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Uncovering the organization of neural circuits with generalized phase locking analysis

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Abstract

Despite the considerable progress of *in vivo* neural recording techniques, inferring the biophysical mechanisms underlying large scale coordination of brain activity from neural data remains challenging. One obstacle is the difficulty to link functional connectivity measures to mechanistic models of network activity. We address this question for the case of spike-field coupling, which quantifies the synchronization between neurophysiological activities observed at two different scales: on the one hand, the action potential produced by neurons, on the other hand a mesoscopic "field" signal, reflecting subthreshold activities. We develop *Generalized Phase Locking Analysis* (GPLA) as a multichannel extension of univariate spike-field coupling that can be interpreted based on neural field models of mesoscopic network activity. GPLA estimates the dominant spatio-temporal distributions of field activity and neural ensembles, and the strength of the coupling between them. We demonstrate the statistical benefits and interpretability of this approach in various biophysical neuronal network models and Utah array recordings. In particular, GPLA, uncovers the contribution of recurrent microcircuits to the spatio-temporal dynamics observed in multi-channel recordings.

Keywords

Spike-field coupling, microcircuits, prefrontal cortex, neural field models, neural mass models, hippocampus, phase-locking.

Introduction

Understanding brain function requires uncovering the relationships between neural mechanisms at different scales (***Einevoll et al., 2019***): from single neurons to microcircuits (***Rasch et al., 2008***, ***2009***), from microcircuits to a single brain area (***Li et al., 2009***) and from a single area to the whole

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brain (***Schwalm et al., 2017***; ***Zerbi et al., 2019***). Therefore, it is crucial to develop data analysis tools to investigate the cooperative mechanisms that connect different levels of organization.

A well-studied example of such a collective phenomenon is oscillatory neuronal dynamics, hypothesized to support computations in the brain (***Peterson and Voytek, 2018***) and various cognitive functions, such as perceptual binding (***Engel et al., 1999***), visual awareness (***Dwarakanath et al., 2020***), attention (***Niebur et al., 1993***) and memory (***Buzsaki, 2006***). These oscillations manifest themselves in Local Field Potentials (LFP), a mesoscopic extracellular signal (***Liljenstroem, 2012***) resulting from ionic currents flowing across the cellular membranes surrounding the electrode. LFP oscillatory activity partly reflects a number of subthreshold processes shared by units belonging to underlying neuronal ensembles and responsible for the coordination of their activity (***Buzsaki et al., 2012***; ***Einevoll et al., 2013***; ***Hagen et al., 2016***; ***Herreras, 2016***). As a consequence, a broad range of empirical investigations support the importance of analyzing oscillatory dynamics observed in LFPs (for reviews see ***Buzsaki et al.*** (***2012***, 2013); ***Einevoll et al.*** (***2013***); ***Herreras*** (***2016***); ***Pesaran et al.*** (***2018***)).

In particular, the synchronization between spiking activity and LFP has been observed experimentally and led to theories of cognitive functions. Notably, attention has been investigated on this basis, and hypothesized to rely on interactions between various neural populations coordinated by network oscillations, which modulate the excitability of target populations so that they spike during time windows facilitating their communication (***Fries, 2005***, ***2015***; ***Womelsdorf et al., 2007***; ***Ito et al., 2011***). However, the exact network mechanisms that possibly allow such scenario to take place remain elusive: are the oscillations endogenously generated through recurrent interactions? And if yes, what is the respective role of excitation and inhibition in this process? While these questions are partly addressed in some brain structures by computational modelling studies, how to validate such models based on large scale in vivo recordings is still at its infancy.

Specifically, common approaches for investigating the spike-LFP oscillatory coupling typically rely on pairwise functional connectivity measurements (***Zeitler et al., 2006***; ***Ashida et al., 2010***; ***Vinck et al., 2010***, ***2012***; ***Jiang et al., 2015***; ***Li et al., 2016***; ***Zarei et al., 2018***) and only describe the empirical relationship between spiking and field activities as synchronized oscillators. Moreover, such pairwise analysis is arguably suboptimal for modern neural recording datasets. Indeed, state-of-the-art multichannel electrophysiology systems (***Dickey et al., 2009***; ***Jun et al., 2017***; ***Juavinett et al., 2019***) allow simultaneous recording of hundreds or even thousands of sites (***Pesaran et al., 2018***; ***Jun et al., 2017***; ***Buzsáki, 2004***; ***Fukushima et al., 2015***), thereby providing an unprecedented opportunity to study the large scale collective organization binding spiking activity of individual units with mesoscopic spatio-temporal dynamics (e. g. wave patterns (***Ermentrout and Pinto, 2007***; ***Ermentrout and Kleinfeld, 2001***)). In particular, this shift in data dimensionality offers the opportunity to go beyond the phenomenological model of synchronization between these activities, to achieve precise account of how network properties shape the detailed spatio-temporal characteristics of this collective phenomenon.

This growth in data dimensionality and complexity requires the parallel development of appropriate models and statistical analysis techniques (***Stevenson and Kording, 2011***; ***O'Leary et al., 2015***; ***Gao and Ganguli, 2015***; ***Williamson et al., 2019***). On the one hand, statistical analysis and significance assessment of parallel spike trains has been shown to be challenging (see for a review ***Grün*** (***2009***)), such that the development of novel, more computationally *efficient* approaches in the high dimensional setting is required. On the other hand, achieving a *mechanistic* understanding, also needs to be *combined* with interpretable biophysical modelling and simulations, which remains largely unaddressed for large-scale neural networks.

Indeed, while methodologies have been developed that elegantly combine frequency-based analysis, multi-variate methods and dimensionality reduction techniques (***van der Meij et al., 2012***; ***van der Meij et al., 2015***; ***van der Meij and Voytek, 2018***), the outcomes remain only interpreted as mere phenomenological models of brain activity, broadly built on the idea that the brain processes information through networks of oscillators coupled at different frequencies. As such, these

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approaches suffer from critical limitations when it comes to providing mechanistic insights. This is chiefly because the outcome of typical multivariate analyses does not easily relate to a biologically realistic understanding of the underlying neural circuits. To go beyond this limitation, a broad range of model reduction approaches are used in physics and biology to simplify a complex model while preserving interpretability (***Transtrum and Qiu, 2016***), and have been used to some extent in neuroscience (***Jirsa and Haken, 1996***; ***Karasözen, 2020***). However, the characteristics of biophysical model reductions and advanced multivariate data analyses need to be carefully chosen to allow mechanistic interpretability of high-dimensional measurements, and have not yet been explored for the case of multivariate spike-field coupling.

We thus develop a "Generalized Phase Locking Analysis" (GPLA) to address the need for an efficient, multivariate method that allows mechanistic interpretation of spike-field coupling data. GPLA characterizes and assesses statistically at once the coupling between the spiking activity of large populations of units and large-scale spatio-temporal patterns of LFP. After demonstrating GPLA's interpretability on toy simulated datasets and statistical benefits with respect to pairwise coupling approaches, we use neural field models to illustrate how this method characterizes key aspects of the underlying neural circuits. In particular, we show how GPLA can untangle the contribution of recurrent interactions to the observed spatio-temporal dynamics. Finally, GPLA's interpretability is exploited in the analysis of Utah array recordings from the macaque prefrontal cortex.

Results

Generalizing spike-oscillation coupling analysis to the multivariate setting

Our analysis relies first on characterizing the coupling between signals originating from a pair of recording channels. On the one hand, we consider the time-varying spike rate $\lambda(t)$ of a given unit; and on the other hand oscillatory activity $L_f(t)$ is derived from the LFP by band-pass filtering in a narrow band of center frequency f. We assume $L_f(t)$ is the complex analytic signal representation of this oscillation, computed using the Hilbert transform (***Chavez et al., 2006***), such that $L_f(t) = a_f(t)e^{i\phi_f(t)}$, where $a_f(t)$ and $\phi_f(t)$ are the instantaneous amplitude and phase of the oscillation, respectively. For our subsequent modelling, $L_f(t)$ need not be associated to an actual oscillatory phenomenon, and reflects the Fourier domain properties of the signal around frequency f. The coupling between these signals can be characterized by the covariance

$$c(f) = \left\langle \lambda(t)L_f(t) \right\rangle = \left\langle \lambda(t)a_f(t)e^{i\phi_f(t)} \right\rangle = |c|e^{i\Phi_c} = |c|\left(\cos(\Phi_c) + \boldsymbol{i}\sin(\Phi_c)\right), \quad (1)$$

where the $\langle\cdot\rangle$ indicates averaging across time and experimental trials. The complex number c then reflects the strength of coupling through its modulus $|c|$, and the dominant LFP phase of spiking through its argument Φ_c (see Figure 1(Top-right)). This coupling measure is a modification of the Phase-Locking Value (PLV) (***Ashida et al., 2010***), and differs from the latter mainly through the incorporation of the amplitude of the oscillation in the averaging, and the absence of normalization by the spike rate. Although $c(f)$ is straightforward to estimate based on observed spike times, leading to the quantity noted $\hat{c}(f)$ (see ***Safavi et al.*** (***2021***)), interpreting its value in terms of the underlying neural mechanisms is challenging, due to the largely unknown specific properties of the considered cell and recording site. Alternatively, synthesizing the information provided by a large number of couplings may provide a more reliable picture of the functioning of the underlying circuits.

Generalized Phase Locking Analysis (GPLA) is introduced as a multivariate statistical analysis technique to estimate the key properties of a matrix $\boldsymbol{C}(f)$ consisting of the pairwise coupling between a large number of units and LFP channels. Given the spike times $\{t_k^m\}$ for unit m and the analytic signal $L_f^n(t)$ that is filtered around frequency f for LFP channel n, the (n,m) coordinate of the coupling matrix $\boldsymbol{C}(f)$ is estimated by summing the values taken by the analytic signal at all spike times (see Figure 1 (Top-left)),

$$\widehat{\boldsymbol{C}}(f)_{n,m} = \sum_k L_f^n(t_k^m). \quad (2)$$

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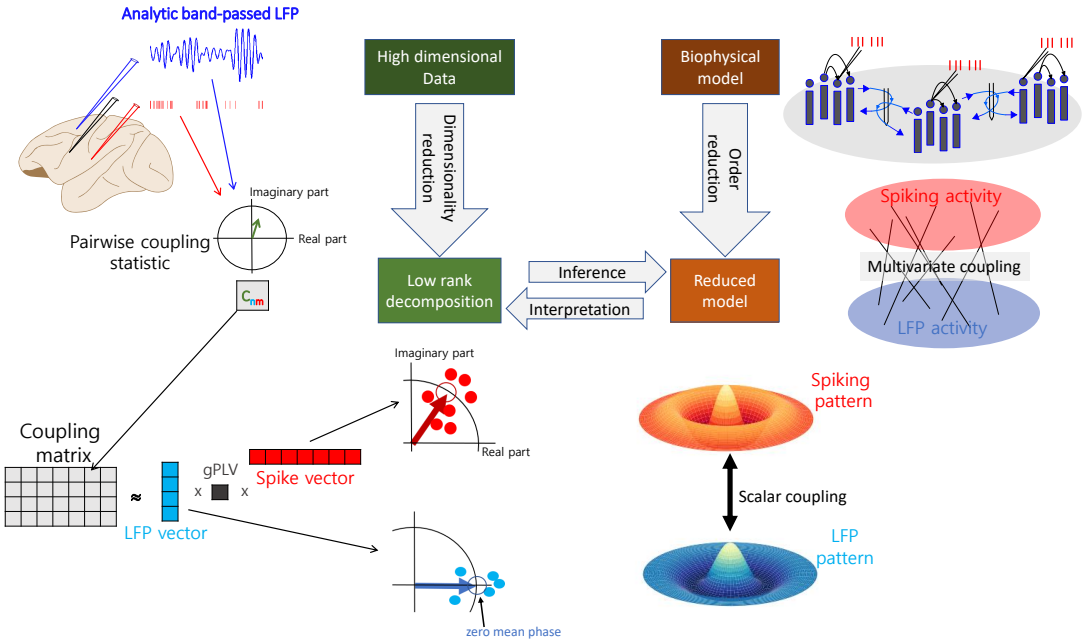

Figure 1. Illustration of the interpretation of spike-field coupling measurements through GPLA. **(Top-left)** A coupling matrix is built from electrophysiology data by gathering pairwise complex phase locking estimates (based on Equation 2) of all spike-LFP pairs in a rectangular matrix. Coefficients (C_{nm}) contain information similar to complex-valued PLV up to a scaling factor: the magnitude indicates the strength of coupling and the angle reflects the average timing of the spike occurrence within the period of the corresponding LFP oscillation. **(Bottom-left)** The coupling matrix can be approximated using its largest singular value and the corresponding singular vectors. Singular vectors represent the dominant LFP (blue array) and spiking patterns (red array) and the singular value (d_1), called generalized Phase Locking Value (gPLV), characterizes the spike-field coupling strength for the phenomenon under study and the chosen frequency. The magnitude of each vector entry indicates a relative coupling of the corresponding unit/channel and the phase indicates the relative timing with respect to other units/channels. By convention, the phase of the LFP vector coefficients' average is set to zero, such that the phase of the spike vector average reflects the overall phase shift of the spike pattern with respect ot the LFP pattern. **(Top-right)** A biophysical model accounts for the underlying network connectivity and dynamics, as well as the measurement process that leads to the collected data. This leads to a theoretical account of multivariate spike-field coupling. **(Bottom-right)** Model reduction entails simplifying assumption leading to a low-rank description of the coupling in the model based on the key mechanistic parameters. This description is compared to the left-hand side low-rank decomposition to infer parameters and interpret the data.

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This multivariate coupling can be as well evaluated for a biophysical model accounting for the underlying network mechanisms and electrophysiological measurements illustrated in Figure 1(Top-left). Next, as schematized in Figure 1(Bottom-left), the coupling matrix is approximated by the term of largest singular value d_1 of its Singular Value Decomposition (SVD) leading to

$$\widehat{C} \quad = U D V^H \quad = \sum_k d_k \boldsymbol{u}_k \boldsymbol{v}_k^H \approx d_1 \boldsymbol{u}_1 \boldsymbol{v}_1^H \,, \tag{3}$$

where $\boldsymbol{v}_k^H$ indicates the transpose conjugate of vector $\boldsymbol{v}_k$. In this expression, the singular value d_1 is a positive scalar, that we will call generalized Phase Locking Value (gPLV), and quantifies the magnitude of the coupling. The associated complex valued singular vectors in this factorization will be respectively called the *LFP vector* $\boldsymbol{u} = \boldsymbol{u}_1$ and the *spike vector* $\boldsymbol{v} = \boldsymbol{v}_1$. As illustrated in Figure 1(Bottom), the spike vector indicates the pattern of coordinated spiking activity most coupled to LFP oscillations, while the LFP vector reflects the dominant spatio-temporal pattern of LFP involved in this coupling. Importantly, the relationship between $\boldsymbol{u}$ and $\boldsymbol{v}$ reflects the phase lag between spiking and LFP activities. Multiplication of both singular vectors by the same unit complex number leads to the exact same approximation as Equation 3, reflecting that GPLA only measures the relative phase between LFP and spikes. To resolve this ambiguity in our analyses, we adopt the convention of setting the phase of the average of LFP vector coefficients $\langle \boldsymbol{u} \rangle = \frac{1}{n_c} \sum_k u_k$ to zero, as illustrated in Figure 1 (bottom). As a consequence, the phase of the mean of the spike vector coefficients $\langle \boldsymbol{v} \rangle = \frac{1}{n_u} \sum_k v_k$ reflects the difference of mean phases between spiking and LFP activities. As illustrated in Figure 1(bottom), the outcome of GPLA is then interpreted based on a reduction of the biophysical model explained in section Reduction of complex models based on linear response theory. Notably, this allows to infer the key network characteristics giving rise to the observed spike-field coupling. See section Detailed GPLA methodology for electrophysiology data in Appendix for more details.

Illustration of GPLA on toy examples

We first illustrate how GPLA provides an intuitive phenomenological model of the coupling between the population of spiking units and LFPs. We use toy simulations in which transient LFP oscillations (Figure 2A) modulate the firing probability in 18 spike trains (attributed to neuron-like units). The firing patterns of these neurons depend on the coupling strength and the delay with respect to the global oscillation. We introduce two simple models in Figure 2C-F, and demonstrate how the resulting spike vector summarizes their structure. For each model, we schematically represent the coupling strength by the line thickness (absence of a line indicates no coupling) and the delay with respect to the global oscillation by the line color (Figure 2C-D, first column). Exemplary spike trains for each model are displayed in the second column of Figure 2C-D overlaid on the magnified version of the oscillation. Model 1 instantiates a global oscillation driving a synchronous population of neurons and this structure is also reflected in the resulting spike vector of the model as all the coefficients collapse to a single point (Figure 2C, third column). Model 3 accounts for the activity of different cell populations that fire together predominantly at three distinct phase values of the LFP and this synchrony is also reflected in the spike vector as the coefficients of the spike vector are clustered together in the complex plane (Figure 2D, third column) i. e. the group to which each unit belongs to is reflected in the phase of the associated spike vector coefficient. In the above cases, the spike vector resulting from GPLA summarizes the coupling structure in an intuitive and compact way. Because this setting has a single LFP channel, this analysis straightforwardly combines univariate coupling measures of each unit. However, statistical analysis of GPLA is different from the univariate case, as we show next.

Statistical benefits of GPLA over univariate spike-field coupling

Beyond the above benefits for interpreting multivariate data, we investigated whether GPLA can be advantageous over its univariate counterpart from a statistical perspective by simulating transient

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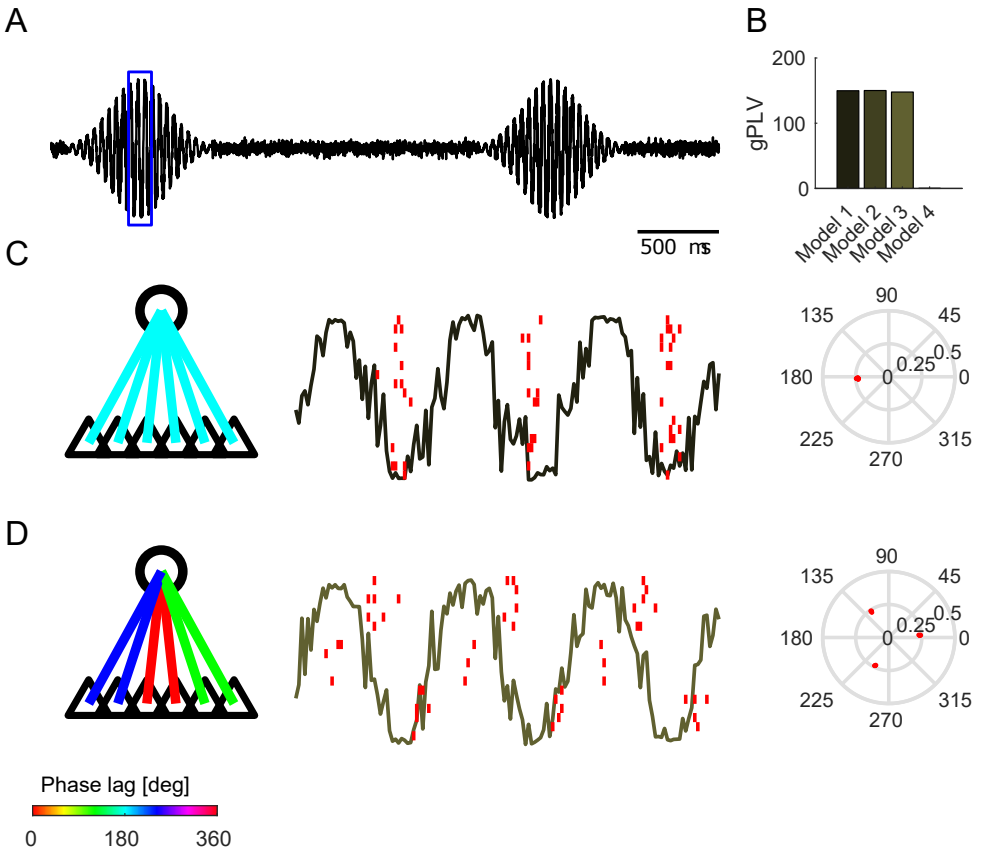

Figure 2. Illustration of GPLA on simple simulations.
(A) Normalized amplitude of LFP-like oscillatory signals. **(B)** gPLVs for different models demonstrated in C-F **(C-D)** Various scenarios of spike-LFP coupling. Left: schematic representation of the modulating LFP oscillation (circle), and 6 representative neuron-like-units (indicated by the triangles). The color of each connecting line indicates the locking phase (see bottom colorbar for color code). Center: LFP-like signals within the window specified by the blue box in A and spikes are represented by overlaid red vertical lines. Right: resulting spike vector is represented in the third column. **(C)** Spiking activity globally synchronized to the trough of the LFP oscillation. **(D)** Three clusters of neurons discharge at different phases of the LFP oscillation (a similar model was also used in Figure 3).

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oscillations (Figure 3A) and phase-locked spikes. The neural populations consisted of 3 groups, each of them locked to a different phase (0, 120, and 240 degrees) of the same oscillation, corrupted with additive noise. An illustrative simulation in the case of low noise and large number of observed spikes is shown in Figure 3B, together with the corresponding spike vector in Figure 3C, providing results similar to Fig. 2E.

For quantitative analysis, we first consider the setting of a single LFP channel and a handful of neurons are the focus of the analysis (Figure 3A-E). Such recordings are still common and valuable in human electrophysiology experiments for understanding cognition (***Mukamel and Fried, 2011***; ***Fried et al., 2014***). The main difference between this simulation and the one presented in Figure 2E is the weaker coupling of individual neurons leading to values at the edge of significance (assessed with the surrogate-based test, see section Significance assessment of gPLV in Appendix). While pooling the spikes from all units into a single spike train to get a *pooled Phase-Locking-Value* (pPLV) may result in a higher statistical power, it requires the distribution of the locking phase to be homogeneous across units (e.g. in the case of Figure 2C, but not for Figure 2D and E). In contrast, GPLA exploits the spike times from multiple neurons to assess the global coupling between spikes and LFPs without requiring such homogeneity. We ran 5000 simulations with only 3 units and compared the coupling assessment based on PLV, pPLV, and gPLV. Figure 3D represents the estimated PLVs, with averages matching the couplings obtained with a larger number of spikes in Figure 3C. Performance of each measure is assessed based on its detection rate, which is defined as the percentage of simulations for which significant coupling is detected, as assessed using spike-jittered surrogate data (see Appendix section Significance assessment of gPLV) and with a significance threshold of 5%. As it is demonstrated in Figure 3E, gPLV detection outperforms the competing approaches (PLV and pPLV).

