Title: Computational Study of Synchrony in Fields and Microclusters of Ephaptically Coupled Neurons

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Abbreviated title: Global and Microcluster Synchrony via Ephaptic Coupling

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Abstract

Neuronal hyper-synchrony is implicated in epilepsy and other diseases. The low frequency, spatially averaged electric fields from many thousands of neurons have been shown to promote synchrony. It remains unclear whether highly transient, spatially localized electric fields from single action potentials (ephaptic coupling) significantly affect spike timing of neighboring cells and, in consequence, population synchrony. In this study, we simulated the extracellular potentials and the resulting coupling between neurons in the NEURON environment and generalized their connection rules to create an oscillator network model of a sheet of ephaptically coupled neurons. Using both models, we explained several aspects of epileptiform behavior not previously modeled by synaptically coupled networks. Importantly, reduction of neuron spacing induced synchronization via single spike ephaptic coupling, agreeing with seizure suppression seen clinically and in vitro via extracellular volume adjustment. Further reduction of neuron spacing yielded locally synchronized clusters, providing a mechanism for recent in vitro observations of localized neuronal synchrony in absence of synaptic and gap junction coupling.
**Introduction**

Neuronal synchrony is implicated in working memory, sensory processing, and attention (???) and diseases like epilepsy, Parkinson’s, schizophrenia, Alzheimer’s, and autism (?). Cortex and hippocampus – due to their laminar structure resulting in large local field potentials (LFPs) – are major research objects in the study of neuronal synchrony and epilepsy (???). Neuronal network hyper-activity and hyper-synchrony underlie activity bursts and spreading excitation, which are related to transient seizure episodes (inter-ictal events) and seizure onset, respectively (????).

The most widely discussed mechanism for pathologic hyper-synchrony in neuronal networks is the remodeling of synaptic connections. Experiments show that loss of inhibitory interneurons and the formation of recurrent connections can lead to hyper-synchrony (?). While synaptic remodeling is likely involved in epileptiform behavior, hyper-synchrony can exist without synaptic connections (?). For example, extracellular medium osmolality changes induce or suppress epileptiform behavior in absence of functioning synapses (????). Even though theoretical and ultra-structural studies have suggested that gap junctions between neurons could explain these observations (????), synchrony can even persist when gap junctions are functionally blocked (?). Therefore non-synaptic, not gap junction-mediated mechanisms for neuronal hyper-synchrony likely exist.

One potential mechanism is ephaptic coupling, or coupling via endogenous electric potentials ($V_e$). Low frequency $V_e$, simulating spatially averaged potentials from many cells, *i.e.* LFPs, can synchronize neurons (????). It is unclear, however, how similar magnitude $V_e$ generated by single action potentials affect population spike timing. Because $V_e$ generated by individual spikes decay quickly with distance and are highly transient, single spike ephaptic coupling is often disregarded (?). However, a theoretical study predicted that single spike ephaptic coupling might significantly alter spike times between a pair of neurons (?). A single action potential can generate both hyperpolarizing and depolarizing $V_e$, dependent on location (??). Ephaptically induced changes to the membrane potentials of nearby neurons show a similar biphasic shape.
It remains unclear how ephaptic potentials and their biphasic signature affect spike timing and network synchronization.

Here, we investigate the effect of single spike ephaptic coupling by first modeling ephaptic coupling between neuron pairs, demonstrating its effects in a small network, and then generalizing pairwise coupling characteristics for an oscillator network. Our results provide a proof of principle that single spike ephaptic coupling synchronizes neurons dependent on neuronal spacing and ephaptic potential shape, and underlies formation of locally synchronous microclusters.

**Glossary**

\[ A \] – Amplitude of rate of ephaptic-like coupling \( g \), \([\mu \text{ms}^{-1}]\)

\[ A_e \] – Peak-to-peak extracellular voltage \( V_e \) at 1 \( \mu \text{m} \), \([\text{mV} \mu \text{m}]\)

\[ A_m \] – Peak-to-peak deflection of membrane voltage \( V_m \) at 1 \( \mu \text{m} \), \([\text{mV} \mu \text{m}]\)

\( \dot{c} \) – Controls the polarity of ephaptic-like potential

\( c \) – Controls the amplitude and polarity of ephaptic-like potential

\( \sigma \) – Parameter combining \( c \) and \( D \)

\( D \) – Dispersion parameter quantifying strength of fluctuations in \( \delta \)

\( d \) – Distance between \( x \) and soma center for NEURON calculations, \([\mu \text{m}]\)

\( d_{m,n} \) – Average minimum distance, used to cluster spike trains

\( \delta_{a,b} \) – Difference in phase between oscillator \( a \) and oscillator \( b \)

\( \delta_\omega \) – Standard deviation of oscillator frequencies in oscillator network, \([\text{s}^{-1}]\)

\( \Delta t_{\text{AP}} \) – Ephaptically-driven change in spike time, measured at peak \( V_m \), \([\text{s}]\)

\( \Delta t_{k,m,n} \) – Smallest time difference from time of spike \( k \) in spike train \( m \) to any spike in spike train \( n \), used in spike train clustering, \([\text{s}]\)

\( f \) – Ephaptic-like potential

\( g \) – Rate of ephaptic-like potential, \([\text{s}^{-1}]\)

\( \phi_i \) – Phase of oscillator \( i \)

\( \phi_e \) – Zero-crossing time of \( f \), \([\text{ms}]\)
$I_{\text{soma}}$ – Membrane currents in the soma, [A]

$\omega_i$ – Frequency of oscillator $i$, [s$^{-1}$]

$\omega_0$ – Mean frequency of all oscillators in oscillator network, [s$^{-1}$]

$N$ – Number of oscillators in oscillator network

$N_s^m$ – Number of spikes detected in spike train $m$

$p^+$ – Probability of up-down ephaptic-like potential

$p(\delta)$ – Probability distribution of phase differences

$R$ – Parameter controlling spacing (density) of oscillators in oscillator network, [$\mu$m]

$r_{ij}$ – Distance between oscillator $i$ and oscillator $j$, [$\mu$m]

$\rho_e$ – Bulk extracellular resistivity, [Ωm]

$S_{m,n}$ – Similarity measure for determining number of clusters

$T_e$ – Zero-crossing time of $g$, [s]

$T_e$ – Refractory period of oscillators, [s]

$V_e$ – Extracellular potential, [mV]

$V_m$ – Membrane potential, [mV]

$v_i$ – Contribution to $V_e$ from straight line segment $i$, [mV]

$v_{\text{soma}}$ – Contribution to $V_e$ from soma, [mV]

$x$ – Location in NEURON model, [$\mu$m]

$z$ – Synchrony statistic

Methods

NEURON simulations

Ephaptic coupling between two neurons. We implemented a reconstructed layer V pyramidal cell model with 176 sections in the NEURON environment, using procedures and parameters of Mainen and Sejnowski (?). This is a multicompartiment model with a high density of Na$^+$ channels in the axon initial segment and hillock. The soma and dendrites contained slow K$^+$ channels, and fast K$^+$ channels were present in the axon and soma. Spontaneous spiking was
achieved by increasing synaptic conductance by 0.2 times the leak conductance and setting the reversal potential to 0 mV in the dendrite compartments \( (? \text{)} \). To achieve repetitive firing without slower dynamics, \( \text{Ca}^{2+} \) currents were removed from all compartments. The resulting membrane currents caused the cell to fire with a regular interspike interval of approximately 15 ms. All membrane currents (capacitive and ionic) were calculated every 0.01 ms. The bulk extracellular resistivity \( \rho_e \) was 400 \( \Omega \text{cm} \).

