# Measuring, Modeling and Modulating Cross-Frequency Coupling: A State Space Modeling Approach to Real-Time Phase Estimation

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## Causal Estimates of Phase

- Understanding the role of phase in neural function requires interventions that perturb neural activity at a target phase, necessitating estimation of phase in real-time
- Current methods for real-time phase estimation rely on bandpass filtering, which assumes (1) narrowband signals and (2) couples the signal and noise in the phase estimate, adding noise to the phase and impairing detection of relation-ships between phase and behavior
- We propose a state space phase estimator for real-time tracking of phase
- We demonstrate in simulations that the state space phase estimator outperforms current state-of-the-art real-time methods
- We also have developed a ready-to-use plug-in for the OpenEphys acquisition system, making it widely available for use in experiments

## State Space Phase Estimation (SSPE)

- We utilize and build upon the approach suggested by Matsuda and Komaki (2017) where data acts as the observation for a linear state space model and the state tracks the analytic signal of the underlying rhythms
- We estimate parameters of the model using an existing segment of data before applying the model in real-time
- For real-time application, given a new observation, we use the Kalman filter to predict and update the state estimate and use this to estimate the phase causally as shown in Fig. 1B and 1C below
- We can use the state covariance to estimate credible intervals for the phase

Matsuda, T., and Komaki, F. (2017). Time series decomposition into oscillation components and phase estimation. Neural computation, 29(2), 332-367.