Beyond better detection of significant coupling, GPLA-based estimation of pairwise couplings based on the approximation of Equation 3 may be more accurate than individual estimates when the data is very noisy and multivariate, benefiting from the SVD procedure to disentangle noise from the ground truth coupling. To demonstrate this, we performed the second simulation (Figure 3F-I), similar to the above, but using 50 LFP channels containing oscillations driving spike-LFP coupling, contaminated by different levels of noise (i. e. adding Gaussian noise with different variances to the transient oscillation, see Appendix for details), and modulating the firing rates of the units, lower firing rates leading to a larger amount of martingale noise for the PLV estimates (***Safavi et al., 2021***). An example LFP trace with (black) and without (blue) noise is exemplified in Figure 3F and an example coupling matrix in the presence of noise is also illustrated in Figure 3G. In this case, the coupling matrix has rank one, as all the units are locked to a single frequency. We ran the simulations with different amounts of LFP noise (indicated on the x-axis of Figure 3H-I), computed the coupling coefficients (similar to Figure 3G) and compared it to ground truth (based on Equation 32). The signal-to-Noise Ratio (SNR) was defined as the ratio of estimation error (the difference between estimated PLV and the ground truth - for more details see section Computing SNR) to coupling strength (PLV) and was used to compare the quality of GPLA-based and univariate estimation (indicated in the y-axis of Figure 3H-I). As this simulation demonstrates, the estimation error of the coupling coefficients is larger for the univariate estimation than for the GPLA-based approach for a broad range of noise levels (Figure 3H-I).

Random matrix theory based significance assessment

While in the previous section, GPLA's significance was assessed using surrogate data, this approach is computationally expensive and provides limited insights into the statistical properties of GPLA estimates. We also investigated this question using mathematical analysis, and exploited it to assess more efficiently the significance of multivariate coupling. Singular values and vectors estimated by GPLA have an intrinsic variability due to the stochasticity of spiking activity, which can be investigated through stochastic integration and random matrix theory (***Anderson et al., 2010***; ***Capitaine and Donati-Martin, 2016***). In the absence of coupling between spikes and LFP, appropriate pre-

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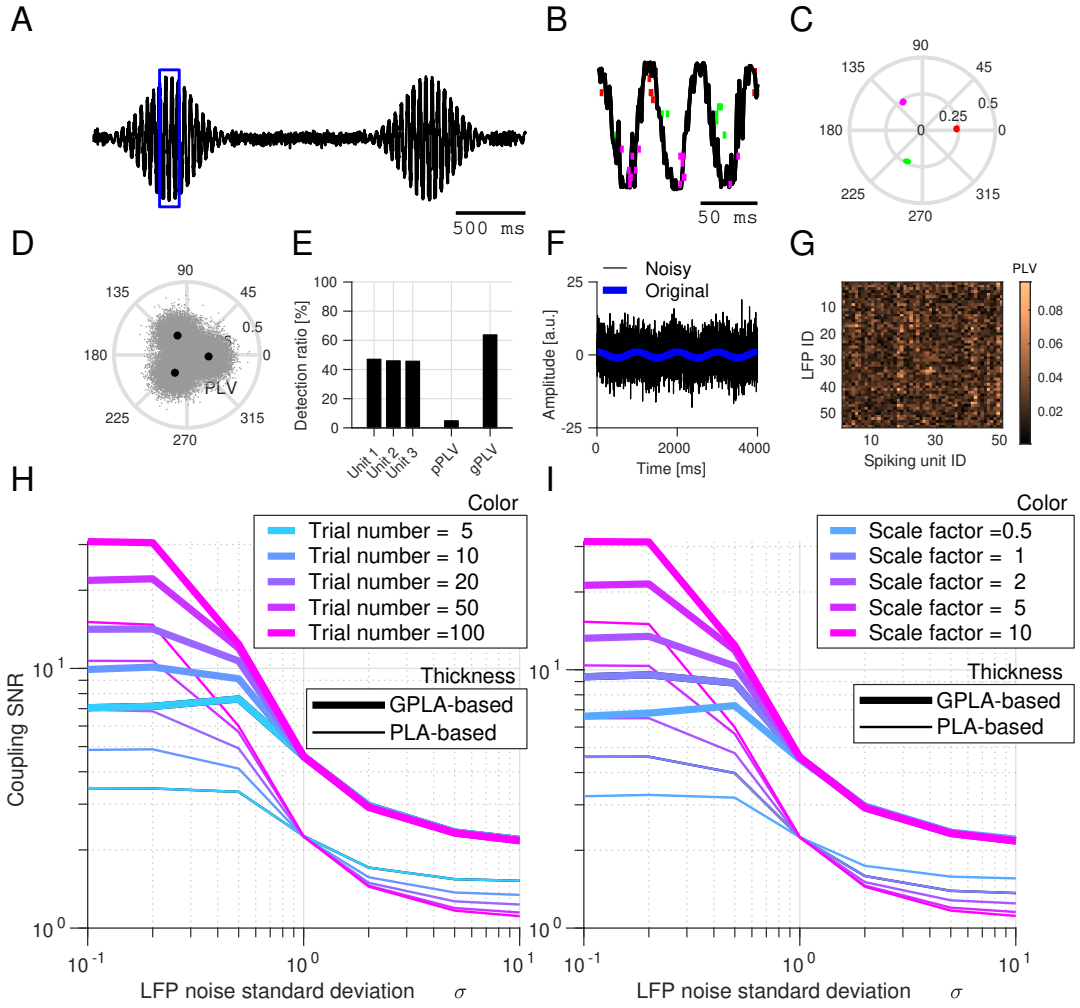

Figure 3. Comparison of GPLA and uni-variate spike-field coupling
(A) Normalized amplitude of LFP-like transient oscillatory signal with additive Gaussian white noise (used in the first simulation). **(B)** LFP-like signal and overlaid spike raster (colored vertical lines – colors indicate populations with the same locking phase) within the window specified by the blue box in (A). **(C)** Spike vector coefficients in the complex plane (colors correspond to B). Each dot represents one coefficient of the spike vector corresponding to a single neuron (note that within each cluster dots are overlapping as they are similarly coupled). **(D)** Complex PLVs represented in the complex plane. Angles indicate the locking phase and the radius the PLV. The gray point clouds indicate the PLV of multiple simulations and larger black dots indicate the average values. **(E)** Performance comparison (in percentage of simulations with significant coupling) of PLV, pooled PLV (pPLV) and gPLV, for three individual neurons. **(F)** Example oscillation, original (blue trace) and noisy (black trace) used in the second simulation. **(G)** Example coupling matrix related to simulation with a large amount of noise ($\sigma = 5$) **(H-I)** Comparison of GPLA-based and PLA-based estimation of PLVs for (H) different number of trials and (I) different levels of firing rate. Signal-to-Noise Ratio (SNR) is defined as the estimation error (the difference between estimated PLV and the ground truth) to coupling strength (PLV).

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processing allows deriving analytically the asymptotic distribution of univariate and multivariate coupling measures (***Safavi et al., 2021***), including the convergence of the squared singular values to the classical Marchenko-Pastur (MP) law (***Marchenko and Pastur, 1967***). Based on the MP law, we can define an upper bound on the largest singular values of the coupling matrix, such that exceeding this bound indicates the significance of the coupling (for more details see Appendix section Analytical test and ***Safavi et al.*** (***2021***)), leading to a *analytical test*.

We assessed the performance of this test on simulated spikes and LFPs with or without coupling as follows. Briefly, we synthesized multivariate LFP activity by linearly superimposing several oscillations ($O_k(t)$ demonstrated in Figure 4A) with different multiplicative weights applied for each LFP channel and generated the spike trains of each unit with Poisson statistics. As for the coupling between spikes and LFPs, $2/5^{\text{th}}$ of the units were coupled to the LFP oscillations (exemplified in Figure 4B), while the remaining units had homogeneous Poisson spike trains (for details see the Appendix, section Simulation of phase-locked spike trains). The estimated coupling matrix computed based on Equation 2 for a simulation with 100 spike trains and 100 LFPs is exemplified in Figure 4C, where we have two coupled populations, one coupled to the lowest-frequency and one coupled to the highest-frequency oscillatory component of the LFP (reflected by the top-right and bottom-left bright blocks of the coupling matrix in Figure 4C and sample spike trains and LFP in Figure 4B).

Computing the SVD of the coupling matrix after application of the preprocessing explained in Appendix, section LFP pre-processing, results in a spectral distribution for the squared singular values, which matches the prediction of the theory (Figure 4D-E). In the absence of coupling between spikes and LFP signals (Figure 4D), the distribution of the eigenvalues closely follows the MP law and in the presence of coupling, the largest eigenvalue exceeds the significance bound predicted by Random Matrix Theory (RMT) (see the Appendix and section Analytical test for more details).

We further quantified the type I and II error of this analytical test. For type II error, we ran the simulations with non-zero coupling between spikes and LFP signals. As shown in Figure 4F, GPLA was able to indicate a significant coupling between spike and LFP even when the coupling strength is as small as 0.05 (no coupling case corresponds to 0 strength and the perfect coupling corresponds to 1). These results also show the performance of the test does not degrade with the increasing dimension of the data through the number of recording channels (Figure 4F). This is in contrast with assessing individually the significance of pairwise couplings, for which correction for multiple comparisons (e.g. Bonferroni) would typically lead to a degradation of the power of the test as the number of units/LFPs increases. This is particularly relevant for weaker couplings as they may lose significance after correction for multiple comparisons. Additionally, we quantified the type I error of the test, by running simulations with no coupling between spikes and LFP and quantified the number of false positives. Our results show that our analytical test has a negligible ($< 5\%$) false positive error (Figure 4G).

We also quantified the performance of the method for estimating the number of populations coupled to different rhythms. In this simulation, the number of coupled populations can be determined by the number of significant singular values (see the Appendix and section Analytical test for more details). Similar to the simulation explained earlier (Figure 4A-C), we simulated multiple (1-10) non-overlapping cell assemblies synchronized to different LFP rhythms (with different frequencies within a narrow range of 11-15.5 Hz). When the coupling was larger than a minimum strength of 0.5, the method was able to capture the number of populations with very low error, MSE < 0.015 (Figure 4H).

Neural field modeling for spike-field coupling

While the above results have addressed GPLA's outcome from a statistical perspective, their mechanistic interpretation requires modeling the underlying neural network dynamics. The basis for this interpretation will be a two-population *neural field model*: a spatially distributed rate model of the activity of two interacting homogeneous populations: excitatory pyramidal cells (E popula-

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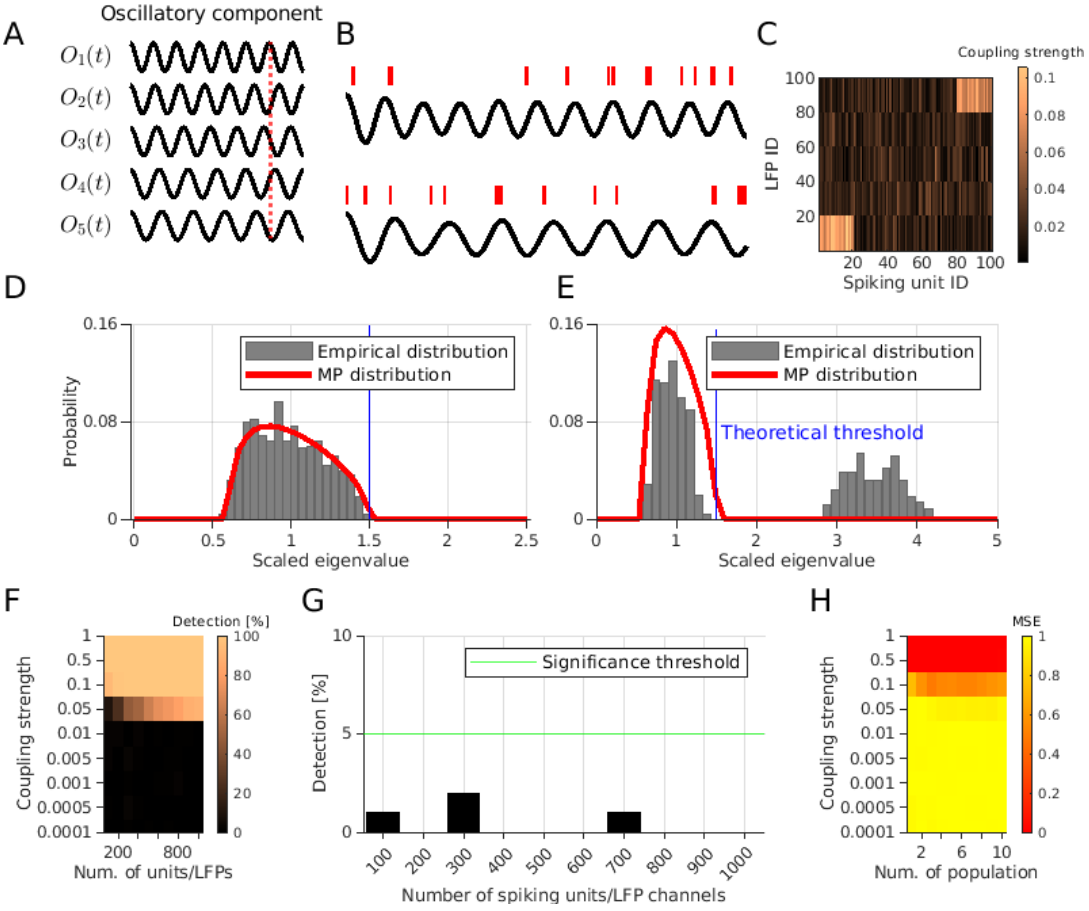

Figure 4. Quantifying statistical properties of GPLA with theoretical significance test.
(A) LFPs are synthesized by mixing several oscillatory components ($O_k(t)$). The vertical red line evidences the phase shift between them. **(B)** Two exemplary spike trains (each from one of the coupled populations) and the corresponding LFPs. In the LFP trace on the top, the oscillatory component with the highest frequency is dominated and for the bottom one, the lowest frequency component is the dominated oscillation. **(C)** An exemplary coupling matrix for a simulation with two coupled populations. **(D-E)** Theoretical Marchenko-Pastur distribution (red lines) and empirical distribution (gray bars) for (D) simulation without coupling and (E) with coupling between multivariate spikes and LFP **(F)** Performance of GPLA for the detection of coupling between spike trains and LFPs for different strength of coupling (y-axis) and different number of spiking units/LFP channels. **(G)** Type I error for different numbers of spiking units/LFP channels (x-axis), quantified as the percentage of simulations wherein a significant coupling between spike trains and LFPs is detected in absence of ground truth coupling. The horizontal green line indicates the %5 threshold. **(H)** Mean-squared-error of GPLA-based estimation of the number of populations coupled to LFP for varying coupling strengths (y-axis) and numbers of coupled populations (x-axis).

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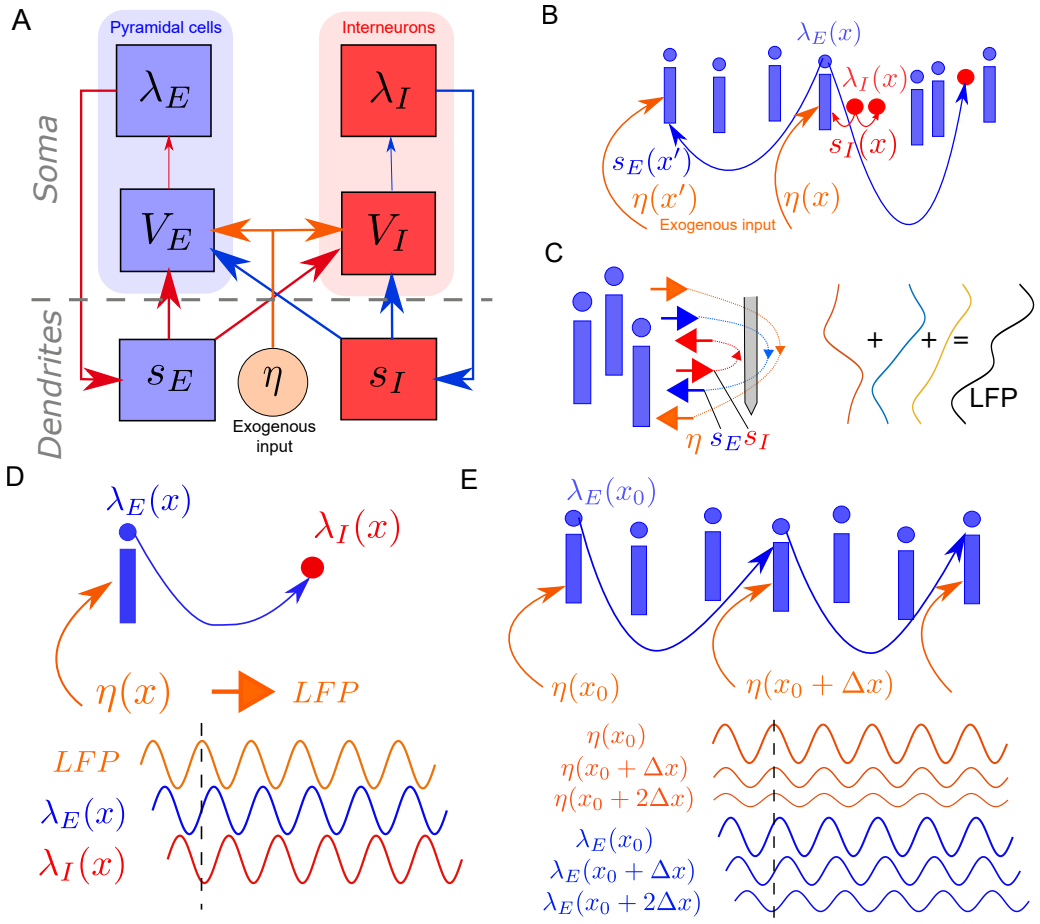

Figure 5. Generative model of spike-LFP coupling.
(A) A two-population neural field model of neural dynamics. V_k, λ_k and s_k indicate respectively somatic membrane potential, firing rate and post-synaptic current for Excitatory (k=E) and Inhibitory (k=I) populations. η indicates the exogenous input to the circuit. Arrows indicates the causal dependence between variables of the model. **(B)** Schematic representation of the model's connectivity: local inhibition and long range excitation, together with the driving by exogenous synaptic currents. **(C)** Schematic representation of the contribution of postsynaptic currents to the electric field, affected by the spatial distribution of synapses over the dendritic tree and the geometry of pyramidal cells. From left to right: Schematic representation of pyramidal neurons, electric field, electrode (gray bar), contribution of each current (EPSC, IPSC and exogenous current, leak current is also contributing to LFP but is not shown) to the LFP profile along the electrode's axis **(D)** Simple microcircuit structure leading to a temporal ordering of the local activities of different kinds $LFP \rightarrow excitation \rightarrow inhibition$ **(E)** Simple microcircuit structure leading to a temporal ordering of activities of the same kind across space: the location receiving stronger exogenous input leads other locations, such that amplitude gradient leads to phase gradients.

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tion) and inhibitory interneurons ("I" population) (***Nunez and Srinivasan, 2006***; ***Wilson and Cowan, 1973***). The model is governed by three basic input-output relations (see Appendix, section Analytical neural field modeling of spike-field coupling) and depicted in Figure 5A: (1) the dynamics of the average somatic membrane potentials V_E and V_I of each population is governed by exogenous post-synaptic currents η originating from other cortical or subcortical structures as well as recurrent excitatory and inhibitory post-synaptic currents (EPSC and IPSC) s_E and s_I; (2) the population spike rates λ_E and λ_I are a function of their respective membrane potentials; and (3) EPSC and IPSC are each controlled by the spike rate of their afferent population (E and I respectively). In the context of large-scale recordings, the neural population can be distributed across one or several spatial directions. Following a classical approximation depicted in Figure 5B, inhibitory connections are assumed local (***Sik et al., 1995***; ***Schomburg et al., 2012***; ***Taxidis et al., 2012***), such that coupling between cells surrounding distinct recording locations happens exclusively through excitatory axons ($s_E(x)$ may depend on λ_E at other spatial locations than x) and the common exogenous input current η.

For the LFP $L(t)$, resulting from the conduction of trans-membrane currents in the extracellular space, we assume the contribution of currents flowing through the membrane of interneurons is negligible, based on the weakness of the anisotropy induced by their dendritic geometry across the population (***Nó, 1947***; ***Lindén et al., 2011***; ***Mazzoni et al., 2015***). The LFP thus results exclusively from pyramidal cell's membrane currents. Which currents (IPSC, EPSC, leak current, exogenous current) affect the most the recorded LFP at a given spatial location depends on multiple factors: the geometry of the cells, the distribution of synapses (inhibitory, excitatory, exogenous) onto them, and the geometry of the electrodes (***Buzsaki et al., 2012***, ***2013***; ***Einevoll et al., 2013***). Figure 5C provides a schematic of how the differentiated location of synaptic boutons over the dendritic tree may result in variable algebraic contributions of each type of current to each recording channel.

Spike-field phase lags for simple network models

The above model is very general, and as such further simplifying assumptions are required in order to make predictions about mechanisms underlying spike-field coupling. First, assuming small-amplitude perturbations in the neighborhood of an operating point, the static sigmoidal conversion of membrane potentials into spike rates (see section Analytical neural field modeling of spike-field coupling in Appendix and ***Jirsa and Haken*** (***1996***)) can be linearized (see Methods and e.g. ***Moran et al.*** (***2007***); ***Ledoux and Brunel*** (***2011***); ***Pinotsis et al.*** (***2012***)). This leads to a linear time-invariant model, whose behavior is fully characterized by its amplitude and phase response to oscillatory inputs at each frequency. This linearized model can already exemplify how the underlying microcircuit parameters influence GPLA properties in simplistic scenarios, thereby allowing their interpretability. First, as illustrated in Figure 5D, we consider a microcircuit receiving exogenous inputs exclusively onto the pyramidal cells' dendrites (no feedforward inhibition), while I cells receive local excitatory inputs, but do not synapse back onto E cells (no feedback inhibition). We assume additionally that subthreshold activity is dominated by the exogenous input currents and proportional to the measured LFP. The lag induced by the membrane potential dynamics results in a positive (frequency-dependent) lag of excitatory activity with respect to the LFP (reflecting the input), while inhibitory activity is itself delayed with respect to excitation. For an exogenous input oscillating at an arbitrary frequency, this implies a phase lag configuration between the (oscillatory) response of these variables.

