Rotational dynamics versus sequence-like responses

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Abstract

In a recent review, Vyas et al. commented on our previous observations regarding the presence of response sequences in the activity of cortical neuronal population and the contribution of such sequences to rotational dynamics patterns revealed with jPCA. Vyas et al. suggested that rotations generated from sequence-like responses are different from the ones arising from empirical neuronal patterns, which are highly heterogeneous across motor conditions in terms of response timing and shape. Here we clarify our previous findings and present new results showing that empirical population data contain plentiful neuronal responses whose temporal structure persists across conditions. The more complex, heterogeneous responses also contain sequence-like responses, which are evident from the analysis of the timing of cross-condition variance. Both consistent and heterogeneous responses contribute to rotational dynamics; therefore, these contributions should be considered when interpreting population rotations. Overall, we do not see any principal contradiction between the neural population dynamics framework and our results pertaining to sequence-like responses. Yet, questions remain regarding the conclusions that can be drawn from the analysis of low-dimensional representations of neuronal population data.

Introduction

In our previous study, we conducted an analysis (Lebedev, Ossadtchi et al. 2019) of multichannel recordings from monkey motor cortex, which Churchland, Shenoy and their colleagues had made available online (https://www.dropbox.com/sh/2q3m5fqfscwf95j/AAC3WV90hHdBgz0Np4RAKJpYa?dl=0) and which they had originally used to substantiate the concept of rotational dynamics – a fundamental type of neuronal processing in many species according to their claim (Churchland, Cunningham et al. 2012). In the rotational dynamics approach, multidimensional neuronal data are processed with a linear transform, called jPCA, designed to generates a set of curved trajectories, one trajectory per arm-movement condition. (In their experiments, each condition corresponded to an arm reaching movement with a distinct path.) If the rotational components obtained with this method account for a substantial percentage of variance in the data, this result is taken as a proof that the neuronal population acts as a dynamical system:

$$\dot{X} = M_{skew}X \tag{1}$$

where X is a six-dimensional vector of principal components obtained from neuronal population activity and $\dot{X}$ is its time derivative. The matrix M_{skew} has imaginary eigenvalues, which corresponds to X rotating around the center of coordinates (Garfinkel, Shevtsov et al. 2017).

