 MCMC-MLE

To initialize the estimation process, Ratcliff & Van Dongen (2011) used MCMC-MLE. In their paper, the method is not described in any detail. MCMC-MLE is a

Figure 3.2: Figure illustrates the DDM parameter estimation process as described by Ratcliff & Van Dongen (2011).

combination of separate generic methods (Markov Chains, Monte Carlo methods and MLE) developed over time, how these methods should be combined with each other to solve the problem at hand is not clear. This makes implementing their estimation process involved. In this section we detail the method along with parameters that worked optimally for us. We start by describing each of these components separately and then combining them to get a reliable initial estimate of the DDM parameters.

3.3.4.1 Monte Carlo Methods

Despite their simplicity, Monte Carlo methods are extremal powerful numerical methods that can be applied to a broad set of problems in optimization, integration and sampling. In our investigation we are specifically interested in computation of expectations, as most problems can be converted into a computation of expectations. Let's say we have a random variable $X \in \mathbb{R}^N$, with probability density function (pdf) $X \sim p(x)$ defined over some set Ω . Let's say we would like to find the expectation of a function $f(X)$, which can be computed as:

$$E[f(X)] = \mu = \int_{x \in \Omega} f(x)p(x)dx \quad (3.17)$$

The Monte Carlo estimate of the expectation can be computed as:

$$\hat{\mu} = \frac{1}{n} \sum_{i=1}^n f(x_i) \quad (3.18)$$

where, $(x_1, \dots, x_n)$ are n -sample of X 's. By the weak law of large numbers, if this expectation exists, then for an arbitrarily small ϵ :

$$\lim_{n \rightarrow \infty} P(|\hat{\mu} - \mu| \geq \epsilon) = 0 \quad (3.19)$$

The variance of Monte Carlo estimate is:

$$Var(\hat{\mu}) = \frac{Var(f(X))}{n} \quad (3.20)$$

i.e., the Monte Carlo method shows $1/\sqrt{n}$ rate of convergence. Even though the integral involved in the computation of the expectation is a multidimensional one, the expression of the Monte Carlo estimate is independent of dimensions. If we attempt to estimate the integral by discretizing the space, the complexity of the problem will rise exponentially with the number of dimensions. The Monte Carlo method essentially solves the *curse of dimensionality* problem. Keep in mind that the variance in the Monte Carlo estimate is directly proportional to $Var(f(X))$. Therefore, in practice, when sampling the X 's, the nature of the function $f(X)$; $X \sim p(x)$ and the number of dimensions play a big role. In the next section we will discuss how the simple Monte Carlo method can be used to solve many practical problems.

3.3.4.2 Integration and Optimization using Monte Carlo methods

Lets say we would like to integrate a function $q(x)$ from a to b and the integral exists but has no analytical solution. The Monte Carlo approximation to the problem can be obtained by converting the integral to an expectation with respect to a uniformly distributed random variable U between a and b :

$$\begin{aligned} & \int_a^b q(x) dx \\ &= (b-a) \int_a^b q(x) \frac{1}{b-a} dx \\ &= (b-a) \int_a^b q(x) p_U(x) dx \\ &= (b-a) E(q(U)) \approx \frac{(b-a)}{n} \sum_{i=1}^n q(x_i); X \sim U(a, b) \end{aligned}$$

Now consider the same function $q(x)$ defined between a to b . We would like to solve the optimization problem:

$$x_0 = \operatorname{argmin}_x q(x) \quad (3.21)$$

The Monte Carlo approximate solution can be obtained by uniformly sampling from U and computing

$$x_0^* = \operatorname{argmin}_{x \in \{x_1, \dots, x_n\}} q(x); X \sim U(a, b) \quad (3.22)$$

It should be clear from the formulation of the problems that choosing the right sampling function, factoring in the shape of the original function $q(x)$ is essential to keep the variance of the estimates low enough to be of any practical use. The essential idea to solve the problem efficiently is to spend more time (i.e. give more density) to the important regions in the sampling space. Many intelligent ways of sampling exist to minimize the variance of estimation including rejection sampling, importance sampling and cross entropy method. The problem with these sampling methods is that they do not scale well with increasing number of dimensions. The MCMC method essentially addresses these issues by generating samples while exploring the sampling space using a Markov chain mechanism which ensures that most time is spent in the important regions in the space. The methods are detailed in the next sections.

3.3.4.3 Markov chains

To carry out MCMC, the random sequence of X_i from the state space Ω are generated stochastically in such a way that they follow the Markovian condition:

$$p(X_{i+1}|X_i, \dots, X_1) = p(X_{i+1}|X_i) \quad (3.23)$$

Specifically, we are interested in a Markov chain where the conditional distribution of X_{i+1} given X_i is independent of i . The marginal distribution of X_1 is called the initial distribution and the conditional distribution of X_{i+1} given X_i is then the stationary transition probability. If the state space is finite, then the transition probabilities can be expressed as a matrix $K(i, j)$ with elements p_{ij} defined as:

$$P(X_{n+1} = x_j | X_n = x_i) = p_{ij} \quad (3.24)$$

and the initial distribution can be expressed as a vector:

$$P(X_1 = x_i) = \lambda_i \quad (3.25)$$

If the state space is uncountably infinite, the initial distribution vector and transition matrix are replaced by unconditional and conditional probability density functions. The most important property of the Markov chain is that if the chain satisfies the conditions for *irreducibility* and *aperiodicity* (discussed later), then the chain will have a stationary distribution $\pi(x)$ and the transition matrix will converge to this distribution as $\lim n \rightarrow \infty$. Aperiodicity implies that the chain is symmetric in time, i.e. transition from X_i to X_j and X_j to X_i are equally probable. This is achieved when:

$$\pi_i p_{ij} = \pi_j p_{ji} \quad (3.26)$$

The chain is irreducible, if it is possible to get to any state from any state irrespective of the current state. This is ensured when the transition matrix satisfies:

$$\pi K = \pi \quad (3.27)$$

Therefore by ensuring these conditions, it is possible to generate samples from the stationary distribution π using the Markov chain. There are many sampling methods based on the Markov chain with the above mentioned properties. We used the Metropolis-Hasting sampling to generate samples which is discussed in the next section.

3.3.4.4 Sampling using Metropolis-Hasting update

Lets say we would like to sample from a distribution $p(x)$, such that the density is known only upto a scaling factor. In other words, $p(x)$ is non-negative and integrates to a finite non-zero value. The Metropolis-Hasting (Metropolis et al., 1953; Hastings, 1970) update works as follows:

- Given the current state x , propose a transition to y , having a proposal conditional probability given x donated by $q(y; x)$
- Accept the transition with probability

$$\min(1, \frac{p(y)q(x; y)}{p(x)q(y; x)})$$

- Else next state is a copy of the current state.

if $q(y; x) > 0$ with probability 1, then this method ensures that the generated chain satisfies the necessary conditions to obtain a stationary distribution $p(x)$. The nature of the conditional density $q(y; x)$ decides how fast the process diffuses through the sampling space. The normal distribution is quite often used as a generic proposal density $q(y; x) = N(x, \sigma^2)$. In this case a large σ results in many rejections while a small σ results in slow diffusion. In the next section we will discuss how these methods can be combined to get a good estimate of parameters of the DDM model from RT data.

3.3.4.5 MCMC - MLE applied to DDM

Given a set of RT observations x , the likelihood that a DDM parameterized by Θ generated it is:

$$\mathcal{L}(\Theta|x) = P(X = x|\Theta) \quad (3.28)$$

The MLE tries to find the Θ_{mle} that maximizes the likelihood of the observed data, i.e.

$$\Theta_{mle} = \operatorname{argmax}_{\Theta} \mathcal{L}(\Theta|x) \quad (3.29)$$

In practice it is convenient to work with the log of the likelihood function. The log function being a monotonically increasing function does not affect the analysis. So the optimization function is changed to:

$$\Theta_{mle} = \operatorname{argmax}_{\Theta} \ln(\mathcal{L}(\Theta|x)) \quad (3.30)$$

The advantage of MLE is that it shows the following important properties:

- Consistency: It converges almost surely to the true value of Θ as the sample size tends to infinity.
- It achieves the CRLB when sample size tends to infinity.

These properties make the MLE an ideal candidate for parameter estimation. If we had access to closed form solution to the MLE expression we would have computed it directly without relying on simulations. For now we will use the MCMC to generate an estimate of the MLE. As the actual value of the likelihood is of little importance, we can construct a likelihood ratio function as:

$$\Lambda(\Theta_0) = \frac{\mathcal{L}(\Theta_0|x)}{\mathcal{L}(\Theta_1|x)} \quad (3.31)$$

the ratio captures how many time more likely the data x is coming from Θ_0 compared to Θ_1 . As we do not have access to a closed form expression for likelihood we have to use a proxy function. We can use the χ^2 measure as described earlier in section 3.3.3 to indirectly measure the likelihood. Formally:

$$P(\Theta|x) \propto \exp(-\chi_{\Theta}^2) \quad (3.32)$$

Therefore the likelihood ratio changes to

$$l(\Theta) = \exp(\chi_{\Theta_1}^2 - \chi_{\Theta_0}^2) \quad (3.33)$$

We now construct a Markov chain on the parameter space Θ using the Metropolis-Hasting update. We take the stationary distribution of the chain to be $p(\Theta) = P(\Theta|x) \propto \exp(-\chi_{\Theta}^2)$. We can generate samples of Θ from the distribution and simply compute the Monte Carlo approximate estimate of the MLE. Note that χ^2 measure is computed via simulations as described earlier. Each simulation requires approximately 10^4 simulated RTs. If we use the previously described simulation method for generating RTs, each RT will require approximately 500 cycles. To get reliable estimates from MCMC-MLE we observed that approximately 500 cycles are required in the Markov chain and another 500 cycles are required to actually estimate the parameters using previously described method. In other words, estimation of parameters based on previous literature require approximately 10^9 operations. Another practical problem using this method is that the data is usually censored due to limitation of time. In case of PVTs the censor time is usually 10 seconds. A much faster and elegant solution to the problem is to directly obtain a closed form solution to the DDM. In the next section we will derive a closed form solution for the DDM and propose a MLE based on it to quickly and efficiently estimate the model parameters from data.

3.4 Improvements in Estimation

3.4.1 DDM: Closed form solution

In this section we derive a closed form solution for the model. The complete distribution for the model is a compound probability distribution which can be derived from Equation 3.11. The resulting distributions are defective (i.e. they have finite mass at infinity), but nonetheless can be used to get a maximum

likelihood estimate of the parameters. Starting from standard diffusion process with drift μ and volatility σ^2 originating at 0 with process termination boundary at a , the distribution of RT is $f(t)$ as derived earlier. Now assuming $\mu \sim N(\xi, \eta)$, the resulting compound distribution is given by:

$$g(t|a, \xi, \eta) = \int_{-\infty}^{\infty} f(t|\mu) p(\mu) d\mu, \quad t > 0 \quad (3.34)$$

$$g(t|a, \xi, \eta) = \int_{-\infty}^{\infty} \frac{a}{\sigma \sqrt{2\pi t^3}} e^{\left\{ -\frac{(a-\mu t)^2}{2\sigma^2 t} \right\}} \left(\frac{1}{\sqrt{2\pi\eta^2}} \right) e^{-\frac{(\mu-\xi)^2}{2\eta^2}} d\mu, \quad t > 0 \quad (3.35)$$

The integration can be done by manipulating the quadratic forms in the exponents to yield:

$$g(t|a, \xi, \eta) = \frac{a}{\sqrt{2\pi t^3(\eta^2 t + \sigma^2)}} e^{\left\{ -\frac{(a-\xi t)^2}{2t(\eta^2 t + \sigma^2)} \right\}}, \quad t > 0 \quad (3.36)$$

$g(t|a, \xi, \eta)$ can be taken to be 0 for $t \leq 0$. Then the cumulative distribution function $G(t|\xi, \eta)$ is given by:

$$G(t | a, \xi, \eta) = \begin{cases} 1 - \Phi\left(\frac{a-\xi t}{\sqrt{t^2\eta^2 + \sigma^2 t}}\right) + e^{\frac{2a\xi + 2a^2\eta^2}{\sigma^2}} \Phi\left(-\frac{a\sigma^2 + 2at\eta^2 + \sigma^2\xi t}{\sigma^2\sqrt{t^2\eta^2 + \sigma^2 t}}\right), & t > 0 \\ 0, & t \leq 0 \end{cases} \quad (3.37)$$

Where Φ is the cumulative distribution function of the standard normal distribution. In the DDM, the distribution Equation 3.36 is shifted because of the non-decision time. Let the shift in distribution be t_0 . Then Equation 3.36 can be appropriately modified to:

$$g(t|a, \xi, \eta, t_0) = \begin{cases} \frac{a}{\sqrt{2\pi t_k^3(\eta^2 t_k + \sigma^2)}} e^{\left\{ -\frac{(a-\xi t_k)^2}{2t_k(\eta^2 t_k + \sigma^2)} \right\}} & , \quad t_k = t - t_0, \quad t_k > 0 \\ 0, & t_k \leq 0 \end{cases} \quad (3.38)$$

As per the DDM, $t_0 \sim U(T_{er} - \frac{S_t}{2}, T_{er} + \frac{S_t}{2})$, the resulting compound distribution will be:

$$r(t | \Theta) = \int_{T_{er} - \frac{S_t}{2}}^{T_{er} + \frac{S_t}{2}} g(t|a, \xi, \eta, t_0) p(t_0) dt_0 \quad (3.39)$$

$$r(t | \Theta) = \left(\frac{1}{S_t} \right) \int_{t-T_{er}-\frac{S_t}{2}}^{t-T_{er}+\frac{S_t}{2}} g(t_k | a, \xi, \eta) dt_k \quad (3.40)$$

$$r(t | \Theta) = \left(\frac{1}{S_t} \right) \left(\int_{-\infty}^{t-T_{er}+\frac{S_t}{2}} g(t_k | a, \xi, \eta) dt_k - \int_{-\infty}^{t-T_{er}-\frac{S_t}{2}} g(t_k | a, \xi, \eta) dt_k \right) \quad (3.41)$$

$$r(t | \Theta) = \left(\frac{1}{S_t} \right) \left\{ G\left(t - T_{er} + \frac{S_t}{2} | a, \xi, \eta\right) - G\left(t - T_{er} - \frac{S_t}{2} | a, \xi, \eta\right) \right\} \quad (3.42)$$

Equation 3.42 captures the defective probability density function for the one-choice DDM. Instead of relying on simulation, the model parameter (Θ) can now be estimated using an MLE. Given a set of observation $\{t_1, t_2, \dots, t_n\}$ the log likelihood of parameter vector Θ can be computed as:

$$\ln \mathcal{L}(\Theta | t_1, \dots, t_n) = \sum_{i=1}^n \ln(r(t_i | \Theta)) \quad (3.43)$$

If the experiment is censored at $t = t^c$, and there are m censored observations along with n uncensored observations the log likelihood will be modified to:

$$\ln \mathcal{L}(\Theta | t_1, \dots, t_n, t_1^c, \dots, t_m^c) = \sum_{i=1}^n \ln(r(t_i | \Theta)) + m \ln(1 - R(t_i^c | \Theta)) \quad (3.44)$$

the minimum negative log likelihood is estimated using interior-point algorithm (Dantzig, 1965). $R(t_i^c | \Theta)$ is computed using trapezoidal numerical integration. For starting the estimation process the boundary a is chosen randomly. Initial value of mean drift ξ^0 and mean non-decision time T_{er}^0 is computed as:

$$\xi^0 = \sqrt[3]{\frac{a\sigma^2}{\sigma_{RT}^2}} \quad ; \quad T_{er}^0 = \mu_{RT} - \frac{a}{\xi^0} \quad (3.45)$$

here μ_{RT} is the mean and σ_{RT}^2 is the variance of observed RTs. These expressions are obtained by assuming a specific condition in the model where $\eta = 0$, $S_t = 0$ (Equation 3.38). The starting values of η and S_t can be chosen as a suitable fraction of ξ^0 and T_{er}^0 respectively based on domain knowledge. We refer to the proposed estimator as MLE based estimator. In the next section we compare the proposed simulation and estimation methods with previously available ones.