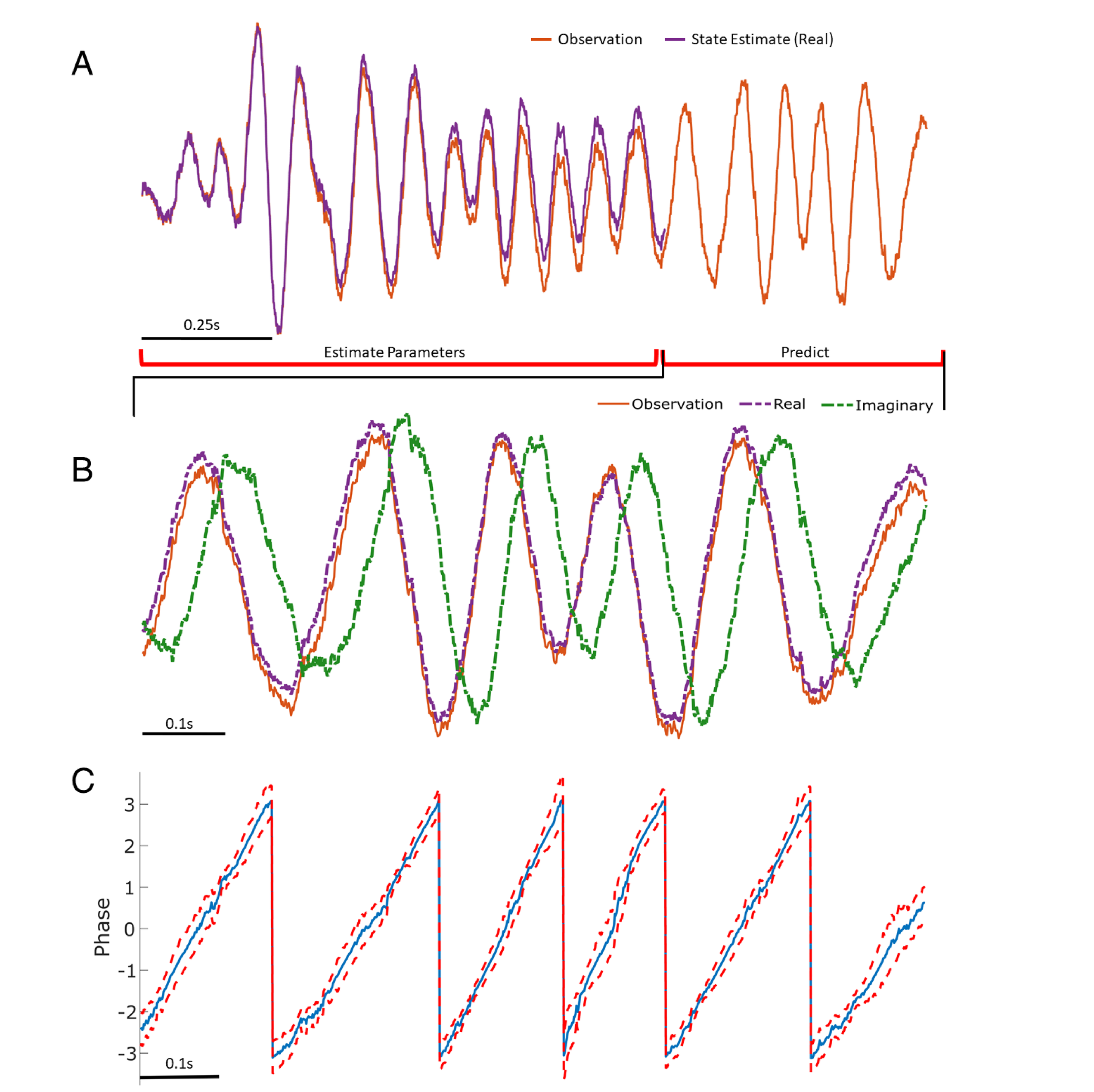


Fig. 1:
**Operation of State Space Phase Estimation Method** Given an observation (A, red), we estimate model parameters in an initial interval of data. At subsequent times, we use the observed data to (B) predict and update the state estimate (purple), and (C) the phase and credible intervals, causally estimated. Note that prediction can be done for any time after parameter estimation; here we show a representative time interval.

