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Evolution of brain–computer interface: action potentials, local field potentials and electrocorticograms

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Brain computer interfaces (BCIs) were originally developed to give severely motor impaired patients a method to communicate and interact with their environment. Initially most BCI systems were based on non-invasive electroencephalographic recordings from the surface of the scalp. To increase control speed, accuracy and complexity, researchers began utilizing invasive recording modalities. BCIs using multi-single unit action potentials have provided elegant multi-dimensional control of both computer cursors and robotic limbs in the last few years. However, long-term stability issues with single-unit arrays has lead researchers to investigate other invasive recording modalities such as high-frequency local field potentials and electrocorticography (ECoG). Although ECoG originally evolved as a replacement for single-unit BCIs, it has come full circle to become an effective tool for studying cortical neurophysiology.

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Invasive brain–computer interfaces (BCI) have primarily evolved over the last decade. Although there are a few earlier examples, the 2000s were really the years when a critical mass of neuroscientists, bioengineers and clinicians came together to make significant advances in the field. Over the last decade there have been numerous technological and neuroscientific advances, but the last decade has also seen an expansion in types of invasive recording modalities used in BCI. This article will discuss the evolution of BCIs from the highly invasive, penetrating, multi-single unit arrays to the more recent meso-invasive, epidural micro-electrocorticographic arrays and their techniques. While the goal of this article is to illustrate the similarities between action potentials (AP), local field potentials (LFP) and electrocorticograms (ECoG) and their evolution over the last decade; the reader may be interested in three recent in-depth reviews that specifically cover either SU BCI [1,2] or ECoG BCI [3].

Single unit neurophysiology and BCI

Much of BCI research today can be traced back to results obtained by systems neurophysiologists studying motor systems over the last 40 years. As early as the 1970s, Fetz and Finocchio were able to operantly train monkeys to modulate individual neurons in primary motor cortex [4]. These results eventually inspired the first human trials of invasive BCIs by Kennedy and Bakay [5]. Likewise, Georgopoulos *et al.* in the 1980s developed the population vector method that allowed researchers to predict arm movement direction in three dimensions from a group of single-unit neurons in motor cortex [6]. This 3D directional encoding by primary motor cortex was further expanded by Schwartz and Moran in the 1990s to include speed, yielding an accurate prediction of 3D hand velocity [7]. Capitalizing on these neuroscientific results, several groups were able to develop real-time, closed-loop, BCI systems capable of controlling multiple degrees-of-freedom (DOF) [8–10]. Initially these systems were tested on non-human primates but by the middle of the decade, single unit arrays were being implanted in humans with motor disabilities for multiple DOF control of a computer cursor [11,12,13••].

This pattern of neuroscientific discoveries fueling new BCI milestones has been a cornerstone of BCI evolution. For instance, a current goal in BCI research today is to control a motorized prosthetic limb such as the DEKA [14] arm with a BCI implant. Patients with upper limb amputations would benefit greatly from a fully functional prosthetic limb. The DEKA arm is a fairly complex machine that contains 10 independent DOF. It has three translational DOF to move the hand to any point in space, three rotational DOF that orientates the hand in space, as well as four DOF within the hand itself for various finger gripping actions. To fully control such a device, ten independent control channels would have to be decoded from the brain. Current state of the art in the BCI community is 4 DOF control in non-human primates. Schwartz and colleagues have trained a monkey to control a robotic limb with 3 DOF of translation and 1 DOF of gripping action from a population of primary motor cortical neurons to perform a self-feeding task [15••]. Although hand orientation has not been implemented in BCI applications yet, the neuroscience research behind

hand orientation is actively being studied. A recent article by Wang *et al*. has shown that individual neurons in primary motor cortex can encode both hand translation and rotation [16] such that a population of proximal arm M1 neurons could be used to control the proximal 6 DOF of the DEKA arm. Likewise, Schieber and colleagues have spent years developing motor cortical encoding models of finger movements [17], and it is just a matter of time before these neuroscience discoveries are implemented in single-unit BCI applications. With the advent of single-unit microelectrode implantations in humans for BCI purposes, scientists are now able to obtain neuroscientific results from neuroprosthetic studies [18•], which will only accelerate BCI research.

Brain movement and tissue reaction to penetrating microelectrodes

In order to record single unit activity, penetrating microelectrodes with roughly 20 μm diameter tips are implanted a few mm down into the brain parenchyma. In primary motor cortex, layer V pyramidal cells are the target neurons for BCI, given their relatively large amplitude extracellular potentials. These pyramidal cells have long apical dendrites that align perpendicular to the cortical surface. During the peak of an action potential, the extracellular current flows from the apical dendrites to the axon hillock yielding a maximal extracellular peak potential midway between these two structures that is detectable not more than 200 μm lateral to the dendritic arbor. Given these relatively small dimensions, stability can be an issue for long-term recording of single unit activity [19,20]. The human brain is a very soft and pliable structure that has a significant amount of motion relative to the skull, even under minor accelerations [21]. To counteract this motion, some microelectrodes (e.g. Utah probes) are designed to sit on top of the brain and float with its relative motion, rather than anchor to the skull.