3.5 Comparison

3.5.1 Methods

The proposed mixed simulation method which is a combination of inverse Gaussian and random walk simulation is compared with previously proposed method by Ratcliff & Van Dongen (2011) relying solely on random walk approximation (from here on referred to as random walk simulation). Since, the modified simulation proposed partly relies on exact sampling method it is guaranteed to be more accurate than previously proposed method based on random walk approximation only. The estimators were compared both in terms of speed and efficiency. Both estimators were checked for any bias in estimation. To carry out the analysis we used six standard parameter sets as shown in Table 3.1.

Set	a	$T_{er}(\text{ms})$	$S_t(\text{ms})$	ξ	η
1	0.09	150	30	1.1	0.20
2		170	40	1.0	0.25
3		190	50	0.9	0.30
4		210	60	0.8	0.35
5		230	70	0.7	0.40
6		250	80	0.6	0.45

Table 3.1: Standard parameter sets

For simulation 20,000 RT samples were generated for each set using both simulation methods. For the estimation analysis we chose all possible combinations of drift and variability in drift (ξ and η) for each set from the table. This allowed 36 combinations of ξ and η for each set in Table 3.1, i.e. a total of 216 estimations. The values for Table 3.1 were arrived at based on observed estimated parameter values for subjects on a PVT before and after sleep deprivation (discussed in later chapters). A 10 minute PVT typically results in 95 responses. Set 6 represents a poorly performing subject while set 1 represents a very fast subject. To make the estimation process realistic, the RTs were generated by simulating a PVT. Three sets of estimation were carried to represent 10 minute, 20 minute and 30 minute PVT session. The analysis was carried out on a run on a contemporary workstation with 6 core Intel Xeon 3.2 GHz processor with 16 GB of RAM. The algorithms were implemented in Matlab R2013b and were vectorized for performance.

3.5.2 Comparison of simulation methods

For the simulation, the step size for random walk approximation was fixed at $\tau = 0.5ms$. The simulations were censored at $t=10$ sec. Figure 3.3 shows the comparison between the two simulators for the 6 sets.

Figure 3.3: Ratio of simulation speeds of *random walk simulation* to *mixed simulation method*. The numbers shown are actual simulation speed of the proposed mixed simulation method in seconds. As we move from set 1 to 6, the mean drift goes on reducing. As a result the proportion of sampled drift that is less than zero also increases. This in-turn reduces the speed of mixed simulation. Under normal circumstances, mixed simulation is two order of magnitudes faster than random walk simulation.

3.5.3 Comparison of estimation methods

For carrying out the χ^2 based estimator we used both the random walk based simulation as well as the proposed mixed simulation method. The estimation speed for all three estimation methods is shown in Table 3.2. The estimation speed for the original χ^2 based estimator with random walk simulation was too slow; therefore, it is reported only for a 10 minute PVT set. Table 3.3 summarizes the mean and standard deviation of error in estimation, where error in estimation e was defined as $e = \Theta - \hat{\Theta}$. The estimates were unbiased based on a one sample t-test at significance level $\alpha = 0.05$. Normalized DDM parameters are shown. The efficiency of both the estimators is similar, although the proposed simulator is an order of magnitude faster and much simpler to implement.

Set	Total estimation time (for 216 estimations)		
	χ^2 based estimator (random walk)	χ^2 based estimator (mixed simulation)	MLE based estimator
10 Min. PVT	≈ 90 hours	12 Hours	12 Minute
20 Min. PVT	N.A.	12 Hours	11 Minute
30 Min. PVT	N.A.	10 Hours	10 Minute

Table 3.2: Estimation speed. The χ^2 based estimator using random walk simulation is the original method as proposed by Ratcliff et al., 2011. As the estimation speed was prohibitively slow, we used the proposed mixed simulation method with the χ^2 based estimator which while still slow, significantly improved speed. The proposed MLE based estimator does not require any model simulation.

Set	Parameter	χ^2 based estimator	MLE based estimator
10 Min. PVT	$T_{er}(\text{ms})$	-1.17 ± 10.8	-0.8 ± 15
	$S_t(\text{ms})$	-1.2 ± 18.8	0.9 ± 15.5
	ξ/a	-0.10 ± 1.42	-0.03 ± 1.57
	η/a	-0.06 ± 0.98	-0.03 ± 1.03
20 Min. PVT	$T_{er}(\text{ms})$	-0.94 ± 9.8	1.4 ± 14
	$S_t(\text{ms})$	-1.2 ± 18	0.9 ± 13.4
	ξ/a	-0.09 ± 1.13	-0.01 ± 1.38
	η/a	-0.07 ± 0.94	-0.09 ± 0.72
30 Min. PVT	$T_{er}(\text{ms})$	-0.25 ± 8.8	0.33 ± 13.5
	$S_t(\text{ms})$	1.4 ± 18.5	1.0 ± 11.9
	ξ/a	-0.08 ± 1.00	0.00 ± 1.00
	η/a	-0.07 ± 0.08	0.03 ± 0.67

Table 3.3: Mean and standard deviation of error in estimation. Drift parameters are normalized.

3.6 Cramer-Rao Lower Bound

The CRLB (Radhakrishna Rao, 1945) measures the lower bound on the variance of estimator. Suppose Θ has to be estimated from the available data x , which is generated according to an underlying distribution $p(x; \Theta)$. Let the estimator denoted by $g(X)$ be an unbiased estimator of $p(x)$. As per the Rao bound, the variance of an unbiased estimator $E(g(X)) = \hat{\Theta}$ of Θ is bounded by the reciprocal of Fisher information $I(\Theta)$. That is:

$$\text{var}(\hat{\Theta}) \geq I(\Theta)^{-1} \quad (3.46)$$

where the Fisher information is computed as:

$$I(\Theta) = E \left[\left(\frac{\partial \ln(\mathcal{L}(x; \Theta))}{\partial \Theta} \right)^2 \right] = -E \left[\frac{\partial^2 \ln(\mathcal{L}(x; \Theta))}{\partial \Theta^2} \right] \quad (3.47)$$

where $\mathcal{L}$ is the likelihood function defined earlier in Equation 3.28. The equations are valid subjected to two regularity conditions:

- (i) For all x such that $p(x; \Theta) > 0$,

$$\frac{\partial}{\partial \Theta} \log p(x; \Theta)$$

exists and is finite.

- (ii) The integration operation with respect to x and differentiation with respect to Θ can be interchanged in the expectation of the estimator.

Here, Θ is assumed to be a scalar. In case it is a vector in $\mathbb{R}^n$, then the variance in estimation will be replaced by a covariance matrix in $\mathbb{R}^{n \times n}$. The bounds on the covariance is:

$$\text{cov}_{\boldsymbol{\theta}}(\mathbf{g}(X)) \geq \frac{\partial \text{E} \mathbf{g}(\mathbf{X})}{\partial \boldsymbol{\theta}} [I(\boldsymbol{\theta})]^{-1} \left(\frac{\partial \text{E} \mathbf{g}(\mathbf{X})}{\partial \boldsymbol{\theta}} \right)^T \quad (3.48)$$

Where I is the Fisher information matrix in $\mathbb{R}^{n \times n}$ with element $I_{i,j}$ defined as

$$I_{i,j} = \text{E} \left[\frac{\partial}{\partial \theta_i} \log p(x; \boldsymbol{\theta}) \frac{\partial}{\partial \theta_j} \log p(x; \boldsymbol{\theta}) \right] = -\text{E} \left[\frac{\partial^2}{\partial \theta_i \partial \theta_j} \log p(x; \boldsymbol{\theta}) \right]. \quad (3.49)$$

In spite of the closed form solution for the likelihood function as derived in Equation 3.43, the derivation of the CRLB is highly involved due to the complex form of the equation. Even if we assume that the covariance structure of estimate has only diagonal elements (i.e. we can compute CRLB with respect to individual parameters assuming other parameters are held constant), the computation of the CRLB is still difficult. Fortunately from the perspective of our investigation, we are not interested in the closed form expression for the CRLB. Instead, much insight can be gained about the practical limitation of the estimator using the maximum likelihood estimator. The MLE asymptotically approaches the CRLB as the available data approaches infinity. Therefore, we design some simulations that would give practical insights into capabilities of the DDM in realistic scenarios.

3.6.1 CRLB estimates using simulations

In this section we are interested in the limitations of the estimator in realistic scenarios. Specifically, we are interested in finding out an approximate estimate of the CRLB and how low the error in the estimates go as we incrementally increase the data size. Getting one set of PVT data is the most ideal, while carrying out more than four PVTs is too cumbersome and unrealistic. Therefore, we compute the errors in MLE estimate as we gather up-to four sessions of standard 10-minute PVTs. To obtain an estimate of the error variance and bias, each PVT was simulated 100 times and the parameters were estimated for each. The error bias and variance can then be computed as:

$$bias_{\Theta} = \Theta_{\mu} = \frac{\sum_{i=1}^{100}(\Theta_i - \hat{\Theta}_i)}{100} \quad var_{\Theta} = \frac{\sum_{i=1}^{100}(\Theta_i - \Theta_{\mu})^2}{99} \quad (3.50)$$

We also obtain estimates with 10,000 simulated RTs. CRLB was estimated using numeric differentiation of the partial derivatives of log likelihood (Equation 3.47) and monte carlo method to obtain the expectation (Equation 3.18). CRLB was computed for each parameter independently (i.e. covariance structure of error is assumed to have only diagonal elements). All estimates were obtained for a fixed parameter set: $a = 0.01, \xi = 1.0, \eta = 0.25, T_{er} = 160ms, s_t = 50ms$. This parameter set represents an average baseline measurement. Notwithstanding the fact that CRLB as well as the performance of the estimator will depend on the exact value of the parameters, this analysis gives an idea of the expected error in estimation without overcomplicating the study with rigorous analysis. Furthermore, the performance of the estimator is essential to gauge the sample size for a given clinical study.

3.6.2 Error estimates: Results

Figure 3.4 shows the standard deviation of error estimates along with the CRLB estimates. Except for range of non-decision time s_t , the error in estimates remain comparatively higher than the lower bound even when data size was increased up-to 10,000 RT samples. The error in the estimates are also important to find out the sample size for a clinical study. For instance, if we want to compare the mean DDM parameters between two groups. Let us assume the following requirements for the study:

- significance level $\alpha = 0.05$.
- power of the experiment $1 - \beta = 0.8$.
- lets say we would like to be able to measure a difference in mean normalized diffusion drift of 1.
- the standard deviation in mean normalized drift within each group is 1.

The sample size n can be computed as:

$$n = 2 * \lceil \frac{(Z_{\alpha/2} + Z_{\beta})^2 2s^2}{(\Delta\mu)^2} \rceil \quad (3.51)$$

where $\lceil . \rceil$ is the ceiling function, Z is the Z-statistic and s^2 is the variance of measurement, which in our case will be the sum of variance within the group (assumed 1 here) plus the variance due to error in estimation (which will depend on how many PVTs we collect). The equation is derived using central limit theorem (i.e. the sampling distribution of mean is distributed normal with mean equal to population mean and standard deviation $\sigma_{sample} = \sigma_{population} / \sqrt{(n)}$. substituting the appropriate value into the equation we get a value of $n=166$ using 1 session of PVT, $n=140$ using 2 sessions of PVT and $n=92$ using 3 sessions of PVT.

3.7 DDM: Limitations

Despite the many advantages of the DDM, there are limitations of the model that must be kept in mind when applied to different studies. There are three key limitations of the DDM:

- (i) All parameters of the model cannot be uniquely identified (Ratcliff & Van Dongen, 2011). From a statistical point of view, it can be assumed that the model has four parameters instead of five and it will not make any difference from the point of view of estimation or simulation. But it is important to keep in mind that each parameter has an underlying neuronal architecture that mediates the decision process. Therefore, a four parameter normalized DDM is not equivalent to a five parameter DDM from a clinical and neuro-biological perspective.

- (ii) The DDM is based on accumulator models which makes the assumption that distinct components of decision process are strictly serial (H. R. Heekeren et al., 2008). This is known to be false from previous experiments. Although, in most situations the assumption has little effect in terms of model fit (Ratcliff, 1978).
- (iii) The model assumes that each RT is IID according to the underlying DDM. Despite the good model fit between measurements and the model it is known that RTs are not independent of each other. The RTs are strongly affected by ISI as well as time on task (H. Van Dongen et al., 2011).

In our investigation, the IID assumption violations could have the most impact. Further improvements in the DDM can be made to accommodate the additional parameters. Currently, there is very little clinical and neurophysiological results available to guide the changes required in the model. In the absence of a model

Figure 3.4: Standard deviation of error as progressively more data is used for estimation. The CRLB estimate shows the lowest possible error achievable with the given amount of data. The analysis is done for a fixed value of parameters that represent an average subject under baseline condition.

that takes into account the temporal and spatial structure of the RTs, we will consider alternate ways of looking at the RT distributions along with the DDM in the next chapters.

3.8 Conclusions

The one choice DDM is a powerful model of perceptual decision making. The availability of simple simulation and estimation methods is essential for the current investigation as well as the clinical community to fully leverage the model for real world applications. We brought to notice the simple observation that the simulation time can be considerably improved by switching between sampling from inverse-Gaussian distribution for positive drifts and falling back on random walk simulation for negative or zero drifts. The novelty of this chapter lies in deriving a closed form solution for the model which did not exist earlier in literature. The closed form solution for the model help gain insights into one choice perceptual decision making and help design more efficient and fast estimators. We used the maximum likelihood estimator, which is a well-established method for parameter estimation to show that the estimated parameters based on the close form solution are in close agreement with previous method based on data fitting. The estimation speed of the MLE based estimator is at-least an order of magnitude faster while maintaining the same level of efficiency compared to previously proposed method. We also derived error estimates and CRLB on estimates which will be very helpful in comparing and setting an upper limit for future improvements in the DDM estimator. The error estimates are also very important in designing clinical experiments. In the next chapter we will use the methods developed here to answer some of the key questions with respect to the DDM applied to study vulnerability to sleep deprivation.

