

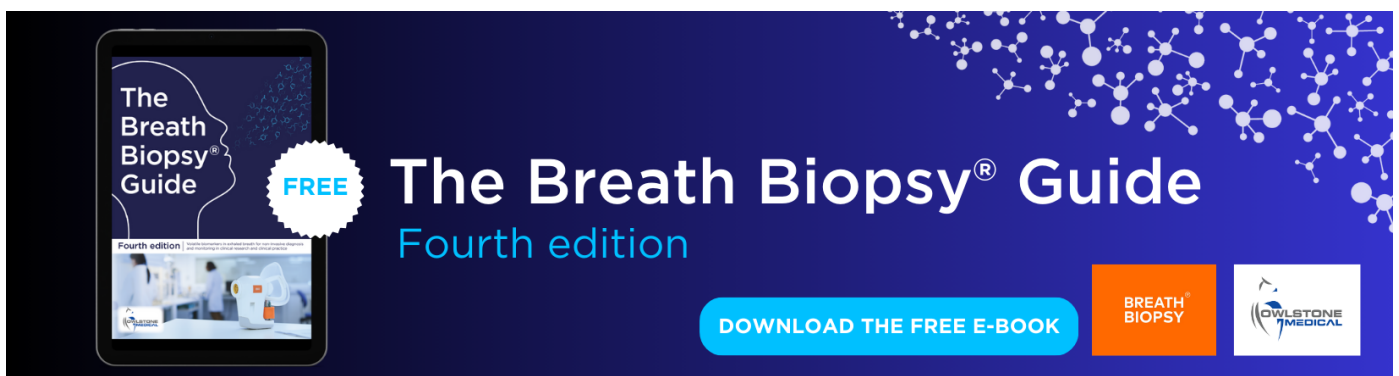
Selection and parameterization of cortical neurons for neuroprosthetic control

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Selection and parameterization of cortical neurons for neuroprosthetic control

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Abstract

When designing neuroprosthetic interfaces for motor function, it is crucial to have a system that can extract reliable information from available neural signals and produce an output suitable for real life applications. Systems designed to date have relied on establishing a relationship between neural discharge patterns in motor cortical areas and limb movement, an approach not suitable for patients who require such implants but who are unable to provide proper motor behavior to initially tune the system. We describe here a method that allows rapid tuning of a population vector-based system for neural control without arm movements. We trained highly motivated primates to observe a 3D center-out task as the computer played it very slowly. Based on only 10–12 s of neuronal activity observed in M1 and PMd, we generated an initial mapping between neural activity and device motion that the animal could successfully use for neuroprosthetic control. Subsequent tunings of the parameters led to improvements in control, but the initial selection of neurons and estimated preferred direction for those cells remained stable throughout the remainder of the day. Using this system, we have observed that the contribution of individual neurons to the overall control of the system is very heterogeneous. We thus derived a novel measure of unit quality and an indexing scheme that allowed us to rate each neuron's contribution to the overall control. In offline tests, we found that fewer than half of the units made positive contributions to the performance. We tested this experimentally by having the animals control the neuroprosthetic system using only the 20 best neurons. We found that performance in this case was better than when the entire set of available neurons was used. Based on these results, we believe that, with careful task design, it is feasible to parameterize control systems without any overt behaviors and that subsequent control system design will be enhanced with cautious unit selection. These improvements can lead to systems demanding lower bandwidth and computational power, and will pave the way for more feasible clinical systems.

Introduction

The idea of using chronically recorded neuronal signals as a means to control prosthetic systems, while having a long history (Fetz 1969, Humphrey *et al* 1970, Fetz and Finocchio 1971, 1972, Fetz and Baker 1973, Fetz and Wyler 1973, Wyler and Fetz 1974, Wyler *et al* 1974, Fetz and Finocchio 1975, Schmidt *et al* 1977, Schmidt *et al* 1978), has recently expanded dramatically. Starting from initial reports of animals

exerting volitional control over computers (Serruya *et al* 2002, Taylor *et al* 2002, Carmena *et al* 2003), the field has grown to include increasingly sophisticated processing of multi-channel neuronal signals (Hatsopoulos *et al* 2001, Kass and Ventura 2001, Schwartz *et al* 2001, Hatsopoulos *et al* 2003, Serruya *et al* 2003, Shenoy *et al* 2003, Kemere *et al* 2004, Paninski *et al* 2004, Helms Tillery and Taylor 2004) and the decoding of those signals to control the motion of devices like robotic arms (Carmena *et al* 2003, Taylor *et al* 2003, Lebedev *et al* 2005).

A system based on these developments has even been deployed in a human with upper spinal cord injuries (Donoghue *et al* 2004).

To date, these systems begin by mapping the relationships between neuronal activity and ‘natural’ behaviors like arm movements. This initial mapping is then transferred without modification to the control of the neuroprosthetic system, generally the motion of a computer cursor. There are two core problems with such an approach. First, a candidate subject for such a system is unlikely to have the natural behaviors to generate such a mapping. Second, there is no guarantee that the nervous system will treat control of a device such as a computer cursor, or even of a robotic arm, the same as control of its own arm. Thus, there may be no easy way to provide the required mapping, and even if such a mapping were provided, that relationship may be less than ideal for controlling an artificial system.