At location \( x \), the extracellular potential \( V_e(x, t) \) was calculated as the sum of individual potentials \( v_i \) generated by all membrane currents:

\[
V_e = \sum_{i=1}^{N} v_i + v_{soma},
\]

where \( v_{soma} \) is the potential due to somatic currents \( (I_{soma}) \). Since the soma is assumed to be spherical, \( v_{soma} \) can be calculated as

\[
v_{soma}(x, t) = \frac{\rho_e I_{soma}}{4\pi d},
\]

where \( d \) is the distance between \( x \) and the center of the soma. Each model section was approximated as composed of multiple straight cylinders, and total current from the section was uniformly distributed across all cylinders in the section. Individual potentials \( v_i \) were calculated for each cylinder. For full details, see \( (? \text{)} \).

The \( V_e \) generated by one ("stimulating") neuron was applied to a second ("receiving") neuron. This was achieved by setting the extracellular potential of the receiving neuron equal to \( V_e \) using the extracellular mechanism in NEURON \( (? \text{)} \). A unique \( V_e \) was calculated for each section of the receiving neuron, and by calculating \( V_e \) at the appropriate locations \( x \) we could vary the proximity and relative position of the two neurons. Except for modifying \( V_e \), the receiving neuron was implemented in NEURON identically to the stimulating neuron. Without ephaptic stimulation, the receiving neuron generated a spike identically to the stimulating neuron. In the pairwise interactions, the electric potential due to the receiving neuron was not accounted for. Its effect is predicted to be small as the receiving neuron fires during the refractory period of
the stimulating neuron. We neglected the effect of a neuron’s $V_e$ on itself (\?)

**Ephaptically coupled small networks in NEURON.** We additionally implemented ephaptically-coupled networks inside NEURON. Ephaptic stimulation was achieved identically to the above pairwise stimulation. $V_e$ at each section of each neuron was calculated by summing the contributions to electric potential from all neurons except the neuron being stimulated. Networks consisted of 16 identical layer V pyramidal cells arranged in a square grid. Spacing was varied to control the strength of ephaptic coupling. Since we employed neuron spacings that were less than the extent of dendritic arbors, neuron segments could possibly overlap, although in practice a minority of segments did (few than 1/2000 of segment-to-segment pairings). Overlapping segments were not included when calculating $V_e$.

We calculated Pearson correlation coefficients between somatic $V_m$ to quantify synchronization between pairs of neurons in the NEURON network (\?). Neurons were simulated for 500 ms, and $V_m$ from the last half of simulations were used to compute correlation coefficients. Neurons were initialized with different $V_m$, which was randomly assigned between $-70 \text{ mV}$ and $-40 \text{ mV}$. All sections in a given neuron were initialized to the same $V_m$. All other initial conditions were identical between neurons.

**Mathematical analysis of conditions for global synchrony**

**Phase relationship between two neurons.** We constructed an analytical mathematical model consisting of a stimulating neuron ($a$) and a receiving neuron ($b$). Both neurons are modeled as simple phase oscillators with phases $\phi_a$ and $\phi_b$, respectively. $a$ fires tonically with a constant frequency, so that $\dot{\phi}_a$ is constant. $\phi_b$ increases with the same intrinsic frequency, but can be altered due to ephaptic potentials received from $a$, $\dot{\phi}_b = \dot{\phi}_a + cf$ (\(f\) – function representing ephaptic potential shape, $c$ – controls the amplitude and polarity of ephaptic-like potential $f$). The phase difference of $a$ relative to $b$, $\delta_{a,b}$, therefore undergoes the following time evolution:

$$\dot{\delta}_{a,b} = \dot{\phi}_a - \dot{\phi}_b = -c f (\delta_{a,b}),$$

(3)
where \( f \) is \( \delta \)-periodic on the interval \([0, 1)\). \( f \) was specified as a function of \( \delta \) based on qualitative features of our NEURON results, to allow general mathematical conclusions. Quantitative parameters were assumed only in later simulations of network dynamics.

Considering the relationship of \( a \) and \( b \), the horizontal axis of Fig. 2 E corresponds to \(-\delta\) in our formulation, and \( \Delta t_{AP} \) on the vertical axis can be seen as roughly proportional to \(-f\). At a specific zero crossing point \( (\phi_e) \), the biphasic \( f \) changes from positive to negative (for up-down potentials). For \( \delta < \phi_e \), the ephaptic potential from \( a \) leads to a pre-dated firing of \( b \) \( (\Delta t_{AP} < 0) \), which corresponds to a reduction of \( \delta \) \( (f > 0, \text{ for up-down potentials}) \). For \( \delta > \phi_e \), the ephaptic coupling leads to an increase of \( \delta \) \( (f < 0, \text{ for up-down potentials}) \). Assuming a continuous and smooth \( f \) that is 0 only at \( \delta = 0 \) and \( \delta = \phi_e \), this means that for up-down potentials, \( \delta^* = 0 \) is a unique, stable steady state, attracting all initial values except \( \delta = \phi_e \), the location of a unique, unstable steady state. Maintaining the same \( f \), setting \( c < 0 \) captures down-up potentials, \( \delta^* = 0 \) is unstable, and \( \delta^* = \phi_e \) is stable. In summary, the globally attractive, stable steady states are

\[
\delta_{a,b}^* = \begin{cases} 
  c > 0 : & 0, \\
  c < 0 : & \phi_e > 0.
\end{cases}
\] (4)

**Conditions for a network-stable synchronous state.** For a network of \( N \) identical oscillators, now with bidirectional ephaptic-like coupling between all oscillator pairs, the condition for a network steady state is that for all \( a \neq b \) \( (a, b \in \{1, \ldots, N\}) \) the \( \delta_{a,b} \) take on a steady state value \( \delta_{a,b}^* \) simultaneously. Based on the fraction of up-down potentials \( (p^+) \), two extreme cases can be analytically investigated. For \( p^+ = 1 \), all \( c > 0 \), and therefore all \( \delta_{a,b} = \delta_{a,b}^* = 0 \); all phase differences vanish and the network-stable state is perfectly synchronous. For the opposite case, \( p^+ = 0 \), all \( c < 0 \), so

\[
\delta_{a,b} = \phi_e \text{ for all } a \neq b
\] (5)
is the condition for a global steady state. For any two oscillators \((a \text{ and } b)\) from the network,

\[
\delta_{a,b} = \delta_{b,a} \iff \phi_a - \phi_b = \phi_b - \phi_a = \phi_e = 0.5
\]  

(6)

must hold in order to fulfill the condition from Eq. 5. Introducing a third oscillator \((c)\), the possibility of a network-wide steady state can be disproved by the following contradiction with Eq. 6:

\[
\delta_{c,a} = \delta_{c,b} \iff \phi_c - \phi_a = \phi_c - \phi_b \iff \phi_b - \phi_a = 0.
\]  

(7)

**Distribution of phase differences in an ensemble of oscillators.** Let \(p(\delta)\) be the distribution of the phase differences of \(N \to \infty\) oscillators relative to a reference phase \(\phi_0\) (all oscillators and the reference phase have the same intrinsic phase frequency). To add a randomizing influence to the ephaptic-like coupling effects, a Fokker-Planck formalism is used (8),

\[
\frac{\partial p}{\partial t} = \frac{\partial}{\partial \delta} \left[ c f(\delta) p(\delta) \right] + D \frac{\partial^2 p}{\partial \delta^2},
\]  