Chapter 4

DDM Parameters and Differential Vulnerability to Sleep Deprivation

4.1 Introduction

In the previous chapter we discussed efficient ways to simulate and estimate the model parameters for one-choice DDM. As discussed earlier, an attractive feature of DDM is that it can predict the response time distribution under different contexts (Ratcliff, 2002) and varying levels of noise (Ratcliff & Tuerlinckx, 2002). Among the numerous studies using the PVT to characterize performance in sleep-deprived persons, there exists only one (Ratcliff & Van Dongen, 2011) that used diffusion modeling to explain behavior. In this chapter, we ascertained if the diffusion model could differentiate persons according to their vulnerability to SD as measured by a decline in psychomotor vigilance. To fill these gaps in our understanding of behavior following SD we posed two questions:

- (i) Are the parameters of the diffusion model differentially affected in vulnerable and resistant participants? and
- (ii) Can diffusion parameters determined *prior* to sleep deprivation predict performance following SD?

The analysis presented in this chapter appears in Patanaik, A., Zagorodnov, V., Kwoh, C. K. and Chee, M. W. L. "Predicting vulnerability to sleep deprivation using diffusion model parameters.", Journal of Sleep Research, 2014. doi: 10.1111/jsr.12166. Used with permission.

4.2 Methods

4.2.1 Subjects

A total of 135 participants (69 females, mean age 21.9 ± 1.7 years) from five different functional imaging studies (Chee & Chuah, 2007; Venkatraman et al., 2007; Chee et al., 2010; L. Y. Chuah & Chee, 2008; L. Y. Chuah et al., 2010) on sleep deprivation contributed behavioral data to this chapter. The 5 studies shared common recruitment criteria and protocol for sleep deprivation. Volunteers had to:

- (i) be right handed,
- (ii) be between 18 to 35 years of age,
- (iii) have habitual good sleeping habits (6.5 to 9 hours of sleep every day),
- (iv) have no history of sleep or psychiatric or neurological disorders and
- (v) have no history of severe medical illness.

All participants indicated that they did not smoke, consume any medications, stimulants, caffeine or alcohol for at-least 24h prior to the sessions. Informed consent was obtained from all participants in accordance to study protocols approved by the National University of Singapore Institutional Review Board.

Participants visited the laboratory 3 times. They first attended a briefing session during which they were informed of the study protocol and requirements and were practiced on the study task. At the end of this session, each participant was given a wrist actigraph to wear throughout the study. The first experimental session took place approximately a week later. The order of the 2 experimental sessions (rested wakefulness and sleep deprivation) was counterbalanced across all the participants and separated by 1 week. This was to minimize the possibility of residual effects of sleep deprivation on cognition for those participants whose sleep-deprivation session had preceded their rested-wakefulness session (H. P. Van Dongen et al., 2003). Sleep duration was verified by actigraphic data and data from non-compliant subjects were not analyzed.

4.2.2 Experimental Details

In the rested wakefulness (RW) session, subjects arrived at the laboratory on scheduled date at 07:30. The PVT was administered at 08:00. For sleep deprivation sessions, subjects arrived at the laboratory on scheduled date at 19:30. They underwent a night of SD under supervision of a research assistant. PVT was administered every hour from 20:00 till 5:00 next morning (10 test periods). For this report only data from the first two periods taken at 20:00 and 21:00 during the wake maintenance zone of the SD session and two test periods at 4:00 and 5:00 following a night of total sleep deprivation were analyzed. We did not compare RW with SD directly because only one data point was available, as discussed in the previous chapter this was too small for our analysis. The first two sessions were labeled Evening before Sleep Deprivation (ESD) and the last two sessions were labeled sleep deprivation (SD). Subjects also rated their subjective sleepiness on the 9-point Karolinska Sleepiness Scale after each PVT test. Through the night, subjects were allowed to engage in non-strenuous activities such as reading, watching videos and conversing. Subjects were instructed to respond as quickly and as accurately as possible. RTs less than 150ms were regarded as false alarms, and they were excluded from analysis. All PVTs administered were of 10-min duration.

4.2.3 DDM parameter Estimation

The model parameters were estimated using a mixed estimation process as detailed in the previous chapter. The MLE based estimator was used to get an initial estimate of the parameters which were fine tuned using the χ^2 based estimator. As discussed earlier, while estimating the parameters only drift ratios ($\xi/a, \eta/a$) are uniquely identifiable. For the sake of simplicity, from this point onwards, in this chapter, we will use drift and drift ratio interchangeably. When comparing the drift parameters across group, it is implicit that they were normalized by the estimated boundary parameter.

4.2.4 Statistical analyses

Group differences were evaluated using an independent samples t-test. To assess the interaction effect of state (ESD or SD) and group (vulnerable or resistant) on

relevant diffusion parameters, a 2×2 factorial design analysis of variance (ANOVA) was employed. Alpha was set at 0.05. To assess the discriminative power of the diffusion parameters a binary logistic regression analysis was performed to classify subjects into vulnerable and resistant groups using baseline data. We used vulnerability as a dependent variable and diffusion model parameters measured in ESD as independent variables. We also tried introducing baseline standard RT metrics to the set of independent variables, anticipating any increase in accuracy. In the set of standard RT metrics, we also included the slowest 10% response speed (RS is reciprocal of reaction time). The slowest 10% RS is known to be correlated strongly with drift parameter (Ratcliff, 2002). The independent variables were introduced one at a time sequentially, using the forward selection method, until the addition of an extra variable resulted in no statistically significant increase in accuracy. A receiver operating characteristic (ROC) curve was obtained by varying the threshold of the logistic function. All analyses were conducted using SPSS version 20 (IBM, Chicago, IL, USA) and Matlab 2013b (The MathWorks, Inc., Natick, MA, USA).

4.3 Results

4.3.1 Identification of vulnerable and resistant subjects

Based on the change in the number of lapses, l , between SD and ESD ($\delta l = l_{SD} - l_{ESD}$), subjects were identified as resistant if they belonged to the lower tertile, and as vulnerable subjects if they belonged to the upper tertile. A lapse was defined as a trial with RT > 500 ms. Resistant subjects ($n=43$) had $\delta l < 4$, and vulnerable subjects ($n=45$) had $\delta l > 12$.

The two groups were similar in age (mean age for resistant group = 22.0 years, std dev = 1.97 years; mean age for vulnerable group = 22.0 years, std dev. = 1.68 yrs; $t_{86} = 0.05$, n.s.), and gender (18 females in resistant group, 22 females in vulnerable group; $\chi^2_1 = 0.43$, n.s.). As expected, across the entire group, sleep deprivation (SD) elicited significant changes in mean and median RT, the reciprocal of RT and lapses compared to the evening before sleep deprivation (ESD) state (Table 4.1). SD had a significant effect on diffusion model parameters (drift, non-decision time) other than within trial variability in drift. Importantly, during ESD, there was no significant difference in any of the traditional RT metrics between the two groups (smallest $p=0.08$, for total lapses; Figure 4.1).

Table 4.1: Standard reaction time and diffusion parameter statistics of study participants. All standard metrics were significantly affected by sleep deprivation. In terms of diffusion parameters, except for standard deviation in diffusion drift, all other parameters were significantly affected.

	ESD(n=135)	SD(n=135)	P-value
Reaction time (RT) statistics			
Mean RT, ms	266 ± 34	442 ± 432	<0.001
Mean response speed, 1/sec	4.0 ± 0.4	3.3 ± 0.6	<0.001
Median RT, ms	249 ± 26	312 ± 138	<0.001
Total lapses	2.6 ± 3.7	15.8 ± 17.9	<0.001
Diffusion parameter statistics			
Drift ξ	0.983 ± 0.246	0.697 ± 0.242	<0.001
Across trial standard deviation in drift η	0.249 ± 0.153	0.222 ± 0.140	0.13
Mean non-decision time T_{er} , ms	157 ± 17	165 ± 22	<0.001
Range of non-decision time S_t , ms	47 ± 16	56 ± 22	<0.001

Overall χ^2 fit for evening before sleep deprivation (ESD) state was 16.8 ± 7.2 and sleep deprivation (SD) state was 17.7 ± 9.7 . Critical value for χ^2 , df = 14 is 26.1.

4.3.2 Effects of state and group on diffusion parameters

Mean diffusion drift: There was a significant main effect of state on mean diffusion drift ξ ($F_{1,172} = 69.4$; $p < 0.001$). Averaged across the two tertiles, diffusion drift was significantly lower in SD state compared to ESD state. Group had a significant main effect on drift, with vulnerable participants having a lower mean diffusion drift ξ than resistant participants, $F_{1,172} = 45.1$; $p < 0.001$. Vulnerable subjects had significantly lower diffusion drift in both ESD ($t_{86} = 2.44$; $p < 0.05$) and SD ($t_{86} = 7.65$, $p < 0.001$) compared to resistant subjects.

The interaction of state and group was significant, ($F_{1,172} = 8.33$ $p < 0.005$) (Figure 4.2). Thus, while both groups showed significant declines in mean diffusion drift following sleep deprivation (vulnerable $t_{88} = 9.02$, $p < 0.001$; resistant: $t_{84} = 3.3$, $p < 0.005$), decline in drift rate was greater in vulnerable than in resistant subjects.

Mean non-decision time: There was a main effect of state on mean non-decision time (T_{er}) ($F_{1,172} = 7.47$; $p < 0.01$); with T_{er} being faster in ESD than during SD. This was modulated by group (group x state interaction ($F_{1,172} = 6.1$; $p < 0.05$)), such that the decline in non-decision times was also significant in vulnerable subjects ($t_{88} = -3.54$; $p < 0.001$, but not in resistant subjects ($t_{84} = 0.11$, $p = 0.91$). There was no main effect of group on T_{er} , $F_{1,172} = 1.45$; $p = 0.23$.

Figure 4.1: Performance metrics measured on the evening before sleep deprivation (ESD). Metrics include mean reaction time (RT), mean response speed ($RS=1/RT$), total lapses and median RT for subjects vulnerable (vul) and resistant (res) to sleep deprivation. Although the resistant group performed better than the vulnerable group in the ESD state, none of the RT metrics were statistically significantly different between the two groups (smallest $p=0.08$ for mean RT). Error bars represent one standard error of the mean.

4.3.3 Predicting vulnerability from baseline data

We observed a classification accuracy of 69.3% at a sensitivity of 65.1% and specificity of 73.3% using baseline normalized diffusion drift (ξ/a), diffusion signal to noise ratio (ξ/η) and mean non-decision time (T_{er}). The baseline slowest 10% RS was observed to be highly correlated ($r = 0.77$, $p < 0.001$) with baseline mean diffusion drift. Despite this, no improvement in classification was observed by addition of any traditional RT measures. The ROC curve is presented in Figure 4.3. The area under the curve was 0.74.

Figure 4.2: Mean estimated diffusion parameters. Estimated for vulnerable (vul) and resistant (res) groups in the evening before sleep deprivation (ESD) and after sleep deprivation (SD). In ESD, vulnerable subjects showed significantly lower ($p < 0.05$) mean diffusion drift compared to resistant subjects. In addition, following SD, vulnerable subjects also displayed significantly lower drift ($p < 0.001$) and significantly higher non-decision time ($p < 0.01$). Both mean diffusion drift and mean non-decision time showed statistically significant group by state interaction ($p < 0.005$ and $p < 0.05$ respectively). Error bars represent one standard error of the mean.

4.4 Discussion

4.4.1 Effect of sleep deprivation on diffusion parameters

Our results replicate and extend the previous finding that single boundary diffusion drift ratio is reduced with sleep deprivation on the standard Psychomotor Vigilance Task. Diffusion drift has also been found to be reduced on a numerosity discrimination task (Ratcliff & Van Dongen, 2009). However, these sleep deprivation related changes in diffusion drift may be context and/or task-dependent. Menz et al. (2012) for example, observed that drift reduced with a decision task in SD for easy but not for hard decisions. Additionally SD appears to affect non-decision diffusion parameters (mean and variance of non-decision times). The latter finding is possibly a result of the greater power of the present study ($n=135$ vs. $n=19$ for one of the original studies) and is consistent with the notion mooted by those

Figure 4.3: Receiver operating characteristic curve obtained by varying threshold of a logistic regression based classifier. Diffusion parameters estimated on the evening before sleep deprivation (ESD) state were used to predict the vulnerability of the subjects to sleep deprivation. The best operating point was found at a true positive (TP) rate of 65% and false positive (FP) rate of 30.7%. The area under the curve was 0.74.

authors that SD can affect multiple cognitive processes (Ratcliff & Van Dongen, 2009).

4.4.2 Difference in diffusion parameters between vulnerable and resistant subjects

The most interesting finding of the present work is that the drift parameter in the evening before sleep deprivation predicted greater vulnerability to SD that was not anticipated by merely observing PVT performance. The latter may have arisen because in the ESD state, diffusion drift rate and non-decision time were

Figure 4.4: Expected median reaction time (RT) for different combinations of mean normalized diffusion drift and mean non-decision time generated by simulating 30 minutes of psychomotor vigilance task (PVT). The variability parameters were fixed at the group average values ($\eta/a=2.62, s_t=52\text{ms}$). Response times (as measured by median RT) of two representative subjects, one vulnerable (vul) and the other resistant (res) to SD were overlaid. Both subjects had the same median RT ($=256\text{ms}$) in the baseline Evening Before Sleep Deprivation (ESD) condition.

affected in opposite directions- vulnerable subjects had longer decision times but shorter non-decision times.

In the ESD state, when the diffusion drift was high, the mean drift and non-decision parameters traded-off without affecting overall observed performance. The effects of varying levels of mean diffusion drift and mean non-decision time on median RT can be modeled (Figure 4.4). The figure was generated by simulating 30 minute PVTs for each pair of diffusion-drift and non-decision time parameters while holding constant variability parameters. The modeled RT of two representative

subjects, one vulnerable and one resistant to SD are shown overlaid on the plot. Both subjects have different mean diffusion drift and non-decision parameters but the same median RT in the ESD state. Modeling showed that as the diffusion drift was reduced, median RT became dominated by the drift parameter and the tradeoff between the parameters became less apparent.

4.4.3 Interaction effect of state and group on diffusion parameters

Both mean diffusion drift and mean non-decision time showed statistically significant group by state interaction. The results suggest that in terms of decision time (i.e. drift parameters) subjects with better performance in ESD state were less affected after sleep deprivation. Furthermore, those with faster decision time performance but slower non-decision times in the ESD state continued to be less affected by sleep deprivation.

The observation that resistant subjects were less affected by sleep deprivation on all diffusion parameters suggests that they may have greater cognitive reserve (Stern, 2002) compared to vulnerable subjects (Bell-McGinty et al., 2004; Y. L. Chuah et al., 2006). This concept has been primarily applied to cognitive aging but has also been shown to be relevant in the context of sleep deprivation (Mu et al., 2005; Chee et al., 2006).

4.4.4 Possible neurocognitive accompaniments of reduced diffusion drift

Although a slower drift rate speaks to slower accumulation of evidence on which to base action, the present experiments and analyses were not designed to examine possible contribution of this mechanism. The experiment that most closely examines rate of processing limitations in the sleep deprived state is one where sleep deprivation was accompanied by a leftward shift in the frequency response profile of fMRI signal in higher visual cortex (Kong et al., 2014). This finding indicates that the maximal rate at which pictures are processed in higher (but not primary) visual cortex is lowered.

