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3D Informatics: High Performance Computing at the Lister Hill Center

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Michael J. Ackerman, Ph.D.
Terry S. Yoo, Ph.D.

U.S. National Library of Medicine, LHNCBC
8600 Rockville Pike, Building 38A
Bethesda, MD 20894

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1 Introduction: Open Science through 3D Informatics

This report describes ongoing efforts at the Lister Hill National Center for Biomedical Communications and the National Library of Medicine to promote, advance, and to provide leadership in non-text, data-intensive informatics. This program concentrates heavily on information science surrounding image data of 2, 3, and higher dimensions. Our mission reaches beyond high dimensional image processing or medical computer graphics; it attempts to synthesize semantic information and dynamic user navigation with visualizations created from real medical data. In the cases where we use models of biological structures, all of these models are generated from sources of real data, firmly grounding this work in the practical aspects of medicine. To adequately describe this research area, we have coined the new term, *3D Informatics*, to encompass the blended notions of information science and medical visualization.

The program's underlying principle is, "Open Source + Open Data = Open Science." We hope to promote scientific accountability, accelerate discovery, and encourage collaborative team research through data sharing, public software, and multidisciplinary research initiatives. Building from the very successful effort in open data of the Visible Human Project, we have conducted a series of initiatives in acquiring additional shareable, public data as well as extensive internal and external projects in open source software development. These efforts have resulted in unqualified successes across the medical imaging research community worldwide. We briefly cover these developments in this report including:

- an update on the Visible Human Project Data (nearly 2,500 licenses worldwide)
- the current status and an assessment of the VHP Insight Tool Kit (ITK) (over 1,500 users in over 40 countries, including the NIH Roadmap National Centers for Biomedical Computing)
- a presentation of the derivative development and follow-on evaluation studies represented by the VHP ITK Algorithms, Adapters, and Data Distribution (A2D2) awards including a review of:
    - CMake (the ITK cross-platform build environment) and its adoption by the K Desktop Environment (KDE) community.
    - the Mayo Clinic Biomedical Data collection (over 100 datasets from dozens of clinical cases across a wide cross section of anatomy, pathology, modality, and pre- and post-operative clinical conditions),
    - the Insight Journal (an online publication with open peer-reviewed which links articles on image analysis algorithms with working source code; over 150 articles have been published since December 2005)
    - VolView release 2.0 (a volume visualization tool for use with ITK, including free licenses)
    - Dart – the regression testing system for open source software development

Beyond a review of our ongoing projects, we describe our current directions in 3D Informatics, including a focused effort for interactive publication of peer-reviewed articles in an online journal incorporating the distribution of integrated public 3D data. We are also planning an expansion of the

VHP collection to cover issues of multiscale data, human variation, and algorithm validation.

2 Overview: 3D Informatics

Since 1999, the NLM Lister Hill Center's Office of High Performance Computing and Communications has been developing a high performance computing program to manage and analyze complex, high-dimensional medical data. More than a single project, this program is built on "pillars of excellence," supporting a broad research umbrella. The general areas of (A) multidimensional image processing, (B) digital modeling and shape analysis, and (C) scientific and medical visualization are the three columns supporting the comprehensive effort in understanding and communicating visual information. Underlying all of this is a traditional informatics foundation of data collection, distribution, and content analysis of volume image datasets (See Figure 1). The individual research areas support the larger program, and like many endeavors, the whole is greater than the sum of its parts. We describe each of the pillars as a support or leg of a structure, and each is required to uphold the mission. Many projects comprise the separate research areas, and each area advances at its own pace depending on the availability of resources and personnel to carry the work forward. Together incrementally, the research areas lift and strengthen our overall effort at the Lister Hill Center, elevating us to provide clearer vision and leadership in the informatics community.

This program is not limited to just three dimensions, and we routinely invoke time varying data

