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# Neurophysiology and Waves

*By Bard Ermentrout and David Pinto*

Spatiotemporally organized waves are among the most ubiquitous activity patterns in the brain. Recent advances in electrophysiology, imaging, and other technologies allow experimentalists to observe these activity patterns simultaneously in the responses of many individual neurons and in the ensemble response of the neural circuit, both in vivo (the whole animal/subject) and in vitro (e.g., cultured cells, brain slices); see Figure 1. By making explicit the process by which wave-like activity emerges from neuronal circuitry, applied mathematics can contribute substantially to our understanding of the dynamics of the brain.

Propagating waves clearly tell us something about the intrinsic circuitry of the brain—for example, its preferred directionality and excitability. Any active medium that is locally connected is able, and indeed expected, to generate wave-like behavior. Recognizing that nature generally tries to exploit the intrinsic dynamics of systems, several investigators have proposed theories as to how wave-like activity might be useful in the brain.

Wave-like patterns are evident in both normal and pathological activity throughout the nervous system. The clearest examples of organized spatiotemporal activity for normal function are *central pattern generators*, which coordinate activity in muscles involved in such motor functions as swimming, feeding, and even breathing. Recordings from the spinal cord of the eel-like lamprey, for instance, show a clear pattern of oscillatory waves that produce the necessary patterns for swimming. Similar waves are observed in the leech and in the crayfish. Other possible roles for waves in normal brain function include establishing the spatial map between the retina and brain during development, scanning sensory inputs for novel features, and encoding target location during motor control.

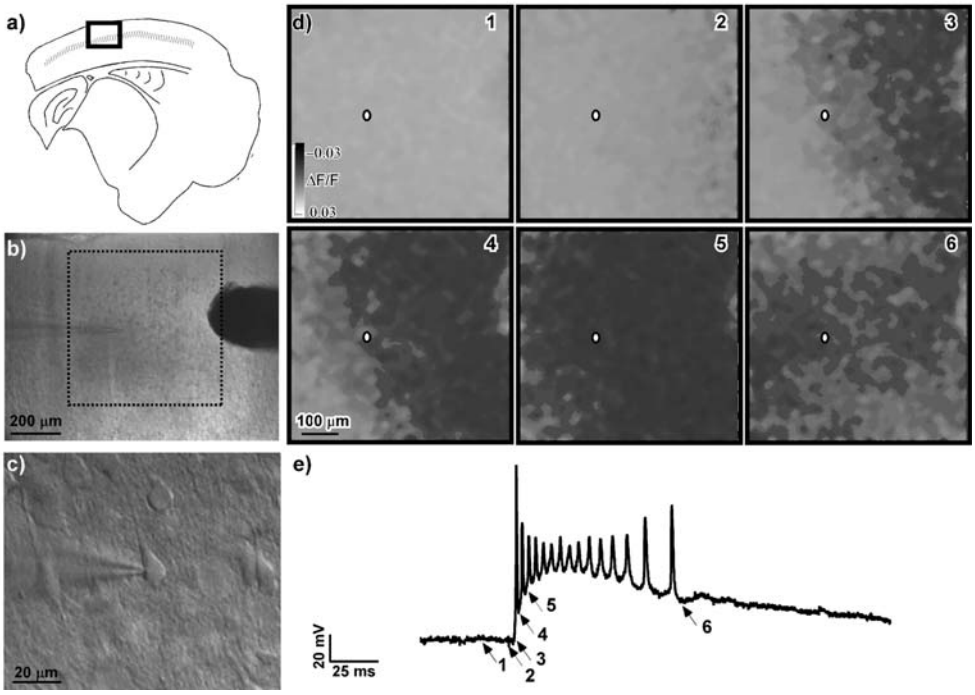


**Figure 1.** *An activity wave in a brain slice from rodent neocortex. Panel (a) is a schematic of a coronal slice taken from one hemisphere of rodent brain. The rectangle outlines the region detailed in Panel (b). Panel (b) is an image of rodent neocortex showing a metal stimulating electrode (right) and a glass recording electrode (left) positioned in the slice. The dashed square outlines the region imaged in panel (d). Panel (c) shows a glass electrode patched onto a single cortical neuron. Panel (d) shows a wave of activation moving across the slice following a brief (200 μs) electrical stimulus. Successive frames are taken at times indicated in Panel (e). Panel (e) is a voltage trace obtained from a cortical neuron located near the white dot in Panel (d). The voltage trace was obtained simultaneously with the activity wave. Waves were induced by bathing the slice in 20 mM picrotoxin to block synaptic inhibition and detected by bathing the slice in voltage-sensitive dye and measuring the change in fluorescence (F). From Sally Duarte and David Pinto, unpublished data.*

