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VIEWPOINT

Complexity and the Nervous System

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Advances in the neurosciences have revealed the staggering complexity of even "simple" nervous systems. This is reflected in their function, their evolutionary history, their structure, and the coding schemes they use to represent information. These four viewpoints need all play a role in any future science of "brain complexity."

From 1.5 kilograms of flaccid matter, convoluted folds, about 100 billion neuronal components, hundreds of trillions of interconnections, many thousand kilometers of cabling, and a short cultural history emerged calculus, *Swan Lake*, *Kind of Blue*, the Macintosh, and *The Master and Margarita*. The brain is often casually described as the most complex system in the universe. What could this mean? Only a decade ago, "complex" simply meant made of many interrelated parts (the word derives from "braided together"). Within mathematics and the physical sciences, the term "complexity" has recently acquired a number of narrower but technical definitions (1). Our task as neuroscientists is to assess how complexity—the concept or the science—can help us better understand the workings of nervous systems. We address this issue from four different, but clearly linked, perspectives.

Teleology

How is the brain's complexity linked to its *raison d'être*? That the brain has a function, which is to protect the individual (or its kin) in its particular ecosystem and to ensure the propagation of its genome, is the most relevant difference from other large physical systems such as galaxies and their tens to hundreds of billions of stars. Brains have "purpose" while star clusters have but brute existence. Does this actually explain why brains are complex? Let us consider what brains do. Brains sense

through many different modalities by extracting relevant patterns (shapes, sounds, odors, and so on) from a noisy, nonstationary, and often unpredictable environment. Brains control and coordinate movements of jointed (limbs) as well as soft (tongues) appendages, form memories with lifetimes that can well exceed those of the molecules holding them, and construct implicit and explicit models of the world and its dynamics. Above all, brains control behavior, the consequences of which can lead to reproductive isolation, speciation, and evolution. Any one of the things that brains do (such as the seemingly simple task of recognizing an odor) invokes many ill-understood neuronal operations, often referred to as "computations." That brains are complex should thus surprise no one, given the complicated and many-faceted tasks they solve.

History

Everything biological must be considered within an evolutionary framework. Today's brains are the result of 0.6 to 1.2 billion years of metazoan evolution (we ignore here unicellular organisms, despite their exquisite regulatory chemical networks). This vast span of time has allowed for a very large number of adaptive steps between our stem ancestors and today's animal cohort. These iterative elaborations might be best captured, perhaps, by the notion of logical "depth" in complexity theory (2). How does an evolutionary perspective help explain brain complexity? We focus on two aspects.

The first is based on the concept of "evolvability." Today's species owe their existence to the ability of their ancestors to adapt and evolve. We can thus assume that evolvability, the capacity of genes to mutate and modify an organism's genotype without

jeopardizing its fitness, must have given a selective advantage to those organisms who had it in higher degree. What features favor evolvability, and do these features engender complexity? Gerhart and Kirschner (3), in their book *Cells, Embryos and Evolution*, describe Conrad's (4) ideas on the subject. Evolvability should be favored by organismic compartmentalization, redundancy, weak and multiple (parallel) linkages between regulatory processes, and, finally, component robustness. These features all imply that evolution can only tinker with a system successfully if many of its constituents and coupling links are not essential for survival of the organism. Hence, the probability of obtaining, through the vagaries of evolution, a brain that does many things well with a single, pluripotent network must be very low. In contrast, the probability of evolving brains with separated subsystems—some for controlling basic functions such as respiration, threat detection, and nursing and others for more subtle functions such as exploratory behavior or memory of places—must be greater. It is therefore reasonable to assume that such indirect pressures should lead to systems replete with specialized circuits, parallel pathways, and redundant mechanisms.

The second issue concerns the relation between optimality and complexity of brain design. Anyone who has studied the performance of neural circuits can only be struck by their efficiency. We, like flies, can detect single photons and, within minutes, adapt to the enormously high photon fluxes of broad daylight (5). The information rate of single motion-sensitive neurons in the fly's brain is close to the fundamental limit set by the spike train entropy (6). Such high efficiency might lead one to think that only simple designs (ones drawn from first principles) could possibly work so well. Not so.