(8)

where \(D = \text{const.}\) quantifies the strength of fluctuations in \(\delta\). At steady state

\[
\frac{\partial p}{\partial t} = 0 \Rightarrow \frac{\partial}{\partial \delta} [\tau f(p^*)] = -\frac{\partial^2 p^*}{\partial \delta^2},
\]  

(9)

where \(\tau = c/D\). The parameters \(c\) and \(D\) are thus described by the single parameter \(\tau\). By separation of variables

\[
p^*(\delta) = \frac{1}{\Sigma} \exp \left[ - \int_{0}^{\delta} \tau f(\delta') d\delta' \right],
\]  

(10)

\(\Sigma\) is a normalization constant that ensures \(\int_{0}^{1} p^*(\delta) d\delta = 1\). To compute \(p^*(\delta)\), an approximated
piece wise linear $f(\delta)$ function is used (Fig. 4 A, inset),

$$f(\delta) = \begin{cases} 
0 \leq \delta < \phi_e/2 : & 2\delta/\phi_e \\
\phi_e/2 \leq \delta < 3\phi_e/2 : & -2(\delta - \phi_e)/\phi_e \\
3\phi_e/2 \leq \delta < 2\phi_e : & 2(\delta - 2\phi_e)/\phi_e, \\
2\phi_e \leq \delta : & 0.
\end{cases}$$

(11)

The $z$ statistic commonly used to quantify synchrony of phase oscillators then is

$$z = \left| \int_0^1 p(x)e^{i2\pi x} \, dx \right|.$$  

(12)

**Ephaptic-like oscillator network model**

$N$ phase oscillators representing ephaptically coupled neurons were placed at random positions in a square with side length $\sqrt{NR}$. The spacing parameter ($R$) effectively defines the oscillator density, $N/\text{Area} = N/(\sqrt{NR})^2 = 1/R^2$. The phase $\phi_i \in [0, 1)$ of neuron $i$ progresses according to

$$\frac{d\phi_i}{dt} = \omega_i + H\left(\frac{\phi_i}{\omega_i} - T_r\right) \sum_{j=1}^{N} \tilde{c}_{j,i} \frac{A}{r_{ij}} g(\phi_j),$$

(13)

with $i, j = 1, \ldots, N$. The intrinsic frequencies ($\omega_i$) were randomly drawn from a normal distribution centered on $\omega_0$ with a standard deviation of $\sigma_\omega$. The other terms represent ephaptic coupling of other neurons $j$ to neuron $i$, which were summed up to give the overall alteration of $\phi_i$ by ephaptic coupling. $r_{ij}$ is the Euclidean distance between neurons $i$ and $j$. The polarity of the ephaptic-like coupling was set by $\tilde{c}_{j,i} = \pm 1$ (i.e. $\tilde{c}_{j,i} = +1$ for ‘up-down’ or $\tilde{c}_{j,i} = -1$ for ‘down-up’, $c_{j,i} = 0$ was used when $j = i$ to prevent oscillators from coupling to themselves). $\tilde{c}$ is analogous to parameters $c$ and $\bar{c}$ in that all determine the polarity of ephaptic coupling, although $\tilde{c}$ does not control the amplitude of coupling. $\tilde{c}_{j,i}$ was randomly assigned for each pair-wise connection, with a probability $p^+$ that $\tilde{c}_{j,i} = +1$ (e.g. $p^+ = 1$ means that all ephaptic potentials have an ‘up-down’ shape). $H(\phi_i/\omega_i - T_r)$ is a Heaviside function, ensuring that the
oscillator $i$ was not affected by ephaptic potentials during a refractory period of duration $T_r$ after crossing $\phi_i = 1$. Outgoing ephaptic potentials were triggered when $\phi_i = 1$ was crossed. At the same time, $\phi_i$ was reset to zero. The three parameters $N$, $R$, and $p^+$ were changed between our different simulations. The fixed simulation parameters are shown in Tab. 1.

The detailed effect of ephaptic potentials of oscillator $j$ on oscillator $i$ was described by

\[
g(\phi) = \begin{cases} 
0 \leq \phi < \omega_0 T_e / 2 : & +1 \\
\omega_0 T_e / 2 \leq \phi < 3\omega_0 T_e / 2 : & -1 \\
3\omega_0 T_e / 2 \leq \phi < 2\omega_0 T_e : & +1, \\
2\omega_0 T_e \leq \phi : & 0.
\end{cases} \tag{14}
\]

$T_e$ is the time at which the ephaptic potential deflection first returns to 0. The coefficient $A$ expresses the amplitude of ephaptic coupling between oscillators at a distance of 1 $\mu$m, which was derived from our NEURON results. It was assumed that $\phi = 0$ corresponds to the resting potential and $\phi = 1$ to the firing threshold for an action potential. For the layer V pyramidal neuron simulated in NEURON, this corresponds to $\approx 20$ mV difference in membrane potential (Tab. 1). Therefore, the amplitude of the change in $\phi$ inflicted by an ephaptic potential at 1 $\mu$m was $A_m/20$ mV, where $A_m$ describes the peak-to-peak deflection of $V_m$ when receiving and stimulating neurons are offset by 1 $\mu$m, as calculated in NEURON. To derive the ephaptically inflicted rate of phase change, this amplitude was divided by the time necessary to reach the ephaptically inflicted deviation, $T_e/2$. Thus,

\[
A = \frac{2A_m}{T_e \cdot 20 \text{ mV}}. \tag{15}
\]

Simulations were executed by iteration through events (transition points in piece wise linear potentials, $\phi_n = 1$ threshold crossings that reset $\phi_n$ to 0, and end of refractory period), increasing numerical efficiency and inherently eliminating step size problems of finite time step methods (e.g. Euler or Runge-Kutta schemes). It is important to realize that, different from the prior analysis of conditions for synchrony, this oscillator network model was based on continuous time
and the detailed interaction of ephaptically coupled oscillators throughout the entire phase cycle. This treatment was no longer based on changes in phase difference after a whole phase cycle of the stimulating neuron.

Population synchrony was calculated with the $z$ statistic,

$$z = \frac{1}{N} \left\{ \sum_{j=1}^{N} e^{\sqrt{-1} \phi_j} \right\},$$  \hspace{1cm} (16)

where $z = 1$ means complete synchrony (all phases $\phi_j$ are equal) and $z = 0$ means complete asynchrony (uniform distribution of phases).

**Simulation of experiments**

To adapt the oscillator network model to experiments with hippocampal slices, an elongated geometry of the oscillator field was introduced (??). The square area was changed to a rectangular area whose long side is ten times the length of its short side, while preserving the relationship that oscillator density was equal to $1/R^2$ (e.g. Fig. 8 A).