Sleep deprivation has been consistently shown to result in reduced recruitment of parieto-frontal and visual extrastriate brain regions during the performance of visual attention tasks (Chee et al., 2010; Lim & Dinges, 2010; Tomasi et al.,

2009) and even in the preparatory phase (Chee et al., 2011). The degree of reduction of activation generally corresponds to impaired accuracy in tasks but only in two studies has greater baseline activation to mark persons relatively more resistant to the negative effects of sleep deprivation (Mu et al., 2005; Y. L. Chuah et al., 2006), in accordance with the cognitive reserve hypothesis. As such, the neural correlates of predictors of vulnerability to sleep deprivation remain to be further characterized. Neuro-imaging studies conducted in the resting state could potentially give more insights. We will address this in a later chapter.

4.4.5 Predictive value of diffusion model parameters

Even though there were statistically significant differences between the vulnerable and resistant group in the baseline ESD condition, it remains to be seen if the diffusion parameters are useful in predicting vulnerability at an individual level. Estimated diffusion parameters are noisy at an individual level, especially when the amount of data is limited. Despite this, logistic regression showed that diffusion parameters have reasonable discriminative power. The addition of traditional RT metrics to the classifier did not improve classification accuracy. Future work should consider using other easily derived physiological measures (for instance heart rate variability; E. C.-P. Chua et al. (2012)) in combination with complex non-linear classifiers, to improve phenotypic characterization of vulnerability to psychomotor vigilance as a result of sleep deprivation. Another way to improve classification accuracy could be to improve the estimates of diffusion model parameters by aggregating more data from longer periods of PVT at baseline; keeping in mind that longer non-standard PVTs are strongly affected by time on task effects, which might negatively affect classification. Ideally, we would like to predict such vulnerability without having to subject participants to sleep deprivation. We will peruse these avenues in the next chapter.

4.4.6 Strengths and limitations

One of the strengths of the present study is its large sample size. We also used an established estimator for model parameter estimation that was validated on simulated data. The comparison between ESD and SD while having some utility in operational settings (Mu et al., 2005) is less ideal than a direct comparison to a well-rested period recorded in the morning hours after waking. As a result of the

test protocol used in the lab, only one such morning measurement was obtained was therefore less readily compared to the SD data (which was averaged across two time-points (Figure 4.5).

It should be remembered that while vigilance decrements are an important and robust measure of performance decline in sleep deprived persons, other cognitive domains may not be similarly affected (H. Van Dongen, Baynard, et al., 2004). Another potential limitation is that we were unable to uniquely identify all the model parameters of the DDM.

We use the term *Sleep Deprivation* to refer to the interaction between homeostatic and circadian processes instead of artificially separating the relative contributions of the two processes. In the real world that the present work speaks to, it remains that increased risk of vehicular accidents occurring at the nadir of the circadian cycle after a night of sustained wakefulness correlates with slowing of PVT performance that the diffusion model parameters in ESD predict.

Figure 4.5: Mean reaction time in milliseconds across sessions. Error bars represent one standard error of the mean.

4.5 Conclusion

Vulnerable subjects have a lower mean diffusion drift but shorter mean non-decision time compared to resistant group in the evening before sleep deprivation.

Possibly as a consequence of possessing greater cognitive reserve, resistant subjects were less affected by SD on both decision and non-decision processes. Diffusion drift can be used to estimate vulnerability to SD prior to experimental manipulation. In the next chapter we will do a systematic analysis to construct a classification system that can predict vulnerability using only baseline measures of psychomotor vigilance. It is clear that the DDM parameters will play a crucial role in such a system.

Chapter 5

Classifying Vulnerability to Sleep Deprivation Using Baseline Measures of Psychomotor Vigilance

5.1 Introduction

In the previous chapter, we showed that subjects categorized as vulnerable or resistant to sleep deprivation differed in their diffusion drift parameters (DDM) derived from PVT RT data sampled at baseline (evening before SD to be precise). In a recent study E. Chua et al. (2014) it was also observed that subjects who are vulnerable to the effects of total sleep deprivation on PVT performance show slower and more variable response times when they are well rested. These results demonstrate that baseline PVT performance carries information about vulnerability to subsequent sleep deprivation, but it remains unclear whether features of rested PVT performance can be used to classify a persons relative performance in the sleep-deprived state. As discussed earlier, one key motivation for the current work is to harness the power of smartphones and wearable devices in the future. To be able to predict vulnerability reliably, the classification system must work on a widely varying experimental situation which is expected when data is collected using these devices at the convenience of the subjects.

The analysis presented in this chapter appears in Patanaik, A., Kwoh, C. K., Chua, E. C. P., Gooley, J. J. and Chee, M. W. L. "Classifying vulnerability to sleep deprivation using baseline measures of psychomotor vigilance", Sleep, 2014. In-Press.

In this chapter we sought to assess the reliability of classifying subjects as vulnerable or resistant to sleep deprivation, using baseline features of PVT performance. We used two independent datasets to carry out our analysis involving PVT data collected from different laboratories under different experimental conditions. We extracted standard RT metrics, diffusion model parameters, and features derived from spectral analysis of RTs, and used a support vector machine (SVM) classifier with stratified 5 fold cross-validation (CV5) to estimate generalization error. The objectives of this work were fourfold:

- (i) Identify and rank candidate features derived from baseline PVT response times that predict vulnerability to sleep deprivation.
- (ii) Select a compact feature set from the candidate features resulting in maximum prediction accuracy, and to measure the performance of this classification model for each dataset.
- (iii) Evaluate the reliability of classification by training the model on one dataset and testing it on another one.
- (iv) Evaluate test-retest performance of classification by training the model using baseline data collected during one study visit, and then testing it using baseline data collected more than 5 months later from the same set of individuals.

5.2 Methods

5.2.1 Subjects

In this chapter we collect additional data from another laboratory. The data used in chapter 4 (135 subjects, 69 females, age 18-25 years) constitutes Dataset 1 here. The experiments for Dataset 1 were conducted in Cognitive Neuroscience Laboratory. For Dataset 2, 45 healthy ethnic-Chinese subjects (3 females, age 22-32 years) were enrolled in a laboratory study at the Chronobiology and Sleep Laboratory as part of a previous study (E. Chua et al., 2014). Dataset 2 shared the same recruitment criteria as Dataset 1 which is discussed in detail earlier (Section 4.2.1). Informed consent was obtained from all participants, and research procedures were approved by the SingHealth Centralized Institutional Review Board.

5.2.2 Sleep deprivation procedures

Dataset 1: As discussed earlier, subjects arrived in the laboratory in three sessions. In this chapter we are specifically interested in the sleep deprivation session, in which the subjects arrived at the laboratory at 7:30pm and were kept awake continuously overnight under supervision of a research assistant. A hand-held 10-min PVT was administered every hour from 8:00pm to 5:00am (10 test periods). Subjects were seated upright during testing and were exposed to ordinary room light. Participants movements were not restricted between PVT tests.

Dataset 2: Subjects underwent total sleep deprivation in a laboratory suite that was shielded from external time cues. Participants arrived in the evening and went to bed at their regular pre-study sleep time. After 8-hours of time in bed for sleep, subjects were kept awake for at least 26 hours using constant routine (CR) procedures, as previously described (Duffy & Dijk, 2002). During the CR procedure, subjects remained in bed in a semi-recumbent position, with exposure to dim ambient lighting (< 5 lux). The PVT was administered every two hours (starting 2.5 h or 4.5 h after wake time) by computer using E-Prime 2 Professional software (Psychology Software Tools, Inc., Sharpsburg, PA). Visual stimuli were presented on an LCD monitor placed on an over-bed table, which allowed subjects to take the PVT while remaining in bed. After undergoing sleep deprivation, participants were invited to return to the laboratory at least 5 months later to complete additional testing. A subset of subjects ($n=34$) took part in the follow-up study. Subjects reported to the laboratory in the mid-afternoon (between 2 6 pm) and completed two 10-min PVTs taken 2 h apart from one another under conditions that were similar to the first study visit. The research protocols for both datasets are summarized in Figure 5.1.

5.2.3 Assessment of vulnerability to sleep deprivation

During total sleep deprivation, cognitive performance usually reaches its nadir in the early morning hours, typically between 4am and 8am, when the sleep homeostat and circadian clock interact to promote high levels of sleepiness (Achermann & Borbély, 1994). This is also the period when sleepiness-related motor vehicle accidents are most likely to occur (Horne & Reyner, 1999). We therefore analyzed PVT performance during this time window as a measure of susceptibility to sleep deprivation. Subjects were categorized as vulnerable or resistant based on a

Figure 5.1: (A) Dataset 1: Subjects ($n=135$) arrived at the laboratory at 7:30pm and stayed awake overnight resulting in total sleep deprivation of 22 h. A 10-min PVT was administered every hour from 8:00pm until 5:00am on the next morning. (B) Dataset 2: After an 8-h opportunity for sleep, subjects underwent sleep deprivation in the laboratory for at least 26 h. Every 2 h, subjects completed a 10-min psychomotor vigilance task (PVT), indicated by the circles. A subset of subjects ($n=34$) participated in a follow up session in which two PVTs were taken in the mid-afternoon. In each dataset, subjects were stratified into vulnerable and resistant groups by performing a median split of PVT lapse data (reaction times > 500 ms) during the last session of sleep deprivation (red circles). Two baseline PVT sessions (green circles) were used to build the classifier for predicting vulnerability to sleep deprivation.

median split on the number of lapses, defined as RTs that exceed 500 milliseconds (Figure 5.1. PVTs marked in red). For Dataset 1, 70 subjects were categorized as vulnerable (≥ 5 lapses). For Dataset 2, 25 subjects were categorized as vulnerable (≥ 23 lapses), of whom 19 completed the follow-up study. The large difference in the median lapse value is likely a result of different experimental conditions between the two studies. The divergence in performance between vulnerable and resistant groups after their usual bedtime is shown in Figure 5.2. For Dataset 1, the first two PVT tests administered at 8:00pm and 9:00pm were used as the baseline. For Dataset 2, the third and fourth PVT sessions, which were taken during the mid-afternoon, were used as the rested baseline, as PVT measurements for the follow up session were available for the same time period.

Figure 5.2: Time course of PVT lapses in vulnerable and resistant groups for (A) Dataset 1 and (B) Dataset 2. Inset: Individual traces show the time course of lapses for each participant who underwent sleep deprivation. Mean $\pm$ SEM are shown.

5.2.4 RT Derived Features

As detailed below, we used a combination of standard RT metrics, features derived from the drift diffusion model (DDM), and spectral analysis of RTs.

5.2.4.1 Standard RT metrics

The most widely used PVT outcome metric is the number of lapses followed by mean RT, mean $1/\text{RT}$, fastest 10% RT, median RT, slowest 10% RT, and the slowest 10% $1/\text{RT}$ (Basner & Dinges, 2011). The reciprocal RT is also referred to as response speed ($\text{RS}=1/\text{RT}$). In an analysis of various PVT outcome metrics during partial or total sleep deprivation, Basner & Dinges (2011) found that metrics involving response speed (RS) and lapses were the most sensitive to sleep loss. It was therefore recommended that these measures be used as the primary outcome measures of the 10-min version of the PVT. In our analysis we considered lapses, mean RT, mean RS, slowest 10% RS, fastest 10% RT, median RT and standard deviation of RT. We also included mean absolute deviation (MAD) from the mean, and $\Delta \text{RT} > 250$, which is the number of consecutive RTs that differ by more than 250ms. The latter was included based on a previous finding that, under baseline conditions, subjects who were categorized as vulnerable to sleep deprivation showed a greater number of consecutive RTs that differed more than 250ms compared to resistant individuals (E. Chua et al., 2014).

5.2.4.2 Metrics derived from DDM

We included the standard normalized drift parameters: mean diffusion drift ξ/a , variability in mean diffusion drift η/a , mean non-decision time T_{er} and range of non-decision time s_t . Again, we implicitly assume that when we refer to the drift parameters they are normalized by the boundary parameter. We also included the parameter ratio ξ/η which is the diffusion drift signal to noise ratio (SNR). This parameter is known to closely track alertness (Ratcliff & Van Dongen, 2011). While estimating the parameters of the model, we combined RT data from two consecutive PVT sessions taken during the baseline rested state.

5.2.4.3 Metrics derived from Spectral analysis of RTs

Given that spatio-temporal features (i.e. structures in the ordering and positioning of the RTs) might not be captured by standard PVT metrics or the DDM, we used discrete wavelet transform (DWT) to extract multi-resolution features from RTs. The DWT effectively addresses the tradeoff between time and frequency resolution in signal analysis and can handle non-stationary signals as well. It decomposes the signal into a hierarchical set of low frequency and high frequency components

called *approximations* and *details* respectively. The DWT is computed by successive low pass and high pass filtering in the time domain. First the samples of RTs, $r[n]$ are passed through a low pass filter with impulse response $g[n]$ resulting in a convolution of the two signals. The signal also goes simultaneously through a high pass filter with impulse response $h[n]$. The outputs then give the detail coefficients ($d[n]$ from high pass filtering) and the approximate coefficients ($a[n]$ from low pass filtering). The filter outputs are then subsampled:

$$y_{high}[n] = \sum_{k=-\infty}^{\infty} r[k] * h[2n - k] \quad (5.1)$$

$$y_{low}[n] = \sum_{k=-\infty}^{\infty} r[k] * g[2n - k] \quad (5.2)$$

The process is applied repeatedly to get multi-level decomposition at different scales (Figure 5.3). We used the Haar wavelet to construct the filter bank. Due to the way DWT operates, the length of the signal has to be a power of 2. The number of RTs collected per PVT can vary widely depending on experimental conditions. The only way to handle the signal is to either truncate them or to extend them. To avoid introducing undesirable artifacts due to signal extensions and maintain consistency across subjects and datasets we considered the last $2^6 = 64$ samples of RTs from each PVT. In the baseline condition, lapses were rare enough and subjects were fast enough to guarantee 64 samples. Samples from two PVTs in the rested baseline were combined together (resulting in uniform sample size of 128) and a 6 level DWT was applied. For each level l the Mean Absolute Value (MAV) was computed as:

$$MAV_l = \frac{1}{N} \sum_{n=1}^N |d_l^n| \quad (5.3)$$

where d_l^n is the n^{th} detail coefficient at level l . RT data was demeaned before application of wavelet transform.

5.2.5 Feature Selection

In any supervised classification problem, identifying the essential features is critical to the performance of the classifier. Some of the features might be irrelevant in the sense that they provide no additional information from the point of view of class

Figure 5.3: A four level decomposition of signal using discrete wavelet transform. At each level, the resolution of the signal is halved.

prediction. Features could also be redundant, i.e. in presence of other relevant features they provide no additional information. Moreover the irrelevant and redundant features increase computational complexity and might introduce noise into the system and reduce the performance of the classifier. Therefore, given a set of features $F = \{f_i, i = 1, \dots, M\}$ existing in $\mathbb{R}^M$ and the target class variable c , feature selection tries to find a subset $S \subset F$ with m features that optimally characterizes c . Ideally we would like to minimize the generalization error of the classifier. The global solution, which might not be unique, could be found by exhaustively searching the feature space. This would require $2^M - 1$ operations. Unfortunately this becomes computationally infeasible even for moderately large values of M . Additionally, since the generalization error has to be estimated from data, large number of searches increases the chances of over fitting especially when the data size is small.

