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# Trial time warping to discriminate stimulus-related from movement-related neural activity

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## HIGHLIGHTS

- A warping method is used to determine best alignment of cell responses to events.
- Bayes factors are used to classify sensory or motor neurons.
- Movement times, firing rate and duration of response are critical in the analysis.

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## ABSTRACT

In tasks where different sensory, cognitive, and motor events are mixed in a sequence it is difficult to determine whether neural activity is related to any behavioral parameter. Here, we consider the case in which two alternative trial-alignment schemes correspond to two different neural representations, one stimulus-related and the other movement-related, using both simulations of neural activity and real recordings in the medial premotor areas during a multiple-interval tapping task called synchronization-continuation task (SCT). To discover whether neural responses are better aligned to sensory or motor events we introduce a family of trial-alignment time-warping functions indexed by a single parameter such that when the parameter takes the value 0 the trials are aligned to the stimulus and when the parameter takes the value 1 they are aligned to the movement. We then characterize neurons by the best-fitting alignment scheme (in the sense of maximum likelihood) under the assumption that the correct alignment would produce homogeneous trials without excess trial-to-trial variation. We use Bayes factors to determine the evidence in favor of sensory or motor neural alignments. The simulations revealed that the variability in neural responses and sequential motor outputs are key parameters to obtain appropriate warping results. In addition, the analysis on the activity of 500 neurons in the medial premotor areas of monkeys executing the SCT showed that most of the neural responses (54.2%) were aligned to the tapping movements instead of the stimuli used to drive the temporal behavior.



## 1. Introduction

The mammalian cerebral cortex has the ability to construct dynamic neuronal representations about sensory events, forthcoming movements, and a myriad of cognitive processes that link sensation to motor execution. Cortical responses in sensory areas show short onset latencies to the presentation of stimuli (Mountcastle et al., 1990; Romo et al., 1996; Nowak et al., 1995; Liang et al., 2002), whereas motor areas show sharp activation profiles before movement onset (Georgopoulos et al., 1982; Crutcher and Alexander, 1990). In contrast, the responses in association areas are less tightly locked to sensory, cognitive, or motor events (Mountcastle et al., 1975; Merchant et al., 2004; Chafee et al., 2007). The picture gets more complicated when we consider that the activity in the cortex exhibits a considerable amount of trial-to-trial variability. In fact, both the shape of the activation profile (Shadlen and Newsome, 1998; Lee et al., 1998; Averbeck et al., 2006a) and the onset latency (Merchant et al., 2001; Nawrot et al., 2003) show different levels of variability across cortical areas for the diverse behavioral aspects of a specific paradigm. Therefore, a critical problem in the cortical physiology of behaving animals is to determine

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whether the response of neurons is related to the different aspects of a task. Different algorithms have been implemented to determine the onset latency of neurons using parametric (Ellaway, 1978; Seal et al., 1983; Davey et al., 1986; Baker and Gerstein, 2001) or nonparametric methods (Sanderson, 1980; Nawrot et al., 2003; Ventura, 2004). Most of these methods take into account the trial-to-trial variability of neuronal activity and can determine with different levels of accuracy the onset response latency, especially to sensory stimuli. However, these methods are not designed to test whether the activity of a cell is associated to the sensory, cognitive, or motor aspects of a task, particularly when the task includes many such events in a sequence.

Here we describe a novel warping method to discover whether the cell responses are better aligned to the sensory or motor events of the synchronization-continuation tapping task (SCT). In this task monkeys synchronize their tapping with pacing isochronous auditory stimuli for a number of intervals, and then continue tapping at the instructed rate without the advantage of the sensory metronome (Repp, 2005; Wing and Kristofferson, 1973). We simulated activity during the four stimuli and four taps of the synchronization phase of the SCT, and restricted the analysis of the recorded neural responses to those cells that showed activity modulations during this task phase (Zarco et al., 2009; Merchant et al., 2011). Every analysis of multi-trial spike-train data begins by introducing some form of temporal alignment across trials. Here, we initially align the trials to the stimuli and write the resulting temporal alignment as a function $[T_0(t)]$. We next let $[T_1(t)]$ be the temporal alignment corresponding to movement and we introduce weighted combinations of these two extreme cases to obtain intermediate alignment schemes $[T_w(t)]$ indexed by a weight parameter $[w]$. We then assume that under the correct alignment the trials will be homogeneous, without excess trial-to-trial variability above that predicted by a Poisson process with a time-varying firing intensity function, and we proceed to find the best-fitting alignment scheme. Finally, for each neuron, we used Bayes factors to evaluate evidence in favor of a sensory or motor alignment (Kass and Raftery, 1995). We found in the simulations that the inter-trial variability of the tapping movements, as well as the magnitude and duration of the neural activity associated to sensory or motor events are critical parameters to obtain proper warping values. Furthermore, the results showed that most neurons in the medial premotor areas of monkeys executing the SCT were aligned to the tapping movements instead of the stimuli used to drive the temporal behavior. We conclude that the present method can be used reliably in a variety of behavioral paradigms where multiple, sensory, motor, and/or cognitive events are intermixed in a sequence, in order to determine to which event the cell responses are better aligned.

