From Baseline to Epileptiform Activity: 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 in the brain the emergence of global behavioral patterns, manifested by electroencephalographic activity, is driven by the 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 a state of baseline physiological activity and the transition from the baseline state to rhythmic, epileptiform activity. We describe principles which explain how this rhythmic activity arises in the form of spatially uniform self-sustained synchronous oscillations. In addition, we show how the rate of spread of the region of synchrony can be predicted and how organization in one spatial region promotes or inhibits organization in another. This provides a plausible explanation of how remote sites can synchronize (kindling-type phenomenon) in the central nervous system. The mechanism of rate-only synchronization without phase synchronization between two separate regions of the brain (with the same or different $\beta$ values) is different from classical phase-locked synchronization. Our theoretical predictions are consistent with the results of human electrocorticographic recordings and functional magnetic resonance imaging (fMRI), in particular with observations that lower-frequency EEG rhythms entrain larger areas of the brain than higher-frequency rhythms. These findings advance the understanding of functional behavior of interconnected populations and might have implications for the analysis of diverse classes of networks.
Introduction

Rhythmic activity in the central nervous system ranges from series of action potentials produced by single neurons, to collective oscillations in small neuronal groups, to complex electroencephalographic (EEG) rhythms arising at the level of large neuronal populations. 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, activity on the population level arises due to collective synchronization of large pools of neuronal cells. This macroscopic behavior is manifested by field-averaged electrical activity that can be recorded on the scalp or directly on the cortical surface, or tracked indirectly using fMRI techniques.

The focus of our study is on the theoretical analysis of such macroscopic synchronized rhythmicity. Experimental studies have shown that global synchronization plays a prominent role in normal brain functioning, in particular the dynamics of sleep and wakefulness. 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. 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 collective functioning of neuronal populations plays a crucial role in a significant proportion of patients with this debilitating disease.

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. 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). This approach,
which emphasizes large-scale statistical properties, has proved useful for gaining insight into global dynamical behavior of neuronal populations.

In particular, WC-type models have recently been used to study existence and stability of traveling waves. \(^5,13,14,15\) Although these studies provided valuable insights into wave dynamics in WC-type neuronal networks, they did not analyze more realistic neurophysiological processes, in particular the formation and evolution of global (EEG) rhythms on the surface of the cortex. \(^2,3\) The analysis of realistic neurophysiological activity in earlier studies has been impeded, at least in part, by the lack of a description of a physiological baseline. \(^16,17\) (As opposed to the mathematical initial rest state, usually represented by zero level of activity, a physiological baseline has non-zero activity\(^18\)). Due to this deficit of knowledge, the pathway from the baseline state to a hyperexcitable state of epileptiform activity has not been studied. Thus, the main objectives of the present study are to examine:

i) how a baseline state of electrophysiological activity (see the next section for the definition of baseline) can be reproduced in a WC-type model, and

ii) how different types of rhythmic behavior, including various synchronized rhythms and epileptiform activity, can arise from the baseline state and spread out spatially due to the interactions of the neural network with various stimuli.

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. We focus on the theoretical understanding of dynamics of epileptiform activity because of its clinical importance, and also because of the experimental data available for validation of our results. \(^3,8\)

Model

We begin by defining a realistic state of baseline physiological activity, which represents activity of the brain in the state of relaxation. In this state, neurons receive some level of spontaneous, weak stimulation by small, naturally present concentrations of neurohormonal substances. \(^19\) The levels of such stimulation vary depending on the relaxation level. In waking adults this state is commonly associated
with alpha rhythm, whereas slower rhythms are usually observed during deeper relaxation and sleep.\textsuperscript{19,20} These rhythms are almost never stationary, with time-varying frequency and amplitude, as well as other a-periodic patterns.\textsuperscript{19} Therefore, the variability of brain activity patterns in such a broadly defined baseline state cannot be described in terms of a single rhythm. As a first step towards modeling a wide range of realistic baseline patterns, we propose the following two-component definition of a baseline state:

I. A time-independent component represented by sub-threshold excitatory activity $E$ and super-threshold inhibitory activity $I$, and

II. A time-varying component which may include single-pulse waves, multi-pulse waves or periodic waves caused by spontaneous neuronal activity.\textsuperscript{19,20,21}

This two-component formulation makes the baseline activity definition sufficiently flexible to allow simulation of a variety of rhythmic patterns observed in the cortex, including alpha and slower rhythms, single-pulse and multi-pulse waves, and the periodic self-production of waves, without periodic forcing or stimuli.\textsuperscript{6,7,13,14,15,19,21} Moreover, this formulation also allows one to reproduce the spontaneous emergence and evolution of different activity patterns without changes in parameters, although such spontaneous transformations previously were considered impossible in this type of model.\textsuperscript{22}

Below we show how this baseline state can be reproduced in a WC-type model. We then describe a plausible theoretical path from the baseline state to large-scale, self-sustained oscillations, which spread out uniformly from the point of stimulus. For this we modify the recent three-variable extension of the Pinto-Ermentrout WC-type model\textsuperscript{13} formulated by Pinto and Troy.\textsuperscript{23} The advantage of the latter model in representing a physiological baseline is in its more realistic and balanced representation of the activities of both excitatory and inhibitory neuronal populations\textsuperscript{24} compared to the earlier, Pinto-Ermentrout model, which did not include the inhibitory activity and thus represented an unbalanced, excitatory (disinhibited) system.\textsuperscript{13,25} Here, we introduce a novel concept of time-independent activation factors which force the system to undergo a transition from an initial “mathematical” rest state to a state of time-independent baseline activity. 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. The variables \(E(x,y,t)\) and \(I(x,y,t)\) represent the average activity (e.g., voltage) levels of the excitatory and inhibitory neuronal populations at the spatial point \((x,y)\) and time \(t\) with long-range (i.e. non-local) connections; \(R\) governs the recovery of \(E\). The network (1) is balanced by positive feedback provided by the activity of the excitatory neuronal population \(E\), and negative feedback of the variables \(I\) and \(R\). This balance is essential for normal functioning of the system. The function \(f(u)\) defines the probability-based, sigmoidal-shaped neuronal firing rate; we approximate \(f\) by the Heaviside step-function; \(\omega_{ij}\) denotes connectivity from population \(i\) to population \(j\) and has the typical connectivity form of an exponentially decaying Gaussian. \(\alpha > 0\) influences the strength of the connections of inhibitory to excitatory neurons. Although \(\alpha\) could be absorbed into \(\omega_{IE}\), we keep it separately for future, more general studies. \(\theta_1\) 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 time-independent baseline activation factors \(\gamma > 0\) and \(\eta > 0\) are introduced as a lumped-parameter representation of intrinsic intra and extracellular biochemical processes, including neurohormonal influences, to force the system to evolve from the “mathematical’ rest to the time-independent baseline. Because our focus is on large-scale functional dynamics (i.e. a large-scale approximation of multiple intra and extracellular processes), the detailed characterization of
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Each individual biochemical process lies beyond the scope of this study. The function $\Psi(x,y,t)$ has three components which simulate three different time-dependent physiological stimuli (see Table 1):

