

# FSG Report

April 2011; FSG met on May 8-9, 2010

The first meeting of the Focused Study Group (FSG) was held at the Portofino Hotel in Redondo Beach on the topic of “*Analysis of Multi-electrode Neural Recordings and Modeling of Neuronal Ensemble Activity*” on May 8-9, 2010. The structure of the meeting and the generated summary report are presented below. Note that the presented summary report is deliberately *very succinct*, since it aims at simply highlighting the key issues. Some elaboration is provided in Appendices and can be expanded over time, if this is deemed appropriate.

## *Purpose*

The FSG meetings are organized by the Biomedical Simulations Resource (BMSR) at the University of Southern California in order to facilitate the rational formulation of future research directions in selected fields of biomedical science and technology by engaging experts within the peer community in a constructive process of thoughtful and far-sighted deliberation. The first FSG meeting on the topic of “*Analysis of Multi-electrode Neural Recordings and Modeling of Neuronal Ensemble Activity*” generated a summary draft report that assesses the state of the art and identifies key challenges as well as future prospects in our collective efforts to *observe, analyze, model and interpret the activity of neuronal ensembles*. This is a topic of emerging importance for systems neuroscience and represents a common interest of the FSG members who are recognized experts in this field. The draft report will be exposed to the constructive comments of additional experts who were not able to attend the FSG meeting and the peer community at large (via the web). The final report will be disseminated broadly.

## *Process*

Since this FSG meeting was the first of its kind for the BMSR, it required careful planning in order to: (a) provide a calm and informal setting; (b) maintain an uninhibited and highly-interactive mode of expressing views and exchanging ideas; (c) prevent meandering of the discussion without stifling the free flow of ideas. The guiding principle was to let free-wheeling discussion determine the course of the FSG deliberations. The members of the FSG panel are all recognized for their expertise, depth of knowledge and balanced judgment. They also represent and understand the scientific perspective and research requirements of the peer community.

The FSG members agreed on the following procedure for the preparation and dissemination of the final report. Each member of the FSG was assigned the task of preparing a few paragraphs on three topics of their choice among the 14 topics selected for elaboration in this report. These paragraphs were sent back to the BMSR and compiled in a comprehensive draft document, which is presented below. This document was then distributed to the FSG members and to additional experts (see name lists at the end of this document) who were unable to attend the FSG meeting for their comments.

Upon receiving the final comments of these experts, a first draft report was prepared and was disseminated to all peers who have participated in this process, soliciting their final comments and their endorsement of a final report that will be posted on the BMSR website for commentary by the broader peer community over a period of six months. The BMSR will undertake to incorporate the commentary of the peer community into the final report – possibly in the form of an Appendix containing the comments of the peer community and responses by FSG members. The final report will be given broad dissemination, including posting on the BMSR website, editorial/correspondence in scientific community newsletters and articles in scientific journals.

## ***Topics***

A list of the specific topics that were discussed during the FSG meeting and will be elaborated in the FSG report is provided below in three clusters: (1) Data Collection, (2) Data Analysis, (3) Interpretation and Utilization.

### **Data collection:**

- key experimental requirements for collection of appropriate ensemble data;
- relations among signal modalities (spikes, membrane potentials and LFPs);
- need for simultaneous recording from separate regions of the brain;
- improvements in spike-sorting methods and robustness to waveform changes.

### **Data analysis:**

- conceptual, mathematical and computational frameworks for comprehensive analysis of ensemble activity and neural encoding;
- development and validation of general methodologies for modeling multi-unit interactions while preserving the “essential complexity” of the neural system;
- modeling of closed-loop interactions and effects of neural feedback;
- electrochemical interactions, neuro-endocrine modeling and neuro-modulation;
- general methods for the design of (near-) optimal neuro-stimulation patterns
- interactions between brain tissue and electronic circuitry.

### **Interpretation and Utilization:**

- conceptual framework for comprehensive understanding of multi-unit activity;
- large-scale simulations of neural networks to test hypotheses and examine mechanisms of neural computation;
- design, testing and evaluation of effective neuroprostheses;
- principles and methods of neural encoding;
- methods of quantifying neural ensemble activity and its connection with behavior.

The FSG also discussed the fundamental issue of “*reductionism versus systems integration in physical and life sciences*”. A thoughtful and stimulating synopsis is provided by Ted Lewis in Appendix 1.

