Teaching neurons how to walk—A BCI Cyber-Physical System

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***Abstract*—Over 8 million people in the US are living with chronic stroke. Existing therapies do not restore lost neuronal function or resources. Here, we aim to develop a bi-directional brain-computer interface that trains human neurons derived from the cells of affected patients to recognize stimuli and respond in a specific manner. We would grow neurons derived from patient induced stem cells on top of a microelectrode array. Using the electrodes, we can both record information about the average network firing rate (steady state) and stimulate the network in a controlled fashion (through the microelectrodes) to adjust and change the average firing rate. Our aim is to train the neural network using electroencephalography (EEG) data.**

I. Introduction

BCI devices are systems that translate brain signals into the control of assistive devices. Bi-directional BCIs can enable brain-controlled movement and artificial sensation in those with complete paralysis after stroke, or facilitate neural repair to augment residual post-stroke functions [3, 4]. However, this only provides a bypass to the injury site and limits BCIs to a smaller proportion of stroke patients with intact cortex. Approaches to improve motor function after stroke such as transcranial magnetic stimulation (TMS) or transcranial direct current stimulation (tDCS) have limited impact and fundamentally fail to replace lost functions. Novel means to overcome these shortcomings are necessary to produce functional recovery.

To this end, a new neurorestorative methodology concept of "engineered neural networks" (ENN) is proposed (Fig. 1). The ENN is envisioned to combine concepts from BCIs, neuromodulation, and cellular replacement. It would be composed of neurons derived from human induced pluripotent stem cells (HIPSCs) and structured to have precise inputs and feedback loops (formed by excitatory and inhibitory neurons). While the cellular component provides novel neural resources, its structure is simultaneously analogous to digital inputs (0's and 1's). This provides "computing resources" with which BCI- and artificial neural network (ANN)-inspired techniques can be used to train the ENN to recognize and decode signals from other brain areas and learn specific behaviors (Fig 2). This process, facilitated by physical interfaces for brain signal acquisition as well as neuromodulation via electrical stimulation, can establish bidirectional communication of the ENN with the remaining brain, thereby replacing the stroke damaged cortex and subserved functions. Additionally, this 'ENN' would serve as an 'intelligence on a chip' device given that the input and output can be adjusted according to the trained task.

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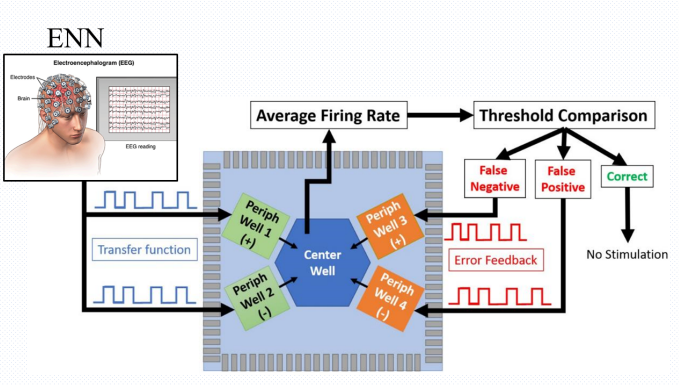

Fig. 1. Schematic of the closed loop process for the CNN. EEG is translated into stimulation pulse trains for Wells 1 (excitatory) and 2 (inhibitory). The resulting average firing rate across all center well channels is compared to transition thresholds for either the move state or idle state. When a false negative/positive state occurs, excitatory/inhibitory feedback is delivered, respectively via tentanic stimulation of wells 3 (excitatory) or 4 (inhibitory).

II. Methods

A. Development of long-term, stem-cell derived neruonal cultures on MEAs

A culture platform consisting of a multi-well microfluidic device over a commercial 256-channel MEA (Multichannel Systems, Reutlingen, Germany) will be fabricated. It's peripheral wells will house isolated populations of either excitatory or inhibitory neurons, while the central well will hold a mixed population. The system will be designed to include at least 25 electrodes within each of the peripheral wells and 100 electrodes within the center well. The overlying microfluidic device will be designed with computer-aided-design (CAD) software, and fabricated in PDMS via commercial foundry. The PDMS cast will be plasma treated and bonded. This platform will be validated with functional and anatomical approaches. Functionally, spontaneous and evoked activity will be recorded from the center well. Specifically, signals will be recorded from each channel using a bioamplifier/stimulator system (Intan RHS, IntanTech, SantaMonica, CA; 20 KHz per channel, 16 bit resolution) with a custom electronic interface that connects with the MEA. First, spontaneous activity will be recorded over a 5-s period. Subsequently, a single electrical stimulation pulse (nominally 10 µA, biphasic, 400 µs pulse width) will be delivered to a peripheral well channel while

