DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
NATIONAL INSTITUTES OF HEALTH

NATIONAL ADVISORY COUNCIL FOR BIOMEDICAL IMAGING AND BIOENGINEERING

Summary of Meeting[1]
May 16, 2008

The National Advisory Council for Biomedical Imaging and Bioengineering (NACBIB) was convened for its 17th meeting on May 16, 2008, at the Marriott Suites Bethesda in Bethesda, Maryland. Dr. Roderic I. Pettigrew, Director of the National Institute of Biomedical Imaging and Bioengineering (NIBIB), presided.

In accordance with Public Law 92–463, the meeting was open to the public from 9:00 a.m. to 12:45 p.m. for the review and discussion of program development, needs, and policy. The meeting was closed to the public from 1:30 p.m. to 3:30 p.m. for the discussion and consideration of individual grant applications.

Council members present:
Dr. Ronald L. Arenson
Ms. Rebecca M. Bergman
Dr. David J. Dzielak
Dr. Richard L. Ehman
Dr. Katherine W. Ferrara
Dr. Don Giddens
Dr. Gary H. Glover
Dr. Percival McCormack

Ex officio members present:
Dr. P. Hunter Peckham, Veterans Administration
Dr. James G. Smirniotopoulos, Uniformed Services University of the Health Sciences
Dr. Andrew Watkins, Centers for Disease Control and Prevention

Council member participated via conference call:
Dr. David Satcher

Council members absent:
Dr. Augustus O. Grant
Dr. Mae C. Jemison

[1] For the record, it is noted that members absent themselves from the meeting when the Council is discussing applications (a) from their respective institutions or (b) in which a conflict of interest may have occurred. This procedure only applies to applications that are discussed individually, not to "en bloc" actions.

Ex officio members absent:
Dr. Anne Plant, National Institute of Standards and Technology
Dr. Judy Raper, National Science Foundation
Mr. Michael Leavitt, U.S. Department of Health and Human Services
Dr. Elias A. Zerhouni, National Institutes of Health

Executive Secretary:
Dr. Anthony Demsey

Also present:
NIBIB staff present for portions of the meeting:

Ms. Lillian Ashley
Dr. Prabha Atreya
Mr. Angelos Bacas
Dr. Richard A. Baird
Ms. Sheila Barrett
Dr. Abesh Bhattacharjee
Ms. Barbara Cantilena
Dr. Zohara Cohen
Ms. Shirley Coney-Johnson
Ms. Nancy Curling
Dr. Emilios Dimitriadis
Ms. Angela Eldridge
Dr. Zeynep Erim
Ms. Cheryl Fee
Ms. Shirley Finney
Ms. Carol Fitzpatrick
Dr. David George
Ms. Pam Glikman
Dr. Valery Gordon
Dr. Ruth Grossman
Dr. John Haller
Dr. John Hayes
Ms. Eunica Haynes
Dr. William Heetderks
Dr. Lori Henderson
Dr. Rosemarie Hunziker
Dr. Chris Kelley
Ms. Mary Beth Kester
Dr. Dale Kiesewetter
Dr. Peter Kirchner
Dr. Brenda Korte
Dr. Lixin Lang
Dr. Albert Lee
Dr. Hector Lopez
Dr. James Luo
Dr. Ying Ma
Dr. Alan McLaughlin
Mr. Todd Merchak
Mr. Nicholas Mitrano
Mr. Larry Morton
Mr. Joe Mosimann
Dr. Peter Moy
Dr. Grace Peng
Dr. Karen Peterson
Dr. Roderic I. Pettigrew
Ms. Katie Serrano
Dr. Belinda P. Seto
Mr. Shaun Sims
Ms. Casey Stewart
Ms. Thomasine Stovall
Ms. Kawannah Taylor
Ms. Florence Turska
Mr. Matt Wise
Ms. Li-Yin Xi
Dr. Yantian Zhang
Dr. Ruixia Zhou

Other Federal employees present:
Dr. David Brown, U.S. Food and Drug Administration
Dr. Chekesha Clingman, U.S. Food and Drug Administration
Dr. Arlette Howard, Office of the Director, NIH
Dr. Lisa Kinnard, U.S. Food and Drug Administration
Dr. Abraham Levy, National Center for Research Resources, NIH
Dr. Kyle Myers, U.S. Food and Drug Administration

Members of the public present for portions of the meeting:
Ms. Jennifer Ayers, American Institute for Medical and Biological Engineering
Mr. Benjamin Beeghly, National Capital Captioning
Mr. Benjamin Corb, American Institute for Medical and Biological Engineering
Dr. Jason Greng, Xigen LLC
Mr. Gareth Hadyk, National Capital Captioning
Ms. Allyson Harkey, NOVA Research Company
Ms. Sarah Oliphant, American Academy of Radiology Research
Mr. Mike Peters, American College of Radiology
Ms. Olivia Propst, NOVA Research Company
Ms. Gloria Romanelli, American College of Radiology
Dr. Bruce Rosen, Harvard University, Massachusetts General Hospital
Ms. Kathy Sedgwick, NOVA Research Company

I. Call to Order: Dr. Anthony Demsey

Dr. Demsey welcomed attendees and called to order the 17th NACBIB meeting. He reminded attendees that the morning session of the meeting is open to the public.

Dr. Demsey specifically welcomed members of scientific society constituencies, including Ms. Jennifer Ayers and Mr. Benjamin Corb of the American Institute for Medical and Biological Engineering and Ms. Gloria Romanelli of the American College of Radiology.

