

Postcards from the brain

Sam Wang describes some of the physics of our most complex organ



Mike Agliolo/Science Photo Library

Brains have long been compared to the most advanced existing technology – including, at one point, telephone switchboards. Today, people often talk about brains as if they were a sort of biological computer, with pink mushy “hardware” and “software” generated by life experiences.

However, any comparison with computers misses a messy truth. Because the brain arose through natural selection, it contains layers of systems that arose for one function and then were adopted for another (even though they do not work perfectly). An engineer with time to get it right would have started from scratch each time, but it is easier for evolution to adapt an old system to a new purpose than to come up with an entirely new structure. Neuroscientist David Linden at Johns Hopkins University has compared the evolutionary history of the brain to the task of building a modern car by adding parts to a 1925 Ford Model T that never stops running.

This complex organ, which is responsible for our thoughts, feelings and awareness, has lured many physicists into applying their own bags of tricks to questions in neuroscience. Some ideas, such as the speculation put forward by Roger Penrose of Oxford University in the UK and Stuart Hameroff of the University of Arizona in the US that brain function is influenced by quantum phenomena, are not taken seriously by neuroscientists. But there are still many respectable roles to be filled by expatriated physicists.

One challenge of neuroscience is to probe brain microstructure and dynamics, which experimentalists can address by designing new techniques. Examples include new methods in optical microscopy and magnetic resonance imaging. Another challenge comes from the very large data sets generated by modern experimental methods, which demand new approaches to analysis. Finally, theoretical principles are waiting to be identified and developed to the point of yielding testable predictions.

Compact dim bulbs

One striking feature of brain tissue is its compactness. In the brain’s wiring, space is at a premium, and it is more tightly packed than even the most condensed computer architecture. One cubic centimetre of human brain tissue, which would fill a thimble, contains 50 million neurons; several hundred kilometres of axons, the wiring over which neurons send signals; and close to a trillion synapses, the connections between neurons.

The memory capacity in this small volume of tissue is potentially immense. Electrical impulses that arrive at a synapse give the recipient neuron a small chemical kick that can vary in size. This variation in synaptic strength is thought to be a means of memory formation. Work at my lab at Princeton University and others has shown that on timescales of less than an hour, synaptic strength flips between extreme high and low states, a flip that is reminiscent of a computer storing a “one” or

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Cleverly done A close-up of the cerebral folds on the surface of a human brain. Folding may reflect optimization to minimize the “wire” length of internal connections.

a “zero” – a single bit of information. These transitions are often triggered by biochemical signals that are generated when the sending and receiving neuron fire in close succession, and jumps in strength may increase the likelihood of the re-occurrence of a particular activity sequence, a repetition that may underpin the first stages of how we store memories and recall past events.

With compactness also comes tremendous efficiency. Your brain uses about 12 W of power, an amount that supports not only memory but all your thought processes. This is less than the energy consumed by a typical refrigerator light, and half the typical needs of a laptop computer. In this sense, we are all dim bulbs.

However, efficiency comes at a cost. Synaptic strength may change in an all-or-nothing fashion, but that is only true for measurements of strength averaged over dozens of signalling events. At any given moment, a single synapse can be remarkably flaky. Even under normal, healthy conditions, synapses release neurotransmitter only a small fraction of the time when their parent neuron fires an electrical impulse. This unreliability may arise because individual synapses are so small that they contain barely enough machinery to function. This may be a trade-off that allows the most function to be stuffed into the smallest possible space, with the idea that a sufficiently large number of synapses can overcome this unreliability. Currently, it is not known whether synaptic unreliability is reflected at the level of behaviour.

Another consequence of the ruthless efficiency required by natural selection is that the amount of wiring used by brains appears to be minimized. Theorists have investigated the total length of input (dendrite) and output (axon) wiring used in brain circuits from animals as diverse as worms and mammals. Wiring typically fills about one-third of mammalian brain tissue’s “grey matter”, where the neurons and synapses are found, and nearly all of its “white matter”, which is made of axons and gets its colour from the insulating fatty sheath that surrounds each axon. This wiring tends to assume a configuration that has close to the least possible total length. For example, in the cerebral cortex, where nearly all of the connections run from one place to another within

the cortex, the grey matter forms a rind that surrounds the white matter. When you look more closely, any given bit of grey matter in the cerebral cortex is layered like a cake, with connections passing from layer to layer. The layers are arranged such that a hypothetical shuffling of the order of the layers would increase the total amount of wiring used, sometimes considerably.

