Improved decoding methods to reduce reaction time in brain-machine interface systems

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SUMMARY: Brain machine interfaces (BMIs) use recorded neuronal activity to establish direct, real-time communication between the brain and external actuators such as prosthetic limbs (Lebedev & Nicolelis, 2006, 2009). Improved understanding of the relationship between modulations in sensorimotor cortical neurons and the complexities of realistic arm kinematics is a critical step in facilitating recovery in patients with motor deficits. Reaction time in the human motor system is a consequence of delays in motor and pre-motor processing steps as well as corticospinal projections. There exist many applications where this inherent response delay is undesirable such as vehicle control and military operations. Faster motor responses, even on the order of milliseconds, can drastically improve safety and performance in many common time-sensitive scenarios. Prior to initiation of movement, neurons in the motor (M1) and sensory (S1) cortices encode information about the timing and type of movement that will be initiated. Extraction of these parameters in real-time enables a reduction in latency between motor plan selection and initiation of movement. In this project, we characterized M1 and S1 neural activity during a reaction-time reaching task and identified highly modulated sensorimotor neuronal subpopulations to optimize our decoding methods and enact BMI operation at reduced reaction times. We were able to create a model that successfully predicts and executes movements to a specified target faster than a monkey itself can execute those same movements. This model proved effective, reaching the correct target for the majority of trials at a faster rate than the monkey model, thus reducing the response time in the execution of planned movement.

Introduction

Sensorimotor defects resulting from neurologic injuries, diseases, or limb loss affect millions of people worldwide. In the United States alone, five million people are currently afflicted with some form of paralysis according to data from Medical News Today (Paddock, 2009). Such paralyzing disorders substantially limit independence, mobility, and communication. Despite severe motor deficits due to damage to the spinal cord, nerves, or muscles, many patients retain fully intact cortical and subcortical motor networks that are capable of motor processing (Mattia et al., 2009). These areas can adapt to new controls due to innate brain plasticity (Hosp & Luft, 2003; Weinstein et al., 2003). To bypass the site of neural lesion, activity from healthy motor regions such as M1 or S1 can be connected to a neural prosthetic through an interface, called a brain-machine interface (BMI) (Lebedev & Nicolelis, 2006). Thus, artificial actuators such as an exoskeleton or artificial limb utilizing neurophysiological signals from undamaged components of the central nervous system allow for direct interaction between the brain and the outside world (Andersen et al., 2004; Jackson et al., 2004; Lebedev et al., 2006). Many research groups are currently pursuing this goal with the hope that BMIs with increasingly sophisticated technologies and decoding strategies will serve to augment partial and full body mobility in paralyzed patients (Andersen et al., 2004; Birbaumer et al., 2007; Fetz, 2007; Lebedev et al., 2006; Mussa-Ivaldi et al., 2003, Nicolelis et al., 2009, Schwartz et al., 2006).

Development of BMI systems

In recent years, there has been much development in the quality of recordings extracted from neuronal ensembles with the aim of creating improved BMIs to drive neuroprosthetics. Initially, single-electrode implants in the brain showed promise for providing the source of signals to drive artificial devices in restoration of mobility after paralysis (Schmidt et al., 1980). Advancing on this technique, the development of the novel electrophysiological model of multi-electrode recordings, such as the Utah Intracortical Electrode Array (UIEA) emerged (Maynard et al., 1996). The UIEA demonstrated the ability of neuronal populations to perform control tasks and showed that the number of neurons present in a recording is significant, as recordings from small populations of neurons rather than single units are more reliable for brain-computer interface application. The introduction of this effective model was almost simultaneous with the development of BMIs (Schmidt, 1980). Chronic implants containing multielectrode arrays in multiple cortical areas of the rhesus monkey’s brain are now able to record extracellular electrical activity of hundreds of neurons (Carmena et al., 2003; Fitzsimmons et al., 2009; Lebedev et al., 2005; Nicolelis et al., 2003; Lebedev & Nicolelis, 2011). With these novel electrophysiological techniques executing simultaneous
recordings from populations of neurons in distinct brain areas, significant information can be derived from ensemble encoding (Nicolelis et al., 1995, 1997, 2003; Kralik et al., 2001; Nicolelis & Ribeiro, 2002).

