A Path to Synchronized Rhythmicity in Large-Scale Neural Networks

Vladimir Shusterman

and

William C. Troy

Cardiovascular Institute and Department of Mathematics
University of Pittsburgh, Pittsburgh, PA

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Address for correspondence:
Vladimir Shusterman
University of Pittsburgh
200 Lothrop Street, Room B535,
Pittsburgh, PA, 15213
Phone: (412) 383-7096
FAX: (412) 647-7979
E-mail: shustermanv@msx.upmc.edu
Abstract

In large-scale neural networks the emergence of global behavioral patterns, manifested by electroencephalographic activity, is driven by self-organization of local neuronal groups into synchronously functioning ensembles. However, the laws governing such macrobehavior and its disturbances, in particular epileptic seizures, are poorly understood. Here we use a mean-field, population network model to describe (i) a baseline state of resting physiological activity, (ii) the evolution from this baseline state to an excitable state, and (iii) the rapid transition from the excitable state to a hyper-exitable state of epileptiform activity through the interactions with time-dependent stimuli. Furthermore, we describe principles which explain how self-organization of local populations arises in the form of self-sustained synchronous oscillations. In addition, we show how organization in one spatial region promotes or inhibits organization in another. These principles are applied to explain a long-standing conundrum of global pattern formation in large-scale neuronal networks in the brain. Theoretical predictions are confirmed by comparison with human electrocorticographic recordings. Our findings advance the understanding of functional behavior of interconnected populations and have broad implications for the analysis of self-assembly in diverse classes of networks.
Introduction

Rhythmic activity in the central nervous system ranges from series of action potentials produced by single neurons,\(^1\) to collective oscillations in small neuronal groups,\(^2\) to complex electroencephalographic (EEG) rhythms arising at the level of large neuronal populations.\(^3\) A multitude of diverse cellular and network processes drive oscillatory activity at these different levels of organization. On the single neuron level electrophysiological activity (i.e. voltage) is determined by the flow of ionic currents across the cell’s membrane, as described by Hodgkin-Huxley type formalism. By contrast, on the population level activity arises due to collective synchronization of large pools (\(10^3\) - \(10^{10}\)) of neuronal cells.\(^3\) Such synchronized activity has been observed in direct cortical recordings obtained in the unanaesthetized cat.\(^4,5\) This macroscopic behavior is manifested by EEG rhythms of field-averaged electrical activity that can be recorded on the scalp, or directly on the cortical surface.\(^2,3,6,7,8\) This organized activity plays a prominent role in normal brain functioning, in particular the dynamics of sleep and wakefulness.\(^9\) Furthermore, synchronized rhythmicity, spreading uncontrollably over large regions of the brain, has been implicated in the pathogenesis of some disorders of the central nervous system, most notably epilepsy.\(^3,10\) Although epilepsy represents a large and heterogeneous group of diseases with different pathophysiological mechanisms, a wealth of evidence from clinical studies strongly suggests that impaired connectivity plays a crucial role in a significant proportion of patients with this debilitating disease.\(^3\)

Mathematical modeling of the dynamics of large-scale neural networks represents a formidable challenge. In particular, when the Hodgkin-Huxley description of single-cell physiology is applied to model behavior at the global level of the entire brain, both theoretical analysis and numerical simulations quickly become intractable because of unmanageably large numbers of interacting variables.\(^11\) Accordingly, to understand rhythmic behavior at this level, it
seems natural to use the coarse-grained (mean) field approach introduced into neuroscience by Wilson and Cowan (WC).\textsuperscript{11,12} This approach, which emphasizes large-scale statistical properties, has proved useful for modeling global dynamical behavior of neuronal populations. For example, Adini et al. and Pinto et al. recently used WC-type models to study existence and stability of traveling waves.\textsuperscript{6,13,14} However, the relationships between this type of model and realistic neurophysiological activity have not been elucidated. Although previous studies provided valuable insights into the dynamics of waves in WC-type neuronal networks, they did not investigate the formation and evolution of global (EEG) rhythms on the surface of the cortex.\textsuperscript{2,3} The analysis of EEG activity in earlier studies has been impeded, at least in part, by the lack of a description of a realistic state of baseline (resting state of low-amplitude electrophysiological activity). In turn, this has precluded analysis of the transition from the baseline state to a hyperexcitable state of epileptiform activity. Thus, a central issue is to understand how such a state of baseline electrophysiological activity can be reproduced in a coarse-grained population model? A second important issue is to determine how different types of normal and pathophysiological phenomena, including various EEG rhythms and epileptiform activity can arise from a baseline state of activity in neuronal networks. Thus, the main objectives of the present study are to understand

