

## **How can we detect and analyze navigation-related low-frequency oscillations in human invasive recordings?**

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**Abstract** Theta oscillations are a prominent semi-periodic fluctuation in the local field potential of the human hippocampus and show important links to areas of cognition like episodic memory and navigation. In this chapter, we begin by characterizing the properties of human hippocampal theta oscillations, which are more bursty and less continuous compared with rodents. Next, we introduce the Better OSCillation Detection algorithm (Whitten et al., 2011) for detecting oscillations based on amplitude and temporal thresholding. We compare BOSC with other oscillatory detection methods, such as those based on dual-amplitude thresholding and hidden Markov models. Additionally, we provide tutorials and a practical guide for oscillation detection for the interested reader. All codes and examples are provided freely in open-source format. Together, these provide researchers with the tools to explore novel questions about the nature of hippocampal navigation-related theta oscillations. As we demonstrate in this chapter, oscillatory detection procedures are extremely helpful for characterizing oscillatory dynamics including burst frequency and burst duration, exceeding beyond the singular dimension provided by amplitude changes measured in the power spectra.

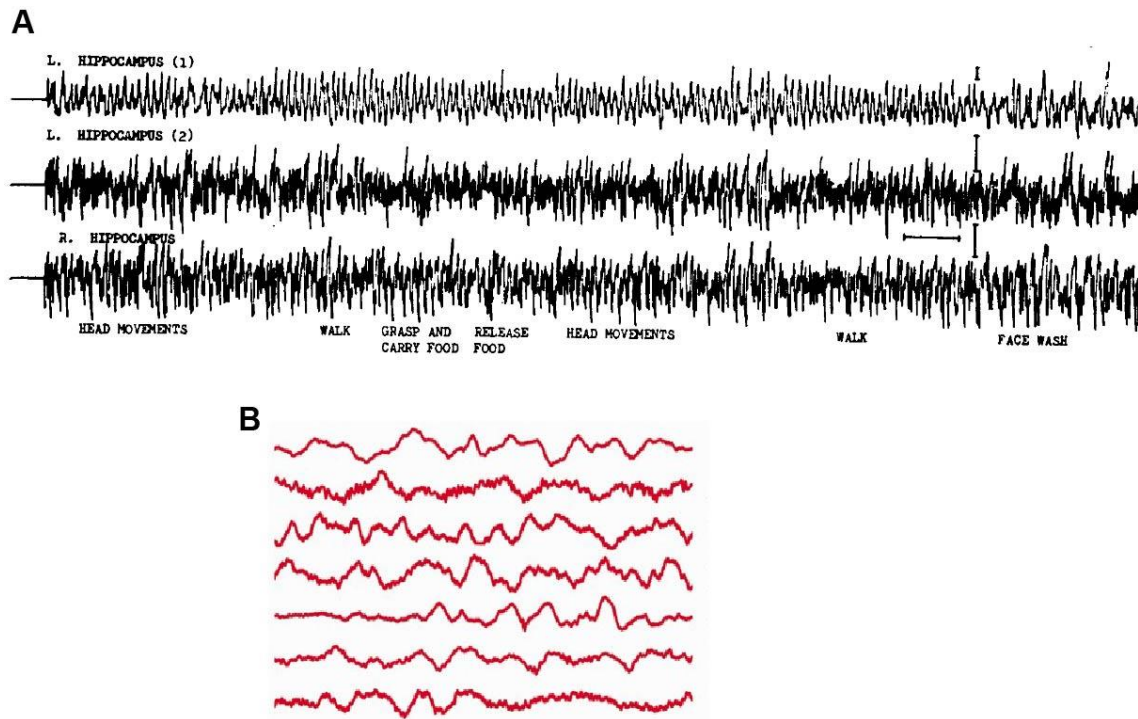
## Introduction

Low-frequency (2-12Hz) oscillations are a prominent signature in the local field potential associated with navigation and memory. In invasive recordings they manifest in medial temporal lobe and neocortex, but they are also observed in noninvasive recordings such as scalp electroencephalogram (EEG). The bursty nature of oscillations, in contrast to the more sustained oscillations observed in animals, prompts the needs to detect and quantify the presence of oscillations. This chapter will first provide a background on neural oscillations as they relate to memory and navigation and include a step-by-step tutorial for detecting neural oscillations using existing algorithms.