Dr. Demsey thanked Ms. Carol Fitzpatrick and Ms. Pam Glikman for planning the meeting and introduced Dr. Pettigrew, who formally welcomed all participants.

II. Director's Remarks: Dr. Roderic Pettigrew

A. Retiring Member

Dr. David Dzielak, who has been a Council member since September 2004, will be ending his tenure with this meeting. Dr. Pettigrew formally thanked Dr. Dzielak for his hard work and commitment to the Council. Dr. Dzielak played an essential role in the early phases of the Institute, communicating the Institute's mission and role in the overall NIH research agenda. Dr. Pettigrew presented to Dr. Dzielak a letter from HHS Secretary Leavitt and a plaque from NIBIB in recognition of his service to the Institute and the Advisory Council.

B. Budget Update

The 2009 NIH budget, as compared to the 2008 budget, has not changed. The 2009 NIBIB

budget, however, includes a 0.5 percent increase over 2008, as requested by the President. There are no significant changes in the planned expenditure of funds.

C. Significant Items

Strategic Plan—Point-of-Care Technologies

NIBIB has continued to pursue its goals as outlined in the *Strategic Plan.* Goal 2 of the *Strategic Plan* focuses on "Targeted research programs in areas of special opportunity or need that take advantage of novel technological advances and scientific discoveries." To that end, NIBIB has focused a small portion of its uncommitted appropriated funds on several areas of high priority interest. One such area has been point-of-care technologies (POCT), which offers an opportunity to advance global health care and improve delivery of health care in a more efficient way by detecting diseases at the initial point of health care provider contact. In point-of-care testing, diagnosis is performed near the patient or at the bedside, often by a minimally trained user, with the aim of timely results for rapid intervention. To make these kinds of tests maximally effective in settings with little infrastructure, an ideal diagnostic test would be affordable, sensitive, specific, user-friendly, rapid and robust, transportable, and deliverable and maintainable to those who need it. In order to support engineering of point-of-care testing, NIBIB has created a point-of-care technology network and funded four development sites, each with a particular focus:

- Rapid Multipathogen Detection for POCT and National Disaster Readiness (University of California, Davis/Lawrence Livermore National Laboratory), focusing on developing technologies to detect various pathogens of concern in national disasters such as methicillin-resistant staphylococcus aureus.
- Center to Advance POC Diagnostics for Global Health (Program for Appropriate Technology in Health [PATH], Seattle, Wash.), focusing on diagnostics for global health, HIV, syphilis, malaria, etc.
- Center for POC Technologies for Sexually Transmitted Diseases (Johns Hopkins University), focusing on sexually transmitted diseases, including HIV.
- Center for Emerging Neurotechnologies (University of Cincinnati), focusing on technologies useful in a neuro-emergency setting.

Representatives from each of the grantee sites met on March 7, 2008, to establish a mode of communication to enhance the network. Dr. Pettigrew will report on progress at a future meeting.

Quantum Grantees

NIBIB has also focused on establishing grants to advance the promise of profound change in the health care system through quantum-level improvements in selected major medical problems. To that end, the Institute has funded five Quantum Grantees to date:

- Karen Hirschi and Mary Dickinson, Baylor College of Medicine: Recreating neurogenesis niches *ex vivo* for transplantation into brain areas affected by stroke.

- Anthony Atala, Wake Forest University Health Services: Utilizing stem cells from amniotic fluid to treat diabetes by regenerating pancreatic beta cells.
- Raoul Kopelman and Dan Orringer, University of Michigan: Developing theranostic nanoparticles to aid surgical resection via targeting, imaging, and PDT of glioma.
- Mehmet Toner, Massachusetts General Hospital: Developing a microchip to detect circulating tumor cells in whole blood for diagnosis and treatment monitoring.
- Shuvo Roy and William Fissell, Cleveland Clinic Lerner College of Medicine: Developing an implantable MEMS-based artificial kidney.

The Quantum Grantees met on March 19, 2008, to share status updates and future plans, and to receive feedback from NIH staff. The total FY07 cost for the five grantees is $5.3 million; Phase II is planned for FY10.

Armed Forces Institute of Regenerative Medicine

The Armed Forces Institute of Regenerative Medicine (AFIRM) was officially announced on April 17, 2008, and reported in *Science*. A multi-agency effort, AFIRM is led by the Department of Defense; NIBIB leads NIH's participation, with a contribution of $500,000 per year over 5 years. The goal of the effort is to bring the power of regenerative medicine to bear on addressing the devastating injuries that members of the armed forces sustain on the battlefield, a practical and important problem for the nation. Two consortia were funded: Wake Forest University (Anthony Atala) and the University of Pittsburgh (Alan Russell); and Rutgers University (Joachim Kohn) and the Cleveland Clinic (George Muschler). (Both Drs. Atala and Kohn are also involved in Quantum Grant projects.) This effort was so well received that the initial funding, $40 million over 5 years, was increased to $80 million. Due to matching funding from other participants, the final funding is $165 million over 5 years.

Meyerhoff Scholarship Program

The Meyerhoff Scholarship Program, at the University of Maryland, Baltimore County (UMBC), is the standard against which other programs are compared regarding effectiveness in increasing diversity among leaders in science and engineering. **Dr. Pettigrew** recently attended the 20th Anniversary celebration of the Program, to which all of the Meyerhoff graduates were invited. The overwhelming majority of graduates have gone on to receive a Ph.D., M.D., or both, and all of the current graduating students have been accepted into Ph.D. and/or M.D. programs. NIBIB looks forward to continuing its support for this successful program.