## Causal Phase Estimation in Simulations

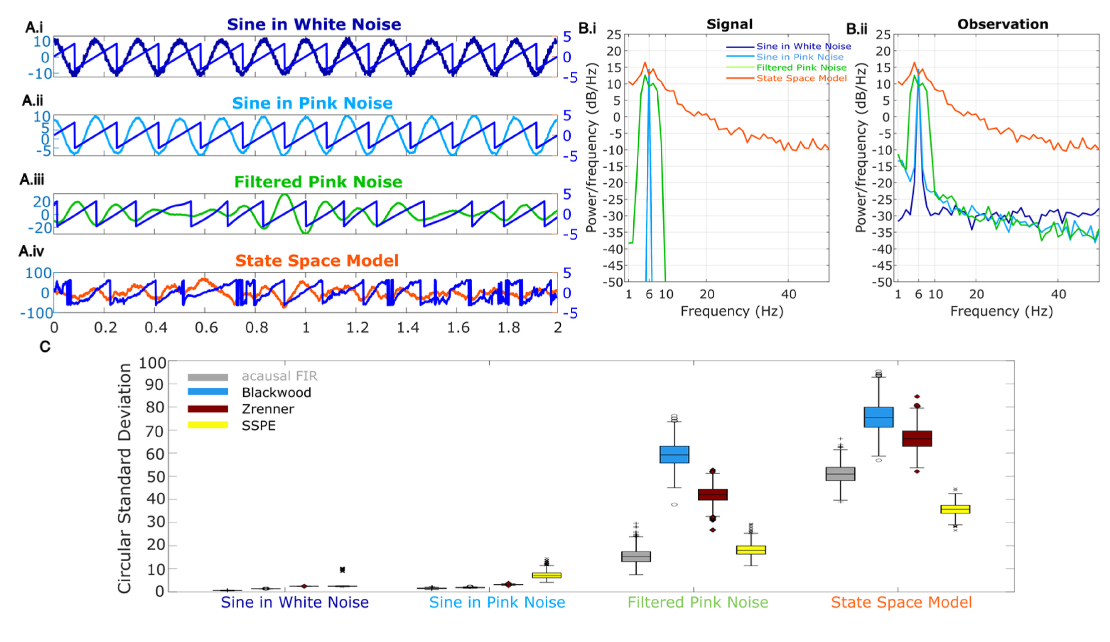


Fig. 2:
**Causal Phase Recovery for Simulated Data**: We simulate data in 4 different ways (see panel A.i to A.iv and B above) to test accuracy in phase estimation under different methods. We compared the SSPE two existing algorithms "Blackwood" and "Zrenner" and an acausal approach "acausal FIR". Both the "Blackwood" and "Zrenner" methods use bandpass filtering and AR forecasting. Phase is estimated under a Hilbert transformer in "Blackwood" and the Hilbert transform in "Zrenner". The "acausal FIR" uses an acausal FIR filter and Hilbert transform to estimate phase. The boxplots shown in C summarize results across 1000 iterations with phase accuracy at 8000 samples on each iteration. We estimated accuracy using the circular standard deviation of difference between the estimated phase and true phase. For simulated rhythms with broad spectral peaks (filtered pink noise and MK model), the SSPE method performs well.

Blackwood, E., Lo, M., and Widge, A. S. (2018). Continuous Phase Estimation for Phase-Locked Neural Stimulation Using an Autoregressive Model for Signal Prediction*. 2018 40th Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBC), 4736–4739.
Zrenner, C., Dragana Galevska, Jaakko O. Nieminen, David Baur, MariaIoanna Stefanou, and Ulf Ziemann. (2020). The shaky ground truth of real-time phase estimation.