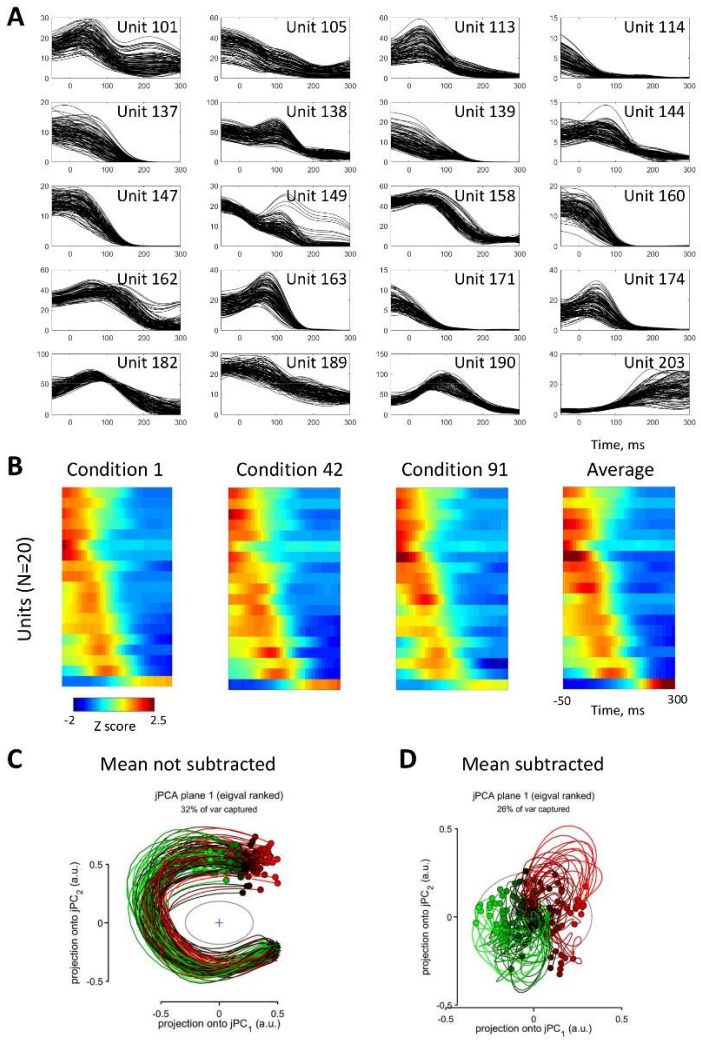

Figure 1. PETHs and jPCA plots for twenty neurons with the highest consistency of PETH shape across conditions. A: PETHs. Each box displays PETHs from different conditions for a single neuron. B: Population PETHs for three representative conditions (left) and the across-condition average PETH (right). Neurons are sorted by the time of peak response derived from the average PETH. C: State-space trajectories for jPCA without the subtraction of mean PETH. D: Trajectories for jPCA with mean PETH subtracted.

Given that Xrotates, its coordinates are oscillating functions of time, and there is a temporal lag (or phase shift) between these functions, which led us to the hypothesis that similar temporal lags could be present in the neuronal population data before it has been processed with jPCA (Lebedev, Ossadtchi et al. 2019). To test this hypothesis, we plotted population perievent time histograms (PETHs) for different conditions, where neurons were sorted by the time of peak activity taken from the cross-condition average PETHs. With this simple procedure, we found a temporal sequence of neuronal responses during the arm reaching task. This sequence persisted across 108 conditions with some variability (see Figure 2 in Lebedev, Ossadtchi et al. (2019)). Based on this observation, we argued that sequence-like responses could be the cause of the rotational dynamics revealed with jPCA. To tackle this idea further, we showed that rotational patterns could be easily obtained with jPCA from a rather arbitrary simulation of neuronal responses that incorporated a requirement that the responses be arranged in a temporal sequence but did not mimic any representation of movement. We concluded that jPCA reveals sequence-like dynamics in neuronal population data, but we were skeptical regarding Churchland's claim that this method elucidates a fundamental mechanisms of cortical motor control.

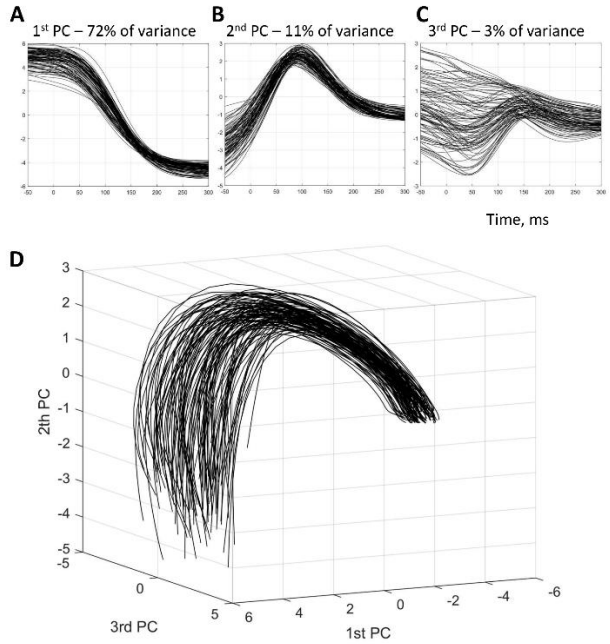

Figure 2. The first three principal components (PCs) for the population of twenty neurons with the highest consistency of PETH shape across conditions. A-B: The first, second, and third PCs. PETHs. D: The first three PCs in 3D.

