THE WHOLE BRAIN ACTIVITY MAP:

Merging Nanoscience and Neuroscience for Technology and Health

Nanoscience and Neuroscience are at a crossroads. Each field is currently booming in its own right, and the two are now on the threshold of an alliance that will mutually and significantly enhance one another. This alliance will provide a wide range of practical benefits.

The Ultimate Goal

The ultimate goal of this project is to construct the **functional connectome map of the human brain**, by assembling a coordinated network of researchers deploying next-generation nanotechnological tools with unprecedented capabilities. Mapping the functional connectome will unravel the fundamental, long-sought paradigms of how the brain computes. Together with these new technologies, this will enable accurate diagnosing, and restoring, of normal patterns of activity to injured or diseased brains; will foster the development of broader biomedical and environmental applications; and will produce a host of associated economic benefits.

What Is the Functional Connectome?

The connectome is a scientific effort currently under way that will give us a detailed anatomical highway map of the brain. The functional connectome, that we are proposing, will make that map comprehensible and useful by telling us about the traffic on those highways. It will map the patterns and sequences of nerve cell firing activity, and in so doing, reveal the brain's code.

Why We Need It

How the brain makes sense of the world is still basically unknown. One major reason for this is the distinct possibility that the neural code is a property that emerges from widespread patterns of nerve cell activity in many parts of the brain at the same time. Current imaging techniques are too local, and either too slow (fMRI) or too blurred (electro- and magneto-encephalography) to record these patterns with enough coverage, detail, and accuracy. If we can obtain higher resolution data over the entire brain, and then correlate the recorded activities with their anatomical circuits and behavioral consequences, we would be in a position to decipher the neuronal code, and to understand how it relates to behavior.

Why Now

Mapping of the functional connectome requires the development of a nanoscale analytical system of unprecedented complexity. Current technology for detecting, storing, and analyzing data of this sort exists to some extent for small brains, but a system of this type that can work at the scale of large animal brains, or even human brains, will require methods and technologies that are now emerging from the first decade of the National Nanotechnology Initiative. Nanosystems offer the only feasible way forward; they will allow for comprehensive coverage, sufficient sensitivity, and minimal invasiveness in neurophysiological research. Nanosystems comprise large coherently engineered

ensembles of nanodevices and nanoparticles, assembled in a fashion yielding capabilities that are immensely greater than the sum of the parts. The technological capabilities for producing such nanosystems *en masse*, can originate by leveraging the immense worldwide resources for producing microchips, and integrating these with bottom up fabricated nanostructures that can report on local neural phenomena with electrical and chemical specificity. The new innovation and capabilities developed in the course of this project will provide utility far beyond the bounds of this project and specific research application. They will open up new industrial avenues for our nation.

Anticipated Benefits

Easily imagined benefits from the project include devices and techniques for diagnosing brain disorders with much greater accuracy and sensitivity than are currently feasible, thus allowing a diagnosis to be made earlier in a disease's progress. Because the project will rely on stimulating nerve cells as well as monitoring their activities, the outcome will point the way towards workable strategies for interventions more refined and longer lasting than those currently used in deep-brain stimulation for Parkinson's disease and chronic depression. Even subtler manipulations can be foreseen for rebalancing circuits that have become imbalanced, as treatments for schizophrenia and autism.

On the engineering side, the nanosystems developed and deployed for this enterprise will have potential uses in a broad range of engineering and environmental applications, where sensitive, miniature, and intelligent systems can fulfill functions that are currently impossible with existing devices. This project realizes the potential for merging of nano- and bio-technology outlined several years ago in a "Nanotechnology White Paper"[1] published by the U.S. Environmental Protection Agency, which stated:

The convergence of nanotechnology and biotechnology with information technology and cognitive science is expected to rapidly accelerate in the coming decades. The increased understanding of biological systems will provide valuable information towards the development of efficient and versatile biomimetic tools, systems, and architecture.