i) how a baseline state of electrophysiological activity can be reproduced in a WC-type model, and

ii) how different types of rhythmic behavior can arise and spread in this setting due to the interactions of the neural network with various stimuli.

To address these important issues, we first define a realistic state of baseline physiological activity to be a state characterized by super-threshold, tonically active inhibitory activity and sub-
threshold, relatively low excitatory activity, as described in experimental studies and recently
summarized by Sloviter.\textsuperscript{15} We then show how this baseline state can be reproduced in a WC-
type, course-grained population model. Using this baseline state as a starting point, we show how
synchronization and loss of synchronization can be predicted by analyzing the interactions
between external stimuli, connectivity, and recovery properties of interconnected neuronal
populations. In particular, we analyze how synchronous oscillations arise and spread during the
course of epileptiform events. We chose to study these events because of their clinical
importance, and also because of the experimental data available for validation of our results. The
model-predicted features of synchronous rhythmic activity are qualitatively similar to those
observed in electrophysiological data recorded from the cortex of the human brain during
epileptic seizures (Figure 2D).\textsuperscript{3,8}

\textbf{Model}

We employ the three-variable extension of the Wilson-Cowan model formulated by Pinto and
Troy.\textsuperscript{16} In order to understand the basic principles underlying the rise and loss of synchronized
rhythmicity, we begin our analysis in one-space dimension. We then extend these results to two
dimensions in order to compare the model predictions with data obtained from electrophysiological mapping of the cortical surface (Figure 2).\textsuperscript{8} The two-dimensional version of
the model consists of the following system:
In this system a spatial unit \((x,y)\) corresponds to a local neuronal population.\(^{12}\) The variables \(E\) and \(I\) represent the activity of the populations of excitatory and inhibitory neurons, which have long-range (i.e. non-local) connections; \(R\) governs the recovery of \(E\). The function \(f(u)\) defines the probability-based, sigmoidal-shaped neuronal firing rate; we approximate \(f\) by the Heaviside step-function.\(^{17}\) To model a state of baseline physiological activity, we introduce time-independent activation factors \(\gamma > 0\) and \(\eta > 0\). After the system evolves from the rest state into the baseline state, we apply time-dependent stimuli \(\Psi\) which have different forms that allow us to study the effects of various types of physiological stimuli; \(\omega_{ij} > 0\) denotes connectivity from population \(i\) to population \(j\); \(\alpha > 0\) influences the strength of the connections of inhibitory to excitatory neurons; \(\theta_1\) and \(\theta_2\) are constant threshold levels for \(E\) and \(I\); \(\tau\) is the inhibitory time constant; \(\varepsilon\) and \(\beta\) determine the rate of change of \(R\).

The general structure of (1.1) consists of a linear part, an integral part, activation factors, and stimuli. Different types of stimuli can induce a variety of changes in the behavior of neuronal populations through a number of physiological mechanisms. These include modifications of neurohormonal concentrations, synaptic transmission, and ionic membrane channel kinetics.
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depending on the type of the stimulus and neuronal populations involved. The integral part represents the effects of activity of all populations through long-range connections. This term is the only source of nonlinearity and non-trivial dynamics in the system. When the activation factors, external stimuli and connection terms are absent, (1.1) reduces to the linear part, and all activity of the network decays to the stable rest state \((E,I,R) = (0,0,0)\).