Resolving the issue of training the system without movements in humans may not be so difficult. It should be possible to ask subjects to imagine that they are performing a task, and from there develop an extraction algorithm for generating movement based on neuronal signals. In fact, this approach has recently proved feasible in teaching trans-radial amputees to open and close a gripper using signals recorded from peripheral nerves (Dhillon *et al* 2004, 2005). Humans, however, are not an appropriate test bed for long-term implant development. A means to ask this same question of, for example, non-human primates, would provide an environment for developing control algorithms and testing specific ideas about the control of artificial systems by the nervous system.

The possible coding differences between natural movements and control of prosthetic devices have been handled by inserting a period of adaptability into the control algorithm itself (Taylor *et al* 2002, 2003). The idea is to track any changes in the properties of neuronal firing as an animal switches from arm movements to control of a computer cursor in 3D. This manipulation produced more direct point-to-point movements and overall shorter movement times. There was also a suggestion that the coding for the neuroprosthetic system was stable from day to day. The parameter space for a neural controller with 50 neurons is difficult to analyse directly. However, random seedings of the tuning parameters produced final parameters that resided in the same regions of the parameter space.

In this paper we describe a system in which we can determine initial tuning parameters for a neuroprosthetic system in primates that have not made any movements. A simple 12 s of recording allows us to generate adequate data to estimate tuning profiles for a set of chronically recorded neurons in M1 and PMd.

For about a third of the neurons, that initial estimate converges quickly to the final value and remains reasonably stable as the animal controls the neuroprosthetic system. For another third of the neurons, the initial estimate of preferred direction converges quickly to 50°–60° from the final determined direction, but the error does still decrease as more data are accumulated for constructing the estimate. For the final third of neurons, the average angle between

the estimated preferred direction and the finally computed preferred direction decreases linearly as more data are used to construct the estimate, suggesting an entirely random relationship between the preferred directions from one instant to the next: the preferred direction in such cells would be an artifact.

In fact, further analysis led us to believe that these three groups of cells may vary in their overall utility to a neuroprosthetic system. One of the open questions in neuroprosthetics is how many channels need to be recorded to produce sufficiently rich signals to perform a useful task. Estimates based on bootstrap analyses of existing data have suggested anywhere from around 100 neurons to nearly a 1000 (Wessberg *et al* 2000, Carmena *et al* 2003, Serruya *et al* 2003, Hatsopoulos *et al* 2004, Sanchez *et al* 2004). In agreement with prior observations, our results here suggest that these numbers could be highly inflated by inclusion of neurons that produce decrements in control (Taylor *et al* 2002, Sanchez *et al* 2004). Therefore, we performed a new set of experiments in which the animals controlled the neuroprosthetic system with a reduced set of neurons in order to directly test how few neurons could be used to reliably control a 3D neuroprosthetic system. For this purpose, we developed a method to measure the contribution of any given cell to the overall control of the prosthetic system: the *individual removal error*. In this metric, larger values imply a more beneficial contribution to the overall control. Thus, we had an animal drive the system using only the 20 neurons with the highest values. Overall, we found that this led to several improvements in control of the system.

Methods

The data reported in this paper are from two rhesus macaques (*Macaca mulatta*) implanted with arrays of microwire electrodes in motor (M1) and premotor (PMd) cortices bilaterally. All procedures described in this paper were approved by the ASU Institutional Animal Care and Use Committee in accord with the NIH Guide for the Care and Use of Laboratory Animals and carried out in AAALACI approved facilities.

Behavioral task

The core task used in the experiments was a 3D center-out task (Georgopoulos *et al* 1986, Schwartz *et al* 1988, Schwartz and Moran 2000, Reina *et al* 2001, Taylor *et al* 2002). We used a virtual reality system in which the animal viewed a 3D arena in a mirror, and manipulated objects in the arena with either hand movement or direct cortical signals. The task consisted of moving a cursor into targets in the 3D environment. The targets were spheres placed at the vertices of a cube oriented in a frontal plane in the workspace, and the cursor was a sphere of a different color that was under control of the animal. Each movement was from the center of the cube to the target and then back to the center. A trial began with the presentation of a target sphere at the center of the workspace. Once the animal had moved the cursor into the center and held it in position for 300 ms, the center target disappeared, and another