Human navigation-related oscillations manifest in various frequencies, covering a range of from 1-12 Hz. The frequency, and prevalence of hippocampal oscillations varied across tasks and species. For example, rodents display 8-12 Hz oscillations in hippocampus associated with movement, while humans display 1-4 Hz oscillations [1, 2]. Typically, theta oscillations in rodent hippocampi are more sustained (Figure 1, adapted from Vanderwolf 1969). In contrast, theta oscillations in humans are more bursty, appearing in the form of bouts [3]. Existing findings suggest that human hippocampal bouts typically last 0.57 seconds, with the range between 0.4s – 0.6s, which is ~3.35 cycles for 6 Hz oscillations [4]. In contrast, 8Hz oscillations in rodents last longer; for example, in a spatial navigation task, the average burst length measured in rats' hippocampal electrodes is ~4.3 cycles [3]. Some frequency variation in navigation-related theta may also relate to differences in sensorimotor inputs between virtual navigation and real-world locomotion. For example, patients with implanted hippocampal electrodes show more electrodes manifesting significant theta bursts in the 8-12Hz theta band compared to virtual desktop navigation, in which oscillations tend to manifest from 1-4Hz [5]. Therefore, when examining intracranial recordings from humans obtained during a spatial navigation task, it is advised to analyze a wider range of 1-12Hz oscillatory activities.

One way to examine navigation-related responses is to analyze the time-frequency power representations. While the absolute power correlates with theta activities in the iEEG data, the absolute power can be confounded by the background noise that is independent

of task-related activities. For example, successful memory encoding and retrieval involves absolute theta power decreases and absolute gamma power increases in human hippocampus [6]. However, the changes in absolute power are often confounded with the slopes of background power spectra (see Figure 2 for an example of background power spectra). This is because background noise also has “power” based on the  $1/f^\alpha$  spectrum. Absolute theta power decreases, for example, can be interpreted as relative theta power increases coupled with an increased tilt of the aperiodic background spectra. Oscillatory detection algorithms, which we will discuss in more detail here, provide a solution by standardizing the quantification of oscillations across electrodes and patients. In the next section we describe the procedure to detect oscillatory activities in intracranial recordings.



**Figure 1.** Navigation-related hippocampal oscillations in humans and rodents manifest differently in frequency and prevalence. (A) Example of 8-12Hz hippocampal oscillations during naturalistic behaviors in rodents. Adapted from Vanderwolf (1969) Figure 4 Panel C. Note the nearly continuous nature of the oscillatory signal. Each row shows example raw traces from one electrode, and the calibrations indicate 1 second of data and 100  $\mu$ V. (B) Example of navigation-related hippocampal oscillations in humans.

Note the less continuous nature of human theta, even during continuous movement (similar to what is shown in rats in A). Adapted from Watrous et al., (2013).

## **1. A practical guide for detecting oscillations from human hippocampal recordings during a navigation task**

In this section, we describe the procedure to detect and quantify the presence of hippocampal oscillations, using deidentified data from Liang et al. (2022). The data is available for download via [https://github.com/liangmingli/chapter\\_scripts](https://github.com/liangmingli/chapter_scripts). The example data are recorded from an implanted electrode in the left anterior hippocampus of a patient undergoing seizure monitoring. The data were collected when the patient navigated in a T-maze in virtual reality on a laptop, and the data contains 48 repetitions of the navigation segments.