Below we describe the evolution of different dynamic states of the system (1.1) summarized in Table 1. Specific mathematical details are provided in Appendix 1.

**Table 1.** Dynamic states of the system and input factors

<table>
<thead>
<tr>
<th>State of the system</th>
<th>Input</th>
<th>Dynamics</th>
</tr>
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<tbody>
<tr>
<td>I. Initial activation</td>
<td>Activation factors: (\gamma &gt; 0) and (\eta &gt; 0), Stimulus: (\Psi = 0)</td>
<td>System evolves from rest towards baseline: (E &lt; \theta_1, I &lt; \theta_2)</td>
</tr>
<tr>
<td>II. Baseline</td>
<td>(\gamma &gt; 0) and (\eta &gt; 0), (\Psi = 0)</td>
<td>System is inactive, stable, non-excitabile: (E &lt; \theta_1, I \geq \theta_2)</td>
</tr>
<tr>
<td>III. Excitable</td>
<td>(\gamma &gt; 0) and (\eta &gt; 0), (\Psi = \alpha \int_{\mathbb{R}^2} \omega_{E} (x',y') dx' dy')</td>
<td>System is inactive but excitabile: (E &lt; \theta_1), and its dynamics are dissociated from (I \geq \theta_2)</td>
</tr>
<tr>
<td>IV. Rhythmic</td>
<td>(\gamma &gt; 0) and (\eta &gt; 0), (\Psi = \alpha \int_{\mathbb{R}^2} \omega_{E} (x',y') dx' dy' + \zeta (x,y,t))</td>
<td>(E) is active, and its dynamics are dissociated from (I \geq \theta_2)</td>
</tr>
</tbody>
</table>
First, it is important to show how a realistic state of baseline physiological activity, characterized by super-threshold, tonically active inhibitory activity and sub-threshold, relatively low excitatory activity\textsuperscript{15} can be reproduced in (1.1) (Table 1, I-II). Mathematically, the baseline state is characterized by

\[ E(x,y,t) < \theta_1 \text{ and } I(x,y,t) \geq \theta_2 \text{ for all } (x,y) \in \mathbb{R}^2 \]  

over a specific time interval. This state is achieved through appropriately chosen activation factors ($\gamma$ and $\eta$) as described below (Principle I). Next, we show how activity can be altered from baseline to an excitable state (Table 1, III), through appropriately timed stimuli $\Psi$. Complete mathematical treatment is provided in Appendix I.

Principles II and III describe mathematical properties that are necessary ingredients required for the transition from the excitable state to hyper-excitable state. This includes high-frequency oscillatory properties of the linear part of the model (Principle II), and global bi-stability properties (Principle III).

We use these theoretical principles to formulate a plausible natural path to synchronized rhythmic activity in the model. In particular, we show how synchronous self-sustained oscillations (SSO) arise, spread, and interact both in numerical experiments and neurophysiological recordings.\textsuperscript{4,8} This analysis provides a theoretical framework that can be useful for understanding dynamic patterns of electroencephalographic activity, including the emergence and temporal evolution of a focus of epileptiform activity.\textsuperscript{8}

**Principle I.** The network can be transformed into a reduced, positive feedback system by appropriately timed external stimuli.
Most biological systems, including neuronal networks, are balanced by a combination of positive and negative feedback control mechanisms.\textsuperscript{18} Similarly, the full network (1.1) is balanced by positive feedback provided by the activity of the excitatory neuronal population $E$, and negative-feedback of the inhibitory activity $I$. This balance is essential for normal functioning of the network.\textsuperscript{2,3,15}

A combination of activation factors and time-dependant external stimuli are required to counterbalance the negative feedback and transform (1.1) into a positive-feedback system capable of self-organization. For simplicity, we assume that $E$, $I$ and $R$ are initially at rest:

\begin{equation}
E(x, y, 0) = I(x, y, 0) = R(x, y, 0) = 0 \quad \text{for all } (x, y) \in \mathbb{R}^2
\end{equation}

In the absence of external input, the solution of (1.1)-(1.2) must remain at the stable rest state $(E, R, I) = (0, 0, 0)$.