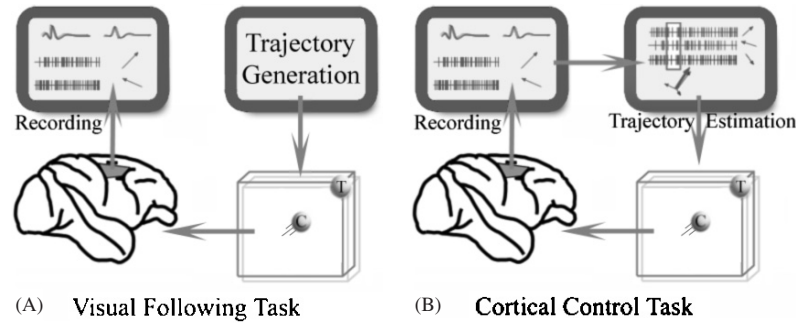


Figure 1. Visual following and cortical control tasks. In both tasks, the animal views a 3D task in virtual reality in which the goal is to move a cursor (C sphere) into a target (T sphere). In the visual following task, we record activity from M1 and PMd neurons as the animal observes the game played by the computer. Based on 12–15 s of data, we compute an initial estimate of the preferred directions for each of the recorded neurons (A). We then switch immediately to cortical control (B), using a population vector based on the initial preferred direction estimates to control the motion of the cursor.

sphere was illuminated. The animal then had 4000 ms to move the cursor into the target sphere. The animals were initially trained in the same virtual reality system to direct the cursor movement by their hands. Once the animals learned the cursor–hand relation, the training for direct cortical control of cursor movement started. After the animals learned to relax their arms during the direct cortical control we started to switch alternately between the hand control and direct cortical control. The neuronal data reported in this paper all come from brain control trials in which the animals’ arms were restrained. Analyses are underway comparing neuronal activity under brain control and arm movement tasks.

Each animal’s fluid intake was carefully regulated, so that the water requirements were met each day in the laboratory. The animal was thus rewarded for correct trials in the task with a small (0.1–0.5 ml) drop of water at the end of each successful trial.

Neuronal data acquisition and processing

We acquired neuronal signals from multi-unit recordings on chronically implanted microwire arrays. The microelectrode arrays were built in-house with 50 micron tungsten wires arranged into two rows of eight wires each. The arrays were implanted 1.5–2.0 mm into cortex in arm areas of M1 and PMd under standard sterile conditions with gas anesthesia (see Taylor *et al* 2002 for details of the implant procedure).

During performance of the behavioral task, signals on each channel were isolated and spike times recorded using a Multichannel Acquisition Processor (Plexon Inc, Dallas TX). Data quality among different channels varied, with some channels producing 2 or 3 well-isolated neurons, and other channels producing only high-frequency multi-unit hash. In this text we use the words ‘units’, ‘neurons’ and ‘cells’ interchangeably to refer to these recordings.

Throughout the work reported in this paper, cursor control was by means of a population vector which mapped the activity of a small ensemble of neurons to three-dimensional motion in real time. The data reported in this paper all come from an experiment in which the cursor motion was driven by the animal exclusively by direct cortical signals.

We opted to use a population vector to provide a mapping from neuronal activity to cursor motion for the reason that it is a simple linear algorithm lending itself to detailed analysis (Georgopoulos *et al* 1983, 1984, 1986, Taylor *et al* 2002, Helms Tillery and Taylor 2004). The firing rates were computed using 90 ms sliding windows at 30 ms increments, zero meaned and then normalized by their maximum zero meaned value.

$$\text{Fr}(un, t) = A + \text{PDc}(un)_x \cdot D_x(t) + \text{PDc}(un)_y \cdot D_y(t) + \text{PDc}(un)_z \cdot D_z(t).$$

The preferred direction for each unit, PDc, was then estimated by a linear regression between the firing rates and the ideal current direction $D(t)$ connecting the cursor to the target location, irrespective of the actual direction of cursor motion. The variable ‘A’ was the intercept and ‘un’ was the index for individual units. The population vector $\text{PV}(t)$ was computed every 30 ms; by summing the neurons’ preferred directions weighted by their instantaneous firing rates (see Georgopoulos *et al* 1986 for details).

$$\text{PV}(t) = \sum_{un} \text{PDc}(un, t) \cdot \text{Fr}(un, t).$$

The population vector was then used to update the location of the cursor in the virtual reality environment.

Initial tuning parameters were established from a *visual following task* (figure 1, left panel). In this task, the animal watched as a custom designed trajectory generator slowly moved the cursor once into each of the eight targets from the center of the cube along a straight line. Each directed movement of the cursor took 1.5 s. Thus, at the end of the visual following task we had around 400 bins (12 s with sliding 90 ms bins every 30 ms) of directional movement data and accompanying spike trains. From this limited sample of data we computed an initial fit of the firing rate to the movement direction in this 3D space, providing us our first estimate for the preferred directions of all the units. We refer to these incrementally estimated preferred directions as the *cumulative preferred directions* (PDc, see below). The *final* PD is indicated as PDf. In this paper, PDf is equal to the PDc computed using the complete set of data.

The data for the fit were accumulated over the first 5 min of data collection. The first presentation, *visual following task*, took approximately 12 s (figure 1, left). Once the first fitting was completed, the task was converted to a cortical control task, where the animal controlled the motion of the cursor directly using a population vector computed from the results of the first fitting (figure 1, right). During the first 5 min of cortical control, we continued performing regressions using the accumulating data to update our estimate of PDc at roughly 30 s intervals. At the end of the 5 min, the final regression produced a PDF for each unit.

