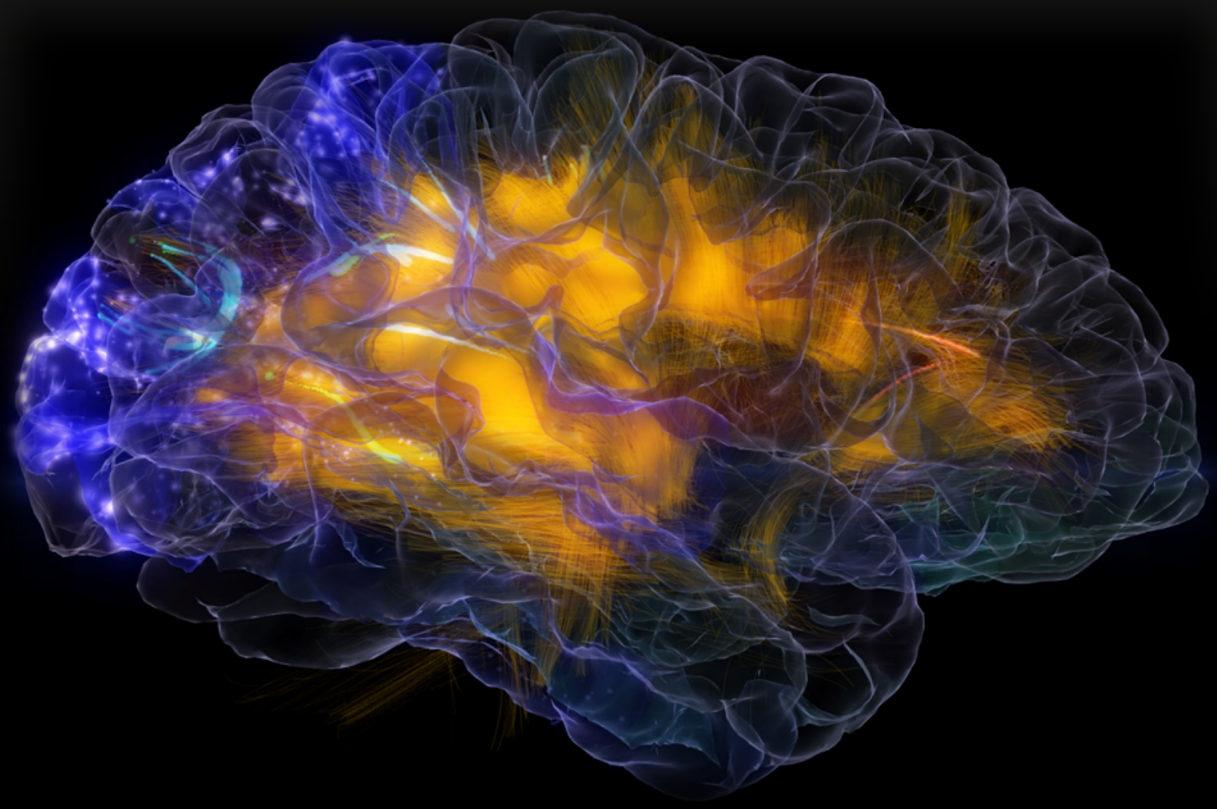

NSF WORKSHOP REPORT

Measuring the Brain: From the Synapse to Thought

2016

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Cover Art: "Glassbrain," by Adam Gazzaley, Roger Anguera Singla, Rajat Jain, Tim Mullen, Christian Kothe, John Fesenko, Oleg Konings and Matt Omernick; University of California, San Francisco.

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Background

Advancing our understanding of the brain has become a United States federal agency-spanning challenge involving a considerable fraction of our nation's research efforts, as exemplified by the multi-institutional thrusts associated with the BRAIN Initiative. The major goals of current efforts include mapping the brain *via* the cell census consortium, and developing a range of new tools and computation methods to enable highly dense measurements of brain function so as to discover emergent properties of neural circuits. From fundamental science to a greater understanding of human health, much of the charge has been led by biological scientists. With unprecedented knowledge and measurement tools becoming available, now is the time to chart a strategic path forward in terms of the roles that chemists will play in achieving this grand challenge.