The transformation begins when the activation factor $\eta$ is of sufficient magnitude to cause the tonic activity of inhibitory neurons $(I)$ to quickly and uniformly exceed its threshold at a critical time $t = T^*$ (Appendix I).\textsuperscript{15,19} In a recent review Sloviter points out, in agreement with Eccles’ view, that dynamical behavior of tonically active inhibitory neurons may play an important role in seizure formation, since “an active inhibitory barrier focuses excitation to its intended target cells”.\textsuperscript{19,15} At an appropriately chosen time $t = T_1$ a stimulus $\Psi$ is applied which causes the $(E,I,R)$ network (1.1) to decouple into a reduced, positive-feedback network (Appendix I). Over the interval $[0, T_1]$ the variables $E$ and $R$ remain practically unchanged because their response time to the activation factors and stimulus is relatively slow.\textsuperscript{19} A rescaling transforms the resultant excitatory $(E, R)$ system into a canonical form:
Here $\omega$ is positive, continuous, symmetric, and normalized so that $\int_{R^2} \omega(x', y')dx'dy'=1$. The parameters $\epsilon > 0$ and $\theta > 0$ are constants; $\beta(x, y)$ represents local recovery properties modulated by stimulus $\Psi_1$ (Appendix I). The function $\beta$ plays a particularly important role in the development of different patterns of electrophysiological activity, including traveling activity waves and the self-assembly of neuronal populations into synchronously oscillating functional groups. This is consistent with Milton's view that "The spatio-temporal dynamics of bulks of neurons depends on the interplay between (i) the magnitude of the neural inputs, (ii) the time course of the relatively refractory rate of the neurons, and (iii) the tightness of the interneuronal connectivity."

**Principle II.** The linear part of the positive-feedback network exhibits decaying, high-frequency oscillations.

Consider the linear part of (1.2):

\[
\frac{\partial u}{\partial t} = -u - v
\]
\[
\frac{\partial v}{\partial t} = \epsilon(\beta u - v)
\]

(1.3)

To understand how high-frequency oscillations arise in (1.3), we let $\beta$ be a constant and examine the effects of the associated eigenvalues $\lambda^\pm = \left((-\epsilon + 1) \pm \sqrt{(\epsilon - 1)^2 - 4\epsilon \beta}\right)/2$ over different ranges of $\beta$. Since $\beta$ is determined by stimulus $\Psi_1$, distinct values of $\beta$ represent
modifications of recovery properties induced by stimuli of various magnitudes. When $\beta$ is small, $\lambda^\pm$ are real and negative. In this case, solutions of (1.3) cannot oscillate and monotonically approach the constant state $(0,0)$ in the $(u,v)$ phase plane. When $\lambda^\pm$ are real, the only patterns of functional activity in (1.2) that can be initiated by a stimulus are solitary traveling waves or wavefronts. When $\beta$ increases and passes the critical value $\beta_* = (1 - \varepsilon)^2 / 4\varepsilon$, the eigenvalues become complex; all non-trivial solutions of (1.3) are now oscillatory and spiral into the constant state $(0,0)$. The frequency of these oscillations is given by $\sqrt{4\varepsilon\beta - (\varepsilon - 1)^2} / 4\pi$; as $\beta$ increases from $\beta_*$, the frequency rises without limit.