# *The FSG Report*

## *April 2011*

### **1. Data collection:**

#### *1.1. Key experimental requirements for collection of appropriate ensemble data*

Although great progress has been made in the fabrication of multi-electrode arrays in recent years, considerable challenges persist in terms of long-term reliable recording, including spatial constancy and stable electrode-tissue interfaces, the scaling-up to larger numbers of electrodes, the issues of conformal recording and adequate spatial sampling and, last but not least, the ability to record reliably at greater depths in the brain.

#### *1.2. Relations between signal modalities (spikes, LFPs, membrane potentials etc.)*

Due to the rapid increase in data storage capacity, it has become increasingly common to record LFP signals together with spiking activity. In addition, calcium imaging is an emerging approach of recording from multiple neurons that requires careful scrutiny in inferring neuronal activity. Thus, understanding the relationship between LFPs, subthreshold membrane potentials, calcium currents and spiking activity of neurons will markedly enhance the amount of information extracted from each experiment. This will require combined theoretical, computational and experimental efforts to model the relationship between single neuron activity, calcium signals and LFPs, as well as to test the validity of the necessary assumptions. Thoughtful commentary on this issue is provided by Ted Lewis in Appendix 2.

#### *1.3. Need to record simultaneously from separate regions of the brain*

The natural trend in understanding brain function is to expand the simultaneous multi-electrode recordings from multiple regions of the brain and to examine their interrelationships with regard to neuronal ensemble activity. This task presents formidable challenges in terms of increasing the number, stability, robustness, reliability and depth of recording channels, as well as providing adequate preprocessing and storing capabilities.

#### *1.4. Improvements in spike-sorting methods and robustness to waveform changes*

Since some practical limitations still exist in current spike-sorting methods and the robustness recordings in the presence of drifts or systematic changes in spike waveform, improvements are possible and highly desirable. This issue also relates to the aforementioned study of the relationship between LFPs and spike trains.

## **2. Data analysis:**

### ***2.1. Conceptual, mathematical and computational frameworks for comprehensive analysis of ensemble activity and neural encoding***

This is probably the most fundamental of the issues pertinent to the rigorous and quantitative study of neuronal ensemble activity. Although significant progress has been made in this regard in recent years, the remaining challenges are numerous and formidable – due to the immense complexity of the problem and the rising expectations of the scientific and medical communities. Thoughtful commentary on the “demarcation problem” and the formulation/validation of scientific hypotheses is given by Ted Lewis in Appendix 3.

### ***2.2. Development and validation of general methodologies for modeling multi-unit interactions while preserving the “essential complexity” of the neural ensemble***

Although this issue is related to the previous one, immediate research challenges concern the development of effective methodologies for the analysis of the vast databases (currently generated in several labs by use of multi-electrode arrays and two-photon calcium imaging) in a manner that leads to increased scientific understanding of neuronal ensemble activity without simplifying the inherent complexity of the problem. Important in this regard is the methodological issue of *nonlinear dynamic modeling of multiple interconnected variables* which is germane to the core research interests of the BMSR.

### ***2.3. Modeling of closed-loop interactions and effects of neural feedback***

Even though this is widely recognized as a key issue in the study of neural function, it has received so far only limited attention due its intrinsic complexity and related methodological challenges. Future efforts should focus on effective methodologies for closed-loop modeling using ensemble point-process data (multiple spike-trains) and elucidating the functional implications of dynamic nonlinear feedback mechanisms.

### ***2.4. Electrochemical interactions, neuro-endocrine modeling and neuro-modulation***

This is also an issue of great importance for the study of the nervous system that has been largely limited to qualitative descriptions due to the lack of appropriate calibrated time-series measurements data. The recent availability of time-series electrochemical data will make possible the quantitative analysis of the dynamics of electrochemical interactions within neuronal ensembles and intermodulation of neural activity, including the critical issues of neuro-endocrine modeling and neuro-modulation.

## **2.5. *General methods for the design of (near-) optimal external neuro-stimulation patterns and interactions between the brain and electronic circuitry***

This is an issue of paramount importance in the growing fields of neuro-prostheses and functional neurosurgery (e.g. Deep Brain Stimulation and its many potential variants). Although the scientific/technological progress in these fields is rather impressive in recent years, a host of important problems remains to be addressed in order to realize the full potential of these approaches and amplify their scientific and clinical impact. Recent technical advances in recording and imaging brain activity from awake behaving animals have confirmed that various neuromodulators (e.g., acetylcholine and dopamine) play critical roles in regulating brain states. The recent development of optogenetic techniques also provide powerful tools for manipulating the neuromodulatory circuits and test their effect on neural function. Since these experiments involve monitoring the activity of large neuronal ensembles, modeling work to link the cellular effects of each neuromodulator with integrated neural function will greatly facilitate our understanding of the brain mechanisms. A related issue is the effect of external stimulation (electrical, magnetic, ultrasound or optical) that requires effective models relating various stimulation parameters to the spatiotemporal patterns of neuronal activation and the resulting neural function.