Recently, the Shenoy group published a new review on neural population dynamics (Vyas, Golub et al. 2020) where they commented on our article:

> *"While it is possible to obtain rotation-like features from non-dynamical models [e.g., sequence-like responses (Lebedev et al. 2019)], such rotations are dissimilar from those observed empirically (Michaels et al. 2016). Perhaps more critically, the hypothesis of sequence-like responses does not account for single-neuron responses, which are typically multiphasic and/or peak at different times for different conditions (e.g., Churchland et al. 2012, figure 2)."*

These comments prompted us to provide several clarifications and conduct additional analyses.

Results

Responses with consistent timing

In our analyses, we inspected more closely the Shenoy group's claim that "the hypothesis of sequence-like responses does not account for single-neuron responses, which are typically multiphasic and/or peak at different times for different conditions (e.g., Churchland et al. 2012, figure 2)". Figure 2 in Churchland, Cunningham et al. (2012) indeed illustrates ten neurons (selected from the data of four monkeys) whose responses are variable across conditions. Yet, we have already shown that, at population level, a consistent sequence of neuronal responses is present in Churchland's data (see Figure 2 in Lebedev, Ossadtchi et al. (2019)). To examine this finding further, here we ranked the neurons in Churchland's population by how consistent the timing of their responses was across the conditions. We quantified cross-condition consistency of response timing as the correlation coefficient for pairs of perievent time histograms (PETHs) for different conditions. This metric detected similar PETH shapes while ignoring the differences in amplitude. We calculated the correlation coefficients for all possible PETH pairs and then used the mean of these values as a measure of consistency for each neuron. The mean correlation coefficient ranged from 0.005 to 0.988 for different neurons (N=218), with the median of 0.494.