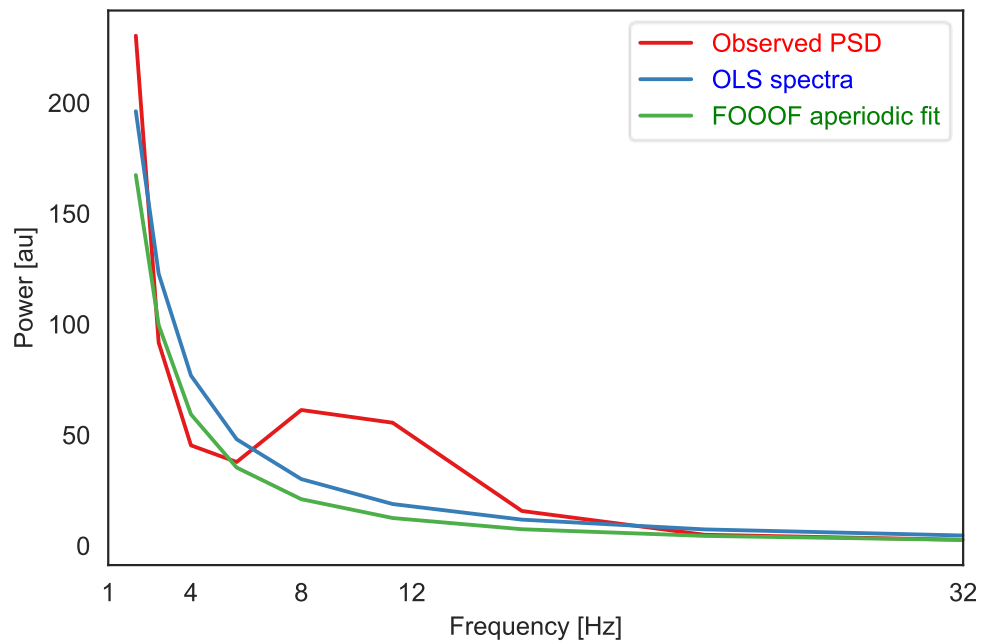
As part of the preprocessing pipeline, filtering, line noise removal, and ictal discharges visual inspection should be done by the researcher. We note that researchers should properly epoch the data dependent on whether the navigation tasks are time-locked or active free exploration. In terms of free exploration, epoching is better implemented after the time-frequency decomposition on the continuous data. For an event-related design, it is better to epoch the continuous data before time-frequency power decomposition, to prevent information leak from temporal smoothing.

Amplitude thresholding is one viable method to detect and quantify navigation-related theta oscillations. They are implemented on the basis of time-frequency decomposition of iEEG data, including BOSC [7], eBOSC [8], and burst detection by neuroDSP [9]. Better Oscillation Detection algorithm detects neural oscillations based on two levels of thresholding: power threshold and duration threshold [7, 10]. The power thresholding identifies timepoints with high oscillatory power, and the duration thresholding reassures that those timepoints when clustered together are sustained based on the number of cycles.

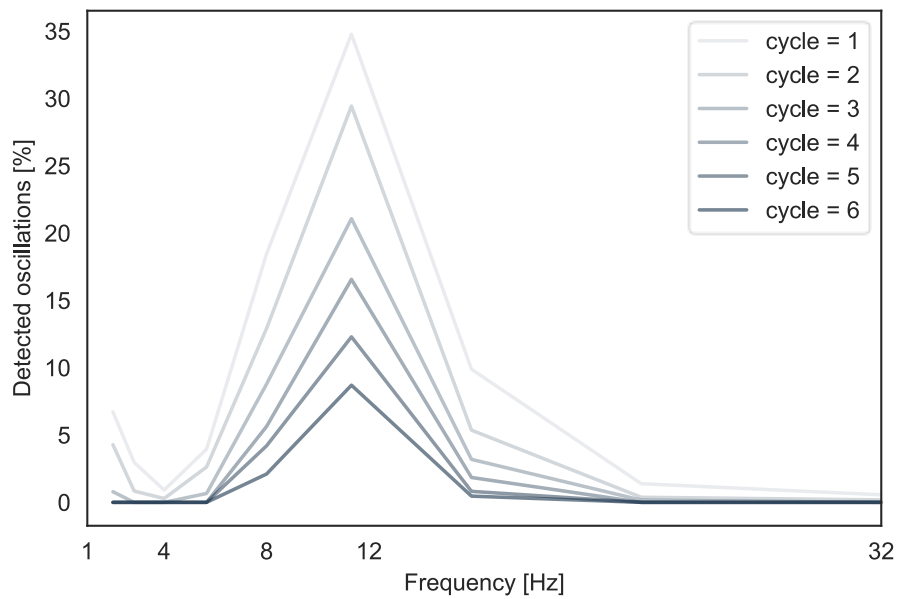
The BOSC library can be downloaded via [https://github.com/liangmingli/chapter\\_scripts](https://github.com/liangmingli/chapter_scripts), contributed by Whitten et al. (2011). The BOSC procedures include

- 1) extracting the time-frequency power,
- 2) estimating the background spectra,
- 3) calculating the power threshold and duration threshold, and
- 4) detecting oscillations.