## **3. Interpretation and Utilization:**

### **3.1. *Conceptual framework for comprehensive understanding of multi-unit activity of neural ensembles***

This is a fundamental issue that has to be addressed before a comprehensive understanding can be attained of how multi-unit activity encodes and processes information in order to secure effective and robust neural function at various levels of integration (from elemental tasks to behavior). The BMSR has advocated the view that the activity of neuronal ensembles and integrated neural functions rely on specific *spatio-temporal patterns* of multi-unit activity (in juxtaposition to simple firing rates), where the timing of the individual spikes and the interactions among them (either intra- or inter-neuronal) are important. This issue cannot be addressed without appropriate multi-unit recordings (explaining its elusive status up to now) but the recent availability of such data makes this fundamental task feasible for the first task.

### **3.2. *Large-scale simulations of neural networks to examine mechanisms of neural information processing***

This is another important issue that has not been properly addressed so far (although several remarkable efforts have been reported) for lack of adequate computational means that enable its

investigation. As such means are becoming gradually available in the form of supercomputing clusters, it is finally feasible to conduct proper large-scale simulations of neural networks postulated on the basis of current scientific knowledge about the structure and function of ensembles of neurons from the molecular to the multi-cellular level. These advanced simulation studies allow the testing of scientific hypotheses pertaining to the integrative function of the nervous system and may also be valuable for *in silico* testing of the potential efficacy of new medications.

### **3.3. *Design, development, testing and evaluation of effective neuroprostheses***

Remarkable progress has been made in recent years in the design, development and testing of neuroprostheses for a broad range of applications from sensory and motor systems, as well as memory and cognitive tasks. However, the enormity of this issue and its potential clinical/medical applications require further intensification of efforts and a broadening/deepening of our scientific knowledge and requisite technologies to achieve these multi-faceted and complex tasks. Specific tasks include expansion of the operational capabilities, robustness, and design methods with regard to scaling-up to a very large number of electrodes for real-time operation.

### **3.4. *Principles of neural encoding and methods for extracting neural codes from point-process data***

This issue pertains to the fundamental question of neural encoding which was also addressed in 3.1 above but focuses on the development of general principles of neural encoding and practicable methods for the extraction of specific neural codes from spatio-temporal point-process data (multi-unit spike trains). This issue has both scientific importance and potential medical/clinical implications in connection with neuroprostheses, functional neurosurgery and interventional neuro-stimulation.

### **3.5. *Alternate approaches to quantifying neural ensemble activity and its connection with behavior***

It is important to explore alternate ways for quantifying neural ensemble activity since the subject matter is vast and probably amenable to various approaches that exhibit relative advantages in different applications. This would allow the scientific/medical community to select the approach that is most suitable in each particular application, including the long-term objective of connecting the advanced neurophysiological studies of neural ensemble activity with observed behaviors in animals and humans.

*Appendix 1: Reductionism vs. Systems Integration in physical and life sciences (by Ted Lewis)*

Perhaps it would be most illuminating to begin a discussion of reductionism with classical geometry, the model of deductive power that inspired Greek philosophers—especially Plato and Aristotle, well before Euclid formalized it in his *Elements*. But it is Euclid’s formalization that provides the nearly complete model for us (lacking just a few elements of modern real analysis) for discussion here. Euclid constructed his geometry in layers. The first layer comprises the definitions, postulates, and common notions of Book 1. From these, he deduces (proves by deduction) an ordered sequence of 48 propositions, each of which is deduced from those that came before. In other words, each proved proposition becomes an axiom in the proofs of subsequent propositions in the sequence. Attempting to understand higher-layer propositions directly in terms of the basic elements (definitions, postulates, and common notions) of Book 1 is not instructive. This may have more to do with the nature of humankind than with any absolute principle. It is clear that the deductive power of human working memory is powerfully leveraged by the process commonly labeled *chunking*, and it is equally clear that the chunking process is layered, or hierarchical. Humans attach names (labels) to complicated phenomena or processes, then manipulate those labels in working memory as they contemplate higher-level systems comprising those phenomena or processes. As they develop the perception of having understood those higher-level systems, they give each of them a label, and so forth. An illustrative example of higher-order thinking would be the inner-ear physiologist contemplating the action of cochlear filters in terms of *convolutions* of *filter kernels* and *input waveforms*. The concepts “*convolution*, *filter kernel*, and *input waveform*” clearly are high level, each involving multi-layered systems of lower-level concepts and definitions. Such contemplations, in terms of a few labels, fit well within Miller’s well-known “*seven plus or minus two*” constraint on working memory -- where our perception of understanding presumably arises. Although we are able to relax the “seven plus or minus two” constraint by using external graphical devices such as chalkboards, it seems that the perception of understanding itself is developed internally—within the “seven plus or minus two” constraint, and then transferred to episodic memory.