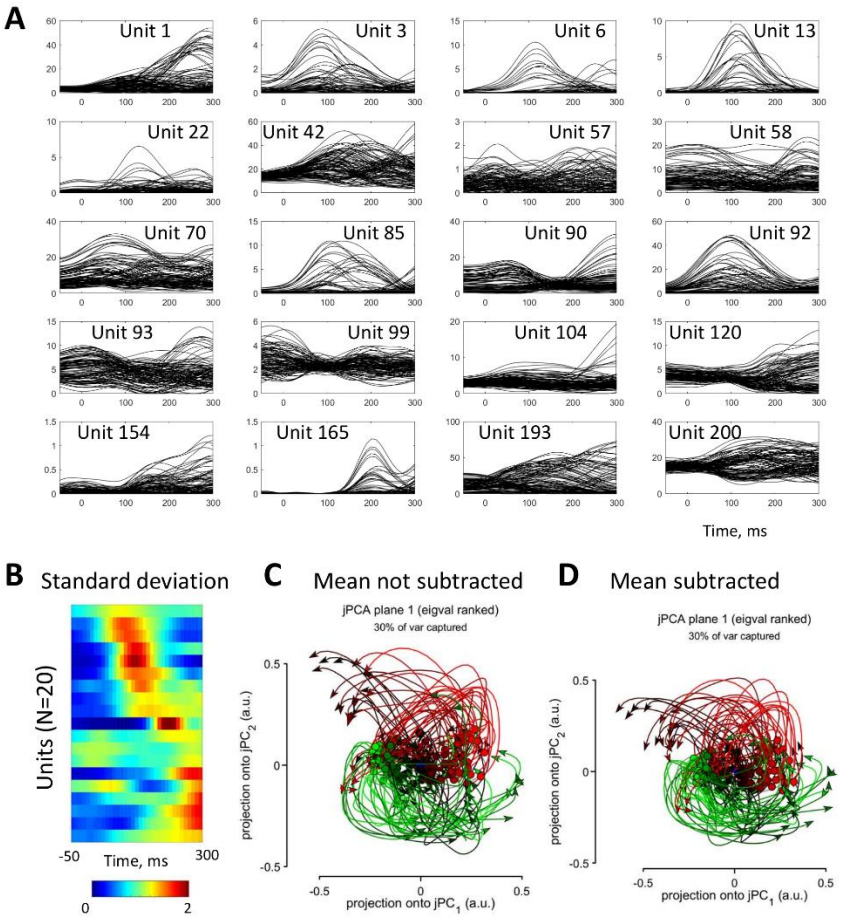

Figure 3. PETHs and jPCA plots for twenty neurons with the lowest consistency of PETH shape across conditions. A: PETHs. Each box displays PETHs from different conditions for a single neuron. B: Color plot of cross-condition PETH variance. Neurons are sorted by the time of peak variance. C: State-space trajectories for jPCA without the subtraction of mean PETH. D: Trajectories for jPCA with mean PETH subtracted.

The neurons with high cross-condition consistency of response timing fit the pattern of "sequence-like responses" the best, provided there is a spread in the occurrences of their peak responses. To assess jPCA results for the neurons of this type, we selected top twenty neurons with the highest mean correlation coefficients between the PETHs (Figure 1). Mean correlation coefficient was greater than 0.90 for all of them. Figure 1A shows PETHs for different conditions for each of these neurons. The PETH shapes are highly consistent across the conditions. Furthermore, after these neurons were sorted by the time of peak response, their population PETHs revealed a temporal sequence that was preserved across the conditions (Figure 1B). jPCA with (Figure 1D) and without (Figure 1C) mean PETH subtraction contained curved trajectories indicative of rotational dynamics. The rotations were especially clear and similar for all trials when mean PETH was not subtracted, whereas two clusters of curved trajectories (colored red and green by Churchland's script) were produced by jPCA when mean PETH was subtracted. Since the subtraction of mean PETH distorts response shape (Lebedev, Ossadtchi et al. 2019), it is not clear whether these two clusters represent any meaningful result.

We next ran a principal component analysis (PCA) for the same twenty neurons with top cross-trial consistency of PETH shapes. The PETHs were highly consistent across the conditions for the first (Figure 1A) and second (Figure 1B) principal components (PCs), which explained 72% and 11% of the variance in the data, respectively. The PETHs for the third PC (Figure 1C), which corresponded to 3% of the variance, were variable across the conditions. The first, second, and third PCs were shifted in phase, which resulted in the curved

trajectories in the 3D plot showing the relationship between these PCs (Figure 2D). These curved trajectories were like the trajectories obtained using jPCA without the subtraction of mean PETH (Figure 1C). Similar results were obtained when 50 or 100 neurons with top consistency of PETHs were selected instead of just 20 (not shown). With the addition of more neurons, the PETHs for the first two PCs became more variable across the conditions while the phase shift persisted between them. The population PETHs remained consistent across the conditions, as well, like in the plots shown in Figure 1B. When neurons ranked 1 through 20, 21 through 40, and so on, were selected for analysis, the consistency of response sequence gradually deteriorated but remained clear till half of the neuronal sample was examined (not shown).

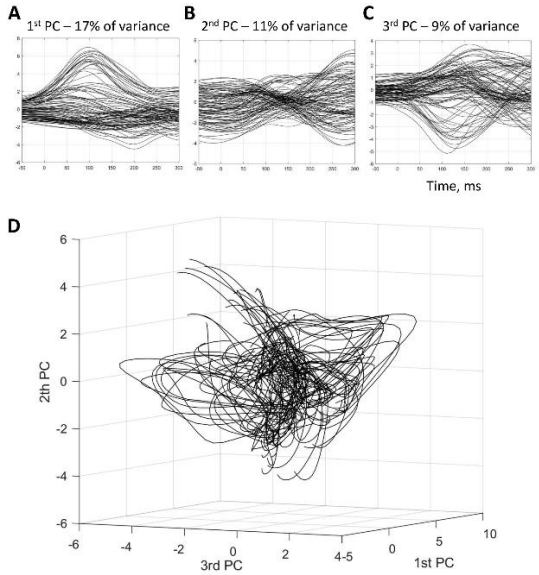

Figure 4. The first three principal components (PCs) for the population of twenty neurons with the lowest consistency of PETH shape across conditions. A-B: The first, second, and third PCs. PETHs. D: The first three PCs in 3D.