After nearly two decades, the ability of highly distributed populations of broadly tuned neurons to sustain the continuous production of motor behaviors in real-time has been evaluated and better-understood (Serruya et al., 2002; Taylor et al., 2002, Wessber et al., 2000). Many studies have demonstrated that cortical neurons modulate their firing during voluntary movements and therefore encode a variety of movement parameters (Georgopoulos et al., 1986, 1992; Ashe & Georgopoulous, 1994; Fu et al., 1995; Sergio & Kalaska, 1998). However, it is well known that individual neurons largely do not demonstrate a one-to-one relationship with any motor parameter (Ashe & Georgopoulous, 1994; Sergio & Kalaska, 1998; Carmena et al., 2003) as they exhibit considerable variability in their neural activity (Lee et al., 1998; Shadlen & Newsome, 1998; Cohen & Nicolelis, 2004; Wessberg & Nicolelis, 2004). Rather, it is the cumulative activity of large and diverse neuronal ensembles that regulates execution of precise movement (Wessberg et al., 2000; Carmena et al., 2003). Incorporating motor, sensory, and cognitive signals, encodings of such activity show high complexity (Cheney & Fetz, 1980; Alexander & Crutcher, 1990; Lebedev et al., 1994; Donchin et al., 1998; Kakei et al., 1999). Therefore, it has been demonstrated that large neuronal populations maintain the ability to generate motor commands during planning and execution of movements despite being disconnected from the body's effectors. Thus, it is possible to extract neuronal signals from real-time recordings of such populations, obtain relevant movement parameters, and utilize them in the control of BMI driven neuroprosthetics (Andersen et al., 2004; Carmena et al., 2003; Chapin et al., 1999; Jackson et al., 2004; Patil et al., 2004; Nicolelis, 2001; Serruya et al., 2002; Taylor et al., 2002; Wessberg et al., 2000; Wessberg & Nicolelis, 2004).

Previous studies have also shown that the arm region of the motor cortex specifically encodes kinematics of reach parameters including velocity (Moran and Schwartz, 1999; Lebedev et al., 2005) and information about movement onset and offset (Lebedev et al., 2008). For example, time-varying speed of movement was represented in cortical activity in addition to the well-studied average directional selectivity, or preferred direction of a single cell (Moran and Schwartz, 1999). In Lebedev et al., 2008, researchers identified neuronal ensembles capable of encoding information regarding temporal intervals during self-paced delay tasks. This neuronal ensemble activity was used to generate predictions that discriminated between delay periods and movement periods of the task. This study, and the study presented in this thesis, seeks to enhance the temporal resolution by which we can extract information from the brain. Neural coding operates at a millisecond time scale and improving BMI efficacy will depend on fast and accurate interpretation of neuronal population activity.

Another factor to consider in the creation of BMIs is the inherent plasticity of the brain and autonomic adjustments. As early as 1960, Clynnes and Kline described the interaction of artificial and biological components. In their work, they discussed, "If man in space, in addition to flying his vehicle, must continuously be checking on things and making adjustments merely to keep himself alive, he becomes a slave to the machine". They sought to create a mechanism by which “such robot-like problems are taken care of automatically and unconsciously, leaving man free to explore, to create, to think, and to feel" (Clynnes & Kline, 1960). In recent research, Mussa-Ivaldi and Miller explore the importance of plastic changes in the brain and rapid feedback in order to enact a more successful BMI. There have been several attempts to induce controlled plastic changes in the brain to simulate how a BMI would react to such a change. Such experiments provide the idea of activating central sensory areas directly using electrical stimulation as a means of reducing feedback delays (Mussa-Ivaldi & Miller, 2003).

Serruya et al. and Taylor et al. utilized paradigms in which subjects receive visual feedback of brain-controlled movement and learning-induced changes in neural activity patterns are tracked (Serruya et al., 2002; Taylor et al., 2002). Serruya discussed use of a linear filter method that is constructed during neuronal control to test whether hand trajectory could be reconstructed from neural activity. Reconstruction accurately reflected hand trajectory, and movement to targets was nearly as good with brain control as it was with hand control, with time required to reach the target only slightly greater with neural signaling. In addition, the study demonstrated that visual and other forms of feedback, paired with a subject’s dynamic learning, can compensate for inaccuracies in a BMI model to provide a voluntarily adjusted control signal. Furthermore, their results demonstrated feasibility for human application with an electrode array suitable for human use (Serruya et al., 2002).