Collaboration with India

Dr. Maharaj Bahn, the Director of India's Department of Biotechnology, recently visited NIBIB. Since his visit, two of his senior advisors have visited to help plan the Indo-U.S. (DBT-NIBIB) Workshop on Low-Cost Diagnostic and Therapeutic Technologies, set for the fall of 2008. The meeting will encourage U.S. and Indian scientists to collaborate in development of low-cost diagnostics and therapeutics, with an eye toward (1) identifying pressing needs and opportunities in the area of chronic diseases and (2) developing a plan of cooperation for

collaborative work. Dr. Pettigrew will report on this further as the Workshop begins to take shape and likely participants are identified.

NIBIB Grantee Wins Pierre Galletti Award

Dr. Nicholas A. Peppas of the University of Texas, Austin, has won the prestigious Pierre Galletti Award, given "for seminal contributions and visionary leadership in biomaterials science and engineering, and for pioneering work on drug delivery that has led to numerous biomedical products and devices." This is the American Institute for Medical and Biological Engineering's highest honor.

Lillian Ashley Retirement

After 42 years of government service, including 6 years at NIBIB, **Ms. Lillian Ashley** will be retiring at the end of the month. Ms. Ashley will be working in the community as a substitute teacher and spending time with family. Dr. Pettigrew expressed his sincere appreciation and admiration for her service and wished her the best.

III. Report on NIH Council of Councils: Dr. Ronald L. Arenson

The Council of Councils (CoC) was established by Dr. Zerhouni under the provisions of the NIH Reform Act of 2006 and is comprised of representatives from various NIH councils. **Dr. Ronald Arenson** represents the NACBIB, and reported on the CoC's most recent meeting.

The CoC advises the NIH Director on matters related to the policies and activities of the new Division of Program Coordination, Planning, and Strategic Initiatives (DPCPSI), established via the NIH Reform Act of 2006, and makes recommendations on the conduct and support of trans-NIH research proposals supported by a Common Fund. The Common Fund replaces the Roadmap and moves it into a new formula. There is no set methodology for growing the Common Fund, but it must at least maintain its previous percentage of the NIH budget. However, if the Common Fund reaches over 5 percent of the budget, a review is triggered. The Common Fund Strategic Planning Report is produced biannually.

At the CoC meeting, Dr. Zerhouni stressed the importance of communication between CoC and individual Institute advisory councils. Three CoC subcommittees have been created that align with the three divisions of the Office of Portfolio Analysis and Strategic Initiatives (OPASI), which is within the structure of DPCPSI and led by Dr. Alan Krensky. The *Division of Resource Development and Analysis* (DRDA) develops and uses analytic tools and information, such as knowledge management and public health need/burden of illness. (Dr. Arenson is on this subcommittee.) The *Division of Strategic Coordination* (DSC) oversees strategic coordination of NIH-wide planning and provides an "incubator space" for trans-NIH initiatives, including the NIH Roadmap and Common Fund. The *Division of Evaluation and Systematic Assessments* (DESA) plans, conducts, coordinates, and supports program evaluations for ICs, trans-NIH initiatives, GPRA, and PART. The next CoC meeting will be November 20–21, 2008, and will focus on obesity and nutrition research as part of the Common Fund initiatives.

IV. Review of Council Procedures and Regulations: Dr. Anthony Demsey

Dr. Demsey noted for the record that a quorum was present for this Council meeting.

A. Council Regulations, Policies, and Procedures

Dr. Demsey summarized elements of the Government in the Sunshine Act and the Federal Advisory Committee Act that govern all Advisory Council meetings. These Acts require the U.S. Department of Health and Human Services to open Advisory Council meetings to the public except when proprietary or personal information is discussed. To comply with these regulations, the NACBIB meeting is open to the public for all but the review of individual grant applications. Dr. Demsey reviewed the guidelines with Council regarding conflict of interest, confidentiality, and lobbying.

B. Future NACBIB Meeting Dates

The next NACBIB meeting is scheduled for September 16, 2008, at the Marriott Suites Bethesda in Bethesda, Maryland. Dr. Demsey asked Council members to inform him of major conflicts with upcoming meeting dates. He also raised the idea that future meetings be held mid-week, in order to avoid the crush of travel out of the Washington, DC, area that occurs on Fridays. The next Council meeting is scheduled for a Tuesday, which can serve as a test case.

C. Approval of the January 25, 2008, NACBIB Meeting Minutes

A motion was forwarded and seconded to approve the minutes of the January 25, 2008, NACBIB meeting with one minor spelling correction. The minutes were approved unanimously with the correction. Dr. Demsey reminded Council that all of the meeting agendas and minutes are available on the Council Web site.

V. Report of the Training and Career Development Working Group: Dr. Don Giddens

The Training and Career Development Working Group met May 16, 2008, at 8:00 a.m. (before the Council meeting). Dr. Richard Baird of NIBIB updated the group on the NIBIB-NSF graduate program. That program is undergoing an external evaluation by a contractor, and a report will be completed this summer. Discussions regarding re-issuance of the program will begin this summer as well.

A general training grantees meeting will be held in June with an expected 175 participants.

Phase II of the NIBIB-Howard Hughes Medical Institute RFA is about to begin. Letters of intent are due May 19, and applications are due June 17. Reviews will take place in the fall, with awards in the spring.

NIBIB has begun tracking personnel in R01 and R21 projects in an effort to understand the number and type of personnel supported by these grants as well as overall grant history. This project will be completed by this summer.