When approximating the background spectra, the original BOSC algorithm uses ordinary least squares linear regression for the estimate. Other alternatives have been proposed and used, such as robust linear regression to exclude outlier values from the power spectra [8], and using recursive Gaussian processes to estimate the aperiodic spectra [11] (see also [Chapter 24](#)). After the background spectra is approximated, power threshold is estimated based on a chi square distribution with 2 degrees of freedom, and a default cutoff is 95% of the distribution. Compared to the OLS linear regression, robust linear regression and recursive Gaussian fitting produce lower power thresholds, i.e., are more sensitive to detecting navigation-related theta oscillations (Figure 2). As for selecting the temporal threshold, shorter temporal thresholds enable researchers to capture the dynamics of shorter oscillatory bouts during navigation, vice versa for longer temporal thresholds (see Figure 3). Three cycles or more is the preferred value for the cycle (temporal) threshold, although a shorter temporal threshold (e.g., 2 cycles) has been used by researchers as well [12].



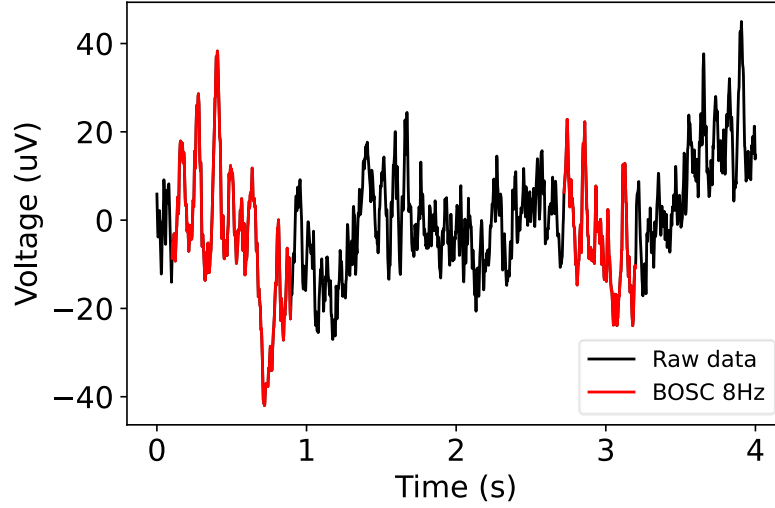
**Figure 2.** Fitting the background spectra using ordinary least square regression and recursive Gaussian fitting processes. The blue solid line indicates the empirical power spectra obtained from the example recordings.



**Figure 3.** Shorter temporal thresholds (i.e., fewer required cycles) yield an estimate of higher oscillatory activities.

After detecting oscillations with BOSC, the outputs are a binary sequence (i.e., timepoints with detected oscillations are noted with 1, otherwise with 0). Averaging the binary sequence yields the measure of oscillatory activities, or the percentage of time detected with oscillations at a given frequency (the  $P_{\text{episode}}$  measure.) Researchers have utilized the  $P_{\text{episode}}$  to investigate the relationship between oscillatory prevalence and spatial navigation [3, 4, 13]. For example, using the BOSC detection algorithm, Vass et al. showed that hippocampal theta prevalence differed between short distance and long distance traversals during navigation.

Further, oscillatory detection algorithms also enable researchers to examine the properties of bursts, such as the burst density, burst duration, and burst amplitudes. Those three aspects of burst dynamics have been implicated as relevant forms of information coding [14]. In the example dataset on trial 11, two oscillatory bursts at 8Hz were identified: one detected around [0.10, 0.90] seconds, and the other burst around [2.72, 3.20] seconds. The first burst lasted approximately 0.79s (6.34 cycles) while second burst lasted 0.48s (3.83 cycles). On average, for the example trial with a four second long duration, approximately 31% of the data was detected with oscillations. To examine the amplitude of 8Hz oscillation, the researcher can simply sample the power series during the timepoints detected with oscillations. Therefore, the BOSC detection algorithm allows researchers to more comprehensively evaluate burst dynamics including burst frequency, burst duration and burst amplitudes. For example, Aghajan et al. (2017) sampled hippocampal activity from one patient with congenital blindness during real-world navigation. Compared to patients with vision, hippocampal theta oscillatory bouts were significantly longer. Therefore, characterization of the oscillatory burst dynamics enables novel insights into how neural oscillations are associated with spatial navigation.



**Figure 4.** Two oscillatory bursts at 8Hz were detected using BOSC in the example dataset, example trial 11. Timepoints detected with 8Hz oscillations are overlaid in red color.

