

The Temporal Organization of Operant Behavior: A Response Bout Analysis

by

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## ABSTRACT

Many behaviors are organized into bouts – brief periods of responding punctuated by pauses. This dissertation examines the operant bouts of the lever pressing rat. Chapter 1 provides a brief history of operant response bout analyses. Chapters 2, 3, 5, and 6 develop new probabilistic models to identify changes in response bout parameters. The parameters of those models are demonstrated to be uniquely sensitive to different experimental manipulations, such as food deprivation (Chapters 2 and 4), response requirements (Chapters 2, 4, and 5), and reinforcer availability (Chapters 2 and 3). Chapter 6 reveals the response bout parameters that underlie the operant hyperactivity of a common rodent model of attention deficit hyperactivity disorder (ADHD), the spontaneously hypertensive rat (SHR). Chapter 6 then ameliorates the SHR's operant hyperactivity using training procedures developed from findings in Chapters 2 and 4. Collectively, this dissertation provides new tools for the assessment of response bouts and demonstrates their utility for discerning differences between experimental preparations and animal strains that may be otherwise indistinguishable with more primitive methods.

## ACKNOWLEDGEMENTS

This research would not have been possible without the support of many others. Federico Sanabria was my tireless and unflappable guide throughout this journey. Peter Killeen provided regular encouragement and continues to serve as a role-model without peers. Tim Cheung supplied the initial impetus and training to explore bout models, and without him my path would have been very different. Janet Neisewander provided regular support and valued advice.

My fellow lab mates Carter Daniels, Elizabeth Watterson, and Gabriel Mazur provided friendship and assistance throughout my studies. For that, I wish them the best in their pursuits.

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## PREFACE

This dissertation represents my cumulative research on response bouts during my graduate studies under Federico Sanabria at Arizona State University (ASU). As such, certain chapters were already published, were under review for publication at the time this dissertation document was compiled, or were being prepared for review. In all cases, I have attempted to keep the format of each study as close to the publication manuscript as possible, although some minor changes were necessary to comply with formatting requirements. For all manuscripts, I was the first and primary author.

Chapter 2 was originally published as “Brackney, R. J., Cheung, T. H. C., Neisewander, J. L., & Sanabria, F. (2011). The isolation of motivational, motoric, and schedule effects on operant performance: A modeling approach. *Journal of the Experimental Analysis of Behavior*, 96(1), 17–38.”

Chapter 5 was, at the time of this writing, under review for publication, co-authored with Federico Sanabria.

Chapters 3, 4, and 6 were being prepared for submission in parallel with this dissertation, and are presented here in “publication ready” format.

Some equations have been repeated across chapters. Notably, the dynamic bi-exponential refractory model (DBERM) is first introduced in Chapter 2 (Equations 2-2 and 2-3). In Chapter 3, the parameterization was changed slightly (Equations 3-1, 3-2, and 3-3), and in Chapter 6 an additional parameter was added (Equation 6-3).

## CHAPTER 1

### GENERAL INTRODUCTION

The primary goal of behavior analysis is to understand why behavior occurs and how it can be controlled (Skinner, 1950). Predicting the probability of behavior is, therefore, a central concern in behavior analysis. Frequently, the probability of behavior is inferred from a *response rate*, the average number of responses in a unit of time. With demonstrable utility, this measure has been the primary dependent variable in highly influential quantitative models of behavior (Herrnstein, 1970; Nevin & Grace, 2000) and applied technologies (Iwata, Dorsey, Slifer, Bauman, & Richman, 1994). Nonetheless, response rate reduces behavior to a single measure, losing useful information. Skinner's (1976) eulogy for the cumulative record objected to simple reductions of behavior, pointing out the plethora of behavioral patterns apparent from simple visual analyses.

Shall we never again see things as fascinating as the slight overshooting when a pigeon switches from the ratio to the interval phase of a mixed schedule, or learns to use a clock in timing a fixed interval, or "sulks" for an hour after a short bout of fixed-ratio responding injected into a long variable-ratio performance, or slowly accelerates as it raps out "just one more" large fixed ratio on a straining [sic] schedule? These "molecular" changes in probability of responding are most immediately relevant (Skinner 1976, p. 218).

Yet Skinner provided few suggestions for how such behavioral patterns could be subject to quantitative analyses, a basic requirement to propel any field past the most basic pitfalls of subjective judgments. Since Skinner's heyday, a plethora of computational and quantitative tools have become easily available that make it possible

to quantify and assess these very patterns with precision. From among the catalog of minutiae seen in the moment-to-moment changes in an organism's response probability, this dissertation focuses on the *response bout*.

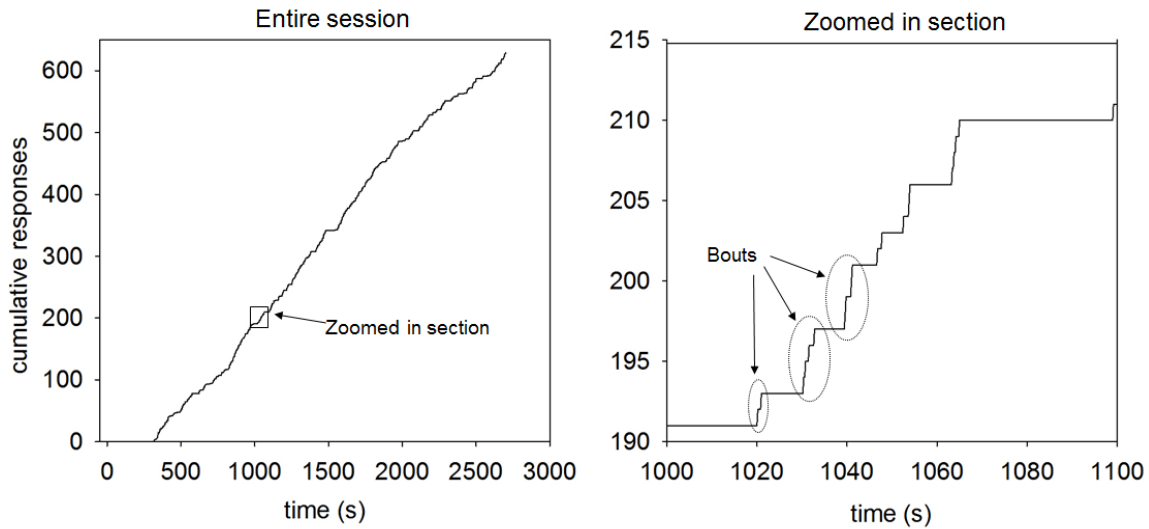


Figure 1-1. Bouts in a cumulative record. The left panel displays a cumulative record of a rat lever pressing on a variable interval (VI) 200 s schedule of reinforcement. The right panel displays a zoomed in portion of the left panel. Bouts are visible in portions where multiple responses appear in quick succession, seen as a steep increase in the slope, followed by a pause, seen as a plateau. Some bouts have been highlighted in the dotted circles in the right panel.

Figure 1-1 shows a rat engaged in bouts of lever pressing. It responds rapidly for several seconds then pauses before beginning again. This dissertation asks and answers multiple questions about bouts. What conditions cause bouts to vary, and in what ways change? What can bouts tell us about how an organism emits operant responses? And finally, how can we measure bouts, and what sort of models can provide useful information about them? In Chapters 2-6, different experimental manipulations and tests of response bouts are described, and new analyses are devised to explore their meaning.

But first, why study bouts to begin with? The remainder of this chapter describes the historical context from which response-bout studies arose and their importance in the experimental analysis of behavior.

### **Basic Units**

To understand the bout, we must first understand the basic experimental unit that feeds the cumulative record: the electric switch closure. As either a rodent lever press or pigeon key-peck, the switch closure has been the de facto standard unit of measurement for operant researchers (Catania, 1998; Ferster & Skinner, 1957; Skinner, 1938). It allows for a discrete quantification of behavior directed toward food acquisition, where the entirety of the behavior of the organism can be collapsed into a single binary dimension. When examined repeatedly over time, this unit yields orderly, highly replicable patterns in the form of cumulative records (Ferster & Skinner, 1957; Zeiler, 1984).

Yet, as a measure of behavior, the switch closure carries with it implicit assumptions that must be readdressed. Most experiments that examine the switch closure assume that every response is functionally equivalent. That is, that each response to the same operandum is uniformly informative and reflective of the same behavior or behavioral process (Shull, Gaynor, & Grimes, 2001; Skinner, 1935). However when, for example, a rat presses a lever, casual observation may reveal considerable variability in the form of the response. Sometimes the rat presses with its left or right front paw, other times it may use its teeth, and on other occasions rub its body against the lever. Should all these behaviors be considered functionally equivalent? Is a right-paw lever press functionally the same as a left-paw lever press, or gnawing on the lever to activate a switch closure? Skinner solved this dilemma by postulating that all behaviors that share a



functional relation with a specific reinforcer, regardless of their topography, are part of a response class and equivalent for analyses (Baum, 2002; Schick, 1971; Skinner, 1935).

The combination of the switch closure analyses with the conception of the response class allowed for the collapse of a wide variety of behaviors into simple, manageable measures that yield orderly relations. However, modern analysis of behavior reveals that not all behaviors strengthened by the same reinforcer are functionally equivalent (Breland & Breland, 1961; Killeen & Pellón, 2013; Mechner, Hyten, Field, & Madden, 1997; Timberlake, 1993) and even ostensibly similar responses to the same lever may be functionally different (Amsel, 1992; Catania, 1971; Shull, 2011). Analyses have revealed an organization of behavior that extends beyond the individual switch closure. For example, Schwartz (1980, 1981, 1986) demonstrated that a series of key-pecks to an array of keys may be strengthened and extinguished in a manner suggesting that the sequence itself is reinforced. Similarly, Bachá-Méndez, Reid, and Mendoza-Soylovna (2007) demonstrated that an extinguished two-lever-press sequence resurged after the extinction of another response at a probability greater than would be expected if each lever press was a functionally equivalent member of a single response class. These studies and others (Fountain, Henne, & Hulse, 1984; Fujii & Graybiel, 2003; Monteiro & Machado, 2009; Terrace, 1991) show that experimentally defined behavioral measures, such as the lever press, do not always correspond well to the behavior that is actually learned. There may be disparities between the experimentally chosen response, such as individual lever presses, and the actual organization of behavior, such as an integrated sequence of multiple lever presses. Understanding what occurs in the operant chamber

may require alternative conceptions of behavior that extend beyond simple discrete response-reinforcer relations.

### **Behavior from States**

An alternative to discrete simple responses is the conception of behavior as a concatenation of states. This approach has found been particularly useful in ethological studies (Patterson, Basson, Bravington, & Gunn, 2009), but can be adapted to explain behavior within the operant chamber. Timberlake's (1993) Behavioral Systems approach treats behavior as a set of systems, that corresponding to a different general type of activity, such as anti-predation or foraging. The occurrence of specific behaviors is dependent on which system is engaged. For example, food deprivation in a rat engages foraging systems which result in a series of food-seeking related behaviors. According to this view, individual responses such as a rat's lever presses under a partial reinforcement schedule, are better treated as one type of activity state resulting from engaging a particular behavioral system. Other researchers have noted the similarity between the natural foraging behavior of rats and their lever-pressing behavior in an operant chamber when the availability of food is probabilistic (Collier & Johnson, 2004; Johnson & Collier, 1994). Engaging the lever may be considered analogous to searching a patch for food, before either giving up to explore another patch (a concurrent lever), to explore the greater environment (engage in away-from-lever activities) or consume found food (the reinforcer). Under this frameworks, the operant lever press for food is a reflection of a food-seeking state that the animal may move in and out of.

Experimental evidence within Behavior Analysis also suggests that operant behavior may be best considered as periods of alternation between states rather than a

series of discrete responses. Early formulations describing the alternation of activity include the matching law (Herrnstein, 1961), and subsequently, Herrnstein's quantitative law of effect (Herrnstein, 1970). The matching law states that the proportion of discrete responses allocated to a single operandum is a function of the proportion of reinforcers obtained from that operandum, relative to the rate of reinforcement for other activities. However, later research has found that the matching law applies equally well to the time allocated to different behaviors (Baum & Rachlin, 1969). These observations helped lead to the suggestion that large “molar” patterns of activity, such as the allocation of responses and time to different activities, are more informative of behavior than the moment to moment, so-called “molecular”<sup>1</sup> dynamics in which each measured response is considered a distinct action to be accounted for (Baum, 2002).

One needs not favor a “molar” or “molecular” approach singularly, however. Whereas purely “molecular” approaches may forgo examining broader patterns of behavior, purely “molar” approaches may miss more nuanced relationships between individually measured responses. In cases where multiple levels of analysis can be dissociated, predictable alternations between different response states and types can be discovered. For example, Killeen, Sanabria, & Dolgov (2009) found that the responding of pigeons on a probabilistic discrete-trial task was best described by a bimodal distribution of key pecks. On each trial, pigeons either did not peck at all, or they made a random number of pecks. These results suggest that on each trial the pigeons were either in or out of a response state. When in the response state, pigeons produced pecks that

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<sup>1</sup> For the biologist, the “molar” and “molecular” terminology of some behavior analysts may be confusing. In this case “molecular” behavior does not reference molecular biology or even physical molecules, but instead a philosophical treatment of behavior with a focus on predicting and describing the occurrence of individual responses.

appear to be generated by a specific random process. These patterns of behavior are not apparent when simply examining the average number of responses per trial or individual responses by themselves.

The alternation between response states is also apparent on free operant tasks to a single operandum. Early research noted that switch closure responses tend to cluster together in time, and that the responses that initiates these clusters are different from responses within these clusters. For example, the rate at which pigeons approach a key to peck is dissociable from the rate at which they actually peck, suggesting that response rate is reflective of at least two different states, one in which the subject engages the key and one in which they do not (Hursh, Raslear, Shurtleff, Bauman, & Simmons, 1988; Nevin & Baum, 1980; Pear & Rector, 1979). Periods of differential engagement also become particularly apparent when examining the behavior of subjects trained on fixed-interval schedules and other timing tasks, which has often been found to conform to a “break and run” pattern. This pattern consists of not responding or responding at a low constant rate followed by responding at a high constant rate after a certain amount of time has passed (Sanabria, Thraillkill, & Killeen, 2009; Schneider, 1969).

Combined, these studies suggest that there is a functional difference between the response that initiates the bout and the remaining responses that complete the bout. The division is readily apparent when behavior is explicitly divided between two operanda: one that initiates the operant and another that either continues or terminates it (Mechner et al., 1997). For example, Mechner and Guevrekian (1962) found that when a timing task required the initiation of the trial on one lever and termination on a second, only the probability of the initiating response was sensitive to food deprivation (see also

Watterson, Mazur, & Sanabria, 2015). Similarly, Corbit and Balleine (2003) found that when training a heterogeneous two-response chain, the initiating response was sensitive to outcome devaluation but the terminal response was not; conversely, the terminal response was sensitive to Pavlovian-instrumental transfer effects but the initiating response was not. The dissociation of response initiation and response execution has also been demonstrated in patterns of neural spiking. The initiation of a response pattern such as a run of responses on a fixed-ratio or initiation of traversing a runway is reflective of specific neural spiking patterns in the dorsal striatum (Fujii & Graybiel, 2003; Jin & Costa, 2010) that are quiescent during the remaining execution of the response pattern, until finally occurring again upon completion. Taken together, this evidence supports a conception of behavior in which subjects alternate between multiple states of engagement, and in which entering a new state initiates a behavioral sequence that persists until reaching some exit criterion. According to this perspective, entering into a new state, and the corresponding initiation of the behavioral sequence, is functionally distinct from executing the sequence.

### **The Response Bout**

The *response bout* is a formalization of the idea that subjects alternate between response states, in this case between a behavioral state in which the subjects engage in the target response, such as the lever pressing, and another state in which the target response does not occur. The temporal clustering of the response is called a bout, and the bouts are separated by pauses during which the subject engages in other activity. Bout-like processes, in which the target response is clustered temporally followed by pauses, have been observed across many disciplines. For example, the rate at which neurons spike are

often described as two alternating Poisson processes, one to describe inter-burst intervals, and another to describe inter-spike intervals (Gerstner & Kistler, 2002; Izhikevich, 2006). In another case, the distribution of swimming durations between turns in *C. elegans* is well described by a mixture of two exponential distributions (Pierce-Shimomura, Morse, & Lockery, 1999), as well as the frequency at which e-mails are responded to (Barabasi, 2010; Barabási, 2005).

In studies of animal behavior, bout-based analyses have been applied to the feeding behavior of many animals (Yeates, Tolkamp, Allcroft, & Kyriazakis, 2001), such as rats (Clifton, Lee, & Dourish, 2000), cows (Tolkamp, Schweitzer, & Kyriazakis, 2000), pigs (Morgan, Emmans, Tolkamp, & Kyriazakis, 2000), and pigeons (Zeigler, Green, & Lehrer, 1971). Researchers studying feeding have long noted that, whereas visits to the feeder may be the measured unit, the total meals, or bouts of feeder-related activity, are more informative. Changes in the distribution of feeding bouts reflect differences in how food is consumed in different species (Zeigler et al., 1971), allowing for response-bout analyses to be diagnostic of different underlying processes.

### **Bouts in the Experimental Analysis of Behavior and the Bi Exponential Model**

Richard Shull conducted considerable early research on the application of response bouts in the experimental analysis of operant behavior (Shull 2001, 2002, 2004; for related treatments, see Killeen, Hall, Reilly, & Kettle, 2002; Kirkpatrick, 2002; Monteiro & Machado, 2009). Shull (2001) conceived of the response cycle as a three-state continuous time Markov chain (see Figure 1-2), in which behavior alternates between a disengaged state away from the operandum, and two engaged states: a visit

state and a response state.<sup>2</sup> When the subject is in the disengaged state, there is a probability  $\text{Pr}(V)$  that after the passage of each arbitrary unit of time, the subject enters the visit state. Within the visit state, there is a probability  $\text{Pr}(R)$  that the subject enters the response state, where a response is made. After completion of the response, the subject immediately returns to the visit state with probability  $1 - \text{Pr}(D)$  or the disengaged state with  $\text{Pr}(D)$ . Figure 1-2 describes this process.

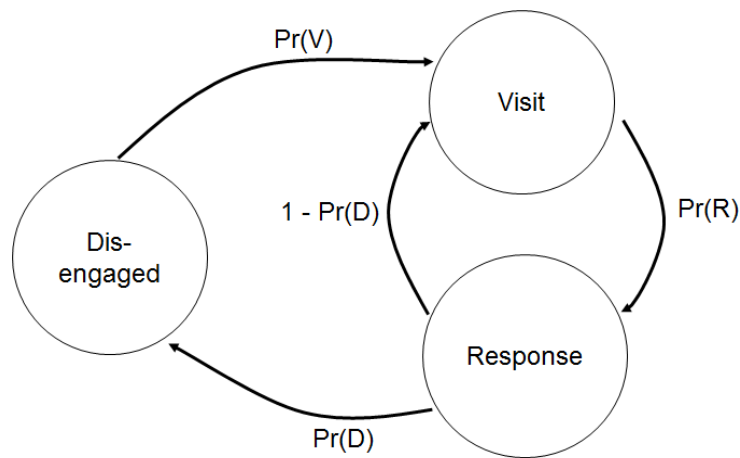


Figure 1-2. Bouts as a continuous time Markov chain (as described in Shull et al., 2001, Figure 2). The visit state is entered with probability  $\text{Pr}(V)$ , and responses engaged with  $\text{Pr}(R)$ . Once a response is made, the subject may return to the disengaged state with  $\text{Pr}(D)$  or return to the visit state with the probability  $1 - \text{Pr}(D)$ .

On a continuous time scale, this Markov model gives rise to two Poisson response-generating processes. The first Poisson process controls the transition from a disengaged state to visit state, whereas the second process controls the emission of

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<sup>2</sup> Note that in this case, a “state” is a formal unit of the Markov model. In previous sections, the term state was used to refer to a more abstract construction in which the subjects were engaged in a specific response. In Shull’s case, “engagement” is actually represented by two formal Markov states.

responses while in a visit. The times between events governed by a Poisson process are exponentially distributed (Ross, 2006), and two alternating Poisson processes, such as in this case, result in a mixture of two exponential distributions of inter-response times (IRTs), one of long IRTs and one of short IRTs. The long IRT distribution corresponds to the bout initiation rate, or how often the animal visits the lever; the short IRT distribution corresponds to the within-bout response rate, or how fast the animal presses while at the lever. The formalization of this model is described beginning in Chapter 2.

Multiple methods have been devised to describe the components of response bouts. Shull and colleagues (2001, 2002, 2004) analyzed response bouts by curve fitting to log-survivor plots of inter-response times (IRTs), or using simple IRT cutoff methods. When the distribution of IRTs are a mixture of two exponential distributions, the corresponding log-survivor function takes on a distinctive "broken stick" shape, characterized by two straight lines connecting at a joint, illustrated in Figure 1-2. The steeper slope nearer the ordinate corresponds to the within-bout response rate, whereas the shallower slope corresponds to the bout initiation rate. With these considerations, Shull and colleagues (2001; 2002; 2004) fit exponential distributions to the straighter portions of each limb of the broken stick using the method of least squares. They then projected the slope corresponding to the bout initiation rate to the point at which it would intercept the ordinate to estimate the proportion of IRTs that are within-bout.



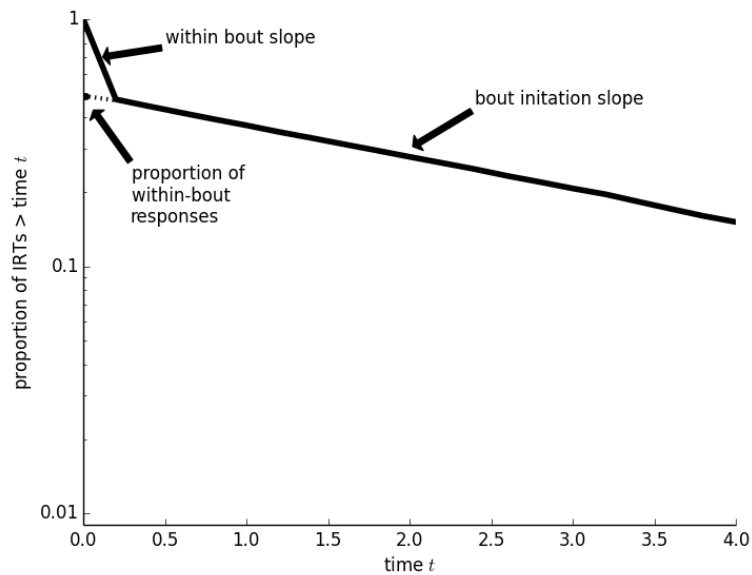


Figure 1-3. A log-survivor plot demonstrating the “broken stick”, which represents the within bout and bout initiation rates. The within-bout response rate is indicated by the upper rightward slope, and the bout initiation rate by the lower leftward slope. The proportion of within bout responses may be estimated by projecting the bout initiation slope to where it would intercept the y-axis, as denoted by the dotted line. The survivor plot indicates the proportion of IRTs (y-axis) that are greater than a certain value,  $t$  (x-axis). For example, in Figure 2, all IRTs are greater than 0 s, therefore, when  $t=0$ , the value on the y-axis is 1. Similarly, only approximately 40% of all IRTs are greater than 1.0 s. When exponential distributed variables are expressed on a semi-log scale, as here, their slopes appear as a straight line.

Using these analytic techniques, Shull and colleagues (2001; 2002; 2004) demonstrated that each parameter of the response bout was differentially sensitive to changes in training and testing conditions, and revealed changes in response patterns that were not apparent from response rates alone. For example, when animals are trained to respond on a variable interval schedule of reinforcement, raising either the rate of reinforcement, the response requirement following the elapsed interval, or the level of food deprivation, all result in an increase in response rate. Despite the similarity in effect on overall response rate, it seems reasonable to hypothesize that these manipulations increased responding through different mechanisms. An increase in behavior due to food

deprivation is not the same as an increase in behavior when more responses are required to earn the reinforcer, yet a simple analysis of response rate would suggest that they are indistinguishable.

Shull demonstrated that these manipulations have unique effects on responding, which the parameters of response bouts reveal. For example, increasing reinforcement rate or food deprivation levels primarily increase bout initiation rate, but influences within-bout response rate and bout length substantially less. In contrast, increasing the number of responses required to earn reinforcement after the end of a variable interval changed the average bout length, but only marginally changed the bout initiation rate (Shull et al., 2001; Shull & Grimes, 2003).

### **Experimental Applications of the Bout**

Just as discrete switch closures reveal shades of actual behavior, behavior itself provides clues to the inner workings of the organism, given the proper analytic tools. The goal of many researchers in behavioral neuroscience is to observe and manipulate behavior and biology, then infer what behavioral processes have been affected. For example, a researcher may infer from a rat's frequent lever pressing for cocaine that the rat is highly motivated to seek the drug. Later, the researcher may apply some treatment that reduces lever pressing for cocaine, such as a new drug thought to decrease cocaine cravings. The onus is on the researcher to demonstrate that their treatment not only reduces the subjects' lever pressing for cocaine, but that it does so *because* it reduces the rats' motivation for cocaine. Treatments that affect behavior in other ways, such as reducing motoric capacity, would be undesirable if the goal is to extend the research to treatments in humans.

The problem of identifying the cause of response decrement poses a problem for behavioral neuroscience researchers employing typical operant methodology. There are many reasons why a rat may stop lever pressing aside from reduced motivation. Changes in working memory, motoric capacity, sensory processing, or any other of a host of processes result in changes in response patterns. However, an examination of simple switch closures aggregated into the most typical measure, response rate, tells us little about the mechanisms responsible for why an animal stops responding.

Typically, a study that wishes to dissociate these different processes will require multiple experiments and behavioral methods, each focused on studying just one of the many hypothetical behavioral processes. Response bouts analyses may provide a less costly method of partitioning out the different sources of change in operant behavior (Johnson, Bailey, & Newland, 2011; Johnson, Pesek, & Newland, 2009; Newland, Hoffman, Heath, & Donlin, 2013; Shull et al., 2001, 2002; Shull, Grimes, & Bennett, 2004; Shull, 2004). By identifying different manipulation with well agreed upon effects (e.g., food deprivation changes motivation or increasing the lever force requirement change the motoric output of the organism) and examining their effects on response bout parameters, we may begin to build a catalog of behavioral processes that are reflected in response bout parameters.

The first major goal of this dissertation was to establish how response bouts are systematically changed due to different behavioral challenges, in particular: by food deprivation and satiation (Chapters 2 and 3) – by training requirements such as response count (Chapters 2 and 5), response duration (Chapter 4 and 6), and response effort

(Chapters 2) – and by breaking the response-reinforcer contingency through extinction and non-contingent reinforcement (Chapters 2 and 3).

By establishing a catalog of bout-parameter changes, these findings may be extended to ask how behavioral processes differ due to less well understood factors, such as a new drug or differences between animal strains. If, for example, a new strain of rat demonstrates differences in bout parameters relative to its control strain, and these differences have been previously shown to be selective the result of motoric challenges, we may then infer that some motoric aspect of the new strain is also different.

The second major goal of this dissertation was to then provide a test case for linking behavioral processes to differences in bout parameters and demonstrating the advantages of bout-based inferences. In Chapter 6, bout analyses are applied to the spontaneously hypertensive rat (SHR), a common animal model of ADHD (Sagvolden et al., 2009), and its control strain, the Wistar Kyoto Rat (WKY). The SHR responds more during operant maintenance and extinction compared to the WKY, yet the cause of these differences are poorly understood (Alsop, 2007). This dissertation assessed how the bout parameters of the SHR and WKY vary, and what behavioral processes may explain the differences. Using those findings, a behavioral “treatment” for the SHR was then devised, in which the SHR was trained to respond more like the WKY.

The third major goal of this dissertation was to develop new models and statistical tools for the assessment of response bouts. The log-survivor plots and complementary analyses traditionally used in the past have significant limitations that needed to be overcome. To better describe response bouts, the dynamic bi-exponential refractory model (DBERM) is proposed in Chapter 2 to take into account the biophysical

constraints of response emission, and how bouts may change over the course of the session. In Chapter 5, alternative versions of DBERM are considered and a new method of estimating the distribution of bout lengths is described. In Chapter 6, DBERM is fit using a hierarchical Bayesian framework (Gelman, 2004; Rouder & Lu, 2005; Shiffrin, Lee, Kim, & Wagenmakers, 2008) that overcomes many of the limitations associated with the inference of between-group parameter differences when using maximum likelihood point estimation (Myung, 2003).

## CHAPTER 2

### THE ISOLATION OF MOTIVATIONAL, MOTORIC, AND SCHEDULE EFFECTS ON OPERANT PERFORMANCE: A MODELING APPROACH.

#### **Abstract**

Dissociating motoric and motivational effects of pharmacological manipulations on operant behavior is a substantial challenge. To address this problem, we applied a response-bout analysis to data from rats trained to lever press for sucrose on variable-interval (VI) schedules of reinforcement. Motoric, motivational, and schedule factors (effort requirement, deprivation level, and schedule requirements, respectively) were manipulated. Bout analysis found that inter-response times (IRTs) were described by a mixture of two exponential distributions, one characterizing IRTs within response bouts, another characterizing intervals between bouts. Increasing effort requirement lengthened the shortest IRT (the refractory period between responses). Adding a ratio requirement increased the length and density of response bouts. Both manipulations also decreased the bout initiation rate. In contrast, food deprivation only increased the bout initiation rate. Changes in the distribution of IRTs over time showed that responses during extinction were also emitted in bouts, and that the decrease in response rate was primarily due to progressively longer intervals between bouts. Taken together, these results suggest that changes in the refractory period indicate motoric effects, whereas selective alterations in bout initiation rate indicate incentive-motivational effects. These findings support the use of response bout analyses to identify the influence of pharmacological manipulations on processes underlying operant performance.

## Introduction

Since Skinner (1938), the rate at which an operant is emitted has served as the principal measure of the effectiveness of reinforcement (Killeen & Hall, 2001, but see Hursh & Silberberg, 2008). Free operant response rate, however, is not a unitary phenomenon. Under most contingencies of reinforcement, operant performance seems to be organized in bouts separated by relatively long pauses. Bout-like organization is evident in break-and-run patterns observed under fixed ratio (FR) schedules of reinforcement (Felton & Lyon, 1966), fixed-interval (FI) schedules (Schneider, 1969), and peak timing procedures (Church, Meck, & Gibbon, 1994; Federico Sanabria et al., 2009). Bout-and-pause patterns are more readily visible in variable ratio (VR; Reed, 2011) and variable-interval (VI) schedules (Conover, Fulton, & Shizgal, 2001; Shull et al., 2001). These patterns suggest that response rate is constituted by two underlying rates—the rate at which bouts are initiated, and the rate at which responses are emitted while in a bout.

Shull and colleagues (Shull et al., 2001, 2002, 2004; Shull, 2004) have shown that the components of operant response rate in VI schedules, bout initiation rate and within-bout response rate, are differentially sensitive to various experimental manipulations. Bout initiation rate, but not within-bout response rate, positively covaries with rate of reinforcement and level of deprivation (Shull et al., 2001, 2002, 2004). The addition of an unsignaled ratio requirement at the end of a scheduled interval increases the probability of remaining in a bout after a response (Shull et al., 2001; Shull & Grimes, 2003; Shull, Grimes & Bennett, 2004). The rate of initiation and the length of bouts decrease with time in extinction (Shull et al., 2002). Taken together, these results suggest that, under VI

schedules, (1) bout initiation rate depends primarily on rate of reinforcement and deprivation, and (2) within-bout response rate is sensitive to schedule demands such as tandem ratio requirements.

The differential sensitivity of the components of response rate to motivational and schedule manipulations (e.g., deprivation level and tandem ratio requirement, respectively) suggests that important psychological processes may be dissociated in nonhuman animals on the basis of critical aspects of operant performance. Such capability has significant implications in behavioral neuroscience, because the isolation of psychological processes is a prerequisite to the identification of their underlying neural processes and structures. In this regard, it would be ideal if the bout-and pause analysis could be extended to dissociate motoric effects in addition to its dissociation of motivational and schedule effects. Indeed, motoric effects are of great concern in biopsychological research, because they are often confounded with changes in motivation (Avila et al., 2009; Salamone, Correa, Farrar, Nunes, & Pardo, 2009; we refer to the experimental variation in these effort requirements as effort or motoric manipulations).

The present study aimed to replicate the schedule and deprivation-level effects demonstrated by Shull and colleagues (2001, 2002, 2004), and to expand upon them by investigating the effect of effort requirement on response rate. We manipulated effort by varying the height and force requirement of the levers, and motivation for food by implementing a 24-hr deprivation period. Our goal was to use the bout-and-pause analysis to characterize the differential effects of motivational (deprivation level), motoric (lever height and force requirement), and schedule (presence/absence of tandem FR requirement) manipulations on response rate, and to identify performance parameters



(bout initiation rate, within-bout response rate, etc.) that are differentially sensitive to these manipulations. Identifying such effects is critical to establish a means of determining whether changes in response rate caused by a drug are due to an alteration in the motivation for the reinforcer or due to changes in motor capacity. To avoid interactions between the treatment drug and the reinforcer—in particular if the reinforcer is another drug—tests are often conducted under extinction conditions (Fuchs, Tran-Nguyen, Specio, Groff, & Neisewander, 1998; Stewart & de Wit, 1987). We therefore introduced a novel, dynamic model to account for changes in model parameters during extinction.

### **A Bout-and-Pause Model of VI Performance**

In a recent series of studies, Shull and colleagues (Shull & Grimes, 2003; Shull, 2004; Shull et al., 2004) analyzed the distribution of VI inter-response times (IRTs) using log-survival analyses, and found evidence that such a distribution is more accurately described as a mixture of two exponential distributions—one characterized by very short, burst-like IRTs, and the other characterized by much longer IRTs. This is consistent with the view that a rat can be in either one of two states during a session—an engaged or a disengaged state (see also Heyman, 1988). When the rat is in the engaged state, it responds at a relatively high rate ( $w$ , within-bout response rate) according to a Poisson process, generating the exponential distribution of short IRTs. After each response there is a constant probability  $(1 - q)$  that the rat will remain in the engaged state and continue to respond at a high rate. There is a complementary probability  $(q)$  that the rat will quit the engaged state and enter the disengaged state. In the disengaged state, the rat may perform responses incompatible with the target response (e.g., locomotion, grooming,

etc.) or may simply be quiescent for a period of time. Once that period of time elapses, the rat will revisit the target operandum to emit a response, thus reentering the engaged state. The target responses that terminate the disengaged state are therefore called bout initiation responses. The exponential shape of the distribution of intervals between bouts implies that bout initiation responses are governed by another Poisson process, albeit one with a much lower rate ( $b$ , bout initiation rate) than the process that controls within-bout responses. Thus, there is evidence that operant responding is not a unitary process, but instead occurs in distinguishable bouts, and that overall response rate is actually a composite of two classes of responses—fast within-bout responses and slower bout initiation responses.

According to this model, the probability density of an IRT of length  $\tau$ ,  $p(\text{IRT}=\tau)$ , in VI schedules of reinforcement can be described by the following bi-exponential distribution (Shull & Grimes, 2003; Shull, 2004; Shull et al., 2004):

$$p(\text{IRT} = \tau) = (1 - q)we^{-wt} + qbe^{-bt}, \quad (2-1)$$

where  $w$  is the mean within-bout response rate;  $b$  is the mean bout initiation rate, and  $(1 - q)$  is the proportion of IRTs that are emitted during a bout;  $q$  is therefore the proportion of IRTs that separate bouts (which is the same as the probability of quitting the engaged state after a response). Overall response rate is thus a composite process controlled by three parameters,  $q$ ,  $w$ , and  $b$ . We call this model the *bi-exponential* model. Note that setting  $q$  to zero (or one) reduces Equation 1 to an exponential distribution, which would be a good description of operant performance not organized in groups of bouts.

## The Refractory Period

Equation 2-1 assumes that after a response is made, an animal can instantaneously make another response (i.e., there is no dead time between responses). This is likely to be incorrect— physical limitations impose ceilings on response rates (Killeen & Sitomer, 2003; Killeen, 1994), which yield a dead, or refractory, period after each response during which the animal cannot make another response (Killeen et al., 2002). This refractory period, which we call  $\delta$ , is longer for responses that take longer to complete, probably like those that involve a higher workload. We included  $\delta$  in Equation 1 as

$$p(IRT = \tau | \tau < \delta) = 0,$$

$$p(IRT = \tau | \tau \geq \delta) = (1 - q)we^{-w(t-\delta)} + qbe^{-b(t-\delta)}. \quad (2-2)$$

We call Equation 2-2 the refractory bi-exponential model. Note that fixing  $\delta$  at 0 in reduces it to Equation 2-1. Figure 2-1 provides a schematic diagram of the refractory bi-exponential model underlying Equation 2-2.

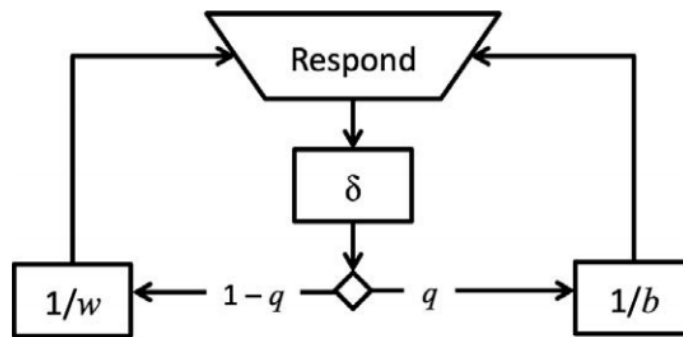


Figure 2-1. A diagram of the refractory bi-exponential model of operant performance. The lever press requires time  $\delta$  to complete. Following a response, the rat either remains in the engaged state with probability  $1-q$  and responds on the lever at rate  $w$ , or exits the engaged state with probability  $q$  and returns at rate  $b$ .

## Predictions

Prior data suggest that food deprivation covaries with the rate at which response bouts are initiated, but not with response rates within bouts in VI schedules (Shull et al., 2001, 2002; Shull, 2004). Accordingly, we anticipated that depriving rats of food would increase  $b$  (bout initiation rate), but not  $w$  (within-bout response rate) or  $q$  (probability of quitting an engaged state after a response), in the distribution of food-reinforced VI IRTs. In contrast, prior data suggest that appending a tandem FR requirement at the end of the VI schedule, which increases the response requirement without substantially affecting rate of reinforcement, mainly increases within-bout response rates and not bout initiation rates (Shull et al., 2001, 2004; Shull & Grimes, 2003). Accordingly, we anticipated that the tandem FR requirement would increase  $w$ , possibly decrease  $q$ , and would not influence  $b$ .

Skjoldager, Pierre, and Mittleman (1993) study provides the most relevant precedent to the motoric manipulation implemented in the present study. They found that increasing the lever height and force requirement prolongs pre-ratio pauses (i.e., reduces rates of engagement) and reduces run rates in a progressive ratio schedule. It is unclear, however, the extent to which the latter effect might have resulted from the longer time it takes to complete more effortful responses, which is reflected in the refractory period  $\delta$  following each response. We thus anticipated that raising the lever and increasing its force requirement would decrease  $b$ , increase  $\delta$ , and possibly decrease  $w$ .

## Method

### Subjects

Six Sprague Dawley rats (*Rattus norvegicus*, designated 505, 507, 517, 519, 520, and 521) naïve to operant conditioning experimentation served as subjects. They were approximately 90 days old and weighed about 350 g at the start of the study. They were housed individually on a 12:12 h reverse light/dark cycle with lights on at 1900 h, and had free access to food and water in their home cage, unless noted otherwise.

### Apparatus

Two experimental chambers (305 mm long, 241 mm wide, and 210 mm high) housed in light- and sound-attenuating compartments were used. The front and rear walls and the ceiling of each experimental chamber were made of clear plastic; the front wall was hinged and functioned as a door to the chamber. The floor consisted of thin metal bars positioned above a catch pan. In the horizontal middle of a side wall (perpendicular to the front and rear walls) was a square aperture (51 mm sides, 15 mm from the chamber floor) to the receptacle for 45-mg sucrose pellets (dustless precision formula F0042; Bio-Serv, Frenchtown, NJ). The chambers were equipped with two retractable levers (MED associates, ENV-112CM) mounted flanking the access to the pellet receptacle. The inside edge of each lever was 8 mm from the closest vertical edge of the receptacle.

One lever (the “low” lever) was located 21 mm above the floor; the other lever (the “high” lever) was 165 mm above the floor and 16 mm below the ceiling. Rats could press the low lever but not the high lever without rearing. Force activation requirements for the low and high lever were 0.05 N and 0.78 N, respectively, except during autoshaping. Force requirements were measured from the tip of the lever using a stylus

force gauge and manipulated by adjusting the spring tension of each lever. Henceforth the high height/force lever will be referred to as the *high workload* lever and the low height/force lever will be referred to as the *low workload* lever. The assignment of high versus *low workload* to the lever closest to the door was counterbalanced across chambers and remained fixed for the duration of the experiment. Extraneous noise was masked by a ventilation fan in each chamber. There was no illumination in the chambers during sessions. Data collection and experimental events were handled by MEDPC™ software and hardware.

## **Procedure**

### **Magazine Training and Autoshaping.**

Each subject completed one session of magazine training, in which 60 sucrose pellets were delivered, response-independently, 1 every 60 s. At the end of the training session, it was verified that all rats ate all of the pellets. Nine sessions of autoshaping were then conducted. Each autoshaping trial started with the extension of a lever, which was retracted after 8 s or a lever press, whichever happened first; lever retraction was followed by the delivery of one pellet. The inter-trial interval (ITI) was 48 s. During autoshaping, both levers were set at the “low” height; lever force activation requirements were both set at 0.15 N. For all other phases of the experiment the lever work requirements were as described in the apparatus section.

### **Phase 1: Maintenance**

Daily experimental sessions were conducted following the autoshaping phase. Each session began with a 5- min acclimation period in which no experimental events occurred. The remainder of the session was divided into trials, each signaled by the

extension of only one of the two levers. The lever closest to the chamber door was always extended for the first trial of each session. The extended lever (high or low) was strictly alternated between trials. Each trial ended and the lever was retracted when a sucrose pellet was delivered or when 300 s had elapsed since the start of the trial, whichever occurred first. Trials were separated by a 15-s ITI during which both levers were retracted.

All experimental sessions lasted for 1 h or 60 trials, whichever occurred first. Sessions ended only after the end of a trial, never during. Sessions were conducted 7 days a week.