Going beyond the relationship between different variables observed at the same location, we study how the activity of the same variable varies across space. For such a scenario, we extend spatially the previous microcircuit scenario (with no feedforward and feedback inhibition), by adding horizontal E-E connectivity with a decreasing strength as a function of distance, and study the activity resulting from a spatially inhomogeneous oscillatory input, with larger input amplitude at a given side (on the left in Figure 5E). Again due to the delay induced by membrane dynamics, this results in the propagation of the activities from one side to the opposite. This leads to an interesting

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relationship between the phase and amplitude of oscillatory activity: the location of largest amplitude is ahead of time with respect to the neighboring locations with smaller amplitudes. Notably, these propagation-like patterns are induced by the network's horizontal connectivity, while the input to the structure does not have phase lags at different locations (***Ermentrout and Kleinfeld, 2001***). These two scenarios indicate that phase and amplitude of oscillatory activities are informative about the underlying microcircuit structure and dynamics. More realistic scenarios will take into account recurrent interactions between cell populations, and these above phases-amplitude relationships become frequency-dependent, as we will see in the next sections.

Reduction of complex models based on linear response theory

In order to analyze these more complex cases, a systematic and quantitative way to link model parameters to the coupling between network activities at a given frequency is required. When Considering the coupling between firing rate ($\lambda_E(x_1,t)$) and field ($L(x_2,t)$) at two locations x_1 and x_2, linearity entails the existence of transfer functions (denoted H_{λ_E} and H_L respectively), linking their respective activity to the time domain Fourier transform of the exogenous input $\hat{\eta}(x,f)$. Crucially, the first singular value approximation of GPLA can be associated to a model reduction that enforces separability of the space and time dependence of the input ($\hat{\eta}(x',t) = n(x')\epsilon(t)$ implying $\hat{\eta}(x',f) = n(x')\hat{\epsilon}(f)$). This leads to both rate and LFP being proportional to the exogenous input at a given frequency, with the following expressions based on the transfer functions:

$$\lambda_E(x,f) = \int H_{\lambda_E}(x,x',f)n(x')\hat{\epsilon}(f)dx' = \psi_E(x,f)\hat{\epsilon}(f) \quad \text{and} \quad L(x,f) = \psi_L(x,f)\hat{\epsilon}(f)\,. \tag{4}$$

such that the coupling between LFP and spikes at respective locations x_1 and x_2 writes

$$C_{x_1,x_2}(f) = \psi_L(x_1,f)\psi_E(x_2,f)^* E(f)\,, \tag{5}$$

where $E(f)$ is the input power spectral density at frequency f and z^* denotes the complex conjugate of z. This shows that the coupling between L at x_1 and λ_E at x_2 is separable in the spatial variables (x_1, x_2), and characterized by two functions of space: one for the field, ψ_L, and one for the excitatory spiking, ψ_E. In particular, as $E(f)$ is a positive number, the phase of C reflects a property of the underlying circuit irrespective of its input, and given by the phase difference between ψ_L and ψ_E at the considered frequency and locations. Importantly, the functions ψ_L and ψ_E also describe the coupling between the same variables at different locations, such that their phase distribution informs about the underlying spatial connectivity. Also ψ_I can be defined in the same way for inhibitory activity and merged with ψ_E.

In practice, we have access to a finite number of spatial measurement points of $C_{x_1,x_2}(f)$ corresponding to electrode channels where L, λ_E and λ_I are recorded. This leads to a rectangular matrix $\boldsymbol{C}(f)$ estimated by GPLA, combining excitatory and inhibitory units. The above separability then implies that $\boldsymbol{C}(f)$ is a rank-one matrix, such that Singular Value Decomposition (SVD) can be used to estimate the coupling properties using the largest singular value and the associated left and right singular vectors, which are spatially discretized approximations of the above functions ψ_L and ψ_E (up to a multiplicative constant). Overall, the spatial distribution of the phase and magnitude of each singular vector is influenced by the underlying recurrent dynamics and its propagation across horizontal connections (shaping the transfer functions such as H_{λ_E} and H_L), as well as the type of currents that dominate the LFP. As we will demonstrate in the next sections, the analysis of these features across frequencies is a rich source of information to validate assumptions about local network organization based on experimental multivariate data.

Application to spike-field dynamics during sharp wave-ripples

The phenomenon of hippocampal Sharp Wave-Ripples (SWR) is one of the most striking examples of neural activity entangling spike and LFP dynamics in multiple frequency bands, attributable to specific mechanisms of the underlying microcircuit (***Buzsáki et al., 1992***). Specifically, SWRs are

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brief episodes observed in hippocampal LFP traces combining a high-frequency oscillation (the ripple) to a low-frequency biphasic deflection (the sharp-wave). Moreover, these LFP activities are well known to be synchronized with spiking activity, with different cell-types firing at specific phases of the ripple oscillation (***Buzsáki et al., 1992***), although spike-field coupling at lower frequencies has also been demonstrated (***Ramirez-Villegas et al., 2015***).

We use simulations of in-vivo SWR described in ***Ramirez-Villegas et al.*** (***2018***) in order to demonstrate what insights GPLA can provide about the underlying hippocampal network mechanisms. The model generates realistic spiking and LFP activity in subfields CA1 and CA3, based on populations of two-compartment Hodgkin-Huxley neurons distributed along two distant one dimensional grids representing the strata of each subfield. In this model, the connectivity of CA3 is characterized by strong recurrent excitatory auto-associational $E-E$ connections, together with $E \rightarrow I$ connections and short-range $I \rightarrow E$ and $I \rightarrow I$ synapses (see Figure 6A for a schematic representation). In contrast, local $E-E$ connections are absent in CA1, but both E and I cells receive feedforward excitation from CA3. LFPs were generated from the total trans-membrane currents using line current density approximation, and measured by two laminar multi-shank electrodes (see Appendix, section Simulation of hippocampal sharp wave-ripples for more details).

We first apply GPLA to a single hippocampal subfield, CA1, as various studies suggest SWRs emerge from it in response to afferent CA2- and CA3-ensemble synchronous discharges (***Csicsvari et al., 2000***; ***Oliva et al., 2016***). In this simulation, LFP and unit recordings are distributed along two orthogonal spatial directions (laminar for LFPs and horizontal for units). We use a total of 157 peri-ripple traces of simulated LFPs and spikes of both populations (inhibitory and excitatory) of duration approximately 1 sec. Exemplary traces of simulated LFP and population firing rate of the CA1 population (pyramidal cells and inhibitory interneurons belonging to CA1) are shown in Figure 6B.

GPLA results for representative frequency bands are provided in Figure 6C-E and for all bands covering the 1-180Hz interval in Figure 6—figure supplement 2. The overall coupling magnitude (gPLV) was significant for all frequencies (Figure 6C), according to both surrogate (based on spike jittering, $p<0.05$) and analytical (based on random matrix theory) tests. In particular, the strongest coupling was detected in the ripple band (80-180 Hz), in line with results obtained with classical univariate techniques on experimental data (***Buzsáki et al., 1992***).

The LFP vectors exhibit a biphasic electric potential profile, typical of laminar recordings (Figure 6D), and corresponding to the field generated by the dipolar geometric arrangement of sources and sinks in the parallel two-compartment models of pyramidal neurons used for this simulation. Notably, the two-compartment approximation has been shown to lead to results comparable to simulations based on passive membrane currents of realistic morphologies (see Figure 6D (right) and ***Ramirez-Villegas et al.*** (***2018***) for more details). To check the quantitative agreement between the LFP vector and the original model of LFP generation in this simulation, we computed analytically the total LFP generated passively by all pyramidal cells using the original LFP simulation code of ***Ramirez-Villegas et al.*** (***2018***), and assuming all cells have identical trans-membrane currents flowing through their somatic and dendritic compartments (see Appendix section Computation of the laminar LFP profile). While the dendritic current reflects the post-synaptic input of the cell, somatic currents are taken opposite to preserve the charge neutrality of each cell. The resulting theoretical LFP profile of the pyramidal population are highly similar to the LFP vector (cosine similarity > 0.97 for LFP vector of all three frequencies in Figure 6D). Note that the sign of the LFP vectors' coefficients results from our convention of setting the phase of its mean to zero (see Figure 1C). As the LFP vector coefficients are divided into two groups of opposite sign, a positive sign is attributed to the set of coefficients that weight the most in the overall sum. In the context of laminar recordings, one could as well adopt a different convention ascribing a fixed sign to coefficients located in the peri-somatic layer (named *stratum pyramidale* in CA1). This would then lead to a sign consistent with classical analyses, e. g. triggered averaging based on spikes or oscillatory peak (***Sullivan et al., 2011***). These results overall suggest that the LFP vector can be exploited to further study the cur-

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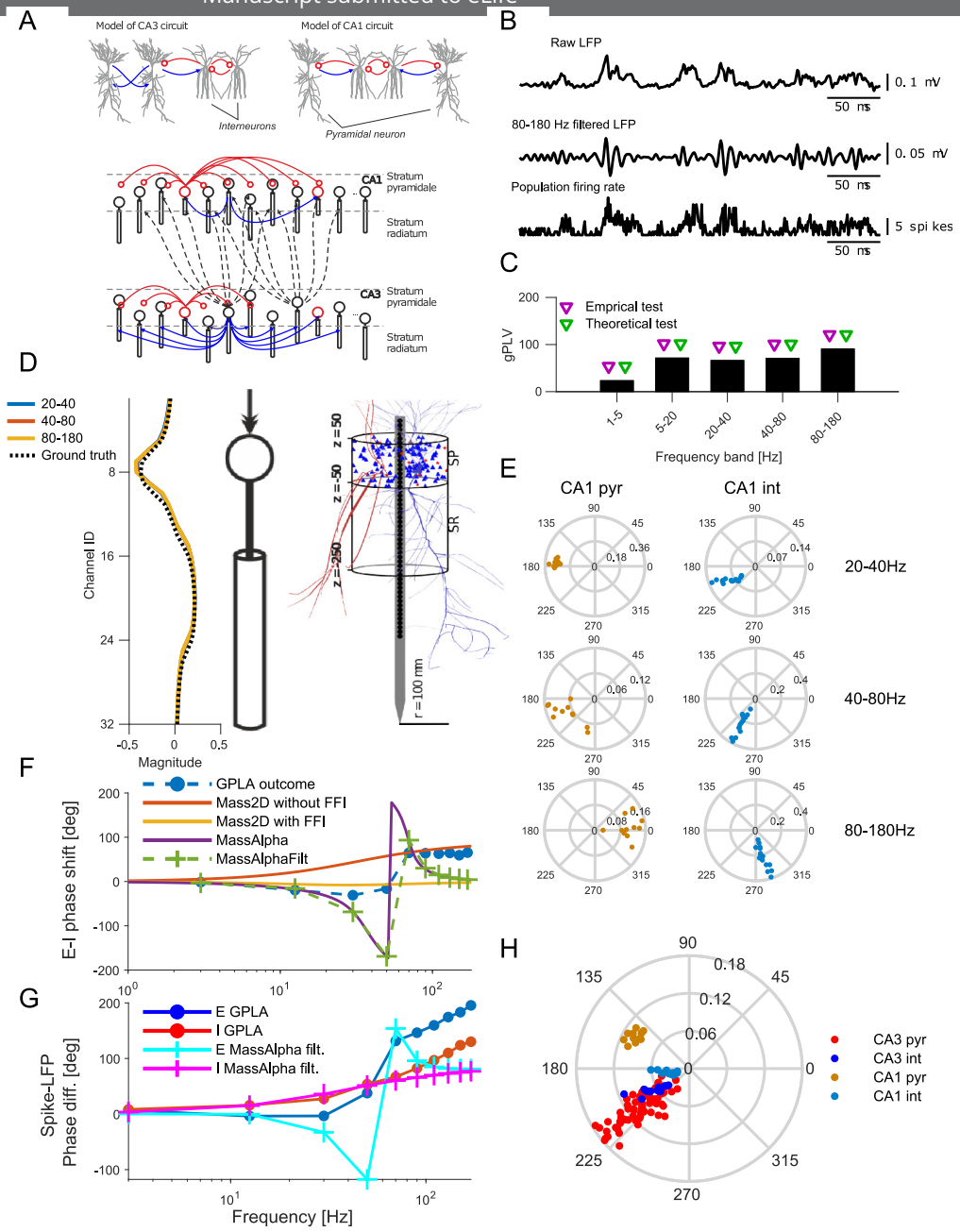

Figure 6. Analysis of hippocampal SWRs generated by a biophysical model
(A) Hippocampal multi-compartment model. Top: Canonical circuits of CA1 and CA3. Bottom: Schematic of the whole model (blue, excitatory connections; red, inhibitory, modified from ***Ramirez-Villegas et al.*** (***2018***). **(B)** From top to bottom: Example broad band CA1 LFP trace, band-pass filtered trace of the CA1 LFP in ripple band (80-180 Hz), and population firing rate of CA1 neurons. **(C)** CA1 gPLVs. Triangles indicate the significance assessed based on empirical (blue triangles, $p<0.05$) and theoretical (red triangles) tests. **(D)** Left: LFP vectors for GPLA of CA1 (blue and red curves are overlapping), with a schematic of the pyramidal two-compartment model. Right: Location of the somata and expample morphologies of each cell type (blue, pyramidal cells; red, interneurons) in an equivalent model with many compartments (right hand-side schematic modified from ***Ramirez-Villegas et al.*** (***2018***)). **(E)** Spike vector coefficients for CA1 in several frequency bands (left: pyramidal cells, right: interneurons). **(F)** Average phase lag between LFP and spike vectors across frequencies for: outcome GPLA on hippocampal SWRs, theoretical analysis of *Mass2D* (without and with feedforward inhibition) and *MassAlpha* neural mass models. Dashed green line indicate *MassAlpha* filtered over the frequency bands used for GPLA. **(G)** Difference between phases of E and I populations based on GPLA the *MassAlpha* neural mass model filtered in the same bands (IPSP was used as LFP proxy). **(H)** Spike vector resulting GPLA jointly applied to CA1 and CA3 in the gamma band (20-40 Hz). The following Figure supplements are available for Figure 6.
Figure supplement 1: Use of EPSP as LFP proxy.
Figure supplement 2: Joint GPLA of CA3 and CA1 activities.
Figure supplement 3: Joint GPLA of CA3 and CA1 activities.

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rent sources and sinks causing the LFP, e. g. through current source density analysis (***Wójcik, 2013***; ***Hindriks et al., 2016***).

The spike vectors components distribution in the complex plane (Figure 6E) support that both E and I cells are synchronized to CA1 LFP in the ripple band (80-180 Hz), but at a different phase, in line with experimental and simulation results (***Buzsáki et al., 1992***; ***Ramirez-Villegas et al., 2018***). This extends our previous observation of Figure 5D to a more realistic case of recurrent E-I interactions. Notably, we observe that while GPLA does not exploit neuron type information, the spike vector can clearly differentiate pyramidal cells from interneurons based on their respective phase in the spike vector, showing that interneurons lead pyramidal cells in lower frequency bands, barring a drastic change in the distribution of phases in high frequencies (see also Figure 6F). This can be used not only for inferring cell types from experimental data (***Varga et al., 2014***), but also to infer the organization and dynamics of neural circuits based on analytical or computational models.

In order to illustrate this second approach, we use the linear response framework (see above section Reduction of complex models based on linear response theory) to predict GPLA's phase in neural mass models of the microcircuit activity with different levels of complexity. In line with (***Ledoux and Brunel, 2011***), we first designed the *Mass2D* model, taking into account somatic time constants (resulting from membrane capacitance and leak currents), but neglecting synaptic dynamics (see Appendix, section Analysis and simulation of two population neural mass models). As a result, *Mass2D* is a 2 dimensional dynamical system, allowing for resonance only through to interactions between pyramidal cells and interneurons (a mechanism exploited in the *PING* model of gamma oscillations (***Traub et al., 1999***)). However, as shown in Figure 6F for typical parameters, and demonstrated analytically (see Appendix, section Analysis and simulation of two population neural mass models) the predicted phase shift across frequencies could neither account for the driving by interneurons in CA1, nor for phase changes in high frequencies (>30Hz). Notably, incorporating strong feedforward inhibition (FFI) did not improve the qualitative match between the analytical predictions and GPLA's outcome. The inappropriateness of *Mass2D* is in line with the current understanding of SWR emergence in CA1 through the pacing of pyramidal activity by delayed I-I interactions (***Stark et al., 2014***), as the model does not account for them.

The emergence of oscillations through I-I interactions is well captured by mathematical models, showing that sufficiently strong delayed recurrent inhibition gives rise to resonance or sustained oscillations (***Brunel and Wang, 2003***). The presence of these oscillations can be accounted for in an extended version of our neural mass model by including an additional synaptic delay and/or a synaptic time constant for I-I synapses (***Ledoux and Brunel, 2011***). We build the *MassAlpha* model that introduces a lag in the post-synaptic dynamics through the use of the so-called *alpha synapses* (see Appendix, section Analysis and simulation of two population neural mass models for details). Interestingly, the resulting E-I phase shift of this model is in qualitative agreement with GPLA estimation (Figure 6F), exhibiting a reversal in the lead-lag relation between populations as frequency grows. This supports the ability of GPLA, combined with appropriate simulations, to capture key characteristics of the underlying circuitry (in this simulation having oscillation dynamics and synaptic delays).

Another interesting property of the network is the phase shift between each individual population and the LFP, which is simply reflected in the phases of the spike vector coefficients averaged across each population (E and I). Given that the LFP is a linear combination of all post-synaptic currents of the network, we can use modeling to evaluate which of these currents is the most representative of the observed spike-LFP phase relation. As shown in Figure 6G (also see Figure 6—figure supplement 1 for EPSP proxy), the choice of the IPSP as an LFP proxy in the MassAlpha model accounts qualitatively, as frequency increases, for (1) monotonous phase increase of the I population, (2) the phase slope reversal of the E population. In contrast, using EPSP as an LFP proxy still fails to reproduce these two aspects (see Figure 6—figure supplement 1), illustrating how GPLA, beyond microcircuit dynamics, may also help address the cellular underpinnings of experimentally observed LFP (***Teleńczuk et al., 2017***). This overall suggests that GPLA combined with neural mass

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modeling of a structure can provide insights into the microcircuit dynamics underlying phenomena as complex as sharp-wave ripples, despite neglecting many biophysical details.

Moreover, GPLA can also provide further insights when concurrent recordings from multiple regions are available. As an illustration, Figure 6H depicts coefficients of the spike vector for the joint analysis of CA1 and CA3 (LFP and spikes of both areas is used for GPLA) showing CA1 and CA3 neurons are all coupled to the field activity with cell-type-specific phases in the gamma band (20-40 Hz) (see Figure 6—figure supplement 3) that are consistent with the GPLAs obtained from individual structures (see Figure 6—figure supplement 2). This suggests that the gamma rhythm has a dominant coherent component spanning the two structures, and thus may support communication between subfields during SWR and consequently memory trace replay, consistently with current hypotheses (***Carr et al., 2012***; ***Ramirez-Villegas et al., 2018***).

Application to spatio-temporal patterns of neural field models

In order to assess the interpretability of GPLA in the context of electrode arrays covering a piece of the cortical surface, we simulated a 2D neural field model as described in Figure 5. We used an exponentially decaying horizontal excitatory connectivity with a spatial scale constant $r_0 = 440\mu m$, following recent analyses of cortical recordings (***Teleńczuk et al., 2017***). The spatio-temporal dynamics was down-sampled spatially on a grid with a step size $\Delta x = 800\mu m$, representing the inter-electrode distance of a putative electrode array of $1.2cm$ size (see Appendix, section Analysis and simulations of neural field models for details). We compared the spatio-temporal dynamics for two choices of connectivity for which the input-free network has a stable equilibrium. First, we consider the *weak inhibition* case (Figure 7A), for which inhibitory (I) cells have weak feedback inhibition ($I \to E$), relative to the self-excitation caused by $E - E$ horizontal connections. The resulting activity is akin to stochastic fluctuations, due to the exogenous input, around a *stable node* equilibrium. Second, in the *strong inhibition* case (Figure 7B), the larger excitability of inhibitory neurons strengthens their influence on excitation and leads to activity fluctuating around a *stable spiral equilibrium*, reflecting a tendency of perturbations to oscillate around this point (Figure 7B) (***Onslow et al., 2014***). In both cases, the computed excitatory population rate is used to simulate the spike train of one excitatory unit per spatial electrode on this grid, in line with the observation that excitatory units are more easily detected experimentally due to their open field configuration (***Logothetis and Panzeri, 2014***). GPLA is then computed between this excitatory spiking activity and different LFP proxies. The results in Figure 7C-H are computed using the total EPSP resulting from horizontal E-E connections as LFP proxy (i. e. excluding exogenous excitation). We observe key differences between the GPLA of the two systems, predicted by linear response theory (see Appendix section Analysis and simulations of neural field models).

First, as reflected in the gPLV values (Figure 7C), spike-field coupling appears stronger in the lower frequency bands in the case of weak recurrent inhibition, while in the case of strong recurrent inhibition we observe a stronger coupling at intermediate frequencies. Notably, the peak of spike-field coupling in intermediate frequencies for strong inhibition is in line with models of the prefrontal cortex with the same enhanced feedback inhibition (***Sherfey et al., 2018***), exhibiting a resonance in the beta range (25Hz).

Second, as demonstrated in the previous neural mass model simulation, the global spike-LFP phase shift may also be informative about the underlying neural circuits. We can compute the average phase shift between the spike and LFP vectors as a function of the frequency band to see a clear difference between the two models. Strong recurrent inhibition leads to phase advance of the spiking activity in the low frequency, in contrast with the weak recurrent inhibition case showing a consistent lag of excitatory spiking across frequencies (Figure 7E).