$$
\Psi(x,y,t) = \begin{cases} 
0 & 0 \leq t < T_1, \\
\alpha \int_{R^2} \omega_{EI}(x',y')dx'dy' & T_1 \leq t < T_2, \\
\alpha \int_{R^2} \omega_{EI}(x',y')dx'dy' + \zeta(x,y,t) & t \geq T_2, 
\end{cases}
$$

where $w_{EI}$ and $\zeta(x,t)$ are positive, uniformly bounded and continuous, and $\alpha > 0$ is assumed to lie in a bounded range. Note that this form for $\Psi(x,y,t)$ represents a small subset of all possible types of physiological stimuli. It was chosen because it allowed for a plausible, simple path to self-sustained rhythmic oscillations, which is the main focus of this study. A number of different stimulus forms have been previously used to induce a variety of patterns, including solitary and multi-bump traveling waves, rotating waves, and spatially uniform self-sustained rhythmic oscillations. Such stimulus-evoked patterns may reflect modifications of neurohormonal concentrations, synaptic transmission, and ionic membrane channel kinetics depending on the type of stimulus and neuronal populations involved. In our model $\Psi(x,y,t)$ is present in both the excitatory and inhibitory parts of (1.1), because in most neural architectures the inhibitory neurons receive the same feedforward projections as the excitatory neurons. However, $\Psi(x,y,t)$ plays a significant role in the dynamics of the system only in the excitatory part.

Thus, the general structure of (1) consists of a linear part, an integral part, baseline activation factors, and time-dependent stimuli. The integral part of (1) 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. We note that when the activation factors, external stimuli and connection terms are absent, (1) reduces to the linear part, and all activity of the network decays to the stable rest state $(E,I,R) = (0,0,0)$. 

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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>
</thead>
<tbody>
<tr>
<td>I. Mathematical rest</td>
<td>$\gamma = 0$ and $\eta = 0$, $\Psi = 0$</td>
<td>$E, I, R = (0,0,0)$</td>
</tr>
<tr>
<td>II. Transition from rest to the time-independent baseline: $0 &lt; t &lt; T^*$</td>
<td>Time-independent activation is introduced: $\gamma &gt; 0$ and $\eta &gt; 0$, Stimulus: $\Psi = 0$</td>
<td>System begins its evolution from the rest state $(0,0,0)$ towards baseline; both $E$ and $I$ remain sub-threshold: $E &lt; \theta_1$, $I &lt; \theta_2$</td>
</tr>
<tr>
<td>III. Time-independent baseline: $T^* \leq t &lt; T_1$</td>
<td>Time-independent activation remains: $\gamma &gt; 0$ and $\eta &gt; 0$, Stimulus: $\Psi = 0$</td>
<td>$E$ remains sub-threshold but $I$ exceeds threshold uniformly: $E &lt; \theta_1$, $I \geq \theta_2$</td>
</tr>
<tr>
<td>IV. Time-varying (physiologically relevant) baseline: $T_1 \leq t &lt; T_2$</td>
<td>Time-independent activation remains: $\gamma &gt; 0$ and $\eta &gt; 0$, and in addition, time-varying activation (i.e. stimulus) is introduced: $\Psi = \int_{\mathbb{R}^2} \omega_{EI}(x',y')dx'dy' + \zeta(x,y,t)$ and the integral term blocks effects of inhibitory population.</td>
<td>$E(x,y,t) &lt; \theta_1$, $I(x,y,t) \geq \theta_2$ Weak, short-time $\zeta(x,y,t)$ component of stimulus may produce different types of waves</td>
</tr>
<tr>
<td>V. Global rhythmic state: $t \geq T_2$</td>
<td>Time-independent activation remains: $\gamma &gt; 0$ and $\eta &gt; 0$, and time-varying activation (stimulus) remains, but the $\zeta(x,y,t)$ component becomes stronger: $\Psi = \alpha \int_{\mathbb{R}^2} \omega_{EI}(x',y')dx'dy' + \zeta(x,y,t)$</td>
<td>$E &lt; \theta_1$, $I \geq \theta_2$ Strong, short-time $\zeta(x,y,t)$ component of stimulus induces the transition from the baseline state to global rhythmicity, including rotating waves and synchronous oscillations.</td>
</tr>
</tbody>
</table>

Throughout, we assume that $E$, $I$, and $R$ are initially at rest. That is,
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We use this initial condition (although this mathematical abstraction is not relevant for a living physiological organism) because (3) is commonly used in computer modeling as a starting point for simulations. Hence, we also use this condition to provide a common “reference point” for comparison of our investigation with previous modeling studies.