Hierarchical clustering (single linkage algorithm) of the oscillators was executed based on the Average Minimum Distance (AMD) between spike trains (spikes detected at $\phi = 1$ threshold), (??). The AMD between two oscillators $m$ and $n$ was calculated as

$$d_{m,n} = \Theta_{m,n} + \Theta_{n,m} = \frac{1}{N_{ms}^n} \sum_{k=1}^{N_{ms}^n} \Delta t_{k,m,n},$$  \hspace{1cm} (17)

where $\Delta t_{k,m,n}^{m,n}$ is the smallest time difference from the time of spike $k$ in spike train $m$ to any spike in spike train $n$ and $N_{ms}^m$ the number of spikes detected in spike train $m$. The number of clusters was chosen by maximal modularity, using the similarity measure

$$S_{m,n} = 1 - \frac{d_{m,n}}{\max_m(d_{m,n})}.$$  \hspace{1cm} (18)
Results

Biphasic $V_e$ with mV amplitude around a spiking neuron

We used a previously published NEURON model of a layer V pyramidal neuron to investigate ephaptic coupling from a “stimulating” to a “receiving” neuron (Fig. 1 A). As per Holt and Koch (⑴) the model was modified to produce an action potential. We calculated the extracellular electric potential ($V_e$) resulting from membrane currents in the stimulating neuron. The action potential began at the soma hillock and axon initial segment, sections of the neuron with Na+ channel densities 100-1000 times greater than other areas, and propagated to the dendrites.

The polarity of membrane currents differed between neuron sections (Fig. 1 B). For example, membrane currents in the soma (and hillock and initial segment) were initially negative, while currents in the dendrites were initially positive. As $V_e$ is the superposition of potentials generated by all currents, $V_e$ could be initially positive or negative depending on location (Fig. 1 C, D). For example, $V_e$ calculated close to the soma was dominated by perisomatic currents in the hillock and initial segment (Fig. 1 C, solid) as compared to $V_e$ close to the apical trunk (Fig. 1 C, dashed).

The amplitude of $V_e$ had an approximately inverse relationship with distance $r$, measured from the centroid of the initial segment and hillock (Fig. 1 D, E). For $r > 100 \mu m$, peak-to-peak $V_e$ was well approximated as $1/r$, while locations closer than 100 $\mu m$ had larger magnitude $V_e$. Sampling locations in three dimensions around the initial segment and hillock, the coefficient of best fit of peak-to-peak $V_e$ was $A_e = 7.7 mV \mu m$, such that peak-to-peak $V_e \approx A_e/r$. Thus we note three characteristics of $V_e$: it can be of large amplitude (> 1 mV), have both depolarizing and hyperpolarizing phases, and has approximate $1/r$ spatial dependency.

The spiking dynamics of nearby neurons can be linked by ephaptic coupling

We next sought to characterize how $V_e$ around a spiking neuron affected $V_m$ in a nearby neuron. Because $V_m = V_i - V_e$, ephaptic coupling deflected membrane voltage $V_m$ in the receiving neuron with the opposite polarity to $V_e$ (Fig. 2 A, B). For this interaction we did not include ephaptic
effects on the stimulating neuron and considered only one way stimulation. Fig. 2 A shows $V_e$ calculated 5 $\mu$m from the stimulating neuron hillock. We sampled the peak-to-peak deflection of $V_m$ in the receiving neuron due to ephaptic stimulation at multiple offsets between the two neurons. Analogous to $A_e$, we computed the coefficient of best fit ($A_m = 1.5$ mV$\mu$m), such that peak-to-peak $V_m \approx A_m/r$. Due to the neurons’ complex topologies there was some variation in peak-to-peak $V_m$ deflection at a given distance (the deflection in Fig. 2 B shows a high amplitude example for $V_m$ deflection at 5 $\mu$m), although in general $V_m$ deflection was well fit with a $1/r$ spatial dependency.

Single spike ephaptic coupling altered spike timing in the receiving neuron (Fig. 2 C). When a 1.5 mV $V_e$ was delivered approximately 1 ms before the peak of the spontaneously generated spike in the receiving neuron (arrow), the spike was advanced by close to 0.4 ms. In general, biphasic $V_e$ with an initial negative part occurring at the hillock led to earlier spike times (solid traces), while an initially positive $V_e$ occurring at the hillock delayed spike times (dashed). Reversing the polarity of $V_e$ at every location of the receiving neuron, and delivering it at the same time, resulted in delayed spike times rather than advanced spike times (Fig. 2 D).

Due to $V_e$ being biphasic, spike timing effects were also dependent on the time at which $V_e$ stimulation was delivered. Changes to $V_e$ by an initial negative part could advance spike times, as the initial negative part of $V_e$ depolarized the membrane potential and triggered a spike. Biphasic traces of $V_e$ with initial negative and subsequent positive part are here referred to as “up-down”, as this is the shape of their effect on $V_m$ in the receiving neuron. The same up-down stimulation delivered 2 ms earlier had the opposite effect, as the subsequent positive part of $V_e$ hyperpolarized $V_m$ and delayed the spike time (Fig. 2 E, solid). Coupling by a biphasic $V_e$ with the opposite polarity (“down-up”), advanced spike times when delivered a few ms before the spike, and delayed spike times when delivered directly before the spike (Fig. 2 E, dashed).
Global synchrony and microclusters emerge in small, ephaptically coupled neuronal networks

We extended the NEURON simulations into a network of neurons that were coupled only ephaptically; again no synaptic or other coupling was implemented. Neurons were organized in a square laminar grid (Fig. A). When spacing between neurons was changed, distinct dynamic phenomena could be observed. At large distances, ephaptic effects were negligible and neuron firing was asynchronous, as measured by small pairwise correlations between somatic $V_m$ (Fig. A). Reduced spacing, e.g. 10 μm, resulted in synchronization between a majority of model neurons (Fig. B). Spacing closer than 5 μm resulted in local clusters of synchronous neurons (Fig. C).

Persistent network synchrony requires homogeneous and specific ephaptic coupling profiles

Because ephaptic potentials are biphasic, an ephaptic potential from one neuron can increase or decrease the phase of another neuron, dependent on their relative phases. We used an analytic model to outline how the shape of the ephaptic potential – up-down or down-up – contributed to synchronization. We first studied two tonically firing neurons ("stimulating" and "receiving" neuron, modeled as phase oscillators) with equal intrinsic firing rates. The firing rate of the stimulating neuron was constant, and therefore independent of the activity of the receiving neuron. The receiving neuron received ephaptic potentials from the stimulating neuron, which altered the receiving neuron’s phase progression. Specifically, for up-down potentials the stable steady state existed at a phase difference of zero, while for down-up potentials the stable steady state was non-zero and equal to the zero-crossing time $\phi_e$. See Methods for a full description. Thus, dependent on the ephaptic potential shape, the two neurons would synchronize or attain a persistent, non-zero phase difference.

For networks of three or more neurons, the shape of the neuron-to-neuron coupling function determines the qualitative phase difference dynamics on the network level. Specifically, a network with only up-down ephaptic potentials has a network-stable steady state in which all neurons are
fully synchronized. In contrast, we mathematically proved that a network with only down-up potentials can not have a network-stable steady. This finding implies that networks with mostly up-down shape potentials would tend towards increased synchrony, while networks with mostly down-up potentials should undergo accelerated desynchronization.

To further investigate this dependence of synchrony on \( p^+ \), we determined phase difference distributions and synchrony in networks with \( N \to \infty \) neurons and stochastic fluctuations in the phase differences. A network with up-down potentials indeed showed an accumulation close to a phase difference of 0 (Fig. 3 A). A network with down-up potentials showed a displacement of the distribution away from zero phase difference, indicating again an active desynchronization (Fig. 3 B). In summary, the fundamental shape of the ephaptic potentials introduces an asymmetry in the effects of ephaptic coupling between pairs of neurons on the microscopic level, which feeds into the macroscopic behavior of the neuronal network. For increasing strength of ephaptic coupling, up-down potentials lead to a stronger synchrony increase; down-up potentials increasingly drive desynchronization (Fig. 3 C).