What is the typical range of detected theta oscillations in humans during spatial navigation? Here, we present several recent publications in the field of human electrophysiology and spatial navigation. During a spatial navigation task, a hippocampal electrode is expected to manifest theta bursts approximately 10-20% of the time (Table 1).

**Table 1.** Studies using BOSC and detecting medial temporal lobe theta oscillations

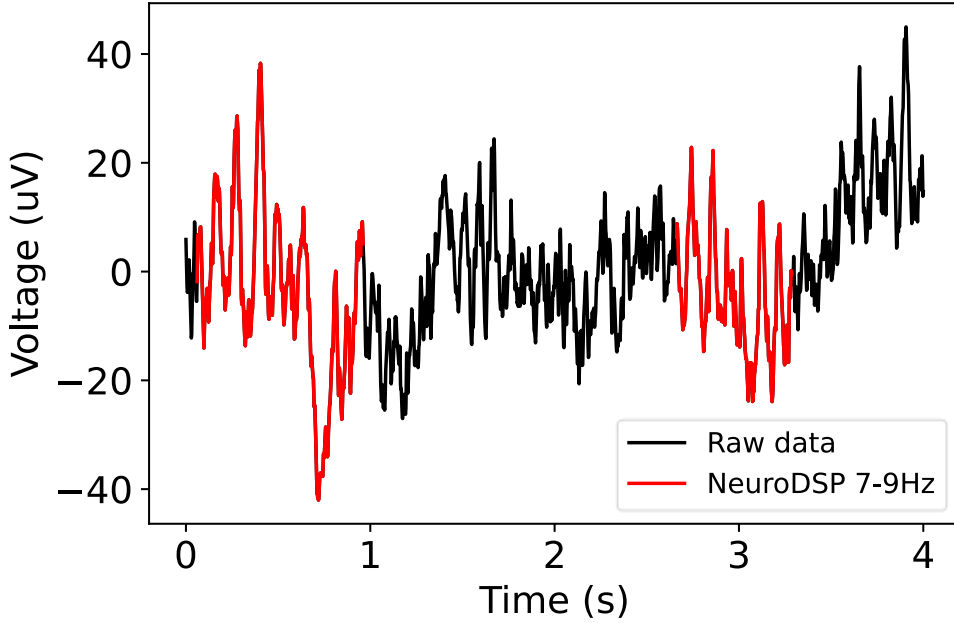
Study	Location	$\theta$ Percentage	Task type
Watrous et al., 2013 [3]	hippocampus	0-16%	Navigation
Vass et al., 2016 [13]	hippocampus	0-30%	Navigation and teleportation
Aghajan et al., 2017 [4]	medial temporal lobe	0-15%	Real-world navigation
Chen et al., 2021[15]	entorhinal	10-20%	Navigation
Kragel et al., 2021 [16]	hippocampus	10%	Recognition memory
Liang et al., 2022 (under review)	hippocampus	0-15%	Navigation and teleportation



## **2. Convergence: detecting navigation-related oscillations using other available methods**

In addition to BOSC [7, 10], as mentioned, there are other methods to cover oscillation detection. Some of these include: 1) using double amplitude thresholding in NeuroDSP [9] <https://neurodsp-tools.github.io/neurodsp/index.html>, and 2) Hidden Markov Model based state inferences of burst status [17, 18], via [https://github.com/OHBA-analysis/Quinn2019\\_BurstHMM](https://github.com/OHBA-analysis/Quinn2019_BurstHMM). In this section we note that we do not intend to give a formal assessment and comparison among the methods for oscillatory detection (see **Chapter 24**).