Non-Obvious Economic Benefits

The economic activities emanating from this project are likely to reach far beyond those related to the outcomes outlined above. We anticipate profound attendant benefits such as occurred in the aftermath of the Human Genome Project. In fact, there are numerous similarities between what is proposed here and the Human Genome Project: it is a comprehensive approach to issues that had previously been treated piecemeal; it requires concerted team effort (unusual for basic researchers); it is a project that will be based on large-scale deployment of new technologies and, as such, requires formidable strategic thinking and the assembly of substantial technological resources; it is an initiative that capitalizes on emerging technologies to open up entirely new realms of scientific inquiry and economic activity; and it falls outside of the current funding programs because of its bridging of distant fields, and its ambitious

[1] http://www.epa.gov/nanoscience/files/epa_nano_wp_2007.pdf

scale. And like the Human Genome Project, the resulting economic benefits are likely to be much broader and greater than anyone imagined, and perhaps will be realized much sooner than anticipated.

A recent report from the Battelle Technology Partnership Practice found that the $3.8 billion investment in the Human Genome Project has generated $796 billion in economic impact.[2] The economic modeling study showed that every dollar invested in the U.S. elements of the project generated $141 in the economy. They estimated that in 2010 alone, academic and commercial genomic sequencing and research supported 310,000 jobs and generated $67 billion in economic output.

This exceptional return on investment is probably an underestimate, since the major anticipated impacts of the Human Genome Project on health care are still merely on the verge of realization. The study's authors conclude that the project is "arguably the single most influential investment to have been made in modern science."

The State of the Art

Although neuroanatomy is a very old science, connectome biology is relatively new. The first complete nervous system wiring diagram was accomplished with the 300 cell nervous system of a model organism, the nematode in the 1980's.[3] The next example is only now coming online for another model organism, the 150,000 neuron brain of the fruit-fly *Drosophila*.[4] A connectome project for the mouse (4 million neurons) is just being launched[5] with an anticipated completion time of at least 5 years, and the prospects for having a human connectome map (100 billion neurons) is decades away.[6] All of these efforts have proceeded slowly because of the painstaking nature of determining the shape of each individual nerve cell. Perhaps surprisingly, the technical barriers to obtaining the functional connectome map are not as daunting, and are much closer to being solved, than for the anatomical connectome map.

Functional mapping can currently be done on the smallest of these brains, the nematode *C. elegans* and the fruit fly *Drosophila*, and on the superficial layers of the mouse brain, but the sensitivity and speed of the recordings is not yet adequate. The tools are proteins or chemical dyes that fluoresce when calcium

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[2] http://www.battelle.org/publications/humangenomeproject.pdf; http://online.wsj.com/article/SB10001424052748704681904576315253143162630.html

[3] White JG, Southgate E, Thomson JN, Brenner S. (1986) The structure of the nervous system of the nematode *Caenorhabditis elegans.* Philos Trans R Soc Lond, SerB, Biol Sci. 314: 1-340.

[4] Chiang AS, et al.. (2011) Three-dimensional reconstruction of brain-wide wiring networks in *Drosophila* at single-cell resolution. Curr Biol. 21: 1-11.

[5] Bohland JW, et al..(2009) A proposal for a coordinated effort for the determination of brainwide neuroanatomical connectivity in model organisms at a mesoscopic scale. PLoS Comput Biol. 5: e1000334.

[6] Sporns, O., Tononi, G., Kötter, R. (2005). "The Human Connectome: A Structural Description of the Human Brain". PLoS Computational Biology 1 (4): e42

levels in the cell change, a technology originally applied to nerve cell recording[7] and more recently combined with advances in microscopy to enable recording from up to 1,000 nerve cells at once in brain tissue up to half a millimeter thick.[8]

The technology for targeted stimulation of nerve cells has existed for many years in the crude form of implanting electrodes into the brain. More recently, a finer grain technique has been developed that uses light-activated proteins to stimulate nerve cells.[9]

Technology has been demonstrated for producing nanoscale probes capable of sensitive and fast responses to changes in voltage.[10,11] This is just starting to be exploited for use in nerve cells, but capabilities for its large-scale integration and production not been assembled, hence its subsequent wide deployment to the neuroscience community has not yet become possible.

