Phase Synchronization May Reveal Communication Pathways in Brain Activity

How is the firing of individual neurons translated into thought, sensory perception or movement? Physicists are joining the quest for answers.

Employing experiments that range from studying isolated pairs of lobster neurons to looking at electrical and magnetic signals from human test subjects, physicists are applying concepts from nonlinear systems, chaos and control theory to improve our understanding of neuronal dynamics. Exemplifying this approach, a collaboration in Germany between neurologists at the University of Düsseldorf and physicists at the University of Potsdam has recently demonstrated the potential of a new nonlinear analysis technique—phase synchronization—for neuronal studies.[1] With this tool, the researchers found evidence in magnetoencephalography (MEG) data for synchronous activity between different parts of the brain and between the brain and the muscles during the tremor of a patient with Parkinson's disease (see the figure below).

The role of synchrony

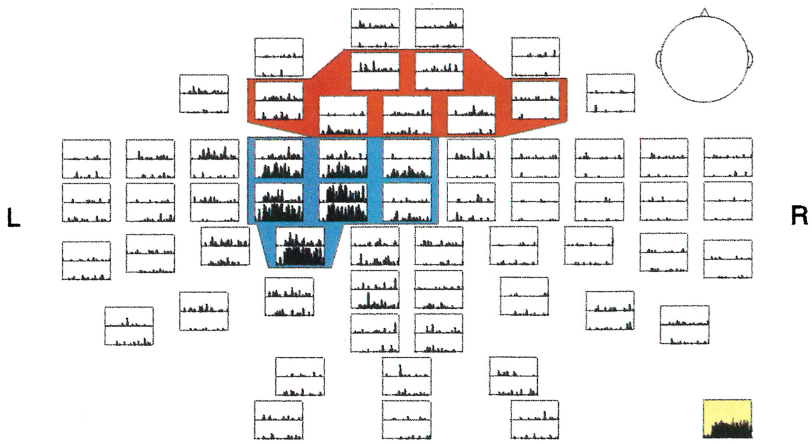
A major focus of the study of neurophysiology is synchronization between neurons, ranging from individual pairs of neurons[2] to much larger scales—within one area of the brain or between different parts of the brain.[3] "All really interesting things that go on in the brain happen in states of partial synchrony," explains neuroscientist and surgeon Steven Schiff (George Mason University). "Otherwise, signals from individual neurons would be independent, and no useful computation would be performed." Too much synchrony, though, may cause dynamical diseases,[4] such as epilepsy or tremor.

One of the challenges facing neuroscientists is to detect such synchrony. For starters, the very term "synchrony" means different things to different people. In the strictest sense, synchronization means that there is a 1:1 correspondence between the states of two coupled systems as they evolve. For systems with different structures or parameters, broader definitions are needed. "Generalized synchrony" means that there exists a functional relationship—possibly a nonlinear one—between the systems,[5] which can still be hard to prove experimentally, according to Schiff.

The traditional measures of synchronization are cross correlation in the time domain and coherence in the frequency domain, both linear analysis tools. The nervous system, however, is composed of highly nonlinear elements. "The nature of the relationship between two systems that are synchronized nonlinearly can be much more complex than when linear synchrony exists," comments Schiff. Jürgen Kurths and the other members of the theoretical nonlinear dynamics group in Potsdam have pioneered the use of a nonlinear tool for measuring synchrony—phase synchronization.

Under appropriate conditions, coupled oscillators can become phase locked, so that their frequencies are in a rational ratio, and therefore so are their phases (up to a constant). Indeed, phase locking is commonly used to stabilize a high-power oscillator using a second, lower-power but more stable oscillator. Kurths's group has extended the idea of phase locking to chaotic oscillators. They have shown that it is possible to calculate the time-dependent phase of a complex signal.[6] Kurths cautions, though, that "you need a dominant narrow-band spectral range"—that is, modulation (possibly complex) around some sort of periodic behavior. However, the origin of the complexity—whether noise or chaos—is immaterial.