Our goal is to show how the system evolves from the mathematical (non-physiological) rest state (3) to a realistic state of baseline physiological activity, as defined at the beginning of this section. As explained above (Table 1), this process consists of two stages. First, the system evolves into the time-independent baseline state (Table 1, part II), where \( E \) and \( I \) have reached constant levels of activity which are uniformly close to their respective time-average levels. Because electrophysiological rhythms (alpha or theta) in this relaxed state are relatively slow, the time-average level of such activity (i.e. excitatory activity \( E \)) would be below its threshold (\( E < \theta_1 \)). Since the excitatory and inhibitory activities are usually reciprocal,\(^{24,33} \) one can assume that this effect is due to the supra-threshold level of the inhibitory activity \( I (I \geq \theta_2) \):

\[
E(x,y,0)=I(x,y,0)=R(x,y,0)=0 \text{ for all } (x,y) \in \mathbb{R}^2
\]  

This non-zero-activity state is more realistic for a living organism than the initial, zero-activity, mathematical rest state. However, the system does not yet exhibit realistic, time-varying, rhythmical behavior. For this reason, we have added the second, time-varying component of baseline. A description of the dynamic process that leads to the baseline state through the activation factors \( \gamma \) and \( \eta \), and appropriately timed stimuli \( \Psi \) is given in the Principle I section. Further mathematical details are provided in the APPENDIX. We also describe two additional mathematical properties which are needed for the transition from the baseline state to a state of epileptiform activity (Principles II and III). These include oscillatory properties of the linear part of the model (Principle II), and global bi-stability properties (Principle III). Finally, we show how a dynamical process, combining the properties described...
by all three Principles, can form a physiologically plausible path to synchronized rhythmic activity in (1). In numerical experiments we demonstrate how synchronous self-sustained oscillations (SSO) arise, spread, and interact, and how these dynamics are consistent with neurophysiological experiments.\textsuperscript{5,8} Our 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}

We now describe three mathematical properties, summarized for clarity in the form of principles, which give sufficient conditions for spontaneous self-organization in (1).

**Principle I. The network can be transformed into a reduced, positive feedback system.**

A combination of the time-independent activation factors and time-dependant stimuli is required to counterbalance the negative feedback of variables $R$ and $I$ and transform (1) into a positive-feedback system capable of self-organization. Recall from (3) that the solution of (1) is initially in the stable ("mathematical") rest state $(E,R,I)=(0,0,0)$. The transformation begins when we let the baseline activation factor $\eta$ be of sufficient magnitude to cause the tonic activity of the inhibitory neurons ($I$) to quickly and uniformly increase to its threshold level $\theta_2$. When this threshold is reached at a critical time $t = T^*$ the system has undergone the transition from rest to the time-independent baseline, and the first step of the transformation is complete (Table 1, I-II).\textsuperscript{17} Details of this transition are given in APPENDIX. Over the interval $[0, T_1]$ the variables $E$ and $R$ remain practically unchanged because their response time to the activation factors is relatively slow compared to that of $I$ (see APPENDIX). For $t \geq T^*$ the system remains in this state until $t = T_1 > T^*$ when a stimulus $\Psi$ is applied which causes the $(E,I,R)$ network (1) to transform into a time-varying baseline state in which the activity of the inhibitory population $I$ is temporarily counterbalanced (Table 1, III). As Table 1 (row III) shows, the integral part of $\Psi$ determines the minimal magnitude of the stimulus required to counterbalance (block) the effects of the inhibitory
neuronal population (when $\zeta(x,y,t)=0$). The magnitude of $\Psi$ remains relatively small as long as its $\zeta(x,y,t)$ component is weak. Such weak stimuli can produce different types of waves depending on $\gamma$, but no self-sustained oscillations. For $t > T_1$ the system remains in this time-varying baseline state until a sufficiently strong stimulus $\zeta(x,y,t)$ is applied at a time $t = T_2$, and subsequently the system dynamics evolve into rhythmic synchronized oscillations (Table 1, IV). In the Appendix we also show how a rescaling transforms the time-varying baseline $(E,R)$ system into the positive-feedback system

\begin{align}
\frac{\partial u}{\partial t} &= -u - v \\
\frac{\partial v}{\partial t} &= \varepsilon(\beta u - v) \\
\int_{R^2}^{\infty} \omega(x-x', y-y') f(u-\theta) dx\,dy + \zeta(x,y,t)
\end{align}

(4)

Here $\omega$ is positive, continuous, integrable, symmetric, and has a typical connectivity form of an exponentially decaying Gaussian such that $\int_{R^2}^{\infty} \omega(x', y') dx'\,dy' = 1$. The parameters $\varepsilon > 0$ and $\theta > 0$ are constants; $\beta(x,y) = \frac{\gamma(x,y)}{const} - 1$ represents local recovery properties modulated by the baseline activation factor $\gamma$ (see Appendix). 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 observations that the time course of the relative refractory rate of the neurons plays an important role in the dynamics of neuronal bulks. Because $E$ and $R$ do not change significantly from the rest level $E=R=0$ over the time interval $0 \leq t \leq T_2$, we assume that

\begin{align}
u(x,y, T_2) &= 0 \\
v(x,y, T_2) &= 0 \\
\end{align}

(5)

Below, in Principles II and III we describe two additional properties of (4) which are needed for the transition from the time-independent baseline to the time-varying baseline state.
Principle II. The linear part of the positive-feedback network \((4)\) exhibits decaying oscillations whose frequency increases without bound as \(\beta\) increases.

To understand how oscillations arise in the linear part of \((4)\) we study

\[
\begin{align*}
\frac{\partial u}{\partial t} &= -u - v \\
\frac{\partial v}{\partial t} &= \varepsilon(\beta u - v)
\end{align*}
\]

We let \(\beta\) be a constant and examine the effects of the associated eigenvalues

\[
\lambda^{\pm} = \left( - (\varepsilon + 1) \pm \sqrt{(\varepsilon - 1)^2 - 4\varepsilon \beta} \right) / 2
\]

over different ranges of \(\beta\). When \(\beta\) is small, \(\lambda^{\pm}\) are real and negative, and solutions of \((6)\) cannot oscillate. Instead, they 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 \((4)\) that can be initiated by the stimulus \(\zeta\) are solitary traveling waves or wavefronts.\(^{15}\) When \(\beta\) increases and passes the critical value \(\beta_* = (1 - \varepsilon)^2 / 4\varepsilon\), the eigenvalues become complex; all non-trivial solutions of \((6)\) are now oscillatory and spiral into the constant state \((0,0)\) in the \((u,v)\) phase plane. The frequency of these oscillations is given by

\[
2\pi \sqrt{4\varepsilon \beta - (\varepsilon - 1)^2} / 4\pi\; ; \text{as} \; \beta \text{ increases from } \beta_* \text{, the frequency rises without limit.}
\]

Principle III. At a critical \(\beta^* > \beta\), bistability occurs in the positive-feedback network: a stable, spatially independent, periodic solution and a stable rest state coexist over a continuous range of parameters.