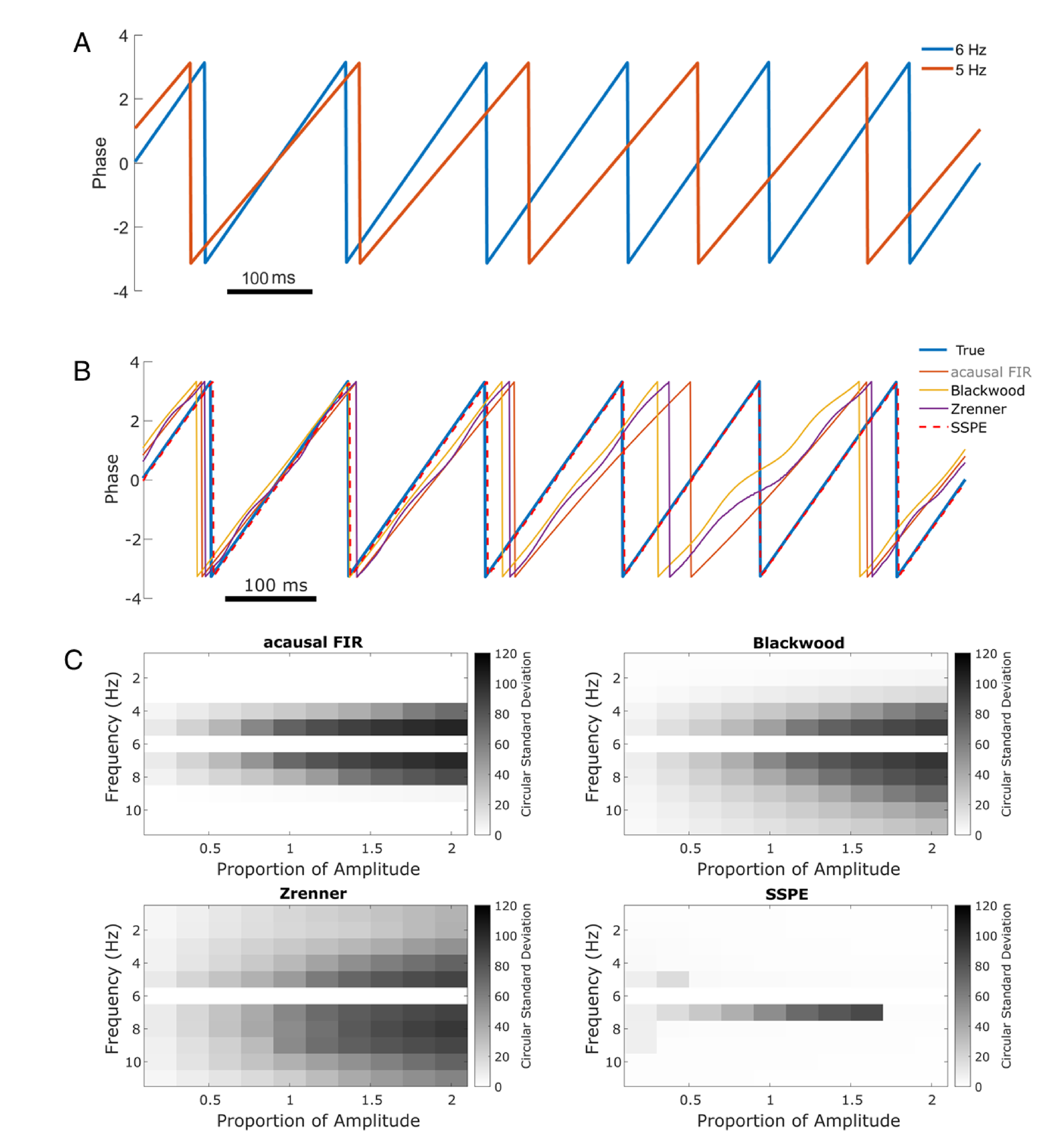


Fig. 3: **Phase Estimation in the Presence of Two Simultaneous Oscillations**: We simulate two slow oscillations at different phases and amplitudes. Pure sinusoids were simulated, the first fixed at 6 Hz and an amplitude of 10 (arbitrary unit) while the second oscillation var-ied in frequency(1-11 Hz) and amplitude (0-50). True phase traces for the two sinusoids in an example case is shown in A with estimated phases for the 6 Hz oscillation in B. We show error as a function of the frequency and amplitude of the second oscillation in C.The error increases as the frequency of the second oscillation approaches 6 Hz (the frequency of the first oscillation). However, the increased error is restricted to a narrower frequency interval for the SSPE method.