A key question addressed during this workshop was "What is the role of chemistry (and, more broadly, mathematical and physical sciences) in moving this grand challenge forward?" As exemplified in the article: "Why recruit more chemists? Neuroscientists don't know all of the chemicals that are active in the brain," in *Chemical & Engineering News*,[1] there are ample opportunities for chemists to contribute uniquely by identifying and investigating the functions of important molecules involved in intra- and intercellular signaling. There are also opportunities for chemists to create new tools and therapeutics that will enable deeper understanding and control of brain function. This workshop articulates a path toward creating novel chemistry-centric tools to enable new understanding of brain organization, activity, and function across the metazoan. The focus on chemistry-associated tool-development differentiated this workshop from many of the prior NSF-sponsored brain-related workshops, as well as other workshops sponsored by the NIH and interagency-related neuroscience/BRAIN Initiative groups, which have focused primarily on genetics, histological imaging, and electrophysiological measurements.

Measuring the spatially and temporally dynamic chemical content of the brain is itself a grand challenge. The brain is a complex organ in which chemical-spatial-temporal processes play crucial roles throughout life. As outlined in the prior decade's 2007 NSF Brain workshop [2] on measurement challenges, a neuron can respond to an external signal by releasing the gaseous cell-to-cell signaling molecule nitric oxide or by opening an ion channel complex; these molecules vary in weight by a million-fold. A nanoscale synapse can be located at the bouton of an axon that is tens of centimeters away from the cell soma to which it transmits information. And, of course, synaptic connections, which function largely through chemical transmission, can vary their efficacy over milliseconds, yet memories can persist for a lifetime. These widely varying chemical, temporal, and

spatial scales are difficult to bridge using existing measurement modalities, leaving many critical measurements unobtainable. The technological challenges associated with *in vivo* imaging, molecular characterization, and speed and spatial resolution of measurements strike at the heart of chemical measurements, and, broadly, the fundamentals of chemistry. The endeavor to characterize the brain chemically is only possible by pushing the boundaries of the core chemical sciences, including synthesis, analysis, and modeling. Hence, it is important today to define the fundamental chemical knowledge that will be needed and the expected results from focusing our efforts as chemists on elucidating brain function. Bridging other disciplines with the chemical sciences is then possible in a thoughtful and impactful manner.

Enormous progress towards these goals has been made but much more remains to be accomplished. It is almost inconceivable that more than a decade into the -omics era, we still do not know the full "parts list" of the brain, nor do we have a complete census of the cell types within this most complex organ in the body. Addressing these and other challenges will be at the heart of chemical measurement efforts that will rely on experts in spectroscopy, spectrometry, separations, electrochemistry, electronics, optics, genetics, and nanotechnology,[3] as well as informatics. The topic is broad; charting a path forward requires multiple viewpoints and disciplines to even begin to address this grand challenge. Our workshop identified the challenges in defining the measurements to be made, developing the technologies that will underlie the characterization process, and designing the tools to enable researchers to catalogue and to retrieve information related to chemical information processing in brains, with each of these areas discussed below.

Research challenges

An overarching challenge for brain science remains: to map the full extent of neurochemical signaling in terms of ***chemical***, ***spatial***, and ***temporal*** encoding of information to define the chemical connectome. It is clear that a diversity of chemical species and processes act together over multiple temporal and spatial domains to govern specific aspects of organismal behavior. Yet current chemical measurements in neuroscience are unable to address the fundamental challenges associated with understanding this complex interplay. Advancing chemical measurements in neuroscience will especially benefit from having the capabilities to do the following:

- Create tools that can be used to determine the parts list of brains, down to individual cells, including metabolomes, peptidomes, metalomes, and proteomes, and to correlate this information with each cell's transcriptome.
- Correlate and decode extracellular chemical signaling in the context of neural firing and, ultimately, complex behavior.
- Develop multimodal dynamic monitoring approaches that embody and integrate neurochemical modes with neural activity modes, e.g., voltammetry with electrophysiology, or microdialysis with regional cerebral blood flow measurements.
- Develop strategies and technologies to enable investigation and, eventually, integration of multiple spatial domains, *i.e.*, subcellular, cellular, local circuitry, neuronal ensembles, brain regions, and entire brains.
- Advance technologies to investigate and, eventually, to integrate multiple temporal domains, *i.e.*, basal *vs.* stimulated extracellular neurochemical levels, monitoring over days to weeks to months to years, and to include continuous monitoring. Enable high-density measurements that encompass not simply greater numbers of sensors but also higher temporal resolution measurements for investigation of biological processes that range from fusion pore opening to behavioral events.
- Integrate technology development with the development (and testing) of underlying theories, including computational models and analytical theories.
- Minimize perturbations of biological systems by measurement processes; create materials chemistry approaches to address problems associated with biofouling and biocompatibility (short term/long term). Move towards minimally invasive or self-healing approaches to reduce artifacts caused by measurements and to enable measurements in humans.
- Fuse neurotechnologies and databases to capitalize on species of fundamental importance in neuroscience research, *e.g.*, *D. melangastor*, *C. elegans*, *A. californica*.
- Create tools that allow a quantitative chemical view of the brain across scales from single cell to "mesoscale" (brain slice and other intermediate *in vitro* preparations) to the living brain. Map quantitative chemical trajectories across key developmental and aging timescales.
- Correlate and integrate disparate measurement modalities (such as combining vibrational spectroscopy, magnetic resonance imaging, and mass spectrometry imaging).
- Study the chemical brain across the species, linking genes, chemistry, and structure.

- Reconcile sparks (electrical brain function), soups (chemical transmission), intracellular signaling, and maps (physical representations of the brain). More efforts are needed to integrate these communities as all aspects are needed to understand processes involved in learning, memory, and behavior.
- Conceive, test, deploy and maintain the cyberinfrastructure to store, curate, and access accumulated knowledge.
- Develop environments to facilitate computational modeling and experimental validations. Discussions with NSF, NIH, and academic participants suggested that new mechanisms are needed to support such data integration, especially to enable data to remain available beyond individual grant periods.
- Integrate global informatics across scales, approaches, and models, making this a recurring workshop theme.

Related challenges impeding success

While the preceding section highlights the scientific needs of measurement science to advance neuroscience research, additional challenges exist. One common refrain was more effective training mechanisms at all career stages to enable researchers to work across disciplines.

Perhaps the largest issue impacting measurement science relates to data issues, and these issues grow larger at the intersection of the measurement science and neuroscience fields. Data archiving, integration, and interpretation issues impact infrastructure, education, and even experimental design. For example, while the large genomic databases are well supported and effective, current neuroscience data repositories do not accept or annotate the newest vibrational images or mass spectrometry images, and most data repositories do not accept the chemical data onslaught. In addition, current data repositories are not effective at keeping up as the types of measurement data evolves. The workshop highlighted data integration and archiving issues with talks from NSF and NIH, where we learned, to the surprise of many attendees, that it is the researchers themselves that need to decide what data to archive and what to delete. The various educational, research, funding, and publishing communities need to work together to understand these issues and chart a path forward.

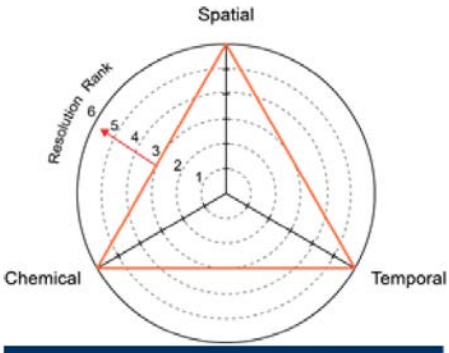
Workshop recommendations

We propose four broad categories in which efforts will address the needs and challenges identified above: research, education, infrastructure, and outreach. For each of these areas we provide some specific recommendations. We emphasize, however, that these areas are not distinct and there are significant (and desirable) overlaps between the categories and synergies to be realized in coupling these activities.

Research

To advance understanding of brains and overcoming these challenges, we need a combination of big science and individual investigator efforts, as well as an overarching informatics effort. We also need to be able to integrate these efforts.

