

The Potential of Multilateral Analyses of Neuronal Activities in Future Brain–Machine Interface Research

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Abstract—Current brain–machine interfaces are based on the implicit assumption that information encoded by neuronal activities does not change despite some recent physiological studies indicating that information encoded by neuronal activities changes. Here, we highlight the necessity for advanced decoding of neuronal activities. Especially, we discuss the advantages of multilateral analyses of neuronal activities, including synchronization and variability.

I. IMPLICIT ASSUMPTION OF CURRENT BMIS

Brain–machine interfaces (BMIs) are expected to provide revolutionary technology that will be of great benefit for the lives not only of people with physical challenges but also of healthy people [1]. BMIs convert neural activity into signals that can control machines, devices, or computers [2]. BMIs represent promising technology to control such devices using only thought, without the need for manipulation of ordinary interfaces such as handles or computer mice.

Current BMIs are based on the implicit assumption that the type of information encoded by brain activities does not change. Many BMI studies using neuronal activities in the cerebral cortex have examined the control of a robot arm [2] or a computer cursor [3] by neuronal activity in motor-related cortical areas such as the primary motor area. The information encoded by neurons used by BMIs exhibits gradual changes along with the adaptation to the task demands under appropriate feedback to the brain [4]. However, once both the neurons and the BMI decoding the neuronal activity have reached an optimum state, the information encoded by neurons remains of a certain type, such as vectors of cursor movement.

II. REPRESENTATIONAL TRANSITION OF INFORMATION ENCODED BY NEURONAL ACTIVITIES

Recent physiological studies have shown that neurons in higher association areas in the cortex are capable of exhibiting rapid changes in the types of information encoded by their activity [4–6]. For example, we have reported that neurons in the monkey prefrontal cortex exhibited representational shifts in behavioral goals encoded by firing rate (Fig. 1) [6,7]. A path-planning task is a demanding task in which monkeys plan

an immediate goal of action to attain a final goal presented early in the preparatory period of the trial (see Methods). A typical prefrontal neuron, referred to as the representational shift neuron, showed changes in firing rate dependent upon its preference for the final goal position early in the preparatory period. Later in the preparatory period, the firing rate of the neuron was dependent on the immediate goals planned by the monkey.

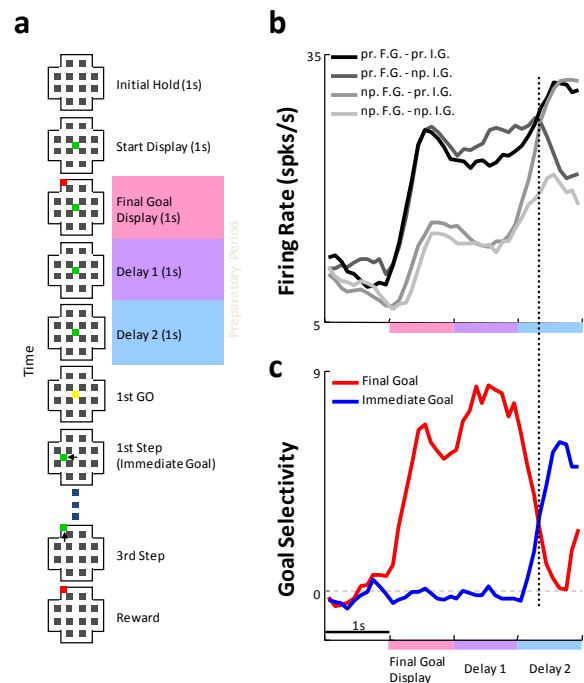


Figure 1. The lateral prefrontal cortex showing a representational shift. a, Path-planning task. The monkey was required to move a cursor step by step to reach a final goal in a checkerboard-like maze on a monitor. After 1 s (Initial hold), a green cursor appeared at the center of the maze (Start display), and 1 s later, a red square was displayed for 1 s, indicating the position of the final goal (Final goal display). After a delay of 1 s, one or two of four possible paths to the goal were blocked. This was followed by another 1-s delay (Delay). Thereafter, when the cursor color was changed from green to yellow (1st go), the animal was required to move the cursor within 1 s to the first position (Immediate goal). Then, the animal had to move the cursor stepwise to reach the final goal, where the animal was rewarded. b, Discharge properties of a prefrontal neuron that represented the final goal position followed by the immediate goal position during the preparatory period. pfd, preferred; n.p., non-preferred; F.G., final goal; I.G., immediate goal. c, The time course of modulation of the final (red line) and immediate goal (blue line) selectivity (see Methods) of the neuron shown in b. Modified with permission from Ref. [8].

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If the abstract information represented in the higher association areas were available for the BMI, innovative

communication could be realized between the brain and various types of machine. For example, it may be possible for the user to provide abstract instructions, such as “feed me,” to a robot arm through the BMI instead of concrete orders, such as to “move right” or “bring the spoon to my mouth.”