Take the wiring of the early visual system of flies. Insects use very small external lenses for optics. To obtain a large field of view, insects

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juxtapose many (1000 to 30,000) lenses as well as their associated neural machinery (ommatidia) (5). This has advantages: An image is constructed from a mosaic of pixels, and no optical pinhole is needed. The eye can be small and yet cover a wide visual field. However, this comes at a price: Tiny lenses are more severely limited by diffraction than larger ones. In most insects, the photons penetrating each ommatidium are guided to hit six main photoreceptors whose phototransducing segments are intermixed. Hence, each one of these six photoreceptors "sees" the same scene, and the global image resolution is given by the spacing between ommatidia. In fly eyes, in contrast, all six photoreceptors have separate phototransducing segments, thereby increasing spatial resolution (5). Because neighboring lenses focus light from overlapping parts of the world, two specific photoreceptors in neighboring ommatidia will catch photons from the same source. To exploit this feature, the axons of these two photoreceptors converge to the same second-order neurons so as to increase efficiency. Conversely, the six photoreceptors within one ommatidium diverge to six different second-order cells (Fig. 1A) (5). As a consequence of this peculiar optimal design, the spatial mapping between consecutive neuronal processing stages needs to be more intertwined in a precise manner. In conclusion, evolution is a remarkable engineer, but imposes complexity.

Structure

Brain complexity is reflected in the complexity of its structural makeup. At the most elementary level, voltage- and neurotransmitter-gated ionic channels of all types are found throughout the animal kingdom. The genome of the worm *Caenorhabditis elegans* contains sequences for 80 different types of potassium-selective ion channels, 90 ligand-gated receptors, and around 1000 G protein-linked receptors (7). The combinatorial possibilities are staggering for a nervous system with only 302 neurons. *Aplysia californica*, a marine mollusk, expresses voltage-dependent glutamate receptors whose actions underlie, at least partly, associative learning in mammalian cortex (8). Dendritic trees in mollusks and insects (9) are as profusely branched and varied as in a primate's brain. The dynamics of the firing of a lobster's neurons are at least as rich as those in mammalian thalamus or neocortex. And neither can be reduced to canonical integrate-and-fire models (10). Exquisite molecular machines endow neurons with complex nonlinear dynamical properties regardless of the animal's size or evolutionary lineage. Moreover, these properties are not static, but adaptively tunable. Cultured neurons artificially prevented from expressing a natural dynamic behavior can rapidly modify their molecular makeup and

revert to their original activity pattern (11). Synaptic properties also are bafflingly varied. Chemical synapses show a host of plastic phenomena whose time-courses span at least nine orders of magnitude, from milliseconds to weeks, providing a substrate for learning and memory (8). Transmitter release is probabilistic and its regulation can depend very precisely on the functional context and modulatory milieu (12). In short, no brain, however small, is structurally simple.

This dizzying variety of mechanisms, this bottomless bag of exquisite molecular and cellular gizmos, appears to be there for one reason—to endow neurons with adaptive, multistable dynamical properties. Their functions, however, cannot be understood without a consideration of the systems in which they lie. Frustratingly, the converse is also true. In a heroic effort, White, Southgate, Thomson, and Brenner (13) mapped the approximately 600 electrical and 5000 chemical synapses connecting the 302 neurons of *C. elegans* (Fig. 1B). Yet, this knowledge by itself failed to provide realistic ideas about the function and dynamics of this minimal nervous system, simply because we know very little about the intrinsic and synaptic properties of its neurons (14). Brain circuits are not Boolean networks, where connectivity is everything. They are not made of static, linear neurons, isotropic nets, or constant connection weights. Recent theoretical work exploring the complexity and dynamics of food-web networks in ecology and incorporating analog connection weights and nonlinear elements (15) might have applicability to neuroscience.