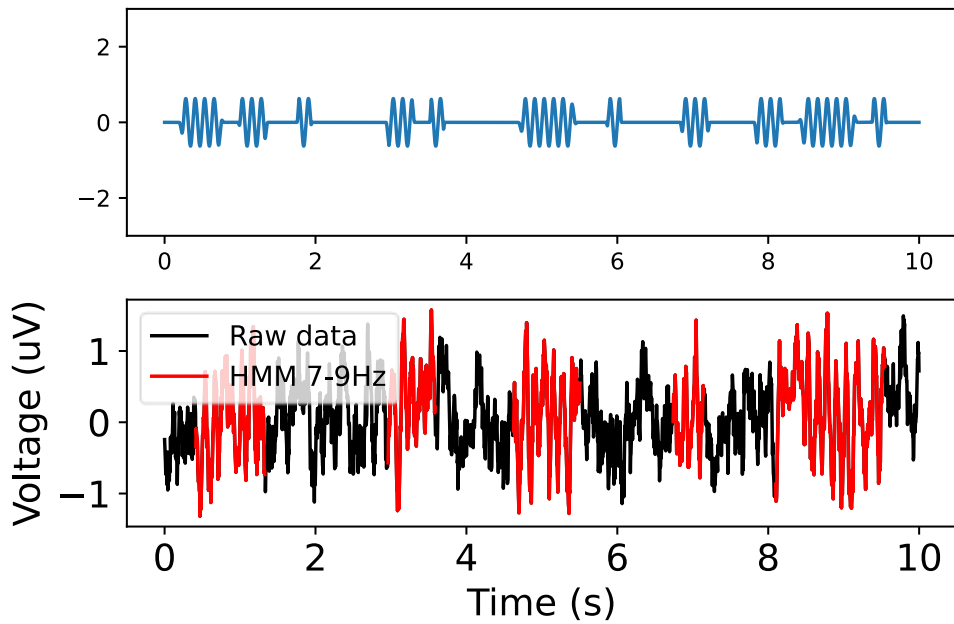
In contrast to BOSC using both amplitude and duration thresholds, NeuroDSP uses only power thresholds but no temporal threshold. The power series will be marked as oscillatory when it goes above the upper power threshold, and then marked as non-oscillatory when it drops below the lower power threshold. Without temporal thresholding, the detected events could include oscillatory bursts that are both short and long. Based on the example dataset, for trial 11, NeuroDSP returned two oscillatory bursts detected at the frequency range of 7-9Hz, similar to the output reported by BOSC: one burst of 0.84s length (6.72 cycles) and the other burst of 0.63 second length (5.0 cycles), and about 38.21% of the data were detected with 7-9Hz oscillations (Figure 5).



**Figure 5.** Two oscillatory bursts within 7-9Hz were detected using NeuroDSP dual power threshold detection. Timepoints detected with 7-9Hz oscillations are overlaid in red color. Compared to the output reported by BOSC (**Figure 4**), both methods discovered two oscillatory bursts with similar timestamps, and both methods detected a similar percentage of 8Hz oscillatory activities (BOSC: 31%, NeuroDSP: 38%). We note that NeuroDSP and BOSC involved different approaches to determining the amplitude threshold(s), and therefore they could produce different detections of oscillatory onsets: note the earlier detected onsets of 8Hz activities in the NeuroDSP outputs compared to that of BOSC.

An alternative method is based on Hidden Markov models (HMM) and Multivariate Autoregressive models [17, 18]. Rather than thresholding with a voltage threshold, oscillatory states are inferred based on empirical observations of time-frequency data and histories of oscillatory states. The idea behind is that compared to a non-oscillatory baseline, oscillatory bursts at distinct frequencies are associated with distinct power spectra, and distinct power spectra can be detected as distinct events/states. The HMM predicts the oscillatory states at each timepoint based on the history of time-frequency representations of past timepoints and the inferred states of past timepoints.

One key parameter for HMM is the possible number of states ( $K$ ), which requires a-priori specification. In Quinn et al. (2019), the authors explored two different  $K$  values: 2 and more than 2. When  $K$  is set to 2, the possible number of states is set to 2, (i.e., oscillatory vs non-oscillatory), and the inference is operated on narrow-banded filtered signals (i.e., 7-9Hz bandpass filtered signal for detecting 8Hz activities). The second approach, where  $K$  is set to be more than 2, is to explore all the possible oscillatory states in the data across multiple frequency ranges. This is suited for research questions that look at multiple oscillatory frequencies in the context of spatial navigation (e.g., theta and gamma activities). One critical difference between the HMM based- and amplitude-threshold-based oscillatory detection is that the output from HMM is ambiguous and requires experimenter interpretation. For example, the HMM will output the posterior probabilities for each timepoint and for each state. But what state(s) belong to theta oscillatory occurrence? Would state 1 or state 2 be the inferred state of theta occurrence? That is the question that will need the experimenter's expertise to answer. Here, to demonstrate the HMM method for oscillatory detection, we simulated 8Hz sinusoids added on top of  $1/f$  noise. HMM-based models detected the simulated 8 Hz oscillatory bursts, and after visual examination, we concluded that state 1 was associated 8Hz oscillatory bursts and state 2 was associated with non-oscillatory timepoints (Figure 6).