- Establish a community-driven "cNeuron" (chemical-neuron) effort to characterize neurons chemically from multiple points of view including from an evolutionary perspective, and in well-defined networks to understand memory and the neuronal control of behavior.
- Support the grand challenge of the emerging concept of the "chemical connectome" to map the full extent in terms of chemical, spatial, and temporal encoding of information inherent in neurochemical modeling. A major effort will be to develop tools that will enable understanding how such information is dynamically encoded.
- While specific calls for interdisciplinary research arise, standing calls for integrated technology and neuroscience efforts remain less common. Encourage such efforts and evaluate the impact to devise new mechanisms that address outstanding needs.
- Enable center-scale efforts that specifically focus on technology development in the mold of Centers for Chemical Innovation.
- Encourage younger chemists to collaborate across disciplines with tailored funding efforts.
- Increase funding for seed projects, particularly involving highly innovative ideas or for ideas where preliminary data are not yet available.



Rank	Spatial (nL)	Temporal (s)	Chemical (# Species)
0	$> 10^4$	$> 10^3$	0
1	10^3-10^4	10^2-10^3	1
2	10^2-10^3	10^1-10^2	2-5
3	10^1-10^2	10^0-10^1	5-10
4	10^0-10^1	10^{-1}-10^0	10-30
5	10^{-1}-10^0	10^{-2}-10^{-1}	30-60
6	$< 10^{-1}$	$< 10^{-2}$	>60

Figure 1 Approach presented by Michael Heien to compare the content of information-rich measurements, and ranking criteria. Mature techniques will meet or exceed the multidimensional rank criteria of an experiment.

Education

Interdisciplinary training and education should be encouraged at all career stages and be widely available to communities at all levels. The following programs will develop a diverse pool of well-trained individuals.

- A number of outstanding "short courses" (offered by Cold Spring Harbor Laboratories, various institutes, on-line, etc.) are available to train researchers about new disciplines, but are perceived as expensive and thus, are not readily available. Encourage individuals to attend these short courses, regardless of rank, by creating both local and national funding mechanisms.
- A need for more quantitative research should be encouraged, a topic well suited to chemistry and the physical sciences. We suggest educational programs, both short- and long-term, specifically focused on quantitative analytical sciences.
- Data archiving is becoming a cultural and scientific issue. We need to train scientists to evaluate their data and decide what should be kept and archived and what the costs are for this. As new data types are acquired, requirements will need to be defined to standardize and to share data and to keep pace.

Outreach

- Establish data hubs, especially with institutions strong in computational sciences and national infrastructure that may already be supported.
- Sharing data across disciplines and models often is not well done. We need to train chemists and neuroscientists to produce and to report data that is important (even negative data), reproducible, and usable by others.
- Encourage K-12 outreach to communicate the
- excitement and importance of interdisciplinary physical science/brain science research. A key goal is to make such science accessible.

Infrastructure

Engineering instrumentation contributes to many areas—new materials, methods, microfluidics, micro- and nanofabrication, cell culture analysis, and more. However, delivery time from new technology to neuroscience labs is too long. We need to speed

technology transfer to focus on translation. This will require coordinated efforts in research, education, and outreach.

- Encourage the development of translational ecosystems by academic-industrial-healthcare partnerships.
- Develop community support mechanisms for scientists to learn how to implement these new technologies by learning from colleagues and collaborators.
- Create long-lasting informatics resources by partnership between institutes, universities, agencies, publishers, and industries. Building on past knowledge and resources is the typical mode for infrastructure, thus loss of knowledge and materials is a significant concern. Indeed, a persisting memory of these brain-related research efforts is desirable.

In addition to these specific recommendations, we emphasize that this workshop sets the stage but requires a follow-up workshop and activities to create a detailed list of charges for the broader ideas presented. In addition to direct follow-up activities as described below, the neuroscience/chemistry community has been staging a number of other activities, including symposia, symposia, and workshops.[4,5]

Follow-up dissemination

- The Executive Summary and workshop report will be available on the web.
- An editorial discussing workshop authored by the workshop exectuive committee (Andrews, Bhargava, Kennedy, Li, and Sweedler) has been published in *Analytical Chemistry*: see Anal. Chem., 2017, 89 (9), 4757–4757. DOI: 10.1021/acs.analchem.7b01364.
- Anne Andrews is leading a group of workshop participants in writing a technology roadmap on new tools by chemists for neuroscience, which is planned for publication in *ACS Chemical Neuroscience*.
- A special session was organized at Pittcon 2017, held March 2017 in Chicago, to disseminate some of the major ideas and discussion points from this workshop. The session, "Measuring the Brain: From the Synapse to Thought," included Sweedler, Andrews, Li, Bhargava, and Eberwine as speakers, representing the breadth of topics at the workshop. The Pittcon symposium was well attended with up to 80 attendees, and provoked a lively discussion.
- A symposium at UIUC is being planned that will continue the discussions raised by the workshop, with a planned date of summer 2017. The symposium will include bioengineering, neuroscience, and chemistry participants.

