BOOKS: NEUROSCIENCE

Interconnected Stories of Brain Rhythms

György Buzsáki

Mircea Steriade's latest book is a monograph written to demonstrate that an understanding of the complex nature of brain operations requires that they be studied in the intact organ. Isolated fragments cannot reveal the actual workings of this supertissue, and our approach to the brain should differ from how we study other organs. Once the precise mechanism of the nephron, the elementary building block of the kidney, was well understood, we learned a great deal about the operations of the kidney and its diseases. But even if we understand the mechanisms of the brain's building blocks, we are still far from understanding the brain itself. Therefore, those who wish to comprehend neuronal systems must study the intact tissue performing its normal functions rather than its mutilated mini version in the dish. That is the message delivered by Steriade, a neurophysiologist at Quebec's Laval University, whose lengthy career serves as an example of how one can carry out cutting edge research without seriously compromising the substrate under study.

The Intact and Sliced Brain
by Mircea Steriade
MIT Press, Cambridge, MA, 2001. 382 pp. $55, £37.95. ISBN 0-262-19456-2.

A main goal of *The Intact and Sliced Brain* is to compare the various methods currently used to investigate brain oscillations (especially those rhythms resulting from interactions between the cerebral cortex and thalamus) and to confront their shortcomings. At the heart of the debate that Steriade reviews is whether these oscillation patterns emerge in a circumscribed brain tissue or require large interconnected systems. The author explains that our brain is in continuous oscillation. The largest amplitude and slowest waves reflect strongly synchronized, cooperative patterns in large aggregates of cortical and thalamic neurons. Steriade pays particular attention to the rhythms observed during sleep: slow oscillation (0.5 to 1 Hz), delta waves (1 to 4 Hz), and sleep spindles (7 to 15 Hz). Neurons do not lose their beat when the brain awakes; instead, a faster (20 to 80 Hz) and much lower amplitude, so-called gamma, oscillation emerges. These fast oscillations, spatially confined and temporally short-lived, are believed to tie together active neuronal assemblies.

What is the best method to reveal the mechanisms and content of these oscillations? This question is not trivial because brain rhythms appear to be as complex as the brain itself. The usual approach to dealing with complexity is to simplify, but Steriade opts to leave the brain intact. His noble choice, however, inevitably allows uncertainty to remain in the explanation of observations. As a result, critical details must be neglected to create communicable theories.

Another choice is to compromise the brain's hardware. The in vitro slice preparation represents such an approach. Although the author acknowledges the large amount of information accumulated by the work on brain slices, he advises us that the conclusions derived from these preparations are often extended too far. Admittedly, the in vitro model of oscillations cannot truly represent the actual phenomenon, and hypotheses generated in simplified preparations must be confronted with experiments in the intact brain. Steriade drives this point home persuasively. But I am unable to resist pointing out that the author's own research provided the basis for allowing such simplification of the hardware.

Gustav Klimt's *Danae*. Behavioral states (such as the sleep portrayed here) that are associated with thalamocortical rhythms, Steriade's principal contribution to neuroscience, can hardly be perfectly understood using only brain slices.

For example, Steriade suggested that the neocortex can generate slow oscillations, the reticular nucleus of the thalamus (a neat collection of fast-spiking inhibitory neurons) can produce sleep spindles, and thalamocortical neurons in isolation can give rise to delta waves. It comes as no surprise that investigators—curious about the complex operations of the brain but limited by the small amount of tissue available in the in vitro preparation—jumped on the opportunity and began to explore the ionic basis of these oscillations. Thanks to the slice preparation, discoveries such as T and h channels rapidly advanced our understanding of thalamocortical oscillations after decades of standstill. So when it comes to the method of choice, I take the blunt advice of my professor of pathology: "The best method is your method, the best hypothesis is your hypothesis."

Steriade presents the intact- versus sliced-tissue dispute embedded in two equally fascinating stories. No one still believes that the thalamus is just a relay device diligently and faithfully transferring peripheral information to the neocortex. But we often fail to remember the names and key events that shaped our current understanding of the thalamus, neocortex, and their interactions. In the first part of the book, Steriade guides us through a century of hard work and thinking by many exceptional intellectuals. Although some of the information he provides can be gleaned from the literature, the most valuable parts of this historical tour are based on his personal observations and discussions with the key players in the extended world of the thalamocortical studies. Many of these scholars advanced their own approaches for studying the brain. One, the author's mentor, Frédéric Bremer, introduced the brain "slicing" (transection) technique to study sleep-wave cycles in his famous *encéphale isolé* and *cerveau isolé* preparations. Against this background, I wonder why Steriade is at odds with recent (thin) slicing techniques.

The second story demonstrates that, like rhythms in the thalamocortical circuit, the theories discussed by the author reverberate, albeit at a much slower pace. First, the neocortex was in charge. After decades of work, the theories shifted to focus on the thalamus. Now the pendulum appears to have slowly swung back to the neocortex, as exemplified by Steriade's considerations of unified corticothalamic networks. I found the commentary on the history and

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context of the research most enjoyable and recommend it to anyone interested in how scientific theories evolve and revolve.

In a short but grand finale, Steriade addresses the question of consciousness. In light of comments such as Francis Crick's claim that "consciousness depends crucially on thalamocortical connections with the cortex" [*The Astonishing Hypothesis* (Scribner, New York, 1994)], someone who has spent a career searching for treasures in this terrain is unlikely to remain neutral on the issue. Steriade does not. He candidly recommends that those interested in the subject read Dostoyevsky, Proust, or Joyce and devote their limited research time to topics that can be defined and successfully attacked. With this delightfully entertaining conclusion, the author has voluntarily distanced himself from the competition in the consciousness battlefield. If the leading expert of the thalamocortical systems advises us to avoid this topic of *ignoramus et ignorabimus*, perhaps we should listen.