Table 1 lists the experimental conditions in the order in which they were presented. Each condition is identified by the schedule on which pellet deliveries were programmed. During continuous reinforcement (FR 1), pellets were contingent on a single lever press. During VI schedules, pellets were contingent on the first lever press following an unsignaled interval that was randomly sampled without replacement from a flat 48-item distribution of intervals, which had a mean of the stipulated VI duration and ranged between 5 and 240 s. The tandem variable-time (VT) 120 s fixed ratio 5 (tandem VT 120-s FR 5) schedule was similar to a simple VI 120-s schedule, but pellets were contingent on the fifth lever press following the interval.

Acute food deprivation was instated immediately after the 27th tandem VT 120-s FR 5 session. Chow was removed from the rats' homecage for 24 h ( $\pm 1$  h). One session was conducted on the tandem VT 120-s FR 5 s schedule under food deprivation. Food deprivation was terminated immediately after this session to minimize the possibility of

chronic food-restriction effects on operant performance (Epstein, Leddy, Temple, & Faith, 2007).

Table 2-1.

*Number of sessions in training and experimental conditions, arranged in chronological order*

Schedule of Reinforcement	Sessions
<i>Phase 1</i>	
FR 1	1
VI 5 s	1
VI 10 s	1
VI 20 s	1
VI 30 s	11
VI 120 s	20
Tand VT 120-s FR 5	27
Tand VT 120-s FR 5 with food deprivation	1
<i>Phase 2</i>	
Tand VT 120-s FR 5	7
Extinction	1

### **Phase 2: Extinction**

Performance was restabilized on the tandem VT 120-s FR 5 schedule for seven sessions, after which one extinction session was conducted. During extinction, only the lever closest to the door was extended after the initial acclimation period; it remained extended for the entire session, with no consequential pellet delivery. The extended lever (high or low workload) was counterbalanced across rats, with 3 rats exposed to each lever.

### **Data Analysis**

Statistical analyses of overall response rates and parameters of the quantitative model were conducted using a within-subject  $2 \times 3$  (workload  $\times$  condition) ANOVA. The two levels of the workload factor were low and high workload. The three levels of the condition factor were VI 120 s (*VT*), tandem VT 120-s FR 5 without food deprivation



(*Tandem*), and tandem VT 120-s FR 5 with food deprivation (*Food Dep*). Dependent measures for each level of the condition factor were the average of the last 4 VI sessions, the average of the last 4 *Tandem* sessions, and the only *Food Dep* session. Because the condition factor was a within subject factor with more than two levels, Mauchly's test of sphericity of the covariance matrix (Mauchly, 1940) was applied. This test verified the homogeneity of variance of the difference scores because violating variance homogeneity can inflate Type I error rates (Myers & Wells, 1995). For terms that violated the sphericity assumption, their degrees of freedom were reduced using the Huynh-Feldt epsilon (Huynh & Feldt, 1970), which countered Type I error rate inflation. When the  $2 \times 3$  ANOVA revealed significant main effects or interactions, paired-samples t-tests (pairing within-subject) were conducted on comparisons of interest. More specifically, when an effect involving the condition factor was found to be significant, follow-up paired-samples t-tests were conducted only between *VI* versus *Tandem* (to assess the effect of the tandem ratio requirement) and *Tandem* versus *Food Dep* (to assess the effect of food deprivation), and not between *VI* and *Food Dep*. The times at which responses were emitted during the single extinction session were also collected, but no between-subject statistical inferences were made.

## **Results Phase 1: Maintenance**

### **Reinforcement and Response Rate**

Panel A in Figure 2-2 shows daily mean reinforcement rates on both low and high workload levers for each manipulation. Panel B in Figure 2-2 shows the mean reinforcement rates averaged over the last four training sessions in the *VI* and *Tandem* manipulations and the mean reinforcement rates from the single *Food Dep* manipulation.

Reinforcement rate did not appear to be affected by either workload or condition: ANOVA failed to detect a main effect of workload,  $F(1, 5) = 1.74$ ,  $p = .20$ , condition,  $F < 1$ , NS, or a workload  $\times$  condition interaction,  $F < 1$ , NS. This indicates that our schedule successfully controlled for reinforcement rates on both levers across schedule/deprivation manipulations. Panel C in Figure 2-2 shows daily mean response rates during *VI*, *Tandem*, and *Food Dep* sessions. Panel D in Figure 2-2 shows mean response rates averaged over the last four *VI* and *Tandem* sessions and the mean response rates from the single *Food Dep* session for each lever. ANOVA found no significant condition  $\times$  workload interaction effect on response rates,  $F = 1$ , NS. ANOVA also found no systematic differences between response rates on the high versus low workload lever (main effect of workload,  $F = 1$ , NS). In contrast, ANOVA found a main effect of condition,  $F(2, 10) = 18.55$ ,  $p < .01$ . A follow-up t-test comparing *VI* versus *Tandem* found that subjects responded more during the *Tandem* condition than during the *VI* condition,  $t(5) = 3.85$ ,  $p < .02$  (left asterisk in Figure 2-2D). A second follow-up t-test comparing *Tandem* versus *Food Dep* found that rats also responded more during *Food Dep* than during *Tandem*,  $t(5) = 3.87$ ,  $p < .02$  (right asterisk in Figure 2-2D), in agreement with the hypothesis that motivation is enhanced by increased food deprivation.

### **Model Selection**

Although statistical analysis suggested that the response rate was not affected by workload, variability in performance between and within subjects may have obscured systematic changes in more fine-grained parameters that underlie overall response rates. We further explored this possibility by considering four variations of a model of IRT distributions (Equation 2-2, Figure 2-1): a single-exponential model, where  $q = 0$  and  $\delta =$

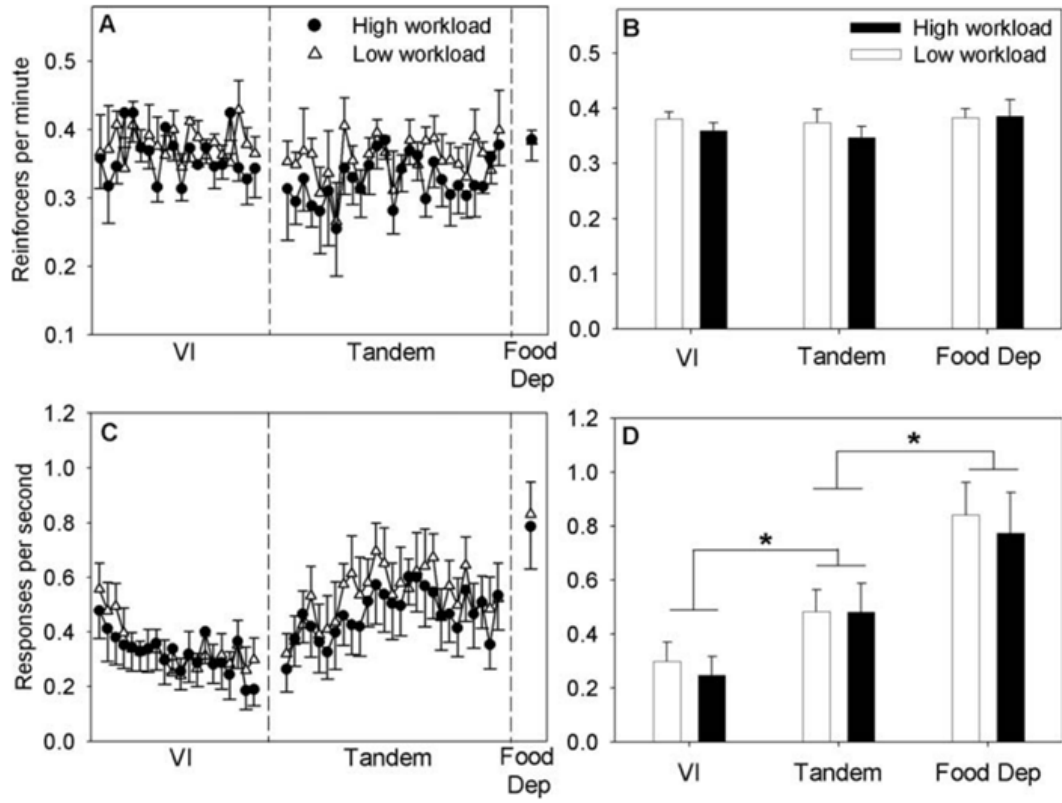


Figure 2-2. Mean reinforcement and response rates Panels A and B are reinforcement rate, Panels C and D are overall response rates. Error bars are the standard error of the mean. for experimental conditions in Phase 1. Left panels show daily means for low and high workload levels. Right panels show means averaged over the last four sessions for *VI* and *Tandem* conditions and the mean for the single *Food Dep* session. Asterisks indicate significant ( $p < .05$ ) effects of condition (schedule/deprivation manipulations).

0; a refractory exponential model, where  $q = 0$  but  $\delta \geq 0$ ; a bi-exponential model, where  $q \geq 0$  but  $\delta = 0$  (Equation 2-1), and a refractory bi-exponential model, where  $q \geq 0$  but  $\delta \geq 0$  (Equation 2-2).

We fitted each model to each rat's daily IRT data on each lever, using the method of maximum likelihood (Myung, 2003). The maximum likelihood estimate (MLE) of each model was the product of the model's daily likelihood estimates across levers and subjects. Akaike Information Criterion (AIC; Burnham & Anderson, 2002; see Appendix

A for a brief explanation of the maximum likelihood method, AIC, and  $\Delta$ AIC) was then used to evaluate the relative goodness of fit of each model. In the present experiment, a trial occasionally timed out before the animal had earned a reinforcer, thus yielding periods that ended without a response. Appendix B provides the expression for the probability that the animal does not emit a response for a given duration.

Table 2-2.

*Minimum daily  $\Delta$ AIC for each of four models of operant performance for each experimental condition in Phase 1.*

Model	VI	Tandem	Food Dep
Single exponential ( $w$ )	3377	6239	25497
Refractory exponential ( $w, \delta$ )	2836	5771	22744
Bi-exponential ( $q, w, b$ )	1097	1700	9622
Refractory bi-exponential ( $q, w, b, \delta$ )	0	0	0

*Note.* Computation of  $\Delta$ AIC is explained in Appendix A. Free parameters are indicated in parenthesis following model names. Note that the food deprivation condition consisted of only a single session.

Table 2-2 shows the minimum  $\Delta$ AIC across daily sessions under each condition for each model. The refractory bi-exponential model (Equation 1-2) was consistently the best model on every training session. The finding that the next smallest  $\Delta$ AIC across all sessions was 1097 means that the refractory bi-exponential model was at least  $e^{548}$  times more likely than the next best model (non-refractory bi-exponential model) on any given day.

To illustrate the goodness of fit of the selected model, Figure 2-3 shows log-survival plots of IRTs (continuous curves) of a typical rat across experimental conditions, along with fitted refractory exponential (dotted) and refractory bi-exponential (dashed) traces. All plots take the approximate shape of a broken stick: a substantial portion of the IRTs is very short (steep portion of the curve on the left side of each plot); the longer IRTs range over much longer intervals (flatter portion of the curve on the right side of

each plot). The refractory bi-exponential model fit the data adequately, and certainly better than the single exponential model. The fitted non-refractory bi-exponential trace (not shown) was almost identical to the refractory bi-exponential trace, except that the former was shifted to the left by 0.1 s. The similarity of both traces highlights the advantage of using a likelihood-based analysis: AIC clearly showed that the inclusion of the refractory period provided a better description of the data. This advantage would have been missed by both visual inspection of the survival function and by fitting a curve to the function using the method of least squares (Kessel & Lucke, 2008).

### **Effects of Parameter Estimates**

To assess the effect of workload, schedule of reinforcement, and food deprivation on refractory bi-exponential parameters, we compared estimates of these parameters<sup>3</sup> across experimental manipulations. This comparison was based on the same  $2 \times 3$  (workload  $\times$  condition) ANOVA used to analyze overall response rates above. The 2 levels in the workload factors were *low* and *high workload*, and the 3 levels in the condition factor were *VI*, *Tandem*, and *Food Deprivation (Food Dep)*. Because our model assumed that each parameter was independent from one another, a separate ANOVA was conducted for each parameter. Estimates for individual rats are shown in Appendix C.

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<sup>3</sup> There are occasional sessions in which 1 animal did not emit bout-like responding – specifically rat 520 on 3 sessions and rat 519 on 1 session under the *VI* condition. On these sessions, these rats' AIC scores from the refractory single exponential model were the lowest. This is because the estimates for  $q$  using the bi-exponential model were so close to 0 that the parameter  $b$  did not account for enough variance to justify its inclusion. This means that the estimates of  $b$  were based on few responses and were thus unreliable. On these sessions, we therefore used the refractory single exponential model for these animals, with  $q = 0$ , and  $b$  for these animals was not estimated. On another 2 sessions under the *Tandem* condition, rat 520 emitted only one response on the high workload lever. We therefore omitted to analyze this rat's IRT data from the high workload lever entirely on these 2 sessions. None of the above atypical responding occurred during the last 4 sessions in each condition, on which statistical analyses were based.

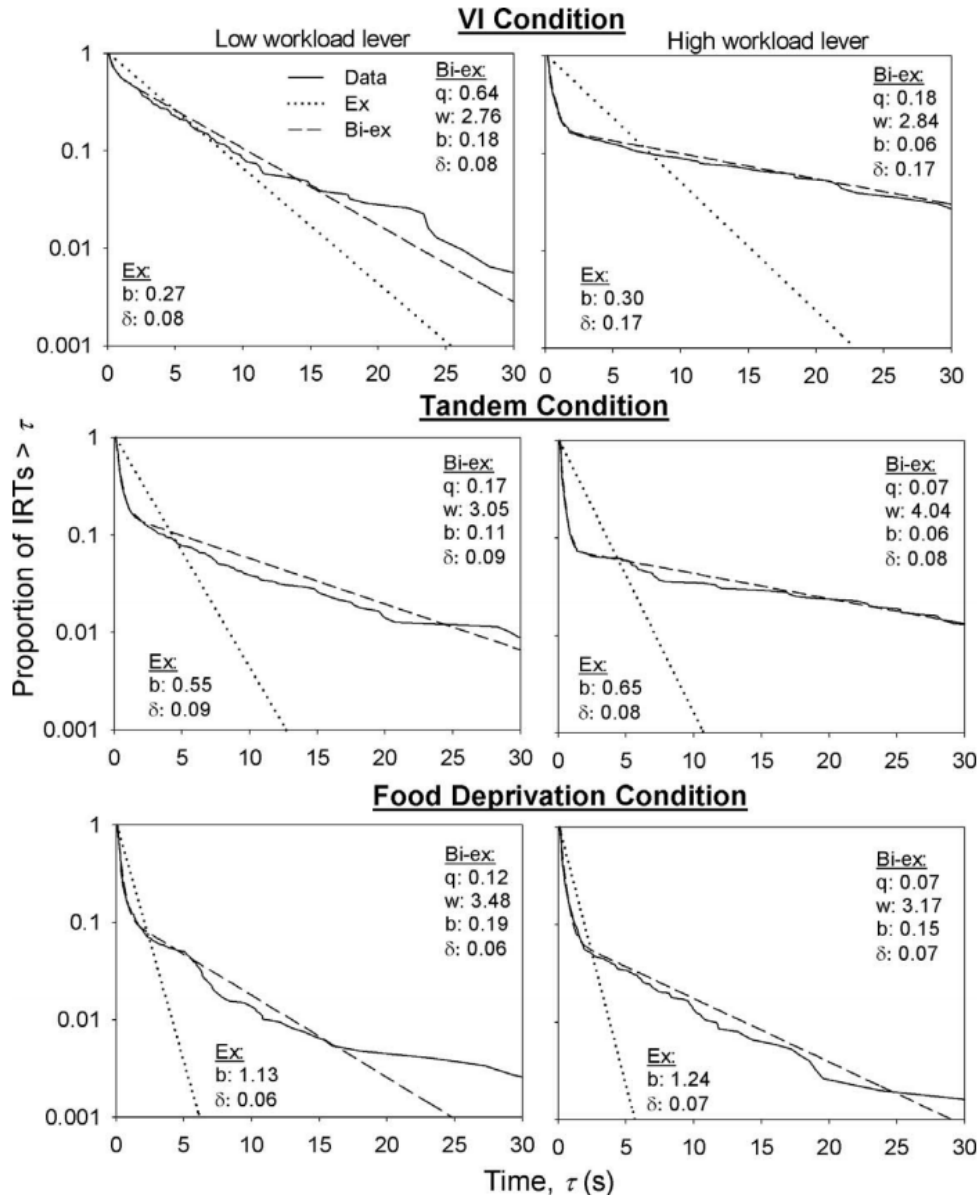


Figure 2-3. Phase 1 log-survival plots of IRTs produced by a representative rat in all experimental conditions (continuous curves). Left and right panels show data from low and high workload levers, respectively. The maximum likelihood fits of the refractory single exponential (Ex) and bi-exponential (Bi-ex) models are also shown. The best fitting parameters for the two models are displayed in each graph.  $q$ : proportion of IRTs separating bouts;  $w$  (responses/sec): within-bout response rate;  $b$  (responses/sec): bout initiation rate;  $\delta$  (sec): refractory period. The rat was selected by ranking the overall response rate on each lever in the last session of each condition in Phase 1 for each rat, then averaging the rank across levers and conditions, and selecting the rat with the third highest average rank.

Panels A and B in Figure 2-4 show the probability of quitting a bout,  $q$ , for each of the two levers. ANOVA found no workload  $\times$  condition interaction effect on  $q$ ,  $F < 1$ , NS. Changing motor workload had no significant effect on  $q$  [main effect of workload:  $F(1, 5) = 1.07$ ,  $p > .30$ ]. In contrast, ANOVA found that  $q$  was significantly affected by condition [main effect of condition:  $F(1.0, 5.1) = 19.64$ ,  $p < .01$ ]. A follow-up t-test comparing *VI* vs. *Tandem* found that increasing ratio requirement reduced  $q$  on both levers,  $t(5) = 4.54$ ,  $p < .01$ , (asterisk in Figure 2-4B). A second follow-up t-test comparing *Tandem* vs. *Food Dep* found that food deprivation did not affect  $q$  significantly,  $t(5) = 1.63$ ,  $p > .10$ .

Panels C and D in Figure 2-4 show mean estimates of the refractory period,  $\delta$ , for each of the two levers. On average,  $\delta$  was systematically higher for the high vs. the low workload lever, although the difference was small (pooled average difference =  $0.033 \pm 0.009$  s)<sup>4</sup>. ANOVA found no workload  $\times$  condition interaction effect on  $\delta$ ,  $F(1.1, 5.3) = 1.96$ ,  $p > .20$ , but it found a significant main effect of workload,  $F(1, 5) = 15.38$ ,  $p < .02$

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<sup>4</sup> Our estimate of  $\delta$  carries a slight bias. This is because maximum likelihood is achieved when  $\delta$  is as large as possible, i.e., at the minimum IRT. However, if  $X$  is an exponentially distributed random variable with rate  $b$  and no refractory period ( $\delta = 0$ ), and if we take  $n$  independent samples from  $X$  (e.g.,  $n$  IRTs from a subject), then  $\min\{X_1, \dots, X_n\}$  will also be exponentially distributed with mean  $1/nb$  (Ross, 2007). Similarly, given a bi-exponential distribution with no refractory period, if we take  $(1-q)n$  samples from the exponential distribution with rate  $w$  and  $qn$  samples from the other exponential distribution with rate  $b$ , then we expect the minimum to be exponentially distributed with mean  $1/[(1-q)nw + qnb]$ . This is therefore our bias when we use the minimum IRT as our estimate for  $\delta$  in the refractory bi-exponential model. We took bi-exponential parameter estimates from the last 4 sessions under the *VI* and *Tandem* conditions and from the single *Food Dep* session, and substituted them into the equation  $1/[(1-q)nw + qnb]$ , where  $n$  is the number of responses emitted by the animal. The average bias pooled across conditions and levers was  $0.005 \pm 0.003$  s, and there was no substantial difference between the biases on the two levers ( $0.002 \pm 0.002$  s). The bias was only ~4% of the average estimate for  $\delta$  (i.e., minimum IRT;  $0.11 \pm 0.01$  s) and was also much smaller than the average difference in  $\delta$  between the high and low workload levers ( $0.033 \pm 0.009$  s). Therefore the bias in the present study was too small to affect any of the findings, and was consequently ignored.

(pound sign in Figure 2-4D), showing that increasing motor workload increased  $\delta$ , as predicted above. The main effect of condition on  $\delta$  was not significant,  $F(1.1, 5.3) = 3.12$ ,  $p > .10$ .

Panels E and F in Figure 2-4 show mean estimates of the within-bout response rate,  $w$ , for the two levers. ANOVA found no significant workload  $\times$  condition interaction effect on  $w$ ,  $F < 1$ , NS. ANOVA found that the main effect of workload was not significant at the .05 level,  $F(1, 5) = 4.50$ ,  $p > .08$ , even though differences in mean  $w$  between workloads may hint that high workloads maintained higher  $w$ . ANOVA found a significant main effect of condition on  $w$ ,  $F(2, 10) = 9.45$ ,  $p < .01$ . A follow-up t-test comparing *VI* vs *Tandem* found that  $w$  increased when ratio requirement was increased,  $t(5) = 4.49$ ,  $p < .01$  (asterisk in Figure 2-4F). A second follow-up t-test comparing *Tandem* vs. *Food Dep* found that food deprivation did not affect  $w$ ,  $t(5) = 0.92$ ,  $p > .35$ .

### **Discussion Phase 1: Maintenance**

A superficial examination of response rate alone indicated that responding on a VI schedule increases if the tandem ratio requirement increases, or if the animals are deprived of food (Figure 2-2, Panels C and D). Both effects, under conditions of constant rate of reinforcement (Figure 2-2, Panels A and B), are replications of well-demonstrated phenomena (Ferster & Skinner, 1957; Shull et al., 2001; Skinner, 1938). Interestingly, no effect of workload on overall response rate was detected. This result is inconsistent with many reports indicating an inverse relationship between force-requirements and response rate (Adair, Wright, Pierce, & Haven, 1976; Alling & Poling, 1995; C. M. Bradshaw, Szabadi, & Ruddle, 1983; Posadas-Sanchez, 2005), although support for this relationship



is not unequivocal (Collier & Jennings, 1969; Elsmore & Brownstein, 1968; Stanley & Aamodt, 1954; Zarcone, Chen, & Fowler, 2007, 2009). Nonetheless, overall response rate is a crude measure of performance: by collapsing all the IRTs into the denominator, response rates neglect the information contained in the distribution of IRTs. We suspected that changes in IRT distribution across conditions would uncover interesting effects, including those produced by changes in workload.

Our first task was to determine the most appropriate characterization of IRT distributions. We thus considered four models, three of which were simplified versions nested within a fourth, more complex model—the refractory bi-exponential model (Equation 2-2). The complexity of this model was well justified by the variance it accounted for and, therefore, it was adopted. The refractory bi-exponential model assumes that responses occur in bouts; it comprises four parameters:  $q$  (the probability of quitting a response bout; its complement,  $1 - q$ , is the probability of continuing in a bout),  $\delta$  (the minimum IRT),  $w$  (the rate of responding within a bout), and  $b$  (the rate of bout initiation).

Finally, we identified substantial changes in refractory bi-exponential parameters caused by changes in experimental conditions. Consistent with Shull et al. (2001), we found that the tandem VT FR schedule maintained higher response rates than the simpler VI schedule because it sustained longer bouts of fast responding (lower  $q$ , higher  $w$ ), even though these bouts were less frequent (lower  $b$ ). Food deprivation selectively increased bout frequency, thus yielding even higher response rates; this also replicated Shull's (2004) findings. We also found that mean response rates obscured three mutually compensating effects of workload: higher workloads yielded less frequent bouts (lower  $b$ )

of responses that took longer to complete (higher  $\delta$ ), but that tended to be emitted at higher rates (higher  $w$ ). Although not statistically significant, the workload-induced change in  $w$  was sufficient to counteract the depressing influence of  $b$  and  $\delta$  on overall response rate.

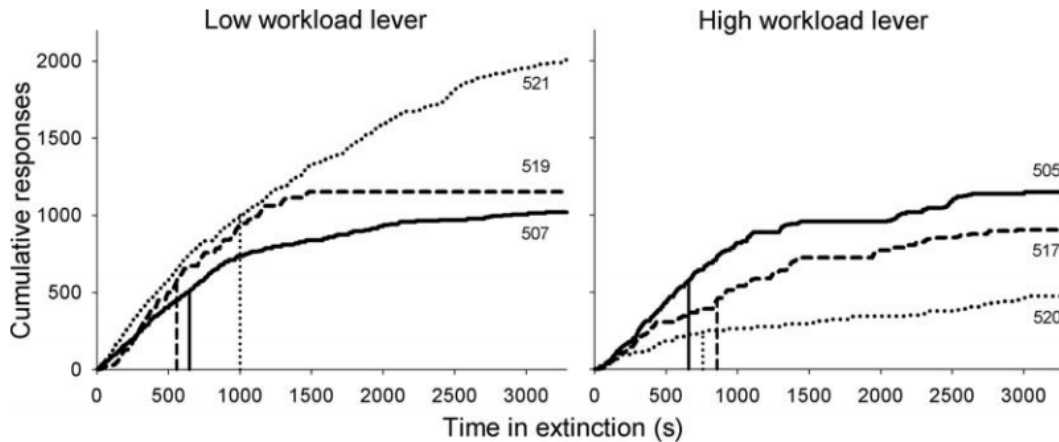


Figure 2-4. Cumulative lever presses emitted during extinction on the low and high workload levers for individual rats. Vertical drop lines indicate the time at which each subject emitted half of its total lever presses in the extinction session. Rat numbers are indicated at the end point of each record.

Among the factors considered in this study, changes in schedule of reinforcement affected only the probability of staying on the lever ( $1 - q$ ) and the rate of within-bout responding ( $w$ ), whereas workload uniquely affected the minimum IRT ( $\delta$ ). Thus, evidence presented here supports the use of  $q$  and  $w$  as indices of schedule effects, and  $\delta$  as an index of motoric effects in food-maintained behavior. Motivational effects, such as those of food deprivation, may be identified by exclusive changes in the rate of bout initiation  $b$ . This means that changes in  $b$  that are accompanied by changes in other parameters may be caused by non-motivational manipulations. As shown in Figure 2-4 Panel H, a schedule manipulation (tandem FR requirement) and a motoric challenge

(higher workload lever) yielded reductions in  $b$ . These non-motivational manipulations also influenced other parameters; only food deprivation influenced  $b$  alone.

### **Results Phase 2: Extinction**

Figure 2-5 shows, in separate plots for low and high workload, the cumulative lever presses emitted by individual rats and the time when half of those lever presses were emitted during the extinction session. On average, fewer responses appear to be emitted during the extinction of high workload lever pressing, although the variability between subjects precludes any meaningful statistical analysis. In contrast, the rate at which responding decayed during extinction, indexed by the half-life of the cumulative response, was similar across workload levels. As in Phase 1, we anticipated that the analysis of response aggregates provided no more than a general semblance of the extinction process. We thus applied the modeling exercise from Phase 1 to the data from Phase 2.

Because the exponential model is a special case of the bi-exponential model, we will focus on generalizing the latter model to extinction performance. Like the maintenance model, the extinction model assumes that responses occur stochastically and independently according to two underlying independent Poisson processes – one with high rate (within-bout) and one with low rate (bout initiation). It is assumed that, during an extinction session, one or more of the following parameters decay exponentially towards zero over time: the probability of remaining in a bout ( $1 - q$ ), the within-bout response rate ( $w$ ), and the bout initiation rate ( $b$ ). The decay of any one of these parameters would yield longer IRTs, and thus reduced response rates, as a function of time in extinction. The nomination of these decay processes is not motivated by

theoretical considerations, but provides reasonable descriptions of the extinction process, given the refractory bi-exponential model.

Specifically, let  $(1 - q_0)$  be the baseline probability of remaining in the engaged state at the beginning of the extinction session,  $w_0$  be the baseline within-bout response rate, and  $b_0$  be the baseline bout initiation rate. Let  $1 - q_t$  be the probability of quitting the engaged state at time  $t$  into the extinction session,  $w_t$  be the within-bout response rate at time  $t$  into the session, and  $b_t$  be the bout initiation rate at time  $t$  into the session. Then:

$$\begin{aligned}
 1 - q_t &= (1 - q_0)e^{-\gamma t} \\
 w_t &= w_0e^{-\alpha t} \\
 b_t &= b_0e^{-\beta t},
 \end{aligned}
 \tag{2-3}$$

where  $\gamma$ ,  $\alpha$ , and  $\beta$ , are the rates of decay of  $(1 - q_0)$ ,  $w_0$ , and  $b_0$ , respectively. The probability of quitting a bout at time  $t$ ,  $q_t$ , is simply  $1 - (1 - q_t)$ . Note that the exponential function is used in Equation 2-3 to describe the decay of parameters as a function of time in extinction, and not to describe the probability distribution of IRTs (cf. Equations 2-1 and 2-2). For simplicity, we assume that if a rat responded at time  $t$  and the next response occurs at  $t + \delta$ , then the parameters  $q_t$ ,  $w_t$  and  $b_t$  are given by Equation 3 and they remain constant between  $t$  and  $t + \delta$ . Appendix D provides expressions for the probability that the animal does not emit a response between its last emitted response and the end of the session. Parameters were estimated for each animal in each experimental condition, based on the joint probability of all IRTs and the “no-response” periods.

Table 2-3.

*List of parameters for the static and dynamic models.*

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<i>Static models</i>	
$\delta$	Refractory period
$q$	Probability of quitting a bout
$w$	Within-bout response rate
$b$	Bout initiation rate
<hr/>	
<i>Dynamic models</i>	
$\delta$	Refractory period
$1-q_0$	Baseline probability of remaining in bout
$w_0$	Baseline within-bout response rate
$b_0$	Baseline bout initiation rate
$\gamma$	Rate of decay of $1-q_0$
$\alpha$	Rate of decay of $w_0$
$\beta$	Rate of decay of $b_0$

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Because parameters  $q$ ,  $w$ , and  $b$  change as a function of time in extinction, we call this model the *dynamic refractory bi-exponential model*, in contradistinction to the *static* model of Equation 2-2. Note that if all three decay-rate parameters ( $\gamma$ ,  $\alpha$ ,  $\beta$ ) are set to zero, the model reduces to Equation 2-2. Table 2-3 lists all the parameters of both static and dynamic refractory bi-exponential models with their meaning, for reference.

We had no *a priori* hypothesis as to which of the parameters,  $(1-q_0)$ ,  $w_0$ , or  $b_0$ , would decay during the extinction session. We therefore used maximum likelihood estimates and AIC to determine the most efficient model. The following models were compared using AIC: (a) single versus bi-exponential ( $q_0 = 0$  vs.  $q_0 \geq 0$ ); (b) non-refractory versus refractory ( $\delta = 0$  vs.  $\delta \geq 0$ ); and (c) all possible combinations of decay rate parameters ( $\gamma$ ,  $\alpha$ , and  $\beta$ ) fixed at zero vs. not fixed at zero. Models with parameters fixed at zero are more parsimonious and are analogous to the “null hypothesis” that those parameters are superfluous (Burnham & Anderson, 2002). The AIC scores for these “null” models would be lower, and hence these models would be favored, if alternative

models that allow these parameters to be free did not account for substantially more variance. There are a total of four single exponential candidate models: two models with  $\alpha$  either free or fixed at zero  $\times$  two models with  $\delta$  either free or fixed at zero. There are a total of 16 bi-exponential candidate models:  $2^3$  models with  $\gamma$ ,  $\alpha$ , and  $\beta$ , each either being free or fixed at zero, and for each bi-exponential model  $\delta$  can be free or fixed at zero, yielding  $2^3 \times 2 = 16$  candidate models. Animals were grouped according to which lever was presented during the extinction session (high vs. low workload); model selection and parameter estimation were conducted for each group separately. AIC analysis showed that the refractory bi-exponential model fit extinction data better than both single exponential models and the non-refractory bi-exponential model.

Table 2-4 shows the five best fitting models for extinction of high vs. low workload lever pressing, as well as the best fitting non-refractory bi-exponential model and the best fitting single exponential model. Model names indicate whether the model is refractory ( $\delta$  is free) and the decay rate parameters that are allowed to vary freely. Each model's  $\Delta$ AIC is shown in parenthesis. The best fitting refractory bi-exponential models were more than  $e^{700}$  times more likely than the best non-refractory bi-exponential model, which was in turn more than  $e^{3500}$  times more likely than the best fitting single exponential model. This provides strong evidence that bout-like responding occurs during extinction, justifying the present fine-grained analysis. The likelihood of each of the top four models for both groups (extinguished on low vs. high workload levers) is fairly similar to each other. In fact,  $\beta$  was the only decay rate parameter that the present data unequivocally suggested needed to be free: for both groups of animals, the best models with  $\beta$  set to zero (ranked fifth in Table 2-4) were more than  $e^{58}$  times less likely than a

similar models with  $\beta$  allowed to be free, providing strong evidence that bout initiation rate declined as extinction progressed. Table 2-4 also shows that models with  $\gamma$  or  $\alpha$  set to zero (ranked second) had low  $\Delta$ AICs. The present data therefore did not provide substantial evidence that the probability of remaining in a bout or the within-bout response rate declined during an extinction session (for model selection criteria, see Appendix A). The model ranked second, underlined in Table 2-4, was therefore selected as best balancing parsimony and goodness-of-fit.

Figure 2-6 shows how IRTs (pauses between responses) changed as a function of time in extinction. The x-coordinate of each point is the time  $t$  when a response was emitted; the y-coordinate shows how long the animal waited until emitting the next response. Note that the y-axis is plotted on a log scale. Also shown are the fitted mean IRTs drawn from the dynamic refractory exponential model selected in Table 4—solid lines represent within-bout IRTs ( $\delta + 1/w_t$ ) and broken lines represent between-bout IRTs ( $\delta + 1/b_t$ ). Note that although the selected dynamic model assumes that  $b_t$  remains constant (flat) between consecutive responses and only increases in discrete “jumps”, the mean IRTs in Figure 2-6 have been joined by a smooth straight line for illustrative purposes. Figure 2-6 clearly shows clusters of rapid within-bout responses with mean IRT of about 0.3 s, intermixed with much slower bout initiation responses with mean IRT of about 10 s at the beginning of the extinction session, and rising exponentially to about 100 s by the end of the session. Rat 519 ceased responding completely at about 1500 s into the session; all other rats showed a more gradual decline in bout initiation rate.

Table 2-4.  
*Best extinction models according to AIC.*

Model rank	Low workload ( $\Delta AIC$ )	High workload ( $\Delta AIC$ )
1	$\delta, \alpha, \beta$ (0)	$\delta, \alpha, \beta$ (0)
2	<u><math>\delta, \beta</math> (0)</u>	<u><math>\delta, \beta</math> (1)</u>
3	$\delta, \gamma, \beta$ (2)	$\delta, \gamma, \alpha, \beta$ (5)
4	$\delta, \gamma, \alpha, \beta$ (2)	$\delta, \gamma, \beta$ (5)
5	$\delta, \gamma$ (250)	$\delta$ (121)
Best non-refractory bi-exp	$\beta$ (2829)	$\beta$ (1483)
Best single exp	$\delta, \alpha$ (12771)	$\delta, \alpha$ (8736)

*Note.* Free parameters are listed for each model; 1-  $q_0$ ,  $w_0$ , and  $b_0$  were free to vary for all bi-exponential models (see Equation 1-3). The best non-refractory and single exponential models are listed for comparison. Selected models are underlined (see Appendix A explanation).

The group mean parameter estimates ( $\pm$ SEMs) of model 2 for each group are presented in Table 2-5. Due to the small group size ( $n = 3$ ), statistical analysis was not conducted on parameter estimates. Nonetheless, there are some noteworthy qualitative inconsistencies and regularities in parameter estimates. The difference in  $w_0$  across workloads was not in the same direction as observed during Phase 1. As the statistical analysis suggested in Phase 1, workload-induced changes in within-bout response rate do not appear reliable. The differences in  $b_0$  and  $\delta$  across workloads, nonetheless, are consistent with the differences observed during Phase 1, thus confirming that higher workload yields fewer bouts of prolonged responses. Absent reinforcement, bouts of more laborious responses do not appear to decline faster in frequency.

### **Discussion Phase 2: Extinction**

The present experiment complements a previous study by Shull et al. (2002). In their study, extinction sessions were separated into blocks of approximately 20 min, with the assumption that model parameters are constant within a block. Then, two separate



analyses were conducted to estimate model parameters for each block, and changes in parameters as a function of block (time in extinction) were visually compared. The first analysis used log-survival plots to fit parameters for each block. However, the authors noted that this method was problematic because the number of IRTs per block became increasingly small, which reduced the reliability of parameter estimates in the later blocks. The second technique imposed an arbitrary cutoff-IRT. All IRTs shorter than the cutoff were classified as within-bout, and all IRTs longer than the cutoff were classified as between-bout. Although Shull and colleagues used this method without any reported issues, the selection of the cutoff-IRT was arbitrary, and has the potential to misclassify pauses between bouts as within-bout IRTs, and vice versa. The present study circumvented these difficulties by generalizing the response-bout model so that any dynamic changes in steady-state parameters can be captured quantitatively. This generalization not only allows parameters to be estimated for individual subjects on a sound theoretical basis, it also has the potential to allow different hypotheses to be explicitly tested using AIC, such as which of the steady-state parameters ( $q$ ,  $w$ , or  $b$ ) change during extinction. The results from the present extinction experiment supported a relatively simple extension of the static refractory bi-exponential model: when reinforcement is discontinued, only the rate of bout initiation declines exponentially over time. Research elsewhere has shown similar effects of extinction on bout initiation, although small decrements in bout length were also reported (Shull et al., 2002; Podlesnik, Jimenez-Gomez, Ward, & Shahan, 2006).

Overall, these findings are consistent with reports of selective effects of rate of reinforcement on rate of bout initiation (J. E. Johnson et al., 2009; Shull et al., 2001). The

evidence supports the notion that reinforcement operates primarily on the initiation of response bouts (G. M. Heyman, 1988), although other studies have shown variations in bout length (Shull et al., 2004) and within-bout response rate (Conover et al., 2001) with rate of reinforcement. The constancy of within-bout “tempo”, for instance, is particularly salient in the flat solid lines of Figure 2-6. As discussed in Phase 1, however, bout initiation appears to be sensitive also to workload and schedule demands. It is yet unclear whether the workload manipulation implemented in this study influenced the rate at which bout initiation declines during extinction.

### **General Discussion**

Our results support the notion that free operant responding under VI schedules is organized in bouts separated by pauses. We effectively extended this notion to characterize extinction as an exponential lengthening of the pauses that separate bouts, which is consistent with prior findings (Podlesnik et al., 2006; Shull et al., 2002). Although we considered two models to account for maintenance and extinction performance (the static and dynamic models, respectively), both models may be special cases of a more comprehensive model. In this more general model, operant performance may be characterized as a propensity to initiate response bouts, which increases with reinforcement and declines with time. Alternatively, the decline in bout initiation may be driven by unreinforced responses, in line with Skinner’s (1938) notion of reflex reserve

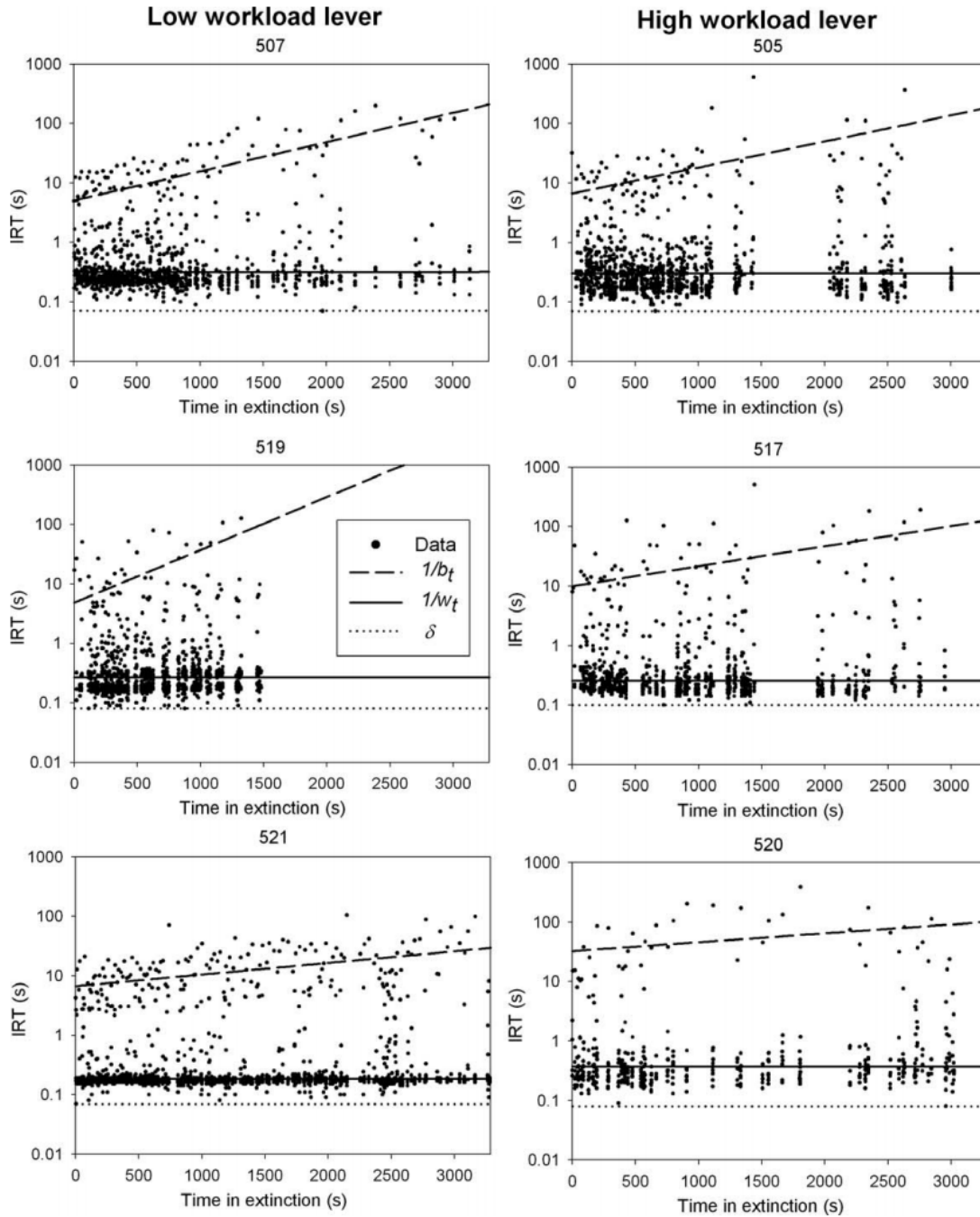


Figure 2-6. Inter-response times (IRTs) as a function of time  $t$  in extinction. The broken, solid, and dotted lines are, respectively, traces of bout initiation rate ( $b_t$ ), within bout rate ( $w_t$ ), and constant minimum IRT ( $\delta$ ), drawn from the dynamic refractory bi-exponential model (Equation 2-5) and fit using the maximum likelihood method. Traces of  $b_t$  have been joined by a smooth straight line for illustrative purposes (see main text).