For our analysis, we first eliminated highly redundant or irrelevant features to focus on a small critical set of candidate features based on minimal-redundancy-maximal-relevance (mRMR) (Peng et al., 2005) for both datasets independently. The mRMR criterion subtracts the minimal redundancy from maximum relevance and can be expressed as:

$$\frac{1}{|S|} \sum_{f_i \in S} I(f_i, c) - \frac{1}{|S|^2} \sum_{f_s, f_i \in S} I(f_s; f_i) \quad (5.4)$$

Where, $I(X, Y)$ is the mutual information (MI) between random variable X and Y and can be computed as:

$$I(X, Y) = \int \int p(x, y) \log \left(\frac{p(x, y)}{p(x)p(y)} \right) dx dy \quad (5.5)$$

We estimated the MI using kernel density based estimation (Bowman & Azzalini, 1997). We used normal kernel function evaluated at 100 equally spaced points. The candidate feature set was constructed by using a first-order incremental search that maximizes the mRMR criterion at each stage. It was observed that the classification accuracy stabilized by the 8th ranked feature for both datasets, when each feature was considered incrementally. Therefore, only the top 8 features were selected as the candidate feature set for further analysis.

Even though a selected candidate feature is deemed relevant, including all such features does not necessarily result in better classification rate as compared to using a smaller feature set. Hence, relevance does not imply optimality (Kohavi & John, 1997). As a result the m best features are not the same as best m features (Cover, 1974). To maximize the accuracy of the classifier, a further compact subset of features was selected from the candidate features using a wrapper based approach (Kohavi & John, 1997). A wrapper is a feature selector that is *wrapped* with the classifier to select features that result in the lowest generalization error. This is very similar to the naive method described earlier, but used on a much smaller candidate feature set employing some heuristic schemes instead of trying out all possible combinations of features. We employed both the incremental forward and backward selection wrapper schemes detailed previously (Kohavi & John, 1997).

5.2.6 Classifier

For classification we have considered support vector machines (SVMs) with radial basis function (RBF) kernel (Vapnik, 2000). SVMs are powerful supervised classification methods with strong theoretical foundations in statistical learning theory and structural risk minimization; thereby leading to good generalization. A standard SVM tries to find a separating hyperplane between two classes that maximizes the margin. For data that is not linearly separable a kernel function is used that transforms the original data to a high dimensional (infinite dimensional in the case of RBF kernel) space, where the data is linearly separable. For a detailed discussion please refer to (Vapnik, 2000). To estimate the generalization error, a stratified 5-fold cross validation (CV5) was used. To find the best SVM parameters a broad level grid search was employed (regularization parameter

$C = [2^0, 2^2, \dots, 2^{10}]$ and RBF kernel parameter $\gamma = [2^0, 2^1, \dots, 2^5]$). As a pre-processing step, features were normalized to unit hypersphere before feeding them to the classifier.

$$\hat{f} = \frac{f}{||f||} \quad (5.6)$$

Where $\hat{f}$ is the normalized feature vector and $||\cdot||$ is the ℓ^2 norm. All analysis were implemented in Matlab 2013b, The MathWorks, Inc., Natick, Massachusetts, United States. We used Matlab version of LIBSVM (Chang & Lin, 2011) in our analysis. The complete feature selection process is summarized in Figure 5.4.

Figure 5.4: Summary of the overall feature selection process. The process was applied independently on both datasets.

5.2.7 Statistical Analyses

Standard RT metrics are known to be stable and reproducible across studies (E. Chua et al., 2014). To test the reproducibility of the DDM parameters, parameters estimated from baseline data of Dataset 1 collected in the first visit

were compared with parameters estimated from the follow up study using two way repeated measures ANOVA with group (vulnerable vs resistant) as the between subject factor and schedule (first visit versus follow up) as the within subject factor.

The variation in DDM parameters for vulnerable and resistant subjects on the evening before and the morning after sleep deprivation has been reported in the previous chapter. As PVT measurements for Dataset 2 were available across the day, DDM parameters were also estimated for the vulnerable and resistant groups at different time of the day. This was also done using repeated measures ANOVA (group as between subject and time of day as within subject factor, with data binned for two sessions of the PVT). For ANOVAs with statistically significant interaction, post-hoc t-tests were used to examine simple effects of group and time. The classifiers were compared using McNemar test with Yates correction. Statistical analyses were performed using SPSS (IBM Corp., New York, NY). Statistical significance was set at $\alpha = 0.05$.

5.3 Results

In each dataset, the top 8 features ranked according to their mRMR score are shown in Figure 5.5. As described in the methods, a wrapper based approach was used to select a subset of features that minimized the generalization error. Below we report classifier accuracy as assessed by cross validation (CV5 accuracy) of features using the optimal feature set.

5.3.1 Model performance in Dataset 1

A CV5 accuracy of 77% was obtained with sensitivity of 85.7% and specificity of 67.7% using five features: diffusion drift ξ , variability in diffusion drift η , range of non-decision time s_t , the number of consecutive RTs that differed by more than 250ms ($\Delta RT > 250$) and wavelet feature MAV_6 (Figure 5.6A). The receiver operating characteristic (ROC) curve and associated confusion matrix are presented in (Figure 5.6A). The area under the ROC curve (AUC) is often used as a single-value representation of overall classifier performance and is equivalent to the probability that the classifier will rank a randomly chosen positive instance higher than a randomly chosen negative instance. For Dataset 1, the AUC for the classifier was 0.75.

5.3.2 Model performance following training on Dataset 1 and testing on Dataset 2

We trained the model on Dataset 1, using the corresponding five features deemed most optimal and applied this feature set to Dataset 2. An accuracy of 71.1% was obtained with sensitivity of 80% and specificity 60%. On varying the threshold for the classifier, a more balanced result was obtained with sensitivity of 72% and specificity of 70% while the accuracy remained unchanged. The ROC and confusion matrix at the default threshold as well as the balanced threshold are presented in Figure 5.7. AUC for the classifier was 0.73.

5.3.3 Model performance in Dataset 2

For Dataset 2, diffusion drift ξ , range of non-decision time s_t and the number of consecutive RTs that differed by more than 250ms ($\Delta RT > 250$) were deemed most important. A CV5 accuracy of 82.2% was obtained with sensitivity of 84% and specificity of 80% using three features: diffusion drift ξ , range of non-decision time s_t and the number of consecutive RTs that differed by more than 250ms ($\Delta RT > 250$). The receiver operating characteristic (ROC) curve and associated confusion matrix are presented in Figure 5.6B. For Dataset 2, the AUC for the classifier was 0.74.

5.3.4 Reproducibility of classification across testing episodes in the same participants

Using the optimal feature set selected in Dataset 2, when the model was trained on baseline PVT data collected during the first visit and then tested on PVT data from the follow-up visit, we obtained an accuracy of 79.4%, with sensitivity of 73.7% and specificity of 86.7%.

5.3.5 Classification using the most sensitive PVT measures

Although standard PVT metrics were not selected by the model, we considered the possibility that such measures might nonetheless carry information about vulnerability to sleep deprivation. Using lapses, mean RS and slowest 10% RS measured at baseline, three measures previously found to be most sensitive to total sleep deprivation³², we obtained a CV5 accuracy of 64.4% on Dataset 1

and CV5 accuracy of 68.9% on Dataset 2. Compared to the best performing features for each dataset, the accuracy of classification using these PVT measures was significantly poorer in the case of Dataset 1 ($\chi^2_1 = 10.2, P < 0.005$) but not significantly different for the smaller Dataset 2, ($\chi^2_1 = 1.8, ns$).

5.3.6 DDM variability across visits and with time; computational performance

Except for across-trial variability in drift η ($F_{1,32} = 4.65, P < 0.05$), DDM parameters were stable across study visits (Figure 5.8). Vulnerable subjects had lower mean drift ($F_{1,32} = 11.6, P < 0.005$) and higher variability in non-decision time ($F_{1,32} = 13.6, P < 0.001$) across both visits compared to resistant subjects. Although DDM parameters were significantly affected by time of the day (Figure 5.9), vulnerable subjects had lower mean diffusion drift ($F_{1,43} = 4.03, P < 0.001$) and higher variability in non-decision time ($F_{1,43} = 27.5, P < 0.001$) irrespective of time elapsed since wake.

The feature extraction process was reasonably quick ($\sim 10 \text{ min /subject}$) when run on a modern workstation, with the majority of time spent estimating the DDM parameters. Overall, the χ^2 DDM fit (at baseline) for Dataset 1 was 19.2 ± 6.1 and for Dataset 2 it was 16.8 ± 7.2 . The critical value for χ^2 , $df=14$ was 26.1.

Figure 5.5: Stratified 5-fold cross validation (CV5) accuracy of the classifier as features ranked by minimal-redundancy-maximal-relevance (mRMR) criterion were incrementally added to the feature set for (A) Dataset 1 and (B) Dataset 2. The top 8 features in each dataset (partitioned by vertical line) were considered for the candidate feature set. The feature set comprised of 5 DDM parameters (mean drift: ξ/a , across trial variability in drift: η , mean non-decision time: T_{er} , variability in non-decision time: S_t , drift signal to noise ratio: driftSNR); 9 standard reaction time (RT) metrics (mean RT, mean response speed (RS), fastest 10% RT, median RT, slowest 10% RS, median RT, standard deviation of RT: std RT, mean absolute deviation of RT: MAD RT and the number of consecutive RTs that differ by more than 250ms: $\Delta RT > 250$); and 6 metrics derived from spectral analysis of RTs (Mean Absolute Value of detail coefficient at level 1 through level 6: MAV_1 to MAV_6).

Figure 5.6: Receiver operating characteristic (ROC) curves obtained by varying the threshold of class membership probability of the SVM classifier for (A) Dataset 1 and (B) Dataset 2 using the best set of features. The best performing point on the ROC curve is marked with a gray circle. Inset: confusion matrix, accuracy, sensitivity and specificity at the best performing point.

Figure 5.7: Performance of the classifier trained on Dataset 1 and tested on Dataset 2 is demarcated by the gray circle on the receiver operating characteristic (ROC) curve. The corresponding confusion matrix, accuracy, sensitivity and specificity are presented below. A more balanced classifier performance was obtained by changing the class membership probability threshold from its default value (marked with a black circle on the ROC). While the accuracy did not improve, the sensitivity and specificity became more balanced.

Figure 5.8: Estimated drift diffusion model (DDM) parameters for vulnerable and resistant subjects estimated from baseline PVT sessions measured across two study visits for Dataset 1. Of the 45 subjects who participated in the first study, 34 returned for a follow up study after at least 5 months following their initial visit to the laboratory. Baseline individual differences in mean diffusion drift and variability in non-decision time were reproducible across study visits. Vulnerable subjects had lower mean drift ($F_{1,32} = 11.6$, $P < 0.005$) and higher variability in non-decision time ($F_{1,32} = 13.6$, $P < 0.001$) across both visits compared to resistant subjects. The across trial variability in diffusion drift appeared to be the only DDM parameter to be affected across the two studies ($F_{1,32} = 4.65$, $P < 0.05$). The ‘#’ symbol denotes significant main effects of group on DDM parameters. Mean $\pm$ SEM are shown.

Figure 5.9: Estimated drift diffusion model (DDM) parameters for vulnerable and resistant subjects across the study period for Dataset 2. DDM parameters were significantly affected by time of day. Vulnerable subjects had lower mean diffusion drift ($F_{1,43} = 4.03$, $P < 0.001$) and higher variability in non-decision time ($F_{1,43} = 27.5$, $P < 0.001$) irrespective of time elapsed since waking. Across trial variability in drift and mean non-decision time showed interesting variations over the period of the day. The combined effect of all the DDM parameters was such that depending on the time of the day, the parameters could act in opposite directions. The dotted vertical line demarcates the usual bed time. Asterisk indicates statistically significant difference ($P < 0.05$).

5.4 Discussion

We observed large between-subject differences in PVT performance during sleep deprivation, such that sleep deprivation vulnerable persons had on average 3-8 times more lapses than members of the resistant group. Although prior studies have identified baseline differences between individuals who are either vulnerable or resistant to sleep deprivation, the ability to predict performance vulnerability using baseline data has not been systematically examined. Here, we examined features beyond summary statistics conventionally used in assessing RTs, including measures derived from the DDM and spectral analysis. Using two independent datasets, we identified a subset of PVT features that can be used to classify relative vulnerability to total sleep deprivation with about 77-82% accuracy.

5.4.1 Features most useful for discriminating vulnerable and resistant participants

Despite substantial differences in the way that PVT data were collected across the 2 studies considered here, DDM parameters and wavelet MAV parameters were among the top baseline features associated with relative vulnerability to sleep deprivation. In terms of best performing features, three features were selected in both datasets: diffusion drift ξ , range of non-decision time S_t and the no. of consecutive RTs that differ by more than 250 ms ($\Delta RT > 250$). Interestingly, none of the standard PVT performance metrics (e.g., mean RT and lapses) were selected when the mRMR criterion was used. The empirical data collected suggest that relative to standard RT metrics, the DDM better captures useful information embedded in RT data that can distinguish persons vulnerable to vigilance decline following sleep deprivation by decoupling RT into distinct components. This is consistent with our previous findings that diffusion parameters measured at baseline predicted vulnerability despite the absence of significant differences in baseline standard RT metrics. This might not be surprising upon inspecting the variation of the DDM parameters for the two groups across the day for Dataset 2 (Figure 5.9). While the mean diffusion drift and range of non-decision time showed statistically significant differences across groups irrespective of time of day, the mean non-decision time and across trial variability parameters showed interesting variations throughout the day. Depending on the time of the day,

DDM parameters moved in opposite directions; i.e. some DDM parameters had a tendency of increasing the RT while others had a tendency to decrease it. In other words, the decision and non-decision components can trade off with each other without affecting overall observed performance. This has also been demonstrated in the previous chapter using simulation (see Figure 4.4).

5.4.2 Classification reliability and reproducibility

PVT outcomes can be affected by multiple factors including experimental conditions, interventions and time of day. Here, we showed that the same set of features appear to be highly discriminatory across datasets. For Dataset 1, five features were selected by the model: diffusion drift ξ , variability in diffusion drift η , range of non-decision time s_t , $\Delta RT > 250$ and MAV_6 . A CV5 accuracy of 77% was achieved using these features. Despite differences in experimental conditions and baseline data acquisition times between the two datasets, the model trained on Dataset 1 and tested on Dataset 2 showed only a small drop in classification performance (71% accuracy). Importantly, the model performed well despite the large difference in the average number of lapses between studies, i.e., the median split on Dataset 1 cannot be directly linked to the median split on Dataset 2. Allowing the threshold to change when the model trained on Dataset 1 was applied to Dataset 2 resulted in a more balanced classification. These results attest to the utility of our classification model for predicting relative vulnerability to sleep deprivation.