The Working Group also discussed the issue of support for foreign students. Foreign-educated researchers currently hold approximately one-half of the NIH intramural and approximately two-thirds of extramural postdoctoral positions. In 1975, Congress mandated a study of national needs for biomedical, behavioral, and clinical research personnel, to be produced every 4 years by the National Academy of Sciences (NAS). The next study would be completed by the end of 2009. NIBIB has asked NAS to evaluate specifically the national need for bioengineers. Hopefully the study will provide an estimate of the future demand for biomedical, behavioral, and clinical researchers and a focus on cross-disciplinary needs such as biophysics, computational biology, and bioinformatics. NIBIB also hopes for a reliable estimate of the future supply of researchers in these areas and recommendations in trainee production rates, in order to evaluate whether supply will meet demand.

Discussion

Dr. Pettigrew asked whether the NAS study is ongoing. Dr. Giddens responded that the study is indeed ongoing and that there is still opportunity for input. Meetings will be held this summer. Dr. Richard Ehman added that the first meeting is May 20–21.

VI. NIBIB Programs in Image Processing and Biomedical Informatics: Dr. Zohara Cohen

Dr. Zohara Cohen outlined the image processing and biomedical informatics portfolios within NIBIB.

The *image process and visualization program* supports (1) development of algorithms and software for post-acquisition image processing and analysis and research and (2) development to optimize display and visualization of images (research on display hardware, models, evaluation analysis for imaging modalities, or image analysis algorithms). Although many other programs support acquisition of images, this program focuses on post-acquisition image processing. This program also includes observer performance studies to understand how people perceive information contained in images.

The *biomedical informatics program* is geared toward supporting development of structures and algorithms to improve the management of quantitative and qualitative biomedical data, including compression, storage, querying, and transmittal. As NIBIB is not unique at the NIH in having a program in biomedical informatics, NIBIB's program in biomedical informatics is intended to support its other bioengineering and biomedical imaging programs.

Dr. Cohen presented statistics on the grants under her management. There are several ways to analyze the portfolio; Dr. Cohen reviewed them by organ, imaging modality, and informatics/computational methods:

- *Organ:* Thirty-five grants look at the brain or central nervous system, 11 grants are cardiothoracic, 8 are musculoskeletal, 1 focuses on the inner ear, 2 look at the eye, and 2 focus on the gastro-intestinal tract. Thirty-four additional grants are crosscutting, which is not surprising given that NIBIB's mission is to enable technologies to support the study of organs and diseases across the NIH.

- *Imaging modality:* An overwhelming number of the grants use MRI (32), microscopy (12), and CT (11). Other modalities include x-ray (4), PET/SPECT (3), ultrasound (1), endoscopy (3), OCT (1), microarray (3), and EEG/MEG (3). Thirteen grants used multiple modalities, and 18 grants were considered "cross-cutting"—the methods could be applied to different imaging modalities. (Note: These categories are not unique; for example, a grant that uses both x-ray and CT was counted in both categories.)

- *Informatics/computational methods:* Seven grants have some particular focus on image enhancement (i.e., removing noise or a motion artifact), and 20 grants focus on segmentation (delineation of critical structures within an image). One of the 19 grants using registration (the alignment of images acquired under two conditions) employs pre-procedural CT data, perhaps high resolution, and bringing it to bear on a procedure being conducted under fluoroscopic guidance. Twenty-one projects are interested in structure morphology, trying to characterize the structure of information in images, while 21 other projects are focused on visualization. Eight grantees are developing methods for feature detection and 14 are employing modeling or simulation to garner extra information. Natural language processing is included in three projects, including one in San Diego in which researchers are attempting to predict outbreaks based on school absenteeism by collecting information from parents who report symptoms. Thirty grants have a software development focus; generally, these researchers are developing software that not only will be used in their work but also will be useful to a broader audience.

Project Spotlight: Patient-Specific Finite Element Model Development—Dr. Nicole Grosland

Dr. Cohen also presented detailed overviews of a few projects from the portfolio, beginning with Dr. Nicole Grosland's work at the University of Iowa. Dr. Grosland and her colleagues are developing patient-specific finite element models. Finite element modeling is a method of studying a complex, irregular structure by breaking it down into small, discrete or finite elements, after which one can apply computational methods to integrate the entire structure, allowing the investigator to understand what is going on in the irregular structure. One of the most challenging and time-consuming steps in this method is breaking down the structure into those elements, a process known as *meshing*. Dr. Grosland is developing an automated method to refine a mesh for the long bones of the hand, work which could have implications for prosthetic design and prediction of fracture risk. The method she uses begins with an atlas, which represents the typical bone shape, and registers the atlas with the images of a particular subject; in that way the edges of the bone are extracted automatically to create the model. The project combines segmentation, registration, and visualization, uses a CT imaging modality, and focuses on the musculoskeletal system.

Project Spotlight: Integrating Data, Models, and Reasoning in Critical Care—Dr. Roger Mark

Dr. Roger Mark, of the Massachusetts Institute of Technology, is leading a bioengineering research partnership integrating data models, reasoning, and critical care. Modern-day intensive care units have so many instruments and monitors collecting large amounts of information that, in some cases, data cannot be integrated or interpreted. Dr. Mark and his colleagues are developing ways to collect these data to make possible advanced methods for monitoring, tracking, and even predicting pathophysiological states. As a first step, they have created the

Multi-Parameter Intelligent Monitoring for Intensive Care (MIMIC) II database. This massive research-enabling database, which supports the development and evaluation of advanced patient monitoring systems, will be made freely available to researchers through PhysioNet (a resource managed by NIBIB's Dr. Grace Peng). To date, MIMIC-II contains 30,000 patient records, 4,000 of which include physiological waveform data. Other data include physiological trends, discharge summaries, nurses' notes, medications, and ventilator settings. Dr. Mark is also currently putting forth particular effort in developing techniques for de-identification of nurses' notes, to ensure patient privacy.