(Catania, 2005). More precisely, the model of bout initiation decline considered in this study was a hybrid of the time-dependent and response-dependent decline models: we assumed that bout initiations decline as time without reinforcement progressed, but the hypothesized clock was only updated with each response. Further research may clarify how the initiation of bouts declines in the absence of reinforcement. We also extended the bi-exponential model to include a refractory period following each response, and demonstrated that it is an informative component of operant performance.

Although the refractory bi-exponential model was capable of describing food-reinforced behavior in rats, it may be somewhat limited in describing the behavior of other species. Pigeon key-pecking has been notoriously resistant to bout-and-pause analyses. Visual inspection of log-survival plots of key-pecking IRTs often fail to reveal a distinct inflection point (Bennett, Hughes, & Pitts, 2007; Bowers, Hill, & Palya, 2008;

Podlesnik, Jimenez-Gomez, Ward, & Shahan, 2006). This divergence in the performance of rats and pigeons suggests that a more flexible model, of which the refractory bi-exponential is a special case, may be necessary to characterize operant behavior across species.

### **Motoric Effects**

When rats were required to press a higher, heavier lever, bout initiation rate declined and the minimum time between consecutive responses (the refractory period  $\delta$  in Equation 1-2) increased. Bout initiation rate is also sensitive to deprivation level and rate of reinforcement (Shull, 2004; Shull et al., 2004), but both were kept constant across workload manipulations. Thus, it appears that workload manipulations had an effect

similar to that of altering deprivation and rate of reinforcement, aside from the more purely motoric effect of lengthening of the refractory period. This is consistent with Posadas-Sanchez's (2005) finding that a higher lever force requirement decreases indices of motivation while increasing indices of response duration. Skjoldager et al. (1993) reported that an increase in lever height and force requirement prolonged pre-ratio pauses and reduced run rates in a progressive ratio schedule. Alling and Poling (1995) replicated these effects in fixed ratio schedules. Pre-ratio pauses are akin to between-bout IRTs—they indicate periods of disengagement from the operandum, and are particularly attuned to motivational manipulations such as those of deprivation level (Malott, 1966). All this evidence converges on the notion that changes in response cost necessarily influence motivation. Therefore motoric effects, which are embedded within changes in run rates, cannot be empirically isolated; they can only be analytically isolated. That is, motoric effects may not be observed without motivational changes, but they may be estimated on the basis of changes in the shortest IRT. The refractory bi-exponential model provides a means for such estimation.

The hypothesis that motoric manipulations imply motivational effects may explain some weaknesses of extant methods of motor-motivational dissociation. One popular method, for instance, consists of estimating the parameters of Herrnstein's (1970) hyperbola from performance across various VI schedules (Bradshaw, Ruddle, & Szabadi, 1981; Glautier, Rigney, & Willner, 2001; Heyman, Kinzie, & Seiden, 1986). A common assumption, derived from early interpretations of the hyperbolic parameters (de Villiers & Herrnstein, 1976), is that the asymptotic response rate  $k$  attained with very high reinforcement rates should be sensitive only to motoric manipulations, whereas the rate

of reinforcement  $r_e$  that yields a response rate of  $k / 2$  should only be sensitive to motivational manipulations. A recent review (Dallery & Soto, 2004) suggests that  $k$  is sensitive to motoric manipulations, but not selectively: it also appears to be sensitive to changes in deprivation level and reinforcer magnitude. In turn,  $r_e$  seems to be sensitive to motoric manipulations under certain circumstances. Motivational effects inherent to motoric manipulations may explain why  $r_e$  is sensitive to motoric manipulations, but not why  $k$  is sensitive to motivational manipulations. A generalization of Herrnstein's hyperbola (McDowell, 2005), similar to that provided by Baum, (1974) for the matching law, appears to account for motivational effects otherwise absorbed by  $k$ . This may be a productive development toward a global account of performance in VI schedules. Local mechanisms similar to those suggested here, however, are not specified by the generalized hyperbola.

### **Schedule Effects**

Rats emitted fewer response bouts when a FR requirement was appended at the end of an interval schedule. These bouts, however, were longer and denser in responses (smaller  $q$ , higher  $w$ ), yielding higher overall response rates. If overall response rate was taken as an index of motivation, we would be deceived into believing that the imposition of a tandem FR schedule increased the motivation to engage the operandum. The reduction in bout initiation rate suggests the contrary: the tandem FR schedule reduced, not increased, motivation. Why would a tandem FR schedule reduce motivation? Longer bouts increase the number of intervening responses between bout-initiating lever presses and reinforcement, and may widen the interval between the two. It is widely acknowledged that delayed reinforcement is less effective in maintaining behavior (e.g.,

Dickinson, Watt, & Griffiths, 1992). More directly relevant to our results, pre-ratio pauses in FR schedules increase with reinforcement delay (Meunier, Starratt, & Sergio, 1979; Morgan, 1972). Although the ineffectiveness of delayed reinforcement has a credit-assignment component (Lieberman, McIntosh, & Thomas, 1979), it is likely to include also a motivational component: delayed incentives are less attractive than immediate ones (e.g., Mazur, 2010). Bout initiation rate may thus be reduced by tandem FR schedules because these schedules yield longer bouts that separate their initiation from reinforcement. This explanation has a significant implication: it suggests that, even though the computer recording the rat's activity may count a bout initiation lever press just as any other lever press, these lever presses are functionally distinct from within-bout lever presses. Despite their topographical similarity, bout-initiating responses and within-bout responses may constitute separate response classes (Schick, 1971). If such were the case, reinforcement of the latter would not completely generalize to the former, and vice versa (see Shull et al., 2004, pp. 76-78, for a related discussion on the bout as a behavioral unit).

Our explanation of reduced bout initiation rates in tandem FR schedules is based on longer bouts. Why, then, do tandem FR schedules yield longer bouts? Probably because fast response bursts are more likely to be reinforced under tandem VT FR than under VI schedules (Killeen, 1969); schedules with a terminal tandem FR requirement selectively reinforce longer bursts. Interestingly, such reinforcement did not appear to generalize to bout initiation lever presses in the present study, supporting the notion that bout initiation and within-bout lever presses are functionally distinct.

Like workload manipulations, schedule manipulations appear to have a motivational and a non-motivational component. The motivational component is related to the resulting delay between bout initiation and reinforcement. The non-motivational component is related to the proximity of within-bout responses to reinforcement. The refractory bi-exponential model identifies changes in the former component with changes in parameter  $b$  in Equation 1-2, and changes in the latter component with changes in  $q$  and  $w$ .

### **Motivational Effects**

Food deprivation selectively increased bout initiation rate (Phase 1), whereas the elimination of reinforcement selectively reduced bout initiation rate (Phase 2). Similarly, Podlesnik et al. (2006) found that prefeeding and extinction reduced bout initiation rate. The results reported here complement the evidence that bout initiation rate selectively covaries with rate of reinforcement (Shull et al., 2001). They suggest that the rat's willingness to engage the operandum, which is driven by hunger, reinforcer availability, and low "price", is expressed in the rate of bout initiation (parameter  $b$  in Equation 1-2). Such general willingness may be described as *operant* motivation, to distinguish it from the more specific notion of *incentive* motivation (Bindra, 1978).

Incentive motivation refers to the approach or seeking behavior elicited by appetitive or conditional stimuli. Incentive motivation is mostly dependent on the properties of the stimulus and on the state of the animal with respect to the stimulus, and is independent of response cost and the interval between response and reinforcer. Operant motivation, instead, is a function of both incentive and response. Response cost may influence operant motivation, as shown by the effects of motoric manipulations, and



longer response-reinforcer intervals are likely to reduce operant motivation, as inferred from the effects of schedule manipulation and rate of reinforcement. Incentive motivation for food, for instance, may be raised by depriving an animal of food or by presenting food (or associated stimuli) to the animal; operant motivation for engaging in food-producing activities may be raised by increasing incentive motivation for food, by reducing the energetic cost of the activities that yield food, or by reducing the time between activities and food. Because incentive motivation is subsumed within operant motivation, changes in incentive motivation may be inferred from concomitant changes in bout initiation rate, but only when response-reinforcement contingencies are kept constant.

Researchers are often interested in drawing inferences about changes in incentive motivation from operant performance. We may want to demonstrate, for instance, that a particular treatment reduces the incentive motivation for cocaine. One way to perform this demonstration is to compare operant performance for cocaine (under maintenance or extinction schedules) with and without the treatment. Based on the results reported here, one would be advised not to compare overall response rates, but to compare estimates of the rate at which response bouts are initiated. Even then, because bout initiation is an indication of operant, not incentive motivation, one would have to rule out motoric and schedule effects that would indirectly affect operant motivation. That is, if the test indicates that only bout initiation rates were affected by treatment, it would constitute positive evidence that the treatment reduced the incentive motivation for cocaine, however if it also affected the within-bout response rate or the minimum IRT, reliable inferences on incentive motivation may not be drawn.

The previous example assumes that the inferences we have drawn from food-seeking behavior may be generalized to cocaine self-administration. Whether such generalization is justified or not will require further research with a wider range of reinforcers (e.g., drugs, access to mates, defense against aversive stimuli) and a variety of operants. The present study has laid out the empirical and analytical methods to assess changes in the components of operant performance, even when the reinforcer is absent. We believe these methods are critical to advancing our understanding of motivated behavior.

## CHAPTER 3

### A BOUT ANALYSES OF OPERANT RESPONSE DISRUPTION

#### **Abstract**

This study investigated how three different forms of operant response disruption - extinction (EXT), non-contingent reinforcement (NCR), and prefeeding (PRE) - disrupt response bouts. In Experiment 1, Wistar Kyoto rats (WKY) were trained on a tandem variable-time (VT) 120 s fixed-ratio (FR) 5 schedule of reinforcement; after stability was established their responding was disrupted for three sessions with one of the three disruptors (EXT, NCR, or PRE). In Experiment 2, Long Evans (LE) rats were trained on a tandem VT 240 s FR 5 to stability, and their responding disrupted with EXT or NCR. In EXT and NCR, response rates declined significantly over the course of the session, primarily due to a declining bout initiation rate in EXT, and to shrinking bouts in NCR. In contrast, a session-wide drop in response rate was observed in PRE, primarily due to a reduction in bout initiation rate at the start of the session. These findings suggest that different forms of disruption impact dissociable aspects of behavior. Theories of behavioral persistence should account for these functional differences, which appear to be obscured in response rate measures.

## Introduction

Operant responding can be disrupted in many ways. A rat's lever pressing for food may be decreased by satiating the animal prior to the experimental session. Alternatively, the response-reinforcer contingency can be broken by withholding the food reinforcer (extinction) or by providing the food independent of the operant (non-contingent reinforcement). Each of these methods decrease response rate, but presumably in ways that are functionally distinct (Bindra, 1978; Bouton, 2004; Lachter, Cole, & Schoenfeld, 1971; Skinner, 1948). This study asks whether the distinct ways in which each of these response disruptors, extinction (EXT), non-contingent reinforcement (NCR), and prefeeding (PRE), change operant responding are revealed by the change in the organization of responses in bouts.

Response bouts are clusters of responses separated by short inter-response times (IRTs), punctuated by longer IRTs (Brackney, Cheung, Herbst, Hill, & Sanabria, 2012; Brackney, Cheung, Neisewander, & Sanabria, 2011; Hill, Herbst, & Sanabria, 2012; J. E. Johnson et al., 2009; Shull et al., 2001, 2002; Shull, 2004, 2011; T. T. Smith, McLean, Shull, Hughes, & Pitts, 2014; Tolkamp et al., 2000). There are three primary characteristics of the response bout: (a) the *mean bout length*, or how many responses the animal makes while in a bout; (b) the *within-bout response rate*, or how fast the animal responds while in a bout; and (c) the *bout initiation rate*, or how frequently the animal begins a new bout.

Brackney and colleagues (2011) used the bi-exponential refractory model (BERM) to estimate bout-organization parameters, showing that those estimates change systematically in response to different reinforcement contingencies and other

experimental manipulations. For example, Brackney et al. (2011) found that depriving a rat of food decreases the overall bout initiation rate, whereas extinction decreases the bout initiation rate gradually over the course of the session, while neither manipulation had an appreciable effect on other parameters. In contrast, increasing the number of responses required to collect a reinforcer increased both the within-bout response rate and the mean bout length.

This study is a partial replication and extension of Brackney et al. (2011). There are several critical differences between Brackney et al. (2011) and the current study. First, in Brackney et al. (2011), the effect of acute food deprivation on normally free-fed rats was examined during variable-interval training (VI), whereas this study examines the effect of acute prefeeding on rats that are normally food-deprived. Second, the current study adds an additional comparison condition, NCR. Third, whereas conditions in Brackney et al. (2011) were confounded by training order, exposure to each disruption condition in the current study was counterbalanced across rats. Fourth and finally, the current study examines response bouts in two strains of rats, Wistar Kyoto (WKY; Experiment 1) and Long Evans (LE, Experiment 2), whereas Brackney et al. (2011) examined the performance of Sprague Dawley rats. WKYs are an inbred strain commonly used as a control strain for the spontaneously hypertensive rat (SHR), an animal model of both hypertension and attention deficit hyperactivity disorder (Sagvolden et al., 2009). WKYs generally display low rates of operant responding, and are sometimes used as an animal model of depression and anxiety (Will, Aird, & Redei, 2003). LE rats are a commonly used outbred strain that originally resulted from a cross between Wistar and wild gray rats (Oiso, Riddle, Serikawa, Kuramoto, & Spritz, 2004).

The primary goal of this study was to assess the relative contributions of each response bout parameter to the decline in responding observed in each response-disruption condition. To achieve this goal, a response-bout model, the dynamic bi-exponential refractory model (DBERM; Brackney et al., 2011; Cheung, Neisewander, & Sanabria, 2012) was fit to responding during maintenance training and to responding during the first disruption session of each condition. Differences between estimates of DBERM parameters during maintenance and disruption were then assessed.

## **Method**

### **Subjects**

#### **Experiment 1**

Twelve experimentally experienced, pair-housed Wistar Kyoto rats (WKY/NHsd, Harlan Laboratories, US) served as subjects. They were approximately one year old [post-natal day, (PND) 336] at the start of the study. The rats were food restricted: 30 min after each experimental session, free access to homecage chow (Harlan 2920X rodent diet) was allowed for 1 h. This feeding regimen remained in effect unless noted otherwise. It maintained subjects at approximately 85% of their *ad libitum* weight based on a logistic function fitted to growth curves provided by breeder.

All twelve subjects participated in several previous experiments and were well trained in lever pressing for sucrose pellets at the start of the experiment. Their experimental histories included training on simple variable interval (VI) schedules, extinction following VI training, latent inhibition, and fixed minimum interval training (Hill, Covarrubias, Terry, & Sanabria, 2011; Mechner & Guevrekian, 1962).

## **Experiment 2**

Ten experimentally naïve Long Evans (LE; Charles River Laboratory, US) rats served as subjects. The experiment started on PND 60. All other details were identical to Experiment 1 unless otherwise stated.

## **Apparatus**

Experimental sessions were conducted in six identical Med Associates® chambers, 305 mm long, 241 mm wide, and 210 mm high. The chambers were housed in sound and light attenuating cabinets, in which a ventilation fan provided white noise at approximately 60 dB. The chambers were arranged according to the standard dual lever configuration – two retractable levers 21 mm above the floor flanked a food receptacle aperture in (51 mm sides, 15 mm from the chamber floor). The walls orthogonal to levers and food receptacle aperture were made of transparent Plexiglas, whereas the remaining two walls were made of aluminum. A houselight mounted outside the experimental chamber provided dim illumination inside the chamber when on. Forty-five mg sucrose pellets (TestDiet™ 5TUT) served as the experimental reinforcers and were delivered into the food receptacle aperture via a pellet dispenser mounted outside the chamber. The experimental equipment was identical in Experiments 1 and 2.

## **Procedure**

### **Experiment 1**

Each daily session began with a 300-s acclimation period, during which no experimental events occurred. Following acclimation, the left lever (farthest from the door) was extended. All sessions were conducted with the houselight off except when noted otherwise. Sessions were 60-min long and were conducted 7 days per week. Due to the

rats' considerable experimental history, pretraining such as autoshaping or chamber habituation was judged unnecessary.

Table 3-1.  
*Experiment 1 phase order by subject.*

Subject	Phase							
3-1	M1	RemT	M2	NCR	M3	PRE	M4	EXT
3-2	M1	EXT	M2	NCR	M3	PRE	M4	NCR
3-3	M1	PRE	M2	PRE	M3	NCR	M4	EXT
3-4	M1	PRE	M2	PRE	M3	NCR	M4	EXT
3-5	M1	NCR	M2	EXT	M3	EXT	M4	PRE
3-6	M1	NCR	M2	EXT	M3	EXT	M4	PRE
4-1	M1	RemT	M2	PRE	M3	EXT	M4	NCR
4-2	M1	NCR	M2	PRE	M3	EXT	M4	NCR
4-3	M1	EXT	M2	NCR	M3	PRE	M4	NCR
4-4	M1	RemT	M2	NCR	M3	PRE	M4	EXT
4-5	M1	PRE	M2	EXT	M3	NCR	M4	EXT
4-6	M1	PRE	M2	EXT	M3	NCR	M4	EXT
Sessions in Phase	13	3	16	3	14	3	13	3

*Note.* The order in which rats experienced each phase progresses from left to right. The number of sessions in each phase is listed in the bottom row. If a subject experienced a disruption condition twice, only the first disruption condition was analyzed. M = maintenance, EXT = extinction, NCR = non-contingent reinforcement, PRE = prefeeding, RemT = remedial VI training.

The experiment consisted of alternating phases of maintenance training (MAINT) and response disruption (Table 3-1). During MAINT, lever presses were reinforced according to a tandem variable-time (VT) 120 s fixed ratio (FR) 5 schedule of reinforcement. Reinforcement was contingent upon the occurrence of 5 lever presses after the elapse of an unsignaled interval that was randomly sampled without replacement from a 12-item list drawn from a Flesher-Hoffman distribution (Fleshler & Hoffman, 1962) with a mean of 120 s. Reinforcement consisted of the delivery of a sucrose pellet and was signaled by a noticeable but brief (0.1 s) flash of the house light.



All subjects began the experiment in MAINT. After each MAINT session, the stability of the response bouts was assessed over a 5-session window. Once stability was detected (see the Appendix E for detection protocols), all rats were switched to a response disruption phase for the following three sessions.

During a response disruption phase, each subject was exposed to a response disrupter for 3 consecutive sessions. There were 3 types of response disrupters:

1. *Extinction (EXT)*. The experimental contingencies were identical to MAINT, except that lever pressing never resulted in a houselight flash or sucrose pellet delivery. Lever presses were recorded but had no programmed consequences.

2. *Non-contingent reinforcement (NCR)*. Pellets were delivered according to a VT 120 s schedule. The experimental contingencies in NCR were similar to MAINT, except that the houselight flash and sucrose pellet delivery occurred at the end of the programmed interval independent of lever pressing. Lever presses were recorded but had no programmed consequences.

3. *Prefeeding (PRE)*. Rats were provided ad-libitum access to their homecage chow for one hour immediately prior to the experimental session. The experimental contingencies were identical to those in MAINT.

During all 3 sessions of a response disruption condition, each rat was exposed to only one response disrupter. The order in which rats were exposed to the response disrupters was counterbalanced (Table 3-1). MAINT resumed on the session immediately following the end of each disruption condition and continued until response-rate stability was reestablished.

The majority of subjects began responding at high rates within the first 7 sessions. However, 3 rats (3-1, 4-1, and 4-3) exhibited low response rates, fewer than 12 responses/min, during the first MAINT phase, in comparison to the other 9 rats that were responding at more than 20 responses/min. In order to establish higher levels of responding, rats responding at low rates were excluded from stability analyses for the first MAINT phases, and introduced to three sessions of remedial training (RemT) instead of the first response disruption phase (Table 3-1). During RemT, subjects were exposed to an ascending schedule sequence of VI 24 s, VI 46 s, and VI 96 s, with a new schedule each day. On the fourth day, RemT was deemed effective in raising response rate, and rats were returned to MAINT.

Due to experimenter error, subjects 3-3 and 3-4 were exposed to PRE twice, and subjects 3-5 and 3-6 were exposed to EXT twice. A fourth treatment phase was added to the end of the experiment to expose all subjects to all treatment conditions. Where subjects experienced a disruptor condition twice, only the first exposure was analyzed.

## **Experiment 2**

In Experiment 2, LE rats were trained on a tandem VT FR, as in MAINT in Experiment 1, and were exposed to two disruptor conditions, EXT and NCR. Because the LE rats were experimentally naïve, they were first exposed to pretraining, which involved chamber habituation (day 1), magazine training (day 2), autoshaping (days 3 and 4), and the gradual decrease in reinforcement rate (days 5-10) until the target tandem VT 120 s FR 5 schedule was reached. During chamber habituation, each subject was placed in its chamber for 1 h; no experimental events occurred, except for the delivery of 5 sucrose pellets at the start of the session. Magazine training consisted of 45 individual sucrose

pellet deliveries on a VT schedule ranging from 45 to 90 s. Autoshaping consisted of 45 daily trials in which the left lever was presented for 8 s followed by a single sucrose pellet delivery; a lever press ended the trial and immediately delivered a sucrose pellet. The inter-trial interval during autoshaping was variable and ranged from 45 to 90 s.

Days 5 to 13 consisted of one day each of the following schedules in consecutive order: continuous reinforcement, FR 5, tandem VT 3-s FR 5, tandem VT 6-s FR 5, tandem VT 12-s FR 5, tandem VT 24 s FR 5, tandem VT 49-s FR 5, and tandem VT 98-s FR 5. On day 14, rats began training on a tandem VT 120-s FR 5, where contingencies of reinforcement were identical to those in Experiment 1.

After 23 days of training on the VT 120 s FR 5 schedule, bout-like responding was not apparent. The mean of the median daily response rate for sessions 13-23 was 51.4 responses/min, with the mean of the daily standard deviation at 28.4 responses/min. In comparison, the overall mean response rate for the WKY during the last 5 sessions of MAINT in Experiment 1 was 28.3 responses/min with a standard deviation of 15.3 responses/min. Examination of log-survivor plots of the IRTs (not shown) suggested that rats were responding at a nearly constant rate without noticeable bouts, as evidenced by no acute deflections in the traces. To allow for detectable bouts, the reinforcement rate was halved, changing the schedule to a tandem VT 240-s FR 5. This produced more appreciable response bouts.

Rats then proceeded to train on the tandem VT 240-s FR 5 for both maintenance components (MAINT1 and MAINT2). Similar to Experiment 1, rats were first trained on the VT 240-s FR 5 (MAINT1) to stability before being exposed to 3 sessions of a

disruption condition (either EXT or NCR; NCR was a VT 240 s instead of VT 120 s). Rats were then retrained on the tandem VT 240-s FR 5 (MAINT2) to stability before being exposed to 3 sessions of the alternate disruption condition. Table 3-2 describes the order and duration of each condition for each rat.

Table 3-2.  
*Experiment 2 phase order by subject.*

Subject	Phase Order			
5-1	M1	EXT	M2	NCR
5-2	M1	NCR	M2	EXT
5-3	M1	EXT	M2	NCR
5-4	M1	NCR	M2	EXT
5-5	M1	EXT	M2	NCR
5-6	M1	NCR	M2	EXT
5-7	M1	EXT	M2	NCR
5-8	M1	NCR	M2	EXT
5-9	M1	EXT	M2	NCR
5-10	M1	NCR	M2	EXT
Session in Phase	24	3	19	3

*Note.* The order in which subjects experienced each phase progresses from left to right. The number of sessions in each phase is listed in the bottom row. Refer to Table 3-1 for abbreviations.

### **Data Analysis**

Response rates generally declined across consecutive disruption sessions within a phase, which indicated that (a) there were fewer responses to model in the first disruption session relative to the second and third, and (b) it would be inappropriate to pool the responses across all three sessions, as their estimated parameters would almost certainly be different. Only performance in the first disruption session of each condition was analyzed because it had the greatest number of IRTs, and the certainty of estimated model parameters is dependent on the number of observations.

## DBERM Parameter Estimation

DBERM assumes that IRTs are generated by a mixture of two independent Poisson processes, which underlie the within-bout response rate ( $w_t$ ) and the bout initiation rate ( $b_t$ ). The mixture weighting parameter,  $p_t$ , is the probability of remaining in a bout after each response, and  $\delta$  is minimum IRT, or response refractory period.

$$\Pr(IRT_t = \tau | \tau < \delta) = 0$$

$$\Pr(IRT_t = \tau | \tau \geq \delta) = p_t w_t e^{-w_t(\tau-\delta)} + (1 - p_t) b_t e^{-b_t(\tau-\delta)}.$$

$$\min(\text{IRT}) \geq \delta > 0; w_t \geq b_t > 0; 1 \geq p_t \geq 0 \quad (3-1)$$

The parameter  $p_t$  is a function of the mean bout length (excluding the bout initiating response),  $L_t$ ,

$$p_t = \frac{L_t}{1 + L_t} \quad (3-2)$$

$L_t$ ,  $w_t$ , and  $b_t$ , at the start of the session (when  $t = 0$ ), are referred to as  $L_0$ ,  $w_0$ , and  $b_0$ , which together constitute the *baseline parameters*. Over the course of the session,  $L_t$ ,  $w_t$ , and  $b_t$ , are assumed to decay exponentially from their starting values at rates  $\alpha$ ,  $\beta$ , and  $\gamma$ , such that

$$L_t = L_0 e^{-\gamma t}$$

$$w_t = w_0 e^{-\alpha t}$$

$$b_t = b_0 e^{-\beta t}.$$

$$L_0, w_0, b_0, \gamma \geq 0; \beta \geq \alpha \geq 0 \quad (3-3)$$

To ease interpretation, the decay parameters are reported as half-lives (e.g.,  $HL_L = \ln(2) / \gamma$ ), the time taken for the parameter to reach half of its baseline value ( $L_0$ ,  $w_0$ , or  $b_0$ ).

To assess how response bouts changed during each disruption condition (NCR, EXT, and PRE) the dynamic bi-exponential model of response bouts (DBERM; Brackney et al., 2011; Cheung, Neisewander, & Sanabria, 2012) was fit to each rat's IRTs using the method of maximum likelihood (Myung, 2003) using custom-written software in Matlab® (MATLAB and Statistics Toolbox Release 2013a, Mathworks, Inc; Natick, MA). For each MAINT condition, DBERM was fit to the aggregate IRTs of the last 5 days of MAINT (i.e., one set of parameters were estimated for the entire 5 days, per subject, per MAINT condition). For each disruption condition, DBERM was fit to the first disruption session individually (i.e., parameters estimates were allowed to vary freely for each subject). When a rat was exposed to the same disruption condition twice (see Table 3-1), the second exposure to that disruption condition (all 3 sessions) and the MAINT condition prior to it were excluded from analysis for that rat.

### **Response Rate Recovery by Simulation**

Monte Carlo simulations were conducted to ensure that the underlying DBERM parameter estimates accurately reflected the observed response rates. The simulation was conducted as follows: for each rat and phase a series of a Bernoulli trials were conducted with a probability according to  $p_t$  (Equation 3-1). A success sampled an IRT from an exponential distribution with a mean of  $1/w_t$ , whereas a failure sampled an IRT from an exponential distribution with a mean of  $1/b_t$ . The sampled IRT then advanced the simulation clock by its respective value, and another trial began. The simulation ended when the session clock exceeded 55 minutes, and the final IRT was removed from the list of simulated IRTs. Each simulation also included enforced pauses that corresponded to post-reinforcement pauses observed for each subject. During those times, the simulation

clock still advanced, but no responses could be produced. One hundred simulations were run for each rat and phase, and then averaged to produce mean predicted response rates.

### **Null Hypothesis Significance Tests (NHST)**

NHST on response rates were conducted in IBM SPSS v22 (Armonk, NY: IBM Corp). To assess whether response rate changed significantly during the first session of disruption in each condition relative to MAINT, responding in each session was partitioned into eight equal-length bins of 6.9 min. The 5 sessions of MAINT per animal prior to the disruption session was collapsed into a single measure per bin by taking the median response rate in each bin. A phase  $\times$  bin (2: phase  $\times$  8: bin) repeated measures ANOVA was then conducted on log-transformed response rates. As the goal of these tests was simply to verify that response rate was generally less in disruption relative to MAINT, post-hoc pair-wise tests using Fisher's LSD were conducted when a significant interaction was observed. Bins between phases were first compared, and if the source of the interaction was not revealed, bins within phases were also compared. Pair-wise test outcomes were only reported for  $p < 0.05$ .

To test whether there was a significant change in DBERM parameters between MAINT and each disruption condition, log-transformed parameters estimated in disruption and in the preceding MAINT were examined with paired t-tests in Matlab® 2013a (Mathworks, Inc; Natick, MA). Because there are seven free parameters in DBERM, a Dunn-Šidák correction for seven comparisons was applied using an expected Type I error rate of 5%. As a result of this correction, p-values less than 0.0073 were reported as significant effects. Due to the stringency of this correction, trends toward significance were reported for  $0.0073 \leq p < 0.05$ .

## Results

### Response Rates

Figure 3-1 displays the response rates for each experiment during MAINT and the first disruption session of each condition.

#### Experiment 1

For EXT, there was a significant phase  $\times$  bin interaction effect on response rate [ $F(7,77) = 2.230, p = 0.041$ ]. Follow-up tests revealed that each bin in EXT was significantly slower than in MAINT. The source of the interaction was then revealed by an examination of each bin in MAINT relative to a central bin (bin 5), and the same analysis in EXT. In MAINT, response rates in bin 5 were only significantly lower than bin 1 and 3, and only significantly higher than bin 8, whereas in EXT, response rates in bin 5 were significantly lower than in bins 1, 2, and 3, and significantly higher than in bins 7 and 8. Combined, these tests indicated that response rate declined more rapidly in EXT than MAINT.

For NCR, there was a significant session by bin interaction [ $F(7,77) = 2.448, p = 0.025$ ]. Follow up tests indicated that response rate was significantly lower in NCR relative to MAINT in all bins but 1 and 7 during NCR relative to MAINT, indicating that response rate was the same at the beginning of the session, but quickly dropped in NCR.

In Experiment 1, PRE, there was a significant effect of phase [ $F(1,11) = 30.927, p < 0.001$ ] and bin [ $F(7,77) = 5.078, p < 0.001$ ]. These results indicated that response rate was lower in PRE than MAINT, but both decreased at approximately the same rate.



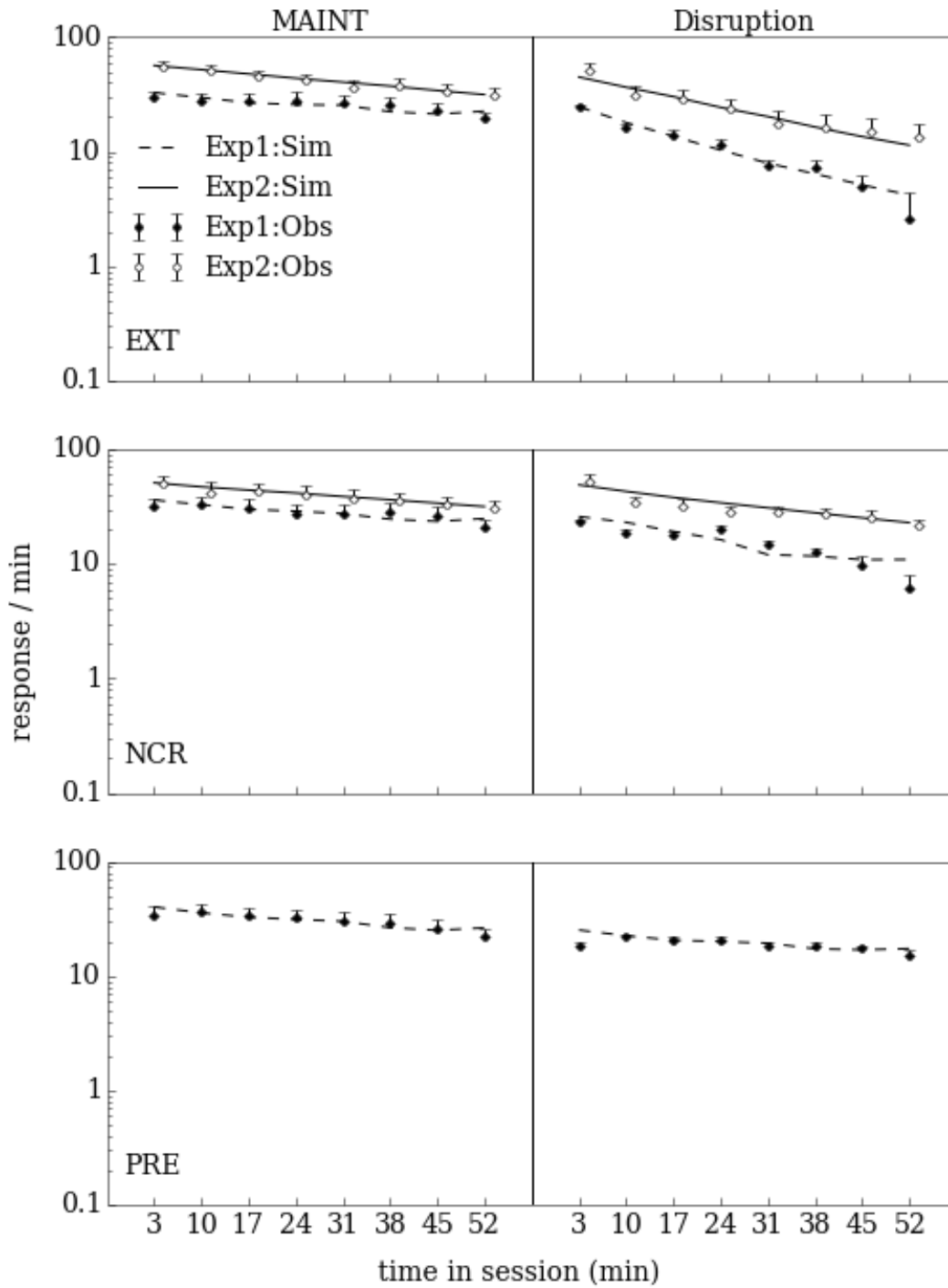


Figure 3-1. Binned response rates during MAINT and response disruption. The markers (filled and open) are the observed response rates for Experiments 1 and 2. The lines (dashed and solid) are the predicted response rates according to the DBERM simulation for Experiments 1 and 2.

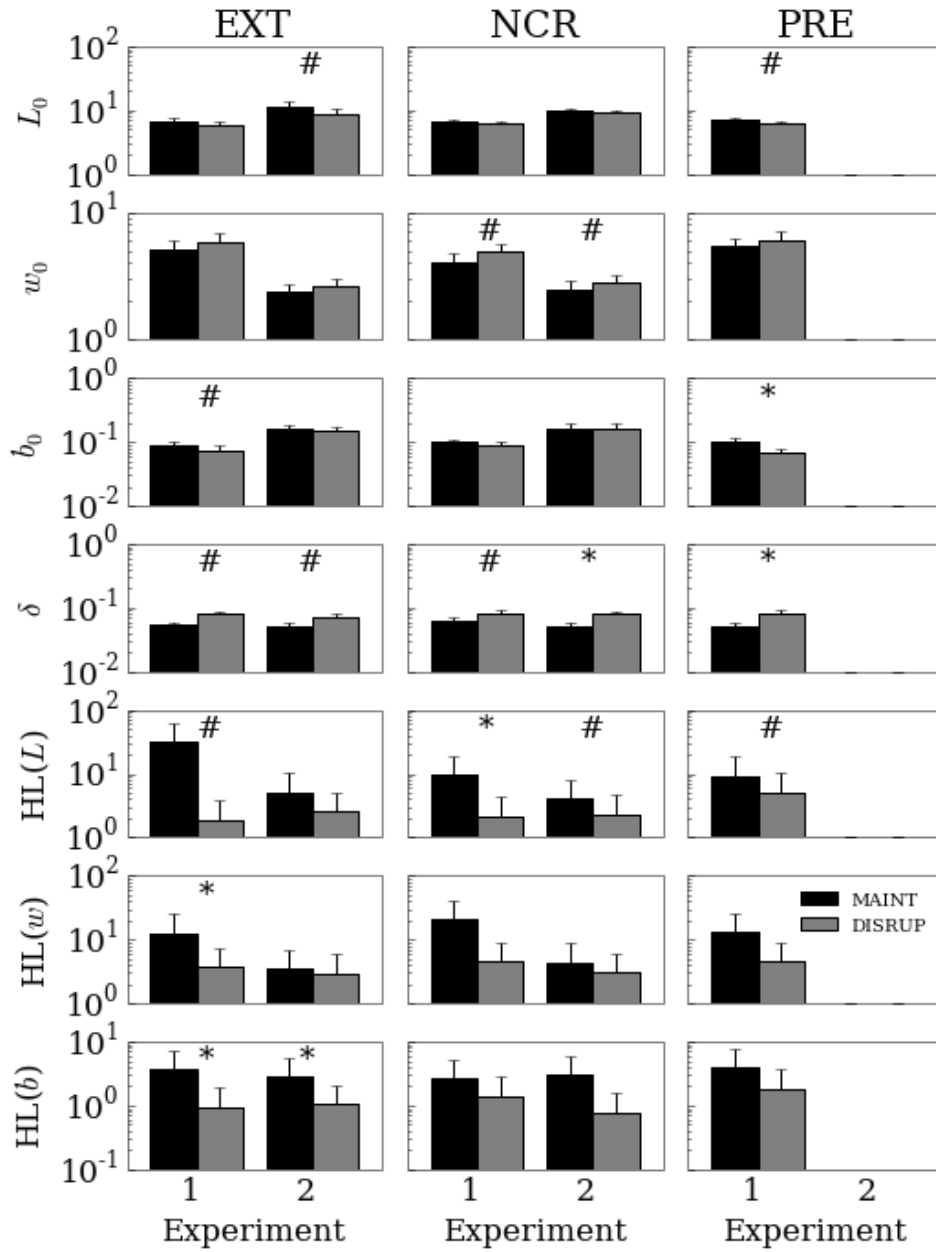


Figure 3-2. Mean DBERM parameter estimates for Experiments 1 and 2. The grey bars are for the disruption condition (EXT, NCR and PRE), and the black bars are the preceding phase of MAINT. Error bars represent the standard error of the mean. The “\*” represents a significant effect of  $p < 0.0073$ , the “#” represents a non-significant trend of  $p < 0.05$ . Units for each parameter are:  $L_0$  = responses;  $w_0$  = responses / s;  $b_0$  = response / s;  $\delta$  = s;  $HL(L)$  = min;  $HL(w)$  = min;  $HL(b)$  = min. There was no PRE for Experiment 2.

## Experiment 2

For EXT, there was a session by bin interaction [ $F(7,63) = 17.523, p < 0.001$ ]. Follow up tests indicated that response rate was significantly lower in EXT than MAINT for all bins except the first. Combined, these results indicate that response rate at the start of EXT was little different from MAINT, but rapidly declined.

In NCR, there was a significant session by bin interaction [ $F(7,63) = 2.64, p = 0.019$ ]. Follow up tests indicated that response rate was significantly lower in NCR than MAINT for bins 2, 4, 5, and 6. Combined, these results indicate that response rate at the start of NCR was little different from MAINT, but rapidly declined during the middle of the session.

## DBERM Parameters

Figure 3-2 displays the mean DBERM parameter estimates for each disruption condition and the preceding phase of MAINT for both experiments.

## Experiment 1

EXT significantly decreased  $HL(\underline{b})$  [ $t(11) = 3.33, p = 0.003$ ], and  $HL(w)$  [ $t(11) = 3.78, p = 0.0066$ ], indicating that the within-bout response rate and bout initiation rates decreased more rapidly in EXT, compared to MAINT. Trends toward significance were also observed for a decrease in  $b_0$  [ $t(11) = 1.926, p = 0.080$ ], an increase in  $\delta$  [ $t(11) = 3.254, p = 0.008$ ], and a decrease in  $HL(L)$  [ $t(11) = 3.033, p = 0.011$ ] in EXT.

NCR only decreased  $HL(L)$  [ $t(11) = 3.28, p = 0.0072$ ], indicating that bout-lengths decreased more rapidly in NCR than MAINT. Trends toward significance were

also observed for an increase  $w_0$  [ $t(11) = 3.144$ ,  $p = 0.009$ ] and an increase  $\delta$  [ $t(11) = 3.179$ ,  $p = 0.009$ ] in NCR.

PRE decreased  $b_0$  [ $t(11) = 6.24$ ,  $p < 0.0001$ ] and increased  $\delta$  [ $t(11) = 5.52$ ,  $p = 0.0002$ ], indicating that initial bout initiation rates were slower and refractory periods were longer in PRE compared to MAINT. Trends toward significance were also observed for a decreased  $L_0$  [ $t(11) = 2.644$ ,  $p = 0.023$ ], and a decreased  $HL(L)$  [ $t(11) = 2.261$ ,  $p = 0.045$ ] in PRE.

## **Experiment 2**

As in Experiment 1, EXT in Experiment 2 decreased  $HL(b)$  ( $t(9) = 7.22$ ,  $p < 0.0001$ ) relative to MAINT. Trends toward significance were also observed for a decreased  $L_0$  [ $t(9) = 3.402$ ,  $p = 0.008$ ] and an increased  $\delta$  [ $t(9) = 2.997$ ,  $p = 0.015$ ].

In contrast to Experiment 1, NCR in Experiment 2 only increased  $\delta$  [ $t(9) = 7.22$ ,  $p = 0.0047$ ] relative to MAINT, indicating that the refractory period was significantly longer. However, trends toward significance were also observed for an increased  $w_0$  [ $t(9) = 2.387$ ,  $p = 0.041$ ] and a decreased  $HL(L)$  [ $t(9) = 2.400$ ,  $p = 0.040$ ] in NCR.