**Emergent behaviors in oscillator networks depend on spatial distribution**

We assessed the relevance of ephaptic coupling in a spatially distributed network of phase oscillators, which serve as simplified representations of ephaptically coupled neurons. The reduced numerical workload of simulating an oscillator network allowed an extensive assessment of larger networks, which was not feasible in NEURON. Connections between the oscillators mimicked ephaptic coupling in three ways: connections took effect in a temporally distributed manner and were biphasic, coupling amplitude scaled with the distance between oscillators as \( 1/r \), and each oscillator was coupled to every other. Examples of the biphasic ephaptic potentials are shown in Fig. 4 A (inset). Their effects on phase progression (Fig. 4 C) are defined in Eqs. 11 and 13. Where known, we assigned model parameters in accordance with literature and common values (Tab. 1). The following parameters were varied between simulations: \( N \), the number of oscillators; \( R \), the distance parameter which sets the density of oscillators and thus also their spacing; and \( p^+ \), the probability that a given ephaptic connection was up-down (as
opposed to down-up). We used the $z$ statistic to indicate population synchrony ($z = 0$ means full asynchrony, $z = 1$ full synchrony).

We found that increasing $N$ and decreasing $R$ led to transitions from asynchronous to synchronous behavior. The transition specifically required a predominance of up-down ephaptic potentials: down-up-dominant and balanced networks did not synchronize ($p^+ = 0.0$ and $p^+ = 0.5$, Fig. 5 A, B), while up-down dominant networks did ($p^+ = 1$, Fig. 5 C). This is in agreement with our earlier predictions of how the qualitative shape of the individual ephaptic potentials determines the establishment or loss of network level synchrony. For intermediate $R$ values, the degree of synchrony was largely dependent on initial conditions (Fig. 5 C).

Closer investigation of the relevance of initial conditions demonstrated a “critical slowing down” of the network’s $z$ dynamics for intermediate $R$. In systems with critical behavior, typically two stable states are attainable by subparts of the system. These subparts can successively entrain larger parts of the overall system, thus leading to global dominance of one stable state. Once a stable state has reached global dominance, it can persist for periods significantly exceeding life times of stable states in subparts of the system. In the oscillator network simulation, global dominance of the asynchronous state is indicated by $z = 0$, and global dominance of the synchronous state by $z = 1$. For low $R$, global asynchrony disappears rapidly and global synchrony persists as a stable global state (Fig. 6 A). Subgroups of oscillators could only stably attain synchrony. Accordingly, no critical slowing down occurs. Instead, the entire network rapidly departs from $z = 0$ initial conditions, frequently attains $z = 1$ within seconds, or remains at $z = 1$ initial conditions. For intermediate $R$, synchronous as well as asynchronous initial conditions persisted for several seconds (Fig. 6 B). Synchrony as well as asynchrony between oscillators are two possible stable states in subparts of the network. Once the whole network was entrained into the synchronous state, emergence of asynchrony became highly unlikely, and vice versa. Because the initial conditions were such network-wide, asynchronous ($z = 0$) or synchronous ($z = 1$) states, these initial conditions persisted for several seconds. For higher $R$, synchrony was lost for all initial conditions (Fig. 6 C). In this case, synchrony in subgroups of oscillators was not a stable state. Thus, only one stable state was possible in
such subgroups, and no critical slowing down could be observed. The network rapidly attained $z = 0$, irrespective of initial condition.

Scanning a range of $R$ in more detail showed three major regimes. Below $R \approx 10 \mu m$, the firing rate was markedly elevated above the oscillators’ intrinsic firing rate ($\approx 20 \text{s}^{-1}$, regime A; Fig. 7 A). An elevated synchrony ($0.5 \leq z < 1$) was present, but full synchrony was not attained. For $R \approx 10 \mu m$, the firing rate had dropped to almost the intrinsic firing rate (Fig. 7 A), while the whole neuronal population was synchronized (regime B; Fig. 7 B). Increasing $R$ beyond $10 \mu m$ led to a reduction of $z$ over the course of the simulation (regime C). To assess how long a $z$ value taken on at a given point in time persisted after this point, we calculated the autocorrelation time ($\tau_{AC}$) of the $z$ traces. Computing the autocorrelation of $z$ and calculating the characteristic exponential decay rate of the resulting autocorrelation function yields $\tau_{AC}$, which is a common statistic for analyzing persistence in a time series (?). $\tau_{AC}$ increased up to a maximum of $\approx 15 \text{s}$, indicating that specific $z$ values persisted for times that exceed the time scale of individual oscillator periods by several orders (Fig. 7 C). For $R \geq 80 \mu m$, the average $z$ was close to 0, and $\tau_{AC}$ took on a constant value of approximately $2.5 \text{s}$.

The dynamics in regimes B and C seem generally in line with our prior reasoning: below a critical $R$, the population synchronized spontaneously, and desynchronized spontaneously above a critical $R$. An alternative explanation would be that, for increasing $R$, the development of synchrony took increasingly long: Below $R \approx 80 \mu m$ synchrony would be attained before the simulation finished, above $R \approx 80 \mu m$ synchrony would have taken longer than the simulation time; for increasing $R$, the development of global synchrony would have taken longer, leading to an increased $\tau_{AC}$. Because simulating for a longer time could never rule out this interpretation, we executed the same simulations, but used perfectly synchronous initial conditions. We found that regime A also exhibited increased firing rate and intermediate $z$ values as observed before (Fig. 7 D, E). In regime B synchrony was maintained throughout the simulation, leading to $z = 1$, while synchrony was spontaneously lost throughout regime C (Fig. 7 E). The loss of synchrony was more pronounced for increasing $R$, indicating a more rapid decrease of $z$ after the simulation is initialized. Lastly, a slight increase in $\tau_{AC}$ was visible when the transition
from regime B to regime C was approached (Fig. 7 F). This indicates occasional reductions of $z$ throughout the simulation, which occurred on a somewhat slower time scale than the individual neurons’ intrinsic firing rate.

In summary, we found three $R$-dependent regimes: (A – sub-critical regime) markedly accelerated firing rate, and intermediate synchrony; (B – critical regime) slightly accelerated firing rate, spontaneous emergence of synchrony across the entire population, and persistence of states of synchrony or asynchrony over extended periods of time; (C – super-critical regime) firing at individual neurons’ intrinsic firing rate, spontaneous loss of synchrony. Regimes B and C are explicable by our prior reasoning. A network stable, synchronous state was established and lost dynamically, which became more pronounced for larger amplitudes of the ephaptic potentials. In regime A, however, we noticed indications of short range synchronization, which could not be assessed using a global measure of synchrony such as the $z$ value.