Whether the SU microelectrodes are anchored to the skull or allowed to translate with the brain, they still must penetrate into the brain parenchyma where they not only cause local neural and vascular damage but also increase the chances for CNS infections [22]. Secondly, SU microelectrodes are typically very stiff mechanically relative to brain tissue, thus, the microelectrodes can irritate the surrounding tissue and initiate a cascade of reactive cell responses, typically characterized by activation and migration of microglia and astrocytes towards the implant site [22]. Continued presence of the microelectrode promotes the formation of a sheath composed partly of these reactive astrocytes and microglia that can have numerous deleterious effects, including neural cell death and an increased tissue resistance that electrically isolates the device from the surrounding neural tissue [23]. So, while single unit activity provides a high fidelity signal for BCI applications, their penetrating microelectrodes provide real challenges for chronic, long-term viability. Several groups are working towards new biomaterials and drug delivery techniques to reduce encapsulation issues in penetrating microelectrodes (see [24,25] for review); however, most of these ideas are yet to be implemented in BCI applications.

LFP gamma band and single unit activity

Given the issues with chronic single-unit microelectrodes, researchers began looking into other invasive recording methods that were not as susceptible to tissue encapsulation, yet yielded a similar high-fidelity control signal for BCI. The gliotic sheath that forms around penetrating microelectrodes has a drastic effect on single unit discriminability. Basically, once the electrode is encapsulated, the local extracellular currents of the firing neuron seek out lower-impedance pathways away from the electrode, rather than flowing through the high-impedance gliotic sheath. This significantly reduces the amplitude of the recorded spike. One simple way to improve signal to noise is to increase extracellular current during an action potential. Since the amount of extracellular current generated by a neuron is correlated to its size, the only pragmatic method to increase signal amplitude is for multiple neurons in the same area to correlate their discharge. The question is which areas of the brain have natural, local correlations in their firing rates, or to put it in neuroscientific terms, which areas of the brain have a columnar organization? Many earlier studies in primary motor cortex suggested that M1 was not organized in a columnar fashion but rather was organized by a series of overlapping homunculi. However, more recent studies that investigated the columnar organization of the encoded movement parameters (i.e. preferred directions) do suggest that primary motor cortex has a loosely columnar organization [26•,27,28].

Given primary motor cortex's columnar organization, the question becomes can the local correlation in neural activity be used for BCI control? To address that question, a couple of important principles needs to be reviewed. First, the typical temporal width of an action potential is around 1 ms while the average firing frequency of a M1 neuron is only 12–14 Hz [29]; thus the chances of any two randomly active neurons firing at the same time is fairly low. However, the spectral power of an action potential has significant frequency components down into the tens of Hz yielding the possibility of correlated single-unit activity manifesting itself in the lower frequency bands (10–300 Hz). Second, the extracellular potentials within the brain are due to both single unit activity and synaptic activity (both excitatory and inhibitory). While the columnar organization of M1 suggests that single unit activity is correlated within an area, it does not necessarily suggest that synaptic activity is also correlated. Given the lower frequency content of synaptic potentials relative to single unit action potentials, researchers began exploring the high gamma band

(70–300 Hz) for signals correlated to single unit activity in primary motor cortex. Several groups have confirmed that high frequency LFPs are well correlated to single unit activity [30,31]; however, no group to date has utilized these techniques in a closed-loop BCI experiment. One reason for this is that while gamma band LFPs could possibly last for years in a chronic implant, it is still highly invasive. As you will see below, with the advent of electrocorticography, researchers can record high gamma band activity from the surface of the brain yielding a safer recording technology over penetrating electrodes.

Subdural electrocorticography (ECoG)

In the previous section, it was discussed that high gamma band activity (70–300 Hz) appears to be well correlated with the surrounding single-unit activity in penetrating microelectrodes. Since most large cortical neurons are orientated perpendicular to the cortical surface (i.e. dendrites on top, axon hillocks below), correlated activity within a cortical column should similarly constructively sum. The optimal location to record this correlated activity would be with a brain surface electrode (i.e. subdural ECoG) centered directly above the cortical column of interest. It is important to note that the optimal location for an ECoG electrode is over a cortical gyrus rather than cortical sulcus since sulcal neurons are oriented parallel to outer brain surface. An advantage for neuroscientists working with ECoG is that human patients are regularly implanted with subdural ECoG grids for the treatment of epilepsy, giving the researchers a unique opportunity to use invasive electrodes in humans. For instance, a recent ECoG study in humans confirmed previous non-human primate findings that high frequency gamma band activity is well correlated to single-unit activity [32•].