Waves are also common in many pathological brain states, such as epilepsy. Focal epilepsy, in particular, is characterized by waves of activity emanating from a local cortical malformation resulting either from injury or from a developmental disorder. Epileptiform activity waves can also be seen in many animal models of epilepsy, both in vivo and in vitro. In most cases, waves are induced experimentally by increasing the excitability of neural tissue with drugs or other manipulations.

Neural waves can be roughly divided into three classes: (i) stationary waves; (ii) active waves; and (iii) oscillation-generated, or phase waves. Stationary waves are spatial patterns that do not propagate—zero-velocity waves. Although their properties are extremely interesting, we focus here on the latter two classes.

Active waves emerge from spatial networks when each local point exhibits the dynamics of an excitable system. Waves of this type—which are responsible for spiral waves in chemical systems, for the movement of flame fronts, and for many other traveling phenomena—are the most familiar to applied mathematicians. In the brain, the best known examples include epileptiform activity waves emanating from diseased or damaged tissue or from experimental brain tissue treated with drugs. In certain tissue slices it is also possible to induce spiral waves and other two-dimensional phenomena.

Phase waves emerge when the local circuitry is intrinsically oscillatory and local heterogeneities, anisotropy, or dynamic instabilities induce phase differences that vary over space. Waves observed in the slug brain, in the visual cortex of the turtle, in the motor cortex of monkeys, and in the central pattern generators of many swimming animals are likely examples of phase waves.

## Modeling Active Waves

How can mathematics help us understand the biology of neural waves? Conversely, can the experimental study of these waves lead to any interesting new mathematics?

Many of the strategies used to analyze the mathematics of brain waves derive from earlier studies of diffusive waves in single neurons. The classic work of Hodgkin and Huxley describing the propagation of activity along the axon of a squid, for instance, is based on the study of a nonlinear reaction–diffusion equation in which the active ionic currents are coupled with linear diffusion of the potential.

Unlike the diffusive coupling in nerve axon equations, waves in cortical networks are produced by coupling that is *synaptic*, i.e., nonlocal. The simplest class of models to have provided insight into the dynamics of traveling waves are *population*, or *firing rate* models. One particularly relevant version of such models has the form:

$$u(x,t) = \int_{-\infty}^{t} \alpha(t-t')F\left[\int_{-\infty}^{\infty} J(x-y)u(y,t')dy - z(x,t)\right]dt'$$
$$\frac{\partial z(x,t)}{\partial t} = \varepsilon[u(x,t) - z(x,t)].$$

The usefulness of this expression is that each term can be related directly to key features of biological cortical circuitry that, in many cases, can be experimentally measured and/or manipulated. In the model, $u(x,t)$ is the firing rate of the neuron at position $x$ and time $t$, $\alpha(t)$ is the time course of individual synaptic interactions, $J(x-y)$ is the pattern of spatial connectivity between neurons, $F(u)$ is the voltage-to-firing rate transformation function, and $z$ is a local "recovery" variable that captures many slow intrinsic processes preventing ongoing activity in single neurons. Together, the equations succinctly express the relation between the synaptic ($\alpha(t)$) and spatial ($J(x-y)$) elements of the circuit, as well as the intrinsic properties of individual neurons ($F(u)$ and $z(x,t)$). This model has been used extensively to explain and predict the behavior of epileptiform activity waves observed experimentally.

In practice, analysis of the firing rate model often begins with the assumption that synaptic dynamics, i.e., $\alpha(t)$, grow instantaneously and decay exponentially, in which case the system can be written as follows:

$$\frac{\partial u(x,t)}{\partial t} = -u(x,t) + F\left[\int_{\Omega} J(x-y)u(y,t)\,dy - \gamma z(x,t)\right] \quad (1)$$
$$\frac{\partial z(x,t)}{\partial t} = \varepsilon[u(x,t) - z(x,t)].$$

Moreover, $J(x)$ is generally taken to be non-negative, symmetric, and integrable on the domain $\Omega$, which could be the real line or the plane, and $F(u)$ is typically monotonically increasing and non-negative, saturating as $u \to \pm\infty$.