BOOKS: EVOLUTION

Growing Trees from Molecular Data

Axel Meyer

Former president Ronald Reagan claimed that if you have seen one redwood tree, you have seen them all. But one doesn't have to wander through an awe-inspiring old-growth redwood forest to know that Reagan was wrong. Every redwood tree is unique, and the same can be said for each phylogenetic tree—a graphical depiction of evolutionary relationships (among organisms or their traits, including DNA and protein sequences). The latter have the great advantage that they do not take hundreds of years to create, but building them well isn't easy and interpreting them isn't straightforward, either. Students and researchers wanting to learn more about the practical aspects of constructing reliable phylogenetic trees from molecular data will find Barry Hall's *Phylogenetic Trees Made Easy* tremendously helpful.

Phylogenetic Trees Made Easy
A How-To Manual for Molecular Biologists
by Barry G. Hall

Sinauer Associates, Sunderland, MA, 2001. 191 pp. Paper, $24.95, £18.99. ISBN 0-87893-311-5.

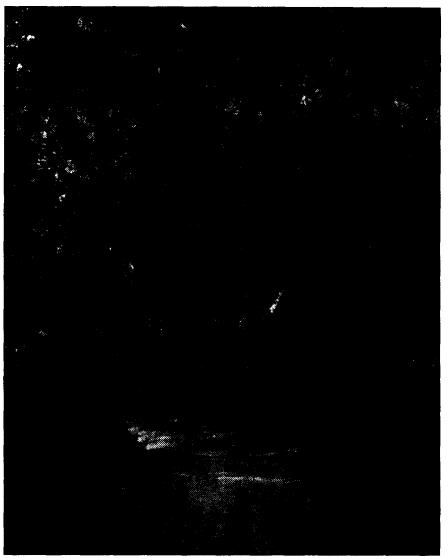
In these days of genomics, phylogenetic trees based on biochemical data abound in specialists' journals in molecular evolution and molecular systematics. They are also found in the journals representing widely diverse fields, from developmental biology to physiology and morphology. Although trees and "tree-thinking" are now all around us, many published phylogenies based on molecular data, especially those in the non-specialist literature, are quite possibly wrong. Errors commonly arise because one cannot simply assume that a gene is a gene is a gene, and the default settings of computer programs often do not do justice to the intricacies of molecular evolution. The pitfalls of tree construction are manifold: the complexity of tree-building methods can bewilder even experts and the choice among alternative analyses is often confusing.

The author, a geneticist at the University of Rochester, offers an excellent, long overdue, and inexpensive "how-to" manual for those wishing to create phylogenetic trees from protein or nucleic acid sequences. His clear explanations of the computer software packages that have become the tools of the trade will allow novices to go beyond the default settings. A series of "learn more about" boxes introduces some of the background theory and includes references to literature that will help users to better understand the assumptions underlying the various analyses and to choose appropriately from among the wide range of parameter settings. In addition, the publisher hosts a Web page (www.sinauer.com/hall) that provides sample files and other utilities to alleviate a beginner's frustrations with correctly formatting files for the different software packages.

Before phylogenetic trees can be built, one must align the molecular sequences (whether those are determined by the user or downloaded from genetic databases). The importance of a correct alignment cannot be overstated—all of the tree-building algorithms depend on it and wrong alignments guarantee incorrect results. ClustalX (*1*) has become the industry standard for alignments, but one must understand the alignment parameters, such as "gap penalties," to evaluate whether the resulting alignment makes sense. Users must know their genes and proteins better than ClustalX does, because they will have to spend time with the computer generated alignment to "refine it by eye"—to ensure, for example, that functional domains are not interrupted by gaps and that the ends are truncated.

Once one trusts the sequence alignment, one can begin to create phylogenetic trees. Of the several sophisticated software packages now available for such analyses, David Swofford's powerful and influential PAUP* (*2*) is the most often used, and Hall discusses it in some detail. The menu-driven Macintosh version of PAUP* is tremendously popular, and rightly so, because it is easy to use; Windows and Unix versions are also available, but these require a higher degree of familiarity with the software and methods because control of the programs relies on manipulation of command lines. (Throughout the book, Hall presents examples using the Macintosh versions of the software he discusses. Although users of Windows and Unix platforms may find this a drawback, the book will still provide them with considerable guidance.) During the last 15 years, the technology available to researchers in the field of molecular evolution has progressed from cumbersome DNA sequencing using radioactively labeled nucleotides to automatic capillary sequencers that permit genome centers to sequence the entire genome of a bacterium in a day. (The increased efficiency has helped expand the field of molecular evolution from studies of the evolution of particular gene families to comparative or phylogenetic genomics.) Similarly, PAUP* has grown from a rather crude DOS program to a slick, deceptively easy-to-use software package that includes a sophisticated graphics interface for presentation of the results. The package allows tree-building by any one of several methods and thus encourages comparisons of the results from different methods. It not only includes neighbor-joining and parsimony, methods which have been widely used for many years, but also sports the more complex maximum likelihood approach.

I think it is fair to say that likelihood methods currently enjoy the greatest popularity among experienced builders of molecular trees, and that the resulting phylogenies are often deemed the most reliable. Unfortunately, these methods are also the most difficult to understand. Therefore users, especially beginners, will appreciate Hall's guid-



Searching for the best tree. Some phylogenetic data sets may leave researchers feeling like the subject of Wynn Bullock's *Child on a Forest Road.*

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