To understand how bistability occurs in \((4)\), we study spatially independent solutions. These solutions satisfy

\[
\begin{align*}
\frac{du}{dt} &= -u - v + f(u - \theta) \\
\frac{dv}{dt} &= \varepsilon(\beta u - v)
\end{align*}
\]
When $0 < \varepsilon < 1$ and the activation threshold $\theta$ is relatively small (e.g. $\varepsilon = 0.1$ and $\theta = 0.1$), there is a second critical value $\beta^* > \beta_*$ such that if $\beta \geq \beta^*$ then (7) has a stable periodic solution (whereas no periodic solutions exist when $\beta < \beta^*$). Examples of such periodic solutions are shown in the 3rd and 4th rows of Figure 1.

Figure 1 also illustrates how system (7) exhibits increasingly oscillatory patterns of solutions as $\beta$ increases from $\beta_*$. These patterns include monotonic damping (top row), damped oscillations (second row), and the transition to bistability in which stable periodic solutions coexist with one or more stable rest states (third and forth row). A standard phase-plane, topological shooting argument can be used to prove the existence of the periodic solutions in Figure 1.

**Figure 1.** Phase portraits (left) and corresponding time plots (right) of spatially independent solutions of (7) when $(\varepsilon, \theta) = (0.1, 0.1)$, $\beta_* = 2.025$ and $\beta^* = 12.61$ **Top row:** When $\beta \leq \beta_*$, all solutions monotonically approach a constant state. **Second row:** When $\beta_* < \beta < \beta^*$, solutions oscillate (rotate around $(0,0)$ in the phase plane) but cannot be periodic. All solutions eventually spiral into a constant state. **Third row:** When $\beta = \beta^*$, a stable periodic solution emerges and coexists with the stable rest state at $(0,0)$ creating bistability in the system. **Bottom row:** As $\beta$ rises past $\beta^*$, the frequency of oscillations of the periodic solutions increases (right plot).
Figure 2. Panel A from top to bottom. Progressive growth of the region of self-sustained synchronous network oscillations in two dimensions (see Supplementary Movies S1 and S2 at http://www.math.pitt.edu/~troy/sync/). Synchronous oscillations that emerge following a stimulus (top) gradually expand outwards, as the entire network synchronizes (bottom).

Panel B. Top. Time series of electrical activity registered by a single electrode shown by a white dot in Panel A. 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.9

Panel C. 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.
Emergence of SSO

We now show how these principles lead to the initiation and spread of self-sustained synchronous oscillations (SSO) in the positive-feedback system (4); for simplicity, this process is analyzed in one dimension (Figure 3). Numerical simulations confirm that the same process holds in two dimensions (Figure 2, A). Because all three principles are invariant with respect to dimension, we conjecture that our results also hold in three dimensions. It is possible to couple two separate three-dimensional systems of the form \((E,I,R)\) together to model interaction across cortical layers.

The first step of the process is described by Principle I (see APPENDIX for details) which shows analytically how appropriate activation factors quickly transform the dynamics of (1) into those of the canonical positive-feedback network (4).

The next step is to understand the dynamics of (4) 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, Panel A). By Principle III, there is a stable, spatially independent, periodic solution (i.e. a bulk oscillation), which causes the solution of (4) to begin oscillating at the point of stimulus. Subsequently, at nearby points, the solution also begins to oscillate; these oscillations become spatially uniform and in-phase over a gradually expanding region, referred to as the SSO region, or equivalently, the region of synchrony (Figure 3, rows 2 and 3) (Supplementary Movie S1 at http://www.math.pitt.edu/~troy/sync/S1).

The rate of 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 4). (The exact point where the concave region starts is given by

\[
\frac{u_t}{u} = -\frac{\varepsilon(\beta+1)}{1+\varepsilon}; \quad u \text{ is negative at this point. However, the maximal concavity of the solution occurs over the time interval on which } u \text{ increases from } 0 \text{ to } \theta. \text{ During this sub-threshold interval, whose length is denoted by } \Delta t, \text{ the solution satisfies (6), which is equivalent to } u_n = -(1+\varepsilon)u_t - \varepsilon(\beta+1)u. \text{ Thus, } u_n \text{ is negative and } u \text{ is concave since } u_t \text{ and } u \text{ are both positive as } u \text{ rises from } u = 0 \text{ to } u = \theta. \text{ Due to concavity, it takes a relatively long time } (\Delta t) \text{ for the activation } u \text{ to reach its threshold } \theta.

From our numerical experiments we observed that during the rise of a solution towards threshold, as the rate of vertical increase slows down due to the concave component, the stable solitary wave emanating from the region of SSO causes the region to expand spatially at a rate proportional to the wave speed. From this initial observation it was natural to expect that the proportionality constant should be the fraction of the time that the solution is concave during one cycle. This led us to conjecture the formula that predicts the rate of expansion of the SSO region, and its validity was borne out by numerical experiment. The rate of expansion of the SSO region is determined by a product of two factors, the fraction \( \Delta t/T \), where \( T \) is period of each oscillation, and the wave speed \( c \):

\[
\text{RATE} = \frac{\Delta t}{T} c
\]

(8)

Our numerical simulations show that \( \Delta t \) gives a 5% error of the numerically computed solutions. Since \( 0 < \Delta t / T < 1 \), (8) shows that the growth rate is slower than the speed of the

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Figure 4. The graph of the activity variable \( u \) during a single cycle of SSO oscillation. When \( u \) rises from the resting state \( 0 \) to the threshold \( \theta \), the shape of the graph is concave. The concavity of \( u \) on this interval, of length \( \Delta t \), is one of the key features determining the rate of expansion of the region of SSO.
traveling waves which is consistent with experimental and clinical observations regarding the spread of epileptic activity. In addition, simulations show that the ratio $\Delta t/T$ and the speed $c$ both decrease as $\beta$ increases (Table 2). The mechanism described above 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.

Table 2. The rate of spread of the region of SSO for different values of $\beta$.