Typical of the many interesting parameters that can be varied in this model is the total strength of recurrent connections:

$$W = \int_{\Omega} J(y)\,dy.$$

If $F$ is piecewise-constant (e.g., a Heaviside step function), we can easily write an explicit formula for the velocity of traveling pulses, which can be compared with those found experimentally. As with many traveling wave problems, there are two values of the velocity $\upsilon$, depending on, say, $W$, which coalesce at a saddle-node point as $W$ gets closer to $W^*$ from above . The slow wave is presumed to be unstable, the faster one stable. This can be proved for the step-function case, but existence and stability results have not been obtained for general $F$. Interestingly, in a recent paper, experimentalists inferred the existence of the slow and fast waves in a clever preparation in which neurons were grown in a one-dimensional array. By altering the strength of the recurrent excitation ($W$), they quantitatively fit the velocity to a simple neural network model.

## Modeling Phase Waves

Systems of local spatially-coupled oscillators can produce a variety of spatial patterns. The easiest way to model such systems is to assume that each point in the medium is locally oscillatory and assign a scalar variable, the phase, to the location. The spatially continuous analogue to an active medium has the form

$$\frac{\partial \theta(x,t)}{\partial t} = \omega(x) + \int_{\Omega} H(x,y,\theta(y,t) - \theta(x,t)),$$

where $H(x,y,\theta)$ is periodic in its third argument and represents the phase coupling, and $\omega(x)$ is the natural frequency. Discrete versions of this system have been the subject of many analyses, and the existence of a variety of types of waves, including rotating waves in two dimensions, has been rigorously proved. For example, if the domain is the real line, $\omega(x) = 1$, and $H(x,y,\theta) = J(x-y)h(\theta)$, the reader can verify that $\theta(x,t) = (1 + \alpha(k))t + kx$, with

$$\alpha(k) = \int_{-\infty}^{\infty} J(y)h(ky)\,dy,$$

is a family of traveling waves. Depending on the shapes of $J$ and $h$, some of these are stable. Such models can explain the emergence of traveling waves in neural systems in which changes in the shape of $h$ are seen with different kinds of coupling.

## Future Directions

Mathematical analysis of wave activity in the brain is in an early and exciting stage. Work presented in just the past few years has established the existence and stability of traveling solutions for spatially extended synaptic networks. These studies parallel similar investigations of systems with diffusive coupling conducted some thirty years ago.

Given the equations that effectively capture simple propagation, one direction for further analysis is to model and explain more complex experimentally observed wave phenomena. In a recent study, one of us (D.P.) demonstrated that experimental waves induced in the slice entail at least three independent dynamic mechanisms, governing wave initiation, propagation, and termination. Modeling and explaining the dynamics for each stage individually would readily translate into new experimental ideas for controlling or curtailing epileptic activity, possibly in a clinical setting.

Another challenge lies in the connection of activity in neural populations with activity in single neurons. As described in several other articles in this issue, the process of neuronal synchrony is closely related to neuronal rhythms and oscillations. The hope for future studies is to bring the two fields together, examining synchrony and rhythmic activity in the context of spatiotemporally propagating phase waves.

Finally, much of the analysis of brain waves has been focused on phenomena in one dimension, such as fronts and pulses. Only recently have investigators begun to examine phenomena that are essentially multidimensional; for example, based on simulations of the two-dimensional analogue of equation (1), spiral waves were induced in a tangential slice (see http://www.jneurosci.org/cgi/content/full/24/44/9897/DC1).

## For Further Reading

[1] O. Feinerman, M. Segal, and E. Moses, *Propagation along unidimensional neuronal networks*, J. Neurophysiol., 94 (2005), 3406–16.

[2] X. Huang, W.C. Troy, Q. Yang, H. Ma, C.R. Laing, S.J. Schiff, and J.Y. Wu, *Spiral waves in disinhibited mammalian neocortex*, J. Neurosci., 24 (2004), 9897–902.

[3] D.J. Pinto, S.L. Patrick, W.C. Huang, and B.W. Connors, *Initiation, propagation, and termination of epileptiform activity in rodent neocortex in vitro involve distinct mechanisms*, J. Neurosci., 25 (2005), 8131–40.

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