Computation of individual removal error

We computed the contribution of each unit's activity to the overall control of the neuroprosthetic system using offline analyses of cortically controlled cursor movements. To begin the analysis, we went through all the bins of online control and computed an error angle for each bin: the angle between the population vector on that bin and a line connecting the cursor to the active target. One at a time, we removed cells from the ensemble controlling the movement, and once again computed for all bins the same error angle. We then averaged the change in error angle following removal of a given neuron from the ensemble. The resulting value was defined as that neuron's *individual removal error* (IRE).

$$\text{IRE}(un) = E_{\text{all}} - E_{\text{all-un}}$$

where E_{all} is the average angular error using all available units and $E_{\text{all-un}}$ is the average angular error computed using all available units except the unit indexed by 'un'. For a given set of units, E_{set} is computed as

$$E_{\text{set}} = \left(\frac{\overrightarrow{\text{PV}}_{\text{set}}(t) \cdot (\overrightarrow{\text{Tgt}}(t) - \overrightarrow{\text{Csr}}(t))}{\|\overrightarrow{\text{PV}}_{\text{set}}(t)\| * \|\overrightarrow{\text{Tgt}}(t) - \overrightarrow{\text{Csr}}(t)\|} \right)$$

$\text{PV}_{\text{set}}(t)$ is the population vectors at time t with all the units in the set. $\text{Tgt}(t)$ and $\text{Csr}(t)$ represent the target and cursor locations at time t , in the virtual reality environment.

Therefore, a good unit for this task and with this algorithm will have a high IRE. Finally, we rank ordered the cells according to their IRE values, and assigned each neuron an *individual removal index* (IRI). This novel measure rank orders the neurons according to their overall importance under any control algorithm.

Results

The data reported here were recorded from an average of 47 units spanning 45 days of recording in one animal (M) and 21 units over 16 days in the second (X). Animal M, from which the 45 days of data were acquired, had extensive exposure to the cortically controlled neuroprosthetics paradigm, whereas the second animal, monkey X, learned the cortical control task specifically for this experiment.

Visual following task

At the beginning of each recording day, while receiving its first daily water allotments, the animal watched as the computer

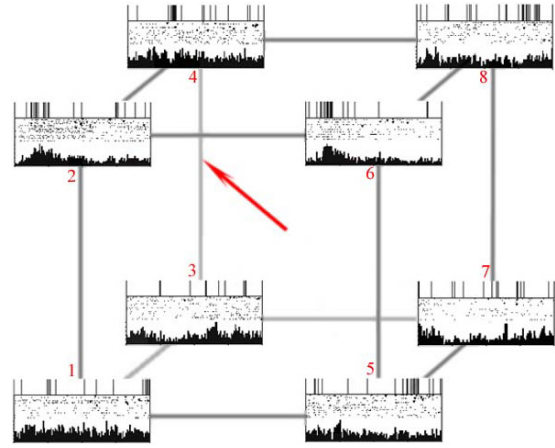


Figure 2. Visual following and cortical control data. Each raster/histogram shows the activity of a neuron during cortically controlled movements to one of the eight target locations. On top of each raster is a single trial record from a set of single trials in the visual presentation. The firing observed in this task close to that expected from the preferred direction (red arrow), with bursts observed particularly during cursor motion to targets 2 and 6.

moved the cursor once into each of the targets. This generally took around 12 s. As the animal watched, we observed that most neurons exhibited some pattern of activation which corresponded with the motion of the cursor in the virtual environment (figure 2). The neuron shown in figure 2, for example, showed a distinct pattern of bursting particularly during movements of the cursor to the upper targets. This pattern bore some resemblance to the activity patterns observed as the animal drove the cursor to each of the targets using cortical activity (rasters and histograms located at each target). This was in reasonable accord with the preferred direction (indicated by an arrow) as determined from the complete data set, which included ten cortically controlled movements of the cursor to each of the eight target locations.

This ability to tune a cortically controlled neuroprosthetic system using only 12 s of recording (one set of movements to each of eight targets) compares favorably with previous experience using an adaptive algorithm seeded with random parameters which has previously been reported to take a series of 15 movements each to the eight targets before the animal could reliably control the motion of the system (Taylor *et al* 2002).

In order to check whether the animal moved its arm during the cortical control and the visual following tasks, we continuously recorded the muscular activity while alternating between arm control and brain control. Figure 3 shows the processed EMG activities from five shoulder and upper arm muscles. EMG activity during both the visual following and the cortical control task periods were negligible compared to that during the arm control task. The raw signals obtained from surface electrodes were filtered (Butterworth band pass, 5th order, 50–450 Hz) and then the RMS values were calculated using 200 ms windows.