There was no PRE in Experiment 2.

## **Discussion**

It is important to acknowledge first that, when compared to MAINT, at least an increasing trend was observed in the refractory period ( $\delta$ ) in all disrupters and experiments. This is likely an artifact of the lower number of responses observed in disruption compared to MAINT. The estimation of  $\delta$  as the shortest IRT observed is biased upwards, because as the number of IRTs sampled declines, the shortest IRT is

likely to be longer (see footnote 4 in Chapter 2). Therefore, disruption effects on  $\delta$  will not be further discussed.

Bout initiation rate appears to decline faster during EXT than during MAINT for WKY (Experiment 1) and LE (Experiment 2) rats. This effect was previously observed in Sprague Dawley rats (Brackney et al., 2011). In addition, within-bout response rates appear to decline faster during EXT than during MAINT in WKY rats. Although, this effect had not been observed before, Brackney et al. (2012) reported an unusual pattern of EXT performance in WKY rats: EXT appears to induce a remarkably fast decline in bout length in this strain (a trend of which was observed also in Experiment 1). It is thus likely that inbred strains of rat such as WKY may display EXT-induced changes in aspects of behavior that are robust to EXT in outbred strains such as LE and Sprague Dawley.

Unlike EXT, NCR did not induce a significant decline in bout initiation rate in either experiment. Instead, NCR appears to induce a faster decline in bout-length (a significant effect in WKY, a trend in LE), and possibly a lower baseline within-bout response rates (a trend in both strains). NCR-induced bout-length effects may be partially explained by adventitious reinforcement of alternative behaviors that compete with the operant (Skinner, 1948). In such case, however, a decline in bout initiation rate would also be expected (T. T. Smith et al., 2014). Alternatively, when reinforcement occurs while a rat is responding within a bout, the sudden reinforcer delivery may interrupt the bout and thus reinforce shorter bouts, with repeated interruptions gradually reducing the average bout length over time. Future research might explicitly examine whether interrupting bouts at different points in their occurrence (e.g., at the initiation versus several responses into the bout) have a differential effect on response disruption.

Whereas estimates of the speed of bout-length decline in NCR, they appear to be robust to PRE. Like EXT, bout initiation rate appears to be sensitive to PRE, but in a very different way. Whereas EXT induced a faster decline in bout initiation rate than MAINT, PRE induced a lower baseline bout initiation rate, but did not decline in an appreciably different way from MAINT. This finding replicates observations by Podlesnik et al. (2006) that prefeeding reduces bout initiation rates, and Brackney et al. (2011) that food deprivation increases bout initiation rates. Combined, these studies suggest that changes in bout initiation rate may serve as an index of changes in operant motivation.

Although all response disrupters decreased response rate, the sources of those differences appear to vary across disrupters, as evidenced by selective changes in response bout parameters. Theories of behavioral persistence, such as behavioral momentum theory (Nevin & Grace, 2000) generally treat these disrupters as functionally interchangeable, assuming response rate as the critical dependent measure to be explained. The present study suggests that focusing instead on the parameters of the organization of behavior may reveal distinct behavioral effects associated with each disrupter.

## CHAPTER 4

### LONGER OPERANT LEVER-PRESS DURATION REQUIREMENTS INDUCE FEWER BUT LONGER RESPONSE BOUTS IN RATS

#### **Abstract**

Operant responding reinforced under variable-interval schedules is organized in bouts. Previous research showed that increasing the work required to produce a response decreases the rate at which bouts are emitted, and increases the minimum inter-response time (IRT). In the current study, the minimum effective IRT was directly manipulated by changing the minimum duration of effective lever presses. Contrary to assumptions of previous models, response durations were consistently variable. Response durations were typically 0.5 s greater than the minimum duration threshold; durations that exceeded this threshold were approximately log-normally distributed. As the required duration threshold increased, rats emitted fewer but longer bouts. This effect may reflect a duration-induced facilitation of a response-outcome association.

## Introduction

Operant behavior appears to be organized in response bouts (Barabási, 2005; Brackney, Cheung, Neisewander, & Sanabria, 2011; Cheung, Neisewander, & Sanabria, 2012; Hill, Herbst, & Sanabria, 2012; Johnson, Pesek, & Newland, 2009; Podlesnik, Jimenez-Gomez, Ward, & Shahan, 2006; Reed, 2011; Shull & Grimes, 2003; Smith, McLean, Shull, Hughes, & Pitts, 2014; Yeates, Tolkamp, Allcroft, & Kyriazakis, 2001; but see Bowers, Hill, & Palya, 2008). Such organization implies that operant behavior can be described using three parameters: the rate at which bouts are initiated ( $b$ ), the rate at which responses are emitted within bouts ( $w$ ), and the mean length of a bout ( $L$ ). Under variable-interval (VI) schedules of reinforcement, rates  $b$  and  $w$  appear to be roughly constant, yielding each an exponential distribution of inter-response times (IRTs) (Brackney et al., 2011). Rates  $b$  and  $w$  may thus be estimated from the distribution of IRTs using the probability distribution function

$$\Pr(IRT_t = \tau | \tau < \delta) = 0$$

$$\Pr(IRT_t = \tau | \tau \geq \delta) = p_t w_t e^{-w_t(\tau-\delta)} + (1 - p_t) b_t e^{-b_t(\tau-\delta)}$$

$$\min(\text{IRT}) \geq \delta > 0; w \geq b > 0; 1 \geq p \geq 0. \quad (4-1)$$

The weighting parameter  $p$  is a function of  $L$ , the average length of a bout without the bout-initiating response;  $p = L / (L + 1)$ .

Brackney et al. (2011) introduced the distribution-shift factor  $\delta$ , which represents the response refractory period. After a response begins, it is assumed that a minimum amount of time,  $\delta$ , must elapse before another response can be started. This parameter represents the time it takes the animal to complete a single response, plus any additional



time it may take to prepare the next response. The reciprocal of the refractory period,  $1/\delta$ , is the absolute maximum response rate an animal can emit, equivalent to the asymptotic response rate of Herrnstein's hyperbola (Cheung et al., 2012; Herrnstein, 1970; Killeen et al., 2002). By subtracting  $\delta$  from all IRTs, changes that alter the time taken to make a response (such as motoric or mechanical constraints on the behavior) can be functionally dissociated from other controlling variables, such as the animal's propensity to respond. For instance, increasing the required work-load (e.g., height and force of a lever) increases  $\delta$  but leaves  $w$  relatively unaffected (Brackney et al, 2011). If  $\delta$  was not estimated, it may be erroneously inferred that work-load reduces the within-bout response rate instead.

Brackney et al. (2011) found that, in addition to increasing  $\delta$ , increasing the required work-load decreased the rate of bout initiations,  $b$ . However, a causal relation, if any, between the altered  $\delta$  and  $b$  could not be determined because the time required to make a response was not directly manipulated.

The primary goal of the current study was to examine how direct manipulations of the required response duration (the effective  $\delta$ ) affected response bout parameters. Rats were trained to respond on a variable interval (VI) 40-s schedule of reinforcement. Responses that met or exceeded a duration threshold of 0.0, 0.4 or 0.8 s (depending on the condition) were signaled by a brief tone and light flash. Only signaled responses could trigger reinforcement after the end of the variable interval.

A secondary goal was to characterize the distribution of response durations emitted under a VI schedule. Whereas Equation 3-1 assumes that the time to emit a

response is constant, direct measurement of lever-press durations have found them to vary from response to response (Fowler, Filewich, & Leberer, 1977; Gharib, Derby, & Roberts, 2001; Gharib, Gade, & Roberts, 2004; Roberts & Gharib, 2006). This study directly examined the distribution of response durations across different duration thresholds.

## **Method**

### **Subjects**

Eight male Wistar rats (WI/NCrI; Charles River Laboratories, US), starting at postnatal day age 74, served as subjects. All rats were pair-housed and had *ad libitum* access to food and water. Subjects were housed with a reverse dark-light cycle (lights off 7 am to 7 pm); experiments were conducted during the dark phase of this cycle. All subjects had previously been trained to respond on left and right levers in an operant chamber on a variable interval (VI) 120-s schedule of food reinforcement. The study adhered to Arizona State University Institutional Animal Care and Use Committee guidelines.

### **Apparatus**

Experimental sessions took place in 8 Med Associates modular test chambers using the standard operant setup. The chambers were enclosed in a light and sound attenuating box with interior dimensions of 30.5 cm x 24.1 cm x 21.0 cm. All test chambers were controlled by MED-PC® IV software (Med Associates, St. Albans, VT). The operant chambers consisted of a clear polycarbonate roof, door, rear, and two lateral walls of aluminum panels mounted to a white polypropylene base. The center panel of one of the walls had a speaker attached to a multiple tone generator and an Eiko 1820

miniature incandescent house light. A liquid dipper with a head entry detector was located centrally on the wall opposite of the speaker. Two retractable levers flanked the dipper; a triple LED stimulus light panel was positioned above each lever. A 0.01-ml cup on the motorized arm of the liquid dipper provided reinforcement, which was a sweetened condensed milk (True Value® Walmart Brand, Bentonville, AR) and water mixture (1/3 milk by volume). The operant chambers had a metal-wired floor and a stainless steel waste pan filled with wood-chip bedding. The levers were set on continuous recording mode so that the duration of lever presses could be measured with a nominal resolution of 0.01 s. A lever press was required to be separated by 0.06 s or more from the previous lever press in order to be counted as a new response. This threshold was selected because 0.06 s was the absolute minimum lever-press IRT previously observed in our laboratory (Brackney et al, 2011). The levers were calibrated to activate when a force of 0.2 (+/-0.05) N was exerted on their edge.

### **Procedure**

Throughout the experiment, lever presses were categorized as either super- or sub-threshold, where the threshold was 0.0, 0.4, or 0.8 s, depending on the experimental condition (Table 4-1). If the lever press duration exceeded the threshold, the response was signaled by a flash of the lights above the lever and a 5-kHz tone sounding for a brief time (0.1 s). For the 0.0 s threshold, every lever presses was immediately signaled.

Daily sessions began with a 5-min acclimation period, during which no experimental events were programmed, followed by the extension of the left lever. Super-threshold lever pressing was reinforced on a VI 40-s schedule. Intervals were sampled without replacement from a 14-item list drawn from a Flesher-Hoffman distribution

(Fleshler & Hoffman, 1962). During reinforcement, the lever was withdrawn, the houselight illuminated and the dipper arm raised. Three seconds later, the dipper arm was lowered, the houselight turned off, and the lever re-extended. Sessions terminated after 80 minutes or 84 reinforcer deliveries, whichever occurred first.

Table 4-1.  
*Duration threshold training conditions.*

Duration Threshold (s)	Cycle	Condition Length (Sessions)
0.0	1	15
0.4	1	13
0.8	1	13
0.0	2	12
0.4	2	12
0.8	2	17

*Note.* Experimental conditions occurred in descending order. When the duration threshold was 0.0 s, a discrete response of any duration met the threshold requirement.

The response-duration threshold varied across 6 experimental conditions (Table 1). During the first three conditions (Cycle 1) the duration threshold was 0.0, 0.4, and 0.8 s. The following three conditions (Cycle 2) were replications of the previous three. Subjects were transitioned from one condition to the next after a minimum of ten sessions, and when the mean response rate and the mean median response duration over the previous five days were judged stable by visual inspection.

### **Data Analysis**

All analyses were conducted on the responses of individual rats, aggregated over the last five sessions of each condition. Equation 3-1 was fit to the distribution of inter-response times (IRTs), using maximum likelihood estimation (Myung, 2003) with custom written MATLAB® (MATLAB and Statistics Toolbox Release 2013, MathWorks,

Inc., Natick, MA) software. IRTs were defined as the intervals between the beginnings of each pair of consecutive super-threshold responses<sup>5</sup>.

ANOVAs were conducted with Prism (GraphPad Software Inc., San Diego, CA). To identify significant effects, a  $2 \times 3$  repeated-measures ANOVA (cycle  $\times$  threshold) was conducted on each variable of interest. Simple main effects were assessed with

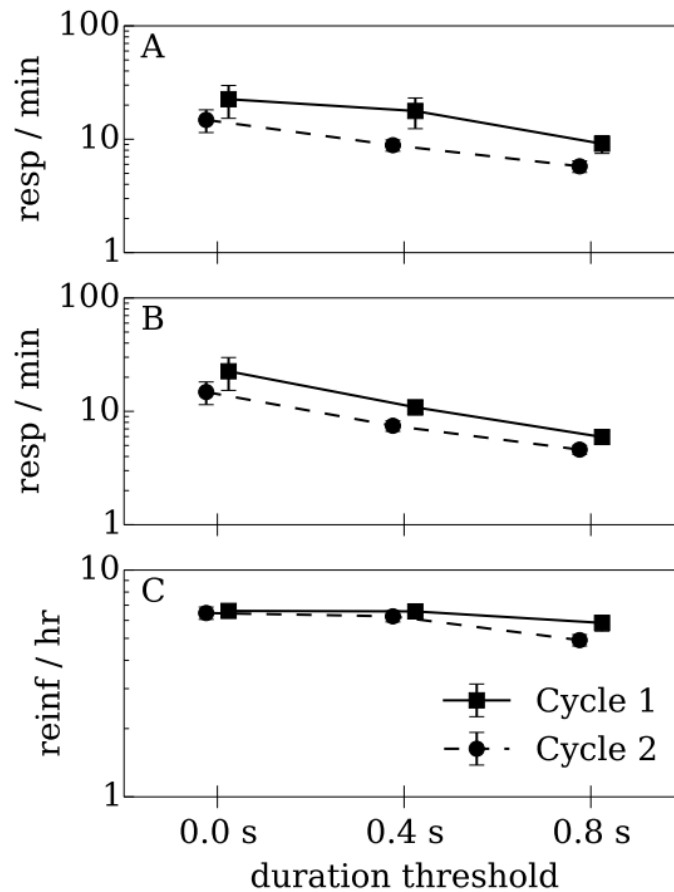


Figure 4-1. Mean median response and reinforcement rates as a function of response-duration threshold calculated over the last five sessions in each threshold condition in Cycles 1 (solid curves) and 2 (dashed curves). (A) Overall response rate, calculated using both super- and sub-threshold responses. (B) Super-threshold response rate. (C) Reinforcement rate. Error bars represent the standard error of the mean.

<sup>5</sup> See Appendix F for a discussion of the exclusive analysis of super-threshold IRTs.

Tukey's honestly significant difference test. Significant effects are reported when  $p < .05$ . ANOVAs were conducted on the log-transformed response rates, reinforcement rates, median response durations, inter-quartile range of response durations, and parameters estimates of Equation 3-1, except  $p$ , which was log-odds transformed. All variables of interest are reported back-transformed; mean bout length is reported as  $L = p / (1 - p)$ . A  $2 \times 2$  repeated measure ANOVA (cycle  $\times$  threshold) was conducted on the arcsine-transformed<sup>6</sup> proportion of responses that exceeded the response threshold for the 0.4 and 0.8 s threshold conditions (all responses were necessarily above the threshold in the 0.0 s threshold condition).

## Results

### Response and Reinforcement Rates

Overall response rate (computed including sub- and super-threshold responses) and super-threshold response rate declined with longer duration thresholds; overall:  $F(2, 14) = 36.64, p < .001$ , super-threshold only:  $F(2, 14) = 37.85, p < .001$  (Figure 4-1A and Figure 4-1B). Both dependent measures also declined between Cycles 1 and 2; overall:  $F(1, 7) = 30.52, p < .001$ , super-threshold only:  $F(1, 7) = 28.53, p < .001$ . Overall response rate declined significantly between the 0.0 and 0.8 s conditions and between the 0.4 and 0.8 s conditions in Cycle 1,  $p < .05$ , and among all conditions in Cycle 2,  $p < .001$ . Super-threshold response rates declined significantly with longer thresholds in both cycles,  $p < .05$ .

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<sup>6</sup>  $y = \arcsin(x^{0.5})$ , where  $x$  is a proportion and  $y$  is approximately normally distributed.

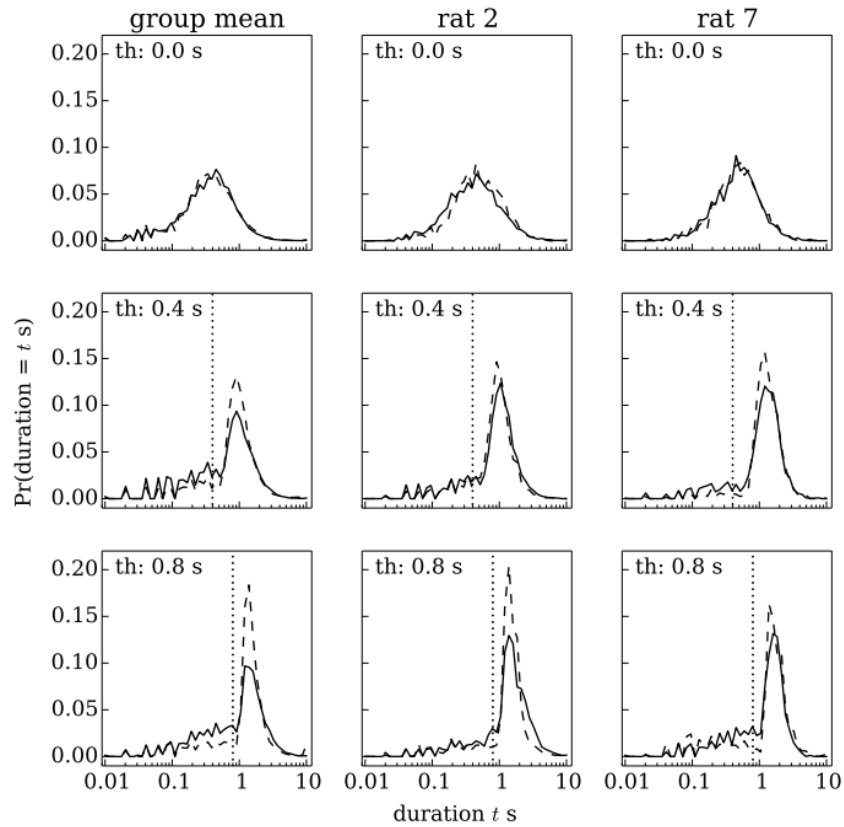


Figure 4-2. Distribution of response durations in the last five days of each threshold condition in Cycles 1 (solid curves) and 2 (dashed curves). The vertical dotted lines indicate the response-duration threshold. The left column are the group means, the middle and right columns are representative rats. The abscissa is on a log scale to highlight the log-normal-like distribution of a portion of response durations.

### Response Durations

Figure 4-2 displays the distribution of response durations for the group, and for two representative rats, in each condition. In the 0.0 s conditions, the distribution of response durations appears approximately log-normal. Longer duration thresholds displaced a large portion of the distribution of response durations rightwards, just above the threshold. For the 0.4 and 0.8 s thresholds, response durations greater than the threshold appear log-normally distributed. Sub-threshold response durations appear to be distributed according to an unknown flatter distribution, which is distinct from the super-threshold durations.

Figure 4-3 displays summary statistics of the duration distributions: the mean ( $\pm$  SEM) of the individual median durations (Figure 4-3A), the interquartile range of durations (Figure 4-3B), and the proportion of durations that met or exceeded the duration threshold (Figure 4-3C).

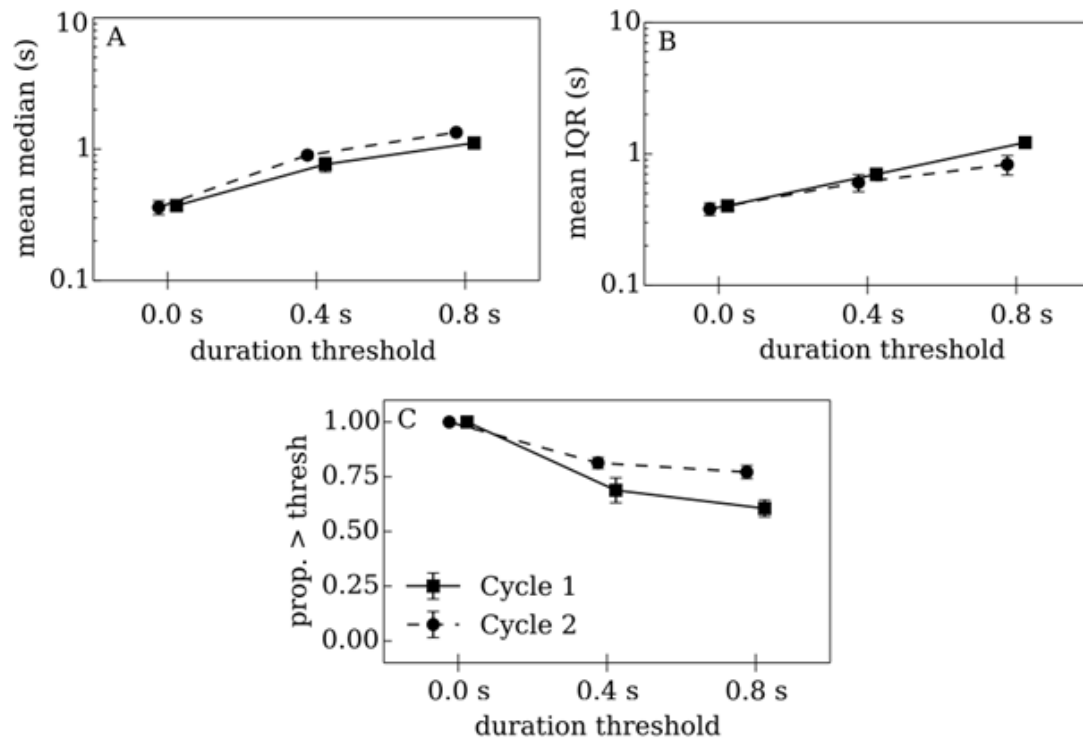


Figure 4-3. Mean of three response-duration distribution statistics as a function of response-duration threshold, calculated over the last five sessions in each threshold condition in Cycles 1 (solid curves) and 2 (dashed curves). (A) Median response duration; across all threshold conditions, the median duration was between 0.32 and 0.54 s longer than the required duration. (B) Inter-quartile range of response durations. (C) Proportion of responses that exceeded the duration threshold; all responses in the 0.0 s condition exceeded the threshold by design. Error bars represent the standard error of the mean.

Median response durations increased with longer duration thresholds:  $F(2, 14) = 219.90, p < .001$ . The interquartile range of the response durations also significantly increased as the threshold increased,  $F(2, 14) = 37.80, p < .001$ , but declined between cycles,  $F(1, 7) = 5.70, p < .05$ . The proportion of responses that exceeded the duration



threshold increased between cycles,  $F(1, 7) = 29.49, p < .001$ . These effects indicate that longer response-duration thresholds resulted in longer, more variable response durations, and point at potential learning effects between cycles.

### **Response Bout Modeling**

Figure 4-4 displays the mean ( $\pm$  SEM) parameter estimates for each condition. Individual parameter estimates for each rat and condition are described in Tables G-1, G-2 and G-3 of Appendix G.

The average bout length,  $L$ , increased with longer duration thresholds,  $F(2, 14) = 11.53, p < .05$ . Significant differences in estimates of  $L$  were observed between the 0.0 and 0.4 s conditions and between the 0.0 and 0.8 s conditions in both cycles,  $p < .05$ . Within-bout response rate,  $w$ , significantly decreased with longer thresholds,  $F(2, 14) = 47.61, p < .001$ , and between cycles;  $F(1, 7) = 14.82, p < .05$ . Significant differences in estimates of  $w$  were observed among all conditions in Cycle 1,  $p < .05$ , and between the 0.0 and 0.4 s conditions and between the 0.0 and 0.8 s conditions in Cycle 2,  $p < .001$ . Bout initiation rate,  $b$ , significantly decreased with longer thresholds,  $F(2, 14) = 34.12, p < .001$ , and between cycles,  $F(1, 7) = 14.89, p < .05$ . Significant differences in estimates of  $b$  were observed among all conditions in both cycles,  $p < .05$ . The refractory period,  $\delta$ , increased with longer duration thresholds,  $F(2, 14) = 2599, p < .001$ , and between cycles,  $F(1, 7) = 28.76, p < .001$ . Significant differences in estimates of  $\delta$  were observed among all threshold conditions in both cycles,  $p < .001$ . When considered together, the

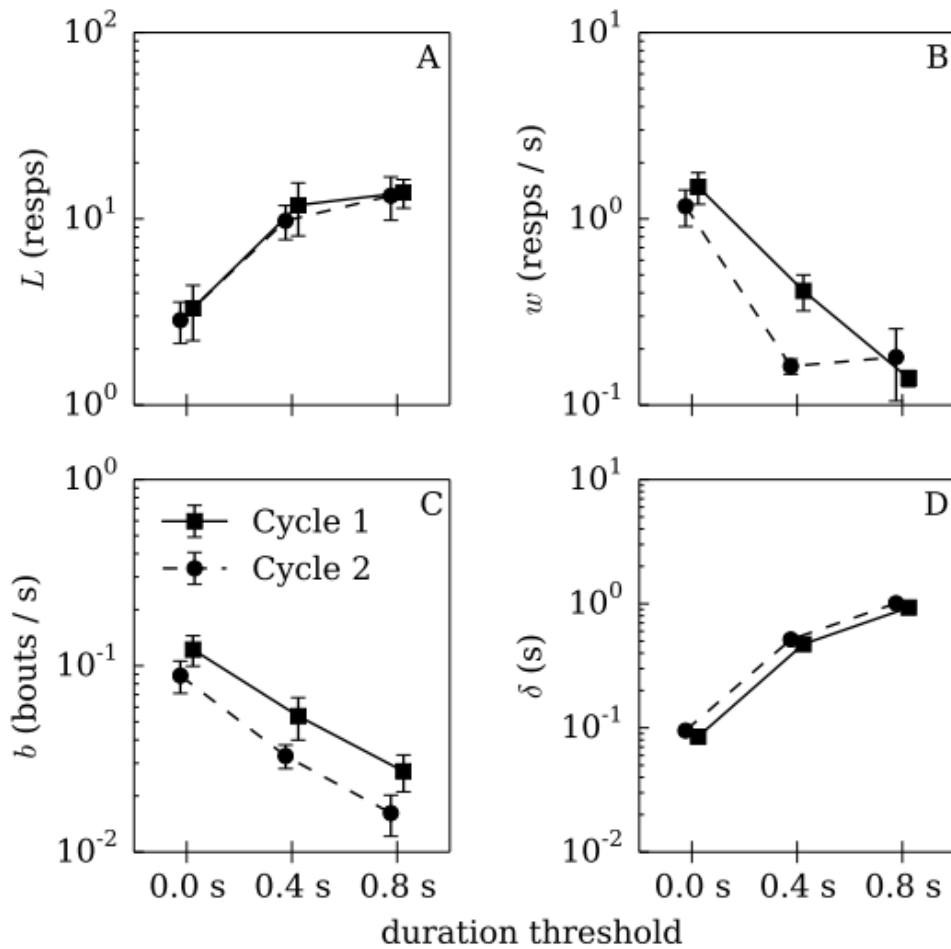


Figure 4-4. Mean BERM parameter estimates (Equation 4-1) as a function of response-duration threshold, computed from super-threshold IRTs in the last five days of each threshold condition in Cycles 1 (solid curves) and 2 (dashed curves). (A) Bout length, not including the bout initiation response; (B) within-bout response rate; (C) bout initiation rate, and (D) refractory period. Error bars represent the standard error of the mean. Estimates for individual subjects are in Tables G-1, G-2, and G-3 of Appendix G.

effects of response-duration threshold on  $L$ ,  $w$ ,  $b$ , and  $\delta$  suggest that longer thresholds yielded fewer but longer response bouts that contained more spaced within-bout responses.

To ensure that the model was providing reasonable fits, log-survivor plots (Shull et al., 2001) of the model predictions were compared to log-survivor plots of the observed

IRTs. Appendix H describes how model predictions were determined. Figure 4-5 displays the log-survivor plots of the group mean and two representative rats for each duration threshold in Cycle 1. As the duration threshold increased, the shape of the log-survivor plot changed from the often-reported “broken-stick” pattern (e.g., Shull et al., 2001) to a straighter pattern. The model faithfully reproduced the distribution of IRTs in the 0.4-s and 0.8-s conditions. In the 0.0-s condition, however, the simulation appears to overestimate the prevalence of the longest, approximately 20%, of IRTs. Because the slope of the right-hand side of the “broken-stick” corresponds to  $b$  (Shull et al., 2001), this divergence suggests that  $b$  may be underestimated in the 0.0-s condition.

### **Reanalyzing the Log-Survivor Plot**

In log-survivor plots of IRT distributions, the vast majority of IRTs are represented in a small space in the upper left hand portion of the plot. This feature of the log-survivor plots helps emphasize the “broken-stick” appearance that is characteristic of bi-exponentially distributed data (Shull et al., 2001), but exaggerates deviations from fit in IRTs corresponding to bout initiations, making it difficult to detect deviations from fit for within-bout IRTs. To identify the range of IRTs over which observation and model diverge, observed and model-predicted IRTs were divided into bins each representing consecutive two percentile slices of the data; the mean IRT for each bin was calculated and plotted. This alternative method of comparing the observed and predicted IRTs allows the full range of IRTs to be more equally represented. The observed and predicted IRTs, organized in percentiles, are shown in Figure 4-6 averaged across rats and for the

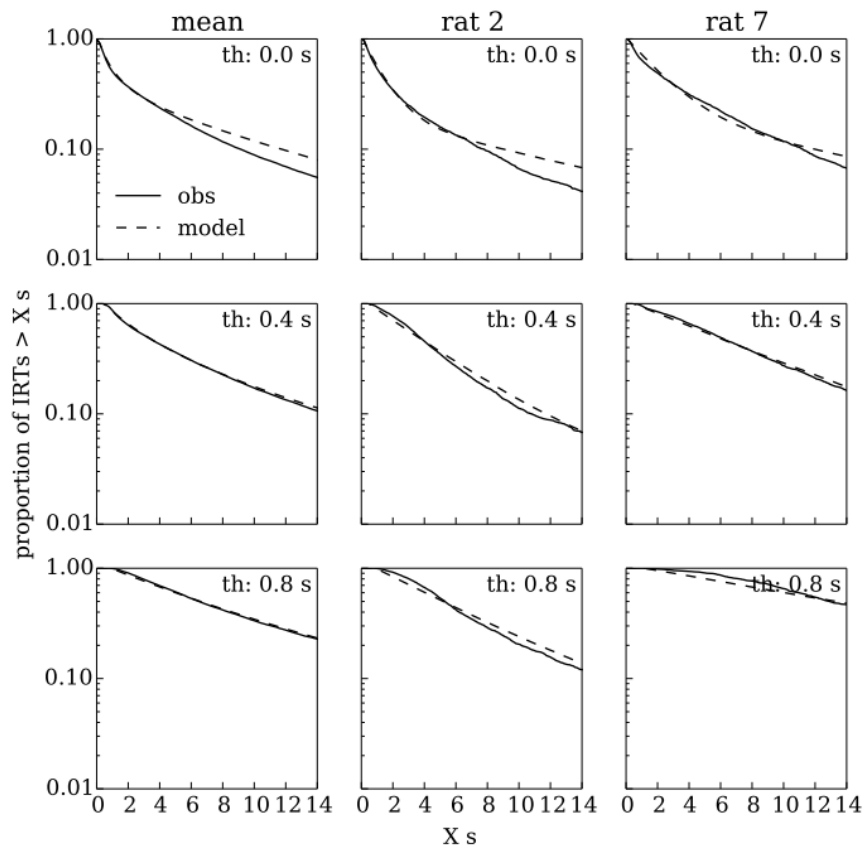


Figure 4-5. Log-survivor plots of super-threshold IRTs demonstrating model fit in Cycle 1. Solid curves correspond to empirically observed IRTs; dashed curves correspond to IRTs predicted by model simulation (see details in Appendix C). Each row of plots corresponds to a different response-duration threshold. The left column is the group mean, the middle column and right columns are representative animals. Although some deviations from the observed data seem prominent from a visual inspection of the plots, they actually comprise only a small proportion of very long IRTs.

two representative rats from Figure 4-5. Figure 4-6 shows little deviation between data and model, suggesting that much of the apparent deviation in Figure 4-5 is due to the “stretching out” of the longest IRTs.

## Discussion

### Longer Refractory periods yield fewer but longer bouts

Prior research has shown that higher, heavier levers yield longer refractory periods between responses and lower bout initiation rates (Brackney et al., 2011),

presumably because they higher-heavier levers take longer to press. To test the hypothesis that longer response durations decrease bout initiation rates, the present study directly manipulated the minimum time required for an effective lever press. Consistent with prior findings, higher response-duration thresholds yielded lower bout initiation rates. Unlike prior studies, however, higher thresholds also yielded significantly longer bouts and lower within-bout response rates.

The unpredicted changes in parameters ( $L$  and  $w$ ) observed in the present study likely stem from three sources. First, the higher work-load condition in Brackney et al. (2011) only increased the mean refractory period from over 0.1 s to less than 0.2 s; the present study increased the required refractory period to 0.4 s and 0.8 s in some of its conditions. This may explain why even though Brackney et al. (2011) report a mean increase in bout length with higher work-load<sup>7</sup>, that increase was not statistically significant.

The second and third sources of divergence between Brackney et al. (2011) and the present results are the strain of rat employed and the schedule of reinforcement implemented. Brackney et al. (2011) trained Sprague Dawley rats on a VI 120-s schedule of reinforcement, whereas the present study trained Wistar rats on a VI 40-s schedule. It is likely that these factors contributed to the differences in mean baseline bout length across studies ( $L < 1.5$  vs.  $> 3.0$  responses in Brackney et al., 2011 vs. the present study), which may have affected the sensitivity of this parameter to changes in refractory period.

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<sup>7</sup> Estimated from parameter  $q$ , where  $L = (1 - q) / q$ .

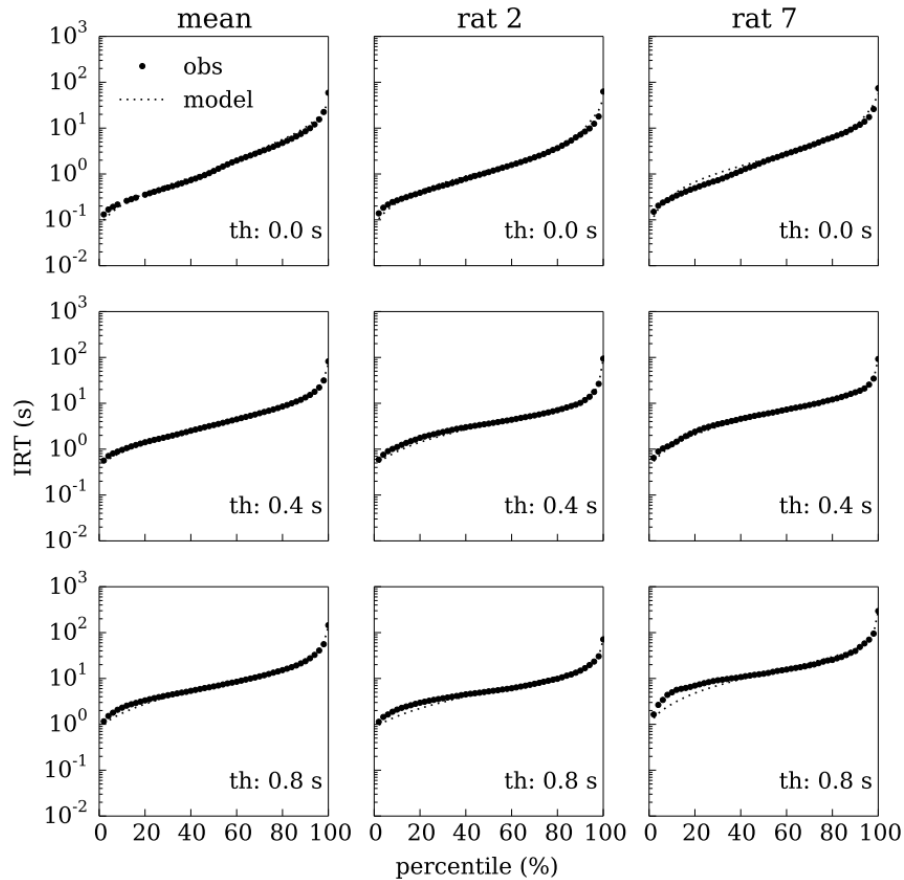


Figure 4-6. Percentile plots of super-threshold IRTs demonstrating model fit in Cycle 1. Each point is the mean IRT for a two-percentile bin of the data. Heavy dots correspond to empirically observed IRTs; dotted curves correspond to IRTs predicted by model simulation. Each row of plots corresponds to a different response-duration threshold. The left column is the group mean, the middle column and right columns are representative animals.

In short, results from both Brackney et al. (2011) and the present study are consistent with the notion that responses of longer duration yield fewer but longer response bouts.

The threshold-induced reduction in bout frequency is somewhat intuitive.

Brackney et al. (2011) suggested that reinforcer deprivation, availability, and response “price” may drive what they labeled *operant motivation*, a general predisposition of the organism to engage the operandum, which is expressed in the bout initiation rate. In the

present study, higher duration thresholds raised the response “price”, thus lowering the bout initiation rate.

The threshold-induced lengthening of bouts is less intuitive. Why would rats persist longer in a bout of more effortful responses? It is well established that the efficacy of a reinforcer declines as a function of time between the reinforced response and the reinforcer (Dickinson, Watt & Griffiths, 1992). This suggests a delay-of-reinforcement gradient; as a response takes a larger fraction of the area under such gradient, it may be more efficaciously reinforced (Hill et al., 2012; Killeen & Sitomer, 2003; Killeen, 1994). Thus, long-duration responses—once initiated—are more efficaciously reinforced, which may be expressed in longer bouts. This hypothesis is consistent with the notion that bout length reflects the strength of the response-outcome association (Hill et al., 2012).

### **Refractory Periods are Variable**

Figure 4-2 and Figure 4-3 reveal that lever presses have variable duration. A considerable minority of recorded responses in the 0.4 and 0.8 s conditions was shorter than the required threshold for reinforcement. Conversely, the median duration typically exceeded the threshold by approximately 0.5 s, which is considerably more than the refractory periods of approximately 0.1 s that are typically estimated when the refractory period is assumed to be static (cf. Brackney et al., 2011).

Training order may have contributed to the high prevalence of sub-threshold responses, as the 0.0 s condition always preceded the 0.4 and 0.8 s condition. Auditory and visual cues signaled when the threshold had been crossed, and subjects adjusted their behavior to meet the new contingencies after a condition switch. However, learned

responses with lower durations may have persisted in their behavioral repertoire. Sub-threshold responses may also have been adventitiously reinforced when they preceded a super threshold response that triggered reinforcement (Catania, 1971; Johansen, Killeen, & Sagvolden, 2007; Killeen, 1994).

Gharib and colleagues' (2001, 2002; Roberts & Gharib, 2006) findings suggest another source of variability in response durations. Roberts and Gharib (2006) hypothesized that decreasing the probability of reinforcement increases the variability in response durations. The rate of earned reinforcers (Figure 4-1) decreased significantly (if by a small margin) as the response threshold increased, which may have increased duration variability.

Regardless of its cause, the variability in response durations is inconsistent with the assumption of Equation 4-1 that, under constant conditions, the refractory period is constant. Instead, it appears that the refractory period is a mixture-distributed random variable with at least two components: a shifted log-normal distribution of super-threshold latencies, and an unknown but flatter distribution of durations that is insensitive to threshold requirement. Future research may determine whether the parameters of this mixture distribution are sensitive to motivational and schedule manipulations, as suggested previously (Faustman & Fowler, 1981; Roberts & Gharib, 2006).

## **Conclusion**

Reinforced responses are organized in bouts. The selective reinforcement of longer response durations not only increases the relative frequency of these durations, it also yields fewer but longer response bouts. Bout-length effects may reflect a duration-



induced facilitation of the response-outcome association. The variability in response durations indicate that, contrary to prior assumptions (Equation 4-1 and Chapter 2), the refractory period between IRTs is not constant. Previous studies have shown that response durations can provide valuable information about the pharmacological and behavioral processes affecting operant performance (Faustman & Fowler, 1981; Liao & Fowler, 1990; Roberts & Gharib, 2006). Future research may explore how the variability of the refractory period is integrated into more comprehensive models of operant performance (e.g., Equation 4-1). Along with the parameters of IRT distribution, the parameters of response-duration distribution may contribute to identify the multiple factors that influence operant behavior.

## CHAPTER 5

### THE DISTRIBUTION OF RESPONSE BOUT LENGTHS AND ITS SENSITIVITY TO DIFFERENTIAL REINFORCEMENT

#### **Abstract**

Response bouts are clusters of responses that occur in rapid succession and are punctuated by pauses during which the response does not occur. Under variable interval schedules of reinforcement, the number of responses in each bout (the bout length) varies among bouts. This experiment was aimed at determining whether the relative rate of reinforcement influenced the relative frequency of bouts of different lengths. Lever pressing in rats was reinforced under a tandem variable time (VT) 150-s fixed ratio (FR)  $X$ , where  $X$  could be 1 or 5 and varied randomly after each reinforcer. Two conditions were included: majority FR1 (mFR1) and majority FR5 (mFR5). In mFR1, 75% of reinforcers had a tandem FR requirement of 1 and 25% had a tandem FR requirement of 5; this distribution was reversed in mFR5. The inter-response times (IRTs) in each condition were fit to the dynamic bi-exponential refractory model of response bouts. The parameters of those fits and the IRTs were then used to simulate probable distributions of bout lengths. The distribution of bout lengths comprised a mixture of short geometrically-distributed bout lengths and long negative-binomially-distributed bout lengths. Long bouts were significantly longer in the majority FR5 condition than in the majority FR1 condition. In conjunction with previous data, the present study suggests that the prevalence of long bouts increases with the proportion of reinforcers with FR5 requirement. These results suggest that bouts of different lengths are sensitive to the rate at which they are reinforced.

## Introduction

Behavior is sensitive to the explicit reinforcement of response patterns that extend beyond simple response-reinforcer relations. For example, animals can be trained to emit inter-response times (IRTs) of a specific durations (Shimp, 1968), response sequences of fixed length (Evenden & Ko, 2005; Mechner & Guevrekian, 1962), and even response sequences that are random (Neuringer, 2002). Even without explicit selection by the experimenter, stereotyped response patterns may emerge (Schwartz, 1982). One such pattern frequently observed across multiple organisms and response types is the response bout, in which multiple responses are emitted in quick succession before engaging in other behaviors (Barabási, 2005; Brackney et al., 2011; Kirkpatrick, 2002; C. A. Morgan et al., 2000; Podlesnik et al., 2006; Shull et al., 2001; T. T. Smith et al., 2014).