It seems clear that the deductive scientific methods of Aristotle and Descartes were inspired by the *Elements*, Descartes by Euclid’s version, Aristotle by an earlier version (perhaps that of Hippocrates of Kos). And in each of those methods, ultimate understanding would be achieved by illumination of the *very first principles*, analogous to the definitions, postulates, and common notions of Euclid’s Book 1. The deductive scientific method would begin, ultimately, with those. But at the dawn of the Western Enlightenment, a new approach emerged, inspired by the likes of Gilbert, Harvey and Galileo—the great empiricists, and described by Bacon in his replacement for Aristotle’s *Organon*. For the science of nature (as opposed, for example, to the science of mathematics), the *New Organon* prescribes observation on nature itself, followed by inductive reasoning, as the route to understanding.

With considerable stimulation and inspiration from colleagues, especially Hooke, Newton wedded these two scientific methods into a two-layered approach -- applying observation and *induction* to establish putative axioms (the laws of motion and the law of gravity) at the first layer, from which propositions (Kepler's laws) could be *deduced* at the second layer. For modern natural science, the *understanding* achieved by Newton's approach was monumental. It was, most arguably, the inspiration for the Enlightenment that followed. It was the answer to Yali's question for Jared Diamond and to the puzzlement of Joseph Needham over China's failure to stay ahead of the West technologically during the 18<sup>th</sup>, 19<sup>th</sup> and 20<sup>th</sup> centuries. And it is the model followed by physical sciences since Newton's time. Most importantly, it eliminates the need for reduction to ultimate first principles. The Baconian side -- observation and induction, allows us to enter the natural world at any level of complexity at which we can make observations.

One might think of Newton's two-layer approach as the *New Reductionism*. Instructive examples in physics are given by the work of Rayleigh on acoustics and the work of Cohen on the properties of solid materials. By deduction, Rayleigh showed that local elastic properties combined with local inertia in solids would lead to spatially extensive propagation of waves (acoustic waves) in those materials. Cohen showed that the elastic moduli and densities of solids could be deduced through quantum mechanics from the structures of their constituent atoms. Thus we have three layers, taken two at a time. Each of these two-layer results gives us a perception of understanding. And each gives us powerful examples of Bacon's ideal: "To learn about nature, look to nature itself, not to books. Then put what you have learned to use for the betterment of humankind." Rayleigh's work allows us to design better acoustic structures -- for improved listening and for many other purposes. Cohen's work allows us to create designer solids -- with desired elastic moduli and the like. On the other hand, Cohen's method does not allow us to predict elastic moduli or densities as precisely as we can measure them. The prudent acoustician, then, would stay with Rayleigh's two layers and use measurements (or tables derived from measurements) rather than Cohen's computations to reveal elastic moduli and densities. From the measured values, reliable estimates of the acoustic properties can be computed. The two-layer approach gives not only the most intuitive understanding for the basic scientist, but also the most reliable results for the applied scientist or engineer working to fulfill Bacon's ideal.

It is our contention that ability to observe ensemble activity, appropriately applied, will gain us access to a fairly high level of complexity in the nervous system. In order to expand those observations into the two-layer approach of the *new reductionism*, we must develop deductive tools and methods to apply to our observations of ensemble activity.

