CONCLUSION

In studying neural oscillations, the analyses we apply are often very complicated, mathematically intensive, and full of assumptions, both explicit and implicit. Therefore, careful consideration of the methods applied to our data is paramount, as seemingly arbitrary choices in the hyperparameters of our analysis (e.g. the minimum number of spikes required for inclusion of a neuron or the length and precise cutoff frequencies of a filter) can have large impacts on the results and ultimate conclusions. Often, in-depth knowledge of the techniques is required in order to appropriately choose hyperparameters and assure the validity of our conclusions. Because considerable effort is required to obtain this knowledge, this means that we will often make honest mistakes in our analysis and as peer reviewers, we often miss the statistical confounds that may underlie highly impactful results. This scientific issue is analogous to a contemporary issue in “fake news” in which data and statistics are either intentionally or ignorantly abused, often in pursuit of an agenda.

There are a few approaches I have found over the course of this thesis work to help alleviate issues I had in trusting my analyses.

1. Deliberate attention to and inspection of raw data is extremely helpful to gaining maximal understanding of our analyses, as complicated methods can often treat our data in ways we do not expect. If we do not understand how we see the ultimate effect by looking at the raw data, there is reason for concern or at least further investigation.
2. Rather than considering the presence of hyperparameters as a “nuisance” that complicates analyses, they can also be valuable tools in order to better understand the data. Hyperparameter settings can be varied, and their effects on the results can be measured in order to better understand the conditions necessary for our results to hold. Suggestion of this approach is a bit ironic, as grid-searching hyperparameters is also a very effective “p-hacking” strategy. Therefore, the efficacy of this approach fully relies on the integrity of the researcher at that moment.
3. In addition to varying hyperparameters, it can similarly be useful to apply multiple methods to our data. When it comes to analyzing neural oscillations, there are several analytic options to choose from (e.g. spectral or cycle-by-cycle analysis), and so this choice should be made consciously. Prior to the work in Chapter 1, I investigated at least six phase-amplitude coupling metrics in order to get a sense of how each of them worked and which, if any, was most appropriate to use with the recordings from the patients with Parkinson’s disease. Applying multiple methods and comparing results not only yields a sense of robustness to our results but also often provides a valuable learning experience.

The choice for the analytic method applied can strongly impact the ultimate conclusion. As discussed in Chapter 1, phase-amplitude coupling analysis and sharpness analysis were capturing the same phenomena in the data. However, the former favored a conclusion of coupled oscillators, whereas we favored the latter conclusion concerning synchrony of transmembrane currents.

In Chapter 2, the choice of developing a time-domain approach to analyzing neural oscillations was very deliberate. As physical processes, including neural dynamics, happen over time (as opposed to being generated in the frequency domain), there are advantages in analyzing signals in this natural domain and directly measure and account for nonstationarities in the dynamics. While it is certainly a biased perspective, I believe that neural oscillations research would be better positioned if the default analysis of these rhythms was based in the time domain using a cycle-by-cycle approach instead of a spectral domain approach. While an analysis based on the Fourier transform has an advantage of computational efficiency, this is no longer as important of an advantage, as computational power is now very cheap.

Conversely, our cycle-by-cycle analysis offers some great features that are advantages over a potential spectral approach. First, our approach directly quantifies waveform asymmetry, which is only indirectly and ambiguously captured in spectral analysis (i.e., similar harmonic patterns can be generated by different oscillators that produce diverse waveforms). Second, cycle-by-cycle analysis inherently runs an oscillation detection algorithm, so oscillatory features are only analyzed on appropriate portions of the signal (i.e., where the oscillation is observable). Third, cycle-by-cycle analysis offers time-resolved estimates of oscillatory features with an appropriate degree of temporal resolution. Not only is symmetry measured for a single cycle, but the estimates of amplitude and frequency are intuitively measured in terms of peak-to-trough voltage and trough-to-trough time, respectively. However, “instantaneous” estimates of amplitude and frequency that are comparatively used offer amplitude and frequency estimates at every point in time. In order to accomplish this, these estimates rely on both narrowband filtering and the complex Hilbert transform. In this approach, both the width of the time window and the behavior on a variety of noisy, nonstationary signals is nonobvious. In Figures 2.5 and 2.6, we demonstrate that the cycle-by-cycle approach can provide more sensitive measures of amplitude and frequency by better differentiating simulated experimental conditions.