Advancing on this, Taylor et al. created a model that incorporates learning-induced changes in neuronal activity during brain-controlled movements, bypassing the need for physical limb movement even while training the model. Researchers explored how visual feedback affects movements derived from cortical signals by comparing movements enacted during closed-loop paradigms (monkeys did not receive visual feedback) and open-loop paradigms (monkeys received visual feedback). Movement trajectories from closed-loops were more accurate on average than open-loops, and animals were able to improve their closed-loop target hit rate over the course of the experiment. These results imply that the subjects learned to modulate their brain signals more effectively when visual feedback was given, consistent with the discoveries of Serruya et al.

Because hand-controlled cursor movements cannot be carried out in patients with movement deficits, a co-adap...
tive movement prediction algorithm was developed. Such a model did not require physical limb movement, and learning induced changes in cell tuning properties were successfully tracked. Individual as well as groups of cells showed substantial differences in preferred directions between the two tasks. These results showed how paralyzed patients could make 3D cursor movements by co-adapting a prediction algorithm to their dynamic cell tuning properties. This study also demonstrates the need to record neuronal activity from brain control elicited movements as well as movements physically enacted by the body in order to create BMIs that function to effectively represent natural movement (Taylor, et al., 2002).

Realizing this, Musallam, et al., sought to extract movement goals from monkeys specifically without the monkeys enacting physical behavior related to the movement. They were able to decode intended goals of three monkeys using neuronal activity from brain-controlled trials as the monkeys positioned cursors on a computer screen independent of physical movement of the body. This demonstrated the ability to use high-level neural signals from the premotor and parietal cortices in driving a neural prosthesis (Musallam et al., 2004). Progress has been made in developing BMI models that can extract increasingly sufficient and valuable neuronal data, but there still remains much more to understand and improve upon in order to create a BMI model capable of producing natural voluntary and autonomous movement in humans.

**Monkey to human models**

In order to execute a BMI driven neuroprosthetic that enacts movements indicative of natural human voluntary movement, numerous facets of movement must be explored. As a close relative to humans, results using rhesus monkeys can provide a reasonable first estimate for what may or may not work in humans. Rhesus monkeys have become the animal model of choice in BMI research although previously, rodents, cats, owl monkeys, and humans have been used (Chapin, et al., 1999, Kennedy and Bakay, 1998; Stanley et al., 1999, Wessberg et al., 2000).

The rhesus monkey is the optimal model for several reasons, including their advanced reaching and grasping abilities and sophisticated hand manipulation skills. They are also able to quickly learn how to voluntarily control the firing rates of individual and multiple neurons in the primary motor cortex if rewarded for generating successful patterns (Schmidt et al., 1978). Additionally, rhesus monkeys have deeply cleft and furrowed brains, making them better models for human neurophysiology than owl monkeys (Carmena et al., 2003; Lebedev et al., 2005). Rhesus monkeys serve as more effective test subjects than human models for widespread research as they are similar in neural complexity and capability, but are less vulnerable to complications (Kennedy and Bakay, 1998). BMIs developed with these animals will provide feasibility for the main safety concerns of long-term implants and estimates of the neuroprosthetics performance. Using rhesus monkeys, numerous studies have demonstrated that signaling from neuronal ensembles during movement related tasks provides substantial information to successfully control a computer cursor or robotic arm (Carmena et al., 2003; Lebedev et al., 2006; Musallam et al., 2004; Serruya et al., 2002; Taylor et al., 2002). Thus, with discoveries from BMI experimentation with monkey models proving promising, BMI technology may be applied to treatment of motor deficits in humans through the use of neural prosthetics in coming years. However, rigorous clinical trials validating the use of BMI control must be established.

Several studies utilizing signaling from neuronal ensembles to control a computer cursor have also been enacted in human models, demonstrating applicability of BMIs for human patients with motor deficits (Kennedy et al., 2000; Leuthardt, et al., 2004; Hochberg, et al., 2005; Patil et al., 2004; Wolpaw and McFarland, 2004). In Kennedy et al., 2000, a neurotrophic electrode that uses trophic factors to encourage growth of neural tissue was implanted into the outer layers of the human cortex for two human subjects in order to synthetically produce speech and typing in patients who cannot effectively communicate. Results indicated that recorded neural signals can drive a cursor across a screen onto targets in order to accurately select icons or letter squares and such tasks demonstrated positive learning curves. The rate at which letters could be accurately selected in order to spell, 3 letters/min, is similar to alternative techniques (Kennedy et al., 2000). Such success yielded hope for BMI models in humans able to enact movements necessary for everyday tasks.