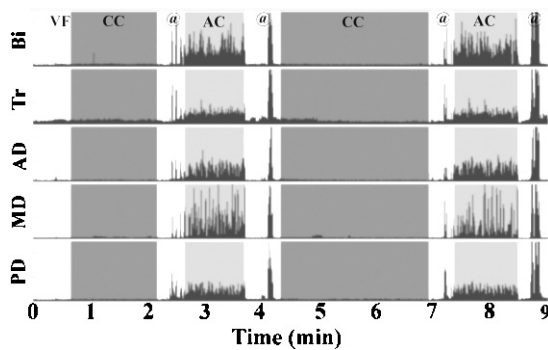


Figure 3. EMG activity was silent during the direct cortical control task. Processed surface EMG activity under visual following (VF), cortical control (CC) and arm control (AC) during a subsequent experiment. Between the tasks, we entered the room to restrain/free the animal's arm. The data were recorded from biceps(Bi), triceps(Tr), posterior (PD), anterior (AD) and medial (MD) deltoids.

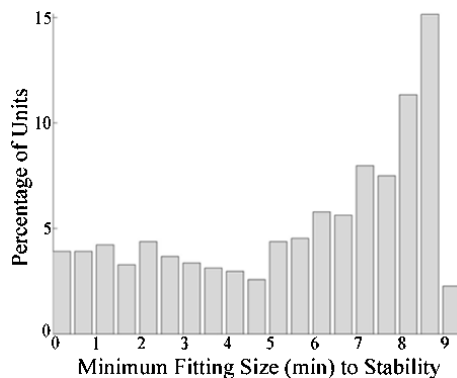


Figure 4. Amount of data required for convergence of preferred directions. The distribution shows how much data, in minutes, needs to be accumulated to estimate the preferred direction of each neuron before the estimated PD falls within 20° of the final computed PD.

Accumulating estimate of PD

The amount of data required for the estimated preferred direction, PD_c, to converge on the final value, PD_f, varied considerably for different neurons. In figure 4 we show a histogram of the size (in time) of the samples that had to be acquired for each neuron until the PD_c converged to a direction within 20° of PD_f. In about 20% of the cases, the estimate calculated with 2 min worth of data was within 20° of PD_f. At the opposite extreme were neurons for which the calculation never produced a particularly stable PD: in these cases, the difference between the PD_c and PD_f decreased slowly until the data set used to fit the PD was complete. This is the property one would expect if the PD were essentially random from one bin to the next. Finally, there are also cells with intermediate properties where the PD_c does converge, but neither rapidly nor to a high degree.

The data shown in figure 4 indicate that not all neurons have equally reliable PDs (see also Sanchez *et al* (2004)), which would suggest that not all neurons contribute equally to the performance of the algorithm. To examine this issue,

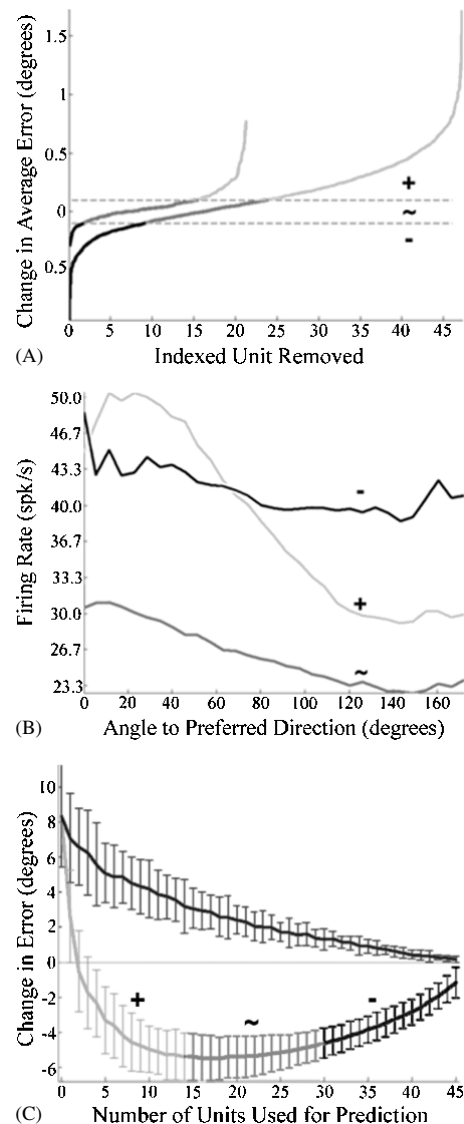


Figure 5. Contribution of individual neurons to overall system performance. (A) The *individual removal error* for the neurons from the two animals plotted against *individual removal index*. The dark, medium and light traces show respectively *negative* (−), *neutral* (∼) and *positive* (+) units. (B) Mean tuning functions for each of the groups shows that neurons with large IRE tend to have high depth of modulation compared to the other neurons, whereas neurons with negative IRE show low depth of modulation on a high background firing rate. (C) Individual neuron contribution to performance is shown in two ways. First, neurons are simply removed from the ensemble and not ranked, providing an estimate of how system performance improves with additional neurons (upper trace). To compute IRE, the neurons are rank ordered according to their contribution (lower trace). In this case the first third produce improvements in performance, whereas addition of the remaining 1/3–2/3 of the neurons produces a decrement in performance.

we computed the individual removal error (IRE) for each of the cells and plotted that value as a function of the individual removal index (IRI).