**Principle III. Bi-stability in the positive-feedback network: a stable, spatially independent, periodic solution and a stable rest state coexist over a continuous range of parameters.**

Spatially independent solutions of (1.2) satisfy

\[
\begin{align*}
\frac{du}{dt} &= -u - v + f(u - \theta) \\
\frac{dv}{dt} &= \varepsilon(\beta u - v)
\end{align*}
\]

When $\varepsilon < 1$ and the activation threshold $\theta$ is relatively small (e.g. $\varepsilon = 0.1$ and $0 \leq \theta < 0.3$), there is a second critical value $\beta^* > \beta$, such that if $\beta \geq \beta^*$ then (1.4) has a stable periodic solution; the proof makes use of high-frequency oscillations in (1.3) described above in Principle II (Figure 1, Appendix II). Thus, changes in $\beta$ (representing changes in the recovery properties of neuronal population modified by a stimulus) cause a succession of dynamic patterns, from monotonic damping to damped oscillations and, finally, a transition to bistability, in which stable periodic solutions coexist with one or more stable rest states. A qualitatively similar succession of
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Dynamic patterns due to gradually increasing parameters has been also described by May in discrete models of insect populations.20

**Emergence of SSO**

We now show how these principles lead to the initiation and spread of SSO; for simplicity, this process is analyzed in one dimension (Figure 2, first column), and computer simulations confirm that the same process holds in two dimensions (Figure 2, 2nd column). Because all three principles are invariant with respect to dimension, we conjecture that our results also hold in three dimensions.

The first step of the process is described by Principle I (see Appendix I for details) which shows analytically how an

![Figure 1. Phase portraits (left) and corresponding time plots (right) of spatially independent solutions of (1.4).](image)
Figure 2. Panels A and B, from top to bottom. Progressive growth of the region of self-sustained synchronous network oscillations in one (A) and two (B) dimensions (see Supplementary Movies S1 and S2). Synchronous oscillations that emerge following a stimulus (top) gradually expand outwards, until the entire network is synchronized (bottom).

Panel C. Top. Time series of electrical activity registered by a single electrode shown by a white dot in Panel B. The first 3 traveling activity waves are followed by 3 SSO oscillations. Horizontal dotted line indicates activation threshold. The initial sub-threshold segment of the traveling wave is convex, whereas that of the SSO is concave. The transition from traveling waves to SSO occurs between the 3rd and 4th cycle. Bottom. Comparison of traveling activity waves (left) and SSO (right) in the model with corticographic data recorded from one of the electrodes located on the surface of the brain during migration of seizure activity across the region of the recording electrodes. The bottom row shows the dynamics of electrical activity recorded directly from an electrode chronically implanted onto the surface of the brain (right parieto-temporal area) during migration of seizure activity across the recording region in a 7-year old female.¹

Panel D. Direct (subdural) electrocorticographic recordings obtained during seizures from chronically implanted electrodes (10 mm center-to-center spacing) on the surface of the left temporal lobe of a 52-year old female.⁸ Note that large-amplitude oscillatory pattern of activity at three neighboring electrodes has identical frequency and phase; the activity is relatively quiescent at the rest of the recording sites. Note also that a slowly rising region precedes each large spike. These properties strongly suggest that an entire region has become synchronized, in agreement with predictions of the model.
appropriate external stimulus quickly transforms the dynamics of (1.1) into those of the canonical positive-feedback network (1.2). The next step is to understand the dynamics of (1.2) when the recovery function $\beta$ is held constant at a level $\beta \geq \beta^*$. To initiate an SSO, a stimulus is applied at an arbitrarily chosen spatial point (Figure 2, Panels A and B). By Principle III, there is a stable, spatially independent, periodic solution (i.e., a bulk oscillation), which causes the solution of (1.2) to begin oscillating at the point of stimulus (Appendix II). Subsequently, at nearby points, the solution also begins to oscillate; these oscillations are spatially uniform and in-phase over an ever-expanding region, referred to as the SSO region, or equivalently, the region of synchrony (Figure 2, column 1, rows 2 and 3) (Supplementary Movie S1).