Due to aforementioned dataset differences, it might be expected that the best set of features selected by the model would be dissimilar across the two datasets. However, we found that of the five features assessed as most optimal for Dataset 1, three were again selected for Dataset 2 (diffusion drift ξ , range of non-decision time s_t and $\Delta RT > 250$). Using these features, CV5 accuracy of 82.2% was achieved. Importantly, when the classifier was trained on PVT data collected during baseline of the first study visit in Dataset 2, performance of the model was similar to that for data analyzed during the follow-up visit (79.4% accuracy). Since the second visit occurred more than 5 months after sleep deprivation, our results suggest that baseline diffusion drift ξ and range of non-decision times s_t show stable between-subjects differences over time. While the best set of features might change depending on the type of classifier employed, the type of heuristic used, and

the definition used for categorizing subject vulnerability, our findings nonetheless demonstrate that DDM parameters, wavelet parameters, and $\Delta RT > 250$ are useful for predicting vulnerability to decline in psychomotor vigilance following total sleep deprivation under laboratory conditions.

5.4.3 Differences between datasets

In Dataset 1, participants were free to walk around when not taking the PVT, and they were exposed to ordinary room light. In Dataset 2, PVT data were collected under conditions that were conducive to poorer performance. Specifically, subjects were restricted to bed in a semi-reclined position in constant dim light. Also, in Dataset 2 we used baseline PVT data collected in the late afternoon, corresponding to the mid-afternoon dip in performance. By comparison, baseline PVTs in Dataset 1 were taken in the late evening, corresponding to the wake maintenance zone when the circadian drive to remain awake is near its peak. The aforementioned experimental differences may explain, in part, the slightly better classification rates in Dataset 2 using a smaller number of features.

5.4.4 Definition of vulnerability to total sleep deprivation

In our analysis, group assignment was based on a median split using the number of lapses in the last session of sleep deprivation. The number of lapses ($RTs > 500ms$) is the most commonly used PVT metric to assess the effects of sleep deprivation on sustained attention. We acknowledge, however, that vulnerability could be defined using other PVT outcome measures, e.g., response speed, or by individualizing the lapse threshold relative to each persons baseline performance. Dividing each dataset into two groups enabled us to build a model that predicts a binary outcome (resilient or vulnerable), but it is important to note that vulnerability to sleep deprivation is a continuous variable. Hence, the decision to split the dataset by the median was arbitrary, and the *most vulnerable* resistant subjects were qualitatively similar to the *most resistant* vulnerable subjects, separated only by a few PVT lapses during sleep deprivation. Despite this limitation, subjects were classified with nearly 80% accuracy. Of note, although resistant and vulnerable groups differed by a few lapses even during the baseline rested state (Figure 5.2), the feature selection process did not select lapses in either dataset. Instead, vulnerability was better predicted by underlying decision and non-decision components of the DDM.

5.4.5 Further improvements in classification

The reliability of estimates for DDM parameters is affected by the size of the data set as has been demonstrated in Chapter 3. To ensure that we had sufficient data for the DDM, we combined PVT RT data across two consecutive 10-min PVT sessions, separated by an hour (Dataset 1) or two hours (Dataset 2). DDM parameter estimates might be further improved by implementing longer PVT sessions (e.g. 20-30 min in duration) or by aggregating data across more PVT sessions. It must be kept in mind, however, that longer-duration PVTs are more affected by time-on-task effects (H. Van Dongen et al., 2011), and adding more PVT sessions might not be practical if our model is to be applied in real-world settings. The classification might also be more accurate if participants are studied under baseline conditions that are conducive to sleep. Adding other easily derived physiological measures, for instance heart rate variability (E. C.-P. Chua et al., 2012), could also potentially improve the performance of the classifier.

5.5 Conclusion

In this chapter, we built a classifier to predict vulnerability in sustained attention during sleep deprivation, using features derived from PVTs taken under rested baseline conditions. We included a range of features including several summary statistics, DDM parameters, and features derived from wavelet transform of the RT sequence. We found that DDM parameters, including decision and non-decision components, the number of consecutive RTs that differ by more than 250ms and wavelet features can be used to discriminate sleep deprivation vulnerable and resistant individuals with an accuracy of 77-82% across datasets. Now that we have shown that there are baseline differences between vulnerable and resistant subjects, and these differences are enough to classify the subjects even under widely varying experimental conditions, in the next chapter we will explore if these differences reveal themselves in resting state conductivities prior to sleep deprivation.

Chapter 6

Baseline resting state connectivity differences between individuals vulnerable and resistant to sleep deprivation

6.1 Introduction

In this chapter we turn our attention to neuroimaging studies. Specifically we are interested in knowing if differences in functional connectivity in the brain are observable in the resting brain prior to SD. We have shown in the previous chapters that such differences are observable in the DDM parameters prior to SD, suggesting intrinsic differences in the structural and/or functional brain. Several studies have also demonstrated baseline neurophysiological differences between participants vulnerable and resistant to sleep loss that could either be detected before exposure to SD or represent a stable trait of the brain. For instance, Mu et al. (2005) showed that participants more vulnerable to SD on a Sternberg working memory task displayed reduced global brain activations than when they were well-rested. In addition, Rocklage et al. (2009) observed differences in distributed white matter (WM) pathways between vulnerable and resistant participants on a simple visual motor task. Although, only a few studies exist (De Havas et al., 2012; Gujar et al., 2010; Sämann et al., 2010) that have examined functional

The analysis presented in this chapter appears partly in Patanaik, A. and Zagorodnov, V. “Connectivity between visual resting state networks predicts vulnerability to sleep deprivation.”, Organization of Human Brain Mapping, 2012. Used with permission.

connectivity differences between rested condition and sleep deprivation. There are no studies that examine these differences between vulnerable and resistant groups. Before we continue, would provide some background to the current investigation.

6.2 Preliminaries

6.2.1 BOLD - fMRI

When neurons in the brain become active, the blood flowing through that area increases. Furthermore the amount of blood that is sent to that area is more than that is required to replenish the oxygen that is used up by the cells. This leads to a local increase in blood oxygenation level. Functional Magnetic Resonance Imaging (fMRI) measures this change in oxygenation level which is therefore referred to as blood oxygenation level dependant (BOLD) fMRI. It is important to notice that fMRI does not measure neuronal activity directly, rather it measures the BOLD signal which acts like a proxy for neuronal activity. This increase in blood flow following brief period of neuronal activity is known as hemodynamic response. Hemodynamic response is slow; whereas neuronal activity typically lasts for milliseconds the increase in blood flow following it may take as much as 5 seconds to reach its maximum. Furthermore the fall (or undershoot) of the hemodynamic response is very slow taking as much as 15 to 20 seconds to reach baseline levels. Fortunately the hemodynamic response can be modelled satisfactorily by a linear time invariant system. This allows for construction of hemodynamic responses from expected neuronal response using convolution. This is very useful in experimental design to find locations in the brain that activate (or deactivate) with a particular experimental task.

6.2.2 Data Acquisition

The data acquisition occurs slice by slice, usually in an alternate order i.e. from top to bottom for one scan and bottom to top for another. The time interval between two scans is called repetition time (TR) which decides the temporal resolution of the data. TR along with in place resolution and slice thickness decides the overall spatial and temporal resolution (Figure 6.1). It is possible to trade off temporal resolution for spatial resolution. The researcher has to decide the parameters based on the aims of the experiment.

Figure 6.1: fMRI data acquisition process. The spatial resolution of the scan is $h \times w \times d$ and temporal resolution is TR .

6.2.3 Data Pre-Processing

Before the acquired data can be analyzed, it must go through some standard pre-processing steps. Slice time correction and motion correction are usually the ones performed first. Slice time correction (Henson et al., 1999) is required because each slice is taken at a different time. Different interpolation algorithms like linear or sinc ($\sin(x)/x$) interpolation can be used to correct for different slice acquisition time, though these are based on the assumption that subject is not moving, which is not true. Unfortunately, any motion correction algorithm must assume that images are slice time corrected! Due to such interdependencies of assumption between slice time correction and motion correction there is no consensus as to which one should be done first. Experience suggests that for short TRs (< 2 sec) slice time correction is not required. Also new MRI machines can acquire interleaved slices, which reduce the need for slice-time correction further.

Next in the pre-processing pipeline is spatial normalization which includes coregistration and normalization. While at the gross level human brain shows remarkable consistency in its overall structure across individuals, it varies widely in size and shape. This makes spatial normalization a necessary step. Coregistration is the process of aligning functional images to high resolution structural image to help identify specific anatomical structures in the functional images. Next the functional image is normalized to a standard space. The Talairach space

(Talairach & Tournoux, 1988) and the Montreal Neurological Institute (MNI)(Evans et al., 1992) space are the two most widely used spaces in the neuroscience community. The normalization process can be achieved using landmark based methods, volume based methods and surface based methods using linear, affine or non-linear registration algorithms. The complete discussion of these is out of scope of this thesis, interested readers are referred to (Holden, 2008). In the last step spatial and temporal smoothing are applied. Spatial smoothing is necessary to increase signal to noise ratio (SNR) to acceptable levels. It also allows for slight mismatch across individuals at the expense of spatial resolution. Temporal smoothing may be required to remove un-interesting temporal signals from the data. Temporal filtering is normally done in frequency domain. For a more detailed discussion of the fMRI processing pipeline reader is referred to (Poldrack et al., 2011) which gives a clear and concise description of fMRI data analysis.

6.2.4 General Linear Model-Finding regions of significant task activations

In task based fMRI analysis the objective is to find brain regions that are significantly activated with the task. This is achieved by entering the task and individual voxel BOLD response into a general linear model (Figure 6.2). The task is normally convolved with hemodynamic response function (HRF) which is the impulse response of the hemodynamic system. In the figure, β_1 accounts for the variability in BOLD signal explained by the task. β_2 accounts for the baseline. The unexplained variance is accounted for by the error. The GLM runs on each of the voxels at the end of which parametric maps are obtained corresponding to each voxel. Statistical significance tests are then performed on these maps to get statistical parametric maps (SPMs). SPM is an image wherein the intensity value represents statistical significance obtained under the null hypothesis of no activation. These SPMs are then thresholded to obtain regions of significant task activations.

6.2.5 Statistical Thresholding Problem of Multiple Comparisons

The easiest way to threshold is to declare a voxel activated if the corresponding SPM intensity exceeded a predefined threshold α derived from null distribution. This is similar to any statistical significance test with significance level α with

clusters rather than individual voxels based on theory of Random Fields (Poline et al., 1997). While useful, Random Fields Theory (RTF) methods have limitations mainly caused by violations of the assumptions it makes (see (T. Nichols & Hayasaka, 2003)), also it requires estimation of smoothness in the data which may not always be reliable. This is where non-parametric permutation tests (T. E. Nichols & Holmes, 2002) come into picture. Permutation tests do not make any assumptions about the data distributions; instead they allows one to directly obtain the null distribution of non-activated voxels. They works under the assumption of exchangeability under the null hypothesis. This is intuitively easy to understand. Take for example, two groups A and B under the null hypothesis that the mean of the two groups are same. If the null is true then data exchangeability holds and data from group A can be exchanged by data in group B. By randomly permuting data between the two groups the distribution of the null can be obtained, statistical tests can then be easily performed. The problem of multiple comparisons in the context of permutation tests is easy to solve using maximal summary statistics over all the voxels. The reason permutation tests were not popular until recently is their heavy computational cost. But with increased computational power at hand, permutation tests are very powerful and should be preferable to other methods.

Cluster based analysis is generally preferred as it can be more sensitive to finding true signal than voxel wise thresholding (see for e.g. K. J. Friston et al. (1996)). No matter which method is used, to carry out cluster based analysis instead of voxel based one must first define the clusters. The cluster threshold is normally arbitrary, yet its exact choice can have significant impact on the results. Threshold free cluster enhancements (TFCE) (S. M. Smith & Nichols, 2009) is a relatively new method which addresses this issue. It implicitly relies on non-parametric permutation tests and is shown to be better than conventional methods especially under low SNR conditions.

6.2.6 Functional Connectivity and Brain Networks

Brain regions do not work in isolation, but rather organize themselves into set of connected networks. This connectivity could be anatomical, functional or effective. Anatomical connectivity is direct axonal connection between brain regions which can be established by diffusion tensor imaging (DTI) studies. Functional

connectivity (K. Friston, Frith, Liddle, & Frackowiak, 1993) is defined as the temporal correlations between spatially remote neurophysiological events, while effective connectivity (K. Friston, Frith, & Frackowiak, 1993) is the influence one neuronal system exerts over another. Functional connectivity is an operational definition while effective connectivity is not. In other words functional connectivity is simply a statement about the observed correlations and does not provide any insight into how these correlations mediate. The distinction between the two connectivity measures is equivalent to the distinction between correlations and causality. The exact definition of effective connectivity is vague as it is always tied to some model of the influence one neuronal system exerts on another. Therefore the validity of effective connectivity is tied to the validity of the model used to describe it. Different models can be used to describe effective connectivity including linear, non-linear models or temporal precedence models like Granger causality models (Roebroeck et al., 2005). Effective connectivity analysis is more difficult to study compared to functional connectivity analysis and usually follows it.

6.2.7 Activations in the absence of task - resting state networks

Functional networks in the presence of task is intuitive to understand and can be easily found using GLM and statistical analysis discussed earlier. What is surprising and counter-intuitive is the presence of such functional networks in the absence of any task (Fox et al., 2005). Furthermore these networks are reproducible across datasets and subjects suggesting a common architecture (Biswal et al., 2010). The brain is constantly active with high levels of activity even when one is not engaged in a focused mental activity. These functional networks also referred to as resting state networks (RSNs) are large amplitude spontaneous low frequency (<0.1 Hz) fluctuations in the fMRI signal that are temporally correlated across functionally related areas. There are 8 to 10 functional networks (Figure 6.3) which show high test-retest reliability (Zuo et al., 2010) and replicability (Shehzad et al., 2009). While there is a common architecture shared by these RSNs, each individual's functional network exhibits unique features and it can provide quantitative phenotypes for molecular genetic studies and biomarkers of developmental and pathological process in the brain. Therefore, the collective set

of these functional networks is referred to as *functional connectome* in line with human genome by Biswal et al. (2010). RSNs have already been quite useful in characterizing pathology and behavior (Zhou et al., 2010; Harrison et al., 2008; Yu-Feng et al., 2007), but their role in SD vulnerability has not been explored. Given our prior findings using the DDM, we believe the intrinsic functional differences will be revealed using the RSN analysis. In the next section we will discuss various ways to find these RSNs.

Figure 6.3: Eight of the most common and consistent RSNs identified by ICA. (A) RSN located in primary visual cortex; (B) extrastriate visual cortex; (C) auditory and other sensory association cortices; (D) the somatomotor cortex; (E) the default mode network (DMN), deactivated during demanding cognitive tasks and involved in episodic memory processes and self-referential mental representations; (F) a network implicated in executive control and salience processing; and (G,H) two right- and left-lateralised fronto-parietal RSNs spatially similar to the bilateral dorsal attention network and implicated in working memory and cognitive attentional processes. Courtesy of Beckmann et al. (2005).