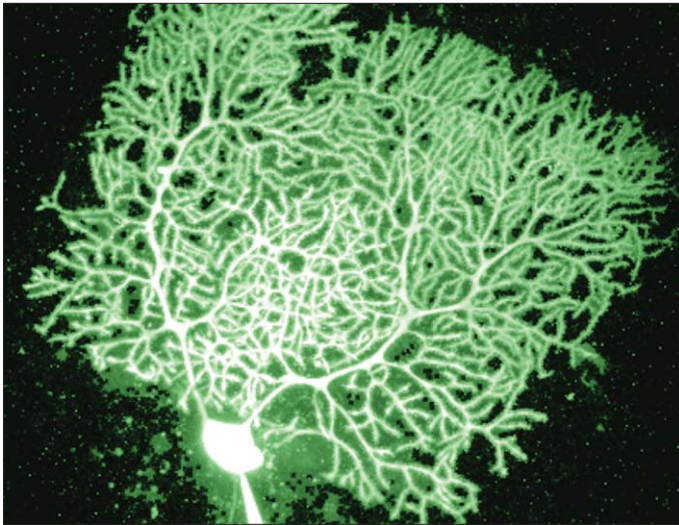
It is not yet known how this wiring is minimized. It is likely that some minimization is predetermined by developmental steps in the form of genetically determined programmes acting through cell biological mechanisms. In addition to pre-programmed steps, the wires themselves may play a self-optimizing role as they grow. Axons growing on a stationary surface have been shown to exert a small amount of force along their length. Such forces can minimize length, in analogy to the way that surface tension acts to minimize the area of soap-film patterns. It has also been suggested that the location of the convolutions on the surface of the brain is determined by such force-generating mechanisms. Just as a sheet with springs here and there would tend to scrunch up, a slab of brain tissue joined at various points by long-distance axons might start to fold.

Other evolutionary constraints may determine the amount of folding, as well as other features of how brain size scales. The mammalian neocortex (also known as cerebral cortex) shows regularities that suggest that brain structure may be subject to universal design constraints. From shrews to whales, mammalian brains vary over 100 000-fold in volume. Over this range, large brains are more folded than small brains: the surface area of the cerebral cortex follows a power law relative to cortical volume that is greater than simple geometry would predict. Using electron microscopy, my group has found that, on average, neocortical axons are wider in large brains than in small brains. The space demanded by these axons is sufficient to account for the increased folding seen in large brains, as well as disproportionate increases in white-matter volume. But why do axons become wider? The conduction velocity of a nerve impulse is known to scale with the thickness of the axon. It may be that widening of axons is driven by an evolutionary need to preserve the time it takes for a nerve impulse to cross the brain.

Watching the brain in action

Another area where physical scientists can make a contribution is in probing how brain tissue processes information. Addressing this issue requires the monitoring of activity in the intact brain and the reconstruction of whole neural-circuit connectivity – two daunting tasks. Physical scientists have entered the fray by inventing a variety of instruments. One breakthrough technology has been multiphoton microscopy, which uses infrared emission from ultrafast lasers. This light does little damage to living tissue and is capable of excellent optical penetration, thus allowing observations in brain tissue, a highly scattering medium. Fluorescent probes, both synthetic dyes and genetically encodable molecules based on green fluorescent protein, have been developed to label neuronal structure. Some probes have been designed to change conformation, and therefore their fluorescent properties, when they bind to calcium ions, which enter neurons when they

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Action-packed A mammalian neuron filled with fluorescent dye and visualized using the physics-based technique of two-photon microscopy.

are active. Indeed, neural activity can now even be imaged in live rodents running on a foam ball floating on jets of air! Other probes allow neurons to be activated or deactivated by light. Taken together, these technologies open the possibility of spying on perturbing neural circuitry in action – an exciting frontier in modern neuroscience.

An outstanding challenge is the full mapping of circuit structure along with the neurochemical identity of the circuit's cellular components, and many researchers are working hard to develop tools to trace these connections in unprecedented detail. One such instrument performs scanning electron microscopy on the face of a block of preserved tissue as it is shaved off layer by layer, thereby generating thousands of images that together contain microstructural information from whole volumes of circuitry. Reconstructing a circuit diagram from the resulting terabytes of data is a daunting task requiring advances in image analysis as well as innovative molecular-biological approaches to identifying specific types of cells. The ultimate goal is the full reconstruction – and eventual understanding – of brain circuits and the processing they perform.

A deeper question

Like many physical scientists, I was drawn to neuroscience by the mysteries of consciousness and thought, and by the promise of a field where the most exciting discoveries lie in the future. I regard neuroscience as a younger cousin to traditional “deep questions” in physics about how the world works, from particle physics (what everything is made of) to cosmology (where it all came from). Neuroscience addresses the issue of how it is that human beings are able to ask any of these questions in the first place.

Today, neuroscience has found its own *raison d'être*. It exists as an area of research that is unusual for the degree to which it draws upon other disciplines, including physics. In 2008 membership of the main US brain-science organization, the Society for Neuroscience, hit an all-time record of nearly 39 000 individuals, close to the American Physical Society's tally of 46 000. Now is the best time ever to have a foot in both camps. ■

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