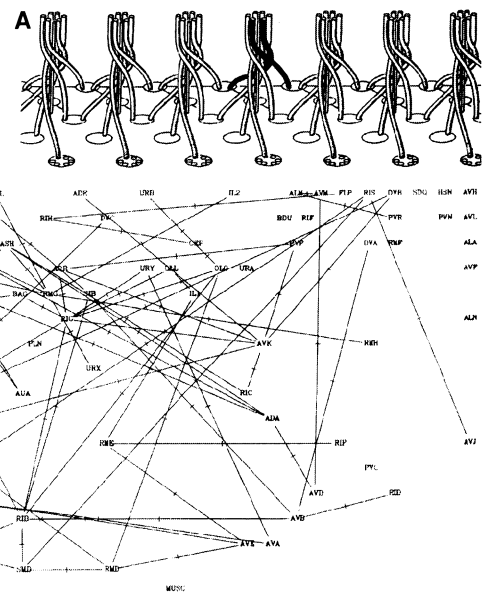
A more realistic accounting of the dynamic

nature of neuronal ensembles and their nonrandom, inhomogeneous connectivity topologies has been incorporated by Tononi and his colleagues into a formal definition of "neuronal complexity" using concepts drawn from information theory (16). These concepts express the degree of interactions between elements of a neuronal population. The complexity of a group of neurons should be low if they fire independently (although total entropy will be high) or if they are all strongly correlated. Complexity will be high if a large number of subassemblies of varied sizes can be formed within the population. Given the nonstationary nature of neuronal activity and our limited ability to sample activity from more than a handful of neurons simultaneously, it remains an open challenge to apply this notion of complexity to spike trains recorded from behaving animals.

Codes and Computation

We are beginning to understand the codes used by spiking neurons to transmit information about the environment from periphery to deeper brain structures. Considered individually, many neurons use an instantaneous firing rate code (17) with a resolution on the order of a few milliseconds. The brain, however, most likely represents the world using neural assemblies, and population codes could be more subtle. Although some neurons integrate inputs regardless of their temporal structure (18), evidence exists that the relative timing of action potentials matters (19), even allowing for combinatorial spatiotemporal codes (20). These alternatives should not be seen as exclusive, but rather as complementary and dependent on the demands of the task the animal must carry out.

Fig. 1. Circuit complexity in nervous systems. **(A)** Projections of photoreceptor axons from the retina (top) onto the lamina (bottom) of the fly's "neural superposition eye." Note the organized divergence of the six main receptor axons within one retinal bundle and their precise rearrangement within six new laminar bundles. [Reproduced with permission from (28)] **(B)** Circuit diagram of the nervous system of the worm *C. elegans* (chemical synapses only). Its 302 neurons have been pooled so that bilateral groups of two to six equivalent neurons are coalesced into single nodes. Connections are represented by lines. Connectivity alone fails to explain or predict circuit function. [Reproduced with permission from (29)]



One well-explored code is that found in the insect analog of the mammalian olfactory bulb (Fig. 2) (20, 21). In this system of about 1000 neurons, individual odors are represented by dynamical assemblies of about 100 neurons, so that information useful to downstream networks and to the animal is decoded from both the identity of the activated neurons and the relative timing of their activity (21). Population codes can thus be combinatorial in both space and time, adding several levels of complexity that are still not widely appreciated.

It is important to emphasize the stark differences between brains and computers. Individual transistors are homogeneous and nonadaptive. The interconnectivity of transistor

gates is very low. In the central processing unit of any microprocessor, one gate is connected, on average, to two or three others. This pales in comparison to interneuronal convergence and divergence ratios, often in the tens of thousands. The standard von Neumann computer architecture enforces a strict separation between memory and computation. Software and hardware, which can be easily separated in a computer, are completely interwoven in brains—a neuron's biophysical makeup is intrinsically linked to the computations it carries out (for instance, to detect temporal coincidence). Furthermore, brains wire themselves up during development as well as during adult life, by modifying, updating, replacing connections, and even in some circuits by generating new neurons (22). While brains do indeed perform something akin to information processing, they differ profoundly from any existing computer in the scale of their intrinsic structural and dynamic complexity.