To utilize such abstract information encoded in the higher association areas, machines require quite high-level abilities. Especially, for a machine to make concrete actions in response to abstract instructions, it has to possess an extremely high degree of autonomy. However, such an advanced machine should have the ability to switch its decoding strategies just in time for the changes in types of information encoded by brain activities. If any signs of changes in the information types can be detected, they may be employed for switching the strategies used for decoding the brain signals.

III. MULTILATERAL ANALYSES FOR DETECTING EARLY WARNING SIGNALS OF REPRESENTATIONAL TRANSITION

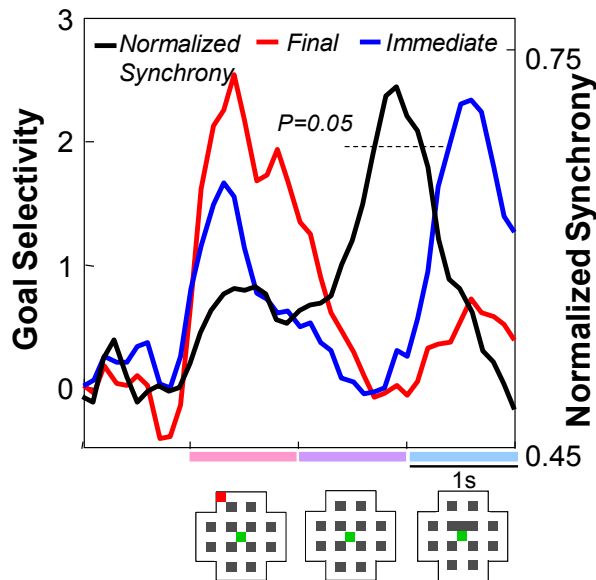


Figure 2. Temporal relationship between synchronization and behavioral-goal selectivity of neuronal activity analyzed for neuron pairs with representational shift neurons. Selectivity for final (red line) and immediate (blue line) goals calculated for the population of neurons with representational shift. Normalized synchrony of each neuron pair was calculated by taking the peak value as 1, and values were then averaged over the preparatory period (black line). Modified with permission from Ref. [6].

The neuronal signal that is usually used for the invasive types of BMI is firing rate or spike count per time window. However, the signals available from raw spike data are not limited to firing rate. Multilateral analyses of raw neuronal data are capable of providing other signals simultaneously, such as correlations between the activities of two neurons or fluctuations in neuronal activity.

Previously, we analyzed the spike correlations of neuronal pairs including the above-mentioned representational shift neurons (see Methods) [6]. We selected neuronal pairs showing significant synchronization and analyzed the time development of the degree of synchronization. This analysis indicated that the times of enhancement of synchronization

were correlated with those of representational shift (Fig. 2). We also analyzed the fluctuations in activity or firing variability of the representational shift neurons (see Methods) [8]. Our preliminary results indicated that the firing variability increased prior to the representational shift. These results suggest that firing synchronization and fluctuations have the potential to serve as early warning signals [9,10] for representational shift or changes in types of information encoded by the firing rate of neurons. Utilizing these multilateral signals may enable rapid switching decoding strategies for neuronal activities.

IV. FUTURE DIRECTIONS FOR BMI RESEARCH

Neurons in the cerebral cortex, especially in higher association areas, are capable of exhibiting rapid changes in the type of information encoded by their activity. Utilizing these changes in activity for BMI would require appropriate switching of decoding strategies. For switching at an appropriate time, signals such as synchronization and/or variability obtainable from multilateral analyses on neuronal activities would be useful.

However, to realize such advanced BMIs capable of rapid switching of decoding strategies, it is necessary to have prior knowledge regarding the types of information encoded in neuronal activity before and after switching. This implies that even such advanced BMIs would be applicable only to routine tasks or tasks in which the working environment or situations are well defined and fully predictable in advance. In contrast, the real environment includes wide varieties of novel situations. To handle such novel situations and resolve the accompanying difficulties, people conceive of various solutions or ideas. It would be quite difficult to decode such novel ideas or the information encoded in the associated neuronal activity.

To decode neuronal information even in novel situations, a process for rapid development of strategies or strategy improvisation in parallel with the decoding process may be indispensable (Fig. 3). This parallel processing seems similar to that involved in decoding the ancient Egyptian hieroglyphs on the Rosetta stone [11]. In that decoding process, the sentences of hieroglyphs were read, while the grammar of the ancient Egyptian language was being determined in parallel based on correlations with the Greek sentences also written on the stone. In a similar way, the whole decoding process for neuronal information in novel situations will require input not only from the brain but also from the environment, such as images or sounds. It will also require a subprocess for rapidly finding new correlations between brain signals and contextual information from the environment. Recently evolving data-mining technologies may also make great contributions to such a subprocess. Neuronal signals from multilateral analyses, such as synchronization and fluctuations, will still be of value by serving as cues for improvising new decoding strategies.