Global and microcluster synchrony emerge in an elongated neuronal field when neuron density is increased

We adapted our oscillator model to the elongated geometry of neuronal fields seen in recent experiments with mouse hippocampal slices. In this geometry, we assessed the development of synchrony in microclusters for different values of the distance parameter $R$ (?). For $R$ values below those that show $z \approx 1$ (sub-critical), the neuronal field separated into localized clusters of synchrony; transient synchrony between the local clusters occurred (Fig. 8 A and B). For $R$ values that show $z \approx 1$ (critical), global synchrony throughout the neuronal field was seen (Fig. 8 C); clusters spanned large parts of the neuronal field and were not as clearly separated any longer (Fig. 8 D). For $R$ values exceeding the range in which $z \approx 1$ (super-critical), no clear pattern of global or local synchrony emerged (Fig. 8 E); correspondingly, random cluster associations occurred, which spanned the entire neuronal field with no apparent spatial order (Fig. 8 F). A more systematic assessment for different values of $R$ confirmed these observations as general patterns (Fig. 8 G). For low $R$ values ($R < 10 \mu m$), few clusters (< 10) occurred, which spanned only small fractions of the neuronal field’s length. For increasing $R$ ($10 \mu m < R < 40 \mu m$), even
Global and Microcluster Synchrony via Ephaptic Coupling

fewer clusters occurred (< 5), which spanned a large part of the neuronal field’s length – as was the case when global synchrony was established within the neuronal field. For higher $R$ values ($R > 40 \mu m$), the number of clusters increased and the clusters spanned large parts of the neuronal field – as observed in Fig. 8 F. Exclusively for $R$ values that led to microclustering, the average firing rate within a cluster increased with the number of oscillators within a given cluster (Fig. 8 H).

Discussion

Functional relevance of single spike ephaptic coupling

We demonstrated that single spike ephaptic coupling could significantly affect spike timing between pairs of model neurons, both in the relatively realistic NEURON environment and a simplified oscillator network. Electric potentials ($V_e$) around a spiking neuron should, by the laws of electromagnetism, affect charged ions and the activity of nearby neurons. However, the effects are generally low magnitude ($V_e < 1 mV$), transient (< 10 ms) and, due to the radial symmetry of $V_e$, nonspecific. For these reasons, the functional relevance of single spike ephaptic coupling are questioned (?). Despite such reservations, recent experiments performed by Anastassiou et al. (?) and Frohlich and McCormick (?) showed that sub-mV changes to $V_e$ can increase synchronization. These stimulating potentials were of similar or lower magnitude to those produced around a single spiking pyramidal neuron (??).

Aside from ? most previous studies of cortical ephaptic coupling used low-frequency (e.g. $1 s^{-1}$) LFP-like stimulating potentials (????). However, neurons are also subject to higher frequency extracellular voltages from single spikes. Intracellular recordings of mouse hippocampal slices show that the fields around a single spiking neuron cause “spikelets”, biphasic voltage deflections, in intracellular recordings of nearby neurons that last at most 10 ms (?). While these spikelets are indeed transient, we showed here that $V_e$ of their magnitude and duration could nevertheless affect spike timing when the receiving neuron is close to threshold (Fig. 2) and synchronize ephaptically-coupled model networks (Figs. , 5-8). For symmetric biphasic
spikelets, as in our model, the effect of ephaptic coupling is thus dependent on the phase of the receiving neuron being close to threshold. This phase-dependence increases the effective specificity of single spike ephaptic coupling. Areas such as the hippocampus have relatively high neuronal densities, increasing the likelihood that a neuron in its “receptive” phase (close to threshold) is in the relevant spatial proximity.

Relevance of profile and distribution of ephaptic-like potentials

Our simplified oscillator network model and simulated networks within NEURON demonstrated that single spike ephaptic coupling could lead to increased synchronization. Additionally, we made testable predictions about the role of the shape of $V_e$ (up-down vs down-up) and how synchronization and neuronal clustering vary as a function of neuronal density. Since a predominance of up-down type ephaptic coupling ($p^+ \approx 1$) was required for the occurrence of synchrony (Figs. 5) we wondered if different geometric arrangements of neurons are more likely to yield $p^+ \approx 1$ and thereby promote synchrony. In our model of a layer V pyramidal cell, the somatic region (soma, hillock, initial segment) produced conditions for $p^+ = 1$ via large contributions from Na$^+$ currents (initially negative $V_e$) followed by slower K$^+$ currents (subsequently positive $V_e$). Fields around the dendrites had opposite polarity ($p^+ = 0$). However, since $V_e$ around the soma was at least an order of magnitude greater than dendritic $V_e$, significant ephaptic coupling strengths were limited to a zone of $p^+ = 1$ around the soma.

Although the shape of the extracellular potential is dependent on the site of action potential initiation (?), empirical recordings and simulations suggest the perisomatic region is the dominant location for $p^+ \approx 1$ (?). A laminar organization, as seen in the cortex and hippocampus, aligns neurons’ $p^+ = 1$ zones and excludes $p^+ < 1$ factors from this region, thereby promoting ephaptic synchronization. Other properties of pyramidal cells, such as their elongate shape that can span up to 1 mm, make them more sensitive to extracellular potentials as compared to other cell types (?). Therefore pyramidal cells organized in a laminar structure, such as in the hippocampus, may be especially susceptible to synchronization from ephaptic coupling.
Ephaptic-like coupling can explain the emergence of synchronized microclusters

For the lowest $R$ values we investigated in our oscillator network, ephaptic-like coupling was strong enough to allow the establishment of locally synchronized microclusters (Figs. 7, 8). Within microclusters, the firing frequency was higher in bigger clusters. Also, clusters transiently aligned their firing patterns with those of other clusters. In dentate gyrus slices from epilepsy model mice where synaptic and gap junction coupling was blocked, the same observations were made (?). Further, the neurons were driven into spontaneous firing by a high extracellular potassium concentration ($[K]=7.5$ mM), matching our model assumptions. We also saw locally synchronized clusters of ephaptically coupled neurons within our NEURON network simulations. These clusters arose spontaneously from asynchronous initial conditions. While the mechanism of microcluster formation was unclear in the experimental study of Feldt Muldoon et al. (?), we demonstrated here that ephaptic coupling is sufficient to explain many details of the experimental observations.

Neuronal spacing and epileptogenesis

Dudek and co-workers suppressed all synaptic communication in rat hippocampal slices consisting of pyramidal neurons, after which they proceeded to control the extracellular volume via control of extracellular osmolality by membrane-impermeant solutes or low osmolality medium (??). Reduction of extracellular volume (corresponding to $R$ reduction in our oscillator model) reproducibly increased the frequency of occurrence of epileptiform dynamics, while increase of the extracellular volume ($R$ increase) abolished occurrence of epileptiform dynamics. These findings by Dudek et al. establish that, under conditions of suppressed synaptic coupling in laboratory experiments, spacing between neurons (as altered by volume compression and expansion) controls the occurrence of epileptiform dynamics on the level of neuronal networks. Our model results – based solely on ephaptic coupling – demonstrate a sufficient and specific mechanism for these observations.

The findings of Dudek et al. do not answer whether synaptic, volume compression-independent
mechanisms take precedence over these non-synaptic mechanisms in humans under live conditions, and how this impacts actual epileptic episodes. Haglund and Hochman investigated a group of patients suffering from cortical and mesial temporal lobe epilepsy for their reaction to furosemide and mannitol administration; administration of furosemide and mannitol increases water content and volume of the extracellular fluid (corresponding to $R$ increase in our model) (?). In agreement with the earlier laboratory findings, mannitol and furosemide administration suppressed the spontaneous occurrence of electrical spikes, the capability of external induction of epileptiform discharges, and the spread of epileptiform activity.