Thus, Churchland's neuronal population contained a sizeable subpopulation with consistent response timing, so the statement that single-neuron responses are "typically multiphasic and/or peak at different times for different conditions" is inexact.

Heterogeneous responses

The neurons with heterogeneous responses, like the ones illustrated in Figure 2 of Churchland, Cunningham et al. (2012), could be found in Churchland's data. To examine the neurons of this type, we selected 20 neurons with the worst cross-trial consistency of PETHs (Figure 3). These indeed had variable PETH shapes (Figure 3A), and the pattern of population PETH did not repeat across the conditions (not shown). Yet, one can notice that the responses, although variable, were not completely void of a temporal sequence. For example, in Figure 3A, unit 3 responded earlier than unit 165, and preferred response times can be seen for the other units, as well. For the response patterns of this kind, the sequence of responses could be visualized by calculating cross-condition PETH variance as a function of time for each neuron, sorting the neurons by the time of peak PETH variance, and then displaying the time-dependent PETH variance as a colorplot (Figure 3B). In this plot, variance peaks (red color) correspond to high variability of neuronal activity across the conditions, that is different responses to different movements – something to be expected for motor cortical activity. Yet, the fact that PETH variability peaked for a certain task epoch indicates that the neuron was especially responsive to movements during that period. The jPCA conducted for this subpopulation of neurons yielded two clusters of curved trajectories (red and green lines in Figure 3B,C) that were only moderately affected by the subtraction of mean PETH.

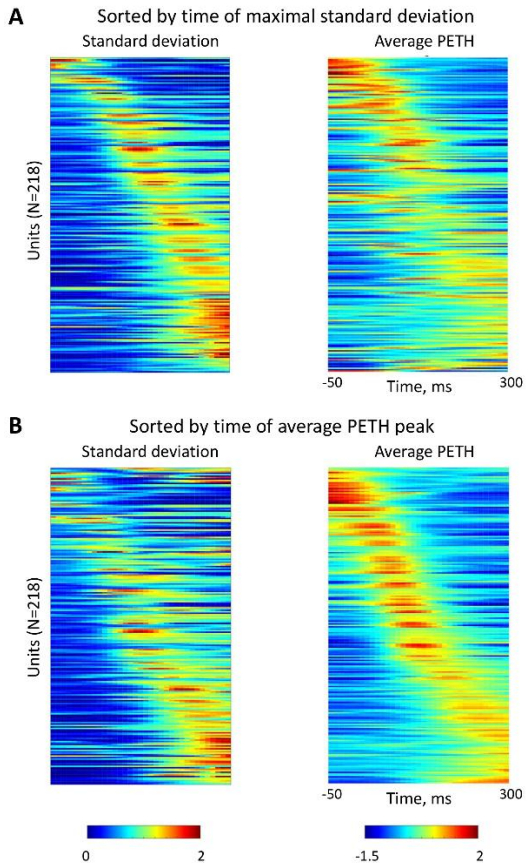

Figure 5. Response sequences defined by the time of maximal PETH variance or PETH peak. A: The sequence was derived from PETH variance (left) and then applied to average PETHs (right). B: The sequence was derived from average PETHs (right) and then applied to PETH variance (left).

The PCA conducted for the 20 neurons with the worst cross-trial consistency of PETHs (Figure 4) revealed high cross-condition variability for each of the first three PCs (Figure 4A-C) which accounted for 17, 11, an 9% of the variance in the data. Yet, clusters of conditions with similar responses can be noticed in these plots, as well as in the 3D plot for the first three PCs (Figure 4D), where clusters of curved trajectories are present. The curvatures are caused by the phase shifts between the PCs.