A major advancement came from the research of Hochberg et al. in 2006 when a tetraplegic human participant in an ongoing pilot clinical trial was able to operate a neuromotor prostheses (NMP) controlled by spike activity from M1 neuronal ensembles. Even years after a spinal cord injury, it was found that neural spiking remained in the M1 arm area and intention of movement could be extracted. A cursor was controlled through extracted neural signals from M1 and the patient was able to open simulated e-mail, operate a television, open and close a prosthetic hand, and perform actions with a multi-jointed robotic arm, all while speaking. NMPs have the potential to be scaled so that parallel commands could be simultaneously extracted from multiple sensors, each in discrete cortical regions. Independent outputs could then emanate bilaterally to both arms and legs, for example (Hochberg et al., 2006).

In order to most effectively and realistically execute motor actions using neuroprosthetics during everyday tasks effectively, feedback from the external environment in which these movements are made is vital. Examples include feedback regarding facets of mechanosensation such as touch and temperature. Such advancements are crucial in situations where visual feedback is insufficient such as picking up a textbook. In order to gauge how much force to exert in lifting the book, mechanosensory feedback is necessary throughout the duration of movement. Missing,
injured, or paralyzed limbs lack sensory input to the CNS, in addition to motor functionality. Recent work has sought to further enhance BMIs by providing a sensory modality to the artificial limb.

To implement sensory feedback into a BMI, a recent study developed a brain-machine-brain interface (BMBl), or simply a BMI system featuring intracortical microstimulation of S1 (O’Doherty et al., 2011). This sensorized BMI, unlike previous motor BMIs, acts to provide information regarding tactile sensory information in the environment explored by the actuated prosthetic limb (O’Doherty et al., 2011). In this novel experimental paradigm, rhesus monkeys enacted upper limb control using a brain-machine-brain interface that controlled the exploratory reaching movements of an external actuator while ICMS of primary somatosensory cortex provided a means for feedback. Distinct temporal patterns of ICMS encoded texture representations of three visually identical textures. Monkeys operated this BMI using activity of motor neurons to move a realistic virtual avatar arm into position to identify and discriminate the unique artificial textures associated with each of three targets. Thus, monkeys were able to identify and experience tactile sensation solely using brain activity and feedback to the cortex.

In his words, Dr. Miguel Nicolelis explains “Such an interaction between the brain and a virtual avatar was totally independent of the animal’s real body because the animals did not move their real arms and hands, nor did they use their real skin to touch the objects and identify their texture. It may be possible to create an exoskeleton that severely paralyzed patients could wear in order to explore and receive feedback from the outside world. Such an exoskeleton would be directly controlled by the patient’s voluntary brain activity in order to allow the patient to move autonomously. Simultaneously, sensors distributed across the exoskeleton would generate the type of tactile feedback needed for the patient’s brain to identify the texture, shape and temperature of objects, as well as many features of the surface upon which they walk.” Such work yields promise for the construction of BMIs that allow patients with motor deficits to regain function that closely parallels that of natural movement and interaction with the external environment.

**Extraction of movement parameters prior to movement onset**

Research into various facets of movement has provided hope for the restoration of autonomous and voluntary movement in patients with motor deficits; yet, there is an incredible amount that must still be learned. The ability to discover and improve the function of BMIs is essentially limitless, and must therefore be explored one step at a time. This research focuses on one specific and crucial facet of planned motor movements; the period following application of a stimulus but prior to the onset of movement, known as the reaction time. Further investigation into the reduction of reaction time would be widely applicable to the successful operation of BMI driven neuroprosthetics in the execution of everyday time-sensitive tasks.

In monkeys, the activity of neuronal ensembles in the motor cortex (M1) during movement has been extensively analyzed, but there is much to be discovered from neuronal activity during the period prior to movement onset. Once cortical neurons demonstrated the ability to modulate their activity prior to movement, researchers have experimented with using these signals to control various prosthetic devices (Craggs et al., 1975; Wolpaw et al., 2004). This window where the movement intention is present but the action is yet to occur is the ideal temporal epoch to derive information for BMIs. Advances in chronic recording electrodes and signal-processing technology reveal the possibility to use these cortical signals in real-time. Real-time BMI systems operate most effectively when salient information is extracted prior to the movement event occurring. Much research has focused on improving this neural decoding algorithms to exploit the biological lead time of motor intentions, including work in rats (Chapin, et al., 1999) and nonhuman primates (Carmena et al., 2003; Moritz et al., 2008; Taylor et al., 2002; Velliste et al., 2008; Wessberg et al., 2000).