## Causal Phase Estimation in Simulations

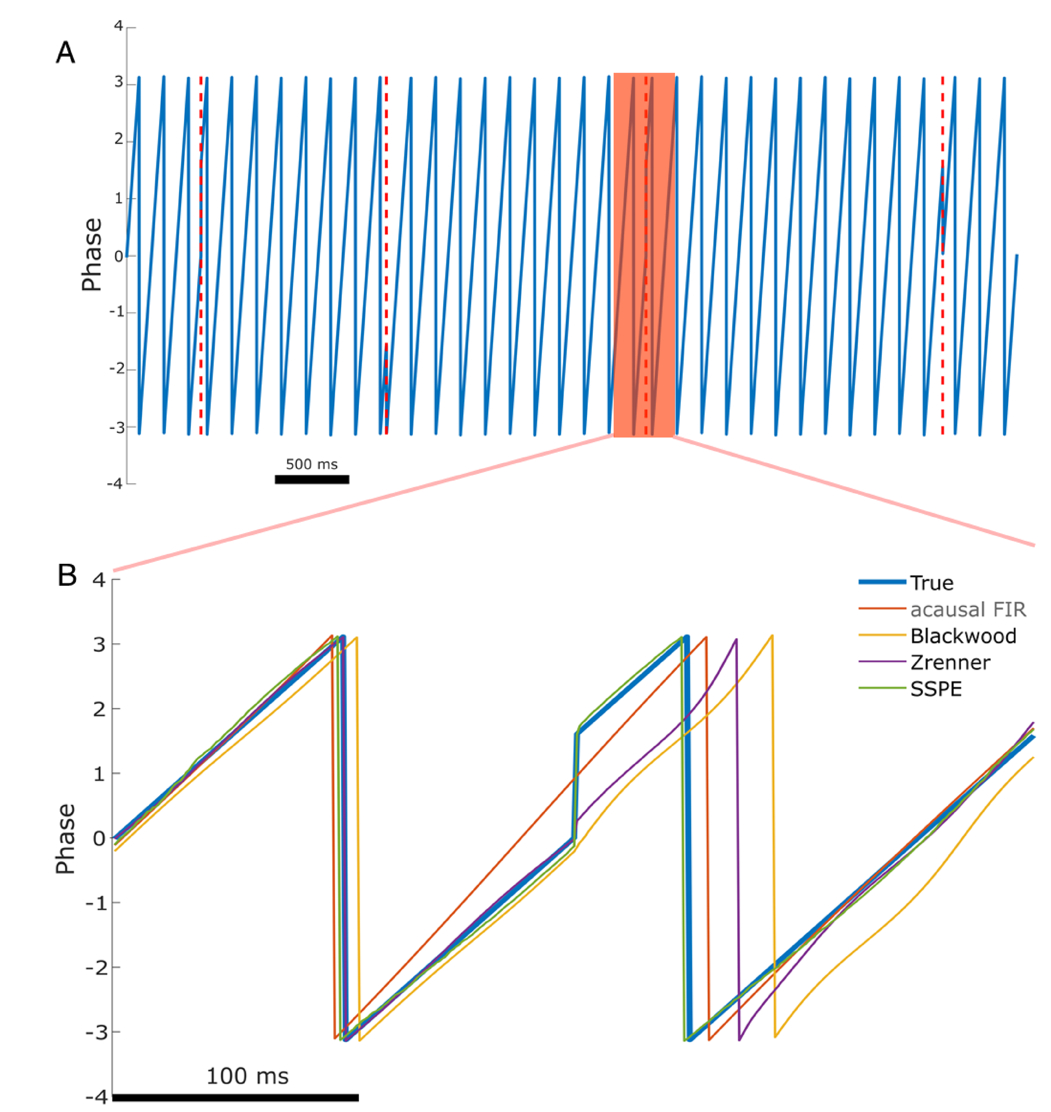


Fig. 4:
**The SSPE accurately tracks phase following a phase reset**: (A) Example phase of a 6 Hz sinusoid (blue) with 4 phase resets (red dashed lines). (B) Example phase estimates (thin curves) and the true phase (thick blue curve) at the indicated phase reset in (A). The SSPE method (in green) tracks the true phase much more closely than other methods following a phase reset.