<table>
<thead>
<tr>
<th>$\beta$</th>
<th>$\Delta t$</th>
<th>$T$</th>
<th>$\Delta t/T$</th>
<th>$C$</th>
<th>$(\Delta t/T)\ C$</th>
</tr>
</thead>
<tbody>
<tr>
<td>12.61</td>
<td>.780</td>
<td>7.248</td>
<td>.108</td>
<td>3.665</td>
<td>.394</td>
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<td>14</td>
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Peskin, and Mirollo and Strogatz describe similar concavity-delay mechanisms in their analyses of synchronized behavior of cardiac cells and populations of fireflies. They found that concavity is a necessary condition for synchronization to occur. In particular, they used the concave component of the curve between the baseline rest state and threshold in the analysis. Here, we have extended their results by introducing a formula that estimates the rate of expansion of the synchronizing region with the use of both the positive part of the concavity and the speed of a stable solitary wave (Supplementary Movie S3 at http://www.math.pitt.edu/~troy/sync/).

The models used by Peskin, and Mirollo and Strogatz 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 SSO phenomenon does not occur. Instead, the solution evolves
into a pulse-shaped traveling wave (Supplementary Movie S3 at http://www.math.pitt.edu/~troy/sync/). However, when an initial stimulus is of sufficient magnitude, oscillations do emerge and spread outwards from the point of stimulus.

The 1st row of Figure 2B shows the time tracing of a solution of (4) at a single recording site (white dot in Figure 2A). 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. This change from convex to concave shape is in agreement with the theoretical predictions that follow from our analysis. 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 2B 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 experiments capture the dynamics of the onset and spread of SSO. In particular, the 2nd row of Figure 2B 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 between the patterns of model-generated (row 1) and neurophysiologic data (row 2) 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 2C 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.\textsuperscript{8} Note that three electrodes record synchronous large-amplitude oscillations, whereas 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 persistent bulk oscillations in an entire spatial region containing the three recording electrodes. It is interesting to compare the frequency of oscillations in panels B (2\textsuperscript{nd} row) and C. The large-amplitude synchronous oscillations entraining the entire region sampled by the three recording electrodes (panel C) are several times slower than those migrating across the region of recording electrodes (2\textsuperscript{nd} row of panel B).\textsuperscript{8} Again, the observation that persistent, spatially uniform oscillations over a relatively large region are associated with the slower rhythm (panel C) agrees with the theoretical predictions of (8).

**A kindling-type interaction.** Every day, a multitude of dynamic patterns of electrophysiological activity emerge, co-exist, interact, and die out in the living brain.\textsuperscript{2} Synchronous oscillations of various frequencies are vital for brain functioning. As Buzsaki and Draghun recently point out, “neighboring frequency bands within the same neuronal network are typically associated with different brain states and compete with each other”.\textsuperscript{2} A kindling-type interaction, in which epileptiform activity spreads from one region to another has been well documented.\textsuperscript{37} To our knowledge, however, such kindling-type phenomena have not been demonstrated in a mean-field model. 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.

The first row of Figure 5 shows distinct disk-shaped regions $D_1$ and $D_2$, which are separated by a “buffer” region, and with two different $\beta$ values, $\beta_1$ and $\beta_2$, such that $\beta^* \leq \beta_1 < \beta_2$. This allows synchronization to occur in both regions.
However, $\beta < \beta^*$ outside and between these regions, so that synchronization does not occur in the buffer region. Since $\beta_1$ and $\beta_2$ are completely independent of each other, the difference between the two beta values can be large and the two regions can synchronize at substantially different rates. 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 the 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 at http://www.math.pitt.edu/~troy/sync/). Because $\beta_1 < \beta_2$, the uniform oscillations in $D_1$ have lower frequency than in $D_2$. However, as formula (8) shows, the rate of synchronization in $D_1$ is faster than in $D_2$. These results give a plausible explanation of how remote sites can synchronize in the brain and, as noted above, are consistent with observations that lower-frequency EEG rhythms entrain larger areas of the brain than higher-frequency rhythms.$^2$ Our finding that synchronization spreads most efficiently at slower frequencies is also consistent with recent fMRI data, corresponding to local-field neural activity,$^4$ which show a stronger spatial response to lower-frequency visual stimuli.$^{38}$

In the second row of Figure 4, the two

\[ \beta_1 = 12.61 = \beta^* \text{ inside the disk-shaped region } D_1 : (x + 20)^2 + y^2 \leq 100; \beta_2 = 15 \text{ inside the region } D_2 : (x - 20)^2 + y^2 \leq 100; \beta = 7 \text{ otherwise.} \]

\[ \text{Bottom row: } \beta_1, \beta_2 \text{ have the same values as above, but now } D_1 \text{ and } D_2 \text{ are close to each other: } D_1 : (x + 20)^2 + y^2 \leq 400, \ D_2 : (x - 20)^2 + y^2 \leq 400. \]

See text for details.
disk-shaped regions have the same $\beta$ values as above, but now $D_1$ and $D_2$ are close to each other and the size of the buffer region is significantly reduced. 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, because the buffer region is small, 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 at http://www.math.pitt.edu/~troy(sync)/). Thus, we conclude that when the buffer is small, the region with higher-frequency oscillations dominates and inhibits synchronization in the slower-oscillating adjacent region.

Our experiments indicate that two complete wavelengths of the traveling wave is the minimal buffer width. When the disks are located closer, the wave emanating from the faster oscillating region enters the other region before the slower oscillating region can emit a wave. Because these waves have to meet in the buffer region to annihilate each other, a smaller buffer region would not allow this annihilation phenomenon to occur. Thus, if the buffer region is smaller than two complete wavelengths of the traveling wave, waves from the faster oscillating region (higher beta) will successfully reach the other region and interfere with the synchronization in that region. We found in our experiments that even a unit-size disk emits traveling waves as synchronization develops and can trigger synchronization in other regions that are located at least two wavelengths away.

If regions $D_1$ and $D_2$ have the same beta values, and an initial stimulus is given at the center of $D_1$ causing synchronization to begin, activity waves are formed and emitted outwards as described above. These waves trigger synchronization in $D_2$, and both regions synchronize at the same rate of oscillations. However, the identical rates of oscillations in the two regions do not necessarily lead to phase synchronization (see Supplementary Movie S6 at http://www.math.pitt.edu/~troy(sync)/). Thus, the rate-only synchronization without phase locking between two regions of the brain observed in our study is different from classical phase-locked synchronization.$^{34,35}$
Conclusions

Our study has shown how a neural network can undergo a series of transformations from the “mathematical” rest to physiological baseline and ultimately, rhythmic, self-sustained epileptiform activity.