Project Spotlight: Lossless Watermarking for Medical Image Security and Confidentiality—Dr. Qiang Wu

Dr. Qiang Wu, of Advanced Digital Imaging Research, LLC, is conducting a Phase II SBIR grant on lossless watermarking, research that cuts across modalities and organ sites and combines image processing with informatics. Data integrity and patient confidentiality are crucial to image-based medical diagnosis, particularly with growing use of teleradiology. In the research setting, DICOM image sharing format is often used, and identification information is stored in a header; however, there is a risk that the header will become detached from the main image data. In clinical practice, the patient information is often actually written into the image in such a way that it cannot be separated; however, this leads to confidentiality issues as well as loss of original image content.

Dr. Wu is exploring reversible and lossless watermarking, in which none of the original image data is lost. A decoder decodes the watermark—which certifies the data itself—and is able to reverse the change made in watermarking, resulting in the original, uncompromised image. The watermarking would also be imperceptible and have excellent payload capacity. Payload, or how much information can be embedded without affecting images irreversibly, is set at a goal of approximately 1,600 characters, considered sufficient for most clinical applications.

NIBIB in the NIH-Wide Informatics Community

NIBIB has strong participation in the NIH-wide informatics community through a variety of avenues: for example, the Biomedical Information Science and Technology Initiative (BISTI). Many NIBIB staff are active participants in BISTI, an NIH-wide consortium that coordinates informatics and biomedical computing research, with a large focus on extramural research. In the past few years, BISTI has released several announcements of funding opportunities, in which NIBIB has participated. Eighteen grants in Dr. Cohen's portfolio are funded through these program announcements.

NIBIB staff are also active in many of the National Centers for Biomedical Computing (NCBCs), which constitute a Roadmap initiative to create centers as building blocks for a national network of biomedical computing. Seven National Centers (the "hubs") are currently funded, all with outside collaborators (the "spokes"). NIBIB also participates in the Software and Data Integration Working Group, which is a major effort related to the NCBCs. This Working Group is developing i-Tools, a conceptual infrastructure to relate all of the tools and data being generated by the NCBCs. Ultimately, the Working Group would like to extend i-Tools beyond the Centers, but the beginning goal is to examine the tools being developed and how they can be

linked to facilitate an investigator's search for an appropriate tool for a particular application. NIBIB is also involved in the NIH Blueprint for Neuroscience Research, which includes 15 ICs. Most of NIBIB's work in this effort falls within imaging and neuroinformatics. For example, the NIBIB-led Neuroimaging Informatics Tools and Resources Clearinghouse (NITRC), in which Dr. Cohen is actively involved, is a clearinghouse for neuroimaging tools and resources—a "one-stop shop" for neuroscientists, end-users, and developers of neuroimaging tools. This Web site includes tools, descriptions, feedback ratings, and discussion groups.

NIBIB is also active in other informatics activities:

- Interagency Modeling and Analysis Group (IMAG)
- Clinical and Translational Science Awards (CTSA) Informatics Coordinating Committee
- NanoHealth Enterprise Initiative
- PhysioNet
- Osteoarthritis Initiative
- caBIG Imaging Informatics Workspace

Dr. Cohen expressed appreciation to the investigators in her portfolio for their innovative ideas, hard work, and accomplishments toward improving human health and reducing the burdens of illness and disability.

Discussion

A Council member asked about NIBIB's role in caBIG. Dr. Cohen responded that NIBIB does not have a major role in caBIG. Dr. Belinda Seto noted, however, that within the National Cancer Imaging Archive, a caBIB imaging project, is the Reference Image Database for Evaluation of Therapy (RIDER) database, which NIBIB cofunds. It is quite likely that without NIBIB funding, the RIDER database would not have reached its current scope.

Dr. James Luo added that there is also a Blueprint initiative for osteoarthritis that attempts to incorporate some of the caBIG and Biomedical Informatics Research Network (BIRN) infrastructures to allow the community to leverage them.

Dr. Heetderks stated that the informatics program tends to be different from other programs because it cuts across so many different Institutes. BISTI, for instance, brings together all of the different Institutes. NIBIB is attempting to interact with the other ICs in two ways: (1) by working closely with individual ICs (e.g., with NCI on caBIG); and (2) by leveraging the infrastructure created through those programs to utilize them for imaging and bioengineering (e.g., using caBIG infrastructure for a nanomaterials database).

A question was raised as to whether computer-aided diagnostics (CAD) is included in Dr. Cohen's portfolio and to what extent NIBIB is involved in CAD systems. Dr. Cohen responded that CAD is indeed part of the portfolio but such grants are assigned to NIBIB only in

cases when the technique is not developed for a particular clinical application. To the extent that there are CAD methods that are crosscutting, NIBIB would support them. However, NIBIB currently focuses on methods for evaluating CAD, as in receiver operating characteristics (ROC) methods. There are currently 10 grants in ROC, examining generalized models for analyzing CAD methods.