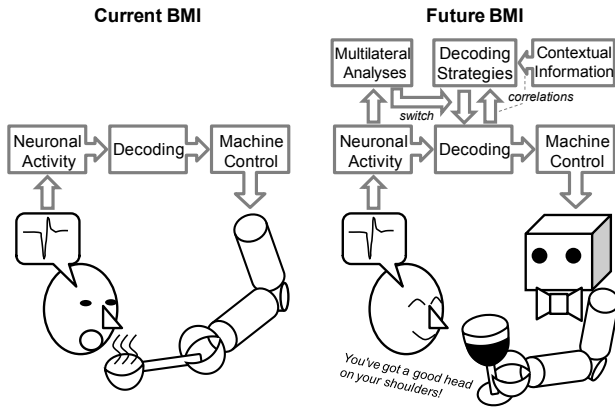


Figure 3. Schematic views for proposed conceptual differences between current and future BMIs.

V. METHODS

A. Behavioral Procedures

Physiological studies were performed on two Japanese monkeys (*Macaca fuscata*) trained in the path-planning task, described previously [12] and in the legend to Fig. 1. Conventional electrophysiological techniques were used to obtain in vivo single-cell recordings from the lateral prefrontal cortex above and below the principal sulcus in the right hemisphere [12].

B. Analysis of Goal Representations by Firing Rate

We focused on neuronal activity during the preparatory period (initial hold, final goal display, delay). For statistical assessment of how the final and immediate goals were related to cell activity, linear regression analysis was conducted using the following regression model: firing rate = $\beta_0 + \beta_1 \times$ (final goal) + $\beta_2 \times$ (immediate goal), where β_0 is the intercept, and β_1 and β_2 are the regression coefficients. The categorical factors for the final and immediate goals were horizontal and vertical directions. The firing rate was calculated as spike counts in 100 ms. The time development of the coefficients was normalized by the significance level of the t -value ($P < 0.05$). Details were also described previously [6].

C. Analysis of Neuronal Synchrony

We used the time-resolved cross-correlation method [6,13,14] to assess changes in the synchrony of neuron pairs independently of changes in the firing rate of individual neurons using the instantaneous firing rate (IFR) estimate to correct for firing rate modulation.

A time-resolved cross-correlation (TCC) histogram was obtained by cross correlating the spike times of two neurons in a pair. This histogram is a plot for spike timing of one neuron within ± 200 ms of when the other neuron fired. The predictor (time-resolved cross predictor; TCP) used to estimate false synchrony caused by fluctuations in firing rate was estimated by cross correlating IFRs. The IFR at each time point was defined from the reciprocal of the interspike interval. Thus, the IFR was obtained for each trial, avoiding detection of false

synchrony caused by intertrial fluctuations. The TCP was subtracted from the TCC at each data point, and this value was summed over the task period to create the standard cross-correlation histogram (CCH).

The CCH was used to select significantly synchronous pairs based on the following criteria: more than 2000 spikes contributed to the cross-correlation estimate, the CCH had a positive peak > 4.41 SDs above baseline ($P < 0.00001$), and the significant peak was within ± 25 ms of the center of the CCH [15].

To examine synchrony in the significantly correlated pairs of spikes over time, we first calculated raw synchrony (RS) by averaging the synchrony magnitudes in the TCC, taken from the half-width area around the peak in the CCH. Similarly, we calculated the firing rate-dependent synchrony (FRDS) as a reference or predictor for synchrony estimated from the firing rate. Then, we calculated the difference between RS and FRDS (divided by the SD of the latter for normalization) and plotted the values as normalized synchrony. Here, we use the term synchrony in place of normalized synchrony for simplicity.

D. Evaluation of Firing Regularity/Irregularity

Interspike interval [ISI] variability was analyzed to determine firing regularity/irregularity. We used a recently developed measure for ISI variability, $L_V R$ [16]. In $L_V R$, the constant, R , which compensates for the effects of the neural refractoriness of a previous spike, was introduced to exclude the influences of firing rate more strictly than local variance, L_V . The mean $L_V R$ was defined as:

$$\langle L_V R \rangle = \frac{1}{n-1} \sum_{i=1}^{n-1} L_V R(i),$$

$$L_V R(i) = \left(1 - \frac{4 ISI_{i+1} ISI_i}{(ISI_{i+1} + ISI_i)^2} \right) \left(1 + \frac{4R}{ISI_{i+1} + ISI_i} \right).$$

ISI was calculated with a time resolution of 1 ms, and n is the number of ISIs during the period of interest. For simplicity, we refer to $\langle L_V R \rangle$ as $L_V R$. We successfully excluded the influence of firing rate using $L_V R$ ($R > 10$ ms) [17].

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