Response bouts emerge spontaneously when behavior is allowed to occur at its operant level, unreinforced by the experimenter (Cabrera, Sanabria, Jiménez, & Covarrubias, 2013); they have also been observed in adjunctive behavior (Ibias, Pellón, & Sanabria, 2014). In the operant domain, bouts are often observed in variable interval (VI) schedules of reinforcement, whether programmed alone (Brackney et al., 2011; Conover, Fulton, & Shizgal, 2001; Shull, 2004; Shull & Grimes, 2003; Shull et al., 2001, 2002, 2004) or concurrently with another VI schedule (Shull, 2011; Smith, McLean, Shull, Hughes, & Pitts, 2014). Bouts can be represented by multiple parameters that are each differentially sensitive to various experimental manipulations. For example, the rate at which bouts occur (the bout initiation rate) is highly sensitive to motivating operations; in contrast, response rate during a bout (the within-bout response rate) and the number of

responses in a bout (the bout length), are relatively insensitive to motivating operations, but are highly sensitive to response requirements (Brackney et al., 2011). Using these parameters, behavioral effects of drugs and poisons (Cheung, Neisewander, & Sanabria, 2012; Johnson, Bailey, & Newland, 2011; Newland, Hoffman, Heath, & Donlin, 2013), and differences between strains of rats (Brackney, Cheung, Herbst, Hill, & Sanabria, 2012; Hill, Herbst, & Sanabria, 2012) and mice (Johnson, Pesek, & Newland, 2009) have been identified.

Response-bout parameters are typically estimated by examining the distribution of IRTs. Across a range of schedules, this distribution appears to conform to a mixture of two shifted exponential distributions, one that characterizes within-bout responding and another that characterizes bout initiation. This mixture distribution constitutes the bi-exponential refractory model (BERM) of operant performance (Brackney et al., 2011; Cheung et al., 2012; Hill et al., 2012), which is expressed mathematically as

$$\Pr(IRT = \tau \mid \tau < \delta) = 0$$

$$\Pr(IRT = \tau \mid \tau \geq \delta) = pwe^{-w(\tau-\delta)} + (1-p)be^{-b(\tau-\delta)}.$$

$$\min(IRT) \geq \delta > 0; w \geq b > 0; 1 \geq p \geq 0 \quad (5-1)$$

Equation 5-1 has four parameters: the within bout response rate ( $w$ ), the bout initiation rate ( $b$ ), the proportion of responses which are within-bout ( $p$ ), and the minimum amount of time required to emit a response and prepare to emit the next ( $\delta$ , or *refractory period*). The mean of within- and between-bout IRTs are, respectively,  $1/(w + \delta)$  and  $1/(b + \delta)$ ; their standard deviations are  $1/w$  and  $1/b$ . The number of responses per bout—i.e., the average bout length—is  $1/(1 - p)$ .

Equation 5-1 does not specify how bout lengths are distributed around their mean. Past models have suggested that bouts lengths are geometrically distributed (Brackney et al., 2011; Shull et al., 2001), but have not provided empirical support (although see Smith et al., 2014 Figures 6B, 7B and 8B). The purpose of the present study was to characterize the distribution of bout lengths in free-operant behavior.

Bout lengths are of particular interest because they appear to reflect the responsiveness of the organism to the response-reinforcer contingency. This inference is drawn from the positive correlation between mean bout-length estimates and the number of responses required to collect reinforcement, typically instantiated by following a variable-time (VT) schedule with a tandem ratio schedule (Brackney et al., 2011; Shull et al., 2001). Various accounts of free-operant performance suggest that reinforcement is facilitated when the response is repeatedly emitted just before reinforcement (Catania, 1971; Killeen & Sitomer, 2003; Killeen, 1994; Killeen refers to this facilitation as response-reinforcement *coupling*). Furthermore, rats with reduced capacity to couple responses to the reinforcer (Johansen et al., 2007) also emit significantly shorter bouts (Hill et al., 2012). It is yet unknown, however, whether the tandem response requirement affects other parameters of the distribution of bout lengths aside from their mean. This possibility was tested in the present study.

Bouts may also have behavioral-unit like properties (Brackney et al., 2011; Shull et al., 2001). If this is the case, bouts of different lengths may belong to different response classes, and the frequency of bouts of different lengths may have some correspondence to the frequency at which they are reinforced (Bachá-Méndez et al., 2007; Schwartz, 1986; Shimp, 1968). Unfortunately, the differential reinforcement of specific bout lengths

cannot be explicitly tested due the probabilistic nature of starts and ends of individual bouts (for extended discussions of bout detection methods, see Brackney et al., 2011; Cheung et al., 2012; Shull et al., 2001; Shull, Gaynor, & Grimes, 2002). Thus, the first step in determining the sensitivity of bout lengths to differential reinforcement is to devise a method to determine whether a particular IRT is within- or between-bout.

Bouts may be defined using an IRT cutoff method (Shull et al., 2001, 2002) where all IRTs  $\leq X$  s, are classified as within-bout; IRTs  $> X$  s are classified as between-bouts, where  $X$  s is the cutoff criterion. Although this method is easy to implement, it has significant drawbacks. In particular, the  $X$  s criterion is both arbitrary and does not take into account potential between- and within-subject variability in pauses separating bouts, thus it is likely to misclassify a substantial number of IRTs.

An alternative method to estimate bout-length distribution parameters is based on estimates of the parameters of a model such as BERM (henceforth, *the parameter-based method*). Given those estimates, the probability that each observed IRT is within-bout can be established. Bout-length distributions can then be estimated by realizing, for each IRT, its probability of being within-bout and simulating the frequency of each bout-length. The main limitation of this method is that bout-parameters must be analyzed *post hoc* by examining the entire population of IRTs within an experimental session, i.e., bout lengths cannot be identified during a session, only after.

Although the parameter-based method for classifying IRTs does not allow the experimenter to program reinforcement for bouts of a specific length, this method may still be useful in inferring the sensitivity of bout lengths to reinforcement. Previous studies (Brackney et al., 2011; Shull et al., 2001) have shown that increasing the fixed-

ratio (FR) requirement that follows in tandem to a variable-interval (VI) schedule increases the average bout length. This effect is consistent with the notion that higher tandem FR schedules may selectively reinforce longer bouts. To that extent, the probabilistic implementation of long and short tandem FR schedules should result in a mixture distribution of long and short bouts. Such mixture distribution may be unveiled by the parameter-based method for classifying IRTs.

To evaluate this possibility, responding was trained on a single lever under a tandem VT fixed-ratio (FR) schedule of reinforcement with probabilistic ratio requirement. In one condition, the majority (75%) of reinforcers were delivered on an FR 5 after the interval elapsed in order to earn reinforcement, while the minority (25%) of reinforcers were delivered on an FR 1 after the interval elapsed. In the other condition, the contingencies were reversed: the majority (75%) of reinforcers required an FR 1 and the minority (25%) required an FR 5. In neither condition was the FR requirement signaled.

A first approximation to the shape of the bout length distributions was obtained using the IRT-cutoff method with various plausible cutoff criteria. These analyses suggested that bout lengths may be geometrically distributed, negative-binomially distributed, or a mixture of both. The parameter-based method was then implemented to estimate the distribution of bout lengths. Geometric, negative binomial, and mixture distributions were fit to the estimated distributions of bout lengths.

## Method

### Subjects

Ten male, pair-housed Sprague Dawley rats (CD-1) that were approximately 90 days old and weighed between 322 and 400 grams at the start of the study served as subjects. They previously participated in another experiment in which they were tested on an object recognition task (Ortiz, Mathewson, Hoffman, Hanavan, Terwilliger, & Conrad, 2014). Prior to the present study, some rats received one intraperitoneal injection of d-cycloserine, a partial N-methyl-D-aspartate (NMDA) agonist, which has been shown to facilitate Pavlovian extinction when applied immediately prior to an extinction session (Walker, Ressler, Lu, & Davis, 2002). Rats 1, 5, 8 and 10 received saline injections, rats 4 and 9 received one 3 mg/kg dose of d-cycloserine, and rats 2, 6 and 7 received one 15 mg/kg dose of d-cycloserine. D-cycloserine was administered to the rats two weeks before they were introduced to operant chambers used in the current study. Because d-cycloserine has a plasma half-life of 70 min in rats (Löscher, Wlaż, Rundfeldt, Baran & Hönack, 1994), its administration was not expected to have any effect on the current operant task, nor were any obvious effects observed.

Rats were housed on a 12:12 h reverse light/dark cycle; all experimental sessions were conducted during the dark portion of the cycle. Rats received *ad libitum* water in their home cage, but were food restricted. They were provided *ad libitum* access to food for only 1 h each day, beginning 30 min after the end of each experimental session.

### Apparatus

Experimental sessions were conducted in 10 identical Med Associates® chambers, 305 mm long, 241 mm wide, and 210 mm high. The chambers were housed in



sound and light attenuating cabinets, in which a ventilation fan provided white noise at approximately 60 dB. The chambers were arranged according to the standard dual lever configuration – two retractable levers (Med Associates®) 21 mm above the floor flanked an aperture (51 mm sides, 15 mm from the chamber floor) that gave access to a liquid dipper (Med Associates®, ENV-202M-S). Only one lever, the one farthest from the door, was operational; it was calibrated to record a press when at least 0.2 N was applied to it. The walls orthogonal to levers and dipper aperture were made of transparent plexiglass, whereas the other two walls were made of aluminum. The dipper well was filled with a freshly-prepared sweetened condensed milk (True Value® Walmart Brand, Bentonville, AR) and water mixture (1/3 milk, 2/3 water, by volume) at the beginning of each session. Each reinforcer was 0.01 ml of the milk-water mixture, delivered by the dipper arm and made available for a 3-s interval. When turned on, a houselight mounted outside the experimental chamber provided dim illumination inside the chamber. Data collection and experimental events were handled by MED-PC™ software and hardware.

### **Procedure**

All sessions were conducted with the houselight off except during reinforcement, when the dipper was raised for 3 s, the houselight was illuminated, and the lever withdrawn. Sessions were conducted once a day, 7 days a week.

### **Pretraining**

Prior to the experiment, subjects were trained to drink from the dipper, press the lever, and to respond on a VI schedule. On the day previous to the first pretraining session, each subject was provided with approximately 1 ml of the milk/water mixture in their home cage in order to familiarize them with the reinforcer. During the first

pretraining session, the houselight remained on, and the dipper was programmed to be in the up position. Three seconds after each head entry to the dipper aperture, the dipper arm was lowered and raised again to refresh the supply of milk in the dipper cup. On the second and third sessions, the dipper was programmed to be in the down position, and head entries illuminated the houselight and raised dipper arm for 3 s. On the fourth, fifth, and sixth pretraining sessions, the reinforcer was paired with the lever extension. The lever was extended for 8 s, followed immediately by its retraction, turning on the houselight, and raising the dipper arm. The dipper remained in the up position and the houselight remained on for 3 s. A press to the lever also immediately withdrew the lever, turned on the houselight, and raised the dipper arm. Inter-trial intervals (ITIs) were randomly sampled from a list of intervals ranging between 10 and 150 s. Training was judged to be complete once the mean latency between lever retraction and the subsequent head entry was shorter than 2.5 s for each subject, or more than 50% of trials concluded with a lever press. All subjects met the criterion within three sessions.

In order to prepare the subjects for the experimental conditions, the next six sessions of pretraining reinforced lever pressing according to the following reinforcement schedules: continuous reinforcement, VI 10-s, VI 20-s, VI 40-s, VI 80-s, and VI 150-s.

### **Experimental Training**

The experiment proper began once pretraining concluded. Each session began with a 300-s acclimation period, during which no experimental events occurred. Experimental conditions were implemented following the acclimation period. Each session was terminated after either 60 min elapsed or 16 reinforcers were delivered, whichever occurred first.

During each session, lever pressing was reinforced on a tandem VT 150-s FR  $X$  schedule, where  $X$  was the ratio requirement. After acclimation and after each reinforcer, the lever was extended. The computer randomly sampled an interval without replacement from a 16-item list generated by a Fleshler-Hoffman distribution (Fleshler & Hoffman, 1962) with a mean of 150 s. The interval began after each reinforcer, and reinforcement was contingent upon the  $X$ th response after the interval had elapsed. The VT 150-s FR  $X$  schedule is similar to a VI schedule, but the number of lever presses required after the interval elapses is  $X$  instead of 1.

The experiment consisted of two conditions: a majority FR 1 condition (mFR1) and a majority FR 5 condition (mFR5). During mFR1, 75% of reinforcers only required 1 response after the VT ( $X = 1$ ) while the remaining 25% of reinforcers required 5 responses after the VT ( $X = 5$ ). In mFR5 the proportions were reversed: 75% of reinforcers required 5 responses and 25% of reinforcers required 1 response. The ratio requirement after each reinforcer was determined by sampling  $X$  randomly without replacement from a 16-item list that contained the numbers 1 (12 items in mFR1, 4 in mFR5) and 5 (4 in mFR1, 12 in mFR5). In this manner, after every reinforcer, interval length and FR requirement selection was random and independent of each other. The selected response requirement was not signaled to the subjects.

Subjects were divided into two groups: the odd numbered rats (1, 3, 5, 7, 9) were assigned to group 'mFR5 first' and the even numbered rats (2, 4, 6, 8, 10) were assigned to group 'mFR1 first'. Each group received approximately equal exposure to both the mFR1 and mFR5 condition, but in opposite order. For the first 27 sessions, group 'mFR5 first' was trained on mFR5 and group 'mFR1 first' was trained on mFR1. For the

subsequent 26 sessions, 'mFR5 first' was trained on mFR1 and group 'mFR1 first' was trained on mFR5.

### **Data Analysis**

Although subjects were trained for 26 or 27 days on each condition, only the last five sessions from each condition (mFR1 and mFR5), when the performance appeared stable, were analyzed. All analyses were conducted with custom written Matlab® code. Model parameters were estimated using maximum likelihood estimation (MLE; Myung 2003); this method identifies the set of parameters that are more likely to produce the observed data.

## **Results**

### **Reinforcement and Response Rate**

Figure 5-1 shows individual changes in response and reinforcement rate between mFR1 and mFR5. Response rate was greater in mFR5 for all rats in mFR5 first (mean difference = 15.58, SEM = 4.91 resp/min) but not in mFR1 first (mean difference = -2.63, SEM = 2.38 resp/min). Changes in reinforcement rate between mFR1 and mFR5 were negligible for both mFR5 first (mean difference = -0.38, SEM = 0.22 reinf/h) and mFR1 first (mean difference = 0.76, SEM = 0.29 reinf/h). This asymmetry in response rate differences between mFR1 and mFR5 suggests that overall response rate was affected by the order in which mFR1 and mFR5 were experienced. However, all subsequent analyses were initially conducted separately on each order condition, and showed only minor differences in response bouts and bout lengths (see individual subject plots of Figure 5-3 and Figure 5-4).

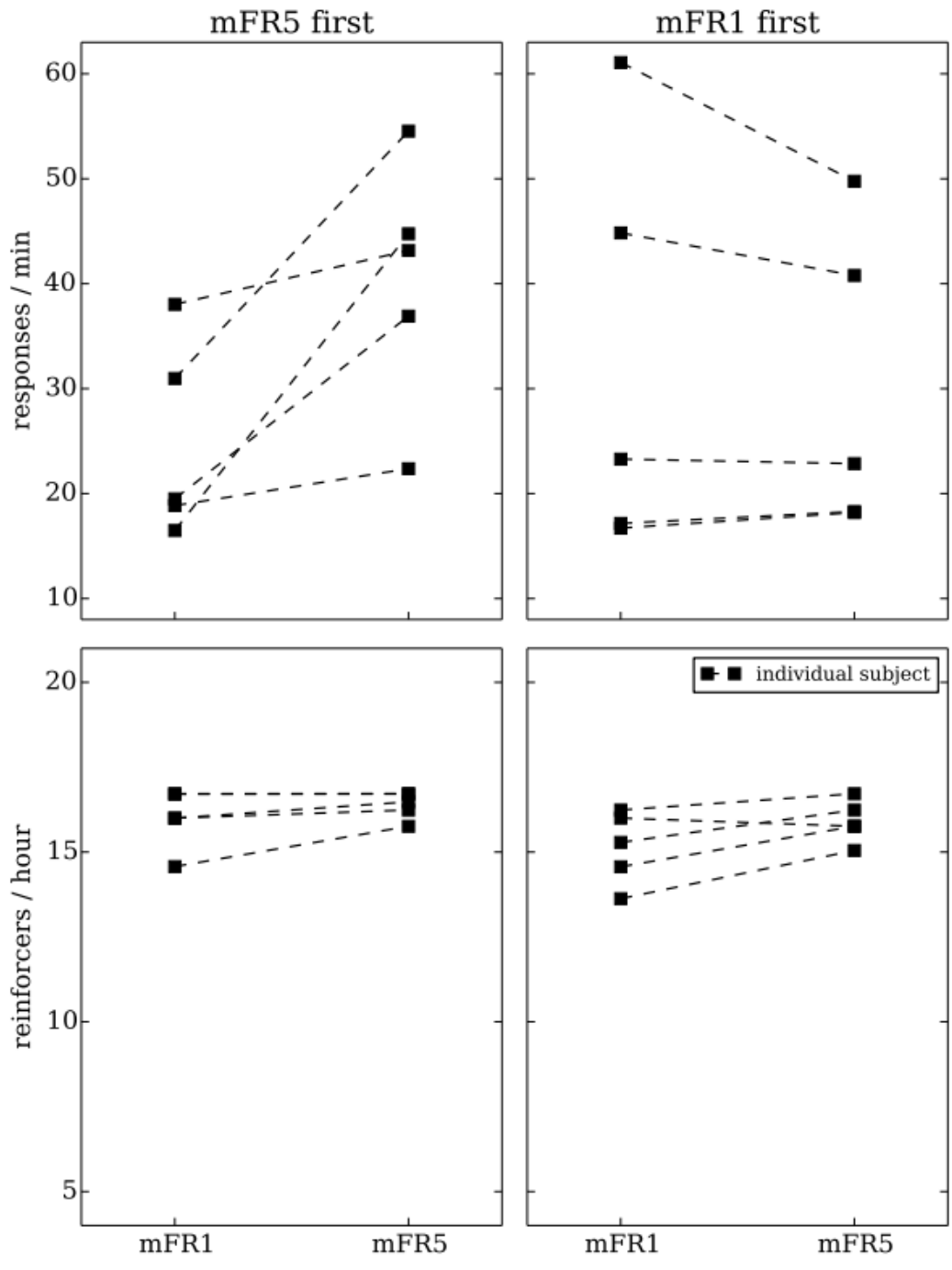


Figure 5-1. mFR1 and mFR5 Response and reinforcement rates. The top panels show the response rates and the bottom panels show reinforcement rates for individual subjects in the mFR1 and mFR5 conditions for groups mFR1 first and mFR5 first. The dashed lines connect individual subjects to highly response rate changes between conditions.

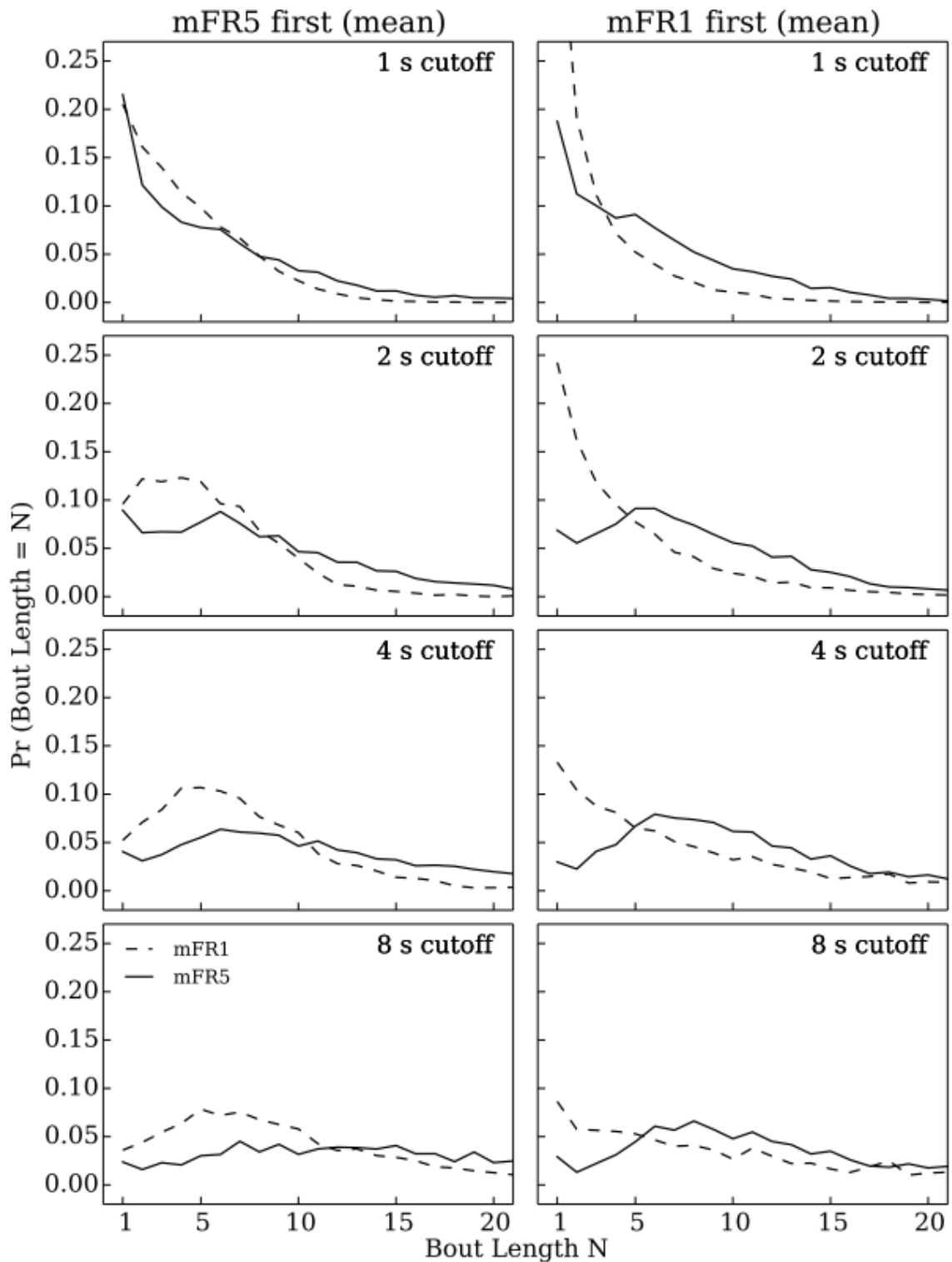


Figure 5-2. Distribution of bout lengths as calculated by the IRT cutoff method (cutoffs 1, 2, 4, and 8 s), averaged over groups (mFR1 first and mFR5 first) for mFR1 and mFR5.

### **Estimation of Bout Lengths by IRT Cutoff Method**

The mean bout-length distribution for mFR1 and mFR5 using IRT cutoffs of 1, 2, 4, and 8 s are displayed in Figure 5-2. The shape of the bout length distribution changed considerably, depending on the cutoff used. When the cutoff was 1 s (top panels), bout-length distributions in both conditions appeared approximately geometric with a mode of 1 response per bout. In contrast, when the cutoff was 8 s (bottom panels), bout-length distributions appeared more peaked, with modal lengths longer than 1. Many of the distributions also appear to have multiple peaks, particularly under mFR5. These distributions informed the nomination of candidate bout-length models described in the Modeling Bout *Lengths* section below.

In the next three sections, an alternative approach to characterizing the distribution of bout lengths is described (the aforementioned parameter method). In those sections, response bout model parameters are estimated to generate probable distributions of bout lengths that are then fit to models of bout length.

### **DBERM Model Selection and Parameter Estimation**

Instead of identifying bouts based on a cut-off method, BERM (Equation 5-1) determines the probability that each IRT is either within- or between-bouts based on characteristics of the entire population of IRTs. When the average IRT lengthens over the course a session, the dynamic version of BERM, DBERM, may be fit to the data to account for changes in the distribution of IRTs (Cheung et al., 2012). For all analyzed sessions ( $N = 100$ ), the mean median IRT in the first half of each session was 0.55 s (SEM = 0.037), whereas the mean median IRT within the second half of each session was

4.87 s (SEM = 1.76). This within-session lengthening of median IRTs supported the implementation of DBERM.

According to DBERM, at time  $t$  since the beginning of a session, the mean within-bout IRT, the mean between-bout IRT, and the proportion of IRTs sampled from the within-bout distribution are, respectively,  $1/(w_t + \delta)$ , and  $1/(b_t + \delta)$  and  $p_t$ ,

$$\Pr(IRT_t = \tau | \tau < \delta) = 0$$

$$\Pr(IRT_t = \tau | \tau \geq \delta) = p_t w_t e^{-w_t(\tau-\delta)} + (1 - p_t) b_t e^{-b_t(\tau-\delta)}.$$

$$\min(\text{IRT}) \geq \delta > 0; w_t \geq b_t > 0; 1 \geq p_t \geq 0 \quad (5-2)$$

The mean bout length at time  $t$  is  $1 / (1 - p_t)$ . For computational convenience, the bout-initiating response is not counted as part of the bout; the adjusted mean bout length at time  $t$  is

$$L_t = p_t / (1 - p_t). \quad (5-3)$$

In order to accommodate changes in response rate over the course of a session, DBERM allows the parameters  $L_t$ ,  $w_t$  and  $b_t$  to decay exponentially over time,

$$L_t = L_0 e^{-\gamma t}$$

$$w_t = w_0 e^{-\alpha t}$$

$$b_t = b_0 e^{-\beta t}, \quad L_0, w_0, b_0, \gamma \geq 0; \beta \geq \alpha \geq 0 \quad (5-4)$$

in which  $L_0$  is the adjusted mean bout length when  $t = 0$  s,  $1/(w_0 + \delta)$  and  $1/(b_0 + \delta)$  are the mean within- and between-bout IRTs when  $t = 0$  s, and  $\gamma$ ,  $\alpha$ , and  $\beta$  are the decay rates of  $L_0$ ,  $w_0$ , and  $b_0$ . In order to determine whether all decay parameters were justified, a series of nested DBERM models were fit to the data (Table 5-1). Each of these models



allowed some of parameters to vary freely while others were fixed at zero. Each model was fit to each individual subject's aggregated IRTs in the last five sessions of each condition (mFR1 and mFR5).

A more general version of BERM is a mixture model of two gamma distributions (Smith et al., 2014),

$$\Pr(IRT = \tau) = p_t \Gamma(h_w, \theta_w) + (1 - p_t) \Gamma(h_b, \theta_b).$$

$$h_w, h_b \geq 1; \theta_w, \theta_b > 0; h_b \theta_b > h_w \theta_w; 1 \geq p \geq 0 \quad (5-5)$$

This bi-gamma model was also compared against DBERM as an account of IRT distributions.

In this model,  $\Gamma$  is the probability density function of a gamma distribution, and  $h$  and  $\theta$  are its respective shape and scale parameters for the within ( $h_w, \theta_w$ ) and between ( $h_b, \theta_b$ ) IRTs. Note that if  $h_w = h_b = 1$ , the bi-gamma model reduces to BERM with  $w = 1/\theta_w$  and  $b = 1/\theta_b$ . The full version of Equation 5-5 was tested, in which all parameters were estimated freely, as well as a version in which  $h_w = 1$  and a version where  $h_b = 1$ . Note that the gamma distribution ( $\Gamma$ ) is distinct from the bout length decay parameter ( $\gamma$ ).

The nested variations of DBERM and the bi-gamma model were compared using the corrected Akaike information criterion (AICc), a model selection criterion that balances goodness-of-fit against parsimony (Burnham & Anderson, 2002). In AICc,  $k$  is the total number of free parameters,  $n$  is the total number of observations, and  $LL$  is the log likelihood of the model,

$$AICc = 2k - 2LL + \frac{2k(k+1)}{n-k-1}. \quad (5-6)$$

The lower the AICCc, the better the model balances a lower number of free parameters with a higher likelihood. The  $\Delta\text{AICc}$  of a model is the difference in AICc between that model and the model with the lowest AICc.

Table 5-1 shows the AICc values for all candidate models. For both mFR1 and mFR5, bi-gamma models had very high AICc, and were thus no further considered. AICc selected DBERM (Equation 5-2) with  $\gamma$  constrained to 0 and all other parameters allowed to vary freely for both mFR1 and mFR5. The selected variation of DBERM assumes IRTs were bi-exponentially distributed, and the within-session decline in IRTs was mainly due to changes in within-bout and bout initiation rates, not due to changes in bout length.

To additionally confirm the validity of the selected model, its predictions were plotted against the observed distribution of IRTs, as displayed in the log-survival plots of Figure 5-3. The figures show that, in general, the model predicts the empirical distribution of IRTs, although there are some noticeable deviations to the fit of lower, between bout limb, which roughly comprises the longest 10% of IRTs. The estimated model parameters for individual subjects in mFR1 and mFR5 are displayed in Table H-1 in Appendix H. Estimates of  $L_0$  and  $w_0$  suggest that rats produced, on average, more and somewhat faster responses per bout at the onset of mFR5 sessions than at the onset of mFR1 sessions. These findings are consistent with prior reports (Brackney et al., 2011). The interval between these within-bout responses ( $1/w_0 + \delta$ ) increased on average by 45% throughout the session. The mean interval between bouts ( $1/b_0 + \delta$ ) was about 5.8 s in both conditions, increasing to  $1/b_{3600} + \delta = 10.9$  s and 13.9 s by the end of mFR1 and mFR5 sessions, respectively.

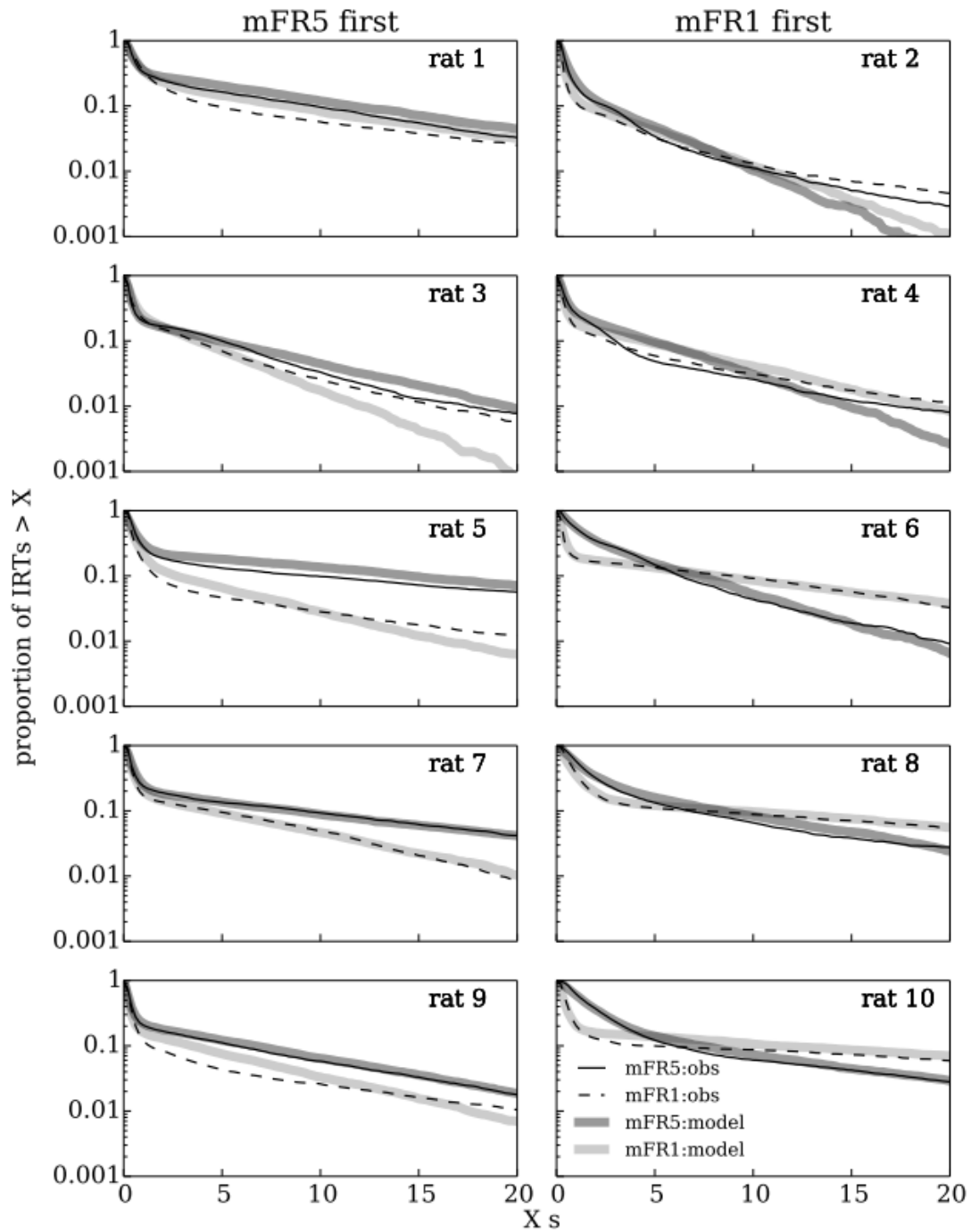


Figure 5-3. Log-survival plots for mFR1 and mFR5 from observed IRTs (obs) and of IRTs predicted by DBERM (model). Model traces have been bolded to help distinguish them from the observed data curves, but the width of the bolding carries no additional significance.

Table 5-1.  
*Comparison of bout model variations.*

Model	$k$	mFR1 ( $n = 71142$ )			mFR5 ( $n = 95085$ )		
		AICc	LL	$\Delta$ AICc	AICc	LL	$\Delta$ AICc
<b>DBERM</b>							
$w_0, b_0, p_0$	30	33746	-16843	1768	26053	-11259	8146
$w_0, b_0, p_0, \delta$	40	32081	-16001	103	19102	-9448	1196
$w_0, b_0, p_0, \delta, \beta$	60	32069	-15974	91	18831	-9325	924
$w_0, b_0, p_0, \delta, \alpha, \beta$	60	31978	-15929	0	17907	-8953	0
$w_0, b_0, p_0, \delta, \alpha, \beta, \gamma$	70	31998	-15929	20	17938	-8949	31
<b>Bi-Gamma</b>							
$h_b, \theta_w, \theta_b, p$	40	32096	-16008	118	20501	-10132	2594
$h_w, \theta_w, \theta_b, p$	40	32116	-16008	138	20541	-10132	2634
$h_w, h_b, \theta_w, \theta_b, p$	50	33757	-16838	1779	26024	-11233	8117

*Note.* Free parameters are listed for each model; other parameters were fixed at zero, except for  $h_w$  and  $h_b$ , which were fixed at 1. AICc was computed for each model, fitted to individual IRT distributions, according to .  $n$  is the number of IRTs observed;  $k$  is the number of free parameters in each model multiplied by 10, the number of rats. Lower AICc indicates higher likelihood, after correcting for free parameters.  $\Delta$ AICc of model  $j$  is the difference between AICc of model  $j$  and the lowest AICc.

### Estimation of the Distribution of Bout Lengths

Distributions of bout lengths were generated for each rat and experimental condition using Monte Carlo simulations. According to DBERM (Equation 5-2), the probability that an IRT of duration  $\tau$  initiated at time  $t$  since session onset is sampled from the within-bout distribution is

$$\Pr_{within}(\tau, t) = \frac{p_t w_t e^{-w_t(\tau-\delta)}}{p_t w_t e^{-w_t(\tau-\delta)} + (1-p_t) b_t e^{-b_t(\tau-\delta)}}. \quad (5-7)$$

Note that Equation 5-7 is simply the within-bout portion of DBERM's likelihood function over its entire likelihood function (Equation 5-2). In the simulation,  $\Pr_{within}(\tau, t)$  served as the parameter for a Bernoulli trial, the outcome of which classified the IRT as either within- or between-bouts. Bout lengths were then calculated as one plus the number of consecutive within-bout IRTs. Because of the computational time required to

conduct the simulation, and because the probability that an IRT was within-bout was typically either < 20% or > 80%, the simulation was run only 5 times for each rat and condition. The simulation yielded a total of 298597 bouts. Simulated bout-length distributions, averaged over 5 runs, are displayed in Figure 5-4. The output of the simulations served as data for modeling the distribution of bout lengths.

### **Modeling Bout Lengths**

Shull (2001) assumed that bout lengths are the outcome of a Markov chain in which the probability of emitting a within-bout IRT is constant. This process generates geometrically distributed bout lengths; the probability that a bout is  $\lambda$  responses long (where  $\lambda$  includes the bout initiation response, and thus must be an integer greater than or equal to 1) is

$$\Pr(\lambda) = p_{geo}(1 - p_{geo})^{\lambda-1}, \quad 0 \leq p_{geo} \leq 1; \lambda \in \mathbb{N}_1 \quad (5-8)$$

where  $p_{geo}$  is the probability of ending the bout after each response;  $\lambda \in \mathbb{N}_1$  indicates that  $\lambda$  is an integer equal to or greater than 1. This model, henceforth referred to as GEO, assumes that after each response, a Bernoulli trial occurs, the outcome of which determines whether the subject exits the bout. The length of many of the bouts generated by the IRT cutoff method in Figure 5-2 and by some of the simulations reported in Figure 5-4 appear to be consistent with Equation 5-8.

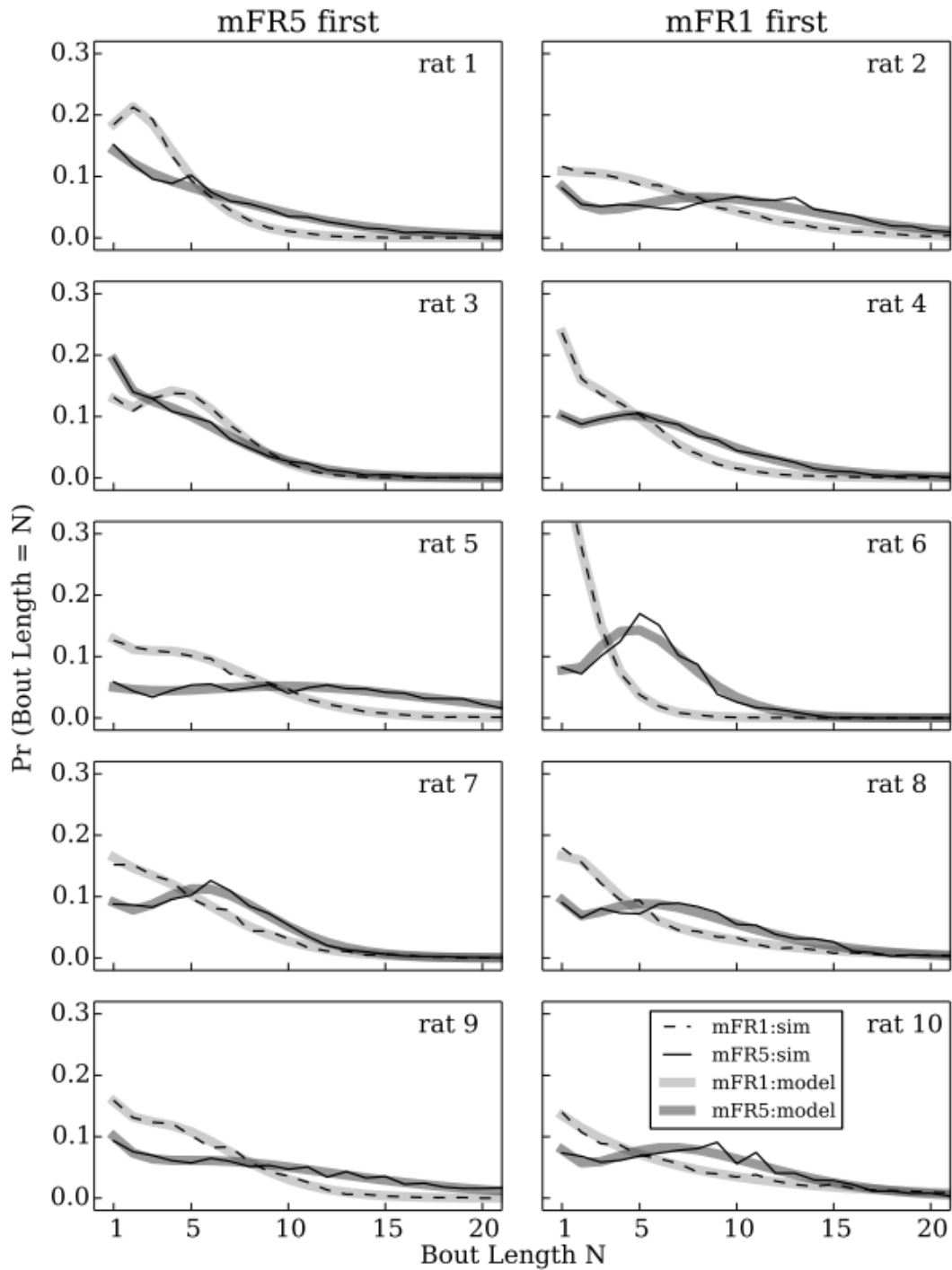


Figure 5-4. Mean bout-length distributions estimations, from 5 runs of a Monte Carlo simulation (sim; Equation 5-6) and predicted by MIX (model; Equation 5-10) for mFR1 and mFR5. The simulation yielded an average of 14930 bouts/rat/condition.

In contrast, many of the bout-length distributions in Figure 5-2 and Figure 5-4 have modes greater than 1. Because all geometric distributions parameterized as Equation 5-8 have a mode of 1 (see Appendix J), these distributions are inconsistent with the assumptions of GEO. A generalization of geometric distribution that accommodates these divergences in the data is the negative binomial distribution. A second model was devised, henceforth NB,

$$\Pr(\lambda) = \binom{\lambda + r - 2}{\lambda - 1} p_{nb}^r (1 - p_{nb})^{\lambda-1} . \quad 0 \leq p_{nb} \leq 1; r, \lambda \in \mathbb{N}_1 \quad (5-9)$$

The middle parenthetical expression is the binomial coefficient. Whereas GEO assumes that exiting a bout results from the failure of a single Bernoulli trial, NB requires  $r$  failed Bernoulli trials, each with failure probability  $p_{nb}$ , to exit the bout. When  $r$  is 1, NB reduces to GEO. Appendix J expands upon the rationale and background of the GEO and NB and explains Equations 5-8, 5-9, and 5-10 in even greater detail.