**Hysteresis of ephaptically mediated synchrony**

Our simulations showed a critical $R$ regime where the asynchronous and the synchronous states persist for prolonged periods once they are established. This could explain experimental observations of prolonged epileptiform and desynchronized phases, without the need to invoke additional slower processes such as changes in the extracellular fluid composition (?).

**Model limitations**

We note a number of limitations in our NEURON and oscillator treatments. First, our NEURON simulations were based on a single type of neuron. It is therefore not clear how far our findings can be generalized to other neuron types. Given that ephaptic coupling mostly advances or delays existing spikes, it’s likely that results here are dependent on similar intrinsic firing rates between model neurons. Second, we assessed synchronization via ephaptic coupling and disregarded all other modes of coupling. This reflects the conditions of the experiments explained by our model. This does not, however, address the dynamic interplay between ephaptic and other modes of coupling (e.g. synapses and gap junctions) in in vivo neuronal networks. Third, the small population of neurons and the simplified two-dimensional rectangular architecture fall short of the geometric complexity of real neuronal architectures. Finally, our model assesses ephaptic coupling only as a physical mechanism, not as an aspect of an information processing system. It remains largely unclear how ephaptic coupling and the resulting synchrony integrate.
with the information processing by neuronal networks.

We used extracellular potentials with a large amplitude – our value for $A_e$ may be larger than in other simulations (e.g. ?). The layer V pyramidal cell we model likely produces extracellular potentials with higher than average amplitude. It is also possible that experimental measures of extracellular voltage are artificially lowered by scarring around the electrode. Further, both the positive and the negative part of $f(t)$ have the same magnitude, while this is not the case for most extracellular action potentials (?).

**Comparison with existent models**

The piece wise linear approximation used in the oscillator network model captures the biphasic shape of the extracellular potential, but not the detailed nuances of the potentials and their dependence on relative neuron position. Together with the decision to model neurons as simple phase oscillators, this is a significant reduction of complexity and realism compared to the physically realistic NEURON simulations. This reduction in complexity made it feasible to treat larger networks. In spite of the reduced realism, our phase oscillator models demonstrated several principles of ephaptic coupling as a mechanism for neuronal synchrony and explained several experimental observations in sufficient mechanistic detail. The observation of global synchrony and synchronized microclusters at different densities of oscillators was also confirmed in NEURON simulations.

A previous study by Park et al. (?) provides complementary insights, addressing the coupling functions between a pair of neurons in more detail. Park et al. first simulated a pair of two-compartment neuron models that are coupled via ephaptic and synaptic connections to derive very detailed coupling functions for a phase oscillator model of the pair of neurons (?). Accordingly, their approximation successfully explains detailed phase-locking patterns observed in the compartment model (?). Thus, for the long-term dynamics of two coupled neurons, Park et al. give a more detailed account.

A number of mathematical models of epileptiform behavior are based on changes in synaptic connections (see ? for review). In one class of models, “rewiring” of the normal synaptic network
is assumed as the main mechanism. Either positive feedback connections (potentiating neuronal activity) are added to the network, inhibitory connections in the network (suppressing excessive activity) are removed, or the neuronal network topology is altered. For example, ? constructed a realistic “virtual dentate gyrus” model. Increasing sclerosis of the dentate gyrus was mimicked by (1) increasing removal of neurons with long-range connections and (2) increasing “sprouting”, the introduction of new synaptic connections. With increasing sclerosis, network topology and dynamics underwent a biphasic change. Intermediate degrees of sclerosis increased long-range connectivity (“small world” network topology) and lead to hyper-excitability of the network, thus supporting epileptogenesis. Severe sclerosis, however, removed long-range connections to such an extent that it broke down effective long-range connectivity, thus preventing long-range spread of activity and hyper-excitability. In another realistic dentate gyrus model based on synaptic connections that was investigated by ?, positive feedback connections, specifically within hubs of granule cells, established epileptogenic microcircuits. Similarly, a simplified model based on a small network constructed by ? could change from quiescence to excitability to epileptogenic behavior by network structural changes. Both models by ? and ? predicted traveling waves of neuronal hyperactivity. In experiment, however, spatially stationary clusters of synchrony and hyperactivity are observed (?).

Berzhanskaya et al. (?) constructed small networks representing hippocampal layers using NEURON. Significant geometric realism was considered in constructing these networks, and pyramidal neurons as well as interneurons were included in the simulation. Model assumptions regarding specific ionic currents, synapse distribution, and the response to external electrical fields were assessed in single neuron experiments (?). This work therefore addresses many of the simplifications we made in our study. However, ephaptic coupling was not considered.

Importantly, experimental studies show that with all synaptic connections silenced, seizure-like synchrony can exist in hippocampal slices (?). Thus, other mechanisms such as ephaptic coupling are likely involved in epileptiform behavior (??). To our knowledge, our study represents the first network model investigating synchronization solely via single spike ephaptic coupling.
Future directions

Additional NEURON simulations realistically implementing extra- vs. intracellular volume changes would deepen our understanding of the connection between volume changes and epileptiform dynamics in neuronal populations. We interpreted $R$, a primary parameter governing the existence of global and cluster synchrony in our simulations, as an effective distance between close-by neurons’ membranes. Presumably, changes in the extra- vs. intracellular volumes would alter the distance between neurons’ membranes, which in turn alters $R$. Following this assumption, we could explain experimental and clinical observations. However, future simulations should be executed where the geometry of the cell membrane is altered to fully assess this hypothesis.

In vitro experiments with slices of neuronal tissue that showed global and cluster synchrony can be extended to assess the effect of extra- vs. intracellular volume changes. Global and cluster synchrony in these experiments was governed by two parameters: addition of positive ions increased the general neuronal activity, while an epilepsy-disposing mutation induced cluster synchrony. Our simulations along with previous experimental and clinical results suggest that the extra- vs. intracellular volume (adjustable via, e.g., sugars that increase medium osmolality) would exert additional control over global and clustered synchrony.

Lastly, our study suggests synchrony caused solely by ephaptic coupling will be less likely where neurons are organized less rigidly into a laminar sheet. Synchrony is often studied in tissues with laminar organization of neurons, because only here electroencephalograms (EEGs) can effectively detect synchrony. Imaging individual neurons in a larger field, however, could confirm or falsify the hypothesis that more irregularly structured neuronal tissues are less likely to develop synchrony solely due to ephaptic coupling.

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Parameter | Name | Value (unit)
--- | --- | ---
A | Ephaptic effect amplitude \(^a\) | 0.06 (\(\mu m \cdot ms^{-1}\))
Spike threshold | Action potential threshold \(^b\) | 20.0 (mV)
\(T_e\) | Time until ephaptic potential returns to 0 the first time \(^c\) | 2.5 (ms)
\(T_r\) | Refractory period \(^d\) | 3.0 (ms)
\(\omega_0\) | Frequency mean | 20 (s\(^{-1}\))
\(\sigma_\omega\) | Frequency standard deviation | 0.20 (s\(^{-1}\))

Table 1: Oscillator network model parameters. \(^a\) Eqn. 15. \(^b\) (?). \(^c\) Numerics. \(^d\) (?)