## SSPE applied to LFP data

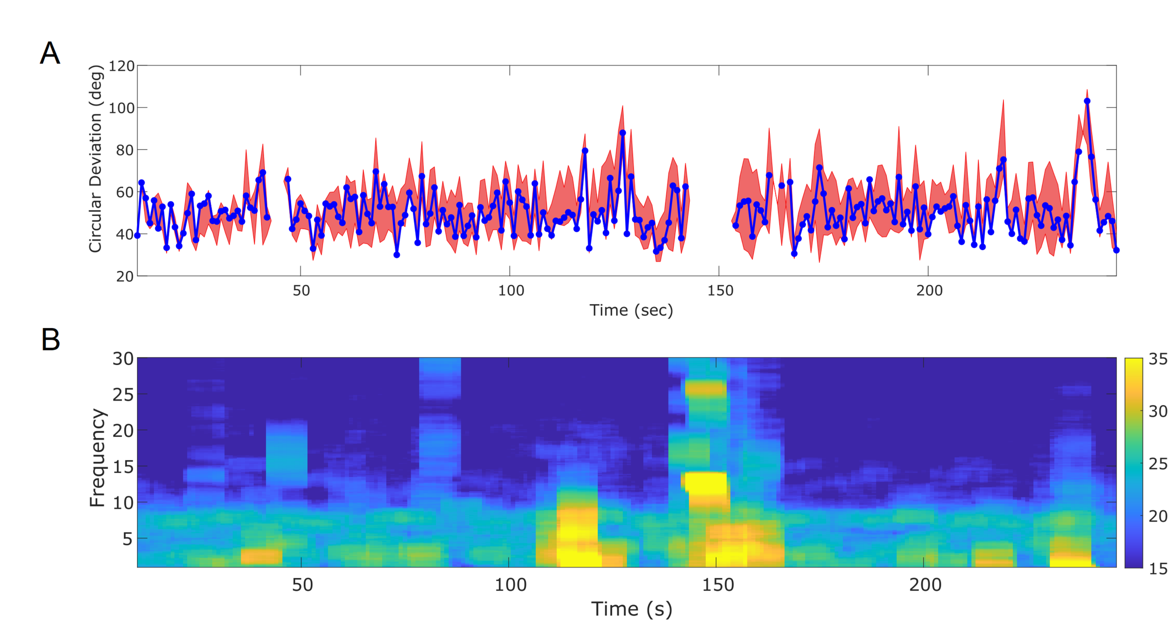


Fig. 5:
**Any interval with a prominent rhythm of interest (here: theta) can be used to fit SSPE parameters.**(A) The phase error for a single instance of the model fit (using data at times 10-20 s, blue curve), and the 90 percent interval for phase error (red bands) at time t derived using parameter estimates from all models estimated with data prior to t. The moments where no error is reported are moments when an acausal approach failed to detect the theta band rhythm. Right: a histogram of circular deviation across all time demonstrating that error remains below 60 degrees in the majority of cases. (B) Corresponding spectrogram of the rodent LFP data (multi-taper method with window size 10 s, window overlap 9 s, frequency resolution 2 Hz, and 19 tapers).