Many of the distributions in Figure 5-2 and Figure 5-4 appear to be bimodal, with one peak at 1 response and another peak at a bout length greater than 1. To account for these observations, a mixture of GEO and NB (MIX),

$$\Pr(\lambda) = (1 - \omega)[p_{geo}(1 - p_{geo})^{\lambda-1}] + \omega \left[ \binom{\lambda + r - 2}{\lambda - 2} p_{nb}^r (1 - p_{nb})^{\lambda-1} \right], \quad 0 \leq p_{nb}, p_{geo}, \omega \leq 1; r, \lambda \in \mathbb{N}_1 \quad (5-10)$$

was developed as a third model of bout lengths. In MIX,  $\omega$  is the weighting parameter that specifies the proportion of bout lengths sampled from the NB;  $1 - \omega$  is the proportion of bout lengths sampled from the GEO. Figure 5-5 represents the MIX model and each of its components as a flow chart.

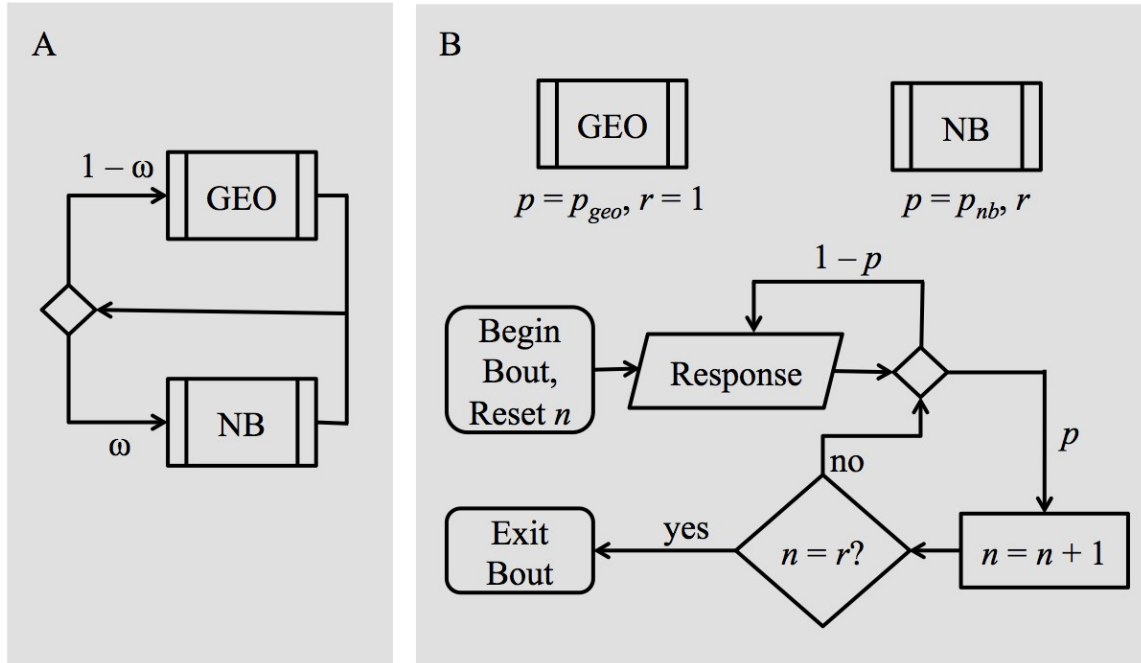


Figure 5-5. Flow-chart representation of the MIX model (Equation 5-10). (A) The model repeatedly chooses between subroutines GEO (Equation 8) with probability  $1 - \omega$ , and NB (Equation 9) with probability  $\omega$ . (B) Subroutines GEO and NB have similar structure, but different parameters. Both begin a bout with a response, followed by a Bernoulli trial. With probability  $p$  ( $p = p_{geo}$  in GEO;  $p = p_{nb}$  in NB), counter  $n$  increases; if  $n = r$  ( $r = 1$  in GEO,  $r \geq 1$  in NB), the bout is exited; otherwise, another Bernoulli trial is conducted. With probability  $1 - p$ , a response is produced followed by another Bernoulli trial.

GEO, NB, and MIX (Equations 5-8, 5-9, and 5-10, respectively) were fit to the aggregate distribution of simulated bout lengths of each individual rat (Figure 5-4) using MLE. Selection among these three models was conducted using AICc (Equation 5-6). Table 5-2 shows that MIX was a substantially more likely model than either one of the alternative models. Figure 5-4 displays the distribution of bout lengths estimated by the MIX model for each rat in each condition overlaid over the mean bout length simulations. Overall, the predicted distribution of bout lengths conforms to the distribution of bout lengths observed from the simulation, without any systematic deviations.



Table 5-2.  
*Comparison of bout-length models.*

Model	mFR1 ( $n = 162144$ )				mFR5 ( $n = 136453$ )		
	$k$	AICc	LL	$\Delta$ AIC	AICc	LL	$\Delta$ AIC
GEO	10	745902	-372940	12370	775784	-387882	24552
NB	20	736586	-368274	3054	759070	-379514	7838
<u>MIX</u>	40	733532	-366726	0	751232	-375576	0

Note. See Table 5-1 for nomenclature.

In order to determine whether training conditions significantly affected the distribution of bout lengths, three separate components of MIX were compared between mFR1 and mFR5: the weighting parameter  $\omega$ , the expected mean of the GEO portion of MIX,

$$\mu_{geo} = \frac{(1-p_{geo})}{p_{geo}}, \quad (5-11)$$

and the expected mean of the NB portion of MIX,

$$\mu_{nb} = \frac{(1-p_{nb})r}{p_{nb}}. \quad (5-12)$$

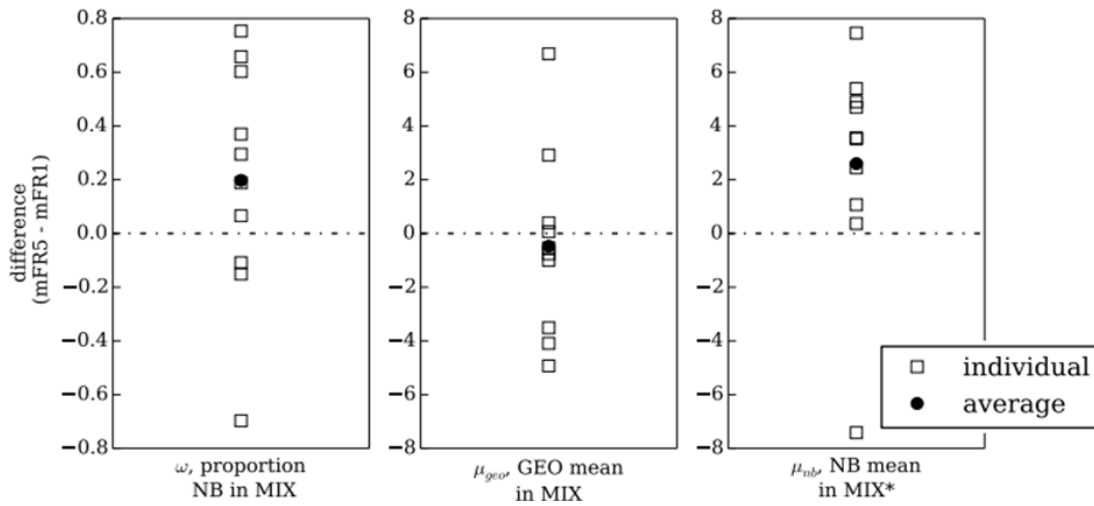


Figure 5-6. Difference in MIX parameter estimates across conditions (mFR5 – mFR1). Squares represent individual differences, circles represents the mean group difference. The “\*” in the x-axis label indicates a significant difference in estimates between mFR1 and mFR5. The dashed lines indicate the expected value if there is no difference between conditions.

Table 5-3 displays estimates of  $\omega$ ,  $\mu_{\text{geo}}$ , and  $\mu_{\text{nb}}$  for each subject and condition. displays, for each rat, the difference in  $\omega$ ,  $\mu_{\text{geo}}$ , and  $\mu_{\text{nb}}$  between mFR5 and mFR1. Condition mFR5 increased  $\omega$  relative to mFR1 for 7 of 10 subjects, and condition mFR5 increased  $\mu_{\text{nb}}$  relative to mFR1 for 9 of 10 subjects. In contrast, there were diverse patterns of change in  $\mu_{\text{geo}}$  between mFR5 and mFR1, with 5 subjects showing an increase in mFR5, 3 showing an increase in mFR1, and 1 subject showing almost no change between conditions. One-tailed Wilcoxon signed rank were conducted to assess whether  $\omega$ ,  $\mu_{\text{geo}}$  and  $\mu_{\text{nb}}$  varied significantly between mFR1 and mFR5. Results indicate that  $\mu_{\text{nb}}$  ( $Z = 1.83$ ,  $p = 0.03$ ) was significantly larger in mFR5 than in mFR1, but there was no significant difference in  $\mu_{\text{geo}}$  ( $Z = -0.92$ ,  $p = 0.82$ ) or  $\omega$  ( $Z = 1.33$ ,  $p = 0.09$ ) between conditions.

Combined, the model fit and parameter estimates indicate that both mFR1 and mFR5 were characterized by two separate populations of response bouts – short GEO-distributed bouts and long NB-distributed bouts. On average, NB bouts were longer and somewhat more frequent in mFR5 than in mFR1.

### **Discussion**

Prior research has shown that operant behavior is organized in bouts, and that mean bout length estimates are proportional to the number of responses required to collect reinforcement (Brackney et al, 2011). These studies, however, did not explicitly examine the shape of the distribution of bout lengths and its sensitivity to response requirements. The purpose of the present study was to examine this parameter of operant performance, which is critical to build a generative models of that postulates behavioral mechanisms responsible for operant learning and performance. A model that assumes that

length of those bouts, would be severely limited.

Table 5-3.  
*MIX model parameter estimates.*

Rat	mFR1			mFR5		
	$\omega$	$\mu_{geo}$	$\mu_{nb}$	$\omega$	$\mu_{geo}$	$\mu_{nb}$
1	0.850	2.076	2.629	0.153	4.987	7.522
2	0.460	4.628	6.486	0.830	1.119	10.042
3	0.811	0.786	4.357	0.702	0.850	4.724
4	0.810	0.251	3.547	0.875	0.650	5.996
5	0.679	1.801	5.794	0.528	8.491	13.253
6	0.318	1.169	1.173	0.921	0.408	4.698
7	0.503	2.448	4.904	0.798	1.449	5.973
8	0.144	5.342	1.607	0.897	0.411	6.999
9	0.626	1.647	5.111	0.814	1.108	9.799
10	0.216	4.905	15.401	0.874	0.813	7.987
Mean	0.542	2.505	5.101	0.739	2.029	7.699
SEM	0.081	0.573	1.270	0.075	0.834	0.850

In the present study, two requirements to collect reinforcement were randomly intermixed within the same session. Sometimes rats were required to emit 1 lever press (tandem VT 150-s FR 1 schedule) after the end of a variable interval; sometimes they were required to emit 5 lever presses (tandem VT 150-s FR 5 schedule). Neither schedule was signaled. Consistent with prior research, as the proportion of FR 5 reinforcement increased, the estimated mean bout length also increased (Brackney et al., 2011).

The estimated mean bout length is, however, not informative of the shape of the distribution of bout lengths. Cursory bout length estimates were established using IRT cutoffs to inform possible bout-length distributions (Figure 5-2), but the use of cutoffs as the sole determinant of bouts has significant limitations (Shull et al., 2002). Due to the probabilistic nature of bouts in a single-operandum study, bout lengths cannot be established deterministically. Instead, expected distributions of bout lengths were estimated on the basis of simulations of DBERM with best-fitting parameters. These

bout-length distributions were best fit by a mixture of geometrically (GEO) and negative-binomially (NB) distributions (MIX model;

Table 5-2). This model suggests that at least two processes govern the generation of response bouts, one that produces short bouts with a mode of 1 response, and one that produces longer bouts with a mode greater than 1. Model estimates suggest that, when a tandem FR 5 requirement was imposed, the long bouts were longer than when a tandem FR 1 requirement was imposed (Figure 5-6).

To further examine the utility of the bout-length mixture model, we reanalyzed the data from Brackney et al. (2011), in which rats were trained to lever press on a VI 120-s and tandem VT 120-s FR 5. Bout-length model selection criteria and parameter estimates are displayed in Appendix K. The MIX model conforms well to the data from Brackney et al. (2011). Estimates of prevalence ( $\omega$ ) and mean ( $\mu_{nb}$ ) of NB-distributed bout lengths from Brackney et al. (2011) are sensitive to FR requirement, similar to the present study. The relation between these variables is more clearly visible when median  $\omega$ ,  $\mu_{geo}$ , and  $\mu_{nb}$  estimates are plotted as a function of the prevalence of FR 5 requirements in the schedule (Figure 5-7). With more frequent tandem FR 5 requirements, the prevalence and mean length of NB bouts tends to increase, whereas the mean length of GEO bouts remains constant and close to 1.6 responses.

The finding that bout lengths are sampled from two separate populations, suggests that bouts of different lengths belong to separate functional response classes. That is, reinforcement of bouts of a particular length seems to differentially strengthen those bouts relative to bouts of other lengths. The hypothesis that reinforcement operates on bouts and not on individual responses is consistent with evidence that bout initiations

increase with rate of reinforcement according to Herrnstein's (1970) hyperbola (Shull, 2011; see also Hill et al., 2012), with evidence that reinforcement operates on responses that precede the one that produces reinforcement (Catania, 1971), and, to some extent, with Killeen's (1994) notion of response-reinforcement coupling. However, one aspect of the present results seems inconsistent with the bout-length-as-response-class hypothesis: If reinforcement of bouts is expressed in a single population of bout lengths centered near the mean of reinforced bout lengths, why would there be two populations of bout lengths when there is only one ratio requirement (1 response in VI 120-s, 5 responses in tandem VT 120-s FR 5)? Determining the origin of bouts that are not explicitly reinforced is a significant obstacle toward explaining the current results. Currently, the information available on the sources of variance in bout length in operant performance is scant. It is yet unclear, for instance, the extent to which variance in bout length is due to variance in the length of bouts reinforced (the same tandem VT FR schedule may deliver reinforcement after bouts of varied length) or due to generalization of reinforcement to bouts of similar length. Controlling these sources of variance in future research may provide a more precise account of the provenance of bouts of various lengths, including those not explicitly reinforced.

The extent to which the MIX model may be more generally applied to other contingencies of reinforcement known to produce bout-like behavior, such as Tandem VT-VR (Shull et al., 2001, 2004) and concurrent VI schedules (T. T. Smith et al., 2014) will require further investigation. For example, Smith and colleagues (2014) provided histograms (Figures 6B, 7B and 8B) of consecutive responses on a single operandum in a concurrent VI VI before changing over to the alternative operandum. The authors argue that this performance is analogous in many respects to response bouts on a single operandum. Their figures show distributions that appear to conform to GEO in some cases and to NB in others, but the merit of neither of these models, nor the MIX model, was quantitatively established.

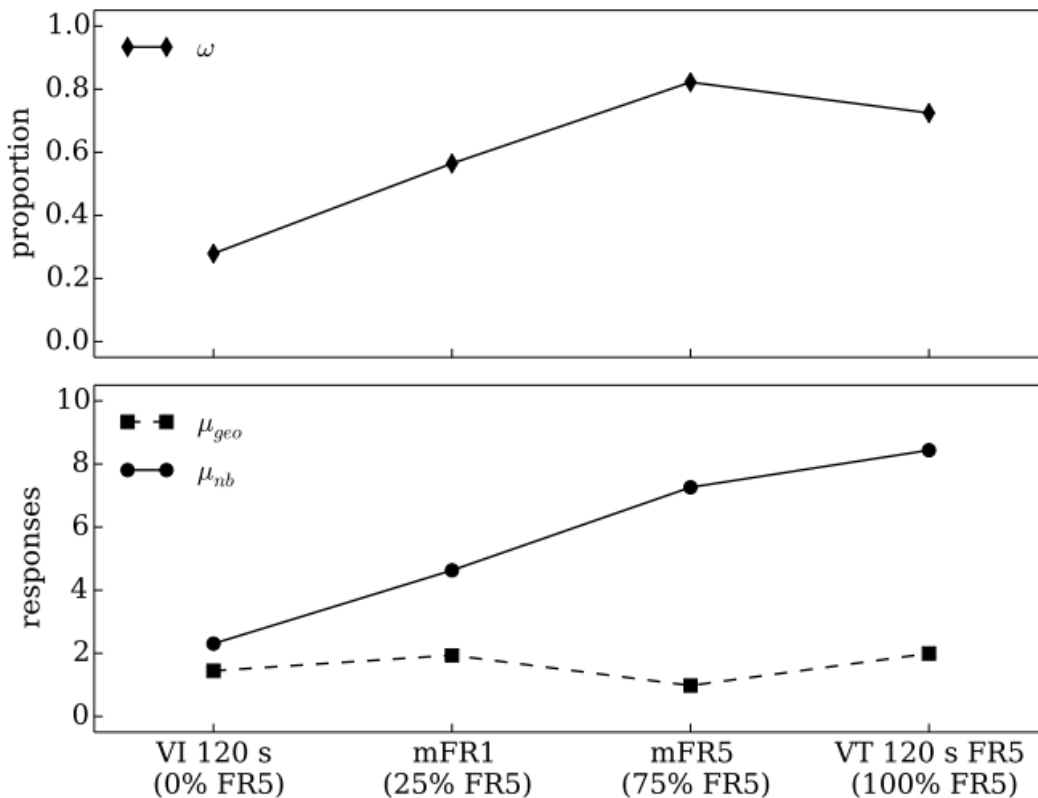


Figure 5-7. Median MIX parameter estimates for VI 120-s and VT 120-s FR 5 (from Brackney et al., 2011) and for mFR1 and mFR5. The percentage of intervals with a tandem FR 5 requirement is noted in the x-axis.

## **Bout Length Estimation Methods**

In this study, we introduce a new, parameter-based method for estimating bout lengths, and contrast its use with the more simple IRT cut-off method. A third method, of intermediate complexity, estimates bout lengths using a more informed cutoff that minimizes classification errors (see Berdoy, 1993, Equation 2). Unfortunately, this method is still too limited, because it does not weigh IRTs based on their probability of being within-bout: an IRT that has a 0.51 probability of being within-bout is weighted in the distribution of bout lengths identically to an IRT that has a 0.99 probability of being within-bout. In contrast, the parameter-based method does not have this limitation.

Another concern related to the estimation of bout lengths is whether their bi-modal distribution is an artifact of DBERM fit to IRTs that change within session. Such artifact is unlikely. First, bi-modal distributions of bout length were also observed using the cut-off method. Second, DBERM does not specify a particular distribution of bout lengths, only the mean bout length  $L_t$ . Finally, if bout lengths were sampled from geometric distributions with parameters varying over the course of the session, the resulting mixture distribution would still have a single mode of 1.

## **Conclusions**

Past research has demonstrated that animals may learn to emit response sequences of a particular length, when such sequences are explicitly reinforced (Evenden & Ko, 2005; Mechner & Guevrekian, 1962), and may even learn to emit two sequences of different length at rates that match their respective rates of reinforcement (Shimp, 1982). The present study extends these findings to response bouts; it suggests that response bouts that emerge from free-operant responding may be shaped by tandem response

requirements. Given that response bouts are visible even at operant level when responding is not explicitly reinforced (Cabrera et al., 2013), it is plausible that, through contiguity, reinforcement selects among bouts of different lengths.



## CHAPTER 6

### ASSESSING OPERANT HYPERACTIVITY IN A RODENT MODEL OF ADHD USING RESPONSE-BOUT MODELING

#### **Abstract**

**Background:** Operant hyperactivity, or the emission of operant responses at an inordinately high rate, has been a frequently observed in children with attention deficit hyperactivity disorder (ADHD) and in a common animal model of ADHD, the spontaneously hypertensive rat (SHR). Prior research used response-bout modeling on the behavioral differences between the SHR and the Wistar-Kyoto (WKY) control strain to identify the core aspects of response bouts potentially responsible for operant hyperactivity in the SHR. This study replicated those performance differences and, based on inferences from response-bout modeling, tested a procedure to attenuate the performance deficits of the SHR.

**Method:** In Experiment 1, SHR and WKY rats were trained extensively on a variable-interval (VI) schedule of reinforcement, and then exposed to a single session of extinction training. In Experiment 2, a new cohort of SHR and WKY rats were again trained on a VI schedule; one SHR group was later trained to depress the lever for at least 0.8 s in order to earn reinforcement. Response bouts were analyzed using the using multiple versions of dynamic bi-exponential refractory model (DBERM) of operant performance. DBERM parameters were estimated using hierarchical Bayesian modeling.

**Results:** Experiments 1 and 2 generally replicated the findings of previous studies that showed that SHRs emit shorter response bouts in VI schedules, but faster within-bout response rates and bout initiation rates than WKYs, and that differences in extinction

performance were primarily due to higher initial bout initiation rates. Furthermore, when SHRs were required to hold the lever down longer during VI training, their performance became more similar to the WKYs, as evidenced by an increase in their bout lengths and a decrease in their within-bout response rates and bout initiation rates.

Conclusions: The operant hyperactivity of SHRs is characterized by short, rapid visits to the lever punctuated by only brief interludes between visits. This hyperactivity can be attenuated by imposing longer response duration requirements, causing visits to become longer, with longer breaks between visits. A change in response-outcome associations may underlie this effect.

## Introduction

Operant learning deficits have been hypothesized to be a core component of attention deficit hyperactivity disorder (ADHD; Luman, Tripp, & Scheres, 2010; Sagvolden, Johansen, Aase, & Russell, 2005). They have been observed in humans with ADHD (Aase & Sagvolden, 2006; Sagvolden et al., 2005) and in a common animal model of ADHD, the spontaneously hypertensive rat (SHR; Brackney et al., 2012; Hill et al., 2012; Johansen et al., 2007; Johansen & Sagvolden, 2005b). When compared to the Wistar-Kyoto (WKY) control strain, the SHR demonstrates deficits in associating responses with reinforcers (Johansen et al., 2007), perseverative responding during extinction learning (Brackney et al., 2012; Johansen & Sagvolden, 2005b), steeper sensitivity to delay of rewards (Hand, Fox, & Reilly, 2010; Sagvolden, Metzger, et al., 1992), and excessive responding at low rates of reinforcement (Hill et al., 2012).

Despite a large body of literature profiling the behavior of the SHR, the causes of their behavioral deficits have not yet been fully determined (Alsop, 2007). Differences in operant learning and performance between rat strains or between experimental conditions are likely multifactorial, and not easily revealed by simple traditional measures (Brackney et al., 2011; Shull, 2011).

Response-bout analyses and their associated models are one set of tools that have proven successful in the determining the sources of variability in operant responding (Brackney et al., 2011; Cheung et al., 2012; Johnson et al., 2009). Under simple schedules of reinforcement, rats typically engage in response bouts—they rapidly press the lever several times before pausing (Brackney et al., 2011; Johnson et al., 2009; Reed, 2011; Shull et al., 2001; Shull, 2011). Four parameters describe the organization of

responses in bouts: the mean number of responses made on the lever before pausing (bout length), how fast the animal responds on the lever (within-bout response rate), how frequently the animal starts a bout (bout initiation rate), and the time taken for an animal to make a single response and prepare for the next response (refractory period).

Sanabria and colleagues (Brackney et al., 2012; Hill et al., 2012) found that, under multiple variable-interval (VI) schedules of food reinforcement, SHRs produce more frequent but shorter bouts of lever presses than WKYs, and that during extinction bouts were gradually shortened for the WKY, but not the SHR. These results conform with previous observations that SHRs are hyperactive in the open field (Hsieh & Yang, 2008; Sagvolden, Metzger, et al., 1992) and have difficulty learning new associations between responses and reinforcer (Johansen et al., 2007; Sagvolden et al., 2005).

The present study aimed at replicating and extending the findings of Hill et al. (2012) and Brackney et al. (2012). In Experiment 1, SHR and WKYs were trained to lever-press on a VI schedule of reinforcement. To assess response-bout parameters, the Dynamic Bi-Exponential refractory model (DBERM) of response bouts was fit using a Bayesian Hierarchical Analysis (BHA). In general, the results confirmed previous findings that SHRs engage in more bouts and respond faster than WKYs during VI training and extinction. Experiment 2 attempted to reduce these strain differences by requiring SHRs to hold down the lever longer to obtain reinforcement. After the SHRs were trained to hold down the lever, their performance became more similar to the performance of WKYs.

## Method Experiment 1

### Subjects

Sixteen male SHR (Charles River Laboratories, US) and 16 male WKY (Harlan Laboratories, US). All subjects were pair-housed with a 12:12 h reverse light cycle (dark from 7 AM to 7 PM). Subjects arrived at the facility on post-natal day (PND) 24. Rats were fed *ad libitum* until PND 36. *Ad libitum* food availability was gradually reduced from 9 h of access on PND 37 to 1 h of access by PND 40. Throughout the rest of the experiment, subjects only had *ad libitum* access to food for 1 h per d, starting 30 min after the end of the experimental session.

### Apparatus

Six standard modular MED Associates (St. Alban, VT) operant chambers were used. Each contained two retractable levers that flanked a food delivery aperture used for reinforcement. The operant chambers were the same as those used in previous SHR studies from our lab (Brackney et al., 2012; Hill et al., 2012). Activation of a liquid dipper delivered 0.01 mL of a sweetened condensed milk (Great Value® brand, Wal-Mart Stores, Inc., Bentonville, AR) and tap water mixture (1/3 milk by volume) to the operant chamber. Operant chamber assignment was counterbalanced across rat strains.

### Procedure

#### Pretraining

Rats were trained to consume the reinforcer and press the lever following the same protocol described Chapters 4 and 5. Prior to the start of the first training session, each rat was given 1 h access to 1 mL of the milk mixture in their homecage for acclimation. On PND 26-28, rats were trained to drink from the liquid dipper in the

operant chamber. On PND 29-30, rats were trained to lever press by pairing the lever presentation with reinforcer delivery. On PND 31, every lever press was reinforced (continuous reinforcement).

### **Variable-Interval Training**

Each variable-interval (VI) session began with a 300-s acclimation period during which no experimental events occurred and the house light remained on. Following the acclimation period, the house light was extinguished and the first trial began. Sessions lasted for either 45 minutes or 18 trials, whichever completed first.

Each VI trial began with the extension of the operative lever. An interval was selected without replacement from a list of 18 intervals generated by a Fleshler-Hoffman distribution (Fleshler & Hoffman, 1962). The first lever press after the selected interval had elapsed was reinforced. Reinforcement consisted of the immediate illumination of the house light and withdrawal of the lever, and the activation of the dipper arm for 3 s after the head-entry IR beam was broken.

On PND 32-36, rats were trained on short VI schedules to familiarize them with the task and prevent early cessation of responding. The mean interval was then increased daily, progressing from 5 s, to 15 s, 30 s, and 60 s. On PND 37, subjects began training on VI 120 s, and remained on that schedule for 41 more days.

### **Extinction**

On PND 79, rats were exposed to a single extinction session (EXT). During EXT, the lever was extended and the house light extinguished after the 300-s acclimation

period, but responding was not reinforced. The lever remained extended without any experimental events occurring for the remaining 40 minutes of the session.

### **Data Analysis**

In order to compare results with Hill et al. (2012) and Brackney et al. (2012), VI training was analyzed over two epochs. Epoch 1 was PND 49-53 and Epoch 2 PND 74-78.

ANOVAs were conducted using IBM SPSS Statistics® v. 22 software. Response rates and reinforcement rates during VI training were analyzed with a  $2 \times 2$  mixed ANOVA with strain (SHR vs. WKY) as the between-subjects factor and epoch (Epoch 1 vs. Epoch 2) as within-subjects factor. Response and reinforcement rates were calculated daily as number of responses and reinforcers emitted divided by the total time during which the lever was extended minus the post-reinforcement pauses (PRPs, the time between the reinforcer ending and the first subsequent response). The individual rats' log median response and reinforcement rates over the five days of each epoch served as dependent variables.

During EXT, the session (after the acclimation period) was broken in eight 5-min bins. An  $8 \times 2$  (bin  $\times$  strain) mixed ANOVA was conducted on log response rates. When appropriate, follow-up post-hoc analyses to the ANOVAs were conducted using Tukey's HSD, and reported when  $p \leq 0.05$ .

### **Model**

DBERM (Brackney et al., 2012, 2011; Cheung et al., 2012) was fit each to inter-response times (IRTs, intervals between consecutive responses without an intervening

reinforcer) in Epochs 1, Epoch 2, and extinction EXT to identify the source of differences in response rates between the SHRs and WKYs' response rates. Cumulative evidence, such as log-survivor analyses, indicate that operant response bouts are often a mixture of two distinct probability distributions; an exponential distribution that explains the within-bout IRTs and another that explains the between bouts IRTs (Brackney et al., 2011; Johnson et al., 2009; Kessel & Lucke, 2008; Shull et al., 2001; Shull, 2011). To describe these IRTs, and how they may change over the course of an experimental session, Sanabria and colleagues (Brackney et al., 2012, 2011; Cheung et al., 2012) developed DBERM, which assumes that free-operant responses are organized in bouts that are governed by four separate parameters: the average bout length,  $L_t$ ; the within-bout response rate;  $w_t$ , the bout initiation rate,  $b_t$ , and the refractory period,  $\delta$ , which describes the minimum amount of time between two responses.  $L$ ,  $w$ , and  $b$  are allowed to change over the course of the session, with their values at time  $t$  represented by  $L_t$ ,  $w_t$ , and  $b_t$ .

$$\Pr(IRT_t = \tau | \tau < \delta) = 0$$

$$\Pr(IRT_t = \tau | \tau \geq \delta) = p_t w_t e^{-w_t(\tau-\delta)} + (1 - p_t) b_t e^{-b_t(\tau-\delta)}.$$

$$\min(\text{IRT}) \geq \delta > 0; w_t \geq b_t > 0; 1 \geq p_t \geq 0 \quad (6-1)$$

Parameter  $p_t$  is the weighting parameter of the mixture distribution, which may be used to compute the average bout length (excluding the bout initiation response),  $L_t$ ,

$$p_t = L_t / (L_t + 1). \quad (6-2)$$

Parameters  $L_t$ ,  $w_t$ ,  $b_t$  are allowed to decline in order to account for within session declines in response rate. At each time point,  $t$ , they decay according to,



$$L_t = L_0 e^{-\gamma t}$$

$$w_t = (w_0 - \Omega) e^{-\alpha t} + \Omega$$

$$b_t = (b_0 - \Omega) e^{-\beta t} + \Omega, \quad w_0, b_0, > \Omega \geq 0; L_0, \gamma \geq 0; \beta \geq \alpha \geq 0 \quad (6-1).$$

in which  $L_0$ ,  $w_0$ , and  $b_0$  are the average bout length, within-bout response rate, and bout initiation rate at the beginning of the session, when  $t = 0$ . They will henceforth be referred to as the *baseline parameters*. Parameters  $\gamma$ ,  $\alpha$ , and  $\beta$  are the decay rates of  $L_t$ ,  $w_t$ ,  $b_t$ , respectively, and will henceforth be referred to as the *dynamic parameters*. To ease interpretation, the decay parameters are expressed as half-lives [e.g.,  $H_b = \ln(2) / \beta$ ].

The parameter  $\Omega$  is the asymptotic response rate that  $w$  and  $b$  approach as the session progresses. The refractory period,  $\delta$ , is the minimum amount of time required to depress the lever and recover, and is expressed functionally as a shift in the exponential distribution of within- and between-bout IRTs. Henceforth,  $\delta$  and  $\Omega$  will be referred to the *ancillary parameters*. Overall, there were a total of 8 DBERM parameters for each rat for each condition (3 *baseline*, 3 *dynamic*, 2 *ancillary*).

Parameters were estimated separately for Epoch 1, Epoch 2, and EXT.

### **Bayesian Hierarchical Modeling**

Parameters were estimated using Bayesian Hierarchical modeling (BHA; Cheung et al., 2012; Gelman, 2004; Griffiths, Kemp, & Tenenbaum, 2008; Shiffrin, Lee, Kim, & Wagenmakers, 2008) on the pooled IRTs within each condition. The application of BHA in conjunction with DBERM is described in detail in previous papers (Brackney et al., 2012; Cheung et al., 2012). By imposing a hierarchical structure onto the data, BHA can account for variability between subjects that would not be possible if DBERM were fit to

each subject individually. It simultaneously uses information at both the individual and group level to fit model parameters, permitting robust between-group comparisons of model parameters fit to individual subjects. This hierarchical assumption asserts that the likelihood of individual model parameters is conditional not just to the performance of an individual subject, but also to the performance of all other subjects in the group, attenuating the effects of extreme values or few data points in individual subjects.

For this paper, it was assumed that the DBERM parameters ( $L_0$ ,  $w_0$ , etc.) of individual rats are sampled from a log-normally-distributed population. The mean [ $\mu_{(\theta)}$ ] and standard deviation [ $\sigma_{(\theta)}$ ] of the population govern the group-level distribution of each DBERM parameter  $\theta$ ; differences in  $\mu_{(\theta)}$  across strains determines the size of strain effects on  $\theta$ .

The posterior distributions of the DBERM parameters and their population hyper-parameters were estimated using a Markov Chain Monte Carlo (MCMC) method (Gelman, 2004), programmed in custom-written software in MATLAB (MATLAB and Statistics Toolbox Release 2013a Mathworks, Inc; Natick, MA). To determine if there was a significant difference between strains for a given DBERM parameter,  $par$ , the distribution of differences between strain posterior means [ $\mu_{dif(par)}$ ] was calculated:

$$\mu_{dif(par)} = \mu_{SHR(par)} - \mu_{WKY(par)}. \quad (6-4)$$

A significant strain effect was identified when the 95% credible interval around  $\mu_{dif(\theta)}$  did not include zero. This meant of the sample estimates of  $\mu_{SHR(par)}$  and  $\mu_{WKY(par)}$ , 95% of the  $\mu_{SHR(par)}$  samples were consistently either large or smaller than  $\mu_{WKY(par)}$ .

### **DBERM Simulation**

A posterior-predictive check was conducted to assess DBERM's goodness of fit. Simulations were conducted using DBERM parameters taken from the MCMC samples comprising each subject's posterior distribution of each parameter. The simulation method is described in detail in Brackney et al. (2012). In brief, the simulation used a Monte Carlo method that repeatedly sampled DBERM-distributed IRTs until the sum of all IRTs sampled exceeded the session length of 40 min (excluding the 300-s acclimation period). Specifically, the simulation repeatedly sampled IRTs from one of two exponential distributions with means of  $1/w_t$  and  $1/b_t$ . Before each sample, the simulation conducted a Bernoulli trial with a probability of  $p_t$  (from Equation 6-2). If the Bernoulli trial succeeded, the IRT was sampled from the distribution with the mean  $1/w_t$ , otherwise the IRT was sampled from the distribution with the mean  $1/b_t$ . After each IRT was sampled, the values of  $p_t$ ,  $w_t$  and  $b_t$  were recalculated according to Equation 6-4 to reflect the current time in session. The PRPs of the animals were included in the simulation by inserting pauses into simulation that reflected the actual observed times and lengths of each animal's PRPs. During those pauses, no IRTs could be generated.

For each subject, 1,000 simulations were conducted. The parameters in each simulation were chosen at random without replacement from the MCMC sample of the posterior distribution of DBERM parameters for individual subjects. To calculate response rates, each simulated session was divided into eight equal length bins, and the number of responses within each bin was divided by the bin length. The median of these response rates were then calculated for each animal, and the mean calculated for the group.

## Results Experiment 1

### Response and Reinforcement Rates

To visualize the correspondence between the observed response rates and those predicted by the DBERM simulations, sessions were divided into eight equal length bins (5 min each), and response rate was calculated for each bin. Figure 6-1 shows the mean ( $\pm$  SEM) of the individual logged median response rates for each bin of Epoch 1, Epoch 2 and EXT.

To assess whether response rates differed significantly between strains and Epochs 1 and 2, A  $2 \times 2$  (Strain x Epoch) mixed ANOVA was conducted. A significant strain  $\times$  epoch interaction effect,  $F(1, 22) = 20.86, p < .001$ , were detected. Post-hoc analyses indicated that SHRs increased their response rate from Epoch 1 to Epoch 2,  $p < .001$ , but WKYs did not.

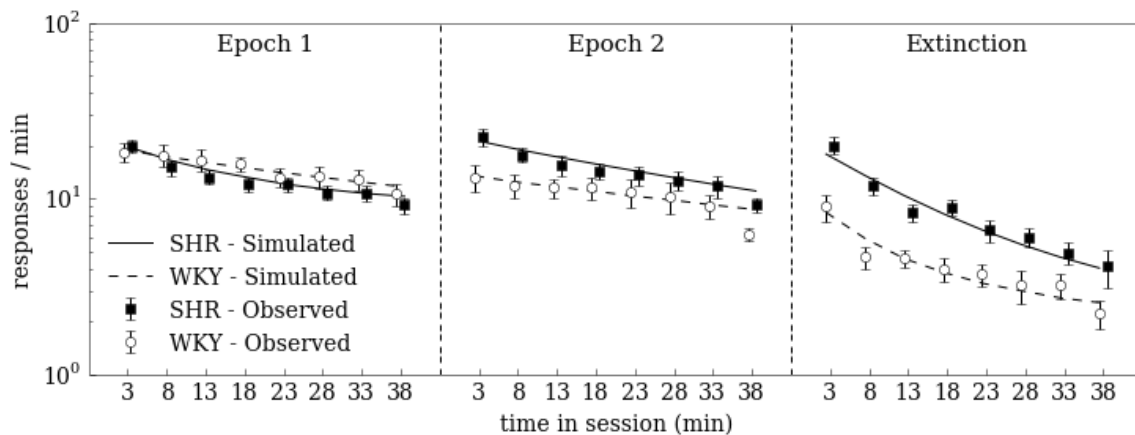


Figure 6-1. Experiment 1 – Group means of individual median response rates during Epoch 1, Epoch 2, and EXT for SHRs and WKYs. The markers indicate the observed response rates, whereas the solid and dashed lines response rates predicted from the DBERM simulation. Error bars represent the standard error of the mean. For comparison with the simulations, sessions were divided into 5 min bins over which response rates were calculated, although ANOVAs were conducted on the medians calculated over the entire session during Epochs 1 and 2.

To assess whether response rates declined during extinction, and whether there was a difference in response rates during EXT between strains, a  $2 \times 8$  mixed-design ANOVA (Strain  $\times$  Bin) was conducted. Significant effects of strain,  $F(1, 22) = 10.80$ ,  $p < .05$ , and bin,  $F(7, 154) = 43.36$ ,  $p < .001$ , were observed on response rates. The strain effect indicates that SHRs responded more than WKYs during EXT.

Similar ANOVAs were conducted on the same factors to assess differences in reinforcement rate, but no differences were found for Epochs 1 or 2.

### **Model Parameters**

DBERM was fit to 58,251, 53,428, and 6,306 individual IRTs for Epoch 1, Epoch 2, and EXT, respectively. Whereas BHA estimated logged parameters, they were back-transformed to the linear scale to ease interpretation;  $\mu_\theta$  on the log scale is the median of parameter  $\theta$  on the linear scale. The medians and 95% credible intervals (CI) of the *baseline* parameters, their half-lives, and the *ancillary* parameters are displayed in Figure 6-2 for each of the three conditions and each rat strain.

In Epoch 1, significant differences between strains were observed for parameters  $L_0$ ,  $w_0$ ,  $b_0$ ,  $HL(w)$ ,  $HL(b)$ , and  $\Omega$ . At the onset of the session, the SHRs engaged in more bouts (higher  $b_0$ ) that were both shorter (lower  $L_0$ ) and contained more responses (higher  $w_0$ ) than those of the WKYs. Moreover, although within-bout response rates declined very slowly [ $HL(w)$  far exceeded the length of the session], they did so more steeply for WKYs than for SHRs. The bout initiation rate decayed faster [lower  $HL(b)$ ] for SHRs than for the WKYs, but it did so to a higher asymptotic rate ( $\Omega$ ).

In Epoch 2, significant differences between strains were observed for parameters  $b_0$ ,  $\delta$ , and  $HL(w)$ . The SHRs engaged in more bouts ( $b_0$ ) than the WKYs, and the SHRs took less time to complete individual responses ( $\delta$ ) than the WKYs. As in Epoch 1,  $HL(w)$  was significantly different between strains, but the calculated half-lives (medians for SHRs = 8,090 min, WKYs = 314 min) indicated that the within-bout response rate did not change appreciably during sessions within Epoch 2.

In EXT, a significant difference between strains was only observed for  $b_0$ , indicating that the SHRs emitted more bouts at the onset of EXT than the WKYs.

In Figure 6-1, the response rates predicted from the estimated DBERM parameters (see *DBERM Simulation* in Methods) are overlaid on the observed response rates. The predicted response rates closely tracked the changes in response rates observed during Epoch 1, Epoch 2, and EXT, thus validating DBERM parameter estimates as reasonable descriptions of the performance of the SHRs and WKYs.

The BHA reached convergence, an indication that sufficient parameter samples were collected, after 30,000, 18,500, and 21,000 MCMC samples were collected for Epoch 1, Epoch 2, and EXT, respectively.