Neural recordings from the M1 region of rhesus monkeys have demonstrated increased activity 200-500ms prior to the onset of voluntary movement (Kubota and Hamada, 1979). More specifically, a temporal segregation was discovered between parameters of direction, target position, and movement distance, with direction related discharge (115ms before movement onset) followed by target position (57ms after movement onset) and movement distance (248ms after movement onset), although some overlap was evident (Fu et al., 1995). Furthermore, it was also found that several of these motor parameters can be represented by a single cell (Fu et al., 1995). From the culmination of extensive research, the direction of movement is encoded by cortical neurons 150-100ms before the onset of the voluntary movement (Georgopoulos, 1995, 1995, 1988, 1989).

Neurons in the primary motor cortex are often characterized by the preferred direction of the cell, i.e. the direction of movement, which corresponds to the largest increases in neural firing rate (Georgopoulos et al., 1989). The directional modulation of neurons is one of the primary motor parameters encoded during the reaction time period and is a parameter with important implications for motor BMIs. Combining the activity of large numbers of directionally tuned cells in M1, an estimate of the intended movement direction can be made, termed the population vector (Georgopoulos et al., 1989). The direction of the population vector (calculated at 20 ms intervals) during the reaction time was able to predict the direction of upcoming movement. Additionally, it has been found that during the reaction time period, target size influenced the slope of the rise in firing rate, and during movement, cortical representations were dependent on movement velocity (Ifft et al., 2011).
Efforts to improve the speed of control for a computer cursor, simulating a shortened reaction time in execution of planned movements, have been the subject of a recent study with monkeys (Santhanam et al., 2006). In a key selection task, monkeys were able to perform center-out reaches of a prosthetic cursor using a BMI driven by unprecedentedly brief neural recordings, on the order of hundreds of milliseconds. A higher performance BMI than previously reported, capable of operating up to 6.5 bits per second or ~15 words per minutes, was demonstrated. The results of this performance implicate a system design, which, in conjunction with other human studies, could substantially increase the clinical viability for BMIs in humans (Santhanam et al., 2006). Other such studies with humans include the development of directional specificity during the reaction time period, with specification evolving over a 200ms time period about 100ms after target presentation (Ghez et al., 1997).

This study aims to advance on previous research conducted on neuronal activity extracted during the reaction time period in order to reduce the time course within which voluntary reaching movements can be executed. The goal of this study is to directly translate neuronal activity into a movement selection, such as the control over movements of a cursor to a decoded target location. This approach is termed end-point control and speeds up actions by bypassing continuous BMI control, favoring discrete outcome selection. The ability of a BMI to correctly predict desired target direction from activity of neuronal ensembles during a specified epoch of the reaction time period was demonstrated. Longer windows yielded more accurate predictions but decreased the number of predictions that can be made per second.

The approach used in the present study is to extract motor commands and identify the intended direction of movement early in the reaction time period. Linear discriminant analysis was employed to make categorical predictions of target location using binned neural activity to train the model. This strategy bypasses the need to predict continuous parameters such as position and velocity. As such, the time required to initiate a movement can be reduced. Using monkeys implanted with multielectrode arrays to record neuronal ensembles, we analyzed the activity of neuronal populations during the reaction time period in order to accomplish the following specific aims 1. Determine the relationship between pre-movement neural activity and the accuracy of classifier predictions of reach direction and 2. Demonstrate that pre-movement activity can be decoded to instruct the intended reach location faster than the monkey’s own movements with high fidelity and accuracy.

**Methods**

*Electrode implants and recording mechanism*

Rhesus monkeys M and N (male, female respectively) were chronically implanted with multi-electrode arrays in right and left hemisphere M1 and S1 according to previously discussed surgical methods (Nicolelis et al., 2003). Two 96 channel microelectrode arrays were inserted into each hemisphere in cortical areas corresponding to representations of arm and leg (Figure 1A). Each array consisted of grids of independently moving electrode triplets, each of which was comprised of electrodes.
of different lengths. This allowed for sampling of neuronal activity from different depths of the cortex. For the purposes of this study, neuronal activity was only recorded in the arm representation area of right hemisphere M1 and S1 in both monkeys. A multichannel recording system was used to amplify, digitize, and filter recorded signals. (Plexon Inc, Dallas, TX, USA). Spike-sorting software utilizing on-line waveform template matching and threshold features was used to sort neuronal spikes.