## Estimating Phase Credible Intervals

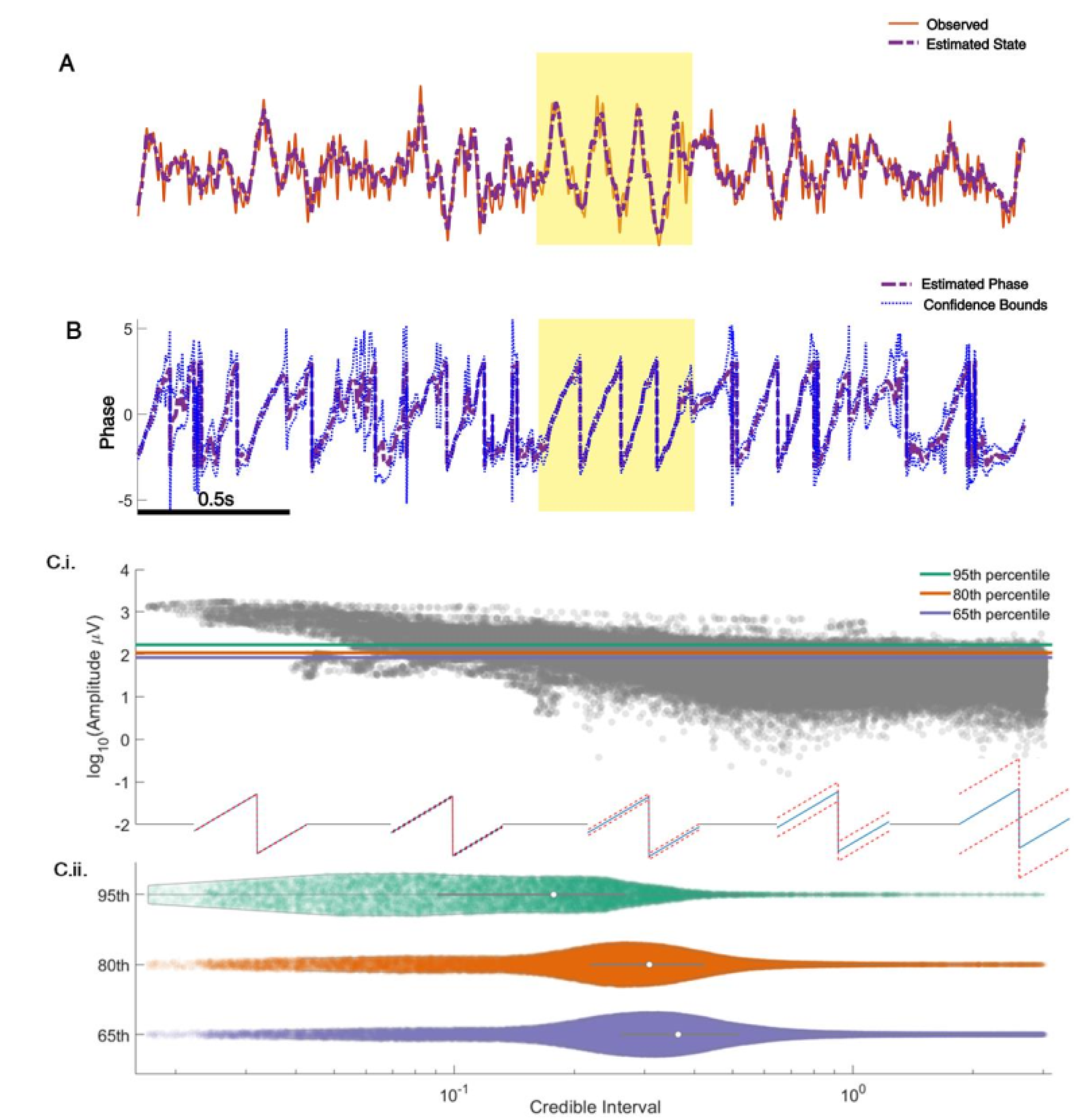


Fig. 6: **SSPE tracks in vivo credible intervals for the phase.**(A) Ex-ample rodent LFP data (red, solid) with a consistent broadband peak in the theta band (4-8 Hz). The estimated state of the SSPE method (purple, dashed) tracks the observed LFP. (B) Phase estimates (purple, dashed) and credible intervals (blue, dotted) for the example LFP data in (A). When the rhythm appears (yellow shaded region) the confidence bounds approach the mean phase; when the rhythm drops out the confidence bounds expand. (C.i) Phase credible intervals versus theta rhythm amplitude for each time point (gray dot). On the x-axis we plot an example cycle of a rhythm with credible intervals, see x-axis of (C.ii) for numerical values of credible inter-vals. (C.ii) Violin plot of credible intervals for thresholds set at the 65th, 80th and 95th percentile of the distribution of amplitude. The distribution of cred-ible intervals increases with reduced amplitude threshold, and all amplitude thresholds include times with large credible intervals.

## Real-time Implementation in TORTE

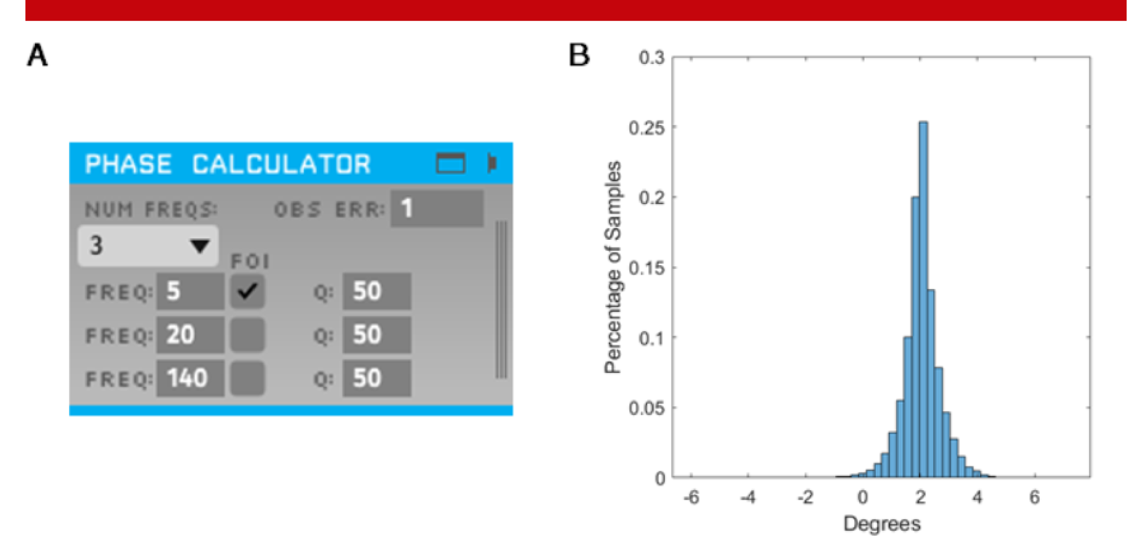


Fig. 7:
**SSPE implementation in TORTE is accurate.**(A) OpenEphys GUI for using SSPE. The user specifies the number of frequencies to track, the center frequencies to track, the frequencies of interest for phase calculation and out-put (FOI), variance for the FOI and the observation error. (B) Histogram of the circular standard deviation between MATLAB (offline) and TORTE (real-time) im-plementations of the SSPE. Small variation results from causal low-pass filtering in TORTE and acausal filtering in the offline phase estimates.

*This work was supported by NIH NIBIB R01EB026938.*