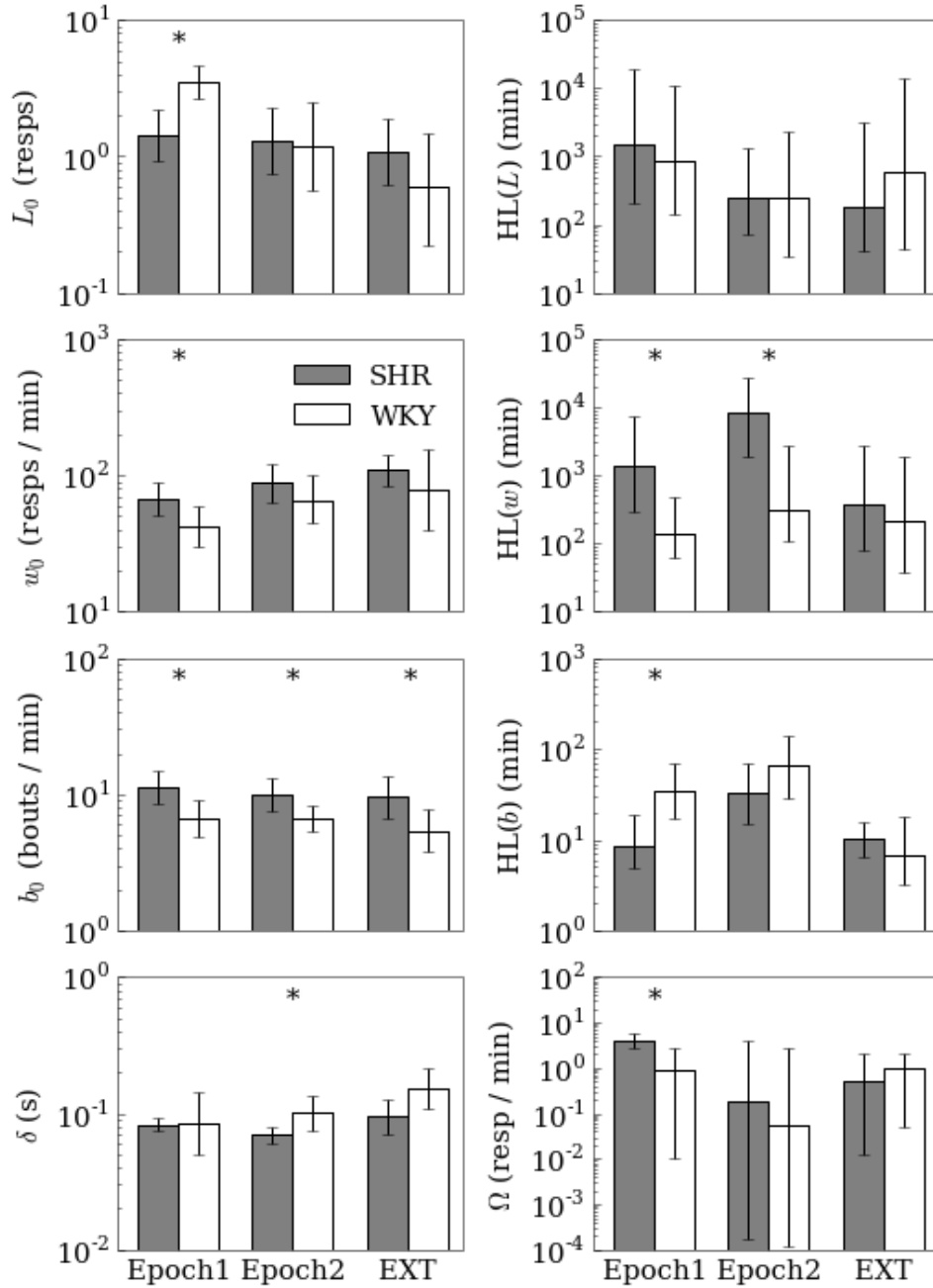


Figure 6-2. Experiment 1 – DBERM parameter estimates for Epoch 1, Epoch 2, and EXT for SHRs and WKYs. Asterisks (\*) indicate significant differences between groups, as determined by the posterior distribution of differences (see *Bayesian Hierarchical Modeling* section of the Methods). Error bars represent the 95% credible intervals.

## **Discussion Experiment 1**

Experiment 1 was a replication and extension of the findings of Hill et al. (2012) and Brackney et al. (2012). Whereas the SHRs and WKYs in those previous studies were trained on multiple variable interval schedules that changed reinforcement rates throughout the session, the subjects in this experiment received prolonged training on only a single VI 120 s.

During Epoch 1, no difference in response rates was observed between strains, similar to Hill et al. (2012). Despite the overall response rate differences, the SHRs engaged in more frequent bouts that were both shorter and faster than the WKYs, also similar to the findings of Hill et al. (2012).

During Epoch 2, SHRs had greater response rates than WKYs, again replicating Hill et al. (2012). An examination of response bout parameters revealed that SHRs engaged in more frequent bouts than the WKYs, which was also found in Hill et al. (2012). However, in Hill et al. (2012), the SHRs also had systematically shorter bouts, which was not replicated here. Regardless of the differences in bout lengths between the two studies, the SHRs still demonstrated greater operant hyperactivity, as evidenced by the increased response rate, which was most likely due to an overall increase in bout initiations.

During EXT of the present study, the SHRs engaged in more frequent bouts at the start of EXT, similar to the results of Brackney et al. (2012). However, in that previous study, bout lengths declined faster for the WKYs than for the SHRs, which was not replicated here.



Multiple factors may have contributed to the differences between the past and present experiments. First, the rats in Hill et al. (2012) and Brackney et al. (2012) had been trained on multiple VI schedules that alternated within each session. In contrast, subjects in the present experiment were trained on a single VI schedule. Second, the response-bout model used in Hill et al. (2012) included neither the *dynamic* nor the *ancillary* parameters of DBERM, which allow a much more accurate characterization of response bouts. Third, Hill et al. (2012) and Brackney et al. (2012) only had six subjects per strain, making inferences on population parameters more susceptible to potential outliers. Fourth, Hill et al. (2012) fit their model to each subject individually using maximum likelihood estimations. In contrast, the current study and Brackney et al. (2012) used a Bayesian Hierarchical framework, which uses information from all subjects to estimate each individual subjects parameters, and further reduces the effect of potential outliers.

## **Experiment 2**

Experiment 1 found that in Epoch 1, SHRs, compared to the WKYs, engaged in more frequent and shorter bouts that contained more responses. In Epoch 2, the SHRs, compared to the WKYs, engaged in more frequent response bouts and took less time to emit individual responses (the refractory period) than the WKYs. Chapter 5 found that increasing the minimum duration for an effective lever press (i.e., increasing the effective refractory period), decreased the frequency of bouts and the within-bout response rate, and increased the length of bouts. Similarly, Brackney et al. (2011) found that the frequency of bouts could be reduced and the refractory period increased by increasing the work required to lever press. To the extent that these findings generalize to the SHRs

performance, increasing the response duration requirement of the SHRs should effectively attenuate their observed operant hyperactivity: it should reduce the frequency of response bouts and increase their length, yielding a reduced overall response rate.

Experiment 2 trained three groups of rats (two SHR groups and one WKY group) to lever press on a VI schedule, similar to Experiment 1. Lever presses for one group of SHRs (SHR-EXP) were required to be 0.8 s or longer in order to earn reinforcement. The second group of SHRs were trained to lever press as normal, without a duration requirement (SHR-CTR). Differences in performance between SHR groups reflected the effect of response-duration requirement. The WKYs were also trained to lever press as normal (WKY-CTR). This group served as reference: response-duration effects were expected to change SHR bout parameters in the direction of WKY bout parameters.

## **Method Experiment 2**

### **Subjects and Apparatus.**

Thirty-two SHR (Charles River Laboratories, US) and 16 WKY (Harlan Laboratories, US) rats were procured for Experiment 2. All rats were male and experimentally naïve. They were treated identically to the subjects in Experiment 1, except when noted otherwise. The experiment was conducted in 16 operant chambers whose assignment was counterbalanced across groups. The chambers were identical to those used in Experiment 1.

## **Procedure**

Subjects were trained to respond on a VI 120 s, as in Experiment 1. In addition, each lever press was signaled by a 0.5 s flash of three LED lights positioned on the wall 2 cm above the lever.

On PND 55, subjects were assigned to their experimental conditions. Sixteen SHRs were assigned to the 0.8-s response duration treatment condition (SHR-EXP). In that condition, a response was only signaled once the lever had been depressed for 0.8 s. Only signaled lever presses could trigger reinforcement.

The WKYs and the remaining SHRs continued to train on the VI 120 s without any change in experimental contingencies, i.e., a lever press was signaled when a lever depression exceeded 0.0 s. Henceforth, this will be referred to as the CTR condition. In this manner, subjects were organized in 3 groups of  $n = 16$  each: WKY-CTR, SHR-CTR, and SHR-EXP.

SHRs were assigned to their groups by assessing their individual response rates for the last five days prior to PND 55. SHRs were sorted into two groups so that the mean and standard deviation of response rates for both groups was approximately equal.

## **Data Analysis**

To mirror the analysis in Experiment 1, responses were analyzed on PND 74-78. The earlier epoch (PND 49-53) was not analyzed because it occurred before subjects were assigned to their experimental conditions. Median response rates, reinforcement rates, response durations, and interquartile ranges (IQRs) of response durations were

measured for individual subjects. Between-group differences in these measures were assessed using ANOVAs conducted in IBM SPSS v22 (Armonk, NY: IBM Corp).

For rats in the EXP condition, only responses that met or exceeded the duration threshold were analyzed. The BHA was conducted using identical methods as Experiment 1, except where stated otherwise in the results.

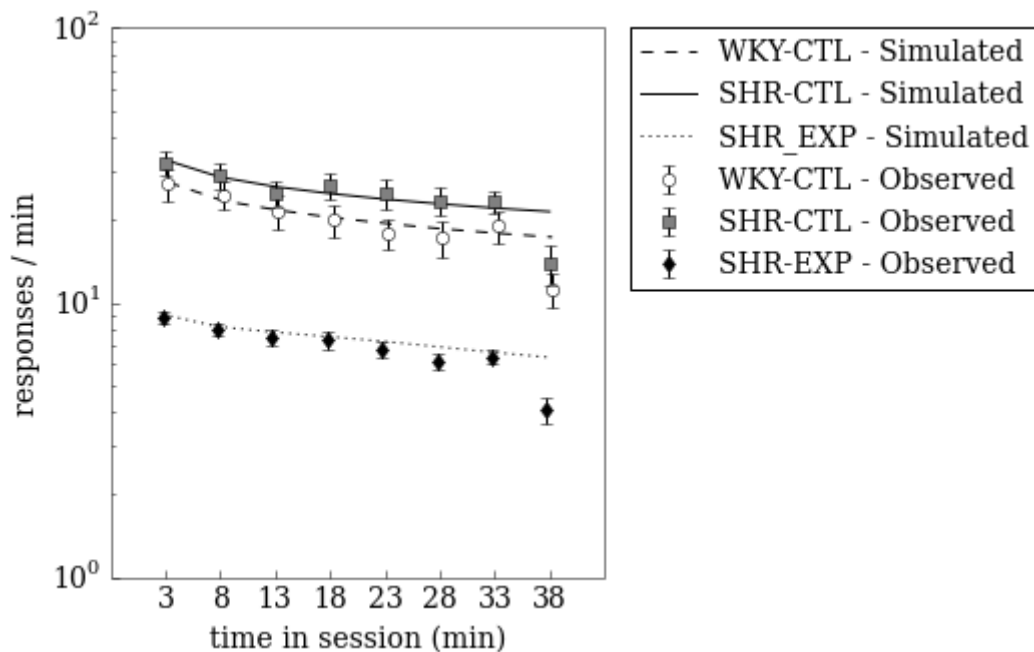


Figure 6-3. Experiment 2 – Group mean of the individual median response rates for WKY-CTL, SHR-CTL, and SHR-EXP during PND 74-78. Error bars represent the standard error of the mean. For comparison with the simulations, sessions were divided into 5 min bins over which response rates were calculated, although ANOVAs were conducted on the medians calculated over the entire session. Simulated response rates are generated from repeated sampling of DGERM.

## Results Experiment 2

### Response and Reinforcement Rate

Figure 6-3 shows the mean (+/- SEM) of the individual log median response rates for each group, divided into 5-min bins. The SHR-EXP group responded at significantly

lower rates than the SHR-CTR and WKY-CTR groups,  $F(2, 45) = 44.18, p < .001$ .

Reinforcement rate did not differ significantly between groups.

### Response Durations

Figure 6-4 shows the mean ( $\pm$  SEM) median and IQR of response durations. Both duration medians and IQRs were greater for SHR-EXP, but there was no significant difference between WKY-CTR and SHR-CTR [median duration:  $F(2, 45) = 68.30, p < .001$ ; IQR:  $F(2, 45) = 46.37, p < .001$ ].

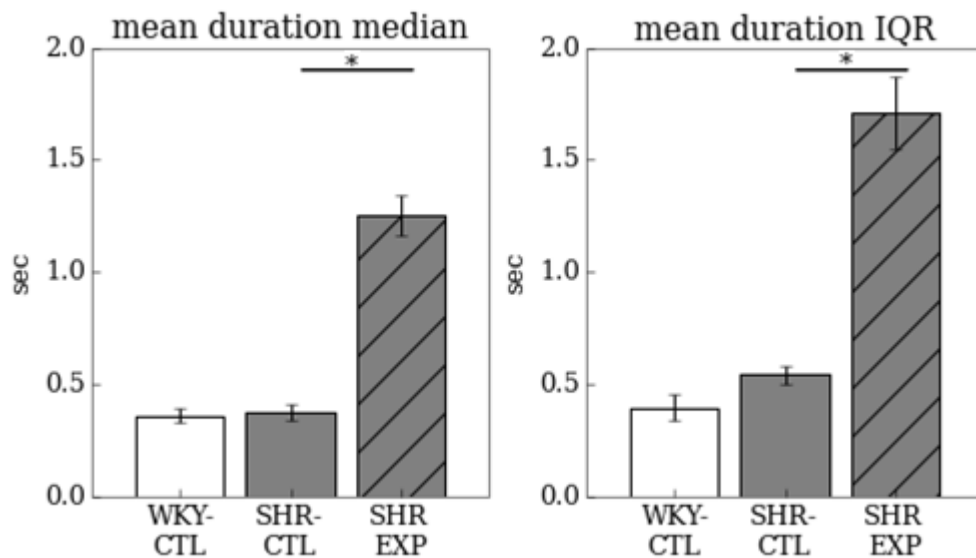


Figure 6-4. Experiment 2 – Group mean of the individual median durations and interquartile ranges (IQR) for WKY-CTL, SHR-CTL, and SHR-EXP during PND 74-78. Asterisks (\*) indicate significant difference ( $p < 0.05$ ) between groups. Error bars represent the standard error of the mean.

### Model Parameters

The IRTs of each group were initially fit to DBERM, as in Experiment 1. Figure 6-5 shows the median and 95% credible intervals (CI) of the *baseline* parameters, their half-lives, and the *ancillary* parameters of each group. The study was concerned with two

primary comparisons. First, parameter estimates from the SHR-CTR and WKY-CTR groups were compared to ensure replication of Experiment 1. Second, parameter estimates from the SHR-CTR and SHR-EXP groups were compared to verify whether the response-duration requirement reversed the effects of strain.

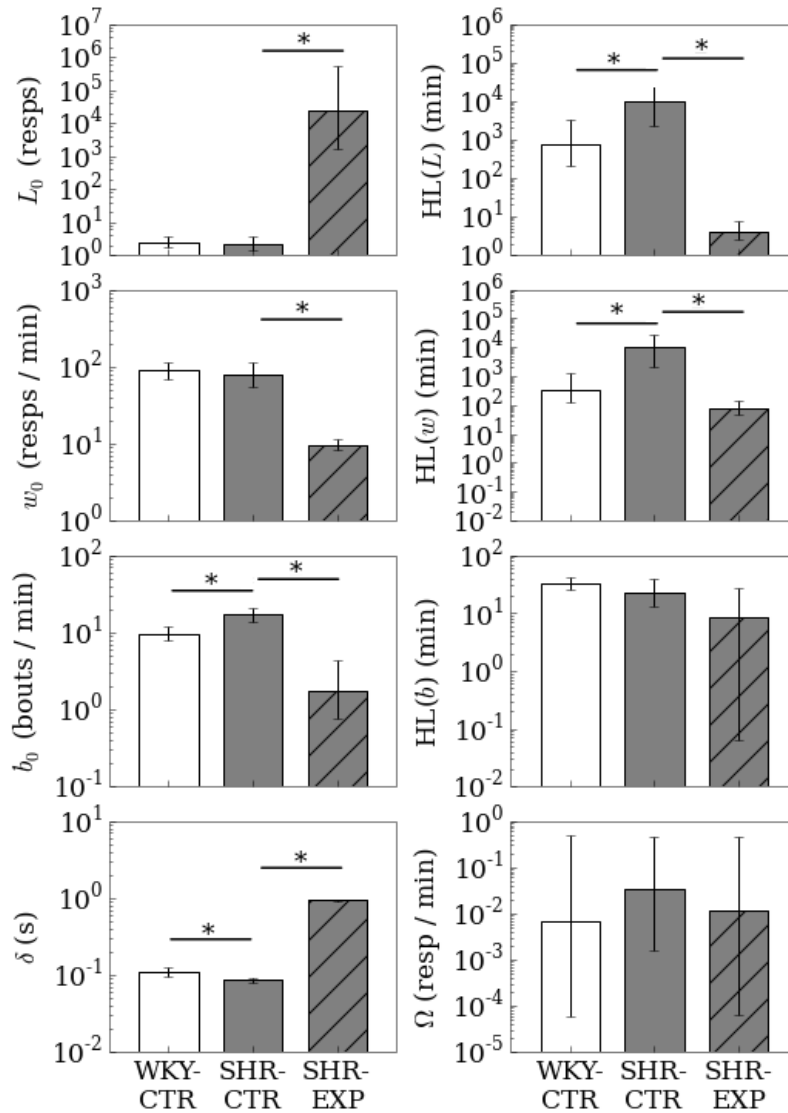


Figure 6-5. Experiment 2 – DBERM parameter estimates for WKY-CTR, SHR-CTR, and SHR-EXP. Asterisks (\*) indicate significant differences between groups, as determined by the posterior distribution of differences. Error bars represent the 95% credible intervals.

A comparison of SHR-CTR vs. WKY-CTR generally replicated the findings of Experiment 1 (Epoch 2). Significant differences between SHR-CTR and WKY-CTR were again observed in  $b_0$ ,  $\delta$ , and  $HL(w)$ , in addition to a significance difference in  $HL(L)$ . The SHR-CTR group engaged in more bouts ( $b_0$ ) than the WKY-CTR group, and the SHR-CTR had a lower refractory period ( $\delta$ ) than the WKY-CTR group. Whereas significant differences in half-lives of both  $L$  and  $w$  were observed, the half-lives were again generally too long (medians  $> 500$  min) to have an appreciable effect on responding.

A comparison of SHR-CTR vs. SHR-EXP indicated a significance difference in  $L_0$ ,  $w_0$ ,  $b_0$ ,  $\delta$ ,  $HL(L)$ , and  $HL(w)$ . When the SHRs were required to depress the lever for 0.8 s, the estimated initial bout length ( $L_0$ ) increased by 10,000 fold, indicating that more than 99.99% of responses were “within-bout” according Equations 6-2 and 6-3. Although estimates of  $HL(L)$  were considerably lower, the high initial values meant that by the half-life, more than 99.99% of response were still within bout.

As an additional check to ensure that DBERM was an appropriate model for the IRTs in Experiment 2, IRT histograms were visually examined for each group (Figure 6-6). The IRTs of SHR-CTR and WKY-CTR appeared approximately bi exponential, as suggested by a general monotonic decrease in the probability of IRTs with a negative concave slope and a long right-ward tail. In contrast, the frequency of IRTs in the SHR-EXP group had a single distinct mode appreciably greater than zero, indicating that the IRTs were not bi exponentially distributed.

Smith and colleagues (T. T. Smith et al., 2014) demonstrated that for some IRT distributions with multiple modes greater than 0 s, a mixture of gamma distributions can adequately account for the data. Given that SHR-EXP's IRTs contained only a single mode within the range of what could reasonably be expected to be that of within-bout IRTs, the following model was postulated:

$$\Pr(IRT_t = \tau | \tau \geq \delta) = p_t \Gamma(\tau; k, \theta) + (1 - p_t) b_t e^{-b_t(\tau - \delta)}$$

$$\min(\text{IRT}) \geq \delta > 0; 1/(k\theta) \geq b_t > 0; \theta > 0; k \geq 1; 1 \geq p_t \geq 0 \quad (6-5).$$

Henceforth, Equation 6-5 will be referred to as the dynamic gamma exponential refractory model (DGERM). DGERM is a modification of Equation 6-1, wherein the between-bout IRTs are described using an identical form to DBERM (Equations 6-1, 6-2, and 6-3), but the exponential distribution of within-bout IRTs has been replaced with a gamma distribution. In Equation 6-5,  $\Gamma$  is the gamma probability density function with shape parameter  $k$  and scale parameter  $\theta$ . Note that  $\Gamma$  is not the bout length decay parameter,  $\gamma$ . When  $k = 1$ , the gamma distribution reduces to an exponential distribution with a rate parameter of  $1/\theta$ .

In comparison to DBERM, DGERM does not contain a within-bout response rate decay ( $\alpha$  in Equation 6-2) or a shift in the distribution of within-bout IRTs by  $\delta$ . The parameter  $\alpha$  was excluded because previous estimates were considered to have a negligible effect on the distribution of IRTs, and because the parameterization of within-bout response rate decay for a gamma distribution has yet to be determined. The parameter  $\delta$  was excluded from the within-bout distribution calculations because the probability of an IRT = 0 s is zero when  $k > 1$ . When a the refractory period,  $\delta$ , is



subtracted from an observed IRT,  $\tau$ , then  $\tau - \delta$  may equal 0. When this occurs, the log-likelihood of any gamma model with  $k > 1$  becomes negative infinity, and all IRTs =  $\delta$  are estimated to be impossible to observe, which is clearly not the case.

To compare the response-bout parameters of the SHR-EXP group against SHR-CTR, Equation 6-5 was fit to the IRTs of all three groups using BHA in a manner otherwise identical to the DBERM fits. The BHA reached convergence after 31,497 samples for DBERM, and 12,000 samples for DGERM.

Figure 6-7 shows the new DGERM parameter estimates. The mean within-bout IRT estimated by the gamma distribution is  $k\theta$ , meaning that the within-bout response rate is  $1/k\theta$ . However, the within-bout IRTs in DGERM are not shifted by  $\delta$ , as they are in DBERM. In order to calculate a post-hoc within-bout responses rate ( $w_{\Gamma}$ ) that is more comparable with DBERM's, the estimated DGERM mean within-bout IRT ( $k\theta$ ) was shifted by  $\delta$ :

$$w_{\Gamma} = \frac{1}{k\theta - \delta}. \quad (6-6)$$

Using DGERM, SHR-CTR had significantly shorter estimates of  $\delta$  than WKY-CTR. Estimates of  $HL(L)$  were also significantly greater for SHR-CTR than WKY-CTR, but not meaningfully so, as the mean bout length declined over the course of the session by less than 0.1 responses per bout in both groups.

In contrast, significant differences between SHR-CTR and SHR-EXP were found between all DGERM parameters, except  $L_0$ . SHR-EXP demonstrated both slower initial bout initiation rates ( $b_0$ ) and within-bout response rates ( $w_{\Gamma}$ ). Notably, estimates of  $w_{\Gamma}$  are approximately equal to estimates of  $w_0$  for DBERM. Although significant treatment

effects were not observed on estimates of  $L_0$ , these estimates for the SHR-EXP group decreased from an excess of 1,000 responses in DBERM to a more reasonable median of 1.8 responses in DGERM.

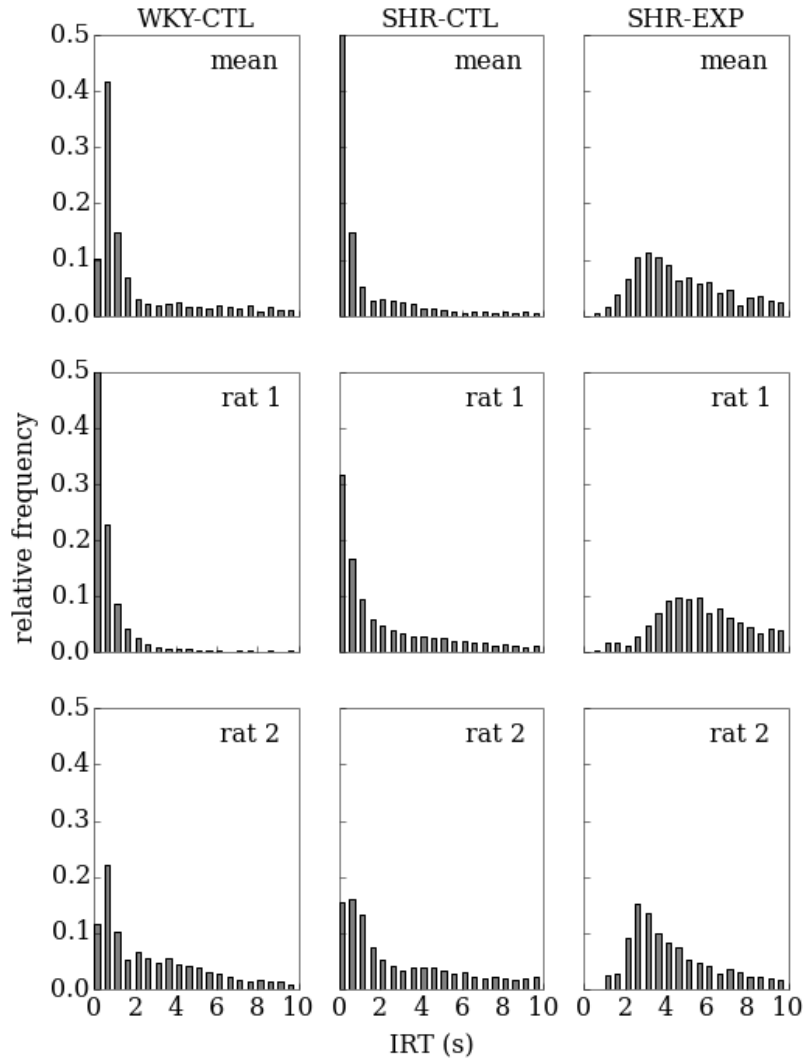


Figure 6-6. Experiment 2 – Histograms of mean IRTs and individual-examples for WKY-CTR, SHR-CTR, and SHR-EXP. Bin size = 0.5 s. The IRT distributions for WKY-CTR and SHR-CTR groups appear generally consistent with a bi-exponential distribution as evidenced by the left-most mode and negatively accelerating decrease in longer IRTs. Although some of the CTL animals appear to have short modes  $> 0$ , this is primarily because the displayed IRTs are not shifted by the refractory period. In contrast, the IRTs of SHR-EXP are non-monotonic, suggesting that an alternative model such as DGERM may be more appropriate.

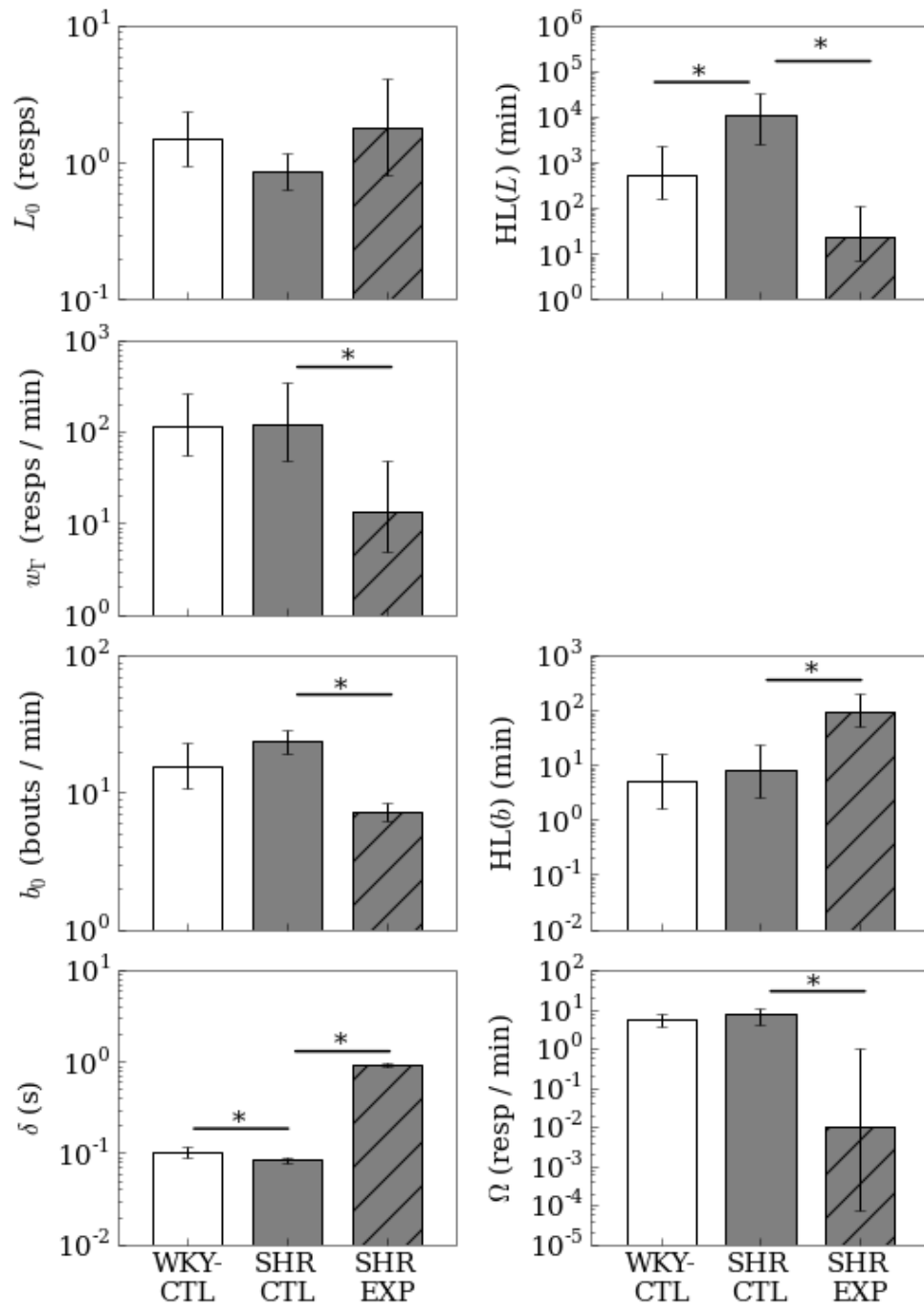


Figure 6-7. Experiment 2 - DGERM parameter estimates for WKY-CTL, SHR-EXP, SHR-EXP. Asterisks (\*) indicate significant differences between groups, as determined by the posterior distribution of mean differences. Error bars represent the 95% credible intervals. The  $HL(w)$  is absent because the  $w$  decay parameter was not part of the DGERM.

Bout-length half lives [HL( $L$ )] were also shorter for the SHR-EXP group, with median half-lives at approximately 10 min for the SHR-EXP group, in comparison to 4682 min for the SHR-CTR group. Conversely, the median half-life of the bout initiation rate [HL( $b$ )] was 3.4 min for SHR-CTR group, compared to 39 min for the SHR-EXP group, indicating that bout initiation rates decreased more rapidly for the SHR-CTR group. The asymptotic response rate ( $\Omega$ ), was also lower for the SHR-EXP group than the SHR-CTR group.

In Figure 6-3, the response rates predicted from the estimated DGERM parameters are overlaid on the observed response rates. The predicted response rates were generated using Monte Carlo simulations, as in Experiment 1, but within-bout IRTs were sampled from a gamma instead of exponential distribution in accordance with Figure 6-5. The predicted response rates closely tracked the changes in response rates observed for each group for all but the final bin.<sup>8</sup>

## Discussion Experiment 2

Experiment 2 asked whether the operant hyperactivity of the SHRs could be reduced by imposing a duration requirement upon their operant responding. To examine this question, one group of SHRs (SHR-CTR) and one group of WKYs (WKY-CTR) were trained to respond typically on a VI schedule, while a third group of SHRs (SHR-EXP) were trained to depress the lever for 0.8 s or more in order to earn reinforcement on the same VI schedule. Experiment 2 was designed for two critical comparisons: WKY-

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<sup>8</sup> Notably similar, if smaller, deviation occurred in Epoch 2 of Experiment 1 as well, but not in Epoch 1 or EXT. Similarly, the WKYs in Chapter 3 (Figure 3-1) showed low bin 8 deviations from the predicted response rates in some phases, but the LE rats did not. In all cases, response rates were calculated in the same way, suggesting that the unpredicted response rate drops in bin 8 may be unique to older SHRs and WKYs.

CTR vs SHR-CTR to ensure replication of Experiment 1; and SHR-CTR vs SHR-EXP to test the effect of the duration requirement.

Figure 6-3 shows that without a response-duration requirement, SHRs emitted higher rates of responding than WKYs, and that the duration requirement reduced the response rates in SHRs. But how do the underlying response bouts differ between strains and change due to duration requirements? Table 1 summarizes the effects of strain (Experiments 1 and 2) and duration requirement (Experiments 1 and 2) on the parameters of response bouts. Each column displays the direction of the observed difference between the typically-trained SHRs (the SHR group in Experiment 1, and the SHR-CTR group in Experiment 2) and the comparison group (WKY group for Experiment 1, WKY-CTR or SHR-EXP groups for Experiment 2). To the extent that the duration requirement decreased operant hyperactivity in SHR, it was expected that differences in response-bout parameter estimates between SHR-CTR and WKY-CTR would be reduced or reversed by the response duration requirement (SHR-CTR vs. SHR-EXP).

Experiment 2 generally replicated the findings of Experiment 1, Epoch 2. When DBERM parameter estimates are compared between the SHR-CTR and WKY-CTR groups, significant differences in the same direction are observed for all parameters, with a single exception. In Experiment 2,  $HL(L)$ , was larger for the SHRs, but not in Experiment 1. However, the estimated  $HL(L)$  for both groups in Experiment 2 represents a negligible change in bout lengths over the course of the session, indicating that although there was a statistical difference, it was not meaningful.

Comparisons of SHR-EXP and SHR-CTR parameters are, on the surface, less straightforward, but can be easily be addressed. Because the distribution of IRTs for SHR-EXP were clearly non-monotonic (Figure 6-6, right panel), DGERM and DBERM were fit to the IRTs of all groups. This raises the question: which model should be used for comparison between groups? An examination of Table 6-1 renders this concern somewhat moot however, as fits of both models suggest similar differences in parameter estimates. When a significant difference in parameters were not replicated between models, non-significant trends in the same direction were still observed with only one exception. With DGERM,  $HL(b)$  was significantly smaller for SHR-CTR than SHR-EXP, but DBERM indicated a positive, though non-significant increase in  $HL(b)$ . In general, the effect in  $HL(b)$ , across models and conditions was equivocal (see also Brackney et al. 2012), suggesting that the primary effects of both duration requirements and strain are tied to other parameters.

Table 6-1 reveals that the directional effect of strain on response-bout parameters closely mirrors the effect of response duration requirements, regardless of whether DBERM or DGERM is used. When a significant difference in a parameter was identified, it was never inconsistent with a significant difference in the same parameter in another column of the table. When significant effects are not replicated within a table row, there was still generally a non-significant trend in the same direction, with few exceptions.

Combined, these results support the hypothesis of Experiment 2: *imposing a duration requirement reduces operant hyperactivity in the SHRs*. The duration requirement lowered response rates in the SHR-EXP group, just as the WKY-CTR group showed lower response rates than the SHR-CTR group. In both cases, slower response

rates appear to be caused by a change a reduction in bout initiation rates, although transient reductions in within-bout responses, asymptotic response rates, and increases in bout-lengths were also inferred.

Table 6-1.

*Relative parameter differences between conditions.*

Param.	Relative to WKY (strain effect)				Relative to SHR-EXP (duration effect)	
	Exp. 1 Epoch 1	Exp. 1. Epoch 2	Exp. 2 DBERM	Exp. 2 DGERM	Exp. 2 DBERM	Exp. 2 DGERM
$L_0$	- *	+	-	-	-*	-
$w_0$ OR $w_T$	+*	+	-	+	+*	+*
$b_0$	+*	+*	+*	+	+*	+*
$\delta$	=	-*	-*	-*	-*	+*
HL(L)	+	=	+*	+*	+*	+*
HL(w)	+*	+*	+*		+*	
HL(b)	-*	-	-	+	+	-*
$\Omega$	+*	+	+	+	+	+*

*Notes.* The left portion of the table displays the differences between the typically trained SHRs (SHR in Experiment 1, SHR-CTR in Experiment 2) relative to WKYs (WKY in Experiment 1, WKY-CTR in Experiment 2) and the right portion displays the differences between typically trained SHRs (SHR-CTR) relative to SHR-EXP. The symbols indicate that the median parameter estimate for the typically trained SHRs (SHR group in Experiment 1, SHR-CTR group in Experiment 2) was greater (+) or lower (-) than the comparison group (either WKY-CTR or SHR-CTR). \*Significant difference between the groups. For Experiment 2, parameter estimates for both DBERM and DGERM were compared. No HL(w) differences are indicated for DGERM columns because within-bout response rate was not permitted to decay in DGERM. The (=) indicates the difference between the estimates was not significant and was smaller than 1%. To the extent that strain effects were consistent across epochs, experiments, and models, symbols should be the same within rows under “Relative to WKY” column. To the extent that the response-duration effect reversed the effect of strain, symbols should be the same within rows under all columns.

### General Discussion

SHRs have been generally reported to be more active than WKYs (Sagvolden, Hendley, & Knardahl, 1992; Sagvolden, Metzger, et al., 1992), including in operant tasks (Brackney et al., 2012; Hill et al., 2012; Johansen & Sagvolden, 2005a; Orduña, García,

& Hong, 2010). The primary goal of the current experiments was to characterize the underlying source of these performance differences, and develop a means to ameliorate them.

### **Experiment 1: Maintenance Differences Between SHRs and WKYs**

Both experiments in the present study provide evidence consistent with the notion that SHRs display operant hyperactivity (heightened responding at low rates of reinforcement) during young adulthood (Epoch 2: PND 74-78) but not earlier (Epoch 1: PND 49-53). These findings are consistent with those of Hill et al. (2012) and Williams and colleagues (Williams, Sagvolden, Taylor, & Sagvolden, 2009a, 2009b). Also consistent with Hill et al. (2012), the response bouts of SHRs in early adulthood (Epoch 1) were shorter but more frequent compared to WKYs. In this study and in Hill et al. (2012), increased bout initiation rates of the SHR persisted into later adulthood. However, in Hill et al. (2012), SHRs in later adulthood demonstrated short bout lengths, whereas only non-significant trends in that direction were found in the present study (Experiment 2). The present study also revealed that the minimum time it takes to complete a response and start a new one (the refractory period) is shorter for the SHR than for the WKY during later adulthood.

The differences between Hill et al. (2012) and the present results are likely due to the differences in schedule design (multiple schedules in Hill et al., a simple schedule in the present study), and the analytic approach that takes into consideration the within-session decline in responding during maintenance. Hill and colleagues (Hill et al., 2012) applied a static bi-exponential model to the IRTs and compared parameter point-estimates. In contrast, this study used models that could account for dynamic changes in



the baseline bout parameters over the course of the session, and applied a BHA framework that accounts for variability in parameter likelihoods across subjects, diminishing the effects of potential outliers and allowing for more robust between-group comparisons (Cheung et al., 2012).

### **Experiment 1: Extinction Differences Between SHRs and WKYs**

Previously, Brackney et al. (2012) found that differences in response rates during extinction between SHRs and WKYs were primarily due to SHRs emitting bouts (a) at a higher rate at the onset of extinction, and (b) whose length persisted longer over extinction training. This study replicated the first effect, and showed a weaker strain effect in the same direction as the second effect. Because Brackney et al. (2012) used same model and model-fitting methods as those used in the current study, the discrepancies between the studies are most likely due to the experimental history of the rats. Whereas the rats in the present study were trained on a simple VI schedule before extinction, the rats in Brackney et al. (2012) were trained on the multiple-schedule design described in Hill et al. (2012).

### **Experiment 2: Effects of Minimum-Duration Requirement on SHR Performance**

Based on prior research (Chapter 4), and the observation the SHRs have shorter refractory periods, we hypothesized that requiring longer responses from the SHRs may result in performance that was more similar to the performance of the WKYs. In particular, it was expected that longer responses would yield fewer response bouts with more responses in each bout, thus reversing the purported source of operant hyperactivity in SHR.

Overall, the present data are consistent with the study's hypothesis. Longer response-duration requirements reduced bout initiation rates and increased the length of bouts in SHRs. In addition, the increased response-duration requirement changed the shape of the IRT distribution. It appears that, partially consistent with Smith et al. (2014), a gamma distribution may provide a more general characterization of within-bout IRTs, particularly when responses take longer to complete.

### **Implications for ADHD**

The refractory period, which has been suggested as an index of motoric capacity (Brackney et al., 2011), was shorter in SHRs than WKYs. The present results are consistent with the notion that operant hyperactivity in SHRs stems, at least partially, from a motoric ability of SHRs to produce responses at very high rates. Notably, however, neither the median response durations nor the IQRs differ across strains, suggesting that the motoric differences in response generation are only observable when examining the fastest responses the rats are capable of producing.

Sagvolden and colleagues (Johansen et al., 2007; Sagvolden et al., 2005) have also suggested that the hyperactivity of SHRs stems in part from an inability to learn responses that are temporally distant from the reinforcer. This hypothesis is consistent with the observation that SHRs produce shorter bouts: for SHRs, the time between each response that initiates a long bout and the next reinforcer may be too long for the latter to strengthen the former, thus selecting only for short bouts (Hill et al., 2012). By requiring individual responses to take longer (Experiment 2), bout initiations become more temporally distant from their reinforcer, and operant hyperactivity may be reduced as the association between hyperactive responses and their appetitive outcomes is decreased.

However, why response-duration requirements increase bout lengths (see also Chapter 4), still requires investigation. Longer responses may be more memorable, increasing their sensitivity to reinforcement (Killeen & Pellón, 2013; Thomas, Lieberman, McIntosh, & Ronaldson, 1983), although this hypothesis has yet to be tested.

## CHAPTER 7

### GENERAL DISCUSSION

#### **Bout Initiations and Motivation**

In Chapter 2, rats that normally had *ad libitum* food access were placed on acute food restriction, and only bout-initiation rates increased. In Chapter 3, rats that normally were food restricted were given *ad libitum* food access, and bout initiation rates decreased. These results are notably similar to those of some discrete-trial preparations, such as the fixed minimum interval (Mechner & Guevrekian, 1962; Watterson et al., 2015), demonstrating that the latency to start a timing task (perhaps analogous to the bout initiation) is sensitive to changes in food and water deprivation, but responding on the task (perhaps analogous to within-bout responding) is not. However, these general effects are reversed when rats are trained on a heterogeneous response chain between two operandums (e.g., a lever press, then a nose poke). There, food deprivation increases the probability to respond on the second action in the response chain, but not the first action (Balleine, Garner, Gonzalez, & Dickinson, 1995). In contrast, Pavlovian instrumental transfer increases the probability to respond on the first action in a chain, but not the second action (Corbit & Balleine, 2003). Disentangling the differential effects of different forms of motivation on responding will require a close look at these ostensibly similar tasks with disparate findings. The first step may be to examine how Pavlovian instrumental transfer, commonly believed to affect incentive motivation, alters response bouts.