Third, the relationship between the spatial variations of modulus and phase of the spike vector is different across these two networks. In the simulation with strong recurrent inhibition, the phase of spike vector coefficients as a function of their modulus for the frequency band associated with maximum gPLV for each model indicates that the phase of the spike vector coefficients decreases

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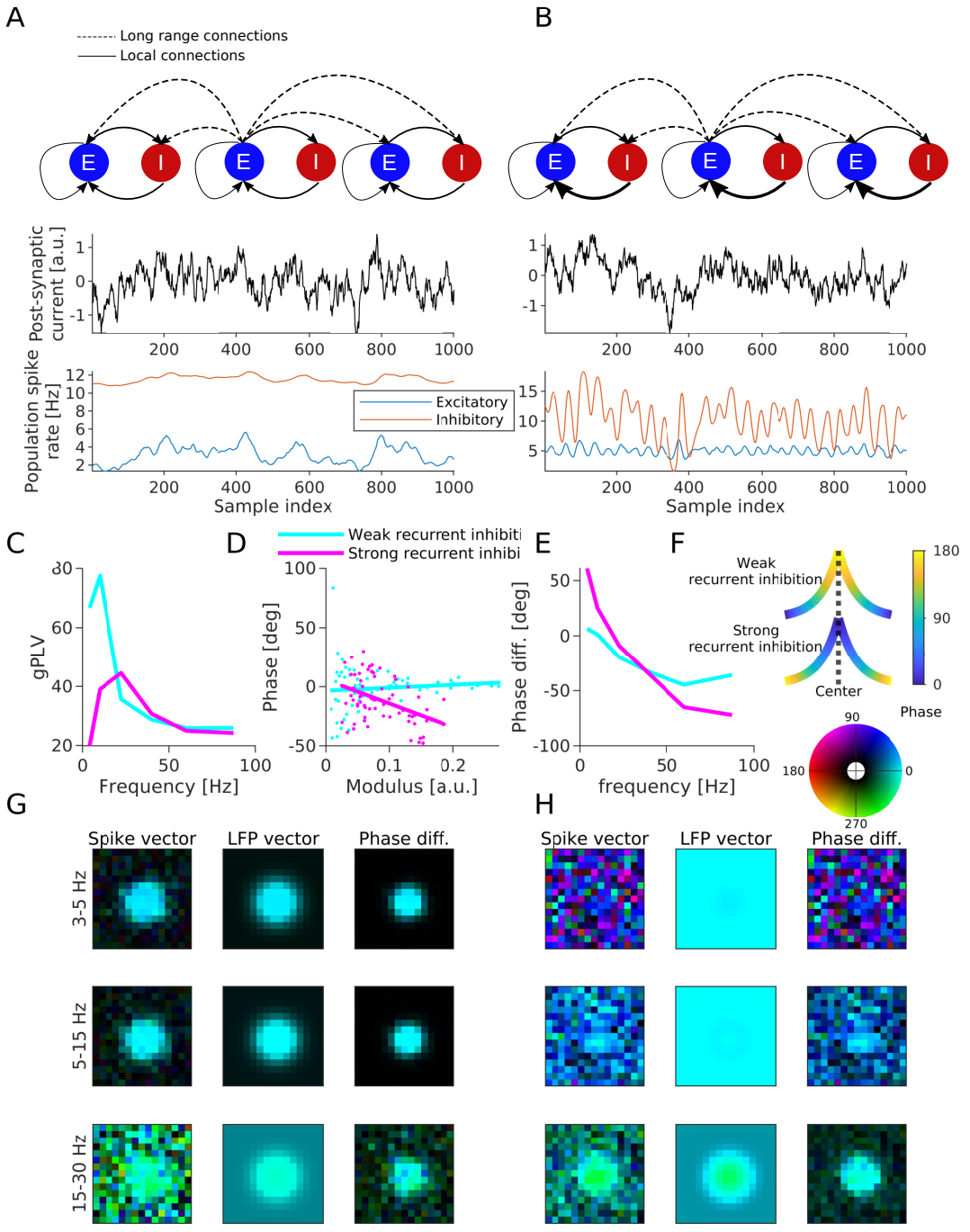

Figure 7. Neural field simulation using EPSP as LFP proxy. (A) Simulation of a neural field with weak recurrent inhibition. Example time course of (from top to bottom) exogenous input, E- and I- populations rates at the center of the neural field (in green, blue and red). **(B)** Same as A for a neural field strong recurrent inhibition, which shows oscillatory dynamics due to increase in recurrent activity. **(C)** gPLV as a function of frequency for both models. **(D)** Phase of spike vector coefficients as a function of its modulus for the frequency band associated with maximum gPLV for both models (each dot one coefficient, and the continuous lines are plotted based on linear regression). **(E)** Shift between the averaged phase of spike vector and averaged phase of LFP vector, as a function of frequency. **(F)** Schematic of the spike vector's phase gradient in the two models according to Equation 6. X-axis is the distance from center and y-axis is the connectivity strength. Line color indicates the phase according to the colorbar on the right. **(G)** Resulting GPLA in 3 frequency bands (indicated on the left) for neural field with weak recurrent inhibition (model schematized in A). **(H)** Same as G for neural field with strong recurrent inhibition (model schematized in B). In both G and H, color of pixel code the values of spike/LFP vector coefficients, with colorbar on top of H. Colors are represented in HSV mode, in which a complex number ($re^{i\phi}$) is represented by hue and brightness of a pixel. Hue of a pixel indicates the phase (ϕ) and the brightness of a pixel indicates the magnitude (r). The following figure supplement is available for Figure 7.

Figure supplement 1: GPLA using IPSP as LFP proxy.

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(i. e. the oscillation lags further relative to the LFP) for larger modulus ($p < 10^{-4}$, F-test on the linear regression model; $N = 69$), whereas, in the simulation with weak recurrent inhibition, phase is not correlated with modulus ($p > 0.3$, F-test on the linear regression model; $N = 69$) (Figure 7D).

This last difference between the two connectivity cases can be directly interpreted based on the spatial maps of spike vector coefficients across the array. Indeed, models exhibit a different radial phase map in both situations (Figure 7G-H), reflecting how phase changes as magnitude decreases when going away from the center (the location with largest input). This gradient can be predicted by theoretical analysis of a one dimensional neural field as we show in detail in Appendix section Spatio-temporal phase analysis in 1D. Briefly, the spike vector can be approximated by the spatial convolution of the input spatial pattern at a given temporal frequency f by a kernel of the form

$$k(x) = e^{-|x|a(f)} = e^{-|x|\mathrm{Re}[a(f)]}e^{-i|x|\mathrm{Im}[a(f)]}. \quad (6)$$

The first term of this kernel has a negative real number multiplied by distance in the exponential that makes the activity decrease away from the locations where exogenous input is the highest, as intuitively expected from the horizontal connectivity of the circuit. In contrast, the imaginary number in the argument of the second term enforces a spatial phase gradient in response to the input, which depends on the sign of the imaginary part of a. If this sign is positive, responses at the location of highest input will be ahead of time with respect to their surrounding in the considered band, as reflected by their larger spike vector phase in the top illustration of Figure 7F. In case $\mathrm{Im}[a]$ is negative, locations with highest input are lagging behind (bottom illustration of Figure 7F). The frequency-dependent complex number $a(f)$ that controls this behavior satisfies the approximate relation (valid at low frequencies, see Appendix section Spatio-temporal phase analysis in 1D)

$$a^2 \approx \frac{1}{r_0^2}\left[1 + \nu_{E\leftarrow I}\nu_{I\leftarrow E} - \nu_{E\leftarrow E} - i2\pi\tau f(2\nu_{E\leftarrow I}\nu_{I\leftarrow E} - \nu_{E\leftarrow E})\right]. \quad (7)$$

with r_0 the above defined spatial scale of excitatory horizontal connectivity, $\nu_{P\leftarrow Q}$ the magnitude of synaptic connectivity from population Q to P. It can be deduced from this expression (taking the square root of this number) that the imaginary part of a will depend on the relative strength of recurrent inhibition onto pyramidal cells, controlled by $\nu_{E\leftarrow I}\nu_{I\leftarrow E}$, with respect to recurrent excitation controlled by $\nu_{E\leftarrow E}$. Intuitively, having $2\nu_{E\leftarrow I}\nu_{I\leftarrow E}$ much larger than $\nu_{E\leftarrow E}$ will tend to suppress the input that created the response, generating a "wave" converging back to the points were the input was highest. The theory also predicts that large values of $\nu_{E\leftarrow I}\nu_{I\leftarrow E}$, as used in the strongly recurrent simulation, can generate strong phase gradients. In contrast, linear stability constrains the values of $\nu_{E\leftarrow E}$ to remain small, reflecting our choice for the simulations, and resulting in a comparatively moderate slope for the weakly recurrent case.

Overall, contrasting these two cases of neural field connectivity shows that modifications of the strength of feedback inhibition are reflected not only in the dominant frequency of spike-LFP synchronization (Figure 7C), but also in the spike-LFP shifts of the GPLA results (Figure 7E), and in the relationship between modulus and phase of spike vector coefficients (Figure 7D). Notably, these observations are being made in absence of specific oscillatory activity nor spatial phase gradient of the exogenous input (which influences the activity synchronously across the array). Therefore, it supports that the observation of complex coordinated activity involving phase spatial gradients, such as oscillations and traveling waves-like phase gradients, may emerge from local recurrent interactions in the recorded regions, instead of resulting from the passive driving by spatio-temporally coordinated activity originating from other brain regions.

As it has been argued in the literature that LFP activity may in some cases reflect inhibitory activity (***Teleńczuk et al., 2017***), we also provide GPLA results when taking IPSP activity as an LFP proxy in Figure 7—figure supplement 1. The variations of GPLA features across the frequency axis witness clear differences with respect to the results of Figure 7C-E, in particular when it comes to the phase difference between spike and LFP phases. This suggest that GPLA also provides information about the neural processes that are reflected in LFP activity.

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Analysis of Utah array data in the prefrontal cortex

After testing the interpretability of GPLA on simulations, we apply it to Utah array (10×10 electrodes, inter-electrode distance $400\mu m$) recordings from the ventrolateral prefrontal cortex of one anaesthetized rhesus monkey (see Figure 8A). LFP signals were preprocessed as described in Appendix, section Animal preparation and intracortical recordings, and multi-unit activity with a minimum of 5 Hz firing rate was used. Recorded signals are exemplified in Figure 8B-F. Exemplary LFP traces are illustrated in Figure 8B. Each trace is recorded from the location specified in Figure 8C. Spike trains are also displayed in Figure 8D (for the same epoch used in Figure 8B). As the analysis is performed in band-limited frequency ranges we also exemplified band-passed LFP signals (together with spikes) in Figure 8E and F. The dataset consisted of 200 trials of visual stimulation (10 sec) and intertrials (10 sec) each 20 sec.

Computing GPLA in different frequency bands revealed that the strongest coupling was in the alpha range (5-15Hz) (Figure 8G). Furthermore, we assessed the significance of coupling with both surrogate and analytical tests (see Appendix, section Significance assessment of gPLV). GPLA above 50 or 60 Hz should be considered with caution, as in high frequencies the spike-LFP relationships may be affected by the contamination of high frequency LFP bands by spike waveforms of units recorded in the same channel (***Zanos et al., 2011***; ***Ray and Maunsell, 2011b***). This may bias spike-LFP coupling towards the specific relation between the spiking of those specific units and the surrounding field, instead of capturing the relation of the underlying population rate to this field, as assumed in neural field models.

Figure 8I-K further shows the spike and LFP vectors for the three frequencies with largest coupling according to their gPLVs (for other frequencies see Figure 8—figure supplement 1). Representing spike and LFP vectors in the complex plane (Figure 8I-K first column), suggests that the relative phases of spike and LFP vectors are different across these three frequencies. To demonstrate the difference more clearly, we fit von Mises distributions to the pooled phase of all coefficients of the vectors (Figure 8I-K second column). The sign of the spike-LFP phase differences changes across frequencies, with spikes ahead of time with respect to LFP in low frequency, while lagging at higher frequencies. This behavior is similar to the above analysis of strongly recurrent neural field model (Figure 7G), when EPSP is taken as an LFP proxy.

The spatial mappings of the LFP and spike vectors on the Utah array (Figure 8I-K, third and fourth column) also demonstrate a spatial structure in the modulus and phase of the LFP and spike vectors, revealing localized regions with stronger participation in the locking, in particular in the beta range 15-30 Hz (green pixels at the middle-top and -bottom in Figure 8K, fourth column). We hypothesize this is due to a higher activation of spatially localized populations, as supported by anatomical studies of the PFC (***Elston, 2000***, ***2003***) and electrophysiological (***Safavi et al., 2018***) studies. In the alpha band (5-15 Hz), exhibiting the strongest coupling between spike and LFP, the spike vector coefficients' moduli are significantly negatively correlated with their phase (Figure 8H ($p < 10^{-6}$, F-test on the linear regression model; $N = 66$). Interestingly, we observe again a similar behavior in the above neural field simulation with strong recurrent inhibition, but not in the simulation with weak recurrent inhibition (Figure 7F). Overall, these results suggest a neural field with excitatory horizontal connections and strong local recurrent inhibition as a plausible model for the recorded prefrontal circuits, in line with what has been suggested by previous modeling work (***Sherfey et al., 2018***, ***2020***). This analysis illustrates how GPLA can support the mechanistic understanding of high-dimensional experimental recordings.

Discussion

In spite of its relevance for assaying the coordination mechanisms of brain networks (***Buzsaki et al., 2012***, ***2013***; ***Einevoll et al., 2013***; ***Herreras, 2016***; ***Pesaran et al., 2018***), the spike-field relationship is still not systematically analyzed in highly multivariate recordings. Potential reasons could be the lack of multivariate methodologies for investigating spike-LFP coupling beyond a single pair of

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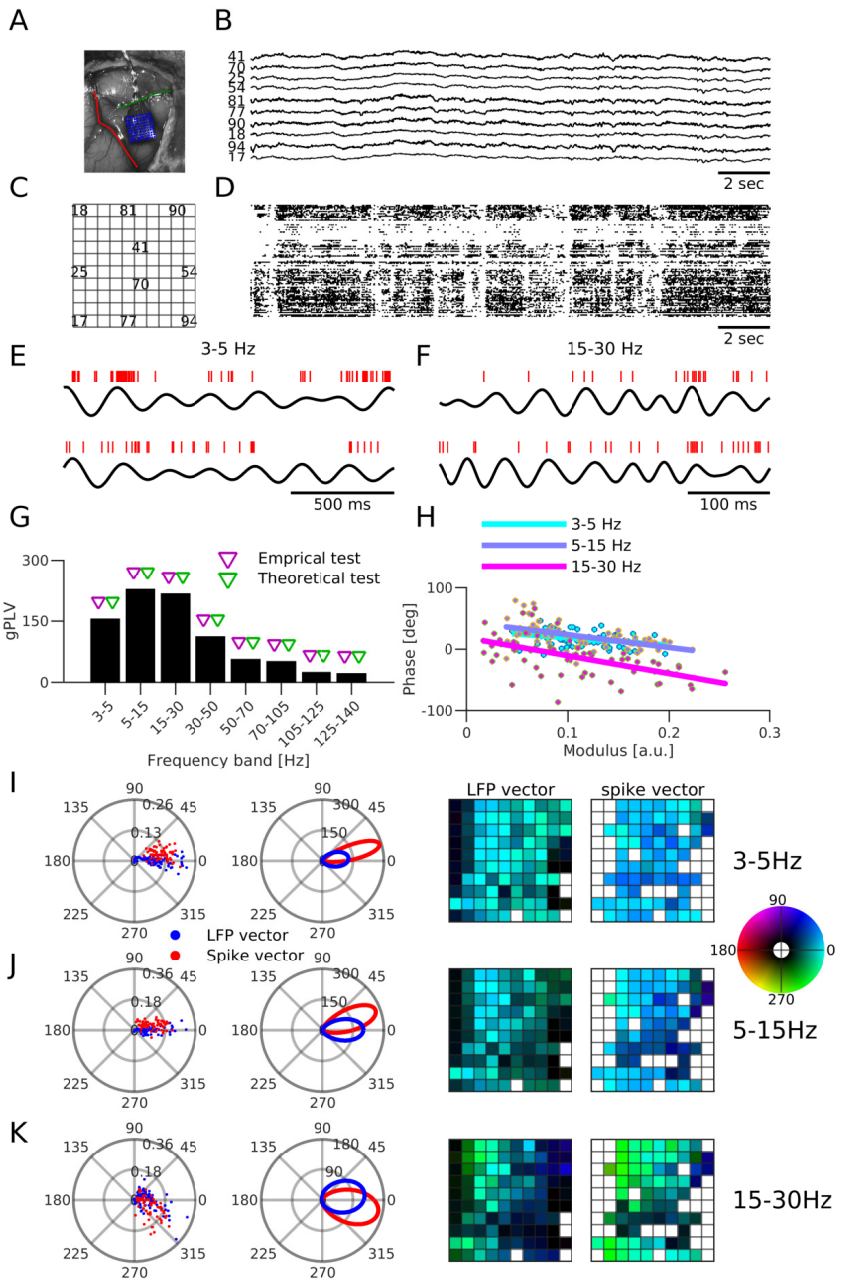

Figure 8. Application to electrophysiological recordings in non-human primate PFC.
(A) Location of the Utah array, anterior to the arcuate sulcus (red line) and inferior to the principal sulcus (green line). **(B)** Broadband trace of the recorded LFP (from the recording channels indicated in C). **(C)** Utah array spatial map identifying channel IDs shown in B. **(D)** Spike rasters for all recorded neurons. **(E-F)** Example spike trains (red bars) and filtered LFP (black traces) in the frequency ranges (E) 3-5 Hz and (F) 15-30 Hz. **(G)** gPLV values. Triangles indicate the significance assessed based on surrogate (blue triangles) and analytical test (red triangles) tests. **(H)** Phase of spike vector coefficients as a function of its modulus for the frequencies indicated in the legend (one dot per coefficient, continuous lines indicate linear regression). **(I-K)** LFP and spike vectors for frequency (I) 3-5 Hz, (J) 5-15 Hz, and (K) 15-30 Hz. First column depicts the LFP (blue dots) and spike (red dots) in the complex plane. Second column depicts the fitted von Mises distribution to phase of LFP and spike vectors. Third and forth columns respectively represent the spatial distribution of phase of LFP and spike vectors values on the array (see C). White pixels in the third column (LFP vector) indicate the recording channels that were not used in the recording and in the forth column (spike vector), white pixels indicate the recording channels with insufficient number of spikes (multiunit activity with a minimum of 5 Hz firing). In the last two columns, colors are represented in HSV mode, in which a complex number ($re^{i\phi}$) is represented by hue and brightness of a pixel. Hue of a pixel indicates the phase (ϕ) and the brightness of a pixel indicates the modulus (r). The colorbar is depicted on the right. The following figure supplement is available for Figure 8.
Figure supplement 1. Analysis of PFC Utah array data.

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spiking unit and a LFP channel, and interpretability challenges.

In this study, we developed the Generalized Phase Locking Analysis (GPLA) as — to the best of our knowledge — the first biophysically interpretable *multivariate* method for investigating the coupling between spatially distributed spiking and LFP activity. GPLA summarizes the coupling between multiple LFP spatio-temporal patterns and multiple spiking units in a compact way. At a given frequency, the spike and LFP vectors represent the dominant LFP and spiking spatio-temporal distribution and the generalized Phase Locking Value (gPLV), characterizes the strength of the coupling between LFP and spike patterns.

We demonstrated that GPLA's outcome features, such as the overall spike-LFP phase shift, the phase shift between different cell types (excitatory and inhibitory), and the spatial phase gradients, provide information about the overall organization of the recorded structure that are not easily quantifiable with simpler measurements.

First, application to realistic simulations of hippocampal SWR revealed various characteristics of hippocampal circuitry with minimal prior knowledge. Second, in order to better interpret spike and LFP vectors' spatial distribution, we also simulated spatially extended neural field models and demonstrate that phase gradients of spike and LFP vectors in these neural field models reflect the underlying microcircuit connectivity (such as the strength of recurrent interactions). Finally, the application of GPLA to experimental recordings suggests a global coupling between spiking activity and LFP traveling wave in vlPFC in line with our simulations of a neural field endowed with strong recurrent inhibition.

Statistical properties of the gPLV were investigated to develop an empirical and theoretical framework for the assessment of the significance of the coupling. The theoretical statistical test built upon Random Matrix Theory (***Safavi et al., 2021***) makes the method applicable to high dimensional electrophysiology data with low run-time complexity, which is important for modern probes such as Neuropixel, featuring 960 recording sites (***Jun et al., 2017***). In contrast, conventional statistical testing procedures based on the generation of surrogate data are computationally expensive as their time required to generate surrogate datasets strongly increases with the number of recorded neurons.

Comparison to existing approaches

To the best of our knowledge, there are very few studies that include the information of multiple LFP channels *and* multiple spiking units for investigating spike-LFP interactions. In particular, among approaches exploiting multiple LFP channels, none fully exploit the statistical relation between spiking activity recorded from multiple sites.

Spike-Triggered Average (STA) of LFP is one of the common multivariate technique for characterizing spike-LFP relationship (***Jin et al., 2008***; ***Nauhaus et al., 2009***). It has moreover been interpreted as a measure of functional connectivity (***Nauhaus et al., 2009***) (but also see ***Ray and Maunsell*** (***2011a***) and ***Nauhaus et al.*** (***2012***)). Although STA can exploit multivariate LFP signals, it can only be computed based on a single spike train, thereby ignoring the information provided by the remaining units. Similarly, even sophisticated extensions of spike-triggered averaging of LFP (***Teleńczuk et al., 2017***) still rely on the information of individual spiking units. In a similar vein, the study of ***Canolty et al.*** (***2010***), which showed that the probability of spiking can be statistically related to the LFP phase in multiple distant regions, was also limited to spiking units taken individually.

This appears clearly as a limitation, because statistical relationship between the spiking activity of different units, such as lags between the activity of different types of neurons (e. g. excitatory and inhibitory neurons) (***Klausberger et al., 2003***) can inform us about the organization of the neural circuit. Notably, this is supported by our simulations and experimental work (***Varga et al., 2014***).