The expansion of the SSO region is determined by an interplay between two key features: i) the speed $c$ of waves that form and propagate outward from the edge of the region, and ii) the concave shape of the graph of the activation variable $u$ as it rises, during each cycle, from the resting state $u=0$ to the activation threshold level $\theta$ (Figure 3). The exact point where concave region starts is given by

$$\frac{u_t}{u} = -\frac{\varepsilon(\beta+1)}{1+\varepsilon};$$

$u$ is negative at this point. However, the maximal concavity of the solution occurs on the time interval on which $u$ increases from 0 to $\theta$; the length of this interval is $\Delta t$. During this sub-threshold interval, whose length is denoted by $\Delta t$, the solution satisfies (1.3), which is equivalent to $u_t = -(1+\varepsilon)u_t - \varepsilon(\beta+1)u$. Thus, $u_t$ is negative and $u$ is concave since $u_t$ and $u$ are both positive. Due to concavity, it takes a relatively
long time ($\Delta t$) for the activation to reach its threshold $\theta$. This creates a delay during which the leading edge of the region of synchrony expands outwards. Simulations show that the longer the delay and the faster the speed of the traveling waves forming at the leading edge, the greater is the rate of expansion. Peskin, and Mirollo and Strogatz describe similar concavity-delay mechanisms in their analyses of synchronized behavior of cardiac cells and populations of fireflies.\textsuperscript{21,22} Their models represent arrays of coupled oscillators, each one describing the repetitive firing of an individual cardiac cell or a firefly. Our model is different because no self-sustained oscillations emerge without an appropriate stimulus. Indeed, if a stimulus at a given point is not sufficiently strong, the resulting solution evolves into a pulse-shaped traveling wave (Supplementary Movie S3). However, when an initial stimulus is of sufficient magnitude, oscillations do emerge and spread outwards from the point of stimulus. The above-described mechanism provides a plausible explanation for sustenance of epileptiform activity without a hypothetical driving source that, despite a number of experimental studies, has never been observed.\textsuperscript{3}

The rate of expansion of the SSO region is precisely determined by a product of two factors, the fraction $\Delta t/T$, where $T$ is period of each oscillation, and the wave speed $c$:

$$RATE = \frac{\Delta t}{T} \cdot c$$

(1.5)

Since $0 < \Delta t / T < 1$, (1.5) shows that the growth rate is slower than the speed of the traveling waves which is consistent with experimental and clinical observations regarding spread of epileptic activity.\textsuperscript{3} In addition, simulations show that the ratio $\Delta t/T$ and the speed $c$ both decrease as $\beta$ increases. Thus, (1.5) predicts that the rate of expansion of the region of synchrony decreases as $\beta$ rises, with the fastest expansion occurring at the critical value $\beta^*$ where the frequency of large-amplitude bulk oscillations is minimal. The ability of slow rhythms to spread over large
regions of the brain has been confirmed experimentally. Thus, the predictions of (1.5) are in agreement with experimental findings and provide a unified, parsimonious explanation for the mechanism by which slow oscillations entrain large regions of the brain.

The 1st row of Figure 2C shows the time tracing of the solution at a single recording site (white dot in Figure 2B). Initially, the recording site is outside of the SSO region. In the time tracing the shape of the sub-threshold section during the first three oscillations is convex, indicating that these oscillations represent traveling waves of activity because the recording site is outside the region of synchrony. However, during the 4th-6th oscillations the shape of the sub-threshold activity has changed from convex to concave, which shows that the leading edge of the SSO region has reached the recording site. Recent neurophysiologic studies in rat hippocampus have confirmed, both in vitro and in vivo, the existence of the sub-threshold slowly rising, concave-form activation that precedes the action potential upstroke. Experimental evidence suggests that this phenomenon represents activation of a sub-population of neurons that escape inhibitory influences due to heterogeneous connections or irregular spread of activity.