Thus, while neurons with heterogeneous response were present in Churchland's neuronal population, these responses were non-uniformly distributed in time: some neurons still responded earlier than the others. Additionally, as evident from PCA that yielded the first three PCs that accounted for 37% of the variance (compare to 86% of the variance for the neurons with high cross-condition consistency), the responses were sufficiently correlated in different neurons to provide reliable data for jPCA analysis. The phase shifts between the PCs originated from the sequence of PETH variance and eventually resulted in the curved jPCA trajectories.

PETH peaks versus variance

It should be noted that defining response sequence based on the time PETH peaks (see Figure 2 in Lebedev, Ossadtchi et al. (2019)) was not profoundly different from defining the sequence based on PETH variance. In Figure 5A, the sequence was derived from PETH variance (shown on the left) and then applied to the color plot showing average PETHs (shown on the right). The sequence of PETH peaks was still present after this operation. Conversely, defining the sequence based on the timing of PETH peaks (Figure 5B, right) did not destroy the sequence in the

plots of variance (Figure 5B, left). In other words, average activity level tended to increase about the same time the variance elevated.

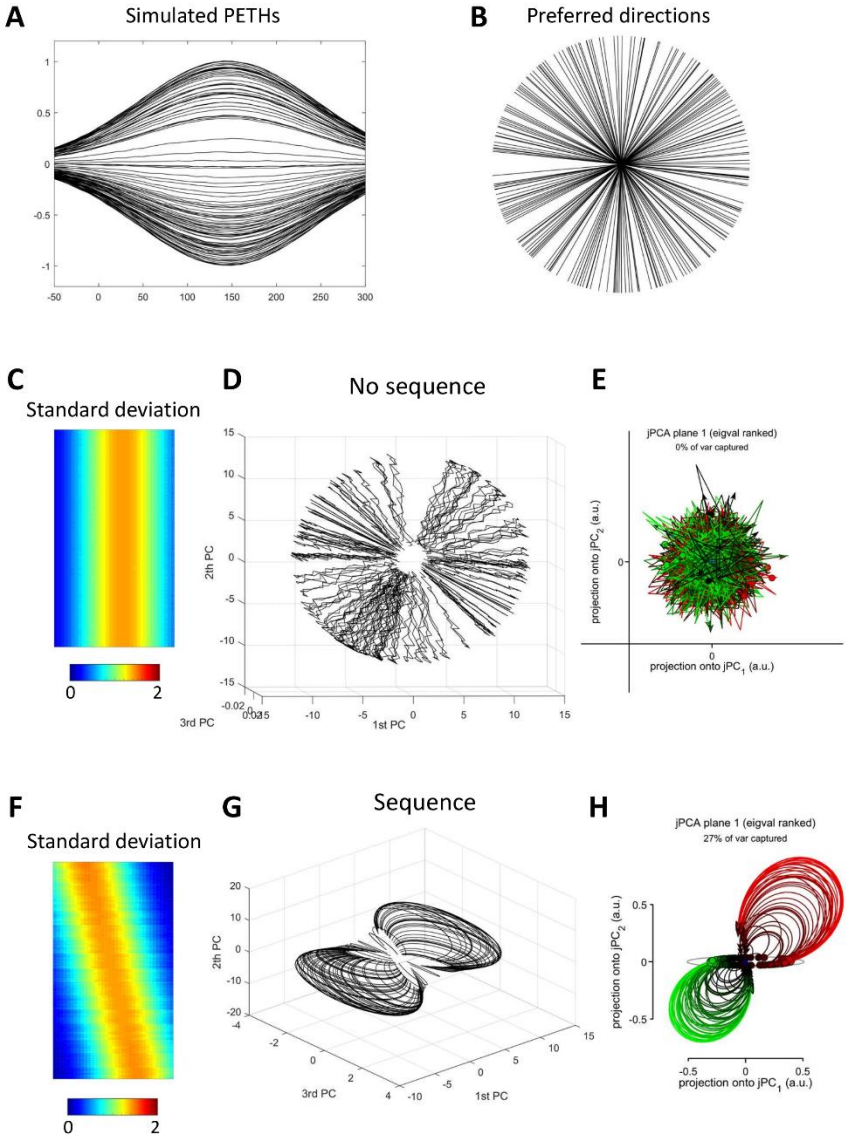

Figure 6. Simulations of cosine-tuned neurons with and without response sequence. A: PETHs for one neuron for different conditions (movement directions). PETH amplitude is proportional to movement angle. B: Preferred directions for the neurons in the population. C: Cross-condition standard deviation. In this population there was no response sequence. D: 3D plot of the initial three PCs. E: jPCA plot. F-H: the same analyses for the simulation of a response sequence.