In figure 5(A) we show the results, in which IRE is plotted as the change in mean error produced by removing

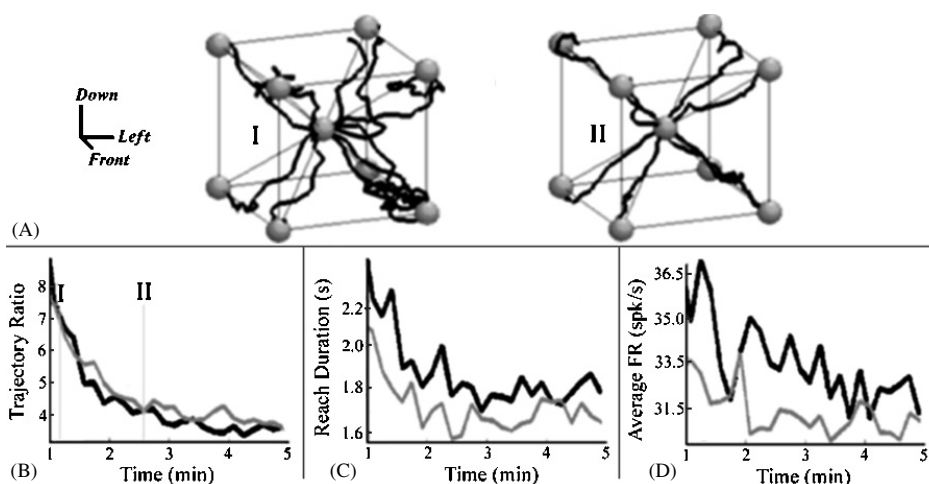


Figure 6. Change in performance as parameters for the control algorithm are tuned. Panel A illustrates individual cortically controlled cursor movements to each of the eight targets at two times following the beginning of tuning: (I) at the end of the visual following task; (II) after 60 s of additional data accumulation. Figures are drawn as shown on the screen prior to reflection in the mirror, leading to a left-handed coordinate system. Panels B, C and D show the general characteristics of the movements (B: ratio of the summed path length and the direct distance from the center to the target; C: the time in seconds taken to reach the targets) and of the entire neuronal ensemble (D: mean firing rate) for the case when the entire ensemble is used (dark) or when just the 20 ‘best’ neurons are used (light).

each indexed neuron individually. The 47 neurons for monkey M (lower trace) and 21 neurons for monkey X (upper trace) clearly varied in their impact on the performance of the cortical control. At one extreme were highly significant contributions to the performance indicated by large positive increases in the error following removal. At the other extreme were neurons which improved the performance of the cortical control when their contributions were removed from the ensemble (negative IRE). We split the complete ensemble into three groups by establishing a threshold at $\pm 0.1^\circ$ change in the performance of the algorithm. The neurons which produced greater than 0.1° increase in the mean error angle when removed from the ensemble were labeled as ‘positive’. Those which caused greater than 0.1° decrease in mean error angle by removal were labeled as ‘negative’, and the remainder were labeled as ‘neutral.’

Units in each of these three groups had distinct characteristics in at least two ways. First, the tuning profiles were distinguishable. Neurons in the *positive* group had well-modulated tuning curves, with a large range between minimum and maximum firing rates, compared with neurons in the other two groups (figure 5(B)). The *negative* and *neutral* groups both had extremely shallow tuning curves. *Neutral* and *negative* cells had another difference: *negative* cells had a much higher background firing rate. Combined with their poor directional tuning, these neurons essentially contributed noise to the control signals.

Generally, estimates of the number of neurons required to meet some performance criterion are generated using random neuron addition with replacement. We performed this simulation, adding randomly selected neurons one at a time and estimating the impact each serial addition would have on the overall performance of the system. The result is shown in the upper trace in figure 5(C). As previously observed in a

number of cases (Carmena *et al* 2003, Hatsopoulos *et al* 2004, Sanchez *et al* 2004), each additional neuron adds a certain element of accuracy to the performance of the system, here measured as the difference between the movement directional error with the full ensemble and the movement direction error with the indicated number of neurons. As expected, the error falls off in a relatively exponential fashion as random neurons are added to the ensemble. We repeated the bootstrap analysis, but this time selecting neurons based on their individual removal error or the order of their IRI (figure 5(C), lower trace). The average decreased steeply with the addition of the first few units from the *positive* group. By the time we had added the first 15 indexed units, the change in error had actually dropped to a negative value: the simulated performance with this subset of units was *better* than the actual performance with the full complement of units. By the time we had added the remaining units, however, the performance had fallen back to the observed value from the complete ensemble. In other words, the final two-thirds of the indexed neurons in this sample impaired the overall performance of the system.