Developing this approach to capture the waveform shape of neural oscillations begs the question of what information about neural activity can be gained from this analytic perspective. Chapter 3 showed that the hippocampal theta cycle features, including its symmetry, contain information about the neuronal firing patterns. However, it is still unclear how these differences in waveform shape may reflect differences in neural mechanisms. This is currently unclear, but could be addressed in future experiments and analyses that are designed to compare the changing shape of the field potential to known behavior-related or physiologically-induced changes in oscillatory circuits.

Currently, I abstractly consider oscillation waveform shape as an observed state variable of a dynamical system defined by the oscillatory generator. The trajectory of this oscillation in phase space changes based on changes in the circuit connectivity, input patterns, extracellular ion concentrations, and the dynamics of transmembrane currents. Changes in this trajectory can be detected as changes in the oscillation waveform shape in addition to the amplitude and frequency. The specific ways in which the waveform shape reflects neural activity are currently unknown, and it is unclear how this will generalize between brain regions.

The pursuit of relating the waveform shape of oscillations to neural mechanisms will greatly benefit from future methodological developments. Not only is a cycle-by-cycle analysis approach being applied to studying waveform shape, but bicoherence has also been applied to show that patients with Schizophrenia have mu rhythms that are less sharp compared to the stereotyped mu rhythms in control subjects [(Bartz et al., 2018; Shahbazi Avarvand et al., 2018)](http://f1000.com/work/citation?ids=6099769,4824273&pre=&pre=&suf=&suf=&sa=0,0).

While the current thesis only considered the waveform shape of a single recording at a time, neural recordings are usually collected with a grid of electrodes. Therefore, methods to analyze the spatial patterns of oscillation waveform shape may provide further insights by extracting spatial information about these features. Multivariate convolutional sparse coding is a promising approach for characterizing this information [(Agarwal et al., 2014; Jas et al., 2017; La Tour et al., 2018)](http://f1000.com/work/citation?ids=6116995,3718997,81556&pre=&pre=&pre=&suf=&suf=&suf=&sa=0,0,0).

The current cycle-by-cycle analysis was limited to four features of oscillatory cycles (amplitude, period, rise-decay symmetry, and peak-trough symmetry), but further features could be defined in order to better distinguish waveforms, such as sine waves and triangle waves. A recent study quantified spectral coupling on a cycle-by-cycle basis by measuring the frequency, power, and timing of gamma oscillations during individual theta cycles in the rodent hippocampus [(Lopes-Dos-Santos et al., 2018)](http://f1000.com/work/citation?ids=6070445&pre=&suf=&sa=0).

Another limitation of this thesis is that it relied on a burst detection algorithm that defined each point in time as either containing or not containing an oscillation. However, this is a false dichotomy, as it is rarely undoubtedly certain whether or not an oscillation is observable in a neural recording at each point in time. Therefore, this work would benefit from a probabilistic oscillation detection algorithm that captures this nuance in oscillation presence (Andrew Watrous, personal communication).

In conclusion, a cycle-by-cycle characterization of neural oscillations can provide a promising complement to the spectral analysis that has led to many discoveries of the importance of rhythms in the brain.

**References**

[Agarwal G, Stevenson IH, Berényi A, Mizuseki K, Buzsáki G, Sommer FT (2014) Spatially distributed local fields in the hippocampus encode rat position. Science 344:626–630.](http://f1000.com/work/bibliography/81556)

[Bartz S, Avarvand FS, Leicht G, Nolte G (2018) Analyzing the waveshape of brain oscillations with bicoherence. Neuroimage.](http://f1000.com/work/bibliography/6099769)

[Jas M, Tour T, Şimşekli U, Re G (2017) Learning the Morphology of Brain Signals Using Alpha-Stable Convolutional Sparse Coding. Arxiv.](http://f1000.com/work/bibliography/3718997)

[La Tour TD, Moreau T, Jas M, Gramfort A (2018) Multivariate Convolutional Sparse Coding for Electromagnetic Brain Signals. arXiv.](http://f1000.com/work/bibliography/6116995)

[Lopes-Dos-Santos V, van de Ven GM, Morley A, Trouche S, Campo-Urriza N, Dupret D (2018) Parsing Hippocampal Theta Oscillations by Nested Spectral Components during Spatial Exploration and Memory-Guided Behavior. Neuron 100:940–952.e7.](http://f1000.com/work/bibliography/6070445)

[Shahbazi Avarvand F, Bartz S, Andreou C, Samek W, Leicht G, Mulert C, Engel AK, Nolte G (2018) Localizing bicoherence from EEG and MEG. Neuroimage 174:352–363.](http://f1000.com/work/bibliography/4824273)