We have also shown that the emergence of synchronous self-sustained oscillations in large-scale population networks can be anticipated when the following three principles hold: 1) The network with both positive and negative control mechanisms can be transformed into a strictly positive-feedback system by activation factors and external stimuli, 2) The linear part of the positive-feedback system exhibits decaying oscillations whose frequency increases without bound as $\beta$ increases, and 3) At a critical $\beta^*$, stable, spatially independent, periodic solution comes into existence and coexists with a stable rest state over a continuous range of parameters. These principles depict sufficient conditions for the spontaneous development of synchronous oscillations in complex, multi-component networks. Furthermore, our study explicitly links the emergence and spread of self-sustained, synchronized oscillatory activity with the modification of recovery properties of the network by stimuli. The mechanism of rate-only synchronization without phase synchronization between two separate regions of the brain (with the same or different $\beta$ values) is new, and it is different from classical phase-locked synchronization.\(^{34, 35}\) 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, as well as the self-sustained periodic formation of traveling waves, and also rotating waves. All of these phenomena have been observed in neurophysiological experiments.\(^{5, 10, 25, 39}\) We address mathematical properties of these types of solutions elsewhere.\(^{15}\)

Note that global oscillations and more complicated behavior have been well documented in WC field models without non-local, spatial terms.\(^{26}\) The novelty of our study is in the analysis of oscillations and dynamical patterns in a WC field model that includes non-local, spatial terms, which make the model more relevant in representing the spatially averaged effects of long-range connections. 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 periodic forcing.\textsuperscript{40,41} Instead, this is a result of the intrinsic dynamics of population networks characterized by strong, long-range connectivity.

Previously, Robinson et al. have reproduced alpha rhythm in a mean field model.\textsuperscript{7} Yet, the self-sustained production of waves (that formed the basis for the alpha rhythm) was due to the direct introduction of a wave equation in the model. Because we could not find physiological rationale for the introduction of a wave equation, we have developed a different, more general and physiologically plausible approach. Our model does not contain a wave equation and it is not based on a presumption that waves exist. Yet, it allows simulation of a broad range of activity patterns, including solitary and multiple waves and self-sustained production of waves (without persistent stimulation), which may give rise to alpha rhythm and other rhythmic patterns. Furthermore, our analysis uncovers a plausible transition from baseline activity patterns to synchronized epileptiform rhythmicity. More elaborate versions of WC-type models, including those of the thalamo-cortical networks with multiple modules and subunits\textsuperscript{42} or detailed synaptic interactions,\textsuperscript{21,43} have also been used to reproduce alpha rhythm and epileptiform activity. By contrast, our model is substantially simpler, hence it is more general and theoretically tractable at the expense of a less detailed description of brain architecture and synaptic interactions. Thus, the novelty of our work is not only in the discovery of rich dynamics (described above) in a simple WC-type model, but in the description of theoretical principles predicting and governing the emergence, spread, and interaction of various activity patterns.

Our findings that rhythmicity can arise in complex, multi-component networks as a result of dynamic, self-organizing behavior without periodic driving force may be relevant to the analysis of slow rhythms in the cardiac, respiratory, and vascular neurohormonal regulation which remain largely unexplained.\textsuperscript{44,45,46} Of particular interest for future studies is to determine the types of networks for which a formula like (8) can predict the rate of spread of the region of synchrony. It also important to determine whether our three principles are not only sufficient, but necessary for spontaneous self-organization. Thus, analysis of theoretical principles and functional behavior of neural networks presented here might
be useful for gaining insights into the origins and spread of epileptiform activity and other important problems of contemporary neuroscience.

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APPENDIX

In this section we show how system (1) which is initially in State I (Table I), mathematically characterized by

\[ E(x,0) = I(x,0) = R(x,0) = 0 \text{ for all } x, \]

undergoes a transition to State III (Table 1) which is mathematically expressed as

\[ E(x,t) < \theta_1 \text{ and } I(x,t) \geq \theta_2 \text{ for all } x \]

For simplicity, we carry out the analysis in one dimension. However, all details are exactly the same in two and three dimensions. We follow a two-step process. First, we make simple, general assumptions on the baseline activation factors \( \gamma \) and \( \eta \), and stimulus \( \Psi \), and determine global bounds on functions and parameters which appear in the model. Secondly, we make use of these assumptions and bounds and carry out the analysis.
Assumptions and global bounds

First, we assume that the activation factor \( \eta(x) \) is stronger than \( \gamma(x) \). Our analysis will show how this assumption contributes to achieving and maintaining sub-threshold level of activity of the excitatory population in the time-independent baseline state (Table I, III). Specifically, we assume the following:

(i) Let \( L > 0 \) and \( \theta_1 \in (\frac{\theta_1}{2}, \theta_1) \) be fixed. Assume that \( \gamma(x) \) is continuous and satisfies

\[
0 < \theta_1 - \theta_3 \leq \gamma(x) \leq L(\theta_1 - \theta_3) \quad \text{for all } x,
\]

where \( \theta_1 - \theta_3 > 0 \) and sufficiently small so that \( \gamma(x) \) is uniformly small.

(ii) For simplicity, we assume that \( \eta(x) \) is constant and has the form

\[
\eta = \int_I \omega_{\eta}(x')dx' + (1 + \delta)\theta_2.
\]

We also assume that the activation factor \( \eta(x) \) is uniformly large for all \( t \geq 0 \). This is achieved by letting \( \delta > 0 \) be large. As we shall show, this causes the activity level of the inhibitory neurons to rapidly increase until a time \( T^* \) is reached where \( I \) uniformly exceeds its threshold \( \theta_2 \). In particular, we will show that the inhibitory activity \( I \) remains above \( \theta_2 \) when \( t \geq T^* \). That is,

\[
I(x, t) \geq \theta_2 \text{ for all } t \geq T^* \text{ and } x.
\]

Physiologically, inequality (A1.5) corresponds to the state of tonically active inhibition.18, 22

Definition of \( \beta \). We define

\[
\beta(x) = \frac{\gamma(x)}{\theta_1 - \theta_3} - 1 \text{ for all } x.
\]