Recognizing that some neurons might actually detract from overall performance of a neuroprosthetic system led us to a series of experiments in which the animal controlled the cursor motion using all of the available neurons, or in separate sessions, controlled the cursor using a reduced set which contained no *negative* cells.

In each of these experiments, task performance improved as we acquired more data and continued to refine the estimated preferred directions, PDc. In figure 6(A) we show example paths to each of the targets in two different phases while adjusting the parameters for the control algorithm. The initial brain-controlled movements to the targets were very unsteady and followed convoluted paths. By the second minute of recording, however, the paths had become much straighter

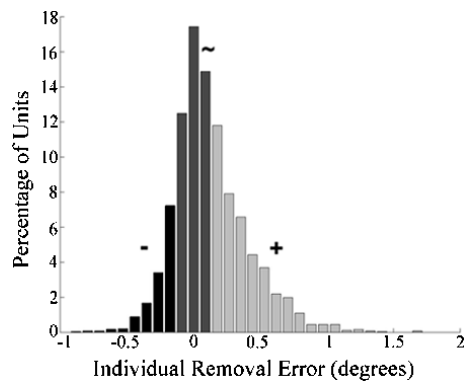


Figure 7. Distribution of individual removal error. The individual removal error computed for varying ensembles of neurons recorded on the same implants in 45 sessions.

and direct, as the animal had evidently gained finer control over the cursor. This is also evidenced in the average ratio of the path length to the distance from the center to the targets (figure 6(B)) as well as the steadily decreasing reach duration (figure 6(C)). In addition, the overall average firing rate across the complete ensemble decreased as the PD calculation progressed (figure 6(D)). All of these observations held whether the cortical control was exerted with the complete ensemble (dark traces) or with a reduced ensemble consisting only of those twenty neurons with the highest IRE (light traces). Notably, both the overall mean firing rates (figure 6(D)) and the movement durations (figure 6(C)) were lower when the animal was using the reduced ensemble of neurons as compared with using the complete set of neurons.

Our classification into *positive*, *neutral* and *negative* groups is not meant to imply that there exist three classes of neurons. Each of the measures employed to characterize the neurons exhibited continuous distributions. For example, the distribution of the *individual removal error* is continuous and single peaked with a mean 0 (mean = 0.14, median = 0.1, standard deviation = 0.3) (figure 7). There is no evidence of three separate peaks corresponding to the three classifications we have applied. Thus, establishing a boundary determining which cells are included or are not included in any control scheme is a qualitative decision.

However, we found a clear relation between the IRE and the stability of the PD estimate. For this purpose, we arbitrarily split the recordings of cortical control into 15 s segments and computed the PD for each segment. We then used the *R* value described in Batschelet (1981) as an estimator of PD stability. We found a correlation of 0.60 between the neurons stability and their IRE.

Discussion

We have developed a simple method in which tuning parameters for the control of neuroprosthetic systems can be estimated in non-human primates without any overt behavior. The only requirements are that (a) the system uses a task for developing tuning parameters that can be performed by a

computer, and (b) the computer's performance be observed by a well-trained and highly-motivated animal. We have limited our discussion to a 3D center-out task, but the general principles should be readily applicable to any task an animal might perform in order to generate tuning parameters.

Our hypothesis regarding the directionally tuned activity we observed is that, as the computer performs the task, the animal is acting volitionally as if it were participating in forcing the cursor into the target. Remarkably, we found that with as little as 12 s of distributed directional data, we could compute a set of parameters which for a subset of neurons were already converging on the final computed preferred direction. In general, stimuli which signal a reward draw the attention of animals, even when interacting with the stimulus increases the wait time for the reward. For example, rats can be conditioned to understand that a ball rolling down a ramp and into a well is a signal for the availability of food. Given the opportunity to participate in the delivery of the ball to the well, the animals inevitably attempt to manipulate the ball's motion on the ramp, despite the fact that the best they are able to do is to delay the delivery of the ball into the well (Timberlake *et al* 1982). In our instance, tapping into the 'will' to move the cursor into the target provides a more direct mapping between neuronal activity and cursor motion than does relating cursor motion to arm movements, and attempting to apply a neural estimate of intended arm movement to the motion of the cursor.

As others have reported (Taylor and Schwartz 2001, Sanchez *et al* 2004), we found that the degree of contribution to overall control varied between neurons. It is not surprising that some neurons do not contribute to the control of movement direction. In even the most generous estimates for coding of movement direction in motor cortex, fewer than 70% of neurons are well tuned. It has been argued that neurons need not have clear explicit relations between discharge patterns and movement to be contributors to movement control (Fetz 1993), but it is somewhat surprising that some neurons cause clear decrements in performance. At first glance, this would appear to require a peculiar pattern of correlations between desired movement and firing rates of the neurons. However, we found that the neurons producing these decrements in control are merely noise contributors with varying bias. In an adequately large sample of neurons, one might expect these noise profiles to balance one another out as long as they were not also subject to internal correlations that were unrelated to movement. Since neuroprosthetic systems to date are dealing with small numbers of neurons, it may be simpler to take these cells out of the mix rather than rely on uniform distributions and non-correlations among the noise.