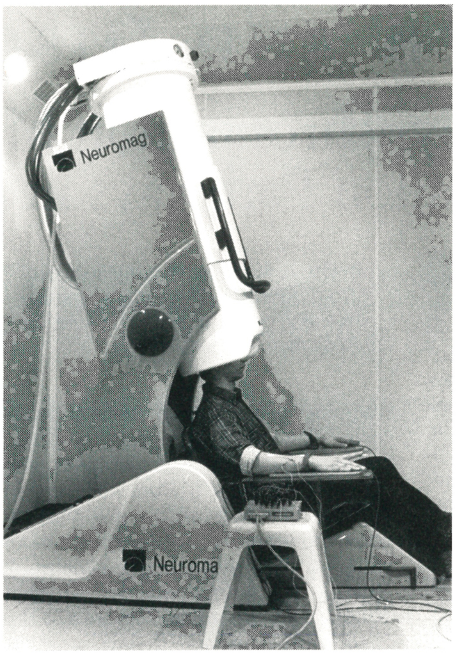
Why look at the phases of signals? "When you compare two complicated signals, the amplitudes are often not correlated," says Kurths, "but if you look at the phases, you do find a relationship." With their technique, Kurths and company can uncover such relationships. In noisy or chaotic systems, there can be phase slips—rapid changes in the relative phase $\phi_{n,m} = n\phi_1(t) - m\phi_2(t)$, where ϕ_1 and ϕ_2 are the phases of the two signals and the variable integers n and m allow consideration of an arbitrary harmonic relationship. Consequently the question of synchronization between the phases can be answered only in a statistical sense. To that end, two quantitative statistical measures of $n{:}m$ phase synchronization, one based on conditional probability and one based on the entropy of the distribution of the relative phase, were introduced.[1] By comparing either measure to that obtained by applying the analysis to surrogate data (filtered white noise), the researchers can determine the values of the indices n and m for



1:2 PHASE SYNCHRONIZATION between brain activity, as measured with 122 magnetoencephalography channels, and the signal (yellow) from the flexor muscle of the right hand during tremor in a patient with Parkinson's disease. Each box shows the extent of synchronization in two channels, measured by the entropy of the relative phase distribution, over a period of 310 s. The tremor begins 50 s into the measurement. The red and blue areas correspond to regions of the cortex associated with voluntary right-side muscle activity. The head is viewed from above. (Adapted from ref. 1.)

which there is significant phase synchronization.

In addition, phase synchronization does not demand one particular requirement that is common to many other analysis techniques: The data do not need to be statistically stationary. For most linear and nonlinear analysis techniques, signals must have constant mean values and power spectra. Many analysis techniques require strong stationarity, where all moments of the time series are constant in time. Biological systems like the brain or the cardiorespiratory system[7] are naturally very far from stationary.



A 122-SENSOR MAGNETOENCEPHALOGRAPH, covering the whole head and housed in a helmet-shaped dewar, is used along with electrodes on the patient's arm and wrist to search for synchronous brain–muscle activity. (Courtesy of Hans-Juergen Bauer.)

Phase synchrony in the brain

Düsseldorf neuroscientist Peter Tass has been looking at phase dynamics in physiological systems in collaboration with Kurths's group since 1994. To investigate phase synchronization in the brain, they have recently teamed up with Alfons Schnitzler's MEG group, which is in Düsseldorf's department of neurology headed by Hans-Joachim Freund. MEG and its cousin, electroencephalography (EEG), are well-suited for the study of neuronal dynamics because of their typical millisecond time resolution. Although EEG electrodes can be placed directly on the head, the bone of the skull distorts the signals, hindering efforts to localize the signal sources. The usual approach, therefore, is to drill holes through the skull and implant the electrodes directly into the cerebral cortex—the roughly 3 mm thick layer of so-called gray matter covering the outer surface of the brain. In contrast, the brain's magnetic field passes through the skull without changing direction. MEG, therefore, can provide better localization of brain activity—typically 5 mm—and it's noninvasive.

MEG uses superconducting quantum interference devices (SQUIDs) to measure the brain's magnetic signals. The device used by the collaboration has 122 channels and covers the entire head. The SQUIDs are arranged in pairs to measure the transverse magnetic field gradients in two orthogonal directions in 61 locations around the head. The entire apparatus, containing the SQUIDs and the pickup coils that couple the magnetic flux to the SQUIDs, is housed in a helmet-shaped dewar that fits over the head (see the photograph above).

The pickup coils inside the helmet are about 3 cm away from the firing neurons of the cortex. Though the detectors are sensitive enough to handle the very small field gradients—typically nanogauss per centimeter—produced at that distance from the brain, they pick up the activity of thousands of neurons in the cortex that are all firing at different times. The task of extracting the weak signals of interest from the large background is critical. Signal averaging has been the common approach, and has been successfully used with MEG data by Bernie Conway and his colleagues (University of Strathclyde in Scotland) and by Riitta Hari and her coworkers (Helsinki University of Technology in Finland) to demonstrate synchronous activity between parts of the brain and voluntary muscle movement.