We will investigate system dynamics for both constant and spatially variable \( \beta \).
Global bounds. We now obtain global bounds which are needed in the analysis of (1): it follows from assumptions (i)-(iii) that there is a value $M>0$ such that

$$
0 < \int_R \omega_{EE}(x')dx' + \alpha \int_R \omega_{IE}(x')dx' + \gamma(x) + \Psi(x,t) \leq M \quad \text{for all } x \text{ and } t \geq 0,
$$

or, equivalently,

$$
0 \leq \beta = \frac{\gamma(x)}{\theta_1 - \theta_3} - 1 \leq K = L - 1 \quad \text{for all } x.
$$

The analysis

Here, we determine the effects of the activation factors $\eta(x)$ and $\gamma(x)$, and the stimulus $\Psi$ on the dynamics of (1). The analysis consists of the following 3 steps:

I. From (1), (A1.2) and assumptions (i)-(iii) it follows that

$$
E_t(x,0) = \gamma(x) > 0, \quad R_t(x,0) = 0, \quad I_t(x,0) = \eta(x) > 0 \quad \text{for all } x.
$$

Thus, $E$ and $I$ begin to increase as $t$ increases from $t=0$. Below we show that if $\eta(x)$ is uniformly large then $I$ quickly increases and exceed its threshold level $\theta_2$. For this we define the reference point

$$
T_0 = \ln(1 + \frac{\theta_1}{K\theta_1 + 2M}),
$$

where $M>0$ and $K>0$ satisfy (A1.7) and (A1.8). Throughout, our analysis will make use of the observation that $T_0$ is independent of $\eta(x)$.

II. We need the following estimates:

$$
|E| \leq \frac{K\theta_1}{2} + M) (e^t - 1) \leq \frac{\theta_1}{2} \quad \text{and} \quad |R| \leq \varepsilon K \frac{\theta_1}{2} (1 - e^{-\varepsilon t}) \quad \text{for all } x \text{ and } 0 \leq t \leq T_0.
$$

To prove (A1.11) we begin with the following observation: for $t \geq 0$, as long as $|E| \leq \frac{\theta_1}{2}$ then the
equation for $R$ in (1) reduces to 
\[-\varepsilon K \frac{\theta_1}{2} \leq R_i + \varepsilon R \leq \varepsilon K \frac{\theta_1}{2}\]
for all $x$ and $t \geq 0$. \hfill (A1.12)

Multiply (A1.12) by $e^{\varepsilon t}$, integrate from $0$ to $t$, and obtain
\[-\frac{K \theta_1}{2}(1-e^{-\varepsilon t}) \leq R(x,t) \leq K \frac{\theta_1}{2}(1-e^{-\varepsilon t})\]
for all $x$ and $t \geq 0$. \hfill (A1.13)

Next, it follows from the first equation in (1), and the global bound (A1.7), that
\[-M + R \leq E_i + E \leq M + R\]
for all $x$ and $t \geq 0$. \hfill (A1.14)

Substitution of (A1.13) into (A1.14) gives
\[-\frac{K \theta_1}{2}(1-e^{-\varepsilon t}) - M \leq E_i + E \leq M + \frac{K \theta_1}{2}(1-e^{-\varepsilon t}),\]
which holds for $t \geq 0$ as long as $|E| \leq \frac{\theta_1}{2}$. Finally, we multiply (A1.15) by $e^{\varepsilon t}$, integrate from $0$ to $t$,
rearrange terms, and conclude that
\[|E(x,t)| \leq (K \frac{\theta_1}{2} + M)(e^{\varepsilon t} - 1) \leq \frac{\theta_1}{2}\]
for all $x$ and $t \in [0,T_0]$. \hfill (A1.16)

This completes the proof of (A1.11).

**Remark.** The estimates in (A1.13) and (A1.16) hold uniformly with respect to $x$ and $t \in [0,T_0]$. These bounds also guarantee that $|E(x,t)|$ and $|R(x,t)|$ remain uniformly small over short intervals of time.

III. We now determine the behavior of $I(x,y,t)$ over the interval $0 \leq t \leq T_0$. From (1) and (A1.4) it follows that $I(x,y,t)$ satisfies $\tau I_i + I \geq (1+\delta)\theta_2$. Solving this differential inequality gives
\[I(x,t) \geq (1+\delta)\theta_2(1-e^{-\tau/\delta})\]
for $t \geq 0$ since $I(x,0) = 0$. At $t = \tau \ln\left(\frac{1+\delta}{\delta}\right)$ we have
\[I(x,\tau \ln\left(\frac{1+\delta}{\delta}\right)) \geq \theta_2\]
for all $x$.
Therefore, there is a minimal $T^* \in (0, \tau \ln(\frac{1+\delta}{\delta}))$ such that

$$I(x,t) \geq \theta_2 \text{ for all } x \text{ and } t \geq T^*. \quad (A1.17)$$

**Remark.** Property (A1.17) represents the population of inhibitory neurons becoming tonically active at $t=T^*$, and remaining tonically active for all $t \geq T^*$.\(^{18,22}\) Below, we analyze the most important implications of (A1.17) for the system’s dynamics.

First, note that inequality $0 < T^* < \tau \ln(\frac{1+\delta}{\delta})$ causes

$$T^* \to 0 \text{ as } \delta \to \infty. \quad (A1.18)$$

In particular, we let $\delta$ be large enough so that $0 < T^* < T_0$, where $T_0$ is the reference point defined in (A1.10). Next, it follows from (A1.17) that the Heaviside function $f(I(x,t) - \theta_2)$ satisfies

$$f(I(x,t) - \theta_2) = 1 \text{ for all } x \text{ and } t \geq T^*. \quad (A1.19)$$

It is important to observe that property (A1.19) implies that

$$\int_R \omega_{IE}(x-x')f(I(x,t) - \theta_2)dx' = \int_R \omega_{IE}(x')dx' \text{ for all } x \text{ and } t \geq T^*. \quad (A1.20)$$