Dr. Cohen added that NIBIB participates in an NIH-wide effort looking at the health impacts of nanomaterials, led by the National Institute of Environmental Health Sciences (NIEHS). Drs. William Heetderks, Lori Henderson, Albert Lee, and James Luo represent NIBIB in that effort by supporting the informatics portion of the project to create a knowledge repository to collect information, characterize nanomaterials, and characterize health effects.

VII. Imaging and Neuroinformatics: Opportunities and Challenges: Dr. Bruce Rosen

Dr. Pettigrew introduced Dr. Bruce Rosen, Professor of Radiobiology and Health Sciences and Technology at Harvard Medical School and Massachusetts General Hospital. Dr. Rosen is well known for his pioneering work in the early development of functional MRI (FMRI) and elucidation of the blood oxygen level-dependent signal phenomenon on which functional imaging is based. In a cover article in *Science* Dr. Rosen was the first to demonstrate a noninvasive technique to image blood flow in the human brain and to allow visualization of sites in the brain responsible for somatosensory functions. Dr. Rosen has received the Gold Medal from the International Society of Magnetic Resonance in Medicine, a distinction also held by two Council members, Drs. Glover and Ehman.

Dr. Rosen expressed appreciation for NIBIB's support of his research and spoke to the Council about opportunities and challenges in imaging and neuroinformatics.

For the presentation Dr. Rosen defined *Informatics* as "the study and application of natural and artificial systems that sense, store, process and communicate information."

Ideally, studies that include informatics will:

- Enable research across different scales different centers, and different modalities. Currently, many new sets of tools are being developed.

- Facilitate ever-larger studies to examine variability in the underlying biology of complex conditions. For example, schizophrenia is likely to be a series of disease variants, and will be better understood when large sample sizes allow the measurement of heterogeneity and complex circuitry.

- Enable conduct of longitudinal methodologies in the face of changing technology.

- Create a means for sharing data that minimizes legal and cultural obstacles.

Current practices for studying complex disease processes pose challenges to researchers. For example, studying changes in hippocampal volume over time in patients who will ultimately develop Alzheimer's disease may involve the use of data from a variety of databases. A trend may be apparent, but the variability and outliers make it difficult to draw inferences. Using a

single scanner at a single research site, would yield decreased variability. The challenge is to obtain a low level of variability in studies of rare diseases, or the genetic influences in diseases like schizophrenia, that require populations beyond those that are available at a single center. Typical clinical studies may include dozens of research sites, each of which may use scanners made by different manufacturers, different models, and different hardware and/or software versions. Even use of the same scanner with the same patient, but at different times, may deliver a different reading. Also, different sites may select different image analysis methods, designed to work reproducibly on some data types but perhaps not others. In order to conduct large studies successfully, the requisite correlates and behavioral, genetic, and chip data should be fully reproducible across all sites—a daunting challenge.

The challenge of registering data from two different scanners can be overcome through enhanced understanding of the scanners and related hardware/software. Corrections can be made for motion or field heterogeneities (B0 or B1), as well as the different magnetic fields used for MR acquisition. Researchers must create common acquisition protocols, develop proper distortion corrections that account for these differences, and examine the differences over time. As part of the BIRN project, Dr. Jorge Jovicich performed multi-site structural MRI data acquisition and calibration studies with many colleagues from around the country, and showed that it is possible to significantly reduce signal intensity variation.

The Alzheimer's Disease Neuroimaging Initiative (ADNI) provides an example for analyzing data across sites and platforms. ADNI scanned over 800 subjects to examine the natural history of patients with Alzheimer's disease, using MRI and other technologies. ADNI has many sites with multiple platforms and field strengths; however, the investigators adapted calibration and standard acquisition tools developed by Dr. Anders Dale and his colleagues as part of BIRN to overcome the challenges of multiple sites.

Preliminary results indicate that acceleration of the rate of change of the size of the cortical thickness over time correlates with Alzheimer's disease. For these patient groups, the ability to view data in detail and to make corrections allows the detection of subtle changes with great sensitivity over short periods of time. For example, these data show that the rate of change in ApoE4 carriers was significantly different from that of non-carriers. A comparison of these data with genetic data allows scientists to tease out genetic influences, such as rate of change in patients with Alzheimer's disease.

While ADNI is an example of what is possible there is still much work to be done. The informatics community must think in more interactive ways about how to design experiments that measure target variables. The analysis pipeline must be considered. Each tool is optimized for a certain type of data acquisition, which determines the pulse sequence. Scanner performance must be taken into consideration, using a closed loop of quality assurance. One of the greatest challenges may be to work with manufacturers to help them view their role as a pre-competitive rather than competitive process.

Successful study design involves a consideration of the interactions between multiple variables, the creation of algorithms to bring all of the information together, data management at many levels and ease of use.

At the enterprise level, a more comprehensive platform is needed that integrates enterprise equipment, databases, and study measures, manages protocols, study designs, and users, and automates quality control and image processing.

Dr. Dan Marcus, of Washington University in St. Louis, has developed XNAT, an extensible neuroimaging archive tool that allows file management, metadata tags, and data- and view-sharing. Dr. Marcus and his colleagues are setting up a database, XNAT-Central, at Washington University, but the application can be disseminated across different enterprises. XNAT-Central is written in an extensible language and can be federated against other national databases.

Dr. Rosen posited an informatics framework for imaging biomarkers. Biomarker language is needed to define the disease, disorder, or trait to be measured; the protocol to obtain a measurable image; the measures that will be extracted from the image; and how the measures translate to a diagnosis. This language must enable a process that can be repeated, validated, automated, and enforced. It is a huge challenge but one that must be undertaken in order to truly reap the most benefit from all of the data.