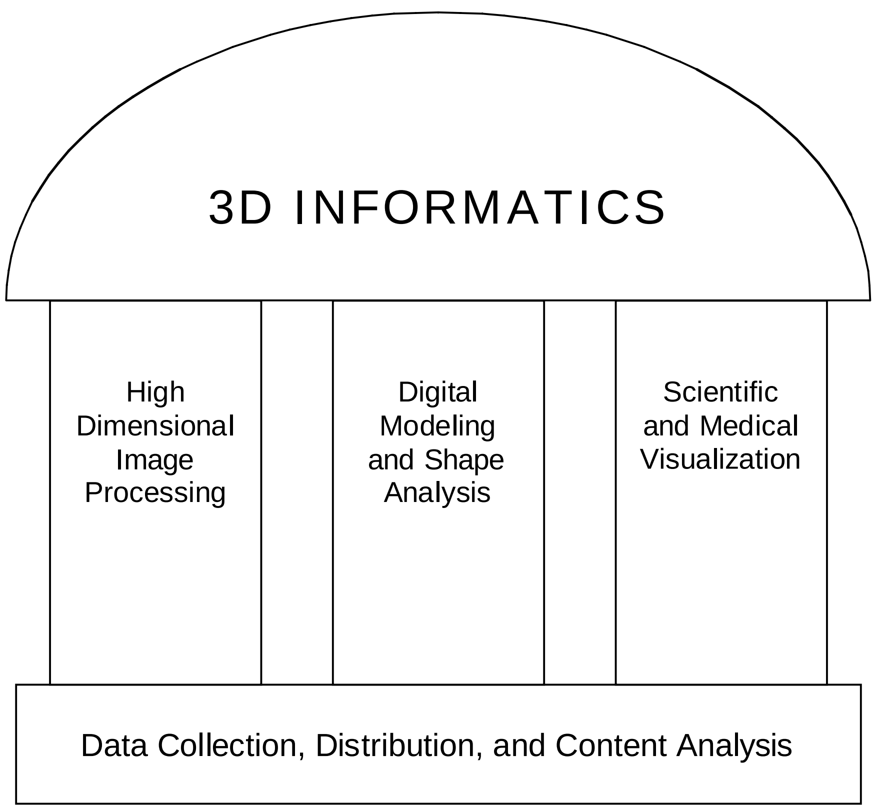


Figure 1. The position of 3D Informatics and its relation to its research subfields. 3D Informatics is defined as the gathering, manipulation, classification, storage, retrieval, representation, navigation, and display of complex, high-dimensional medical data.

and multimodal radiological information in our investigations. Much of our work has been performed in collaboration with faculty and research scientists from across the country. We have begun the exploration of the infrastructure and organizational issues surrounding volume data archives. We are continuing our research in volume image segmentation, registration and analysis. Furthermore, we have executed a project to study non-photorealistic rendering methods for the portrayal of medical information using computer-generated medical illustration techniques. Our ultimate goal is to broaden our focus to incorporate information and models at a variety of scales, permitting the analysis of complex information across disciplines linking non-visual information with images and admitting the use of information that is studied at the microscopic or nanometer scale to be incorporated in models and simulations at the system or organism level.

3 Background

While the term, *medical informatics*, has come to represent the general functions of medical librarianship and data mining of medical information, it has typically not included the important fields of radiology, computer image analysis, or digital image synthesis. The term "computational biology" as it is used today is a contraction of "computational *molecular* biology," and the term applies almost exclusively to molecular sequencing and the study of protein structure. *Bioinformatics* is an even more narrow term applying to database management and data mining for genetics and proteomics. All of these perspectives on our field often preclude the important dimensions of medical imaging, visualization, and digital modeling and simulation at all levels and scales, from the interaction of complex organic molecules and enzymes, through cellular organization and function, to the broad issues of physiology at the systems and organism scale represented by the field of gross anatomy.

We submit that these narrow viewpoints are detrimental to their respective constituents, limiting the scope of their individual investigative groups to a restricted and bounded area of research. By its nature though, the concept of *informatics* encompasses the "big picture," and it should be inclusive rather than exclusive of multiple disciplines. A medical library, as an institution, is a repository of multidisciplinary scope, archiving the knowledge of a very broad alliance of interests. Medical Informatics and Bioinformatics rarely include the areas of visualization, modeling, simulation, image processing, and data analysis, seldom incorporating them directly into their curricula. The NLM/LHC Office of High Performance Computing and Communications is pioneering this mission as a new domain, *3D Informatics* [Yoo 2005a]. We define 3D Informatics as follows:

3D Informatics: the science concerned with the gathering, manipulation, classification, storage, retrieval, representation, visualization, analysis, navigation, and display of complex, high-dimensional data. This data may include more than three independent dimension, including position, time, and scale. The data may also represent many more than one dependent dimensions, including multi-channel data (*e.g.*, the RGB values of the Visible Human Project color cryosection data).