### ***Appendix 2: Relation between LFPs and spike recordings (by Ted Lewis)***

There are numerous non-spiking inter-neurons in the brain, and one might argue that slow or graded potentials are important elements of the computational processes of the brain. This was

the argument made by Bullock in his classic paper “Neuron Doctrine and Electrophysiology” and in the sequel “The Neuron Doctrine, Redux” nearly fifty years later. Bullock’s argument in that first paper had been based on extensive observations, by several observers, of the intracellular activities in cells of the nine-neuron cardiac ganglion of *Homarus americanus*. In its day, neuron for neuron, it was arguably the most thoroughly understood ganglion on earth. The fact that its cells were linked by electrical junctions as well as chemical synapses made it irreducible, in a formal sense, and thus not easily addressable through reductionist analysis. The quantitative details of its properties would be determined by all of the elements of all of its cells; none would be determined by a proper subset of those elements. Engineers are familiar with this problem -- frequently labeled the *problem of loading*, and they solve it by introducing buffered boundaries (e.g., large impedance mismatches or nearly unidirectional transduction processes) between elements. To simplify two-layer reductionist analysis in neural systems, one needs to locate natural buffers (with processes that isolate the source of activity from the load). Two candidates are chemical synapses and spiking axons. To the extent that the state of the post-synaptic cell does not feed back directly through the synapse, the synapse buffers the sending cell from its load (the post-synaptic cell). To the extent that the states of the axon’s target do not feed back through the axon to affect the states of its proximal regions and cell body of origin, the axon buffers the sending cell from its target. The boundaries of elements at the lower layer of a two-layer analysis would be determined by the presence of putative buffered boundaries at their places of input and output. If, like those of the lobster cardiac ganglion, the inter-neurons of the brain are coupled by unbuffered junctions, then the most propitious place to begin studies of ensemble activity would seem to be axon bundles (e.g., white matter).

***Appendix 3: The demarcation problem and the formulation/validation of scientific hypotheses***  
(by Ted Lewis)

In geometry and in mathematics in general, first principles (e.g., the definitions, postulates and common notions of Euclid’s Book 1) are taken to be given or true by definition. In the two-layer approach to reductionism in natural science, on the other hand, modern philosophers of science generally agree that the descriptions of material properties and behavior (i.e., the descriptive models, hypotheses or laws) postulated for each of the two layers must be derived from observation (empirical evidence) and, therefore, be contingent (neither true nor false by pure logic or definition alone). Furthermore, they generally agree that these descriptions (frequently labeled *descriptive hypotheses*) must be testable with doable experiments or observations. These are the three quintessential features of descriptive hypotheses in natural science: (1) basis in empirical evidence, (2) contingency, and (3) testability.

Modern philosophers of science generally identify a second kind of hypothesis, the *explanatory hypothesis*, a synthesis of descriptive hypotheses at the lower layer that will putatively explain one or more descriptive hypotheses (representing properties or behaviors) at the higher layer. The explanatory hypothesis is tested by deductive analysis. In the manner of Newton, this analysis begins with the relevant descriptive hypotheses at the lower layer being raised to the

level of axioms. Although they may play the same role in this analysis as propositions or theorems do in the mathematical sciences, the descriptions of properties or behaviors at the higher layer stand on their own empirical bases and are not contingent on proof of derivability from properties and behaviors at the lower layer. In other words, analysis tests the explanatory hypothesis, not the higher-layer descriptive hypotheses (for astronomers, Kepler's laws would stand on their own, without Newton's synthesis). Furthermore, passing the test does not guarantee validity of the explanatory hypothesis; one still faces the specter of affirmation of the consequent. And this is where Ockham's razor comes in.

Thus we have a quintessential difference between the natural sciences and the mathematical sciences. There is at least one more: An axiom in the mathematical sciences need not have any of the three features required of a descriptive hypothesis in natural science. By widespread conventional practice, there seem to be other differences -- descriptive models in natural science need not be parametric; and deductive analysis in natural science need not have the formal structure required of it in the mathematical sciences. Instead, it may take the form of simulation, employing either parametric or nonparametric models. In whatever form it takes, affirmation of the consequent remains its major pitfall.

***The roster of the Focus Study Group (FSG) in alphabetical order:***

**Berger, Theodore,** *Biomedical Engineering & Neuroscience, University of Southern California*

**Dan, Yang,** *Neuroscience, Molecular & Cellular Biology, University of California, Berkeley*

**Deadwyler, Sam,** *Neuroscience, Physiology & Pharmacology, Wake-Forest University*

**Fetz, Eberhard,** *Neuroscience, Physiology & Biophysics, University of Washington*

**Georgopoulos, Apostolos,** *Neuroscience, Neurology & Psychiatry, University of Minnesota*

**Lewis, Ted,** *Electrical Engineering and Bioengineering, University of California, Berkeley*

**Marmarelis, Vasilis,** *Biomedical and Electrical Engineering, University of Southern California*

**Mehta, Mayank,** *Neuroscience & Astrophysics, University of California, Los Angeles*

**Schreiner, Christoph,** *Neuroscience, University of California, San Francisco*