NIBIB is a multimodality universe. All of the different kinds of data—optical, electrophysiological, or neurochemical—must be integrated in order to answer the complex questions set before the scientific community. Ultimately, the definition of informatics is "tools to accelerate new discoveries by creating and fostering a new collaborative infrastructure and culture." Dr. Rosen challenged the Council to test this hypothesis: enabling sharing will engender sharing.

Dr. Rosen thanked his colleagues who provided slides.

Discussion

A Council member noted that there is currently a heated debate surrounding interoperability standards, which he observed at the recent Society for Imaging Informatics in Medicine (SIIM) meeting in Seattle. It is important to integrate the health care enterprise, because much of it to date has been clinically focused. Efforts such as DICOM must be fit into newer paradigms, such as service-oriented architectures. NIBIB is uniquely positioned to help bridge the developing science and clinical databases and create ways to share imaging and clinical data. Large-scale studies rely on data sharing.

Another Council member suggested that the biggest impediment to data sharing is the difficulty in extracting information from multiple databases. The technology world seems to have found solutions to many of the underlying problems. One problem lies in the exchange of sensitive patient information; however, many electronic commerce systems use a class of algorithms called *secured digital hash algorithms* or *digital signatures*, which are accredited by the Federal Government and assign to sensitive information a unique identifier that cannot be inverted. There is almost no discussion of using these algorithms in health care. If NIBIB or another organization could provide tool sets and operational procedures for using these algorithms, it would contribute greatly to solving the data sharing issue.

VIII. ROC Analysis, Image Assessment Methodologies, and Biomarker Validation: Dr. Kyle Myers

Dr. Peter Kirchner introduced Dr. Kyle Myers, Director of the Division of Imaging and Applied Mathematics at the Center for Devices and Radiological Health at the Food and Drug Administration (FDA). She is also Director of the Laboratory for the Assessment of Medical Imaging Systems (LAMIS), an interagency collaboration between NIBIB and the FDA Center for Devices and Radiological Health that was created in January 2004. Last year, Drs. Myers, Pettigrew, and Seto received a special citation from the Commissioner of the FDA for their collaborative efforts.

Dr. Myers reported on the current state of the science in image assessment and high dimensional biomarker evaluation and highlighted some areas of current consensus on the need for research. Recent reviews suggest that there remain many problems of study power and bias in scientific studies, and that faulty statistical analyses could jeopardize findings for many cancer trials.

Biomarkers—as defined by Dr. Myers—are one or more measurements of disease status. Images can be considered high-dimensional biomarkers. Likewise, the new high-dimensional array technologies can also be thought of as images and, thus, biomarkers.

There is a science of image or array assessment, many aspects of which are mature. The field has been building since the 1960s, when Kurt Rossmann contemplated the best approach for making use of image phosphors, which were new technologies being added to the exterior of direct film in the early days of the film screen transition. He wanted the scientific community to appreciate that the value of one system over another depended on the targeted inference from the images. For example, if the task is to determine the size of a needle, sharpness would be paramount; if the task is to detect low-contrast objects, resolution can be sacrificed to reduce noise.

There are two broad uses of biomarkers:

1. *Classification*, in which one assigns a patient to one of a finite number of disease states or categories (e.g., presence or absence of an analyte; lung nodule detection; malignant versus benign breast mass).

2. *Quantitation*, in which one estimates on a continuous output scale indicating degree or extent of disease (e.g., quantifying tumor size or change in response to therapy; time to progression; degree of stenosis; activity in a volume).

Often, a hybrid method is used, in which an estimation/quantitation task will influence classification. In the task-oriented framework, it is necessary to conduct biomarker validation, or the demonstration that inferences made on the basis of biomarkers (data, measurements, images, arrays) are correct. It is important that the value of biomarkers used in making inferences generalizes from small study (pilot data) to pivotal study. In this way, investigators can have better use of resources in designing appropriate pivotal studies that provide needed study power.

The ROC (receiver operating characteristic) curve measures the ability of a biomarker or test to separate two populations (e.g., non-diseased versus diseased). Making a diagnosis requires setting a threshold, with patients to the right categorized as “diseased” and patients to the left,

"non-diseased". A two-by-two truth table of decisions versus truth state for a 50/50 distribution will give a true-negative fraction of 0.5 (specificity) and a true-positive fraction of 0.95 (sensitivity). The ROC space is a plot of the true-positive fraction versus the false-positive fraction. If the diseased/non-diseased threshold is moved toward higher specificity, it is at the expense of sensitivity, and some diseased cases will be missed. If it is moved toward higher sensitivity, it is at the expense of specificity, and there will be more false-positives.

Unique issues arise in the assessment of imaging biomarkers and other high-dimensional datasets, because the scientist is faced with a mass of information coming out of the modality or modalities. It is necessary to have some way to move from the patient data to diagnosis via a process that in the current radiology environment often involves a human observer.

A number of strategies can be used to elicit diagnostic scores from human observers. Radiologists have been trained to speak in terms of patient management scales or action items, but they also would like more information that can be used to train radiologists and other observers to use levels of certainty with which an ROC curve can be mapped. The assessment community is working toward a consensus on how to fulfill the needs of both clinicians and scientists.