The dynamic behavior described above has also been observed by Towle et al. in human studies of electrical activity in the brain. The 2nd row of Figure 2C compares the dynamics of electrophysiological activity at a single site in the model with activity registered by an electrode chronically implanted directly onto the surface of the human brain. This human subject undergoes an electrocorticographic recording during migration of seizure activity across the region of recording electrodes. These unique experiments capture the dynamics of the onset and spread of SSO. In particular, the 2nd row of Figure 2C shows how a pattern of electrical activity changes from traveling waves when the seizure activity is outside of the recording electrode, into large-amplitude, self-sustained oscillations (SSO) when the seizure activity is directly under the electrode. Note the remarkable similarity in the patterns of model-generated and neurophysiologic
data showing traveling waves and bulk oscillations (SSO). During each upstroke concavity is clearly visible in the sub-threshold interval of the SSO patterns but not in the traveling waves. Figure 2D shows electrophysiologic data obtained from an array of electrodes chronically implanted on the surface of the brain in another human subject also suffering from intractable epilepsy. Note that three electrodes record synchronous large-amplitude oscillations; activity is relatively quiescent at the rest of the recording sites. The uniformity of frequency and phase strongly suggests that the large-amplitude synchronous oscillatory activity represents bulk oscillations in an entire region containing the three recording electrodes. Comparing Panels C and D, one also observes that the large-amplitude synchronous oscillations at the three recording sites in Panel D are several times slower than those in the 2nd row of Panel C. The observation that the slower rhythm in Panel D spreads and synchronizes a relatively large region is in line with the theoretical predictions of (1.5).

Figure 4. Interaction between low-frequency and high-frequency SSO in distinct regions. **Top row:** $\beta_1 = 12.61 = \beta^*$ inside the disk-shaped region $D_1 : (x + 20)^2 + y^2 \leq 100$; $\beta_2 = 15$ inside the region $D_2 : (x - 20)^2 + y^2 \leq 100$; $\beta = 7$ otherwise.

**Bottom row:** $\beta_1$, $\beta_2$ have the same values as above, but now $D_1$ and $D_2$ are close to each other: $D_1 : (x + 20)^2 + y^2 \leq 400$, $D_2 : (x - 20)^2 + y^2 \leq 400$. See text for details.
Interaction. Every day, a multitude of dynamic patterns of electrophysiological activity emerge, co-exist, interact, and die out in the living brain.\(^2\) Synchronous oscillations of various frequencies are vital for brain functioning. As Buzsaki and Draguhn recently point out, “neighboring frequency bands within the same neuronal network are typically associated with different brain states and compete with each other”.\(^2\) Thus, it is important to understand how synchronization in one region promotes or inhibits synchronization in another.

To investigate the rules of interaction between neighboring regions, we consider distinct spatial regions with different synchronization properties (Figure 4). We define disk-shaped regions \(D_1\) and \(D_2\) with two different \(\beta\) values, \(\beta_1\) and \(\beta_2\), such that \(\beta_2 < \beta_1 \leq \beta^*\). This allows synchronization to occur in both regions. However, \(\beta < \beta^*\) outside and between these regions, so that synchronization does not occur. An initial stimulus is given at the center of \(D_1\) (left). As the solution synchronizes in \(D_1\), activity waves propagate outwards and trigger synchronization in \(D_2\). Subsequently, the SSO region \(D_2\) also starts emitting activity waves. Because the region between \(D_1\) and \(D_2\) is relatively large, the activity waves coming from \(D_1\) meet and annihilate the waves coming from \(D_2\). In this “buffer” region, synchronization is not possible since \(\beta < \beta^*\). The end result is that the regions \(D_1\) and \(D_2\) remain synchronized at two distinct frequencies (Supplementary Movie S4). Because \(\beta_1 < \beta_2\), the uniform oscillations in \(D_1\) have lower frequency than in \(D_2\). However, the rate of synchronization in \(D_1\) is faster than in \(D_2\) (formula 1.5). This is consistent with observations that lower-frequency rhythms entrain larger areas of the brain than higher-frequency rhythms.\(^2\) Furthermore, evidence of activity waves spreading from a point of stimulus to distant brain regions has recently been confirmed in human subjects.\(^24\)