**The baseline state system.** Because of (A1.20), observe that when $T^* \leq t < T_0$, the $(E,R)$ component of the solution of (1) satisfies

$$\frac{\partial E}{\partial t} = -E - R + \int_R \omega_{EE}(x-x')f(E(x)-\theta_1)dx' - \alpha \int_R \omega_{IE}(x')dx' + \gamma(x) + \Psi, \quad (A1.21)$$

$$\frac{\partial R}{\partial t} = \varepsilon (\beta E - R).$$

Below, we explain the effects of the different components of $\Psi$ on the dynamics of (A1.21). Our goal is to describe the time sequence of events that transforms (A1.21) to the time-varying baseline state. In particular, we will show how our choice of $\Psi$ causes the form of system (A1.21) to undergo a sequence of switches at the times $T_1$ and $T_2$ which satisfy (see (2) and Table 1)
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\[ T^* < T_1 < T_2 < T_0. \] (A1.22)

First, recall that \( \Psi(x, y, t) = 0 \) on the interval \( T^* \leq t < T_1 \) (Table 1, II), hence (A1.21) becomes

\[
\begin{align*}
\frac{\partial E}{\partial t} &= -E - R + \int_R \omega_{EE}(x - x') \cdot f(E - \theta) \, dx' - \alpha \int_R \omega_{EE}(x') \, dx' + \gamma(x), \\
\frac{\partial R}{\partial t} &= \varepsilon (\beta E - R).
\end{align*}
\] (A1.23)

The dynamic behavior of \( E \) and \( R \) is governed by (A1.23) when \( T^* \leq t < T_1 \).

**Switch 1.** At \( t = T_1 \) the stimulus changes from \( \Psi = 0 \) to \( \Psi = \alpha \int w_{IE} \), and this causes (A1.21) to switch its form from (A1.23) to

\[
\begin{align*}
\frac{\partial E}{\partial t} &= -E - R + \int_R \omega_{EE}(x - x') \cdot f(E - \theta) \, dx' + \gamma(x), \\
\frac{\partial R}{\partial t} &= \varepsilon (\beta E - R).
\end{align*}
\] (A1.24)

We refer to (A1.24) as an excitable system (Table 1, III) since \( \omega_{EE} \) only describes connections between populations of excitable neurons, and the activity \( I \) of the inhibitory neurons plays no role in its dynamics when \( t \geq T_1 \). The dynamic behavior of \( E \) and \( R \) is governed by (A1.24) when \( T_1 \leq t < T_2 \). Note that the system is inactive since \( E < \theta \) on \( T_1 \leq t < T_2 \).

**Switch 2.** At \( t = T_2 \), we add a strong, instantaneous stimulus \( \zeta \) to the previously applied stimulus \( \Psi = \alpha \int w_{IE} \). We let \( \zeta \) satisfy

\[
\zeta(x, t) = \begin{cases} 
A e^{-t^2} & t = T_2 \\
0 & t > T_2
\end{cases}
\] (A1.25)

This causes (A1.24) to switch its form to
\[
\frac{\partial E}{\partial t} = -E - R + \int_{R} \omega_{ee}(x-x') f(E-\theta_{i}) dx' + \gamma(x) + \zeta(x,t),
\]
\[
\frac{\partial R}{\partial t} = \varepsilon(\beta E - R).
\]

When \( t \geq T_{2} \), the dynamic behavior of \( E \) and \( R \) is governed by (A1.26). To analyze the dynamics of (A1.26), it is convenient to re-scale the variables and parameters by setting

\[
u = E - \frac{\gamma(x,y)}{1+\beta}, \quad v = R - \frac{\beta \gamma(x,y)}{1+\beta}, \quad \omega = \omega_{ee}, \quad \theta = \theta_{i} - \frac{\gamma(x,y)}{1+\beta}.
\]

This transforms (A1.26) into the canonical, excitable form of equation (4).

Recall from (A1.6) that \( \beta = \frac{\gamma(x)}{\theta_{i} - \theta_{3}} - 1 \). This, and (A1.27) imply that \( \theta = \theta_{3} \) in (4). The dynamic behavior of system (4) depends on the stimulus \( \zeta \) and the functional form of \( \beta \). Detailed analysis of the behavior of (4) in different ranges of constant values of \( \beta \) is described in sections 3 and 4 of the main body of the manuscript; the effects of spatially variable \( \beta \) are shown in section 5. In these sections we show that there is a critical value of \( \beta^{*} \) such that, when \( \beta \geq \beta^{*} \), large-scale synchronous oscillations occur when \( \zeta(x,T_{2}) \) is of sufficient magnitude. Other types of functional activity that arise when \( \beta < \beta^{*} \) are also described in the main body of the manuscript. Since we apply stimulus \( \zeta \) at time \( t=T_{2} \), we need to estimate the values of \( u \) and \( v \) at \( t=T_{2} \). It follows from (A1.6) and (A1.27) that

\[
u(x,T_{2}) = E(x,T_{2}) - (\theta_{i} - \theta_{3})
\]
\[
v(x,T_{2}) = R(x,T_{2}) - (\gamma - (\theta_{i} - \theta_{3}))
\]

From (A1.13) and (A1.16) we conclude that

\[|E(x,T_{2})| << \frac{\theta_{i}}{2} \quad \text{and} \quad |R(x,T_{2})| << K \frac{\theta_{i}}{2}
\]

From (A1.28) and (A1.29) we obtain the estimate
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\[
-\frac{3\theta}{2} + \theta_1 \leq u(x,T_2) \leq -\frac{\theta}{2} + \theta_3 \quad (A1.30)
\]

Since we assume (see (ii)) that \( \theta_3 \approx \theta_1 \) and \( \theta = \theta_3 \), we can approximate (A1.30) with

\[
|u(x,T_2)| \ll \frac{\theta}{2} \text{ for all } x. \quad (A1.31)
\]

Similar reasoning gives the estimate

\[
|v(x,T_2)| \ll K \frac{\theta}{2} \text{ for all } x. \quad (A1.32)
\]

The estimates given in (A1.31) and (A1.32) imply that \( u(x,T_2) \) and \( v(x,T_2) \) are approximately zero when \( T_2 - T^* > 0 \) is small. Hence, for computational simplicity we assume that

\[
u(x,T_2) = v(x,T_2) = 0 \quad \text{for all } x. \quad (A1.33)
\]

At \( T_2 \) we apply the stimulus \( \zeta(x,T_2) \) to the system (4) with initial values given in (A1.33). If the stimulus \( \zeta(x,T_2) \) is strong enough and \( \beta \) is in an appropriate range, synchronous self-sustained oscillations are initiated at the point of stimulus and spread outward. The detailed description of this process is given in the main body of the manuscript.
References