All studies were conducted with a protocol approved by the Duke University Institutional Animal Care and Use Committee and were in accordance with the NIH guidelines for the Care and Use of Laboratory Animals. Behavioral task

Monkeys M and N were trained to control the position of a computer cursor in a two-dimensional reaching task using a hand-held joystick. X (left-right) and Y (forward-backwards) positions of the joystick were translated to the X (left-right) and Y (up-down) positions of the cursor on the display screen, placed 45 cm from the monkeys’ eyes (Figure 1B). They performed center-out movements to peripheral targets, similar to a previous human study studying pointing movements (Smyrnis et al., 2000). The joystick was placed on the side of the working hand (left), at waist level. The left hand was chosen to hold the joystick because the quality of neuronal recordings was better in the right hemisphere of each monkey.

The monkey positioned its hand on the joystick to initiate a trial. If hand contact was broken with the joystick, the trial was discarded. Once the monkeys touched the joystick, a computer cursor (diameter of 0.5 cm) and a circle (diameter of 3cm) appeared at the center of the screen. The monkey then moved the cursor inside the circle, holding the cursor steady for a random interval between 800 and 1500ms (Figure 1D). After this interval concluded, the central circle disappeared and a peripheral target appeared at angles 45°, 135°, 225°, or 315° degrees on a thin circle aligned on the center of the screen. The monkey was required to move the cursor to this peripheral target, a thickened arc of 8, 15, or 22 degrees (Figure 1C). When the cursor crossed the target from the inside of the circle out, a juice reward was given. If the cursor was moved outside of the boundary of the circle without crossing the target, the trial was terminated and a 500ms timeout was given. There was a 5s limit to each trial. Three sessions in monkey M and four sessions in monkey N were used for analysis.

Data analysis

**PETH Analysis**

Neural activity was analyzed using peri-event time histograms (PETHs) aligned on target onset (Awiszus, 1997). Action potential (or spike) timestamp data from the experiments was recorded for offline for each cell. Bins of PETH represent number of spikes occurring in discrete increments of time over the task interval and were 25 ms in width. For each neuron, PETHs were calculated for each rewarded trial and averaged across trials for each possible movement direction (4 possibilities). For each neuron, this average modulation profile was normalized by subtracting the mean bin count and dividing by the standard deviation of the cells’ bin count. After normalizing, PETH depicts the statistical z-score, or the modulations as a fraction of the overall modulations.

**Neural decoding**

Linear discrimination analysis (LDA) is a linear classifier that uses a history of training data to make categorical predictions (Fisher, 1936). In the present study, LDA was used to decode the movement direction of a single trial from neuronal activity sampled across the task interval. A sliding window approach was used, where input for the LDA classifier was a vector of neural data, indicating the number of spikes occurring during a 100ms window for each cell. The window was slid at 25ms time steps from 500ms before and 1000ms after target appearance. The data was divided up such that 80% of trials for a given session serve as sample data, and 20% as training data for the decoder. LDA predicted variables of movement direction 1–4 (corresponding to 45°, 135°, 225°, and 315°, respectively) from ensembles of neurons. The accuracy of the LDA prediction analysis (fraction correct) was evaluated by dividing correct predictions by the number of possible correct predictions. The fraction correct was found at each time step of the sliding window throughout the length of the trial using M1 cells for monkey N and M1 and S1 cells for monkey M (Figure 3).

**Response profile**

An analysis was conducted to determine neuronal firing rates that exceeded an empirically determined threshold. First, the recorded spikes across a session for each cell were binned into 50ms bins. The mean spikes per bin were averaged across all neurons to generate population activity. To obtain the neuronal firing threshold value, we computed the mean population activity over a full session for each monkey. We defined threshold to be the initial time when population activity exceeded mean firing rate+2 standard deviations (Figure 4). This data was then analyzed with movement onset to determine the alignment between nearest threshold crossings (T0) and movement onset (M0). Movement onset was subtracted from nearest threshold crossing and the difference was obtained for each trial for monkeys M and N (Figure 5). The metric T0 – M0 was computed to better understand the temporal relationship between these two events. A t-test was performed on the distribution of T0 – M0 to determine if it was significantly shifted from 0 mean, as we would expect.