Tass and company show that phase synchronization can uncover synchronous behavior in MEG time series data. They have demonstrated this capability with data from a patient in the early stages of Parkinson's disease, a degenerative disorder of the central nervous system. One characteristic of the disease is involuntary shaking—tremor—at a frequency of 3–8 Hz that occurs in repose and is seen primarily in the hands and less commonly in the feet, lips and jaw. Although the principal degenerative process is known to involve a loss of the neurotransmitter dopamine, how the degeneration causes tremor is not well understood.

One of the Düsseldorf neurologists, Jens Volkmann, had previously used MEG studies with other colleagues to demonstrate that specific parts of the brain normally associated with voluntary muscle activity show tremor-synchronous activity.[8] That analysis relied on traditional, linear techniques. By looking for phase synchronization between different parts of the brain and between brain and muscle activity during the tremor, the new collaboration not only confirmed the synchronous activity in motor-related parts of the brain, but was better able to localize the regions of synchronized behavior and was able to follow the temporal evolution of that behavior.

The first patient the researchers studied was a 36-year-old male in the early stages of Parkinson's, so that tremor—in this case, of the right hand—was the only significant abnormality present. The activity of the muscles flexing and extending the right fingers was recorded using electrodes attached over the muscles and filtered between 5 and 7 Hz to extract the principal tremor frequency component. MEG data were filtered within the same range and additionally at the first harmonics (10–14 Hz).

The researchers used both of their synchrony statistics to search for $n{:}m$ synchronization in the time series. During the tremor, they found 1:1 phase locking between the flexor and extensor muscles, which they had expected. They also found 1:2 synchrony between cortical activity and each of the two muscles. The primary regions of cortical synchronization were in two regions on the left side of the brain that are normally associated with voluntary right-side muscle movement (see the figure on page 17). The two regions of the cortex were also 1:1 phase-locked together. Furthermore, both the brain–muscle and brain–brain synchrony appeared only with the onset of the tremor, and their strengths were found to decrease as the tremor faded. Additional studies of other patients with Parkinson's have shown similar phase-locking results.

The value of nonlinear analysis

Revealing tremor-related synchronous brain–brain interaction by means of nonlinear phase synchronization analysis would not have been possible with only linear analysis, says Tass. "The standard tool, coherence analysis, would have found relationships between a synchronous area and almost all other regions of the cortex." Solving the difficult problem of determining the pattern of firing neurons that produced the measured MEG signals—necessary for obtaining detailed information about the location of tremor-synchronous activity—is still under way.

"This isn't isolated work, but a harbinger of things to come—applying the ideas of nonlinear dynamics to signals from neurons," comments Lou Pecora (Naval Research Laboratory). "The tools of nonlinear dynamics have the power to give you information you can't get from standard techniques."

Phase synchronization is but one nonlinear dynamics tool being brought to bear on the question of neural communication. Tools inspired by the concept of fractal dimension from chaos theory have been used to predict the onset of epileptic seizures.[9] (See PHYSICS TODAY, July 1998, page 9.) And other researchers, such as Peter Grassberger's group at the John von Neumann Institute for Computing in Jülich, Germany, are working on concepts for detecting weak, statistical forms of synchrony.

"The main merit of Kurths's work is that it shows a possible direction for quantifying synchronization phenomena in complex neurological systems," says Thomas Schreiber (University of Wuppertal), who also uses nonlinear analysis techniques to study physiological systems. "It doesn't pretend to provide the final answer, but often you're at a loss about what to look for. Phase synchronization may be a way to go."

Schiff, a fellow researcher of synchrony in the nervous system, concurs. "The phase synchrony technique will appeal to many in neuronal dynamics, since it can pick up synchronization that can't be seen by linear tools," he says. "It opens windows to phenomena not currently accessible."