Next Steps

By analogy to the role played by *C. elegans* and *Drosophila* in troubleshooting and laying the foundations for the Human Genome Project, these model systems will play a similar role in part of our progression towards the human functional connectome. On this front, we will start with existing technology (calcium imaging and state-of-the-art microscopy) to produce initial functional connectome maps. The same technology will be used on a piece of mouse brain cortex (10,000 cells) that is thin enough to be imaged. A key element in our strategy, which will permit us to determine the input and output for each nerve cell, is the ability to stimulate in a targeted and controlled manner. This will be done with the existing optogenetic technology, which is available for all three model organisms.

In parallel, on a second front, we will develop and deploy a new generation of integrated nanoscale probes that combine integrated electrophysiological and photonic technologies. We will also pursue development of new classes of nanoparticles permitting optically based neurophysiological stimulation and recording from local, very selectively targeted regions of neuronal tissue. Together these nanotechnologies will enable simultaneous observation and stimulation across deep, vast, and previously-inaccessible regions in the brain, and thus enable the construction of a full functional connectome map. We will strategically assemble resources to enable robust mass-production of systems

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[7]Smetters D, Majewska A, Yuste R. (1999) Detecting action potentials in neuronal populations with calcium imaging. Methods. 18: 215-221.

[8]Nikolenko V, Watson BO, Araya R, Woodruff A, Peterka DS, Yuste R. (2008) SLM Microscopy: Scanless Two-Photon Imaging and Photostimulation with Spatial Light Modulators. Frontiers in Neural Circuits. 2: 5.

[9]Fenno L, Yizhar O, Deisseroth K. (2011) The development and application of optogenetics. Annual Rev Neurosci. 34: 389-412.

[10] See, for example, Du J, Riedel-Kruse IH, Nawroth JC, Roukes ML, Laurent G, Masmanidis S. (2010) High-Resolution Three-Dimensional Extracellular Recording of Neuronal Activity With Microfabricated Electrode Arrays. J. Neurophysiology 101(3): 1671, and references contained therein.

[11]Du J, Roukes ML, Masmanidis S (2009) Dual-side and three-dimensional microelectrode arrays fabricated from ultra-thin silicon substrates. J. Micromechanics Microengineering19(7): 075008

that utilize these tools in a highly reproducible manner, multiplexing them at unprecedented scale, and deploying them to newly-assembled networks of researchers who will become capable of mapping the functional connectome.

The Way Forward

Perfecting the technological capabilities, mass-producing the requisite nanosystems, and assembling the collaborative research networks that will use them constitutes the core vision for the primary organizing phase of this effort. The initial research phase consists of producing the preliminary functional maps in model systems, outlined above. Beyond these immediate next steps, we envision working towards the ultimate development of subsequent generations of untethered, nanoscale neural probes that can locally acquire, process, and store accumulated data, and that would ultimately be configurable into a communications network within the tissue. Such device networks could potentially address the long-standing problem of how to obtain sufficient coverage in deep tissue layers. These networks of "intelligent" nanosystems would also be capable of providing specific responses to externally applied signals, or to their own readings of brain activity. Their responses could be used to trigger nerve cell activity in a measured manner, and could comprise the first steps in controlled restoration of normal patterns of activity in damaged brains. This would initially be done in animal models for brain injuries, such as TBI and PTSD, or for psychiatric disease.

The Authors

A group of scientists, whose research spans neuroscience, nanoscience, genomics, and systems biology have collaborated to produce this document. This group – Paul Alivisatos (LBNL and UC Berkeley), George Church (Harvard U.), Ralph Greenspan (UCSD), Michael Roukes (Caltech), and Rafael Yuste (Columbia U.) – formed at a recent workshop exploring the juncture of nanoscience and neuroscience that was organized by The Kavli Foundation, the Gatsby Charitable Foundation, and the Allen Institute for Brain Science. The workshop was held in September, 2011 at Chicheley Hall, home of the Kavli Royal Society International Centre, UK.