**Temporal effects on LDA prediction quality**

We sought to determine the effect of bin size on the quality of LDA predictions. Neuronal data was organized into 100ms bins, and four separate analyses were conducted using 1–4 bins, corresponding to a window length 100–400ms. The first bin always began 400ms prior to movement onset. The time was chosen because the mean
reaction time of these trials was approximately 500ms. The average across bins was taken and input into the decoder representing the mean firing rate for each neuron from the population of cells for the 100-400ms window of time. LDA once again predicted the movement direction from ensembles of neurons with 20% of trials serving as training data and 80% of trials serving as sample data for the decoder. Fraction of correct predictions was individually calculated for each separate analysis of bin size. Analysis was conducted on four sessions for monkey N and two sessions for monkey M using both M1 and S1 cells (Figure 6).

Executing accurate movements faster than the monkey

Our previous analyses yielded promise for a model that can decode a monkey’s pre-movement brain activity in order to instruct the intended reach location of each trial. We next sought to evaluate whether this information could be decoded and used to execute accurate movements towards a target faster than the monkey was able to execute such movements. LDA was used to generate predictions, with 30% of trials serving as training data and 70% as sample data. For each rewarded trial, LDA was used to predict movement direction from consecutive bins of neuronal data. Thus, LDA was applied at 100ms intervals, or bins, and the corresponding neuronal activity was decoded to determine the intended reach location at the earliest possible time interval while still maintaining accuracy for each trial.

An algorithm for the computer model was constructed. Every 100ms (10 Hz) from the time of target appearance (TA) until the time of entry into the target, a prediction of movement direction was made. If three consecutive predictions of a discrete movement direction were found between the nearest target appearance (TA) and TA + 800ms, it was determined whether 1. The prediction was correct and 2. The prediction was made prior to the time that the monkey reached the target. If both criteria were satisfied, the computer model was given a ‘point’. If the prediction of movement direction was incorrect or the monkey reached the target before the prediction was made, the monkey model was given a ‘point’. If three consecutive bins were not found between TA and TA + 800ms, we sought to find 2/3 bins with the same movement direction from the time period of TA + 800ms to entry into the target. If 2/3 bins with the correct movement prediction were found and the above two criteria were satisfied, the computer model was given a ‘point’. If not, a ‘point’ was given to the monkey model for that trial.

Thus, for every trial, if the LDA model was able to make an accurate prediction of intended reach location prior to the time that the monkey reached the target, the computer model received a point and ‘won’ that trial. However, if the computer model made either an incorrect prediction of movement or the monkey reached the target faster than an accurate prediction could be made, the monkey received a point and ‘won’ for that trial. For every trial, a single point or ‘win’ was given to either the computer or monkey model— whichever was able to execute the correct movement faster. Analysis was conducted on four sessions in monkey N and two sessions in monkey M using both M1 and S1 cells (Figure 7).

Results

Data were collected from four daily recording sessions in monkey N (2126 trials) and from three sessions in monkey M (1305 trials). Neural activity was recorded from 64-69 M1 neurons (range depends on different

Figure 2: Neuronal activity by cell during course of trials for monkey N.
Greatest neural activity occurred after target onset for most cells.
Figure 3: Fraction correct predictions of movement direction during the course of a trial.

3A., 3B., 3C. Values became significant upon onset of target appearance (confidence interval with standard deviation (SD) of 2, dashed line represents chance prediction value).

3D., 3E., 3F. Mean onset of movement for each session for either M1 or S1 cells (confidence interval with SD of 2, dashed line represents mean value).

3G., 3H., 3I. Entry into target for each session for either M1 or S1 cells (confidence interval with SD of 2, dashed line represents mean value).
In conducting a typical response profile, neural activity of the population was examined in the absence of temporal information about the behavior (see Methods). Neural activity throughout the course of the session from both monkeys was analyzed to depict a population response profile (Figure 4). Activity was averaged over the full population to yield mean response and response greater than 2 standard deviations above the mean (signifying threshold crossing). Population activity demonstrated sufficient amounts of threshold crossings throughout the course of the session for both monkeys, with data from monkey N shown (Figure 4). Further analysis was subsequently conducted on the temporal correlation between movement onset and nearest threshold crossing. We observed a rapid increase in firing rate that often occurred shortly prior to movement onset. In other words, a significant, detectable burst across the recorded subpopulation of neurons was seen at 318.3±711.6 (monkey N, p<0.05) and -179.9±1854.4 (monkey M, p <0.05) prior to movement onset (Figure 5).