Data such as the VHP male and female images illuminated the need for software tools and methods that admit the analysis, rendering, and visualization of large data. The multi-channel nature of the data also suggests an increasing need for managing multi-valued, rather than scalar, volume data. Beyond the basic processes of rendering anatomical structures from annotated data, there remain the fundamental problems of aligning multimodal data and the extraction of valuable features from the disparate streams of information. Finally, pressure is mounting from quarters such as developmental biology to find new ways to utilize static data such as the VHP male and female datasets in dynamic models that can demonstrate the progression and regression of disease, portray patterns of gene expression over time, and represent physiological processes from biomechanics to electric field propagation in the study of cardiac and neural function. Incorporating the broad surfeit of information in medical analysis has become part of the charter of the Program on 3D Informatics. Beyond the VHP data, NLM is responding to the movement of related fields toward data aggregation and distribution. Our program is positioned to address these diverse concerns.

4 Project Significance

The field of bioinformatics may be at a crossroads. The traditional research areas of gene sequence storage, searching, and retrieval may be slowing as a burgeoning research area, even though universities nationwide appear to be searching for candidates with expertise in this area to fill faculty vacancies. The shift from infrastructure building to applications development is becoming profound as commercial ventures and academic institutions alike begin repositioning their research in drug discovery, patient specific medical treatment, and basic research in gene expression. To meet these new challenges, it may not be enough to simply pursue a strategy of data mining. Rather, the modeling and simulation of biological, medical, and physiological processes as well as the visual representation of these mechanisms at all scales (from nano to macro) may emerge as some of the key research areas of the next ten years. The opportunities in these areas as well as the need for additional cross-disciplinary infrastructure in the form of open-access data collections is reinforced by a recent NIH-NSF report [Johnson 2006, Moorhead 2006, Munzner 2006].

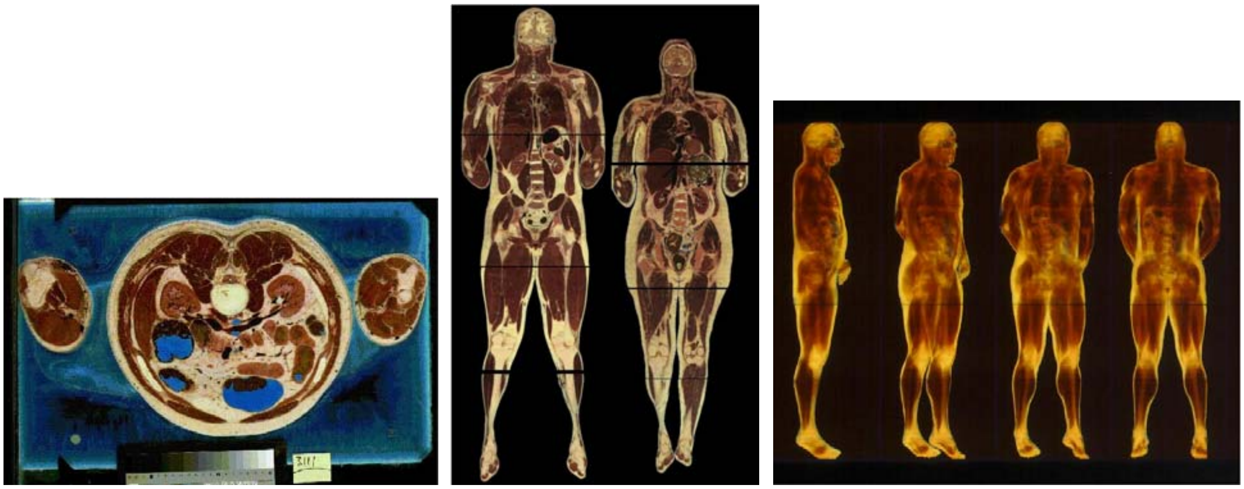
Our goal is to establish one of the premier laboratories in medical image analysis and medical computer graphics in the country here at the Lister Hill Center. Our opportunities to attract visiting researchers and sponsor collaborative research have been demonstrated in the past few years as our program has been building from its early successes. In addition, since the research domain of connecting medical volume data, visualization, user interaction, and data modeling is relatively young, our program can make salient changes to the field. Through our emphasis on open, reproducible science we have shown that we can influence this field using our external programs, directing the community toward open source and open access.

5 Status Report

The HPCC Office has supported interrelated internal and external programs in 3D Informatics that support and complement one another in a general mission of directing the field through data collection and open-source software development. Though ongoing, OHPCC has had considerable success in this domain, creating and sponsoring tools that have begun to influence not only our target domain, but which have also been adopted in other areas of computer science.