Simulations

To verify the proposed mechanism for rotational dynamics in populations of neurons with heterogeneous responses, we ran a simulation (Figure 6), where conditions (N=108) represented directions of center-out movements (from 0 to 360 degrees) and neurons (N=218) were modeled as having cosine tuned directional tuning. The same shape of PETH was chosen for all neurons (Figure 6A), and its amplitude was proportional to movement angle. Preferred directions were randomly selected from the range 0 to 360 degrees (Figure 6B). We first simulated

a population with responses in individual neurons occurring simultaneously (Figure 6C). For this population, rotations were found neither in the plot depicting three initial PCs (Figure 6D) nor the jPCA plot (Figure 6E).

Next, we simulated a neuronal population with a sequence of responses (Figure 6F). The preferred directions were kept the same as in the previous analysis. For this population, rotations were visible in both the plots depicting PCs (Figure 6G) and the jPCA plot (Figure 6H).

Discussion

Here we conducted additional analyses in response to the comments of Vyas, Golub et al. (2020) regarding our paper (Lebedev, Ossadtchi et al. 2019). Although Vyas et al. asserted that we proposed sequence-like responses as an alternative to dynamical models of population activity, this is not what we suggested. We did not advocate any non-dynamical model that would oppose the dynamical-system framework of Shenoy and his colleagues. In fact, unlike Michaels, Dann et al. (2016), we did not propose any physiologically plausible neuronal model at all. We started with analyzed Churchland's data (i.e., empirical observations), where we found evidence of sequence-like responses. This finding was not new; several previous studies reported similar neuronal patterns (Georgopoulos, Kalaska et al. 1982, Luczak, Barthó et al. 2007, Lebedev, O'Doherty et al. 2008). The novel finding of ours was the observation of a response sequences that was preserved across different movement conditions. While it was tempting to interpret such a sequence in terms of consecutive stages of neuronal processing, we thought that the dynamical-system explanation proposed by the Shenoy group was plausible, as well.

As to the comparison of representational and dynamical models conducted by Michaels, Dann et al. (2016), we consider their work an effort in the right direction but we have little to add to this topic simply because we did not examine how the neurons in Churchland's dataset encode motor parameters. (And we could not because the dataset does not contain kinematics data.) Yet, there appears an important point of agreement between us and Michaels and his colleagues, as they concluded that "incorporating variable latency offsets between neural activity and kinematics is sufficient to generate rotational dynamics at the level of neural populations". The same judgment was expressed by the reviewer of our manuscript who wrote that it was obvious that "state-space rotation is equivalent to a preserved sequence of neural activity". Since there appears to be a consensus on the issues of sequences producing rotations and sequences being present in empirical data, we suggest that "sequence-like responses" should not be considered as something completely different from a "dynamical model" or an "empirical observation". We instead suggest that an investigation of response sequences should be viewed as a complementary analysis to the population methods that reduce data dimensionality, such as jPCA.

Looking into how response sequences (taken from experimental data or simulated) could be helpful to validate the results obtained with jPCA and similar methods, which are often hard to interpret. For instance, we described cases where there was a clear sequence in neuronal responses but jPCA did not return rotations because it incorporated a subtraction of cross-condition mean response (Lebedev, Ossadtchi et al. 2019). Algorithmic components of this kind could significantly alter the results an mislead a researcher that relies exclusively on a complicated population analysis. For instance, Michaels, Dann et al. (2016) permutated their data and then generated rotational patterns – a procedure that could have resulted data that was ill conditioned for jPCA. Yet, they drew their conclusion from the state-space plots.