In the bottom row of Figure 4, the two disk-shaped regions have the same \(\beta\) values as above, but now \(D_1\) and \(D_2\) are close to each other. Again, an initial stimulus given at the center of
D_1 causes synchronization to begin; in turn, activity waves are formed and emitted outwards. These waves trigger synchronization in D_2, and activity waves are also emitted from region D_2. However, in the absence of a buffer region, the activity waves from D_2 enter D_1 and quickly annihilate synchronization in D_1. The end result is that synchronization persists only in region D_2 (Supplementary Movie S5). We conclude that in the absence of a buffer zone the region with higher-frequency oscillations dominates and inhibits synchronization in the slower-oscillating adjacent region.

These investigations studied synchronization of integrate-and-fire systems of coupled oscillators. For a comprehensive review of the relationships between these models see Gerstner.\textsuperscript{25} In contrast, our study doesn’t assume that the system consists of a discrete collection of coupled oscillators. Instead, we the Wilson-Cowan and Amari approach, in which 1) the coarse-grained system is spatially continuous and 2) in the absence of connections and stimuli, the system doesn’t exhibit self-sustained oscillations.

Conclusions
We have shown that the emergence of self-organization in the form of synchronous self-sustained oscillations in large-scale population networks can be anticipated when the following three principles are met: 1) The network with both positive and negative control mechanisms is transformed into a strictly positive-feedback system by external stimuli, 2) The linear part of the positive-feedback system exhibits decaying high-frequency oscillations, and 3) A stable, spatially independent, periodic solution coexists with a stable rest state over a continuous range of parameters. These principles depict necessary conditions for the spontaneous development of
synchronous oscillations in complex, multi-component networks, and in particular, in a variety of large-scale networks with long-range connections, the so called “small-world” networks. In contrast to previous studies, we have found that the self-organization process does not depend on the presence of noise or a priori built-in array of coupled oscillators. Instead, this is a result of the intrinsic dynamics of population networks characterized by strong, long-range connectivity. Furthermore, our study explicitly links the emergence and spread of self-organized activity with the modification of recovery properties of the network by external stimuli. Of particular interest to general audience is the derivation of a specific formula that accurately predicts the rate of spread of the region of synchrony using the most fundamental features of the dynamical system, which makes it applicable to diverse classes of networks.

As \( \beta \) varies from 0 to \( \beta^* \), our model is capable of reproducing a number of dynamic phenomena, including wave fronts, solitary and multi-bump waves, the self-sustained periodic formation of traveling waves, and also rotating waves. All of these phenomena have been observed in neurophysiological experiments. We address the existence and stability of these types of solutions elsewhere.

The principles described here also have broad implications for the study of biorhythmicity in general. While some biological oscillators, such as the cardiac pacemaker cells, have been identified, others remain elusive despite a number of experimental studies devoted to their search. In particular, the origins of slow rhythms in the cardiac and vascular neurohormonal regulation remain largely unexplained. Our analysis shows that biorhythmicity can arise in complex, multi-component networks as a result of a dynamic, self-organizing behavior which does not require local oscillators acting as a driving force. Instead, such self-sustained biorhythms represent a functional pattern of the network activity itself, which exists only when the network infrastructure and connectivity are intact. This explains why the attempts of finding individual
biological oscillators and isolating them from the network are often unsuccessful. Probing the origins and functional behavior of biorhythms is an important area of further development and applications of the principles described in the present study.
References


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14 D. Pinton, Jackson, Wayne………………………………………………………………………