The standard clinical electrodes used for ECoG monitoring in epilepsy patients typically have diameters on the order of a few mm. This is a much larger dimension than a typical cortical column; thus, the cortical activity recorded by ECoG electrodes is a summation of a fairly large area of the brain. Therefore, most studies involving subdural ECoG use gross motor movements to determine tuning parameters. In the first closed-loop, ECoG-based BCI study subjects quickly learned to modulate high frequency gamma rhythms in motor cortical areas and in Broca's speech area to control a one dimensional computer cursor in real-time [33]. Subsequent studies have achieved 2D control of a computer cursor using the upper arm region of motor cortex for one dimension and the hand region of motor cortex for the other dimension [34,35]. Other investigators have had success using gamma band activity from auditory regions of cortex to control a computer cursor [36]. Those subjects would simply imagine a certain sensation (i.e. note played on a piano) which would modulate gamma band activity on a distinct electrode(s). In addition to using ECoG as an effective BCI modality, researchers are using it as a neuroscientific tool to investigate new hypotheses on cortical population representations. For instance, researchers have used ECoG in humans to identify novel hand movement representations in ipsilateral motor cortex [37] and individual finger representations in contralateral motor cortex [38•].

There were two primary reasons for the rapid evolution of ECoG research over the last few years. First, BCI researchers were searching for an effective recording modality that was less invasive and more stable than penetrating microelectrodes, yet provided an accurate representation of population-level, single-unit activity. Recent longitudinal studies in monkeys have shown that ECoG is a robust and stable recording modality for BCI applications [39••]. The second reason for the rapid evolution of ECoG is the ability to perform neurophysiological studies in humans. Distinctly human traits such as speech and language processing cannot be analyzed in any animal model and require invasive electrodes to elucidate novel findings [40]. Subdural ECoG has come full circle in its evolution. What started out initially as a method to avoid some of the complications of penetrating microelectrodes in BCI studies is now a valid neuroscience tool for studying population activity in the brain.

Epidural electrocorticography (EECoG) and neural plasticity

One of the primary benefits of subdural ECoG is that the recording electrodes are placed on the surface of the brain rather than in the brain tissue. As mentioned earlier, there is significant relative motion between the brain and the overlying skull [21]. The three layers of the meninges (dura, arachnoid, and pia) essentially buffer this relative motion. The pia is fixed to the brain while the dura is attached to the skull. The middle layer (arachnoid) is designed to strain between these layers and buffer these motions. Subdural electrodes placed on the surface of the brain and routed out through the dura mater to the skull still interfere with this natural buffering system. Furthermore, subdural electrodes are placed inside the CNS leaving a pathway for infection (e.g. encephalitis). Studies using epidural ECoG electrodes (EECoG) can eliminate both of these potential problems. By placing electrodes on the surface of the dura, the electrodes can safely anchor to the skull/dura complex alleviating the irritating effects of brain/skull motion. Likewise, the outside layer of the dura is part of the peripheral immune system reducing the chances of initiating an infection in the CNS. The downside of placing electrodes on the surface of the dura is the electrodes are slightly further away from the brain. However, since dural electrical conductivity is similar to cerebral spinal fluid (i.e. low resistivity), epidural recordings are very similar to subdural recordings.

Since EECoG is not a standard clinical recording modality, the first studies using this technique were applied in non-human primates [41•]. In these experiments, two electrodes were randomly chosen to control the vertical and horizontal speed of a 2D computer cursor. The animals quickly learned to trace circles on a computer screen by modifying the power in the 65–100 Hz band under these two EECoG electrodes. The randomly chosen electrodes were not initially directionally tuned, rather the monkey had to learn this mapping through biofeedback and neural plasticity. Previous single unit studies have shown that neural plasticity plays a huge role in BCI performance improvement [10,42•] and this is certainly the case in EECoG BCI. However, there are some distinct differences between single-unit BCI plasticity and EECoG plasticity. In SU experiments, the subject modifies the firing rates of individual neurons to improve performance. However, a recent study has shown that in order to increase gamma band activity in ECoG, a subject can either increase the firing rate in the population under the electrodes or increase the coherence in the spiking neurons [43••]. This modeling study clearly showed that increasing synchronous activity had a much greater impact on simulated ECoG high gamma band activity than simple average firing rate increases. The EECoG BCI study mentioned above [41•] clearly showed that the monkeys modified their control band (i.e. 65–100 Hz) more than other frequency bands on the control electrodes. If the monkeys were simply increasing firing rate throughout the population, one would expect a broadband change in activity. The distinct frequency band changes within overall gamma band suggest that the monkeys may be modifying synchronous activity in the population for control. Future studies will certainly delve more into these questions, but it seems interesting that ECoG has evolved from a single-unit BCI substitute to an ideal tool for investigating synchrony and plasticity in populations of neurons.

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