In Chapter 2, bout initiations are interpreted as an index of motivation. However, throughout this dissertation, bout-initiation rates changed due to almost all manipulations,

indicating that either motivation is changing in all cases or that altered bout-initiation rates reflect a more general effect.

Multiple researchers have suggested that sequences of responses may acquire behavioral unit-like properties (Bachá-Méndez et al., 2007; Schwartz, 1981; Shimp, 1982; Shull et al., 2001; Shull, 2011; Terrace, 1991). If bouts were the units of behavior emitted by the organism, any perturbation to behavior would be expected to affect the probability of the whole bout (bout-initiation rate) regardless of the cause. With only a single exception, this was observed for all the manipulations described in Chapters 2-5. The debate about the existence of theoretical units of behavior (Bachá-Méndez et al., 2007; Graybiel, 1998; Schwartz, 1981; Shull, 2011; Thompson & Zeiler, 1986) and their role in response-bout formations will not be solved exclusively with the data in this dissertation, but they do suggest that the rats learn a behavioral pattern that extends beyond individual lever presses.

### **Motoric Indices, the Refractory Period, and Response Durations**

In Chapter 2, the refractory period ( $\delta$ ) was introduced as a novel response-bout parameter. Across all experimental manipulations, the refractory period only changed when the required lever force and lever height was increased (Chapter 2, though see Chapter 3), suggesting that it is an appropriate index of the motoric constraints of the organism. However, this interpretation comes with caveats. The refractory period represents the amount of time it takes the animal to complete a response and reassert their position in space enough to initiate a new response. It is estimated as a static point for any set of IRTs, but Figure 4-3 shows that response durations are variable. This suggests that refractory periods may also be variable, and if so, the current DBERM parameterization

will require improvement. Future bout-modeling research may attempt to explain IRT variability as a function of both the variable duration of the response and the variable time between the completion of the response and the initiation of the next response. More precise accounting of response durations in DBERM may then provide a better index of motoric challenges than a static refractory period.

### **Response Requirements and Contingencies of Reinforcement**

Three distinct response requirements were manipulated in this dissertation: (a) the number of responses required after the end of a variable interval (Chapters 2 and 5); (b) the response duration required (Chapters 4 and 6); and (c) the lever force and lever height, or response effort (Chapter 2). Whereas explicit motivational manipulations only changed the bout initiation rate, response requirement manipulations changed the bout lengths, within-in bout response rate, and/or the refractory period. Combined, these results suggest that while bout initiations reflect the general probability of the reinforced behavior pattern, the bout lengths, within-bout response rates, and refractory periods reflect the behavioral pattern selected for by reinforcement.

This interpretation is further supported by the bout-length distributions in Chapter 5. Using a novel method, the chapter showed that bout lengths are sensitive to varying response requirements within the same session. As the proportion of trials that require 1 response after the end of the variable interval vary relative to the proportion of trials that require 5 responses after the end of the variable interval, so do the proportion of short and long bouts.

Future research might replicate the findings of Chapter 5 using additional methods. Although the analytic techniques implemented in Chapter 5 are superior to more traditional methods, such as the IRT cutoff, it still relies on multiple models and simulations, each of which carries its own assumptions. A two-lever preparation in which bouts are initiated on one lever and terminated on a second lever may provide an empirical method of determining bout lengths, instead of inferring them from a model's IRT distributions. However, the extent to which bouts produced by two levers reflect the same behavioral processes as bouts on a single lever will require investigation.

### **Breaking the Response-Reinforcer Contingency**

How response bouts change during extinction and non-contingent reinforcement was investigated in Chapters 2 and 3. The dynamic parameters ( $\gamma$ ,  $\alpha$ ,  $\beta$ ; Equation 2-3) were first introduced in Chapter 2 to allow the average bout length, within-bout response rate, and bout-initiation rate to decay over the course of the session.

In Chapters 2 and 3, bout initiation rate decay was found to increase during extinction, indicating that extinction is primarily due to a gradual reduction in bout frequency. In contrast, non-contingent reinforcement increased bout-length decay, possibly due to the interruption of the response bout and reinforcement of competing behaviors. These findings support the notion that extinction leaves behavior relatively intact in the animal's repertoire (Bouton, 2004; Winterbauer & Bouton, 2011), and provides a possible explanation for why non-contingent and/or alternative reinforcement may more effectively eliminate a target behavior than extinction alone (Cooper, Heron, & Heward, 2007; Zeiler, 1971)

## **DBERM Assumptions and Alternative Models**

In Chapter 2, BERM (Equation 2-1) was first introduced, and the hypothetical process that underlies BERM's assumptions are illustrated in Figure 2-1. It later became obvious that the process described in Figure 2-1 was not necessarily accurate. Although that process produces IRTs that are perfectly described by BERM, the assumption that a single Bernoulli trial (as implicated by the center, diamond node) decides whether the next IRT is within or between bouts is not an explicit assumption of any mixture model. Chapter 5 revealed this error quite clearly, when it was found that bout-length distributions were not always geometric. Although Figure 2-1 is based on an inaccurate assumption, it had no impact on actual parameter estimation.

Beginning in Chapter 5, and again in Chapter 6, an alternative model in which one or both of the exponential distributions in the mixture model were replaced with a gamma distribution. The model provides a good account of IRT distributions that have modes greater than the minimum IRT, but integrating the decay components and/or the refractory period of DBERM with a gamma-based model is problematic (Chapter 6). Future research may investigate how to incorporate these unique aspects of DBERM with the more flexible gamma-based models.

## **SHRs and the Bayesian Hierarchical Estimation**

In Chapter 6, the BHA method of estimating DBERM parameters is introduced, which provides multiple advantages over maximum likelihood point estimation. BHA simultaneously uses information at both the individual and group levels to fit model parameters. By generating distributions of parameter estimates instead of single points, it becomes possible to conduct between-group comparisons while taking into account the



inherent uncertainty of parameter estimates (Gelman, 2004). Although BHA is a powerful model estimation technique, complicated models such as DBERM are computationally expensive to fit and require the development of custom-built modeling programs. Future research may extend the experimental manipulations of Chapters 2-5 using BHA.

### **Conclusions**

This dissertation demonstrated the sensitivity of IRT distributions to a variety of perturbations and challenges. Combined, these data lead to two primary conclusions. First, lever presses are organized into bouts, and the frequency of bout initiations reflect the overall probability of behavior. Second, bout lengths, within-bout responses rates, refractory periods, and response durations reflect the specific behavior patterns selected for by the contingencies of reinforcement.

The prototypical measure of behavioral probability in operant research is response rates (Killeen & Hall, 2001; Skinner, 1966). In every experiment in this dissertation, except one (NCR; Chapter 3), changes in overall response rate were found to be concordant with similar changes in bout initiation rates. Furthermore, manipulations that could reasonably be postulated to *only* change the general probability of behavior, such as changing motivation or extinction, only reliably changed bout initiations rates. These findings are consistent with prior research that indicate that the matching of response rates to their reinforcement rates (Baum, 1974; Herrnstein, 1961) can be explained primarily by bout initiation rates (Shull, 2011). Combined, these multiple lines of evidence suggest that common overall changes in behavior probability are specifically due to changes in the probability of bouts, but not responding within a bout.

Manipulations that changed the requirements to earn reinforcement (changes in response count/force/height/duration) caused specific changes in bout lengths, within-bout response rates, and refractory periods. When the required number of responses increased, bout lengths and within-bout response rates increased. When the lever was made more difficult to press, the refractory period lengthened. When the response duration requirement was increased, bout lengths grew longer and within-bout response rates decreased. When the contingencies of reinforcement were varied to select for a mixture of short and long bouts, the proportion of long bouts increased as reinforcement for more responses increased. In concert, these findings reveal how different contingencies of reinforcement select for different patterns of responding, and suggest that response bouts may better reflect the learned behavior of the rat than the simple frequency of individual lever presses.

Chapters 2-6 provided multiple lines of evidence leading to these conclusions, but as with any scientific endeavor, new questions spring forth as old ones are answered. If response bouts are selected for by the contingencies of reinforcement, why are the within-bout IRTs and bout-lengths so variable from bout-to-bout? To the operant researcher accustomed to counting discrete lever presses, the dynamic, moment-to-moment changes in response bouts may be disconcerting. However, the static nature of the lever press is an illusion perpetrated by our standard measurement procedures. As Figure 4-2 illustrates, a closer look at differences between individual responses reveals their variability.

Skinner (1935) recognized the trouble variability posed to behavioral classification efforts, and neatly sidestepped the need to formally account for behavioral variability by instead postulating that all responses that share a common reinforcer belong

to the same *response class*. Responses were declared functionally equivalent if they resulted in the same consequence, regardless of their physical form. Since then, multiple lines of research (Amsel, 1992; Ibias et al., 2014; Killeen & Pellón, 2013; Mechner et al., 1997; Shull, 2011; Sidman, 2000) have revealed that different types of responses may share the same reinforcer, while maintaining distinct functional relations with that reinforcer. For example, Killeen and Pellón (2013) demonstrated how different behaviors (e.g., lever pressing versus schedule-induced drinking) are selected by the same reinforcer, despite occurring at different timescales with different sensitivities to the reinforcement. While such studies do not invalidate the usefulness of the conceptual response class, they demonstrate that class-membership is controlled by more than simply sharing the same reinforcer, and additional membership criteria need to be discovered.

Just as a speciated population of animals is variable between individuals, may change over time, and is best categorized by examining properties of the population as a whole, the same is true of operant responses (Skinner, 1981). To identify the population or class membership of an operant and locate the natural lines of fracture between behavioral events, behavioral variability, and how it changes, must be explained. This dissertation accounted for the natural variability in inter-response times (IRTs) of the lever-pressing rat using response-bout models. Its findings support previous studies (Cheung et al., 2012; Shull et al., 2001, 2004) showing that IRTs may naturally divide into two distinct populations, within-bout IRTs and bout-initiation IRTs, and show that the reinforced operant is not fixed like a unit on a yardstick, but is instead probabilistic and hierarchically organized (Dezfouli et al., 2014). Reinforcement affects the probability of bouts, as well as the pattern of activity that makes up the bout.

Many more questions regarding the nature of response bouts remain. For example, what are the conditions under which bouts occur? Operant bouts are most frequently studied during variable interval (VI) reinforcement. These reinforcement schedules allows the organism to emit many responses, while relative few of them are directly responsible for activating the reinforcer. Bouts within the operant chamber may form simply because a sequence of tightly spaced responses occurred in close proximity to reinforcement. A simple test of this hypothesis would be to reinforce only the terminal response when its follows a sufficiently long IRT (a tandem VT-differential reinforcement of low rates; VT-DRL). If bout-like responding does not occur under such a schedule, this would support the hypothesis that bouts are the result of reinforcing a series of short IRTs. However, the “bursting” of rats trained on simple DRL schedules (Doughty & Richards, 2002), despite explicit reinforcement of the opposite, suggests that bouts cannot be explained by accounts of IRT reinforcement alone (Peele, Casey, & Silberberg, 1984; Rachlin, 1978).

Strain differences among rats may provide some clues about the origin of response bouts. Notably, SHRs often produce shorter bouts than WKYs, which is consistent with the hypothesis that SHRs have a decreased capacity to associate delayed responses with the reinforcer (the delay-of-reinforcement gradient hypothesis; Sagvolden, Johansen, Aase, & Russell, 2005). Under this hypothesis, few responses would be associated with the reinforcer, yielding shorter bouts. Because the bout initiating response is then temporally closer to the reinforcer, it would also acquire more strength, explaining the occurrence of more frequent bouts in the SHRs. If this hypothesis is correct, more memorable responses (Lieberman et al., 1979; Thomas et al., 1983) should also increase

the bout lengths of SHRs. This is a possible explanation for why increasing the response-duration requirement increased bout lengths (Chapters 4 and 6). Experiments that increase the salience or otherwise signal the occurrence of responses prior to reinforcement may validate this hypothesis.

None of these hypotheses, however, can explain why within-bout response rates (e.g., Chapter 3, Experiment 1) and bout lengths (e.g, Brackney, Cheung, Herbst, Hill, & Sanabria, 2012) extinguish in some cases, but not in others (e.g., Chapter 2). Multiple lines of research have suggested that operant resistance to change may be a function of learning to integrate multiple responses together into an action sequence chunk (Dezfouli et al., 2014; Fujii & Graybiel, 2003; Graybiel, 2008; Ostlund & Balleine, 2008). Under this hypothesis, responses early in training are each encoded separately, and mediated by the dorsal medial striatum (DMS; the primate caudate homolog). As training progresses, consecutive responses become encoded as a single action, or chunked, which is mediated by the dorsal lateral striatum (DLS; the homolog of the primate putamen). The similarities between bouts, and action sequence chunks has been noted previously (Dezfouli & Balleine, 2012), and may explain differences in the extinction of response bouts under different preparations and rat strains. If responses within a bout become encoded a single action pattern, they may be expected to also extinguish as a single action pattern, evidenced by only a reduction in bout initiation rates. In contrast, if responses within a bout are encoded individually, bout lengths and within-bout responses should also decline over the course of extinction.

The bouts/chunking hypothesis is testable through multiple experiments. The formation of response bouts may be accompanied by additional physiological changes

associated with chunking (Fujii & Graybiel, 2003; Jin & Costa, 2010; Smith & Graybiel, 2013; Yin & Knowlton, 2006). Lesions to the DLS, but not to the DMS, may then alter the distribution of bout lengths (see Chapter 5). Whereas geometrically distributed bout lengths (Chapter 5) may be indicative of bouts in which individual responses are encoded separately and each response is produced independent of the previous (in accordance with Figure 1-2), bouts in which sequences of responses are encoded as a group may create more peaked distributions of bout-lengths (in accordance with Figure 5-5). Greater resistance to extinction may then be observed when bouts are encoded as an integrated unit, as opposed to individual responses (Dezfouli & Balleine, 2012).

From the data presented in the previous chapters, it is clear that bout analyses provide a powerful alternative to the simple assessment of discrete responses. Responding is always variable, and models that account for that variability will be more useful than those that treat it as unexplained noise. The next step is to explain the causes of that variability, to explain why bouts occur and change in some cases, but not others, and to describe the underlying behavioral and biological processes responsible. The experiments proposed in this section may take us far along that path, and reveal more about the nature of bouts and operant conditioning.

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APPENDIX A

MAXIMUM LIKELIHOOD METHOD AND AKAIKE INFORMATION CRITERION

(CHAPTER 2)

The maximum likelihood method consists of maximizing the probability of the data (i.e., the joint probability of all of the observed IRTs and the observed “no-response” periods for each individual rat in a session) given each model, by adjusting model parameters. The maximized probability is known as the maximum likelihood estimate (MLE). The Akaike Information Criterion (AIC) is then used to select between candidate models (Burnham & Anderson, 2002; for examples of its use, see Avila et al., 2009; Killeen, Sanabria & Dolgov, 2009; Sanabria, Acosta, Killeen, Neisewander, & Bizo, 2008; Sanabria & Killeen, 2008). The AIC for a model is computed as  $AIC = 2k - 2\ln(MLE)$ , where  $k$  is the total number of free parameters, i.e., the number of parameters allowed to vary in the model, multiplied by the number of subjects. For example, Equation 4, in which  $q$ ,  $w$ ,  $b$ , and  $\delta$  are allowed to vary freely, applied to 10 subjects, involves  $k = 4 \times 10 = 40$ . The model with the lowest AIC ( $AIC_{MIN}$ ) represents the best balance between likelihood (high MLE) and parsimony (low  $k$ ).  $\Delta AIC$  was computed for model  $i$  as  $\Delta AIC_i = AIC_i - AIC_{MIN}$ . As a rule of thumb, if  $\Delta AIC_i > 4$  the evidence for model  $i$  is considered weak relative to the model with the lowest AIC (the best fitting model). This is because the likelihood of model  $i$  relative to the best fitting model is  $\exp(\Delta AIC_i/2)$  (Anderson & Burnham, 2002), and with  $\Delta AIC_i > 4$ , it is at least  $e^2 \approx 7$  times more likely to observe the data using the best fitting model than using model  $i$ . Following this rule, the simplest model (lowest  $k$ ) with  $\Delta AIC_i < 4$  was favored

APPENDIX B

PROBABILITY OF THE INTERVAL BETWEEN THE LAST RESPONSE IN A  
SESSION AND THE END OF THE SESSION (CHAPTER 2)



Let us assume that the animal emitted its last response of the session at time  $L$ , and that the session ended at time  $S$ . Then, under the assumption of the dynamic refractory bi-exponential model, the probability that an animal emits no responses between  $L$  and  $S$  is:

$$p(\text{no response between } L \text{ and } S \mid S - L < \delta) = 1$$

$$p(\text{no response between } L \text{ and } S \mid S - L \geq \delta) = (1-q)e^{-w(S-L-\delta)} + qe^{-b(S-L-\delta)} \quad (\text{B-1}).$$

For non-refractory models, fix  $\delta$  at 0. For single exponential models, fix  $q$  at 1.

## APPENDIX C

### REFRACTORY BI-EXPONENTIAL MODEL PARAMETERS (CHAPTER 2)

The following tables show estimates of  $q$ ,  $\delta$ ,  $w$ , and  $b$  in separate tables. Estimates are shown separately for each individual rat in each experimental condition. Estimates were obtained for each daily session. For the *VI* and *Tandem* conditions, the mean estimate of the last 4 sessions is shown.

Table C-1.

*Estimates of parameter  $q$  (probability of quitting a response bout).*

Rat	Low workload lever			High workload lever		
	VI	Tandem	Food Dep	VI	Tandem	Food Dep
505	0.52	0.16	0.12	0.11	0.09	0.08
507	0.26	0.14	0.14	0.25	0.13	0.15
517	0.48	0.15	0.17	0.32	0.13	0.13
519	0.43	0.24	0.20	0.73	0.14	0.14
520	0.67	0.12	0.07	0.75	0.13	0.10
521	0.47	0.16	0.15	0.38	0.13	0.13

Table C-2.

*Estimates of parameter  $\delta$  in seconds.*

Rat	Low workload lever			High workload lever		
	VI	Tandem	Food Dep	VI	Tandem	Food Dep
505	0.08	0.08	0.06	0.10	0.09	0.07
507	0.09	0.07	0.09	0.11	0.07	0.08
517	0.08	0.08	0.08	0.06	0.13	0.16
519	0.18	0.10	0.06	0.27	0.08	0.06
520	0.18	0.10	0.09	0.28	0.09	0.08
521	0.06	0.06	0.06	0.17	0.09	0.09

Table C-3..

*Estimates of parameter  $w$  (within-bout response rate) in responses per second.*

Rat	Low workload lever			High workload lever		
	VI	Tandem	Food Dep	VI	Tandem	Food Dep
505	2.07	3.31	3.48	2.34	4.69	3.17
507	1.91	2.91	3.16	1.71	3.79	3.54
517	5.31	3.11	2.59	3.14	8.60	17.13
519	1.06	4.03	4.48	4.17	5.69	5.43
520	1.15	3.90	3.14	2.52	3.09	3.17
521	2.27	6.09	7.30	3.90	9.56	9.98

Table C-4.

*Estimates of parameter b (rate of bout initiation) in responses per second.*

Rat	Low workload lever			High workload lever		
	VI	Tandem	Food Dep	VI	Tandem	Food Dep
505	0.20	0.13	0.19	0.11	0.06	0.15
507	0.34	0.19	0.23	0.11	0.18	0.21
517	0.17	0.08	0.24	0.12	0.06	0.09
519	0.14	0.11	0.28	0.05	0.10	0.33
520	0.08	0.03	0.05	0.04	0.02	0.03
521	0.25	0.23	0.33	0.18	0.11	0.23

## APPENDIX D

PROBABILITY OF THE INTERVAL BETWEEN THE LAST RESPONSE IN A  
SESSION AND THE END OF THE SESSION, ACCORDING TO THE DYNAMIC  
MODEL (CHAPTER 2)

Let us assume that the animal emitted its last response of the session at time  $L$ , and that the session ended at time  $S$ . Then, under the assumption of the dynamic refractory bi-exponential model, the probability that an animal emits no responses between  $L$  and  $S$  is:

$$p(\text{no response between } L \text{ and } S \mid S - L < \delta) = 1$$

$$p(\text{no response between } L \text{ and } S \mid S - L \geq \delta) = (1 - q_L)e^{-w_L(S-L-\delta)} + q_L e^{-b_L(S-L-\delta)},$$

(D-1)

where  $q_L$ ,  $w_L$  and  $b_L$ , are calculated by substituting  $L$  into  $t$  in Equation 2-5. For non-refractory models, fix  $\delta$  at 0. For single exponential models, fix  $q$  at 1.

APPENDIX E

RESPONSE RATE STABILITY ESTIMATES (CHAPTER 3)

To assess the stability of response bouts, each individual subjects' session IRTs were fit to BERM (Equation 2-2) by maximum likelihood estimation using custom-written Matlab® software. For each parameter  $L$ ,  $w$  and  $b$ , a simple linear regression over sessions was fit to estimates pooled across subjects on that day. Therefore, three linear regressions (one each for  $L$ ,  $w$ , and  $b$ ) were estimated for each moving window of five sessions. Fit was determined by the method of minimizing the residual sum of squares. AICc (Anderson and Burnham, 2002; Hurvich & Tsai 1989) was then used to assess whether the arithmetic mean of each BERM parameter of the past five days was a better fit than the linear regression. If the AICc value of the fit to the arithmetic mean was four or more less than the AICc value of the fit to the regression, then the past five day sequence of parameter estimates were judged to be stable. If the parameters  $L$ , and  $b$ ,  $w$  were all found to be stable, a treatment condition was initiated on the following day.



APPENDIX F

SELECTION OF SUPER-THRESHOLD IRTS FOR ANALYSIS (CHAPTER 4)

Model fits were conducted only on the IRTs between super-threshold responses to more accurately reflect operant performance as it is typically recorded. In most operant protocols, it is likely that animals regularly produce behaviors that belong to the target response class, but go unnoticed by the experimenter. When a discrete switch closure constitutes the functional response that triggers reinforcement, there may be a multitude of behaviors that are either adventitiously reinforced due to their temporal proximity to the response that triggered reinforcement (Catania, 1971; Killeen & Pellón, 2013), generalizations of the functional response (e.g., response that are topographically similar to the target, but do not meet the reinforcement criterion), or simply induced by the reinforcement protocol. When lever tension is tightened to increase the force needed to depress the lever, as in Brackney et al. (2011), the subject may continue to emit responses that no longer fully depress the lever and hence go unrecorded. Zarcone, Chen, and Fowler (2007, 2009) demonstrated this methodological challenge by programming reinforcement contingent upon exerting a certain force on a force-plate transducer. In these studies, a significant proportion of responses was below the force threshold, and would not have been identified with a more typical operandum. For these reasons, functionally ineffective sub-threshold responses were excluded from response-bout modeling.

APPENDIX G

BERM PARAMETER ESTIMATES FOR INDIVIDUAL SUBJECTS

(CHAPTER 4)

This appendix includes the estimates of individual parameters of the bi-exponential refractory model (BERM, Equation 4-1), for each threshold condition and cycle. Estimates were obtained using the method of maximum likelihood. The units for  $L$ ,  $w$ ,  $b$ , and  $\delta$  are responses, responses/s, bouts/s, and s, respectively.

Table G-1.  
*Threshold = 0.0 s.*

Rat	Cycle 1				Cycle 2			
	$L$	$w$	$b$	$\delta$	$L$	$w$	$b$	$\delta$
1	10.65	2.23	0.27	0.08	3.21	2.10	0.17	0.08
2	4.11	0.79	0.08	0.09	1.03	0.86	0.08	0.11
3	0.88	1.75	0.14	0.08	1.35	2.25	0.08	0.09
4	3.31	0.87	0.10	0.09	2.23	1.19	0.14	0.10
5	1.14	1.27	0.08	0.08	3.32	0.30	0.03	0.12
6	0.85	3.11	0.09	0.09	1.94	0.75	0.06	0.08
7	4.18	0.44	0.06	0.09	7.82	0.19	0.03	0.10
8	1.34	1.40	0.17	0.08	1.95	1.71	0.13	0.08
mean	3.31	1.48	0.12	0.08	2.86	1.17	0.09	0.09
median	2.33	1.34	0.10	0.08	2.09	1.03	0.08	0.09
SEM	1.16	0.31	0.02	< 0.00	0.76	0.28	0.02	0.01

Table G-2.  
*Threshold = 0.4 s.*

Rat	Cycle 1				Cycle 2			
	$L$	$w$	$b$	$\delta$	$L$	$w$	$b$	$\delta$
1	3.33	0.82	0.14	0.47	18.80	0.15	0.04	0.48
2	22.94	0.24	0.02	0.47	9.69	0.18	0.03	0.51
3	0.70	0.76	0.09	0.47	2.17	0.18	0.04	0.49
4	10.19	0.48	0.05	0.47	12.51	0.25	0.05	0.47
5	7.59	0.18	0.02	0.49	7.52	0.15	0.01	0.47
6	3.27	0.48	0.05	0.47	5.99	0.15	0.02	0.48
7	33.85	0.14	0.02	0.47	17.60	0.09	0.01	0.69
8	12.88	0.19	0.05	0.47	3.81	0.14	0.05	0.53
mean	11.84	0.41	0.05	0.47	9.76	0.16	0.03	0.51
median	8.89	0.36	0.05	0.47	8.61	0.15	0.03	0.49
SEM	4.01	0.10	0.01	< 0.00	2.17	0.02	0.01	0.03

Table G-3.  
*Threshold = 0.8 s.*

Rat	Cycle 1				Cycle 2			
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	$L$	$w$	$b$	$\delta$	$L$	$w$	$b$	$\delta$
1	21.30	0.17	0.04	0.87	33.83	0.13	0.01	0.88
2	20.11	0.17	0.03	0.91	13.03	0.10	0.01	0.92
3	10.90	0.13	0.01	0.88	21.71	0.08	0.01	1.01
4	18.89	0.19	0.03	0.93	11.63	0.13	0.01	1.16
5	6.60	0.15	0.02	0.87	0.40	0.74	0.04	0.88
6	4.38	0.10	0.02	0.89	5.52	0.10	0.02	1.15
7	21.42	0.06	0.01	1.17	14.22	0.07	0.00	1.12
8	7.01	0.15	0.06	0.93	6.12	0.08	0.02	0.95
mean	13.83	0.14	0.03	0.93	13.31	0.18	0.02	1.01
median	14.90	0.15	0.03	0.90	12.33	0.10	0.01	0.98
SEM	2.59	0.01	0.01	0.04	3.72	0.08	0.00	0.04

APPENDIX H  
IRT SIMULATIONS (CHAPTER 4)

Simulations were conducted to obtain the predicted distribution of IRTs from the fitted model (Equation 4-1). Although determining the expected inverse cumulative distribution (i.e., a survivor plot) is a simple matter of integrating over the probability density function, determining the mean IRT for each percentile bin is more complicated. To keep estimation techniques identical for both the survival plots (Figure 4-5) and percentile plots (Figure 4-6), IRT-generation simulations were used for both types of plots.

Each simulation used a Monte Carlo method in which a series of Bernoulli trials were generated. After each success [with probability  $p = L / (L + 1)$ ], an IRT was sampled from an exponential distribution with a mean of  $1/w$ ; after each failure (with probability  $1 - p$ ), an IRT was sampled from an exponential distribution with a mean of  $1/b$ . The refractory period,  $\delta$ , was then added to the IRT. The sampled IRT then advanced the session clock by its respective value, and new trial then began. The session continued until the session clock exceeded the maximum session length of 3,160 s (the 84-min session time minus the 5-min acclimation period); the vector of IRTs was truncated to exclude the final IRT, which advanced the session clock beyond the session length. One hundred sessions were simulated for each rat and condition; the generated IRTs were then aggregated to produce the model prediction traces for the log-survivor and percentile plots in Figure 4-5 and Figure 4-6.

APPENDIX I

DBERM PARAMETER ESTIMATES (CHAPTER 5)



Table I-1.

*Individual DBERM parameter estimates.*

Rat	$L_0$ (responses)	$w_0$ (responses /s)	$b_0$ (bouts/ s)	$\delta$ (s)	$\alpha$ ( $s^{-1} \times 10^{-3}$ )	$\beta$ ( $s^{-1} \times 10^{-3}$ )
<i>Majority FR1 (mFR1) Condition</i>						
1	2.623	2.896	0.143	0.09	0.208	0.208
2	5.383	2.434	0.315	0.07	0.058	0.160
3	3.689	4.207	0.169	0.07	0.018	0.018
4	2.913	3.576	0.286	0.08	0.130	0.144
5	4.631	2.325	0.078	0.04	0.205	0.205
6	1.154	1.310	0.218	0.09	0.000	0.000
7	3.786	3.380	0.093	0.08	0.097	0.097
8	4.791	1.017	0.174	0.08	0.219	0.511
9	3.856	4.169	0.155	0.03	0.135	0.136
10	7.622	0.709	0.109	0.09	0.108	0.294
Mean	4.045	2.602	0.175	0.07	0.118	0.177
SEM	0.552	0.402	0.027	0.01	0.025	0.046
<i>Majority FR5 (mFR5) Condition</i>						
1	5.416	2.149	0.176	0.09	0.302	0.539
2	8.570	3.988	0.255	0.07	0.059	0.185
3	3.515	3.371	0.273	0.07	0.000	0.190
4	5.302	4.496	0.183	0.08	0.094	0.113
5	11.047	2.417	0.197	0.04	0.093	0.475
6	4.382	4.571	0.091	0.09	0.056	0.068
7	5.146	3.345	0.155	0.08	0.052	0.116
8	6.466	1.541	0.059	0.08	0.112	0.112
9	8.316	5.271	0.277	0.03	0.316	0.489
10	7.212	2.927	0.059	0.09	0.170	0.170
Mean	6.537	3.407	0.175	0.07	0.125	0.246
SEM	0.719	0.375	0.027	0.01	0.034	0.057

*Note.* In some instances,  $\beta = \alpha$ . This is because  $\beta$  was constrained to be equal or higher than  $\alpha$ , so that  $w_t$  would be higher than  $b_t$  at all times. When relaxing this constraint yielded better fits, the best solution within these constraints was a single rate of decay for both  $w_t$  and  $b_t$ .

APPENDIX J

BERNOULLI TRIALS, GEOMETRIC AND NEGATIVE BINOMIAL  
DISTRIBUTIONS, AND THEIR RELATION TO THE LENGTHS OF BOUTS  
(CHAPTER 5)

Geometric and negative binomial distributions describe the results of a series of Bernoulli trials, which may be thought of as analogous to a series of “coin flips” where the probability  $p$  that a coin falls “heads”—i.e., a “success”—may take any value between 0 and 1. The geometric distribution

$$\Pr(x) = p(1 - p)^x \quad 0 \leq p \leq 1; x \in \mathbb{N}_0 \text{ (J-1)}$$

describes the probability that  $x$  failures will be observed before a success. In the GEO bout-length model (Equation 5-7), a failure is expressed as remaining in a bout and making another within-bout response; a success is expressed as leaving the bout. Because bouts must have at least one response, the number of failures in a bout of length,  $\lambda$ , is  $\lambda - 1$ . According to Shull et al.’s (2001) original model, the decision to remain within-bout or exit the bout after each response is determined by a simple Bernoulli trial, and hence bout lengths are distributed according to GEO.

A fundamental property of a geometric distribution is that its mode is always zero or 1, depending on the parameterization of geometric distribution. In Equation J-1, the mode is 0, and when applied to bout lengths, which always have at least one response, the mode is 1.

When bout lengths have a mode greater than 1, GEO becomes insufficient to describe the data. An extension of the geometric is the negative binomial (NB) distribution,

$$\Pr(x) = \binom{r + x - 1}{x} p^r (1 - p)^x \quad 0 \leq p \leq 1; x \in \mathbb{N}_0; r \in \mathbb{N}_1 \text{ (J-2)}$$

which specifies the probability that  $r$  failures will occur before  $x$  successes. As in GEO, each NB success is expressed as a within-bout response. In contrast to GEO, however, NB failures do not necessarily correspond to exiting the bout. In NB, each failure increases a counter,  $n$ ; bouts are exited only when  $n = r$ ; if  $n < r$ , another Bernoulli trial occurs. As in GEO, NB bouts must have at least one response, so the number of failures in a bout of length  $\lambda$  is  $\lambda - 1$  (Equation 5-9).

For simplicity, the discrete form of the negative binomial distribution function is noted in Equations 5-8 and 5-9. However, parameter estimation was actually conducted with an extension of the negative binomial distribution function that allows  $r$  to take on non-integer values,

$$\Pr(BL = \lambda) = \frac{\Gamma(r+\lambda-1)}{\Gamma(r)\Gamma(\lambda)} p_{nb}^r (1 - p_{nb})^{\lambda-1}. \quad 0 \leq p_{nb} \leq 1; r > 0; \lambda \in \mathbb{N}_1 \text{ (J-3)}$$

This extension prevents parameter estimates from being interpreted simply in terms of Bernoulli trials, however it also simplifies parameter estimation, as estimating discrete parameter values using standard optimization algorithms in Matlab® is non-trivial.

APPENDIX K

ESTIMATES OF BOUT-LENGTH DISTRIBUTION PARAMETERS FROM  
BRACKNEY ET AL. (2011) (CHAPTER 5)

Model selection and parameter estimates were based on “low” lever data from Brackney et al. (2011). The “low” lever condition is more similar to the training conditions in the present study and to typical training conditions.

Table K-1.  
*GEO, NB, and MIX model fit statistics.*

Model	$k$	VI ( $n = 42013$ )			Tandem ( $n = 34881$ )		
		AICc	LL	$\Delta$ AIC	AICc	LL	$\Delta$ AIC
GEO	6	135638	-67814	442	198062	-99024	4794
NB	12	135650	-67814	454	198074	-99024	4806
<u>MIX</u>	24	135196	-67574	0	193268	-96610	0

Note. See Table 1 for nomenclature.

Table K-2.  
*MIX parameter estimates.*

Rat	VI 120 s			Tandem VI 120 s FR5		
	$\omega$	$\mu_{\text{geo}}$	$\mu_{\text{nb}}$	$\omega$	$\mu_{\text{geo}}$	$\mu_{\text{nb}}$
505	0.605	0.111	1.214	0.756	0.314	6.07
507	0.091	2.83	3.901	0.597	2.065	7.535
517	0.139	0.848	2.709	0.693	1.924	11.274
519	0.385	39.103	6.363	0.769	0.455	6.152
520	0.737	1.815	0.477	0.83	2.199	14.328
521	0.173	1.077	1.902	0.523	2.554	9.337
Mean	0.355	7.63	2.761	0.695	1.585	9.116
SEM	0.109	6.306	0.868	0.047	0.389	1.322

APPENDIX L  
CURRICULUM VITAE (ABRIDGED)

### **Education**

PhD in Neuroscience, Arizona State University, 2009-2015 (graduation date: 8/2015)

MS in Behavior Analysis, University of North Texas, 2006-2009

BS in Psychology, Drake University, 2001-2005

### **Google Scholar Profile**

<https://scholar.google.com/citations?user=WslBsCkAAAAJ&hl=en>

### **Research Papers**

Watterson, E., Daniels, C.W., Watterson, L.R., Mazur, G.J. Brackney, R.J., Olive, M.F., & Sanabria, F. (2015). Nicotine-induced place conditioning and locomotor activity in an adolescent animal model of attention deficit/hyperactivity disorder (ADHD). *Behavioral Brain Research*, 291, 184-188.

Daniels, C. W., Watterson, E., Garcia, R., Mazur, G. J., Brackney, R. J., & Sanabria, F. (2015). Revisiting the effects of nicotine on interval timing. *Behavioral Brain Research*, 283, 238-250.

Vaidya, M., & Brackney, R.J. (2014). Interactions between equivalence relations and the development of analytic units. *Psychological Record*, 64(4), 681-691

Brackney, R.J., Cheung, T.H.C., Herbst, K., Hill, J.C., & Sanabria, F. (2012). Extinction learning deficit in a rodent model of attention-deficit hyperactivity disorder. *Behavioral Brain Functions*, 8(59).

Brackney R.J., Cheung, T.H.C, Neisewander, J.L. & Sanabria, F. (2011). The isolation of motivational, motoric, and schedule effects on operant performance: a modeling approach. *Journal of the Experimental Analysis of Behavior*, 96(1), 17-38.

### **Research Presentations (Talks)**

Brackney. R.J. (April 2015). Beyond the single lever press: a close look at bouts of behavior (Invited address). *Four Corners Association of Behavior Analysis, Annual Conference, Santa Fe, NM.*

Brackney, R.J., Cheung, T.H.C., & Sanabria. F. (May 2013) Behavioral processes contributing to the generation of bout-like responding. *Association of Behavior Analysis International: Annual Convention, Minneapolis, MN.*

Brackney, R.J. (September 2012). Enhancing neuroscience by dissecting behavior (Invited address). *4<sup>th</sup> Arizona State University & Barrow Neurological Institute Neuroscience Research Symposium. Phoenix, AZ.*

Vaidya, M. & Brackney, R.J. (November 2009). Do equivalence relations influence the development of analytic units? *Association of Behavior Analysis International: International Conference. Oslo, Norway.*



### **Research Presentations (Posters)**

Brackney, R.J., & Sanabria, F. (May 2015). What's in a bout? Functional manipulations of response rate components. *International Association for Behavior Analysis Annual Conference*.

Gerkin, R.C., Brackney, R.J., & Smith, B.H. (April 2015). Molecular nearest neighbors determine mouse behavioral generalization to overlapping odorant Mixtures. *Association for Chemoreception Senses Annual Conference*.

Brackney, R.J., Gerkin, R.C., Der-Ghazarian, T., Dai, K., & Smith, B.H. (April 2014). Olfactory stimulus generalization and habituation in the mouse: What makes two odors different? *Association for Chemoreception Senses Annual Conference*.

Brackney, R.J., Wilson, C. Moritz, A., & Sanabria, F. (May 2012). The local dynamics of a human concurrent choice preparation. *Society for the Quantitative Analysis of Behavior Annual Conference*.

Brackney, R.J., Hill, J., Herbst, K., & Sanabria, F. (May 2011). Extinction in an animal model of ADHD: A bout-response analysis identifies deficits beyond baseline performance. *Society for the Quantitative Analysis of Behavior Annual Conference*.

Scherbarth, A., Murrell A., Smith, R.G., Kapadia, V., Carlson. B., Lamancusa, M., Smith C.M., & Brackney, R.J. (May 2010). Evaluation of skill maintenance and external validity in a behavioral parent training program. *International Association for Behavior Analysis Annual Conference*.

Brackney R.J., Cheung, T., Neisewander, J., & Sanabria, F. (February 2010). A bi-exponential model of response-bout analysis under differential effort requirements. *Arizona State University Graduates in Earth, Life and Social Sciences Annual Conference*.

Brackney, R.J., Vaidya, M., & Arntzen, E. (May 2008). Extinction following schedules of continuous, intermittent and non-contingent reinforcement. *International Association for Behavior Analysis Annual Conference*.

Klipec, W.D., Scheider, B., Brackney, R.J., Stanley, K., Schwabe, J., & Young, B. (April 2005). The rat P300 ERP to signaled occurrence and omission of expected reinforcers following extended training. *Drake University Undergraduate Research Conference*.

Klipec, W.D., Brackney, R. J., Sounhein, K., Mejia, R., & Dolezal, A. M. (April 2005). The Effects of methamphetamine and cocaine on rats' Y-Maze performance using directional vs. visual cues. *Drake University Undergraduate Research Conference*.

### **Other Presentations**

Brackney, R.J., Cheung, T.H.C., Sanabria, F., & Lundberg-Kenrick, D. (December 2012). The bi-exponential refractory model of operant performance. *Online at* <http://www.youtube.com/watch?v=TkPiModqaIg>

### **Teaching Assistantships at Arizona State University**

BIO 202 – Human Anatomy and Physiology II (03/2015 – 05/2015) Supervisor: Delon Washo-Krupps

BIO 201 – Human Anatomy and Physiology I (01/2015 – 03/2015) Supervisor: Delon Washo-Krupps

BIO 361 – Animal Physiology Lab (08/2014 – 12/2014) Supervisor: Joanna Henry

PSY 101 – Introduction to Psychology (01/2014 – 05/2014) Supervisor: Robert Short

PSY 101 – Introduction to Psychology (08/2012 – 12/2012) Supervisor: Lynda Mae

PSY 290 – Research Methods Lab (01/2012 – 05/2012) Supervisor: Anita Pedersen

PSY 290 – Research Methods Lab (08/2011 – 12/2011) Supervisor: Heather Cate

PSY 230 – Introductory Statistics (05/2011 – 07/2011) Supervisor: Craig Nagoshi

PSY 230 – Introductory Statistics (01/2011 – 05/2011) Supervisor: Gary Groth

PSY 101 – Introduction to Psychology (08/2010 – 12/2011) Supervisor: Heather Cate

### **Honors and Awards**

School of Life Sciences Travel Grant, Arizona State University (05/2010)

Jump Start Grant, Arizona State University (03/2010)

Neuroscience Graduate Fellowship, Arizona State University (08/2009)

Doug Fields Memorial Research Grant, University of North Texas (04/2009)

Student Government Association, Raupe Grant, University of North Texas (08/2008 & 01/2009)

Donald L. Whaley Memorial Scholarship, University of North Texas (08/2008 & 01/2009)

College of Public Affairs and Community Service Travel Grant, University of North Texas (05/2008)

UNT Grant, University of North Texas (08/2006 & 01/2007)

Donald L. Whaley Memorial Scholarship, University of North Texas (08/2006 & 01/2007)

Dean's List, Drake University (01/2005 - 05/2005)

Psi Chi, Psychology Honor Society, Drake University (01/2003 – 05/2005)

Presidential Scholarship, Drake University (08/2001 – 05/2005)

### **Non-Academic Professional Work Experience**

Residential Support Worker for *Crossroads Counseling and Training* (06/2005 – 06/2006, Fairbanks, AK)

Pharmacy Technician for *Fred Myer Pharmacy* (06/2003 – 08/2003, Fairbanks, AK, )