The analyses that we conducted here provide additional explanations to how sequence-like responses contribute to what Churchland and his colleagues called rotational dynamics (Churchland, Cunningham et al. 2012). They used jPCA method to extract rotational patterns from neuronal population activity and argued that the existence of such patterns constitutes a proof that monkey motor cortex acts like a dynamical system. While the dynamical system idea is currently popular, we think that the results generated with dimensionality reduction methods need scrutiny, particularly with respect to their relationship to the activity patterns of individual neurons within the population.

In their response to our work, the Shenoy group was skeptical regarding response sequences being the main cause of rotational dynamics. They also called sequence-like responses a non-dynamical model even though their own data contain such sequences. In this paper, we provided additional evidence showing that Churchland's dataset contains neurons whose response timing is highly consistent across conditions (Figure 1). Previously the Shenoy group emphasized that motor cortical neurons have heterogeneous response patterns and did not describe the neurons with consistent responses.

For the highly consistent neurons, a sequence of responses can be easily revealed with a simple analysis of response peak timing. These neurons fit Churchland's original description of "an unexpected yet surprisingly simple structure in the population response" as they exhibit remarkably similar responses for all arm-movement conditions. Yet, Churchland, Shenoy and his colleagues have expressed dissatisfaction with this simple population pattern (Churchland, Cunningham et al. 2012) because it corresponds to "rotations that are similar for all conditions". They reasoned that "in such cases one fails to gain multiple views of the underlying process, making it difficult to infer whether rotations are due to dynamics or to more trivial possibilities". We respectfully disagree with this assessment because, in our opinion, cross-condition consistency fits the dynamical system framework quite well. For example, Figure 1C depicts state-space trajectories for the neurons with consistent responses. These trajectories resemble the state diagram for a pendulum (see Figure 1c in (Vyas, Golub et al. 2020)), and even a dependence of the trajectory on the initial state can be noticed.

The other point of disagreement is related to the way Churchland et al. dealt with "rotations that are similar for all conditions". To remove these rotations, they subtracted cross-condition mean PETHs from the PETHs for each condition. In the case of the neurons with consistent responses, this procedure simply removes most of the data and leaves noise (e.g. compare Figure 1C and Figure 1D), so it is unclear what one is supposed to gain with this method. The gain is not clear either for the neurons that are "multiphasic and/or peak at different times for different conditions". In this case, mean PETH is likely to be highly noisy. Additionally, mean PETH could be dominated by the strongest responses contributed by a few conditions (e.g. preferred-direction response). In addition to these considerations, it is unclear how a dynamical system defined by equation 1 could perform subtraction of the mean PETH.

The point the Shenoy group made about the neurons with heterogeneous responses merited a special consideration. A sequence of responses was not clear for the neurons of this type was not clear when looking at the sequence of PETH peaks. Yet, after we defined the sequence using the timing of PETH variance, it became clear that neuronal modulations did not occur randomly in time but followed a sequence instead. This sequence eventually translated into the curved jPCA trajectories.

Overall, we do not see any principal controversy between the neural population dynamics framework (Vyas, Golub et al. 2020) and our results pertaining to sequence-like responses. Yet, in our opinion, questions remain regarding the interpretation of low-dimensional representations of neuronal population data.

Methods

The data and jPCA code were downloaded from the Churchland lab's online depository

(https://www.dropbox.com/sh/2q3m5fqfscwf95j/AAC3WV90hHdBgz0Np4RAKJpYa?dl=0). The dataset contained PETHs for each neuron and each condition. jPCA was run with the following MATAB commands:

```
times = -50:10:300;                                    (4)
jPCA_params.numPCs = 6;
[Projection,Summary]=jPCA(Data,times, jPCA_params);
```

PETHs were standardized by subtracting the mean (for all conditions) and dividing by the standard deviation (also for all conditions).

Acknowledgement

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