Apart from work that specifically target spike-field coupling, a body of methodological studies by van der Meij and colleagues use a somewhat similar ideas to ours, namely extracting a dominant frequency coupling structure with dimensionality reduction techniques (***van der Meij et al.,***

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2012; *van der Meij et al., 2015*; *van der Meij and Voytek, 2018*). In spite of the similarities with these methodologies from a data analysis perspective, our investigation of spike-LFP coupling further leads to a mechanistic interpretation of mesoscopic activity, since it relates subthreshold to supra-threshold activity. To the best of our knowledge, this combination of dimensionality and model reduction reveals properties of the recorded circuits, such as the contribution of recurrent interactions to the spatio-temporal dynamics, that were not accessible otherwise.

Limitations and potential extensions

One limitation of GPLA is that it considers the underlying networks dynamics to be fixed for the analyzed data. Although the application of GPLA on simulation of Hippocampal Sharp Wave-Ripples demonstrates that an application on even such transient and aperiodic signals is insightful (Figure 6), but certainly due to the non-stationarity of neural dynamics, the time-resolved analysis of spike-LFP data (that likely required further methodological development) may improve our understanding of the underlying processes. As an alternative, it is however possible to apply the present methodology to portions of recordings containing identified transient phenomena, such as hippocampal Sharp Wave-Ripples, that are likely key to understand brain function (*Harris, 2005*; *Buzsaki, 2010*). For example, as LFPs result from the superposition of electric potentials from multiple sources and can capture various *coordinated or cooperative* phenomena, LFP decomposition techniques can temporally isolate these epochs of coordinated activity and application of GPLA to these epochs can characterize how each neuron is participating in the collective activity and/or to what degree, it is coupled to the larger-scale dynamics.

Another limitation comes from the nature of SVD, leading to orthogonal singular vectors that may or may not capture distinct physiological processes, which lead to mostly limiting GPLA to the dominant phenomenon reflected in the largest SV and corresponding vectors. However, simulations used in Figure 4 demonstrates in simple cases that subsequent SVs may reflect well isolated participating neuronal population.

Furthermore, GPLA can also be improved by exploiting a better univariate estimation method. Various novel methodologies for assessing pairwise spike-field coupling have been developed in recent years (*Grasse and Moxon, 2010*; *Vinck et al., 2010*; *Lepage et al., 2011*; *Vinck et al., 2012*; *Jiang et al., 2015*; *Zarei et al., 2018*; *Li et al., 2016*) each providing some improvements over classical measures such as PLV. For instance, *Zarei et al.* (*2018*) proposed a bias-free estimation of spike-LFP coupling in the low firing rate regime. Replacing the coefficients of coupling matrix (Equation 15) with these improved pairwise estimates may bring those benefits to GPLA as well. Nevertheless, the pairwise estimate used in the present paper also to normalize the coupling matrix in a way that allows the design of an analytical test to quickly assess the significance of the coupling. Alternative pairwise coupling estimates should be adapted to the requirement of the Random Matrix Theory to preserve the statistical benefits of our approach. This typically requires knowing the asymptotic distribution of the coupling statistics and devising and appropriate normalization thereafter. In case the new coupling measures are not adaptable to the analytical test, the Surrogate-based test remains applicable at the expense of heavier computational costs.

Neuroscientific interpretation of GPLA

Due to the complexity of the structure and dynamics of spatially extended neural networks, interpreting the outcome of statistically sound approaches such as GPLA in terms of biological mechanisms remains challenging. Thanks to the analysis of neural mass/field models, we could link several features of GPLA to a mechanistic interpretation. First, we applied this strategy to simulations from a biophysically realistic model of hippocampal ripples in order to use a system for which the underlying mechanism are well understood, but more complex than the neural field models used to interpret GPLA results. Despite the discrepancy between models, this showed that increasing the complexity of neural mass models using properties that are qualitatively in line with the key ground truth underlying mechanisms (e. g. inhibitory synaptic delays), allowed reproducing quali-

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tatively GPLA results of these simulations, making the approach more interpretable. This allowed in particular (1) to show the LFP vector reflects the laminar distribution of field potential generated by current dipoles, (2) to link the phases of the spike vector to cell types and recurrent I-I dynamics,

Next, we used neural field simulations in order to find interpretations of GPLA characteristics that can be exploited in the context of cortical electrode array recordings. This is an important step as the mechanisms underlying spatio-temporal phenomena observed *in vivo* remain largely elusive. While keeping the complexity of these models minimal (using exponentially decaying horizontal excitation and local inhibition), we could already observe that altering the microcircuit structure resulted in non-trivial qualitative modifications of GPLA's outcome, in particular regarding the phase gradients of spike and LFP vectors across the array. Finally, our analysis of Utah array recordings suggests the key GPLA features exhibited in simulation can also be estimated in real data and provide insights in the underlying organization of the recorded circuits.

Overall, the simple rate models we investigated have the benefit of lending themselves to approximate analytical treatment, providing direct insights into the role played by network parameters in GPLA characteristics. However, refinements of these first analyses are possible by improving the biological realism of population models and will allow checking the robustness of our simplifying assumptions. In particular, neural data recorded with multi-electrode arrays may be investigated in light of the knowledge about the horizontal connectivity of the structure, which may not be monotonous (for example see recent findings on non-monotonous correlation structure in V1 (***Rosenbaum et al., 2017***) and PFC (***Safavi et al., 2018***)).

More generally, a mechanistic interpretation of GPLA results in a given structure strongly relies on the accuracy of the assumptions made to perform analytical and/or computational modeling. We have shown neural mass models can approximate the population behavior of rather complex dynamics, such as sharp-wave ripples, and further sophistication of mass models will certainly help generalize the interpretability of GPLA analysis to include more biophysically realistic results (***Jirsa and Haken, 1996***; ***Qubbaj and Jirsa, 2007***; ***Costa et al., 2016***). The investigation of more complex models will benefit from incorporating systematic parameter estimation approaches, taking inspiration from inference techniques that have been developed for modelling the activity of one or several neurons (***Ladenbauer et al., 2019***; ***Gonçalves et al., 2020***) and combining them with the present model and dimensionality reduction approaches to ensure tractable estimation.

Ultimately, our results supports the ability of GPLA to interpret distributed information processing in higher-tier cortical areas such as PFC and hippocampus where investigating distributed spike-LFP interactions has proven key to elucidating the mechanisms of cognitive functions such as working memory (***Liebe et al., 2012***; ***Markowitz et al., 2015***), memory consolidation and spatial navigation (***Taxidis et al., 2015***; ***Fernández-Ruiz et al., 2017***). This approach is thus likely to provide further insights about the coordination mechanisms involved in such cognitive functions in various experimental settings.

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Author contribution

Conceptualization, S.S., T.I.P., M.B.; Methodology, S.S., J.F.R.-V. and M.B.; Software, S.S. and M.B.; Formal Analysis, S.S. and M.B.; Investigation, S.S., T.I.P., V.K. and M.B.; Resources, N.K.L.; Data Curation, S.S., T.I.P., V.K., and M.B.; Writing - Original Draft, S.S. and M.B.; Writing - Review & Editing:

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Appendix

Contact for reagent and resource sharing

Further information and requests for reagents and resources may be directed to and will be fulfilled by the Lead Contact, Dr. Michel Besserve (michel.besserve@tuebingen.mpg.de).

Experimental model and subject details

The neural data used in this study were recorded from the ventrolateral prefrontal cortex (vlPFC) of one anaesthetised adult, male rhesus monkey (macaca mulatta) by using Utah microelectrode arrays [Blackrock Microsystems (***Maynard et al., 1997***)] (more details on these experiments are provided in a previous study exploiting this data by ***Safavi et al.*** (***2018***)). All experiments were approved by the local authorities (Regierungspräsidium) and were in full compliance with the guidelines of the European Community (EUVD 86/609/EEC) for the care and use of laboratory animals.

Method details

Detailed GPLA methodology for electrophysiology data

GPLA proceeds in several steps: preprocessing of multi-channel LFP signals, construction of the coupling matrix, and its low-rank approximation. Finally, parameters of this low-rank approximation are standardized following specific normalization conventions allowing their easy interpretation and comparison. These steps are described in the following subsections.

LFP pre-processing

Prior to computing couplings, the LFP signal is pre-processed, first by filtering in the frequency band of interest. The choice of the filter bandwidth for the purpose of extracting the instantaneous phase or analytic signal in a particular band is subjected to a trade-off. On one hand, the signal requires a narrow enough band-pass filtering to provide us a proper estimate of the phases (***Chavez et al., 2006***). On the other hand, the filtered signal should preserve the temporal dynamics in the frequency of interest. The second step is extracting the analytical signal using the Hilbert transform, resulting in a complex-valued signal containing both the amplitude and phase of LFP. In the optional third step (see section Necessity of whitening and post-processing), we whiten the LFPs. We need to decorrelate LFP signal recorded in the different channels by applying a whitening operator. Whitening is only necessary to be able to use tools from Random Matrix Theory (***Anderson et al., 2010***) for the purpose of statistical analysis, otherwise generalized phase locking value, spike and LFP vectors all should be calculated in the original space to allow us interpreting the GPLA outputs in the channel space. For more detail on the rationale for the inclusion of the whitening step see section Analytical test and ***Safavi et al.*** (***2021***).

We consider LFPs and spiking units are recorded repeatedly over K trials, and each trial has length T (number of time-points). We represent LFPs of trial k by $L^{(k)}$, which is a $(n_c \times T)$ matrix, where n_c is the number of LFP recording channels. To simplify the notations, by $L^{(k)}$ we refer to analytical signals, i. e. band-passed in a particular frequency range and Hilbert transformed signals. We denote the collection of $N_m^{(k)}$ spike times of unit m at trial k by $\{t_j^{m,(k)}\}_{j=1\dots N_m^{(k)}}$ ($\{t_j^{m,(k)}\}$ contains the time-point indices of the LFP data for which spikes occur).

We introduce a *reduced-ranked* whitening operator which is a modified version of the conventional whitening that decorrelate the data, in this case, LFP signals. We customized this procedure in order to accommodate GPLA's needs, i. e. (1) avoid over-amplification of noise components of LFP (which are reflected in smaller eigenvalues of LFP covariance matrix) in the whitening operator, and (2) eliminate factors of variability that are not consistent across trials.

In our *reduced-ranked* whitening, we first reduce the rank of the LFP covariance matrix, by truncating the eigenvalue decomposition of LFP covariance matrix. We choose the number of components such that 99% of variance is explained with the reduced rank covariance matrix. In order

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to find the number of components that 99% of variance of LFP covariance matrix, we concatenate LFPs of all trials into a larger $n_c \times KT$ matrix, denoted by L and compute the eigenvalue decomposition of the covariance matrix,

$$\mathrm{Cov}\,(L) = \frac{1}{T} L L^H\,, \tag{8}$$

where $.^H$ indicates the transpose complex conjugate (should be noted that, analytical signal L, is a complex-valued matrix). We denote the number of components needed to explain 99% of variance of LFP covariance matrix by n_c^{eff}. We find the reduced number of components, n_c^{eff}, based on all trials, and we use n_c^{eff} to define the whitening operator of individual trials. The reduced rank single-trial LFP covariance matrix is denoted by $\mathrm{Cov}^{\mathrm{red}}\left(\mathrm{L}^{(\mathrm{k})}\right)$, and computed as follows

$$\mathrm{Cov}^{red}\left(L^{(k)}\right) = \sum_{p=1}^{n_c^{eff}} \lambda_p^{(k)} x_p^{(k)} (x_p^{(k)})^H\,, \tag{9}$$

where $\lambda_k^{(k)}$ and $x_k^{(k)}$ respectively denote the eigenvalue and eigenvectors of the LFP covariance matrix of trial k. We denote the whitened LFP of trial k by $L_w^{(k)}$, and compute it as follows,

$$L_w^{(k)} = (\Lambda^{(k)})^{\frac{-1}{2}} (X^{(k)})^H L^{(k)}\,, \tag{10}$$

where $\Lambda^{(k)}$ is a $n_c^{eff} \times n_c^{eff}$ diagonal matrix containing the eigenvalues of the above single-trial reduced rank LFP covariance matrix, and $X^{(k)}$ is a is a $n_c \times n_c^{eff}$ matrix containing the eigenvectors $x_k^{(k)}$.

Coupling matrix

Given the spike times of a single spike train $\{t_j^{(k)}\}_{j=1\ldots N^{(k)}}$ and $L_w^{(k)}$ a single channel pre-processed LFP analytic signal (as explained in section LFP pre-processing) and its phase ϕ ($= \angle L$), the conventional measure of spike-LFP coupling, Phase Locking Value (PLV), defined as follows:

$$PLV = \frac{1}{N^{tot}} \sum_{k=1}^{K} \sum_{j=1}^{N^{(k)}} \exp\left(i \phi_{t_j^{(k)}}^{(k)}\right)\,, \tag{11}$$

where, i is the imaginary unit ($i^2 = -1$), and $N^{(k)}$ is the number of spikes occurring during the trial k, N_{tot} is the total number of spikes occurred across all trials, i. e.

$$N^{tot} = \sum_{k=1}^{K} N^{(k)}\,. \tag{12}$$

In addition to PLV, we introduce a similar coupling statistics, denoted by c,

$$c = \frac{1}{\sqrt{N^{tot}}} \sum_{k=1}^{K} \sum_{j=1}^{N^{(k)}} L_{t_j^{(k)}}^{(k)}\,, \tag{13}$$

to be used when the theoretical significance test is intended to be used (see section Analytical test). The coupling statistics c is different from PLV in two ways, First, in PLV only the phase information from the continuous signal is used, while for c, we use both the phase and amplitude of the LFP signal. This is motivated by evidence that inclusion of the amplitude can improve the coupling measure (***Denker et al., 2007***, ***2011***) by weighting the contribution of spikes in the coupling measure by the LFP amplitude at the correspond spike time, as well as by theoretical considerations (see Appendix section Analytical test for more details). The second difference is, for c we have normalization by square root of the number of spikes rather the number of spikes (division by $\sqrt{N^{tot}}$ in Equation 13 versus N^{tot} in Equation 11). Basically, a scaling by $\sqrt{N^{tot}}$ is needed to normalize the variance of entires of the coupling matrix to 1, in order to be able to use tools from Random Matrix Theory (***Anderson et al., 2010***) (see ***Safavi et al.*** (***2020***) for more details).

A multivariate generalization of the coupling statistics, could be achieved by collecting the coupling statistics between all spiking units and LFP signals. Given spike times $\{t_j^{m,(k)}\}_{j=1\ldots N_m^{(k)}}$, $\phi_w^{(k)}$ LFP

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phase, and $L_w^{(k)}$ the analytical LFP, we can define the coupling matrix $\boldsymbol{C}$, based on PLV (Equation 11) as follows,

$$(\boldsymbol{C})_{n,m} = \frac{1}{N_m^{tot}} \sum_{k=1}^{K} \sum_{j=1}^{N_m^{(k)}} \exp\left(\boldsymbol{i}(\phi^{(k)})_{n,t_j^{(k)}}\right), \tag{14}$$

or based on c (Equation 13),

$$(\boldsymbol{C})_{n,m} = \frac{1}{\sqrt{N_m^{tot}}} \sum_{k=1}^{K} \sum_{j=1}^{N_m^{(k)}} (L^{(k)})_{n,t_j^{(k)}}, \tag{15}$$

where m, j and n respectively indicate the index of spiking unit, index of spike time and index of LFP channel and N_m refers to number of spikes recorded in spiking unit m [1].

Let n_c and n_s be the number of LFP channels and number of spiking units, respectively, $\boldsymbol{C}$ is thus a $n_c \times n_s$ complex-valued matrix (or $n_c^{eff} \times n_s$ if whitening is applied). As n_c (or n_c^{eff}) and n_s are not necessarily equal in electrophysiological datasets, the coupling matrix is not square in general.

Our coupling matrix is thus designed as a multivariate generalization of univariate coupling measures in order to capture the overall synchronization between the spiking activity and the phase of a global oscillatory dynamics in a given frequency band.

Low rank decomposition

Each column of the coupling matrix $\boldsymbol{C}$ has a common spiking unit whose locking is computed with respect to different LFP channels (called LFP vectors). Conversely, each row collects the phase locking values of all spiking channels to a common LFP reference channel. In order to achieve a compact and interpretable representation of this high dimensional object, we compute the Singular Value Decomposition (SVD) of the coupling matrix of the form

$$\boldsymbol{C} \quad = U D V^H \quad = \sum_{k=1}^{p} d_k u_k v_k^H, \tag{16}$$

where (d_k) is a tuple of positive scalars, the singular values (SV), listed in decreasing order. The complex valued vectors u_k and v_k are, respectively, the n_c/n_c^{eff}- and n_s-dimensional singular vectors associated to a given SV d_k. One important property of SVD is that keeping only the first term in Equation (16), with SV d_1, achieves the best rank-one approximation of the matrix, $\boldsymbol{C} \approx d_1 u_1 v_1^H$, in the least square sense (***Datta, 2010***, Theorem 7.29).

Post-processing

In order to make the outputs of GPLA interpretable, we introduce a few post-processing steps. An unwhitening and rescaling procedure is introduced to reverse some normalization discussed in previous sections LFP pre-processing, Coupling matrix, and Low rank decomposition, and a rotational transformation is introduced in order to represent the singular vectors in a more interpretable fashion.

Representation of singular vectors: Following the conventional mathematical representation of SVD in Equation 3, U and V are unitary matrices i. e. $U^H U = I$ and $V^H V = I$.[2] This implies that all singular vectors are unit norm, and all the information regarding the strength of coupling is absorbed in the singular values on the diagonal matrix D. As explained in main text (see sections Reduction of complex models based on linear response theory and Generalizing spike-oscillation coupling analysis to the multivariate setting), the relative magnitude and phase of singular vectors coefficients can be used to interpret the *relative* contribution of individual LFP channel and individual spiking unit to the coordinated pattern captured by the largest singular value.

We can summarize the coupling matrix with three quantities:

$$\boldsymbol{C} \sim (gPLV).v_{LFP} v_{spike})^H. \tag{17}$$

[1] Reader can also refer to ***Safavi et al. (2020***, Section 4) for a different formulation of computing the coupling matrix.

[2] For spike vector, V, should be noted that, V is a unitary after appropriate normalization that was discussed in the previous paragraph

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However the coefficient of both singular vectors can be rotated of the same arbitrary angle in the complex plane, as the rotation transformation in the complex plane does not change the SVD factorization, i. e.

$$udv^H = udv^H e^{-i\theta_0} e^{i\theta_0} = e^{-i\theta_0} ud \left(e^{-i\theta_0} v\right)^H . \tag{18}$$

We exploit this free parameter to make the GPLA more neuroscientifically interpretable by rotating both spike and LFP vectors with $-\overline{\phi_{LFP}}$, where $\overline{\phi_{LFP}}$ and $\overline{\phi_{spike}}$ are the average spike and LFP phases, defined as,

$$\overline{\phi_{LFP}} = \angle \sum_{i=1}^{n_c} (v_{LFP})_i \,, \tag{19}$$

$$\overline{\phi_{spike}} = \angle \sum_{i=1}^{n_u} (v_{spike})_i \,. \tag{20}$$

The rationale behind it is to center the coefficient of the rotated LFP vector ($\widetilde{v_{LFP}} = v_{LFP} e^{-i\overline{\phi_{LFP}}}$) around zero phase in the complex plane and the rotated spike vector, $\widetilde{v_{spike}} = v_{spike} e^{-i\overline{\phi_{LFP}}}$, preserves the angular difference of Φ_d of the spikes with respect to the LFP, defined as

$$\Phi_d = \overline{\phi_{LFP}} - \overline{\phi_{spike}} \,. \tag{21}$$

With this chosen convention, we obtain the final GPLA factorization

$$C \sim (gPLV).\widetilde{v_{LFP}} \widetilde{v_{spike}}^H . \tag{22}$$

We can also apply the phase difference between average LFP and spike vectors (Φ_d) to gPLV as it can summarize the overall phase shift between LFP and spikes. Given that gPLV is always a real positive value, by this convention, we add an extra information to gPLV.

We thus define a *complex gPLV* ($\widetilde{gPLV} = gPLV e^{-i\Phi_d}$) which its magnitude indicate the coupling strength between spikes and LFPs as in phase locking value (PLV) and its angle indicates the overall phase difference between spiking activity and LFP which is similar to locking phase in classical univariate phase locking analysis. This is an arbitrary choice to some degree, neverthelss it allows to interpret the GPLA output very similar to classical univariate phase locking analysis.

Needless to mention, when the magnitude of gPLV is small, this overall phase difference is not meaningful (similar to the case where PLV is small, the locking phase is not meaningful).

Unwhitening: As discussed in section LFP pre-processing, due to theoretical considerations, and in particular for applicability of our analytical significance test (see Significance assessment of gPLV), we whiten the LFPs prior to any other processing. In order to retrieve the original structure of the LFP i. e. retrieve all the correlations that were present in the original LFP signals but was diminished by the whitening, we need to revert the whitening i. e. unwhitening the LFP vector resulting from GPLA. This can be achieved by computing the unwhiten operator and apply it to the LFP vector,

$$v_{LFP}^{unwhiten} = W^{-1} v_{LFP} \,, \tag{23}$$

where W^{-1} is the unwhitening operator. In order to find this operator, we first we concatenate whitened LFPs of all trials (resulting from Equation 10) into a larger matrix L_w ($n_c^{eff} \times KT$). Then we estimate W^{-1} by using a linear regression with unwhitned and whitened LFPs (W^{-1} is the $n_c \times n_c^{eff}$ matrix of coefficient for regression).