Figure 1: Characterizing electric potentials around a spiking neuron. A) Multicompart-ment, 3D layer V pyramidal cell model (?). Duplicate model cell is shown in gray. B) Summed membrane current \(I_{tot}\) for all compartments of the apical trunk, soma (including the hillock and initial axon segment), and the basal dendrites. C) Two characteristic extracellular potentials \(V_e\). One is calculated at a distance 10 \(\mu m\) from the hillock (black) and the other approximately 80 \(\mu m\) from the soma near the apical trunk (dashed). The peak-to-peak \(V_e\) close to the apical trunk is highlighted. D) \(V_e\) for 30 locations in the \(x, y\) plane of the neuron in A. Each trace is 3 ms in duration, and the scale bar is 1 mV. Traces are plotted at the spatial locations at which they were calculated. The soma is centered at \((0,10)\). E) Peak-to-peak amplitude of \(V_e\) as a function of distance from the hillock. Locations were sampled along the \(x, y,\) and \(z\) axes at regular intervals. The \(1/r\) best fit line (least-squares) and equation are shown.

Figure 2: Ephaptic coupling in NEURON. A) Stimulating potential \(V_e\) calculated 5 \(\mu m\) from stimulating neuron hillock. Additional traces were created by multiplying \(V_e\) by coefficients 0.5 (solid thin), 0 (solid thick), -0.5 and -1 (dotted). B) Ephaptic stimulation while receiving neuron is at resting membrane voltage. Receiving and stimulating neurons were separated by 10 \(\mu m\). Arrow shows start of ephaptic stimulation. C) Ephaptic stimulation while receiving neuron is close to threshold. Identical ephaptic stimulation as in B. The arrow shows the start of ephaptic stimulation. Up-down \(V_m\) deflections advance the spike, while down-up delay it. Time \(T = 0\) corresponds to the peak of \(V_m\) with no ephaptic stimulation (nil). D) Quantification of C. Data points are generated by multiplying stimulating \(V_e\) by a scalar coefficient between 1 and -1, as in A-C. E) Effect of varying start of ephaptic stimulation (arrow in A-C) on spike timing. Both up-down and down-up \(V_m\) deflections can advance and delay the spike. Arrow in E corresponds to arrows in A-D.

Ephaptically coupled network in NEURON. A) Ephaptically-coupled network of 16 neurons arranged in a square 4x4 grid with 5000 \(\mu m\) spacing. Top: Schematic of laminar network. Neurons plotted to scale. Center: Grey-scale plot of \(V_m\) for all 16 neurons. \(V_m\) color code is shown on very right of the figure; action potential peaks are white lines. Simulations were run in the NEURON environment. Bottom: Pairwise correlations between all neurons in the network (Pearson correlation coefficient). B) Same as panel A, but for a network with 10 \(\mu m\) spacing. Top: For clarity, only somas are shown (not to scale). C) 3 \(\mu m\) spacing.
Figure 3: **General conditions for synchrony.** A, B) Different effect of up-down vs. down-up ephaptic potentials ($\tau > 0$ vs. $\tau < 0$, respectively), coupling strength (absolute magnitude of $\tau$), and different temporal profiles ($\phi_e$) on synchrony of the phase difference distribution ($p(\delta)$). $\tau = +5000$ in panel A, $\tau = -5000$ in panel B. $\phi_e = 0.01, 0.02, \ldots, 0.1$ are indicated by shading from black to gray. C) Mean $z$ value for different $\tau$ ($\phi_e$ same as in other panels.)

Figure 4: **Network model schematic for three coupled neurons.** A) Geometric arrangement and ephaptic potentials defining the connections. The amplitude $A/r_{b,c}$ is larger because $r_{b,c} < r_{a,b}$. B) Oscillator phases without coupling ($R \to \infty$). C) Oscillator phases with coupling.

Figure 5: **Occurrence of synchrony in the network model.** The $z$ statistic of synchrony depends on the number of neurons ($N$), distance parameter ($R$), and the fraction of up-down potentials ($p^+$). 12 simulations per data point, $z$ calculated from 2500 to 3500 ms, shown are arithmetic means. Initial phases were either uniformly distributed (thin lines) or fully synchronized (heavy lines). $p^+$ indicated above panels A), B), and C).

Figure 6: **Hysteresis in population synchrony and asynchrony.** $N = 100$ oscillators were started with all $\phi = 0$ (grey lines) or with uniformly distributed $\phi$ (black lines). A) For low $R$, all simulations develop towards synchrony ($z = 1$). B) For intermediate $R$, the initial synchrony level persists. C) For high $R$, all simulations approach asynchrony ($z$ close to 0). Simulation parameters: $p^+ = 1$, $N = 100$, square geometry was used.

Figure 7: **Influence of distance parameter $R$ on global synchrony.** $N = 200$ oscillators with only up-down potentials ($p^+ = 1$) was initialized with random phases (A-C) or synchronized phases (D-F). Statistics calculated are average frequency of individual neuron spikes ($f$, panels A and D, gray line indicates intrinsic frequency of $20\text{s}^{-1}$), synchrony ($z$, panels B and E), and the autocorrelation time of the $z$ time course ($\tau_{AC}$, panels C and F). An elongated geometry was used, simulations run for up to $N \cdot 6000$ iterations or until 40 s elapsed time, statistics calculated for $t \geq 2\text{s}$. (Gray boxes) individual simulation runs, (solid lines) arithmetic mean of individual simulations.

Figure 8: **Distance parameter $R$ controls global and microcluster synchrony in simulated hippocampal slice experiments.** A) Raster plot of $N = 150$ phase oscillators with $R = 5\mu$m; oscillators sorted by increasing $y$ coordinate. B) Neuron locations corresponding to A (gray crosses) with indications of detected cluster membership (polygons enclose clusters, dots indicate cluster membership). C, D) Same as A and B, respectively, but for $R = 35\mu$m. E, F) Same as A and B, respectively, but for $R = 150\mu$m. G) Number of detected clusters over a range of $R$ (solid lines – mean, dashed lines – 10th and 90th percentile; $N = 200$, 30 simulations per $R$ value). H) Span of clusters over a range of $R$. The span of a cluster is the $y$ difference between the two neurons located most distal along the $y$ axis, and is given as a fraction of the overall span of the whole neuronal field (same line styles and simulation parameters as G). I) Average firing rate across cluster member neurons vs. cluster size (number of neurons within cluster) for different $R$ ($N = 200$, 30 simulations per $R$ value). $p^+ = 1$, $\phi \sim U$ for all simulations.
A. Diagram of a neuron with labels for distal dendrites, apical trunk, basal dendrites, soma, hillock, initial segment.

B. Graph showing total current (nA) over time (ms) for apical trunk, soma + initial segment, and basal dendrites.

C. Graph showing total current (nA) and V_e (mV) over time (ms) for near soma and near apical trunk.

D. Grid of small diagrams showing variations in y (µm) and x (µm).

E. Graph showing peak-to-peak V_e, V_{p2p} vs r, distance from hillock (µm), with equation V_{p2p} = A_e/r and A_e = 7.7 mV µm.
A \( \phi_a(t) \)

B \( r_{a,b} = r_{b,c} = r_{c,a} = \infty \)

C \( r_{a,b} = r_{a,c} = 8 \mu m, r_{b,c} = 4 \mu m \)
(A) $p^+ = 0$

$N=25, \phi\sim U$
$N=50, \phi\sim U$
$N=75, \phi\sim U$
$N=100, \phi\sim U$
$N=25, \phi=0$
$N=50, \phi=0$
$N=75, \phi=0$
$N=100, \phi=0$

(B) $p^+ = 0.5$

(C) $p^+ = 1$
\[ \phi_0 \sim U \]

\[ \phi_0 = 0 \]