Workshop Details

This NSF-supported workshop took place on October 12-13, 2016, at the Federal Building in Arlington, Virginia.

The workshop was co-chaired by Professors Rohit Bhargava and Jonathan Sweedler (University of Illinois at Urbana-Champaign), with input from an organizing/executive committee composed of Anne Andrews (UCLA), Robert Kennedy (University of Michigan), and Lingjun Li (University of Wisconsin).

Attendants

This list of participants includes 33 individuals from academic and other research institutions, eleven staff members from the NSF, and four staff from the NIH. The final list of workshop participants included the following individuals:

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Agenda

Day 1: October 12, 2016

Time	Session Description
8:00 am	Registration
8:15 am	Welcome Session • Workshop overview and charge, Jonathan Sweedler • NSF: the interface between chemistry and neuroscience, Angela Wilson • The BRAIN Initiative and the role of chemistry research, Anne Andrews
9:00 am	The Grand Challenges in Understanding the Brain: Integrating models, technologies, and scale, from fundamental to clinical *Martha Gillette*, Leonid Moroz, Anne Andrews
10:00 am	Break
10:15 am	Characterizing the cells making up the brain: a cell census *Jonathan Sweedler,* Jim Eberwine, Yong Yao
11:45 am	Working lunch Creating a parts list of the brain *Lingjun Li*, Jeff Agar, Tom Neubert, Sean Bendall
1:15 pm	The dynamic brain: sampling and measuring brain chemistry *in vitro* and *in vivo* *Michael Heien*, Adrian Michael, Leslie Sombers, Jill Venton, Ryan White
3:00 pm	BREAK
3:15 pm	Advances in molecular imaging *Rohit Bhargava*, Conor Evans, Fahmeed Hyder, Partha Basu

Day 2: October 13, 2016

Time	Session Description
8:00 am	Sensors around neurons and in the brain Christy Haynes, David Berkowitz, Tim Glass, Lin Tian, Mande Holford
9:25 am	Engineered structures Robert Kennedy, Albert Folch, Han Xue, Hang Lu, Steve Weber
10:50 am	BREAK
11:00 am	Opportunities in data analysis, informatics and integration Scott Sternson, Badri Royam, George Komatsoulis, Bill Miller
12:30 noon	Working Lunch Summary from the sessions, discussions and workshop integration
3:30pm	Adjourn

Citations:

[1] Andrea Widener *"Why recruit more chemists? Neuroscientists don't know all of the chemicals that are active in the brain,"* **Chemical & Engineering News 94**(22), 22-23, 2016.

[2] *Brain Science at the Interface of the Biological, Physical and Mathematical Sciences, Computer Science and Engineering: Analysis of New Opportunities*, March 5–6, 2007.

[3] Alivisatos, A. P., Andrews, A. M., Boyden, E. S., Chun, M., Church, G. M., Deisseroth, K., Donoghue, J. P., Fraser, S. E., Lippincott-Schwartz, J., Looger, L. L., Masmanidis, S., McEuen, P. L., Nurmikko, A. V., Park, H., Peterka, D. S., Reid, C., Roukes, M. L., Scherer, A., Schnitzer, M., Sejnowski, T. J., Shepard, K. L., Tsao, D., Turrigiano, G., Weiss, P. S., Xu, C., Yuste, R., and Zhuang, X. *Nanotools for neuroscience and brain activity mapping.* **ACS Nano 7**, 1850-1866, 2013.

[4] Andrews, A. M. *Why monitor molecules in neuroscience?* **ACS Chem. Neurosci. 8**, 211-212, 2017.

[5] http://onechemistry.jhu.edu/index.php/symposium/2017-2/, *"One chemistry symposium: Chemistry's role in the brain initiative,"* Johns Hopkins University, March 2017.


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