Rescaling: As introduced in Equation 13, coefficient of coupling matrix are normalized by the square root of number of spikes. This choice of normalization, is different from the one use in conventional PLV (Equation 11). This will lead to inhomogeneous weighting of spiking units according to their variability of their firing rate. To avoid this potentially misleading weighting, we divide the spike vector by the square root of number of spikes,

$$v_{Spike}^{rescaled} = v_{Spike} \oslash \vec{N} \,, \tag{24}$$

where $\oslash$ is (entrywise) Hadamard division and $\vec{N} = \{N_m^{tot}\}_{m=1,\ldots,n_s}$, which is a vector consist of total spike counts (similar to Equation 12) of all the neurons (indexted by m) used in GPLA. Furthermore,

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to preserve the original norm of the spike vector (unit magnitude), we also need to normalize the spike vector by its norm,

$$v_{Spike}^{final} = \frac{v_{Spike} \oslash \vec{N}}{\left\| v_{Spike} \oslash \vec{N} \right\|}. \tag{25}$$

Necessity of whitening and post-processing

The whitening (and the subsequent post-processing) is necessary to have the advantage of applicability of the analytical significance test. LFPs are typically very correlated signals, and such correlation will be reflected in the magnitude of the singular values (and consequently gPLV), therefore, by whitening such correlations will be removed prior to investigating spike-LFP coupling. Nevertheless, multivariate analysis of spike-LFP coupling with GPLA even without whitening can still be beneficial for investigating spike-LFP relation sip (see Figure 3). If statistical testing based on surrogate data is intended, it is possible to skip the whitening step and proceed directly with the constructing the coupling matrix and low rank estimation. In that case, entries of the coupling can be filled by conventional PLVs (see Equation 14), or other choices of spike-LFP coupling measures (***Grasse and Moxon, 2010***; ***Vinck et al., 2010***; ***Lepage et al., 2011***; ***Vinck et al., 2012***; ***Jiang et al., 2015***; ***Zarei et al., 2018***; ***Li et al., 2016***) (also see the section Limitations and potential extensions for further elaboration). In this case, whitening of the LFP can be skipped and subsequent "Unwhitening and rescaling" discussed in section Post-processing is not necessary anymore.

Optional normalization for gPLV

As gPLV is a singular value of a matrix, it grows with the dimensions of the coupling matrix. This makes the comparison of gPLV resulting from different datasets difficult. For instance, assume the hypothetical situation of having two datasets recorded from two homogeneous populations of neurons, if the strength of coupling is the same in two populations, the populations with a larger amount of recorded neurons (therefore larger dimension of the coupling matrix) will have larger gPLV. Certainly, this can be misleading for investigating the spike-LFP coupling with GPLA when datasets with variable number of spiking units and/or LFP channels. To overcome this issue we suggest normalizing the gPLV to become independent of the size of the neural population (dimension of the coupling matrix) and the number of channels. When we consider the the entries of coupling matrix, C, to be PLV (LFPs are not whitened and Equation 14 is used for constructing the coupling matrix), pairwise coupling static is bounded ($|PLV| \leq 1$). When all the entities of the coupling matrix C attain their maximum value, gPLV will also gain the maximum possible value. Therefore, we can exploit it to normalize the gPLV. For a coupling matrix having maximum coupling for all pairs ($(C)_{n,m} = 1$ and C, a $n_c \times n_s$ matrix), then $gPLV_{max} = \sqrt{n_c n_s}$. Therefore, if we normalize the original gPLV by the maximum value it can achieve ($gPLV_{max} = \sqrt{n_c n_s}$, calculated is based on the dimensionality of matrix C), then the gPLV will be bounded by 1 as well. Moreover, with this normalization, gPLV is also comparable to PLV (if we have a homogeneous population of neurons, otherwise these quantities are not comparable).

Significance assessment of gPLV

In order to statistically assess the significance of coupling between spikes and LFP based on gPLV, we develop a surrogate- and a Random Matrix Theory (RMT)-based statistical testing framework exposed in ***Safavi et al.*** (***2020***). Hypothesis testing based on the generation of surrogate data is a common method for significant assessment in neuroscience. Nevertheless, not only generating appropriate surrogate data can be challenging (for a review see ***Grün*** (***2009***)), but also computationally expensive. This motivates the development of an analytical test exploiting minimal computational resources.

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Surrogate-based test

In contrast to uni-variate methods for which the distribution under a null hypothesis is more likely to be (possibly approximately) derived based on theoretical analysis (e.g. Rayleigh test for PLV (***Fisher, 1995***, Chapter 4)), such approaches are usually unavailable in multi-variate settings (nevertheless, we have developed one for gPLV, see section Analytical test). Following a common alternative approach, we build the null distribution by generating many surrogate datasets ***Grün*** (***2009***). The resulting gPLVs values forms an empirical H_0 distribution that can be used to compute the p-value for statistical assessment of the significance gPLV in the data. Importantly, the choice of the appropriate surrogate data according to characteristics of neural data is critical. For instance, generating surrogate data by shuffling inter-spike-intervals (ISI) is not an appropriate method when we have non-stationarity in firing rates (***Grün, 2009***).

In this work, we used an *interval*-jittering rather than a *spike-centered*-jittering[3], as the former was reported to be more reliable for detecting temporal structures in spike data (***Platkiewicz et al., 2017***). We devised the two following spike-jittering-based methods for GPLA. We also verify the appropriateness of our jittering approaches with various simulations (see the Results).

Simple interval jitter: Each surrogate dataset is generated by jittering all the spikes (from all neurons) with a particular jittering window (or dither width). In the interval jittering, per each spike, a new spike time is drawn within the jittering window around the spike. The timing of jittered spikes should be drawn from a uniform distribution. The size of the jittering window can be specified by the frequency wherein the spike-LFP coupling is being investigated. The smallest jittering window (or dither width) that can be used in order to destroy the temporal structure potentially exists in the range of frequency-of-interest. In the phase-locking analysis of electrophysiological data we usually extract the analytic signal or instantaneous phase of LFP by applying Hilbert transform on band-limited LFP signals (***Chavez et al., 2006***). The central frequency of the band-limited filter can be used for specifying the jittering window (or dither width), i. e. jittering window is the inverse of this central frequency.

Group preserved jitter: Similar to "simple interval jitter" we generate each surrogate dataset by relocating all the spikes within a window. For each surrogate data, we first divide the spike trains into equally-sized windows. Then we circularly shift the spike sequence within each window for all neurons together using a uniformly distributed time shift. Notably, we use a single random value for circular shifting of all neuron's spiking within the window. This size of this window should be chosen similar to the previous method ("simple interval jitter") i. e. based on the central frequency of the band-limited filter. The rationale behind this method of generation surrogate data is *relative* timing of the spikes could be associated to a large degree to the ansamble activity irrespective of the coupling to the LFP. Therefore, the relative timing of the spikes might not be impaired in the absence of coupling to global dynamics of the LFP. With "group preserved jittering" the relative timing is preserved and the coupling to the LFP is destroyed.

Analytical test

Challenges in generation of surrogate data (***Grün, 2009***) and considerable increase in the dimensionality of datasets (***Pesaran et al., 2018***; ***Jun et al., 2017***; ***Buzsáki, 2004***; ***Fukushima et al., 2015***), suggest that deriving mathematically (asymptotic) properties of GPLA under the null hypotheses, as is done for univariate testing (e. g. Rayleigh test for PLV (***Fisher, 1995***, Chapter 4)) is an interesting alternative.

In a companion work (***Safavi et al., 2020***), by using martingale theory (***Aalen et al., 2008***) we derive an asymptotic distribution for the entries of the coupling matrix in fairly general settings. Furthermore, by exploiting RMT (***Anderson et al., 2010***) we can find a good approximation of the distribution of eigenvalues (or singular values) of the coupling matrix in absence of coupling between spikes and LFPs. This provides a null hypothesis for the statistical testing of the largest eigenvalues (or singular values) of the coupling matrix, which corresponds to gPLV in our setting.

[3]Interval- and spike-centered-jittering are also known as hard and soft dithering respectively.

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Table 1

Figure num.	Osc. type	Num. of oscillatory components	Equations
Figure 2	Transient	1	14,31
Figure 3 A-C	Transient	1	14,31
Figure 3 D-I	Sustained	1	31,32
Figure 4 A-G	Sustained	5	15,31
Figure 4 H	Sustained	1-10	15, 31

As mathematical details are described in ***Safavi et al.*** (***2020***), we restrict ourselves to a brief explanation. When the LFP signal is whitened, and under a null hypothesis reflecting an *absence of coupling*, the coupling matrix which is constructed based on Eq 13, asymptotically converges to a matrix with i.i.d. complex standard normal coefficients (***Safavi et al., 2020***, Theorem 2), and the Marchenko-Pastur (MP) law then provides an approximation of the distribution of its squared singular values (***Safavi et al., 2020***, Theorem 3).

This law (***Marchenko and Pastur, 1967***) has the density

$$\frac{d\mu_{MP}}{dx}(x) = \begin{cases} \frac{1}{2\pi\alpha x}\sqrt{(b-x)(x-a)}, & a \le x \le b, \\ 0, & \text{otherwise}, \end{cases} \tag{26}$$

with $a = (1-\sqrt{\alpha})^2$ and $b = (1+\sqrt{\alpha})^2$ which are the upper and low bounds of the support of the distribution. Based on on the these bounds we can define a significance threshold, θ_{DET}, for the largest eigenvalue of hermitian matrix, $\boldsymbol{S} = \frac{K}{n_u}\boldsymbol{C}\boldsymbol{C}^H$:

$$\theta_{DET} = (1+\sqrt{\alpha})^2 . \tag{27}$$

The null hypothesis can be rejected if, the largest eigenvalue of $\boldsymbol{S}$ (denoted by ℓ_1) is superior to the significance threshold:

$$\ell_1\left(\boldsymbol{S}_n\right) > \theta_{DET} . \tag{28}$$

Therefore, there is a significant coupling between the multi-channel spikes and LFPs, if

$$gPLV > \sqrt{n_u \theta_{DET}} . \tag{29}$$

As mentioned above to be able to use the result of ***Safavi et al.*** (***2020***, Theorem 3), we need to whiten the LFP signal first, as described in LFP pre-processing. Furthermore, satisfying this theorem requires the coupling matrix to be normalized appropriately based on the spike rate of each unit (as defined in Equation 15).

For computing α on neural data, the *reduced ranked* $n_c^{eff} < n_c$ entailed by the whitening procedure (see LFP pre-processing more details), the *effective* dimensionality of the coupling matrix changes from $n_c \times n_u$ to $n_c^{eff} \times n_u$ (which depends on the spectral content of the LFP). This leads to a modification of Equation 27 as follows:

$$\theta_{DET} = (1+\sqrt{\alpha_{eff}})^2 , \tag{30}$$

where $\alpha_{eff} = n_c^{eff}/n_u$.

Simulation of phase-locked spike trains

We use simulated phase-locked spike trains and noisy oscillations as a toy model to demonstrate the potential applications of GPLA. The core principles of simulations used in both Figure 2, 4 and 3 are explained in the following paragraphs and the specializations used for individual figures are provided at the end (also summerized in table 1).

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For generating phase-locked spike trains, we adopt the method introduced in (***Ashida et al., 2010***). As the model has already been described elsewhere we restrict ourselves to a brief explanation. We sample the spike times from an inhomogeneous Poisson process with rate $\lambda(t)$,

$$\lambda(t) = \lambda_0 \exp\left(\kappa \cos(2\pi f t - \varphi_0)\right) , \tag{31}$$

where φ_0 is the locking phase of the spikes with respect to the oscillation, κ is the concentration parameter of the spikes around the locking phase, that specify the strength of coupling between spikes and the oscillation, λ_0 is propositional to the average firing rate over time ($\lambda_0 I_0(\kappa)$ is the average firing rate), and f is the frequency of oscillatory modulation of the spike trains.

Furthermore, we can also derive an analytical expression for the complex-valued PLV to be used as ground truth PLV (used in Figure 3),

$$PLV^* = e^{\mathbf{i}\varphi_0} \frac{\int_0^\pi \cos(\theta)\exp(\kappa\cos(\theta))d\theta}{\int_0^\pi \exp(\kappa\cos(\theta))d\theta} = e^{\mathbf{i}\varphi_0}\frac{I_1(\kappa)}{I_0(\kappa)} , \tag{32}$$

where PLV^* indicate the ground truth value, and the I_k's denoting the modified Bessel functions of the first kind for k integer (see e. g. ***Abramowitz et al.*** (***1972***, p. 376)):

$$I_k(\kappa) = \frac{1}{\pi}\int_0^\pi \cos(k\theta)\exp(\kappa\cos(\theta))d\theta . \tag{33}$$

For the simulation used in Figure 4, we construct the LFP by superimposing $N_{osc} \leq 10$ oscillatory components $O_j(t) = e^{2\pi \mathbf{i} f_j t}$, $j \in \{1, \dots, N_{osc}\}$ that the frequency of oscillations are limited in range of $[f_{min}, f_{max}]$. Each LFP signal is a weighted sum of these oscillatory components. We can represent these weights in a $(n_c \times N_{osc})$-variate matrix (we call it *mixing matrix*, and denot it by W), where each row of mixing matrix indicate the weights for the corresponding LFP channel. Thus, the synthetized multichannel LFP ($\mathbf{\Psi}(t) = \{\psi_l(t)\}_{l=1,\dots,n_c}$) can be written as the product of the mixing matrix (W) and the oscillatory basis ($\boldsymbol{O}(t) = \{O_j(t)\}_{j=1,\dots,N_{osc}}$),

$$\mathbf{\Psi}(t) = W\boldsymbol{O}(t) + \boldsymbol{\eta}(t) , \tag{34}$$

where $\boldsymbol{\eta}(t)$ is additive white noise on both real and imaginary parts.

In this simulation, the frequency of the oscillatory components range from 11Hz to 15 Hz, and the mixing is the following,

$$W = \begin{bmatrix} \boldsymbol{w}_d & \boldsymbol{w}_0 & \cdots & \cdots & \boldsymbol{w}_0 \\ \boldsymbol{w}_0 & \boldsymbol{w}_d & \boldsymbol{w}_0 & \cdots & \boldsymbol{w}_0 \\ \boldsymbol{w}_0 & \boldsymbol{w}_0 & \ddots & \ddots & \boldsymbol{w}_0 \\ \boldsymbol{w}_0 & \ddots & \ddots & \ddots & \boldsymbol{w}_0 \\ \boldsymbol{w}_0 & \cdots & \cdots & \boldsymbol{w}_0 & \boldsymbol{w}_d \end{bmatrix} . \tag{35}$$

where $\boldsymbol{w}_d = w_d \mathbf{1}_{N_g}$ and $\boldsymbol{w}_0 = w_d \mathbf{0}_{N_g}$, $w_d = 1$ and $w_0 = 0.1$ ($\mathbf{1}_{N_g}$, is a $(N_g \times 1)$-variate all-one column vector). This simple structure of the mixing matrix (which is close to a block diagonal matrix) implies that each LFP channel contains one dominant oscillatory component with a specific frequency (as in each row, there is only one oscillatory component with large coefficient w_d and a specific frequency).

For the simulation used in Figure 3A-C, oscillations originate from a single oscillatory source, but in order to make transient rather sustained oscillations, they were multiplied by a Gaussian window (with the size of 20 cycles of oscillation) around random events. The timing of transitory events was governed by a homogeneous Poisson process. Moreover, the spiking activities are phase-locked to the phase of the oscillations as the spike times were drawn from an inhomogeneous Poisson process with the rate specified in Equation 31. For the rest of the simulations in Figure 3 a single sustained oscillation has been used.

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Simulation of hippocampal sharp wave-ripples

The model was introduced and described in ***Ramirez-Villegas et al.*** (***2018***). We thus restrict ourselves to a brief explanation of the characteristics that are the most relevant to GPLA analysis.

Network architecture

We use a model of part of the hippocampal formation, accounting for the dynamics of CA1 and CA3 subfields during non-Rapid Eye Movement (non-REM) sleep. Cells of each subfield consist of 150 units (135 pyramidal neurons and 15 interneurons), arranged on a one dimensional array, along the x-axis. The connectivity of CA3 is characterized by strong recurrent excitatory auto-associational pyramidal-pyramidal connections, together with pyramidal-interneuron connections and short-range and interneuron-pyramidal synapses. In contrast, CA1 connectivity is implemented as a "feedback and reciprocal inhibition" circuit, including only pyramidal-interneuron, interneuron-pyramidal, and interneuron-interneuron synapses, all located in their peri-somatic region (see Figure 6A for the schema of the model)

Cell dynamics

Each neuron is modeled with two compartments: dendritic and axosomatic, the dynamics of each follows a Hodgkin-Huxley type (conductance-based) equation (***Pinsky and Rinzel, 1994***; ***Traub and Miles, 1995***). Notably, they include a non-linear slow dendritic calcium channel responsible for the bursting activity.

Computation of the laminar LFP profile

The procedure for computing laminar LFP profiles was also described in ***Ramirez-Villegas et al.*** (***2018***). Briefly, the trans-membrane current of each compartment of each cell is modeled as a line source (***Schomburg et al., 2012***) that were placed with the equal distance across the horizontally in a Stratum Pyramidale (SP) of $100\mu\mathrm{m}$ thickness, with an axosomatic compartments height of $80\mu\mathrm{m}$ for both pyramidal neurons and interneurons (***Traub and Miles, 1995***). Total dendritic arbor height of pyramidal cells was $200\mu\mathrm{m}$, corresponding to the CA1 Stratum Radiatum (SR). LFPs were captured through two multi-channel electrodes (mimicking laminar probes), each with 16 recording sites disposed along the vertical axis (denoted by z), 20 $\mu\mathrm{m}$ apart covering the simulated axosomatic and apical dendritic fields of CA1 and CA3. Each electrode crosses the corresponding linear cell arrangement (perpendicularly) in its middle.

The extracellular medium is modeled as a uniform and isotropic ohmic conductor with resistivity $\rho = 333\Omega\mathrm{cm}$. The potential in the extracellular medium is governed by the Poisson equation $\nabla^2\phi = \frac{1}{\sigma}\frac{d\xi}{dt} = -\frac{I_t}{\sigma}$, where $\sigma = \frac{1}{\rho}$ is the conductivity of the extracellular space $\left[\frac{\mathrm{S}}{\mathrm{m}}\right]$. With these assumptions, the extracellular potential $\phi\left(y_0, r, t\right)$ at the algebraic depth z_0 and a radial distance r, measured over the compartment's length limits (z_1 and z_2, respectively indicate the algebraic depth and the bottom of the top of the cylindrical compartment with length $L = z_2 - z_1$) can be computed by

$$\phi\left(z_0, z_1, z_2, r, t\right) = \frac{1}{4\pi\sigma L}\int_{z_1}^{z_2}\frac{I\left(t\right)}{\sqrt{\left(z - z_0\right)^2 + r^2}}\mathrm{dz} = \frac{1}{4\pi\sigma}\frac{I\left(t\right)}{L}\ln\left[\frac{\sqrt{\left(z_1 - z_0\right)^2 + r^2} - \left(z_1 - z_0\right)}{\sqrt{\left(z_2 - z_0\right)^2 + r^2} - \left(z_2 - z_0\right)}\right]. \quad (36)$$

after solving the integral with standard procedures. Accounting for the contribution of all compartments and cells, the total extracellular potential $\phi_{\mathrm{tot}}\left(z_0, t\right)$ at a given depth z_0 is

$$\phi_{\mathrm{tot}}\left(z_0, t\right) = \sum_i\sum_j \phi_{i,j}\left(z_0, z_{1,i,j}, z_{2,i,j}, r_{i,j}, t\right)\ , \quad (37)$$

where $\phi_{i,j}$ is the potential generated by the total transmembrane current of the jth compartment of the ith cell, located at radial distance $r_{i,j}$ from the electrode.

Note that since the neuron models considered in this work are two-compartmental, charge conservation within the cell implies that the total absolute somatic transmembrane currents equal the

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absolute of the total dendritic transmembrane currents (which also follows the charge conservation principle), leading to a dipolar distribution of the LFP contribution for each cell.

Equations 36-37 describe the way LFPs are simulated (as the low-frequency parts of the extracellular potential) in the original biologically realistic model that generated the LFP data we use for GPLA analysis. We also exploit it to provide an approximative LFP laminar profile for the population of pyramidal cells based on this equation, by injecting the same constant current to all cells and compartment of the linear arrangement, but having opposite signs for the axosomatic and dendritic compartment to respect charge neutrality and thus the dipolar structure (Figure 6D (broken line)).

Neuron exclusion criterion for GPLA

To reduce the small sample bias caused by a low number of spike events, we only use neurons that had a minimum average firing rate of 3 Hz firing. Nevertheless, using all neurons did not change the results significantly. For instance, in Figure 6G (in contrast to Figure 6A-F and H where excluded neurons based on their firing), to be compatible with the neural mass model we did not exclude any neuron.

Analytical neural field modeling of spike-field coupling

In order to justify and interpret our approach, we use a rate-based neural field model. Units are grouped in populations according to their cell-type on spatial localization. Spiking activity of a specific population p at possibly multidimensional location x is represented by its average spike rate $\lambda_p(x,t)$. Simultaneously, the LFP $L(X,t)$ is recorded at locations reflected by possibly different coordinates X.

Rate model of circuit dynamics

We follow classical neural field models, stating that the rate of each population evolves as a monotonous function of the membrane potential, itself controlled by post-synaptic currents (PSCs). Dynamics of the membrane potential V_p of each population p, is assumed to be governed by the following differential equation:

$$\frac{dV_p}{dt}(x,t) + \tau_p V_p(x,t) = \alpha_p \eta(x,t) + \sum_k \nu_{p\leftarrow k} s_k(x,t)\,, \tag{38}$$

where η represents the post-synaptic current generated by the external input (for which no spiking activity is available), s_k the normalized[4] post-synaptic current from the afferent population k, whose effect on target population p is scaled by synaptic strength $\nu_{p\leftarrow k}$.

The relationship between the normalized post-synaptic current at location x and spiking activity of the afferent population activity is modeled by spatio-temporal integration (***Wilson and Cowan, 1973***; ***Somers et al., 1995***; ***Jirsa and Haken, 1996***), possibly taking into account the propagation speed v_0 along the axons

$$s_k(x) = \int c_k(x,X)\lambda_k(x, t - |x-X|/v_0)dX, \tag{39}$$

where the connectivity kernel $c_p(x,X)$ models the density of synapses of neurons whose soma is located at target location x, with afferent neurons having their somas at location X. The integral covers the spatial domain where units' somas can be found, and may thus be 1-, 2- or 3-dimensional depending on the model. The kernel c_k reflects the spatial spread of axonal arborizations and as such can be approximated based on anatomical studies.

The elements finalizing the description of the state of the system are the relations between each population's membrane potential and rate, modeled by

$$\lambda_p = a_p(V_p)\,, \tag{40}$$

[4]By "normalized", we mean that s_k is a numerical quantity independent of the target population, possible target-specific differences in the PSCs being taken into account in the connectivity parameters $\nu_{p\leftarrow k}$, without loss of generality.

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where a_p is a typically sigmoidal activation function (these are the only non-linearities considered in our neural mass equations), leading to the overall dynamical system represented in Figure 5A.