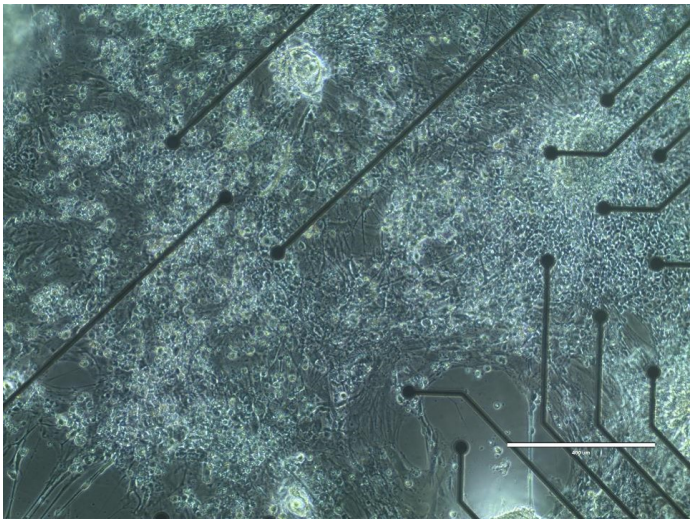

Fig. 2. 100x Zoom light microscope photo taken of the cultured MEA. A dense network of neuronal processes as well as the electrodes they sit upon are visible.

evoked responses are recorded in the center well over a 5-s period. This procedure will be repeated until each channel has undergone 50 stimulations. Channels will be stimulated sequentially in a random fashion with an interleaved 5-s spontaneous activity period. To determine the post-synaptic effect, spontaneous and evoked firing rates will be calculated for each channel. Firing rates will be defined as the number of action potentials (APs) per second, where individual APs will be detected using our unsupervised wavelet-based AP detection algorithm. For each channel, the firing rate across all repetitions will be compared between the spontaneous and evoked conditions using a rank sum test.

1) Training of Neurons using EEG Data: Healthy human subjects (n=10) will undergo 64-channel EEG recording (256 Hz) and follow computerized cues to perform 10-min of alternating trials of foot dorsiflexion or idling (30 s per trial, 20 trials total). This training EEG data will be later used to train the CNN to recognize the idling or dorsiflexion brain states. The CNN will placed inside a CO2 incubator and connected to an amplifier/stimulator system. EEG data will be converted into stimulation patterns and delivered to the CNN while its center well's activity is recorded. First, one excitatory and one inhibitory peripheral well will be designated as excitatory and inhibitory inputs, respectively. A mapping procedure will then determine how to map EEG channels into MEA input channels as follows. The EEG data will be analyzed to determine the magnitude of the movement-related desynchronization (reduction in μ [8-12 Hz] and [12-35 Hz] band power due to transitioning from idle to foot dorsiflexion states). We will then convert signals from each EEG channel into excitatory/inhibitory stimulation pattern. Each channel's EEG signal will be band-pass filtered at 8-35 Hz. Power envelopes, Pμ,(t), will then be extracted by low-pass filtering. Due to movement induced desynchronization, we expect the Pμ,(t) to be higher during idling trials and lower during foot-dorsiflexion trials, especially for channels above the motor cortex contralateral to the moving foot. A state machine describing the setup is shown in Fig 3.

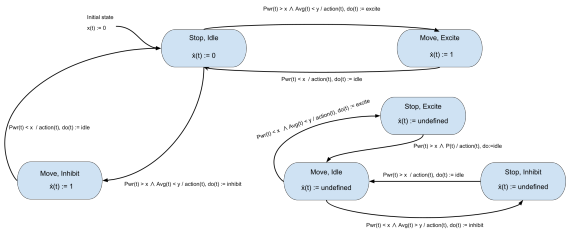

Fig. 3. A composition state model of the proposed ENN machine with standard hybrid model notation.

III. Conclusion

With the ENN, we have taken the concept of the nerual network to it's roots in brain physiology. Using physical neurons we intent to create an 'intelligence-on-a-chip' design that can be trained to produce learned outputs for any given electrical stimuli. While this has been achieved previously using rat brain neurons, the advantage of using human stem-cell derived neurons is the ability for these trained cells to eventually integrate with their host without rejection. The CNN is expected to initially have poor ability to recognize EEG underlying idling/foot dorsiflextion. During training, the decoding error rate and the need for error-driven feedback are expected to decrease. By the end of training period (up to 10 days), the CNN should reach high accuracy in EEG recognition (¿95 percent) and this level of performance is expected to generalize to real-time validation. This benchmark is chosen as it matches the decoding accuracy that can be achieved with conventional machine learning approaches for binary EEG classification. Indeed, one of the biggest challenges faced by AI and ML is learning efficiency and power consumption. AlphaGo was trained on a dataset that a human player would have to play 175 years continuously to match. Training AlphaGo required the same amount of energy one would need to sustain the metabolism of an active adult human for a decade. The lofty goals envisioned in the field cannot be accomplished without advances in computing efficiency which organoid intelligence strategies can provide. While there is a long way to combining these two fields, we hope this is a start.

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