Figure 6.4: spatial-Independent Component Analysis (sICA) decomposition of group data.

6.2.8 Finding Group and Subject RSNs

Finding RSNs is not as straight forward as finding task related functional connectivity since there is no task to correlate with. There are two distinct approaches to handle the problem:

- (i) seed based analysis, and
- (ii) multivariate analysis.

Each has its own advantages and limitations. In case of seed based analysis a seed voxel or a cluster of voxels is chosen and its (average) time-course is correlated with rest of the brain. While simple to compute, seed based correlation analysis has serious limitations. The obvious one is the selection of seed voxels unless there is a strong prior hypothesis based on which a selection of seed voxels can be done there is no objective way of specifying them. Other not so apparent problem is effect of nuisance variables like global brain signal (Zarahn et al., 1997), motion and physiological noise which while of no importance to the analysis can have strong distributed influences on large parts of the brain, and therefore can severely contaminate the seed based analysis. The only way to alleviate this problem is to regress out the time-course of nuisance variables from the fMRI data. Correct estimation of these nuisance parameters is essential for the success of seed based correlations.

Multivariate methods act on the whole data matrix decomposing it into components. While there are many matrix decomposition methods the one that makes most sense in this context is spatial Independent Component Analysis (sICA) (van de Ven et al., 2004). In sICA the data matrix is assumed to be a linear mixture of spatially independent maps and their corresponding time-courses. In other words if X is the data matrix in $\mathbb{R}^{m \times n}$ where m is the number of time points and n is the number of voxels, then

$$X = AS \tag{6.1}$$

Where S contains statistically independent spatial maps in its rows and A which is the mixing matrix contains the associated time-course in its column. Sources are estimated by iteratively optimizing an un-mixing matrix $W = A^{-1}$ so that some measure of independence is maximized between the rows of $S = WX$. Kurtosis and negentropy are commonly used measure of independence. The standard ICA model presents problem in thresholding as it lacks any noise model. Consequently statistical significance of estimated sources is no longer possible within the framework of null-hypothesis testing. A probabilistic ICA (pICA) model has been developed (Beckmann & Smith, 2004) that includes a noise term in the standard ICA model. By providing measures of error for estimated components statistical inferencing and thresholding becomes possible. Beckmann & Smith (2004) used a Gaussian-Gamma mixture to model the noise and signal and then use an alternative hypothesis test to threshold. Usually single subject data is not sufficient to get good estimates of S , therefore data from multiple subjects are temporally concatenated (Figure 6.4) to get good estimates. Subject ICA maps can then be obtained using dual regression (Beckmann et al., 2009). Working of dual regression is simple; the ICA group maps are used as regressors to estimate individual time-course. These estimated time-courses are then used as regressors to estimate individual component maps. This is shown graphically in Figure 6.5. Now that we have a good background of functional connectivity and RSN analysis, in the next section we will move onto the experiment.

Figure 6.5: In dual regression individual time-courses are estimated first, which are then used to estimate individual spatial maps. Image courtesy of Beckmann et al. (2009)

6.3 Materials and methods

6.3.1 Participants

Twenty one right-handed, healthy adults (12 females, mean age = 21.3 years, stdev = 1.3 years) participated in this study. Informed consent was obtained from all participants in compliance with a protocol approved by the National University of Singapore Institutional Review Board. These participants were part of a larger study investigating the impact of SD on selective attention (Chee & Tan, 2010). They were selected from a pool of university students who responded to a web-based questionnaire and met the following criteria:

- age from 18 to 35 years,
- be right-handed,
- weigh between 45 to 95 kg,
- have good habitual sleep (6.5 to 9 hours of sleep every day),

- have no history of sleep or psychiatric or neurological disorders and have no history of severe medical illnesses.

The sleeping habits of all participants were monitored throughout the 2-week duration of the study and only those whose actigraphy data (Actiwatch, Philips Respironics, MA, USA) indicated habitual good sleep (i.e., they usually slept no later than 1:00 AM and woke up no later than 9:00 AM) were recruited for the study. All participants indicated that they did not smoke, consume any medications, stimulants, caffeine or alcohol for at least 24 h prior to scanning.

6.3.2 Study procedure

Participants made three visits to the laboratory. The first was a briefing session, during which they were informed about study protocols and requirements. Each participant then underwent two experimental sessions, once during rested wakefulness (RW), and once following a night of SD. The order of sessions was counterbalanced across participants, and sessions were separated by 6 to 9 days in order to minimize the residual effects of SD in those who completed the SD session first.

For the RW session, participants arrived at the laboratory at 07:30. One PVT assessment was then administered at 08:00. For the SD session, participants arrived at the laboratory at 19:30, having stayed awake the entire day without napping. They were subsequently monitored in the laboratory until 05:00 the next morning. The PVT was also administered every hour from 20:00 till 5:00 next morning (10 sessions). Participants also rated their subjective sleepiness on the 9-point Karolinska Sleepiness Scale and mood on a 10-point Likert-type scale after each PVT assessment. Between each test bout, participants were permitted to engage in non-strenuous activities such as reading and watching videos. Similar to previous chapters, participants were then split into two groups-vulnerable and resistant, based on a median split of the total number of lapses in the last sessions of SD.

6.3.3 Imaging methods

R-fMRI scan images were acquired on a 3 Tesla Tim Trio system (Siemens, Erlangen, Germany) fitted with a 12-channel head coil. Foam padding was used to restrict head motion. A gradient echo-planar imaging sequence was used with

a TR of 1.5 seconds, TE of 30 ms, field of view of 192×192 mm and matrix size of 64×64 . Parallel image reconstruction with GRAPPA was enabled and an acceleration factor of $2x$ was engaged. Twenty eight oblique axial slices (4mm thick with 0.4 mm inter-slice gap) parallel to AC-PC line covering whole brain were acquired. High resolution coplanar T1 anatomical images were also obtained for co-registration purposes.

6.3.4 Data analysis

The acquired R-fMRI images were preprocessed using FSL version 5 (S. M. Smith et al., 2004). The following preprocessing steps were applied: motion correction (Jenkinson et al., 2002), removal of non-brain structures from echo planar imaging volumes (S. M. Smith, 2002), spatial smoothing using Gaussian kernel of 4mm full width half maximum (FWHM) to increase signal to noise ratio, high pass temporal filtering of FWHM 150s to remove low frequency drifts and low pass temporal filtering of FWHM 5s to remove any high frequency noise. The functional scans were then registered to MNI152 standard space by using affine registration at resolution of 4mm (Jenkinson et al., 2002).

For each subject, the preprocessed and normalized fMRI images were concatenated across time to form a single 4D image. This group data was then processed using pICA (Beckmann & Smith, 2004). In our analysis we restricted the ICA output to 20 components, which is consistent with previous work on low dimensional ICA (S. M. Smith et al., 2009).

The default mode RSN and two left and right frontoparietal RSNs were identified by visual inspection. Subject-specific RSNs were obtained from group RSNs using dual regression (Beckmann et al., 2009). To obtain group statistical maps, voxel-wise random effects analysis was performed using a one sample t-test. Regions of interest (ROIs) were determined using joint expected probability distribution (Poline et al., 1997) with height ($p < 0.001$) and extent ($p < 0.001$) thresholds, corrected at the whole brain level. Participants were then split into two groups vulnerable and resistant, based on a median split of the total number of lapses in the last sessions of SD. Average connectivity between these two groups was compared using a two sample t-test restricted (masked) within the network as defined by the group statistical maps (ROIs). Threshold was set at ($p < 0.05$) corrected using a threshold free cluster enhancement (S. M. Smith & Nichols,

2009). The analysis was repeated on R-fMRI scans obtained in the last session of SD. Finally the difference in connectivity between RW and SD for all participants was also obtained for those RSNs that showed a statistically significant difference in connectivity between the two groups.

6.4 Results

Based on the total number of lapses in the last session of SD, the median split was found at 2 lapses. This resulted in 10 participants in the vulnerable group (lapses > 2) and 11 in the resistant group (lapses ≤ 2). The number of lapses in RW was not significantly different between the two groups ($t_{19} = 1.75$, $p=0.10$, *n.s.*). Group ICA statistical maps corresponding to DMN and frontoparietal networks for both groups are shown in Figure 6.6.

6.4.1 Functional connectivity differences between vulnerable and resistant groups in RW

Resistant participants had significantly stronger ($p<0.05$, corrected) connectivity compared to vulnerable participants in the right-frontoparietal RSN (see Figure 6.7) when they were well-rested. The cluster showing significant differences in connectivity was located in Brodmanns area (BA) 40 in the ventral right posterior parietal cortex (rPPC) (peak location MNI: 40,-52,40; cluster size 512 mm^3). There were no significant differences in RSN connectivity within the DMN network.

6.4.2 Functional connectivity differences between vulnerable and resistant groups in SD

Resistant participants continued to have stronger connectivity ($p<0.05$, corrected) in the right-frontoparietal RSN (see Figure 6.8) compared to vulnerable participants after SD. The cluster of significant difference in connectivity was also located in the ventral rPPC (BA 40), the same region identified in the RW state. However, the cluster size was bigger after SD compared to RW (1472 mm^3) and the peak location was slightly shifted (MNI: 42,-54, 32). No other significant clusters were found.

Figure 6.6: Group ICA statistical maps corresponding to the default mode network and left and right frontoparietal networks are shown. The statistical maps were thresholded using joint expected probability distribution with height ($p < 0.001$) and extent ($p < 0.001$), corrected at the whole brain level.

6.4.3 Functional connectivity changes from RW to SD in vulnerable and resistant groups

Only the right-frontoparietal RSN showed a difference in connectivity between the vulnerable and resistant groups both in RW and after SD. Figure 6.9 highlights regions of the brain that displayed significant ($p < 0.05$, corrected) decline in connectivity across states (from RW to SD) for the right-frontoparietal RSN across all participants. Large parts of the orbitofrontal cortex (OFC) and parts of the left PPC also showed significant ($p < 0.05$, corrected) decline in connectivity after SD (Table 6.1). The rPPC region however did not show any significant decline in connectivity with SD. There were also no significant differences in connectivity decline between the

Figure 6.7: Locations within the right-frontoparietal RSN (demarcated by red boundary) which show significantly stronger connectivity for resistant subjects compared to vulnerable subjects in baseline rested wakefulness condition. Error bars show Mean $\pm$ SEM.

resistant and vulnerable groups.

Table 6.1: Clusters showing significant decline in connectivity in the right-frontoparietal RSN across states (RW SD) for all subjects.

Anatomical Region	Peak Voxel					Volume (cc)
	BA	T	x	y	z	
Middle frontal gyrus right	10	5.6	38	54	-8	22.6
Middle frontal gyrus left	10	6.2	-26	66	-12	8.5
Ventral left-PPC	40	5.8	-34	-62	36	3.3

Figure 6.8: Locations within the right-frontoparietal RSN (demarcated by red boundary) which show significantly stronger connectivity for resistant subjects compared to vulnerable subjects after sleep deprivation. Error bars show Mean $\pm$ SEM.

6.5 Discussion

To our knowledge, this is the first study that has examined differences in baseline functional connectivity between individuals vulnerable and resistant to sleep loss. We found statistically significant differences in functional network connectivity between participants vulnerable and resistant to SD, even in the well-rested condition. The vulnerable group had significantly lower connectivity compared to the resistant group in the ventral rPPC area (BA 40) in the right frontoparietal RSN. Interestingly, this difference in connectivity persisted after SD and did not show any further decline.

Figure 6.9: Locations within the right-frontoparietal RSN that show significant decline in connectivity across the rested wakefulness and sleep deprived states (RWSD), for all subjects.

6.5.1 Reduced functional connectivity in the ventral right PPC region as a marker of vulnerability to SD

In the previous chapters we have shown the importance of mean drift diffusion parameter (which models the rate of accumulation of noisy evidence in a one choice decision task like the PVT) in discriminating between vulnerable and resistant subjects. The posterior parietal cortex (PPC) has been shown to play a vital role in such decision making processes (Platt & Glimcher, 1999; Snyder et al., 1997). In addition, the ventral PPC region is also implicated in visuospatial attention (Babiloni et al., 2007). Specifically it enables attentional capture and reorientation to salient and behaviorally relevant stimulus and is known to have a dominant right hemispheric lateralization (Hodsoll et al., 2009; Hutchinson et al., 2009; Mevorach et al., 2006; Stevens et al., 2005). The observed difference in connectivity of the ventral rPPC within the right frontoparietal RSN, which remained unaffected by SD could be a marker of an intrinsic property of the group which exists irrespective and independent of state (RW or SD). This complements our findings in the previous chapters that DDM parameters in the rested conditions are predictive of vulnerability to SD.

6.5.2 Role of frontoparietal network

Connectivity differences were primarily observed in the frontoparietal network. Activations in the frontoparietal network regions are implicated top-down biasing of visual attention. The frontoparietal network is also known to flexibly couple

with the DMN and its anti-correlated dorsal attention network (DAN) typically activated during a task (Spreng et al., 2010). The frontoparietal network regions have also been implicated in differential performance between vulnerable and resistant participants. Chee & Tan (2010) observed increased signal in frontoparietal regions on a visual selective attention task with varying stimulus contrast to modulate perceptual difficulty. It was further observed that sleep-deprived vulnerable participants showed reduced top-down frontoparietal signals with this reduction being particularly significant during SD lapses. Here, we also observed a reduction in connectivity in large portions of the frontoparietal RSN after SD which supports previous findings. This reduction was however not significantly different between vulnerable and resistant participants.

6.6 Conclusions

This study sought to examine functional connectivity differences between individuals vulnerable and resistant to sleep loss prior to SD exposure, without the need for participants to perform a particular task. We demonstrated that there were significant differences in resting-state connectivity within the right-frontoparietal RSN between vulnerable and resistant groups. Furthermore, this difference in connectivity did not appear to be influenced by SD. The brain regions showing significant difference between the groups are implicated in visual attention and visuo-motor integration, regions crucial to information accumulation and visio-motor integration. It is clear that the differences between vulnerable and resistant group are intrinsic properties of the brain as revealed by both this functional connectivity analysis as well as previous DDM analysis. These findings will help elucidate a better understanding of subject-specific vulnerability to SD.

Chapter 7

Summary and Outlook

7.1 Summary

Sleep is an important aspect of human life with nearly 30% of life spent sleeping. It has strong bi-directional relationship with health. Sleep or rather the lack of it, has enormous economic and health impact. The modern lifestyle is only exacerbating the situation which is evident from the progressively decreasing sleep duration. Given that cognitive effects of sleep deprivation vary considerably but stably across subjects, it is of paramount importance that the mechanisms that underly this differential vulnerability be understood. While some work has tried to understand the mechanisms of differential vulnerability, progress has been slow, and due to the relatively recent discovery of the phenomenon (2004) there is huge scope for further research. Guided by the DDM, this thesis provides a fresh perspective to the problem.