**Figure 6.** Detecting 8Hz simulated oscillatory bursts using Hidden Markov models [17, 18]. In the top panel, the simulated 8Hz bursts is plotted, and the simulated bursts are added to  $1/f$  noise for follow-up oscillatory detection. In the bottom panel, timepoints detected with 7-9Hz oscillations are overlaid in red color.

### 3. What do we mean by “oscillation?”

The mathematical definition of an oscillation refers to a continuous periodic signal that can be decomposed into frequency, amplitude, and phase. In most applications, such oscillations are approximated as sine and cosine functions using the Fourier Transform. As is fairly clear from our examples above, however, the “bursts” of signals discussed above cannot be considered “oscillations” in the strict sense because they are not continuous in terms of their cycles. Consistent with this, comparing Fourier methods with methods that better account for the burstiness of these signals within the local field potential (such as BOSC) suggest that Fourier methods generally do a comparatively poor job at characterizing these signals [19].

This raises the question then why we even call such signals “oscillations” when they are clearly not, even in rodents, continuous cycles resembling sine waves. The answer to this question appears to be part nomenclature: early efforts to characterize these time-varying signals in scalp EEG and invasive recordings applied Fourier methods [20, 21] thereby assuming oscillatory signals in the stricter mathematical sense. This assumption, however, is not necessarily problematic as Fourier methods can still approximate aperiodic signals as well, and almost any function for that matter, although the numbers of coefficients can become unwieldy [22]. As mentioned, the accuracy of characterizations that assume a periodic continuous signal is weaker than methods that allow for bursts (such as BOSC or NeuroDSP). Perhaps more importantly though for our present consideration is that the term “oscillation” is incorrect.

As an alternative, we suggest the term “semi-periodic fluctuation” (SFP) in the local field potential. This term helps capture the idea that such signals are indeed periodic for bouts but then taper off (for reasons that have yet to be revealed). The term “fluctuation” helps to capture another issue which is that the amplitude of these bursts also varies from cycle to cycle and burst to burst. This is also in contrast to a classic sine wave in that the

amplitude should be constant and therefore something that can be approximated with a single number. While we think it is likely that the term “oscillation” will persist, it is important to be aware that the signals we have discussed, particularly in humans, are not “oscillatory” in the classic Fourier sense but rather semi-periodic and varying in amplitude.

One could ask why such signals might be “bursty” in the first place, and why human signals might be more bursty than those of other species, like rats. While the reasons have yet to be uncovered, one possibility is that brief bursts of periodic fluctuations actually carry more information than long continuous bursts. This can be seen from the Fourier perspective described above; a continuous signal requires 3 parameters to describe it in Fourier space: frequency, amplitude, and phase. A semi-periodic fluctuation requires many more parameters to capture both the aperiodic nature and the fluctuating amplitude of the signal. Likely, such bursty signals are more adept at transiently coordinating disparate brain regions compared to a continuous signal, which would lead to entrainment and potentially seizures [23, 24]. While these ideas remain speculative, they provide some initial ideas about why “oscillations” may not be oscillatory at all.

#### **4. Conclusions**

Hippocampal low-frequency oscillations are often found when humans perform a spatial navigation task. Such low-frequency oscillations have been demonstrated to be relevant for the formation of spatial representations and the coding of multiple spatial variables. While power can provide some degree of the prevalence of navigation-related oscillations, the transient and bursty nature of human hippocampal low-frequency oscillations necessitates the needs of oscillatory detection performed on the data. Implementing oscillatory detection on the obtained intracranial recordings can quantify the amount of oscillations in the signal and allows for the extraction of parameters regarding burst frequency, burst duration, and burst amplitude. Oscillatory detection is mostly performed via amplitude thresholding, where timepoints with sufficiently high oscillatory power are considered “oscillatory”. The amplitude thresholding sometimes is accompanied by temporal thresholding to identify oscillatory bursts that last longer than a

specific number of cycles. Alternative approaches to oscillatory detection also include Hidden Markov model-based approach, in which the oscillatory states are inferred rather than yielded from thresholding. Oscillatory detection can generate new analyses and insights for spatial cognition research, allow for the standardization of oscillatory prevalence across electrodes and participants, and most crucially, incorporates the transient nature of low-frequency semi-periodic fluctuations in humans vs. animals.

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