From synaptic currents to LFPs

The local field potential is the lower frequency (<150Hz) part of the electrical potential recorded in the extracellular space, generated by the transmembrane currents (***Einevoll et al., 2013***). Considering that active currents mostly reflect spiking activity, whose dynamics lies mostly above the typical LFP frequency range, we approximate the LFP as resulting from the linear superposition of passive membrane currents triggered by post-synaptic input currents (***Mazzoni et al., 2015***), leading to the equation

$$L(y,t) = \sum_p \int f_{p,e}(y,x)\eta(x,t)dx + \sum_{p,k} \int f_{p,k}(y,x)s_k(x,t)dx\,,$$

where $f_{p,k}(.,x)$ represents the electrical field spatial distribution generated by trans-membrane currents of the p cells with soma located at x, resulting from exciting them with post-synaptic unit currents of population k. Note due to charge neutrality of the cells, trans-membrane currents across the membrane of individual cells sum to zero, such that input currents at the levels of synapses are compensated by opposite trans-membrane currents away from them, typically leading to dipolar current distributions. Along the same lines, $f_{p,e}$ is the distribution associated with post-synaptic current resulting from exogenous inputs to p cells. Differences between these fields according to the afferent populations are due to the respective distribution of their synaptic button over the efferent cell, preferentially targeting either the peri-somatic or distant dendritic sites, as illustrated in Figure 5C. These field distributions are assumed dominated by currents originating from pyramidal cells, due to their individual and collective geometric arrangement (***Nó, 1947***; ***Lindén et al., 2011***; ***Mazzoni et al., 2015***), such that we can simplify the above equation to obtain

$$L(y,t) = \int f_{E,e}(y,x)\eta(x,t)dx + \sum_k \int f_{E,k}(y,x)s_k(x,t)dx\,. \tag{41}$$

Spike-LFP relation

Analysis of the frequency response of neural network models is a useful approach to understand their characteristics and underlying mechanisms (***Ledoux and Brunel, 2011***; ***Sherfey et al., 2018***). In our case, this can be performed analytically by linearizing Equation 40 around an operating point, the neural field model becomes a linear time-invariant system controlled by the exogenous input $\eta(t)$. We can thus compute transfer functions for each variable of the system that will determine their response to a sinusoidal exogenous input at frequency f, based on the computation of temporal Fourier transforms of the signals. For a given signal, $s(t)$ the temporal Fourier transform at frequency f is given by

$$S(f) = \mathcal{F}_t[s](f) = \int_{\mathbb{R}} s(t)e^{-i2\pi ft}dt\,.$$

By applying the Fourier transforms on the left- and right-hand-side of dynamical equations, we can derive transfer functions linking the responses of each network variable to the exogenous input at a given frequency. We provide in Table 2 a list of time-domain variables and their corresponding notations for their time-domain Fourier transform, used in analytical developments.

Specifically, for a general exogenous input signal with time-domain Fourier transform $\mathcal{E}(X,f)$, where f denotes the temporal frequency, we obtain the input-output relation for population rates and LFP activity L

$$\lambda_p(x,f) = \int H_{\lambda_p}(x,X,f)\mathcal{E}(X,f)dX \quad \text{and} \quad L(y,f) = \int H_L(y,X,f)\mathcal{E}(X,f)dX\,.$$

A major simplification of this expression occurs when the exogenous input is separable in time and space,

$$\eta(X,t) = n(X)e(t))\,, \tag{42}$$

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Table 2. List of neural field and mass model variables (k indicates neuron population (afferent in case of synapse property))

Description	Symbol	Temporal Fourier transform	Equation
Exogenous input (spatio-temporal)	$\eta(x,t)$	$\mathcal{E}(x,f)$	38
Exogenous input (temporal)	$e(t)$	$\mathcal{E}(f)$	42
Spike rate	$\lambda_k(x,t)$	$\Lambda_k(x,f)$	43
Membrane potential	$v_k(x,t)$	$V_k(x,f)$	43
Synaptic activity	$s_k(x,t)$	$S_k(x,f)$	38, 39,41
Activation function	$a_k(x,t)$	$A_k(x,f)$	40

Table 3. List of neural mass model parameters

Parameter name	Symbol	Value (*Mass2D*)	Value (*MassAlpha*)
E membrane time constant	τ	$10ms$	$10ms$
I membrane time constant	δ	$5ms$	$10ms$
$E \leftarrow I$ synaptic strength	$\nu_{E\leftarrow I}$	0.01	0.3
$I \leftarrow E$ synaptic strength	$\nu_{I\leftarrow E}$	0.5	0.3
Alpha synapse time constant	σ	n.a.	$4ms$
$I \leftarrow I$ synaptic strength	$\nu_{I\leftarrow I}$	n.a. (accounted for in δ)	20.0

leading to $\mathcal{E}(X,f) = n(X)E(f)$ after temporal Fourier transform. This simplifying assumption models a number of typical inputs to the structure, including sinusoidal standing waves ($\eta(x,t) = n(x)e^{i2\pi ft}$) and traveling plane waves ($\eta(x,t) = e^{i(2\pi ft - kx)}$). This results in a simple expression for the covariance estimated across experimental trials between *rate* and LFP at two possibly different spatial points (x,y)

$$\left\langle L(y,f)\lambda_p(x,f)\right\rangle = \left(\int H_L(y,X,f)n(X)dX\right)\left(\int H_{\lambda_p}(x,X,f)n(X)dX\right)|e(f)|^2 .$$

in which the input intervenes only as a multiplicative positive constant, and which is separable in both space variables x and y. As a consequence, the rank one approximation of the covariance between spiking units and LFP channels activity estimated by GPLA is informative about the microcircuit properties, as we explained in the Appendix describing the analysis of the neural mass and neural field models.

Analysis and simulation of two population neural mass models

General description

The generic dynamic model of Equation 38 is exploited to describe network activity at a single location (i.e. we neglect the spatial extent of the considered structure) containing two cell types: pyramidal (E) and inhibitory (I), leading to the linear equations:

$$V_E + \tau_E \frac{dV_E}{dt} = \nu_{E\leftarrow E}s_E - \nu_{E\leftarrow I}s_I + \eta \quad (43)$$

$$V_I + \tau_I \frac{dV_I}{dt} = \nu_{I\leftarrow E}s_E - \nu_{I\leftarrow I}s_I + \alpha\eta \quad (44)$$

where $\boldsymbol{\nu}$ is a matrix gathering the non-negative synaptic strengths between populations, η the exogenous input to the network, with $\alpha \geq 0$ controlling the ratio between feed-forward excitation and inhibition. The term $\nu_{kj}s_j$ is the population averaged post-synaptic potential from population j to population k. In order to study quantitatively the effect of connectivity changes in the microcircuit, in this expression of the post-synaptic current, we isolate the synaptic strength coefficient $\nu_{k\leftarrow j}$, from a perisynaptic activity, that summarizes the dynamical processes occurring pre- and post-synaptically (synaptic delay, time constant induced by the post-synaptic channel conductance, ...). In the simplest case we assume peri-synaptic activity s_j can be approximated by the spike rate of

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population j, λ_j (up to a multiplicative constant that is absorbed by ν_{kj}). Alternatively, we model synaptic dynamics by a linear differential equation controlled by this rate (see model *MassAlpha* below).

The neural mass models will be analyzed with linear response theory, such that the a_k's of Equation 40 will be linearized around an equilibrium point of the dynamical system (that can be computed for vanishing input $\eta = 0$), and the resulting multiplicative constants will be themselves absorbed in the connectivity matrix ν, leading to replacing Equation 40 by

$$\lambda_k = V_k \,. \tag{45}$$

Next we describe the two linearized neural mass models exploited to interpret GPLA results of hippocampal simulations (see Figure 6). Parameter values for both models are reported in Table 3

Mass2D: E-I interactions without synaptic dynamics

Starting from Equation 43 and using Equation 45, the linearized system can be trivially reduced to the two-dimensional dynamical system (up to rescaling of the connectivity matrix coefficients)

$$\lambda_E + \tau \frac{d\lambda_E}{dt} = -\nu_{E\leftarrow I}\lambda_I + \eta \,, \tag{46}$$

$$\lambda_I + \delta \frac{d\lambda_I}{dt} = \nu_{I\leftarrow E}\lambda_E + \alpha\eta \,. \tag{47}$$

where τ and δ are time constants derived from membrane time constant τ_k and recurrent synaptic connection ν_{kk}. Linear response analysis then relies on the Laplace transform (with Laplace variable p) of these equation

$$\Lambda_E(p) + \tau p \Lambda_E = -\nu_{E\leftarrow I}\Lambda_I + N(p) \,, \tag{48}$$

$$\Lambda_I(p) + \delta p \Lambda_I = \nu_{I\leftarrow E}\Lambda_E + \alpha N(p) \,. \tag{49}$$

For the case of *no feedforward inhibition* ($\alpha = 0$), this leads to the ratio of excitatory to inhibitory activity in the Laplace domain

$$\frac{\Lambda_E}{\Lambda_I}(p) = \frac{\delta p + 1}{\nu_{I\leftarrow E}} \tag{50}$$

resulting in excitatory activity being in advance of $\tan^{-1} 2\pi f \tau$ with respect to inhibitory activity at frequency f.

For the case of strong feedforward inhibition ($\alpha = 1$), this leads to

$$\frac{\Lambda_E}{\Lambda_I}(p) = \frac{\delta p + 1 - \nu_{E\leftarrow I}}{\tau p + 1 + \nu_{I\leftarrow E}} \tag{51}$$

such that the phase shift between population is of constant sign across frequencies, but may be positive or negative depending on the exact parameters' values governing the E-I dynamics. Plots summarizing these situations are provided in Figure 6D.

MassAlpha: E-I interactions with alpha type synaptic impulse response

Together with Equation 43, we include in addition a non-trivial synaptic dynamics in the form of the differential equation (assuming same dynamic for both AMPA and GABA synapses),

$$\sigma^2 \frac{d^2 s_k}{dt^2} + 2\sigma \frac{ds_k}{dt} + s_k = \lambda_k \,, \tag{52}$$

This corresponds the classical *alpha synapse* used in computational models (e.g. implemented in the *NEURON* software (***Carnevale and Hines, 2006***)), modeling the response to a single spike with the alpha function

$$s(t) = \frac{1}{\sigma^2} t e^{-t/\sigma} \,. \tag{53}$$

By combining these equations with linear activations (Equation 45), the dynamics of the circuit is summarized by a 6-dimensional state-space model that can be studied analytically with linear response theory.

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Analysis and simulations of neural field models

When taking into account the spatial extension of the network, neural mass models can be extended to neural field models, where the variables described above possibly depend on space. Consider one or two spatial dimensions tangential to the layers of the network (assuming a layered organization like the hippocampus or cortex), the key phenomenon that should be additionally modeled is then the coupling between activity in different locations of the network entailed by horizontal connections. In line with the literature and to simplify the analysis, we will consider only the excitatory connections are spatially extended. With respect to the above generic neural field model Equations 38-40, equations pertaining to synaptic activity and rate need only to be specified. We use the model introduced by ***Jirsa and Haken*** (***1996***, Equation 15) with a spatial diffusion term with characteristic distance r_0 and axonal propagation speed $v_0 = r_0\gamma$, which takes the form of a damped wave equation:

$$\frac{1}{\gamma^2}\frac{\partial^2 s_E}{\partial t^2} + \frac{2}{\gamma}\frac{\partial s_E}{d\partial t} + s_E - r_0^2\Delta s_E = \lambda_E + \frac{1}{\gamma}\frac{\partial \lambda_E}{\partial t}\,, \tag{54}$$

where Δ is the Laplacian operator, while $s_I = V_I$ to encode purely local inhibition, eliminating redundant multiplicative factors.

To specify Equation 40, we use sigmoid activation functions for both AMPA and GABA synapses,

$$\lambda_E = \frac{Q_E}{1+\exp(-\chi_E.(V_E - V_{th,E}))}\,, \tag{55}$$

$$\lambda_I = \frac{Q_I}{1+\exp(-\chi_I.(V_I - V_{th,I}))}\,, \tag{56}$$

whose parameters (maximum rate Q_k, spiking threshold $V_{th,k}$ and excitability χ_k for population k) are adjusted in order to obtain different types of dynamics, either evolving around a stable equilibrium point (model *FieldStable*) or with a clear oscillatory activity (model *FieldOsc*).

Spatio-temporal phase analysis in 1D

Before simulating 2D neural field models with an explicit method, we investigate analytically properties of a simplified 1D model. In this case, the partial differential Equation 54 corresponds to an exponentially decaying connectivity, with axonal propagation speed $v_0 = r_0\gamma$, such that the resulting post-synaptic current takes the integral form (see ***Jirsa and Haken*** (***1996***, Equation (14)))

$$s_E(x,t) = \frac{1}{2r_0}\int \exp(-|x-X|/r_0)\lambda_E(X, t-|x-X|/v_0)dX\,. \tag{57}$$

If we take the neural field equation in the context of horizontal connection along non-myelinated axons ($v_0 \sim 1m/s$, $r_0 < 1mm$), the typical value of γ is beyond 1000 such that if we focus on frequencies below $200Hz$, we may neglect for the temporal derivatives of the partial differential equation. This leads to the following approximation for the dynamics of excitatory post-synaptic current.

$$s_E - r_0^2\frac{\partial^2 s_E}{dx^2} = \lambda_E\,. \tag{58}$$

In an unbounded 1D medium, assuming that activities vanish at large distances, we can use the spatial Fourier transform $\widehat{f}(t,z) = \mathcal{F}_x[f(t,x)](z) = \int_{\mathbb{R}} f(t,x)e^{-2i\pi zx}dx$ to derive the expression of s_E as a function of λ_E

$$\widehat{s_E}(t,z) = \frac{1}{1+(2\pi z)^2 r_0^2}\widehat{\lambda_E}(t,z)\,. \tag{59}$$

In order to get back to the original spatial position domain, we use a general Fourier transform relation for an arbitrary complex parameter a such that $\mathrm{Re}[a] \geq 0$:

$$\mathcal{F}_x\left[\frac{1}{2a}e^{-|x|a/r_0}\right](z) = \frac{r_0}{(2\pi z r_0)^2 + a^2}\,, \tag{60}$$

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This formula can be inverted, considering an arbitrary complex number b, and defining $\sqrt{b}$ to be the unique complex number such that $\sqrt{b}^2 = b$ and $\mathrm{Re}\sqrt{b} \geq 0$, we get

$$\mathcal{F}_z^{-1}\left[\frac{r_0}{(2\pi z)^2 r_0^2 + b}\right](x) = \frac{1}{2\sqrt{b}} e^{-|x|\sqrt{b}/r_0}\,, \tag{61}$$

For the particular case $b = 1$, we get $\sqrt{b} = 1$, which, in the spatial position domain, leads to

$$s_E(t,x) = \int_{\mathbb{R}} \lambda_E(t,y) h_{r_0}(x-y)dy = h_{r_0} * \lambda_E(t,x)\,, \tag{62}$$

where $*$ denotes spatial convolution and $h_{r_0}(x) = \frac{1}{2r_0} e^{-|x|/r_0}$. This reflects that horizontal connectivity generates EPSCs corresponding to a spatial smoothing of the excitation rate spatial distribution.

After linearizing around the operating point of the network (absorbing again the resulting multiplicative constant in the connectivity matrix), we obtain the equation of the dynamics by modifying Equation 38 (assuming neither long range nor feedforward inhibition)

$$\lambda_E(t,x) + \tau \frac{d\lambda_E}{dt} = \nu_{E\leftarrow E} s_E(t,x) - \nu_{E\leftarrow I}\lambda_I(t,x) + \eta(t,x)\,, \tag{63}$$

$$\lambda_I(t,x) + \delta \frac{d\lambda_I}{dt} = \nu_{I\leftarrow E} s_E(t,x)\,, \tag{64}$$

where the synaptic strength values incorporate multiplicative constants resulting from the linearization of Equations 55-56. By computing the temporal (with frequency variable f) and spatial Fourier transform of each equation, we get (using $p = i2\pi f$)

$$\widehat{\Lambda_E} + \tau p \widehat{\Lambda_E} = \nu_{E\leftarrow E}\widehat{S_E} - \nu_{E\leftarrow I}\widehat{\Lambda_I} + \hat{H}\,, \tag{65}$$

$$\Lambda_I(t,x) + \delta p \widehat{\Lambda_I} = \nu_{I\leftarrow E}\widehat{S_E}\,. \tag{66}$$

Eliminating $\widehat{\Lambda_I}$ we get

$$(1+\tau p)\widehat{\Lambda_E} = \left(\nu_{E\leftarrow E} - \nu_{E\leftarrow I}\frac{\nu_{I\leftarrow E}}{1+\delta p}\right)\widehat{S_E} + \hat{H}\,. \tag{67}$$

Combined with the spatially Fourier transformed horizontal connectivity Equation 58 (using $k = i2\pi z$)

$$(1 - r_0^2 k^2)\hat{S}_E = \widehat{\Lambda_E}\,, \tag{68}$$

this leads to

$$\widehat{S_E} = \frac{1}{1+\tau p}\frac{\hat{E}}{-r_0^2 k^2 + 1 + \frac{1}{1+\tau p}\left(\frac{\nu_f}{1+\delta p} - \nu_{E\leftarrow E}\right)}\,, \tag{69}$$

where we define the *feedback inhibition gain* $\nu_f = \nu_{E\leftarrow I}\nu_{I\leftarrow E}$.

Introducing our time-space separability assumption on the exogenous input

$$\eta(x,\,t) = n(x)\epsilon(t) \tag{70}$$

leads to

$$\widehat{S_E}(z,\,f) = \frac{1}{1+i2\pi\tau f}\frac{E(f)\hat{n}(z)}{-r_0^2(2\pi z)^2 + 1 + \frac{1}{1+i2\pi\tau f}\left(\frac{\nu_f}{1+i2\pi\delta f} - \nu_{E\leftarrow E}\right)}\,, \tag{71}$$

By defining

$$b = 1 + \frac{1}{1+i2\pi\tau f}\left(\frac{\nu_f}{1+i2\pi\delta f} - \nu_{E\leftarrow E}\right)\,, \tag{72}$$

and using the inverse spatial Fourier transform of Equation 61, we get

$$S_E(x,\,f) = \frac{1}{2r_0\sqrt{b}}\frac{E(f)}{1+i2\pi\tau f} n(x) * e^{-|x|\sqrt{b}/r_0}\,, \tag{73}$$

Assuming the exogenous input does not impose a spatial phase gradient to the structure (i.e. $n(x)$ is positive real for all locations up to a multiplicative constant), the phase gradient at a given frequency will be controlled by the imaginary part of $\sqrt{b}$. Specifically, to investigate qualitatively the

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phase gradient around a peak of activity of the exogenous input, we assume that $n(x)$ is a dirac at $x = 0$. Then the spatial variation of the phase around $x = 0$ take the form

$$\phi(x) = -\frac{|x|}{r_0}\mathrm{Re}\left[\sqrt{b}\right] . \tag{74}$$

This dirac approximation, does not match well our simulations (using a Gaussian shape spatial input distribution). However, computing spiking activity form S_E based on Equation 58, to obtain the spatial distribution of the spike vector, will have a deblurring effect compensating the convolution by $n(x)$ in Equation 75, making in closer to a Dirac. As a consequence, we will interpret the data based on the following approximation

$$\lambda_E(x,\, f) \approx C\frac{1}{2r_0\sqrt{b}}\frac{E(f)}{1 + \boldsymbol{i}2\pi\tau f}e^{-|x|\sqrt{b}/r_0} , \tag{75}$$

up to a multiplicative constant C.

In order to investigate the qualitative effect of the microcircuit connectivity on this spatial gradient, we assume $\tau = \delta$ and use a low (temporal) frequency assumption of the form $f << 1/\tau$, such that we can exploit a first order expansion for the fractions containing the term $\tau p << 1$. This leads to the approximation

$$b \approx 1 + (1 - \boldsymbol{i}2\pi\tau f)\left(\nu_f(1 - \boldsymbol{i}2\pi\tau f) - \nu_{E\leftarrow E}\right) \approx 1 + \nu_f - \nu_{E\leftarrow E} - \boldsymbol{i}2\pi\tau f(2\nu_f - \nu_{E\leftarrow E}) . \tag{76}$$

Simple geometric considerations show that the sign of the imaginary part of b is the same as the sign of its square root, such that under our simplifying assumption, the sign of the gradient taken algebraically from center ($x = 0$) to surround ($|x| > 0$) is the sign of

$$2\nu_f - \nu_{E\leftarrow E} , \tag{77}$$

showing that strong feedback inhibition will tend to put the populations surrounding $x = 0$ in advance with respect to this center point, while weak feedback inhibition (with respect to feedback excitation), will to generate a phase lag of the surround with respect to the center.

Neural field simulation in 2D

While the above analysis is much easier to perform in 1D, in most structures (and in particular cortex), the domain spanned by horizontal connectivity is better approximated by a 2D domain, which can also be sampled by modern electrode arrays. We thus simulate the dynamics of such 2D system to get insight into the characteristics revealed by GPLA analysis in this context. We use simplified notations for the 2D (in space) time-varying scalar fields $V(t, x, y) = s_E((x, y), t)$ and $I(t, x, y) = \lambda_E((x, y), t)$. Let Δx and Δt be the spatial and temporal grid spacings, and $V^n_{j,l} = V(n\Delta t, j\Delta x, l\Delta x)$ the discretized field. We use a Forward Time Centered Space (FTCS) finite difference scheme to simulate the above neural field model (***Fletcher, 1991***). FTCS relies on making the approximations

$$\frac{\partial V}{\partial t}(t, x, y) \approx \frac{1}{\Delta t}\left(V^{n+1}_{j,l} - V^n_{j,l}\right) , \quad \frac{\partial^2 V}{\partial t^2}(t, x, y) \approx \frac{1}{(\Delta t)^2}\left(V^{n+1}_{j,l} + V^{n-1}_{j,l} - 2V^n_{j,l}\right) , \tag{78}$$

$$\text{and} \quad \frac{\partial^2 V}{\partial x^2}(t, x, y) \approx \frac{1}{(\Delta x)^2}\left(V^n_{j+1,l} + V^n_{j-1,l} - 2V^n_{j,l}\right) . \tag{79}$$

Applying these approximations to Equation 54, leads to an explicit scheme for the field values at time $(n + 1)\Delta t$ based on all values at time $n\Delta t$ and $(n - 1)\Delta t$.

$$V^{n+1}_{j,l} = \frac{1}{G + 1}\left((G - 1)V^{n-1}_{j,l} + 2V^n_{j,l} + G^2\left(R^2\left(K_\ell *_d \boldsymbol{V}^n\right)_{j,l} + I^n_{k,l} + \frac{1}{G}\left(I^n_{k,l} - I^{n-1}_{k,l}\right) - V^n_{j,l}\right)\right) , \tag{80}$$

where $G = \gamma\Delta t$, $R = r_0/\Delta x$ and $K_\ell *_d$ denotes the discrete 2D spatial convolution with the discrete Laplace operator

$$K_\ell = \begin{bmatrix} 0 & 1 & 0 \\ 1 & -4 & 1 \\ 0 & 1 & 0 \end{bmatrix} . \tag{81}$$

The parameters chosen for both models presented in main text are reported in Table 4.