5.1 The Visible Human Project

In 1989, the NLM Board of Regents empowered an *ad hoc* panel of experts that recommended that NLM should take in the rapidly evolving field of electronic imagery. In 1991, the University of Colorado School of Medicine was awarded a contract resulting in the acquisition of the NLM Visible Human Male and Female (VHP) data sets. NLM makes the data sets available under a no-cost license agreement over the Internet. The VHP male data set contains 1,971 digital axial anatomical images obtained at 1.0-mm intervals (15 Gbytes), and the VHP female data set contains 5,189 digital images obtained at 0.33-mm intervals (39 Gbytes) (See Figure 2). The optical data is supplemented by a complete series of clinical radiographic data including multiple MRI studies as well as X-ray CT images [Spitzer 96].



a. b. c.

Figure 2. Three small-scale rendered views of the Visible Human Project data. 2a: A sample axial slice from the male dataset. The male dataset is 15 GBytes, consisting of 1,971 axial cryosections, with a 1.0 mm spacing. The female dataset is 39 GBytes, consisting of 5,189 axial crysections with a 0.33 mm spacing. 2b: The male and female datasets stacked with a sample coronal slice displayed. 2c: Four volume rendered views of the VHP male dataset.

The Visible Human Project image data sets are designed to serve as a common reference for the study of human anatomy, as a set of common public domain data for testing medical imaging algorithms, and as a test bed and model for the construction of image libraries that can be accessed through networks. The impact and value to the medical imaging community of having access to a whole digital human male and female specimen cannot be overstated. Derivative products from the VHP datasets include textbooks, software, research programs in human modeling and simulation, and an array of imagery, graphics, and visualizations depicting the organization of the human body using modern techniques. Four VHP Conferences have been supported by the NLM. The Visible Human data sets are available through a free license agreement with the NLM. The data sets are being applied to a wide range of educational, diagnostic, treatment planning, virtual reality, and virtual surgeries, in addition to artistic, mathematical, legal, and industrial uses. The Visible Human Project has been featured in more than 800 newspaper articles, news and science magazines, and radio and television programs worldwide. NLM has documented over 900 publications in the scientific and technical literature that discuss the Visible Human Project and its derivative products covering a period from January 1987 through March 2007.

The Visible Human Project, having been sustained through multiple initiatives, remains alive and well [Ackerman 2000]. Since the introduction of the data sets, NLM has issued over 2,450 licenses in over 49 countries. Roughly half of those licenses have been issued in the past four years, demonstrating that the demand for these data remains strong. The continuing impact of this pioneering work is also reflected in the development of projects modeled after the VHP such as the Visible Korean Human [Chung 2005, Park 2006] and the Chinese Visible Human [Zhang 2005, 2006]. As recently as 2004, DARPA ran the Virtual Soldier program which built its central thoracic model of human anatomy from the VHP male dataset (see: http://www.virtualsoldier.us/). VHP continues to thrive and contribute to a global research community.

5.2 Other Programs in Data Collection and Distribution

The VHP is not the only study of volume image data collection conducted by the NLM. OHPCC has maintained a series of important projects to study the issues surrounding data collections for 3D Informatics research.

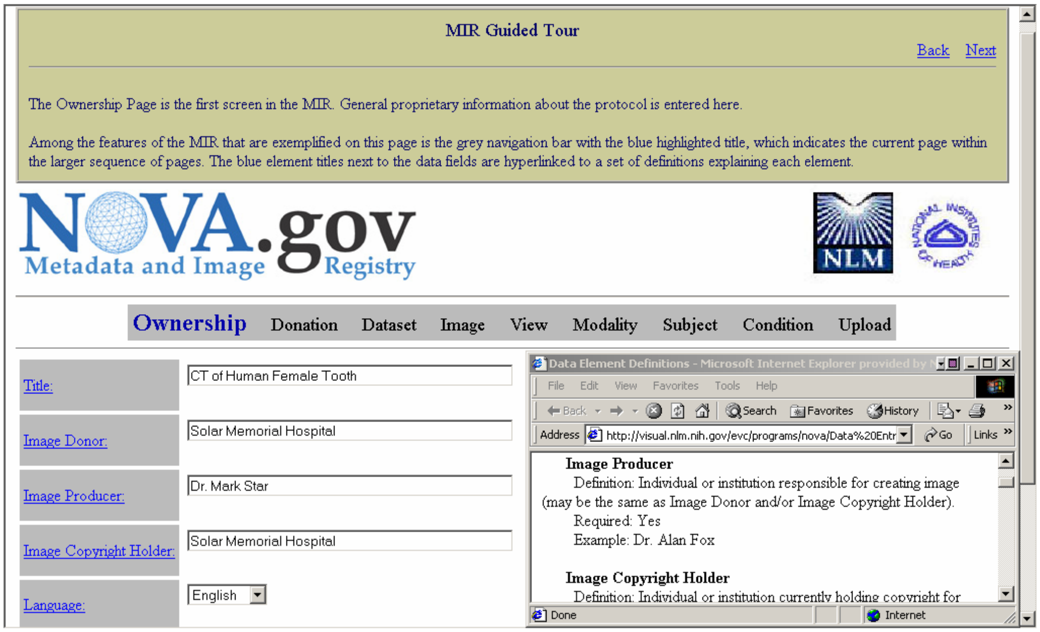


Figure 3: A screenshot of the Metadata Image Registry entry screen with Data Element Definitions present.