We start off by first making improvements in the estimation and simulation of the DDM and understanding its limitations in Chapter 3. The current implementation of the model is considerably simpler and faster than previous methods. We believe, with the current improvements and ease of implementation, the clinical community will find the model attractive for application to wide range of experiments. In chapter 4, we explore if the DDM parameters are discriminative between the vulnerable and resistant groups. We observed that not only were the DDM parameters significantly different between the vulnerable and resistant, they were capable of measuring these differences even when the standard measurements like mean RT and lapses failed to measure any such difference. We showed using simulations that decision and non-decision components of the DDM can trade off with each other, resulting in similar overall performance despite significant

differences in the underlying decision components. This tradeoff is especially important at high drift rates which is observed in the baseline conditions before sleep deprivation. We also observed that subjects with lower diffusion drift were also affected more by sleep deprivation, hinting at possible lower availability of cognitive reserve for information processing. We further showed that a simple logistic regression based classifier could classify the upper and lower tertile of subjects ranked by their vulnerability to SD using the DDM parameters. We systematically carried this analysis further in Chapter 5. We used a set of features including standard summary statistics, DDM parameters and wavelet parameters. A minimum redundancy maximal relevance measure in conjunction with wrapper based heuristics was used to find a set of most discriminative features. DDM parameters, $\Delta RT > 250$ and wavelet features were selected as most important features. Using the best set of features we achieved an accuracy of 77%. This was achieved using rested vigilance data collected prior to sleep deprivation in the late evening, corresponding to the wake maintenance zone when the circadian drive to remain awake is near its peak. The model trained on this dataset and then tested on a completely independent dataset taken under completely different experimental conditions showed a respectable accuracy of 71%. When the feature selection process was applied independently to this dataset, again the same set of features appeared as most important. An accuracy of 82% was achieved on this dataset. We also tested the repeatability of the classification by testing the model on a set of follow up subjects. Our results showed that prediction of cognitive vulnerability to SD can be reliably and robustly done using DDM parameters along with $\Delta RT > 250$ parameter.

In Chapter 6, we moved our attention to functional resting state connectivity. We showed that brain regions involved in visual attention and visuo-motor integration showed significantly reduced functional connectivity for vulnerable subjects compared to resistant subjects and these differences persisted after sleep deprivation. These differences were observed in the resting state in the absence of any task. The imaging analysis suggests that these differences are intrinsic to the group. The involvement of the brain regions implicated previously in information accumulation and visuo-motor integration in a task free condition squarely ties the observation to the results obtained using the DDM analysis.

7.2 Future Work

In this thesis, we provide a good foundation for future experiments to build upon. There are two clear directions in which we see future research ahead. One in the direction of improving vulnerability classification accuracy and other in the direction of gaining fundamental understanding of the mechanics of differential vulnerability. Naturally, both directions will complement each other. Before we discuss these possibilities, there are a few issues which need to be clarified.

7.2.1 Absolute scale for vulnerability

We have shown in Chapter 5 that performance on a PVT is strongly influenced by the experimental conditions. Defining vulnerability as the relative ranking within a group which undertook the PVT under similar experimental conditions is straightforward. For realistic scenarios where vulnerability prediction can be of use, strictly controlling the experimental conditions could be impractical. Therefore, a suitable way to compare psychomotor vigilance across groups need to be formulated. This will in essence provide an absolute scale for quantifying vulnerability. Analytically, the task of comparing performance of two datasets or subjects is essentially that of finding the change in threshold or bias. We have shown that the model trained on one dataset and tested on another dataset which was taken under notably different experimental conditions worked reasonably well. This suggests that the information about this bias is embedded within the RT distribution. One possible way to address the issue is to construct a mapping from DDM parameters estimated in the sleep deprived condition to an absolute scale of vulnerability. To be able to achieve this, psychomotor vigilance data for the same group of subjects in two or more different experimental conditions can be collected. The stability and reliability of such mapping must be demonstrated fully before it will be given any credence by the clinical community.

7.2.2 Prediction under field conditions

In our investigation, data was collected under controlled laboratory conditions. If the experimental conditions are unconstrained, then the sources of variability will increase which could adversely affect classification reliability and accuracy. For vulnerability predictions in real world scenarios, the system need to perform

well under widely varying experimental conditions. While our results show that predictions are robust to varying experimental conditions across two datasets it remains to be seen how it performs on wider sets of data. One of the key difficulties in vulnerability experiments (or for that matter any experiment involving sleep deprivation) is the difficulty and cost in acquiring ground truth data, as it involves subjecting participants to a full night of sleep deprivation. Based on the discussions with our collaborators, most sleep laboratories measure PVT data after sleep deprivation as a part of the study. What remains missing is the baseline psychomotor vigilance data. While relatively less time consuming, collecting rested data from these subjects is still logistic challenge and financially costly. One way to address the issue is to build a web/mobile PVT application and reaching out the participants for whom ground truth is already available to give the PVT at their own convenience using their own computer or mobile phone. This will naturally provide a realistic unconstrained data acquisition condition to test the prediction model. We have made some headway in this regard, which is discussed in Appendix A.

7.2.3 Improving classification accuracy

One of the easiest way to improve classification is possibly by collecting more data at baseline condition. This can be done either by increasing the duration of each PVT or by collecting more PVTs. Each route has its own distinct challenges. The problem with collecting multiple PVTs is that it limits the practicality of the whole endeavour as sufficient gap must be provided between PVTs to avoid the effects of time on task. On the other hand, increasing the time of PVTs will increase the influence of time on task. This is problematic from the point of view of DDM analysis as the IID assumptions will be strongly violated. Experiments could be designed to understand how the effects of time on task differ between the two groups which will shed some light to the problem. Another way to handle the problem is to explicitly model the effects of time on task within the DDM. Given the importance $\Delta RT > 250$ metric, an autoregressive model for the drift can be used: $\xi_t = \beta \xi_{t-1} + error$, although this should ideally be dictated by experiments.

In our investigation we used an SVM for classification which is a well established classification method. As our goal was to show the practicality of classification, we avoided using more complex classification systems. Small improvements in classification can be expected by using more advanced classification methods. An

analysis comparing a set of state of the art classification systems can be carried out. Such analysis will be more meaningful as more data is collected.

7.2.4 Understanding the mechanics of differential vulnerability

Our investigation has shown that the information accumulation systems in the brain play a vital role in the observed performance difference between subjects after sleep deprivation. It remains to be seen how experimental manipulation of the functioning of these neural circuits modulates the performance of the subjects after sleep deprivation. This could be achieved using a transcranial magnetic stimulation of the neural circuits deemed important and observing how it affects performance after sleep deprivation. Diffusion MRI can be carried out to test if the functional connectivity differences observed between vulnerable and resistant subjects are mediated by underlying structural differences in the brain. Pharmacological interventions can be carried out to gain understanding of the molecular basis of differential vulnerability. Clinical experiments involving humans are costly, time consuming and pose risks to the subjects. We believe our thesis will provide guidance to the clinical community in designing the right experiments and asking the right questions.

7.3 Conclusion and Final Thoughts

In conclusion, we streamlined the DDM estimation and simulation process by deriving a closed form solution for the DDM and studying its statistical properties. We showed that the resistant subjects had significantly lower diffusion drift compared to the vulnerable subjects even before any exposure to SD. Such differences were also observed in the resting state connectivity within the right-frontoparietal RSN and appeared to be unaffected by SD. The specific brain regions that showed significant difference between the groups are implicated in visual attention and visuo-motor integration, regions crucial to information accumulation and visio-motor integration, suggesting a stable and intrinsic functional and/or structural basis for the observations. We demonstrated that the various DDM parameters could act in opposing directions. This is especially important in the rested condition, when the effect of the individual DDM parameters can completely cancel each other out resulting in similar observed reaction time responses even

when the underlying DDM parameters are significantly different. We systematically showed that the DDM parameters are the most important behavioural metrics for predicting vulnerability to SD using rested data collected prior to SD. The prediction is reliable across time and datasets and robust to varying experimental conditions.

Research at the forefront of science is increasingly becoming multi-disciplinary with researchers from widely different fields collaborating together to solve a problem. The advantage of such diverse collaborations is that the researchers bring very different perspectives of looking at the same problem and consequentially very different solutions to address them. We believe our work will attract a wide range of researchers to study vulnerability to sleep deprivation. Predicting and understanding the dynamics of differential vulnerability to sleep deprivation is only going to be progressively more important in the increasingly sleep deprived society.

Appendix A

Effective PVT Data Acquisition

In this work we have shown that subjects vulnerable to sleep are fundamentally different from resistant subjects as revealed by DDM and imaging studies. Furthermore, the vulnerability can be reliably predicted under varying experimental conditions using baseline PVT data. The predictive capability could further improve with integration of other vital bio-signals like heart rate, body temperature, perspiration etc. Wearable bio-sensor devices can already measure these signals in conjunction with smartphones. Therefore, a software based cross platform PVT data acquisition system could be an invaluable tool to push this research work further to large population in cost and time effective way. In the next section, we will discuss the current solutions available and their shortcomings, technical difficulty in developing such a system and finally we present the solution that we have developed to address the issue. As the challenges involved are primarily technical, we have moved the discussion out of the main text of the thesis.

A.1 Existing PVT Data Acquisition Systems

- **PVT-192** (Ambulatory Monitoring Inc., Ardsley, New York USA) is the gold standard in PVT acquisition. It is a hardware based solution with claimed latency of 1 ms. The currently quoted price of the device is \$2500.
- **PVT Laptop System** (Pulsar informatics inc., Philadelphia, Pennsylvania USA) for Windows. Currently priced at \$1399 per unit.
- **Software App** (Pulsar informatics inc., Philadelphia, Pennsylvania USA) available on iPad. Currently priced at \$99 per app download plus additional yearly membership charges to access data on cloud.

- **PC-PVT** (Khitrov et al., 2014), is a free software based solution available on Windows platform. The software primarily targets laboratory settings and is not meant for direct use by the subjects or end user. Being developed in Matlab, it requires a download of a hefty 400 MB Matlab runtime to work.

The high price of the commercial solutions make it infeasible to conduct future experiments on large scale. Additionally, the commercial solutions are available on limited platforms. The only free solution available currently runs on desktop system running Windows and is not geared to be used directly by the subjects. We intend to solve the problem by developing a software solution that is user friendly and cross platform. In the next section we discuss the primary challenges in developing such solution.

A.2 Technical Challenges

The key challenge in developing a software based solution capable of running on general purpose hardware is the requirement of keeping the latencies to within a few milli-seconds. As an average PVT RT is only 250 ms, and the intra-subject variability in RT is estimated to be 29 ms (Rupp et al., 2012), for reliable use the latencies of the system at-least be within 10 ms. In a general purpose hardware there are three primary sources of latencies:

- (i) Latencies due to pooling rate of input device. Standard desktop keyboard and mouse are pooled at 250 Hz (source: Intel inc., Santa Clara, California - USA). High end gaming devices are pooled as fast as 1000 Hz. Smartphones usually have 100Hz scan rate for touch screens (source: Cypress Semiconductor Corporation, San Jose, California - USA).
- (ii) Latencies due to processing time of the software application. This could range from less than a millisecond on a desktop system to as high as 100ms on smartphones.
- (iii) Latencies due to refresh rate of display screen. This in almost all cases is 60 Hz.

All these latencies can add up to 100 ms or more, which is unacceptable for a PVT acquisition system. In fact, most smartphones show latencies in this range for a simple touch-to-respond application (Figure A.1). The problem is further exacerbated by the widely varying hardware and software configuration between available devices. Careful design of the software is essential to keep the latencies in check.

Figure A.1: Latencies in response for some of the flagship tablet devices. Courtesy of Agawi TouchMarks, used with permission.

A.3 Design Considerations and Possible solutions

As the PVT involves a relatively simple animation, the processing latencies can be kept minimal by utilizing hardware acceleration for graphics using multi platform Open GL libraries (Silicon Graphics, California - USA). Latencies due to pooling rate of the input device and refresh rate of the display device are strongly tied to the hardware. While these cannot be reduced at a software level, they can be accounted for. For this, precise timing information is required for peripheral devices.

Fortunately, for display devices there is a vertical blanking interval, also known as VBLANK, which is the time difference between two consecutive screen refreshes.

Open GL exposes the VBLANK via `glFinish()` API (Application Programming Interface) call. By precisely measuring the delay in the animation, reaction time measurements will account for display latencies. Similarly, if the average latency for input device is known, it can be subtracted from RT to reduce average latency. Unfortunately, neither timing information nor pooling rates are available for input devices on most platforms. As a result, they will continue to affect the latencies of the system. One possible way to solve the problem is to hardcode the latencies on a per system basis. This could be possible on certain devices (for instance on Apple, due to limited hardware models).

Other than keeping latencies to minimum, another important design consideration is the choice of development environment. The space of computing devices is highly fragmented both in terms of hardware and software. Each platform offers its own choice of software development kit (SDK) and programming language. Developing independently for each platform is prohibitively costly and time consuming. Moreover, it constitutes an essential wastage of resources as the same task has to be repeated in multiple programming languages. After careful considerations, C++ along with the Qt user interface framework (Digia, Helsinki - Finland) was selected for developing the system. C++ allows high performance and both high and low level access to underlying hardware and Qt framework makes it easy to develop the system in a platform agnostic way.

A.4 Quick PVT: A Cross Platform PVT Software Solution

The PVT software solution named *Quick PVT* was designed targeting Desktop systems running Windows, Linux or iOS and also mobile platforms including Android, iOS, Windows Phone and Blackberry. Screenshot of the application running on a Windows system and on an Android phone is shown in Figure A.2. The application size varied between 14 to 20 MBs. Special attention was paid to keep the user interface minimal and very easy to use for the subjects and end users. As the data is generated at the user end, to avoid any data tampering, the SHA1 hash of the original data along with a secret key is stored. This would allow the researchers to validate the authenticity of the data received.

A.5 Conclusion

We believe our work will be of considerable interest to both the clinical and machine learning community. Looking at the present trends, it appears that fatigue risk management using distributed and cloud enabled computing devices will be an emerging industry. Consequently, the *Quick PVT* software will help researchers to take our work further in this direction. We have left the precise measurement of observed latencies and other fine-tuning of *Quick PVT* on different platforms as a future exercise.

Figure A.2: Screenshot of *Quick PVT* running on a Desktop system on Windows and on a smartphone running Android.

Publications

- (i) Patanaik, A. and Zagorodnov, V. “Connectivity between visual resting state networks predicts vulnerability to sleep deprivation.”, Organization of Human Brain Mapping, 2012
- (ii) Patanaik, A., Zagorodnov, V. and Kwoh, C. K. “Parameter estimation and simulation for one-choice Ratcliff diffusion model.”, Symposium on Applied Computing-Association for Computing Machinery (SAC-ACM) Special Interest Group on Applied Computing (SIGAPP), 24-28 March 2014. doi: 10.1145/2554850.2554872 (AR: 24%, Tier: A)
- (iii) Patanaik, A., Zagorodnov, V., Kwoh, C. K. and Chee, M. W. L. “Predicting vulnerability to sleep deprivation using diffusion model parameters.”, Journal of Sleep Research, 2014. doi: 10.1111/jsr.12166 (IF: 3.8)
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