It is worthwhile noting that the overall firing rate of the entire recorded ensemble was decreased by removing the *negative* neurons (figure 6(C)). There is no clear evidence that the mean firing rate and mental sense of effort are correlated, but given the higher metabolic cost of increased neuronal activity, it seems prudent to capitalize on choices which can produce the desired signal outcome with lower overall neuronal activation.

The rapid convergence of a subset of the neurons to a stable preferred direction, and the fact that this subset is also the

subset that contributed most significantly to the performance of the system also suggests that the notion of adaptation in the context of remapping activity from arm movements to neuroprosthetic systems might be somewhat misleading. The term implies that there is a steady graded change in the firing properties of neurons as the nervous system learns to use that set of neurons for an alternative purpose. This is similar to the often invoked plasticity that could make design of signal extraction algorithms for these systems very forgiving: as long as the system provides a reliable and readily determined mapping between neuronal activity and device motion, the central nervous system will be able to adjust to accommodate.

None of the experiments performed to date have required long-term use of the neuroprosthetic devices, but the extremely rapid convergence of our tuning algorithm suggests that, rather than an adaptive change, the use of a neuroprosthetic system could be treated as a fundamentally different problem by the brain. If this is true, then two observations should be possible: (1) rapidly switching the demands placed upon the motor and premotor cortices, from 'natural movements' to control of neuroprosthetic systems, should produce rapid changes in the firing properties of neurons in the CNS; and (2) choosing a set of parameters based upon this alternate tuning should produce much more rapid improvements in control of the prosthetic device.

In fact, the first observation has been made in several other contexts: notably in the context of attempting to determine the primary parameters encoded by the firing of neurons in motor cortex. A standing debate in this area is whether firing in motor cortical neurons encodes abstract kinematic parameters such as the direction of hand movement in space, or rather kinetic parameters such as muscle or endpoint forces. Two approaches taken to this issue have been sophisticated data analyses and direct experimental manipulation of these variables.

In the case of direct manipulation of control variables, instead of a clear and clean answer, inevitably the core result has been that, on average, the properties of neurons in M1 fall somewhere between the two expected parameter spaces. In Scott and Kalaska (1995), for example, the authors attempted to determine whether neurons in M1-coded arm movement in terms of hand trajectory or joint angle by altering the posture of otherwise equivalent movements. They found changes in the tuning profiles of M1 neurons, but no changes that conclusively showed that the coding was in terms of either joint space or hand path.

While other authors have reported that neurons in M1 and PMd are tuned to the visual location of a target (Ashe and Georgopoulos 1994, Fu *et al* 1993, 1995), we believe that our results reflect something that is dissociated from movement *per se*. We are proposing that there is no permanently fixed primary parameter encoded by neurons. Instead, the parameter or parameters encoded depends on task one is asking the motor system to perform. If the goal of a task is point-to-point movements, then a primary parameter could be the direction of hand movement in space. If one asks the system, instead, to exert fine control over force at the endpoint, then the system will focus its resources on that goal (Georgopoulos *et al* 1992, Massey *et al* 1992). In the case of our experiments, if the

system is asked to control the motion of an artificial device, then the system will encode the motion of that device: a result hinted at when animals were alternately asked to control a computer cursor with effectively instantaneous response or a robotic arm with slower and anisotropic responsiveness (Taylor *et al* 2003).

An example of how the system might change coding properties depending on task demands was visible in one series of experiments requiring adaptation to a transient large amplitude force perturbation: both motor and somatosensory cortices have been found to recruit larger numbers of task-related neurons as the adaptation proceeds, but then to level off once the animal has learned to deal with the adaptation (Cai *et al* 2004, 2005, Weber and He 2004). The primary parameters involved in the movement, hand movement direction, forces, force directions, were present prior to the perturbation. Why then did the number of neurons encoding these parameters change? We would propose that the reason is that the computational demand on the system vis-à-vis these parameters has increased.

At this stage, there are no clear hallmarks that would identify how neurons might be recruited as task requirements change. In this paper we have reported a method to objectively estimate the influence of each neural unit under any control algorithm for a 3D prosthesis. Applying our method to a population vector-based system; we have found that only small portion of units contributed positively to control. The remaining neurons essentially added noise to the computation. This leads to the conclusion that the design of neuroprosthetic systems will require careful analysis of the properties of available neurons for control.

The successful outcome of these experiments shows that future designs for neuroprosthetics should select a subset of the available units most effective for use with the prosthetic designed for a specific task. This alleviates the engineering problem of high bandwidth requirement. After selection, only the most useful units should be amplified, transmitted and decoded for use with the neuroprosthetic. This is a significant departure from the current approach of weighting each unit according to their contribution which requires the transmission and processing of all available units. The observation from our experiment that the selected units are stable on each day suggests the feasibility of quickly identifying a subset of units for information extraction and control on at least a daily basis, if not for a longer period. As shown in this study, this initial tuning of the system could be done successfully without any overt movement from the patient.

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