## 2. Materials and methods

### 2.1. Animals

Two male monkeys (*Macaca mulatta*, 5–7 kg BW) were trained to tap on a push button in the SCT. Neurophysiological recordings were carried out in the MPC during performance of the task using a system with 7 independently movable microelectrodes (1–3 MΩ, Uwe Thomas Recording, Germany, see Merchant et al., 2011). Single-unit activity was extracted from these recordings using the Plexon off-line sorter (Plexon, Dallas, TX). All the animal experimental procedures were approved by the National University of Mexico Institutional Animal Care and Use Committee and conformed to the principles outlined in the Guide for Care and Use of Laboratory Animals (NIH, publication number 85-23, revised 1985).

### 2.2. Synchronization-continuation task (SCT)

The SCT used in this study has been described before (Merchant et al., 2008; Zarco et al., 2009). Briefly, the monkeys were required to push a button each time stimuli with a constant interstimulus interval were presented, which resulted in a stimulus–movement cycle. After four consecutive synchronized movements, the stimuli were eliminated, and the monkeys continued tapping with the same interval for three additional intervals. Monkeys received a reward if each of the intervals produced had an error < 35% of the target interval. Trials were separated by a variable inter-trial interval (1.2–4 s). The target intervals, defined by brief auditory (33 ms, 2000 Hz, 65 dB) stimuli, were 450, 550, 650, 850, and 1000 ms, and were chosen pseudo-randomly within a repetition. Five repetitions were collected for each target interval. For the warping analysis we only used the data of the four stimuli and their corresponding tapping movements of the synchronization phase of the task. We analyzed 500 neurons that showed a minimum discharge rate of 4 Hz and showed task related activity based on an ANOVA where the discharge rate was the dependent variable and the task epoch (initial control key holding period [500 ms] vs. the synchronization phase) was the factor.

### 2.3. Time warping

In this work, we propose a warping transformation (Wang and Gasser, 1999) to determine whether the activity of a cell was better aligned to sensory or motor events during the SCT. We defined the time of sensory events as the instant in which the auditory stimulus was presented. The time of motor events was defined as the moment in which the monkey tapped on the button. Hence, we only used the behavioral information and cell activity recorded during the synchronization phase of the SCT. The goal of this analysis was to find the cell alignment that produced the smallest intertrial variability. The method has the following steps:

(1) The action potential times $\{t_{i,j}\}$ were initially aligned to the stimulus times $\{S_{i,1}, S_{i,2}, S_{i,3}, S_{i,4}\}$, where $i$ correspond to the trial repetition and $j$ to the spike number. In addition, we defined the following transformation in order to align the action potential times $\{t_{i,j}\}$ to the motor events $\{M_{i,1}, M_{i,2}, M_{i,3}, M_{i,4}\}$:

$$T_i(t) = \frac{L_{j+1} - L_j}{M_{i,j+1} - M_{i,j}}(t - M_{i,j}) + L_j \quad \text{when} \quad M_{i,j} \le t \le M_{i,j+1} \quad (1)$$

and $\{L_1, L_2, L_3, L_4\}$ were landmark references. $L_1$ was the average reaction time of the monkeys for the first stimulus during cell recordings, whereas $L_2$ to $L_4$ were defined as the target interval duration (i.e. 450, 550, and 650 ms). This transformation was performed for each trial across the five interval durations in the SCT.

(2) The warping transformation was:

$$T_w^i(t) = wT_i(t) + (1 - w)t \quad (2)$$

that depended on the parameter $w$. When $w = 0$ the responses were aligned to the sensory events $S$. When $w = 1$ the responses were aligned to the motor events $M$. $w$ values between 0 and 1, in steps of 0.1, produced alignments between $S$ and $M$ events.

(3) The average spike density function $r_w(t)$ for every interval duration across trials was computed using the following equation for a particular $w$.

$$r_w(t) = \frac{1}{N}\sum_{i=1}^{N}\sum_{j=1}^{n_i}\frac{1}{\sqrt{2\pi}\sigma}e^{-\frac{(t - T_w^i(t_{i,j}))^2}{2\sigma^2}} \quad (3)$$