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Table 4. List of neural field model parameters

Parameter name	Symbol	Value (*weak Rec.*)	Value (*strong Rec.*)
E membrane time constant	τ_E	$20ms$	$20ms$
I membrane time constant	τ_I	$20ms$	$20ms$
E-E synaptic strength	$\nu_{E\leftarrow E}$	0.2	0.2
I-I synaptic strength	$\nu_{I\leftarrow I}$	0	0
$E \rightarrow I$ synaptic strength	$\nu_{E\leftarrow I}$	0.2	0.2
$I \rightarrow E$ synaptic strength	$\nu_{I\leftarrow E}$	1	1
E excitability	χ_E	1	1
I excitability	χ_I	0.1	3.33
E sigmoid threshold	$V_{th,E}$	0	0
I sigmoid threshold	$V_{th,I}$	0	0
E maximum rate	Q_E	$20Hz$	$20Hz$
I maximum rate	Q_E	$20Hz$	$20Hz$

Quantification and statistical analysis

Parameter estimation of von Mises distribution

The von Mises distribution (VM), which is also known as "circular normal" distribution is the counterpart of the Gaussian distribution for circular data (***Fisher, 1995***, Chapter 3). We used it for various purposes in this work (e. g. to model the spiking probability to synthesize phase-locked spike trains).

The VM distribution takes the form,

$$p(\phi|\varphi_0,\kappa) = \frac{1}{2\pi I_0(\kappa)} \exp\left(\kappa\cos(\phi-\varphi_0)\right), \tag{82}$$

where $I_0(\kappa)$ is the modified Bessel function of order zero (Equation 33). In Figure 8 and 1, we fit a VM distribution to the pooled phases of spike and LFP vectors coefficients. We use a maximum likelihood (ML) method for estimating the two parameters of the VM distribution, φ_0 and κ (***Fisher, 1995***). The ML estimation of φ_0 is simply the sample mean direction, denoted by $\bar{R}$ (for spike-LFP data is the locking phase). Maximum likelihood estimation of, $\widehat{\kappa}$, is the solution of following equation:

$$A_1(\widehat{\kappa}) = \bar{R}, \tag{83}$$

and A_1 is a ratio of two modified Bessel functions:

$$A_1(x) = \frac{I_1(x)}{I_0(x)}. \tag{84}$$

Approximate solutions are available for $\widehat{\kappa}$ (***Fisher, 1995***, sec. 4.5.5)

$$\widehat{\kappa} = \begin{cases} 2\overline{R} + \overline{R}^3 + 5\overline{R}^5/6 & \overline{R} < 0.53 \\ -0.4 + 1.39\overline{R} + 0.43/(1-\overline{R}) & 0.53 \le \overline{R} < 0.85 \\ 1/\left(\overline{R}^3 - 4\overline{R}^2 + 3\vec{R}\right) & \overline{R} \ge 0.85 \end{cases} \tag{85}$$

where $\overline{R}$ is the resultant length of the phases.

Computing SNR

In Figure 3H-I, in order to compare GPLA-based and PLA-based estimation of pairwise couplings, we define signal-to-Noise Ratio (SNR) as the ratio of estimation error to coupling strength (PLV) and it was used to compare the quality of GPLA-based and univariate estimation.

For the PLA-based estimation, SNR is the ratio of PLV to its estimation error. To compute the SNR for the GPLA-based estimation, the following procesure has been used: 1- Compute PLVs for all pairs of spiking units and LFP signals (based on Equation 14). 2- Construct the coupling matrix with

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the obtained PLVs, as shown in Figure 3G. 3- Obtain the rank-one approximation of the coupling matrix via GPLA (which is based on SVD at core). 4- Compare the elements of the approximated coupling matrix to the ground truth PLV, and compute the SNRs similar to PLA-based computation.

Animal preparation and intracortical recordings

The methods for surgical preparation, anesthesia, and presentation of visual stimuli for the Utah array recordings have been described in previous studies (see ***Logothetis et al.*** (***1999***, 2002); ***Belitski et al.*** (***2008***); ***Safavi et al.*** (***2018***)).

Data collection

Neural signals were recorded with a NeuroPort Cortical Microelectrode Array (Blackrock Microsystems, Salt Lake City, Utah USA). An array was implanted in the inferior convexity of the prefrontal cortex (see ***Safavi et al.*** (***2018***) for more details). The arrays are 4mm $\times$ 4mm with a 10 by 10 electrode configuration. Neural signals recorded from 96 of the available 100 electrodes. Neural activity was recorded in 200 trials. Each trial consisted of a 10s period of movie presentation, followed by 10s of a blank screen (inter-trial).

LFP extraction

The raw signals were low-pass filtered using an 8th order Chebyshev Type 1 filter with a cut-off frequency of 200Hz and a pass-band ripple less than 0.05dB. Forward and backward filtering was used to minimize phase distortions caused by the filtering. Next, the filtered signal was decimated to a sampling frequency of approximately 500Hz.

Spike detection

For detecting multi-unit spikes, the raw signal was band-pass filtered using a minimum–order finite impulse response (FIR) filter (***Rabiner et al., 1975***) with pass-band cut-off frequencies of 600Hz to 5800Hz and stop-band cut-off frequencies of 400Hz and 6000Hz, with at least 65dB attenuation in the stop-bands and less than 0.002dB ripple within the pass-band. The amplitude threshold for spike detection was set to 5 standard deviations above the average of the filtered signal (***Quiroga, 2007***). To spare computational costs, the standard deviation of the signal for each channel was estimated using a smaller, randomly chosen section of the filtered signal. Spike times with inter-spike intervals less than the refractory period of 0.5ms were eliminated.

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Figure supplements

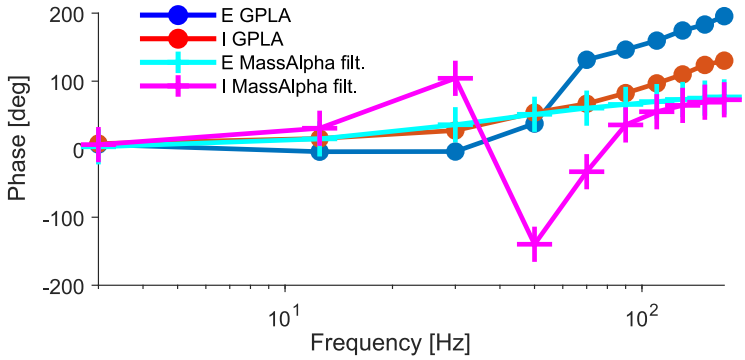

Figure 6 – Figure Supplement 1. Use of EPSP as LFP proxy.
Difference between phase of excitatory and inhibitory neurons/populations based on GPLA and the excitatory and inhibitory populations in the MassAlpha neural mass model. In this simulation EPSP has been used for the LFP proxy.

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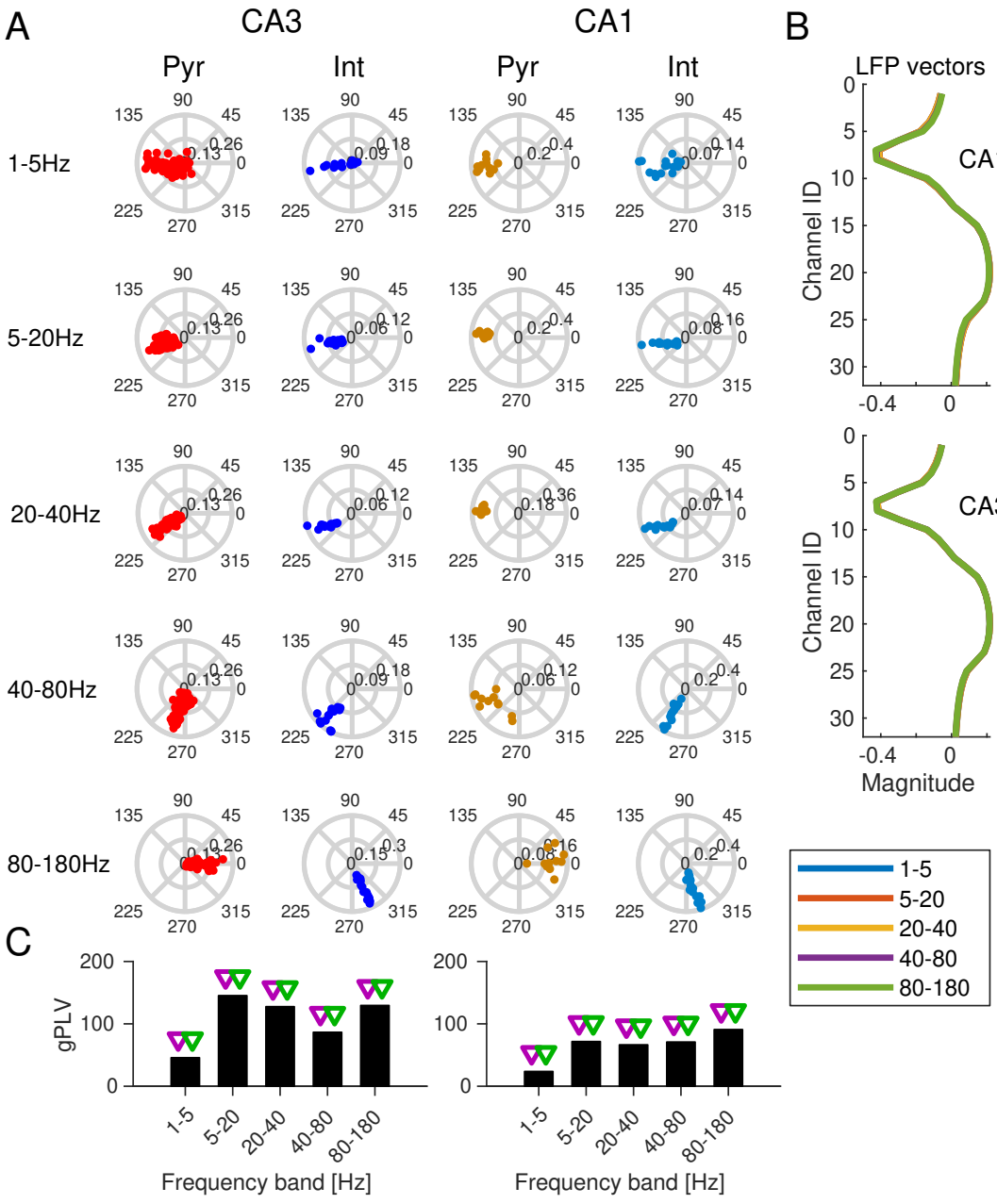

Figure 6 – Figure Supplement 2. Joint GPLA of CA3 and CA1 activities.
(A) Spike vectors represented in polar plots similar to Figure 6E, but for all frequencies (indicated on the left). **(B)** LFP vectors, similar to Figure 6D, but for all frequencies (indicated in legend in the bottom). **(C)** gPLV for different frequency ranges of LFPs, similar to Figure 6C. Triangles indicated the significance assessed based on empirical (blue triangles, with significance threshold of 0.05) and theoretical (red triangles) tests. (left) for CA3 and (right) for CA1.

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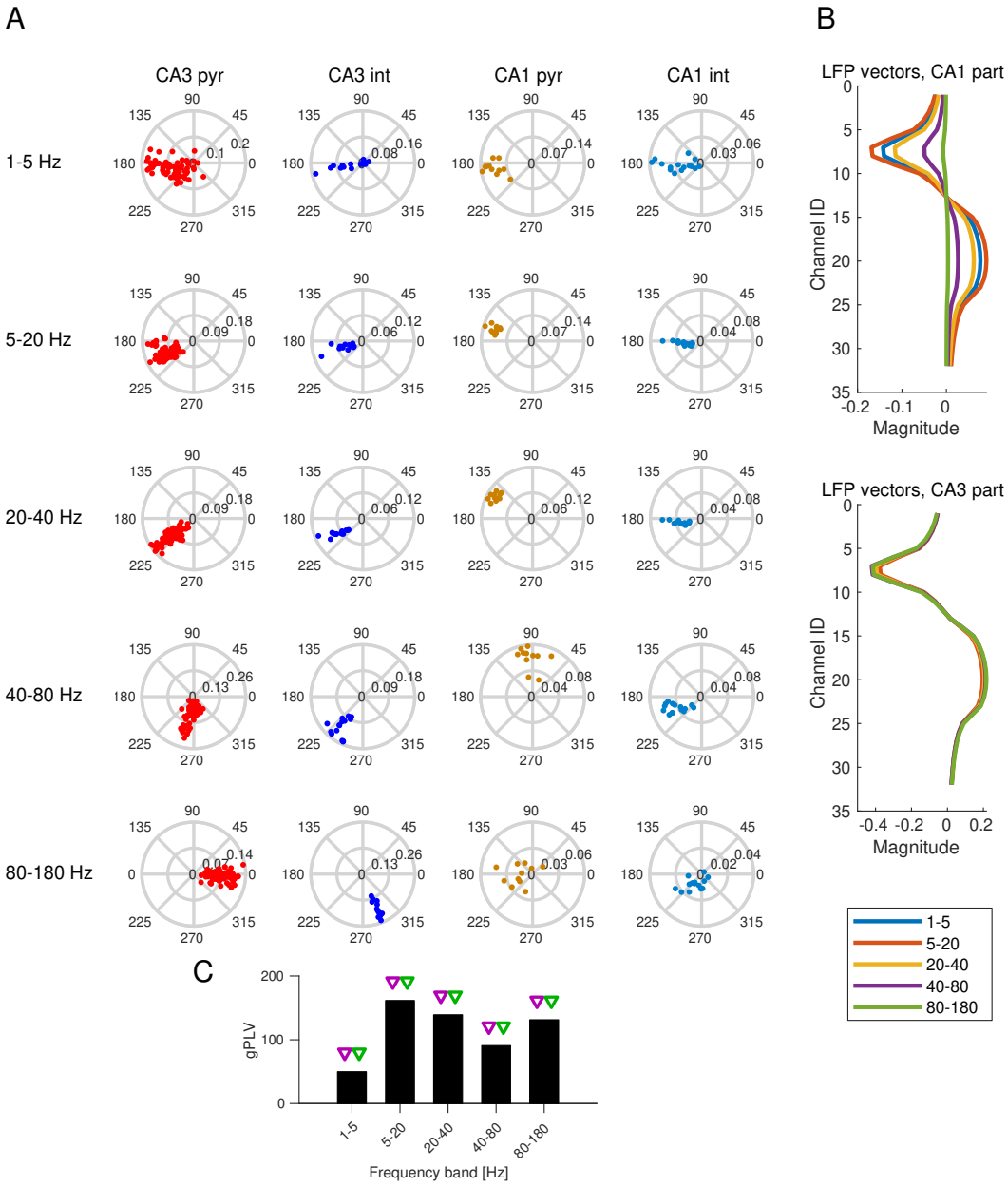

Figure 6 – Figure Supplement 3. Joint CA1-CA3 analysis of hippocampal SWRs generated by a computational model

(A) Spike vectors represented in polar plots similar to Figure 6E, but for all frequencies (indicated on the left). **(B)** LFP vectors, similar to Figure 6D, but for all frequencies (indicated in legend in the bottom). **(C)** gPLV for different frequency ranges of LFPs Figure 6C. Triangles indicated the significance assessed based on empirical (blue triangles, with significance threshold of 0.05) and theoretical (red triangles) tests.

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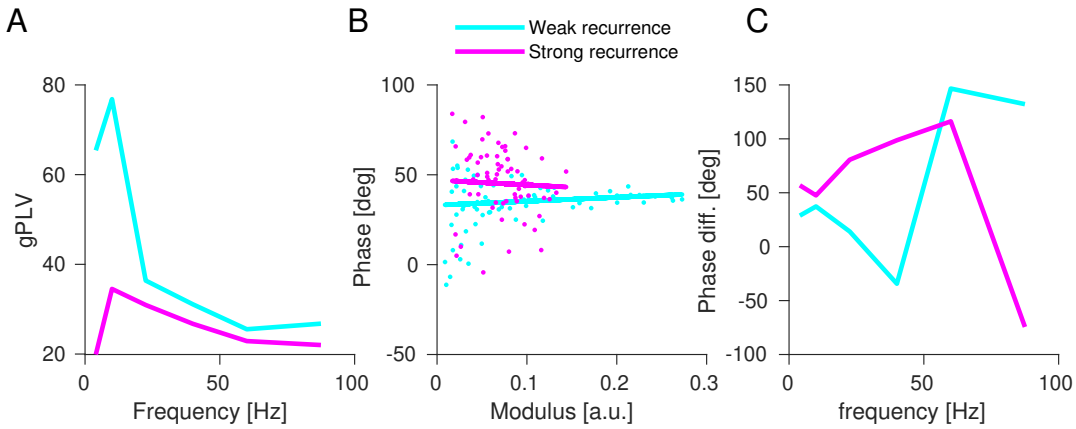

Figure 7 – Figure Supplement 1. GPLA using IPSP as LFP proxy.
To be compared with Figure 7C-E. **(A)** gPLV as a function of frequency for both models. **(B)** Phase of spike vector coefficients as a function of its modulus for the frequency band associated with maximum gPLV for each model (each dot one coefficient, and the continuous lines are plotted based on linear regression). **(C)** Shift between the averaged phase of spike vector and averaged phase of LFP vector, as a function of frequency.

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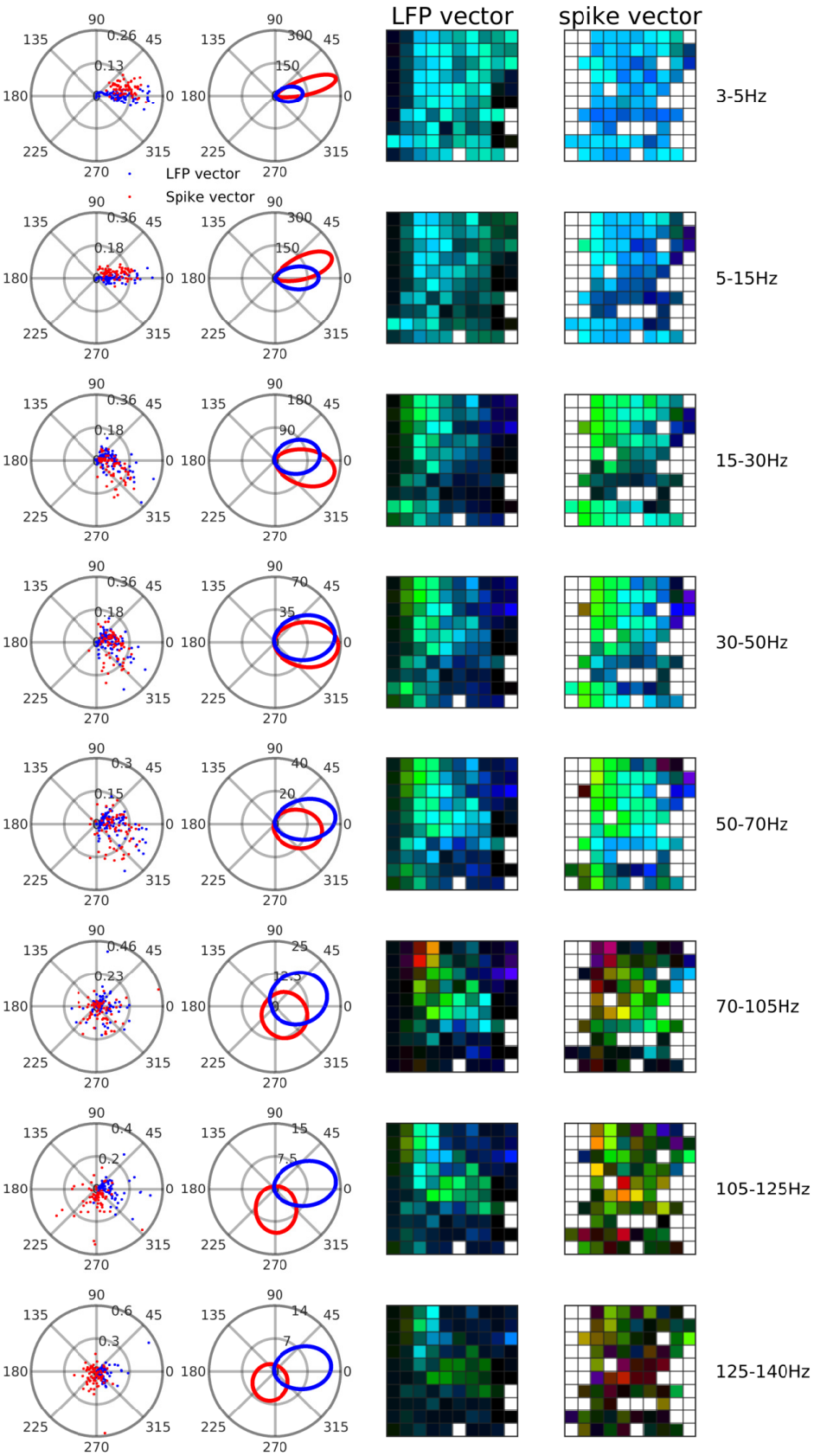

Figure 8 – Figure Supplement 1. Analysis of PFC Utah array data
LFP and spike vectors for frequencies indicated on the right. First column depict the LFP (blue dots) and spike (red dots) in the complex plane. Second column depict fitted von Mises distribution to phase of LFP and spike vectors. Third and forth column respectively represnting phase of LFP and spike vectors which remapped to real configuration of electrodes on Utah array (see Figure 8C).