Complexity: A Useful Framework?

While everyone agrees that brains constitute the very embodiment of complex adaptive systems and that Albert Einstein's brain was more complex than that of a housefly, nervous system complexity remains hard to define quantitatively or meaningfully. A bee's brain for instance, with about a million neurons and stupendously intricate microcircuits (23), controls very elaborate behaviors (24). The brain-to-body-mass ratio of sharks and rays is very close to that of mammals, and much greater than that of bony fish, amphibians, or reptiles. The size of the neocortex in toothed whales, normalized for its body size, ranks with that of primates above all other mammals (25). If forced, how would you rank complexity among these brains?

Any realistic notion of brain complexity must incorporate, first, the highly nonlinear, nonstationary, and adaptive nature of the neuronal elements themselves and, second, their nonhomogeneous and massive parallel patterns of interconnection whose "weights" can wax and wane across multiple time scales in behaviorally significant ways. For now, perhaps the most obvious thing to say about brain function from a "complex systems" perspective is that continued reductionism and atomization will probably not, on its own, lead to fundamental understanding. Each brain is a tremendously heterogeneous patchwork. Understanding function of any of its parts requires a precise knowledge of its constituents but also of the context in which this part operates.

Finally, what of any possible link between the complexity of nervous systems and those most tantalizing of phenomena, consciousness and subjective experience? Tononi and Edel-

man (26) propose that the existence and expression of consciousness is related to complexity. A positive correlation between complexity, as measured across large neuronal ensembles over a fraction of a second or longer (16), and consciousness is not implausible. Alternatively, it is at this time equally plausible that consciousness arises out of a novel feature of certain types of brains, some cellular or circuit property with a unique molecular, anatomical, or physiological signature (27). Only time will tell if and how the mind arises out of "complex" brains.

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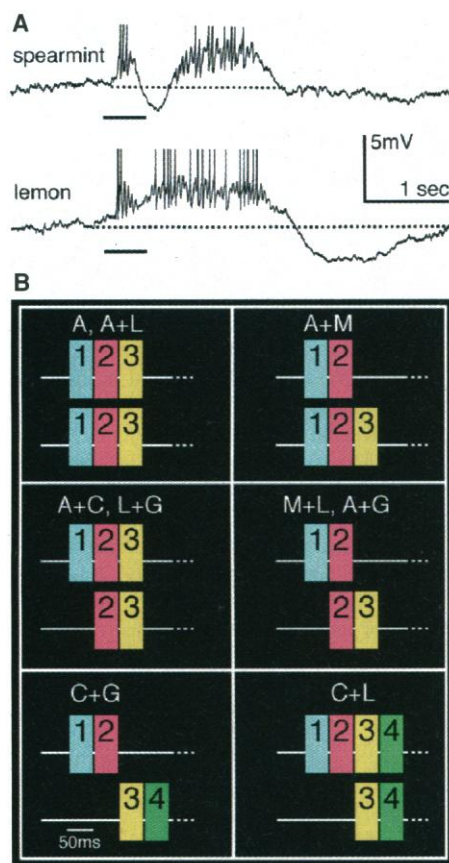


Fig. 2. Neural code complexity. (A) Intracellular recordings from a projection neuron in the locust antennal lobe, in response to two odors (spearmint and lemon). Note the highly dynamic and stimulus-specific voltage waveforms composed of slow (nonperiodic) and fast (periodic) modulations as well as action potentials (clipped) (data from G. Laurent). (B) Simultaneously recorded pair of projection neurons and their responses to nine different odor blends (capital letters), grouped in six spatiotemporal patterns. Each colored box represents the occurrence of a spike within a 50-ms window. Each number or color represents the rank order of a spike in the temporal sequence. Odor quality information is contained both in the identity of the activated neuron subset and in the timing of each neuron's recruitment. The code is thus a combinatorial spatiotemporal code. [Adapted from (20)]