Images contain a lot of data, but there are sources of variability (e.g., patient biological variability, protocol differences, platform differences, display conditions, artifacts) that must be accounted for. Also, observers are often variable, across time and each other. In a 1996 reader variability study by Craig Beam, Peter Layde, and Dan Sullivan, the investigators mailed film screen mammograms to 108 randomly chosen mammographers from the Mammography Quality Standards Act database, who were asked to assign a management score; the observer operating points were then plotted. The results showed no unique ROC operating point, no ROC curve. This becomes a problem when, for example, a new technology such as fulfilled digital mammography is compared against a traditional technology; it is difficult to assess whether a computer-aided diagnosis adds value when also looking for a change in performance in the midst of enormous uncertainty.

Validating biomarkers and competing technologies in the midst of such variability requires random-effects or multivariate ROC analysis, called multi-reader multi-case (MRMC) ROC. MRMC ROC is a way of collecting data and analyzing the components of variance to see where that variability originates, so that when ROC curves and the areas under them are presented, true error bars that account for all sources of variability exist and the variability's source and relative strength is known. MRMC ROC gives total uncertainty in ROC estimates from range of case difficulty, reader skill, mindset, and their interactions; it is essential for testing significance of difference in competing modalities and for developing sampling strategies for larger studies.

Dr. Myers provided an example of a fully crossed design, in which every reader reads every case under both modalities. MRMC ROC calls for statistical re-sampling. The first practical solutions involved statistical re-sampling and applied a classical analysis of variance (ANOVA) to the design, but since then there have been many new innovations in this area. Brandon Gallas, a colleague of Dr. Myers' at LAMIS, has developed direct solutions that are being incorporated into the well-known MetS ROC package. A statistical solution tool would examine missing data, determine the expected statistical power of the test, and explain which paradigm is necessary to

use in terms of numbers of readers and cases to achieve a particular error bar on the figure of merit.

CAD algorithms are written because a scientist has a group of images and asks a radiologist what features should be included in the program. Then, the programmer works with the algorithm and the data set until the right answer is achieved. This is not true validation. A validated algorithm:

- Gets right answers on the training dataset.
- Gets right answers on an independent dataset.
- Improves the radiologists' performance in observer (laboratory) studies.
- Improves the radiologists' performance in clinical testing.

Stand-alone performance refers to computer performance. Most algorithms, though, are developed for use by a human. The next level of validation, then, is to examine whether the output data actually helps the human user; to achieve that validation, studies must be conducted with users. There are unique issues in assessing machine algorithms. The same algorithm can provide a different answer on two different test datasets. For example, early in the development stage, high performance estimates are often drawn from the easiest cases: the sickest of the sick and the wellest of the well. Different test cases will give case variability due to a range of case difficulty.

Training variability is another source of variability that is often overlooked. First, a reasonable architecture for an algorithm is developed—with a set of classifier rules and a certain type and number of features—and then the developer "trains" the algorithm. Typically, developers use sets of cases from each of the two categories (i.e., diseased, non-diseased) and feed them to the algorithm, which learns to separate them. The algorithm's performance improves as it sorts through more and more cases (assuming no test variability). The performance of the algorithm also greatly depends on what kinds of training cases are used.

The same components of variance for human observers apply to assessment of machine algorithms:

- Different samples of test cases will yield random measures of a fixed algorithm's performance ("Case" variability).
- For same learning machine design, different training cases will give different algorithms ("Reader" variability).
- Algorithm output must be thresholded to determine what regions to mark ("Mindset").
- Different algorithm designs correspond to different imaging modalities.

Therefore, MRMC is relevant and important in algorithm development.

When using multiple biomarkers, these algorithms often contain tens of thousands of features, and researchers do not know which features will eventually distinguish populations. Because the relationship of these features to disease or each other is unknown, dimension issues arise. Dr. Myers indicated that assessment science is not "data rich". There are many features available but not many samples from cases; therefore, researchers cannot understand the sources of variability, creating a high potential for fragility, or the instability of a classifier. The small amount of obtainable data is split into training and testing cases and results in big error bars.

Dr. Myers advocates a three-level approach, with data mining at the forefront:

- Pre-clinical research (biological, chemical, pharmaceutical), then data mining for feature and architecture selection.

- Pilot study: Use new samples to estimate mean performance and training and testing uncertainties from a finite size of training and testing sets. At the end, train again with entire available set—this defines the interim classifier.

- Use total uncertainties to design a pivotal study.

Images and other high-dimensional datasets that require humans or machines for interpretation have layers of complexity added to ROC methodology that require the research community to develop tools for examining these sources of variability. Some validated methodologies and software are still needed to address multiple lesions and responses per case, missing or uncertain truth, and partial area measures. The assessment community needs to choose judiciously when to conduct large-scale trials and when to make use of modeling.

Dr. Myers thanked her LAMIS colleagues who are working to bring these kinds of ideas to fruition.

VIII. Adjournment

The open session of the NACBIB meeting was adjourned at 12:45 p.m.

IX. Closed Session

This portion of the meeting, involving specific grant review, was closed to the public in accordance with the provisions set forth in Section 552b(c)(4) and 552b(c)(6) Title 5, U.S. Code and 10(d) of the Federal Advisory Committee Act, as amended (5 U.S.C. appendix 2). The closed session was adjourned at 3:30 p.m.

X. Certification

We certify that, to the best of our knowledge, the foregoing minutes and attachments are accurate and complete.[2]

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Anthony Demsey, Ph.D.
Executive Secretary,
National Advisory Council for Biomedical Imaging and Bioengineering
Director,
Office of Research Administration
National Institute of Biomedical Imaging and Bioengineering

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Roderic I. Pettigrew, Ph.D., M.D.
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[2] These minutes will be approved formally by the Council at the next meeting on September 16, 2008, and corrections or notations will be stated in the minutes of that meeting.