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References

1. P. Tass *et al.*, Phys. Rev. Lett. **81**, 3291 (1998).
2. C. M. Gray, W. Singer, Proc. Nat. Acad. Sci. **86**, 1698 (1989). S. J. Schiff *et al.*, Phys. Rev. E **54**, 6708 (1996). R. C. Elson *et al.*, Phys. Rev. Lett. **81**, 5692 (1998).
3. S. L. Bressler *et al.*, Nature **366**, 153 (1993).
4. J. Bélair *et al.*, eds, *Dynamical Disease: Mathematical Analysis of Human Illness*, AIP, New York (1995).
5. N. F. Rulkov *et al.*, Phys. Rev. E **51**, 980 (1995). L. M. Pecora *et al.*, Phys. Rev. E **52**, 3420 (1995).
6. M. G. Rosenblum *et al.*, Phys. Rev. Lett. **76**, 1804 (1996).
7. C. Schäfer *et al.*, Nature **392**, 239 (1998).
8. J. Volkmann *et al.*, Neurology **46**, 1359 (1996).
9. K. Lehnertz, C. E. Elger, Phys. Rev. Lett. **80**, 5019 (1998). J. Martinerie *et al.*, Nature Med. **4**, 1173 (1998). S. J. Schiff, Nature Med. **4**, 1117 (1998).

Deep under the South Pole, a Novel Telescope Records Ultrahigh-Energy Astrophysical Neutrinos

Neutrinos that have escaped from the hottest cauldrons in the cosmos are being captured in 18 000-year-old ice.

A neutrino telescope buried under a mile of ice at the South Pole has been recording the interception of very high energy neutrinos (typically 10^{12} electron volts, or 1 TeV) for two years now. The AMANDA (Antarctic Muon And Neutrino Detector Array) collaboration has begun reporting its first results at meetings in recent weeks. A preliminary pass through the first four months of data harvested in 1997 has already yielded about 20 unambiguous neutrino events. So one can expect AMANDA, in its present configuration, to yield about 100 events per year above its neutrino-energy threshold of roughly 50 GeV.

AMANDA is a collaboration of a dozen institutions in the US, Sweden, Germany and Belgium. The spokesmen are Steven Barwick (University of California, Irvine) and Christian Spiering (DESY Institute for High Energy Physics, in Zeuthen near Berlin).

The 50-kiloton Super Kamiokande in Japan, largest of the water-Čerenkov detectors in a man-made container, is limited by its size to the measurement of neutrino energies less than about 10 GeV. (See PHYSICS TODAY, August 1998, page 17.) At higher energies, the neutrino sky has been *terra incognita*. The idea of recording the collisions of very energetic astrophysical neutrinos by deploying Čerenkov-light (or even acoustical or radio) detector arrays in large *natural* volumes of water or ice has been under discussion since the 1960s. With the exception of the relatively small Russian facility at Lake Baikal in Siberia, AMANDA is the first such high-energy neutrino telescope to begin operation. In almost a decade of running, the pioneering Baikal array has recorded only a handful of neutrino candidates. In more benign climes, the ambitious DUMAND project off the coast of Hawaii was canceled by DOE in 1996, after three years of installation efforts plagued by an inhospitable ocean and unanticipated cutbacks in logistics support. NESTOR, a Greek-German-Italian-Russian-Swiss undertaking, is currently under construction off the Ionian coast of the Peloponnisos. A similar French–British project, named ANTARES, expects to begin deploying detectors off Marseilles next year.

"It's a funny way to scan the heavens," says DUMAND survivor Robert March (University of Wisconsin–Madison). "Instead of putting your detectors on a mountain top, you bury them deep under water or ice, and then look *downward* for things coming up through the Earth." One has to perform these antics because one can't look directly for the elusive, electrically neutral neutrinos. What one actually observes is the Čerenkov light generated in water or ice by the passage of relativistic charged particles—mostly muons—produced by neutrino collisions (at painfully low rates) with nucleons in or near the detector volume.

Any such scheme, however, would come to grief if one didn't have a way of eliminating the overwhelming background of cosmic-ray muons that have nothing to do with the high-energy neutrinos one wants. Burying the detector deep does greatly attenuate the cosmic-ray muon flux; but that's not nearly enough. The detector array must have directional resolution good enough to distinguish between muons coming down from above—all of which are fatally suspect—and those coming up from below. Only a neutrino could make its way through the Earth; cosmic-ray muons have ranges in material of, at most, tens of kilometers.

Why bother?

Good directional discrimination is essential for much more than just weeding out cosmic-ray muon background. A fundamental goal of the new discipline of high-energy neutrino astronomy is the detection and study of point sources in and beyond our galaxy. Neutrinos, unlike photons, are not subject to absorption in the environs of the source, the Earth or the intervening medium. Nor, unlike charged cosmic rays, are their points of origin obscured by bending in the Galactic and intergalactic magnetic fields. The most energetic charged cosmic rays, though they may suffer only negligible magnetic bending, are presumed to lose significant energy over long extragalactic distances by pion production in collisions with cosmic-microwave-