It was determined that threshold crossings occurred before movement onset for both monkeys N and M. A t-test was conducted for both monkeys M and N yielding highly significant results, affirming that neural ensembles...

**Figure 4:** Population response profile.
4A. The recorded spikes across a session for each cell were binned into 50ms bins; population activity reflects the mean spikes per bin when averaged across all neurons for a single session. Sufficient threshold crossings were observed to conduct further analysis on the temporal relationship between movement onset and nearest threshold crossing. Both M1 and S1 cells from monkey N are depicted for one session.
4B. Select portion of the session (Movement onsets represented on the x-axis).

**Figure 5:** Alignment of firing onset and movement onset. Movement onset was subtracted from nearest threshold crossing. Both monkeys M and N showed rapid firing onset (first instance of exceeding the + two standard deviation threshold) on average prior to movement onset (p<0.05).
5A. Monkey N, all cells.
5B. Monkey M, all cells.
peaked in activity prior to movement onset.

Temporal effects on LDA prediction quality

LDA analysis was used as a classifier to predict behavioral direction from neuronal ensembles using window lengths of 100-400ms. For all four sessions for monkey N, fraction of correct predictions increased with increasing window length. Similar results were observed using two trials from monkey M, with an increase in the quality of LDA predictions as the length of the window was increased (Figure 6).

Executing accurate movements faster than the monkey

Four sessions from monkey N were used for analysis. Two sessions from monkey M were used for analysis. For the majority of trials, the computer model was able to decode intended reach location from neuronal activity to execute movements to a target; successfully completing a trial faster than the monkey could complete the same trial. Our results demonstrate that pre-movement activity can be effectively decoded to determine intended reach location, reducing the amount of time needed for a movement to be executed. Monkey M exhibited a higher percentage of tested trials. This is likely due to the superior quality of neuronal data extracted from analysis from monkey M because of the greater number and quality of cells used for recording (Figure 7).

Discussion

We were able to create a model that can successfully predict and execute movements to a specified target faster than a monkey itself can execute those same movements. The computer model proved extremely effective, successfully reaching the target and completing the majority of trials at a faster rate than the monkey model. This demonstrates the ability to accurately execute movements in a reduced amount of time, effectively eliminating a portion of the response time in planned movement. In addition, this method eliminates the time necessary to complete the movement itself, as the target is reached almost immediately after an accurate prediction is made. Thus, we accomplished our second aim by demonstrating that pre-movement activity can be decoded to instruct the intended reach location faster than the monkey’s own movements with both high fidelity and accuracy.

In order to determine feasibility for such a model, we conducted several analyses on the neuronal activity prior to and during movement. Each analysis yielded useful information that was utilized in order to develop our computer model. From the PETHs analysis it is evident that there are several components of reaction time. The first is a brief period of neuronal response after target appearance, during which no elevated activity is observed. A second interval after appearance of the target commonly consists of increased cell activity. Maximum activity is reached approximately 300-400ms after target appearance, although it is varied between neurons. Results from the LDA analysis show a performance equal to chance before target appearance and predictions reach statistically significant values less than 100ms after target appearance while the brain is processing the stimulus and generating a motor command, consistent with previous
Executing movements in a reduced amount of time has widespread applicability to a range of fields such as machine control, video gaming, and competitive athletics. Most importantly, it is applicable to real-life scenarios where a fast response is necessary, such as operating vehicles and responding to dangerous situations. We are currently working on an advanced model using solely neural activity that is able to make predictions without any time related information. Such a model would have prediction windows aligned on threshold crossings so that it can be implemented in real-time. This model is likely to be effective as threshold crossings are strong predictors of movement onset. Thus, the next step in this research is the development of a BMI that generates continuous predictions in real-time as a monkey model executes movements. With success from such experiments, this model could then be applied towards human clinical trials. With the discoveries presented in this research, we can ultimately improve reaction time to allow for more natural function with neuroprosthetic devices, and enact faster movements in time-critical situations.