Metadata and Image Registry

In 2002, the 3D Informatics group combined resources from the NLM Library Associates Program and the NIH Summer Internship Program to explore the concept of an online volume image database. Two library associates (C. Twose and T. Lee) accepted a spring project to study privacy, regulatory, and technical aspects of medical volume data collections. Their work included background investigations and interviews with a broad cross-section of potential users including internists, radiologists, anatomists, and computer scientists. They also explored the emerging HIPAA regulations, the commercial imaging standards such as DICOM 3.0, and existing examples of online public archives. The result was a design of a public archive including the necessary metadata for browsing, searching, and data entry. During the summer of 2002, two undergraduate interns (D. Leiman and A. Fletcher) joined the team and began the implementation of a pilot digital archive based on the design from the associates. The resulting initial modest collection has ten datasets, an HTML infrastructure, and an XML superstructure for organizing the collection. Figure 3 shows the data entry page for this site. This work was published as an NLM Associates Project report as well as a refereed publication at the 2003 SPIE Medical Imaging Conference in San Diego [Leiman 2003]. Further work on XML-based data indexing was carried out in the summer of 2003, and published in 2004 [Fletcher 2004].

The Mayo Clinic Collection

In 2003, NLM funded a project through the VHP ITK effort for the collection of a broad data archive for the support of medical imaging research. This project was executed with the Mayo Clinic, Biomedical Imaging Resource. By 2004, the Mayo Clinic provided over 100 datasets collected across dozens of animals and clinical cases representing a wide cross section of anatomy, pathology, modality, and pre- and post-operative clinical conditions. The entire collection is organized as a web site using HTML links and pages to provide a user-friendly, searchable index to the datasets. (See Figure 4).

The Mayo Clinic collection contains 3D MRI data of a human hand in motion, capturing dynamic motion of the complex carpal bones of the wrist. Also, in addition to a sampling of different pathologies such as 3D brain tumor datasets and 3D scans of aneurysms and other arterial-venous malformations, the collection includes 3D microscopy data of a dissected human temporal bone containing the middle and inner ear at very high resolution for the study and pedagogical presentation of the anatomy and physiology of the human auditory system. Animal studies include a dynamic moving 4D canine cardiac sequence, a whole mouse micro CT scan with 20 micron resolution, and CT scans of two dolphin heads [Holmes 2005]. The resulting collection is another demonstration of the commitment of the HPCC Office to the open distribution of public imaging research data.

5.3 The OHPCC 3D Informatics Group

In 1999, the Board received a broad report including a project titled, “Imaging Tools for the Visible Human.” Based on that report and employing the comments from the Board of Scientific Counselors, the Office of High Performance Computing and Communications has worked to create a comprehensive internal laboratory in 3D Informatics, we have grown from a single researcher to a small lab with three investigators (one principal and two contract personnel). Our laboratory has ongoing research collaborations with former medical informatics faculty fellows from Ohio State Univ., Brigham Young Univ., UNC-Charlotte, and the University of Maryland Baltimore County. In the past seven years we have hosted over a dozen summer graduate fellows and NIH Summer Interns in addition to the four Summer Faculty Fellows. We maintain a variety of associations with neurosurgeons, radiologists, forensic pathologists, and computer scientists nationwide. Dr. Terry Yoo has directed all the work performed by the Program on 3D Informatics.

An important step in creating an imaging lab for the Lister Hill Center has been the establishment of an applications development center. The former Learning Center for Interactive Technology has been redesigned as the OHPCC Collaboratory where a variety of computing resources are now available. A succession of high performance computing facilities have been configured for the Collab, beginning with a multiprocessor SGI Challenge series computer, followed by an Itanium-based SGI Altix multicore, multiprocessing system. Currently, the Collab uses an XGrid employing an array of between 14 and 27 CPUs, permitting the development of parallel implementations of our compute-intensive algorithms. Immersive displays with stereo viewing capabilities and a Desktop Phantom haptic user interface are available in the Collab and have been used in the past to demonstrate OHPCC Next Generation Internet projects for the BoSC.

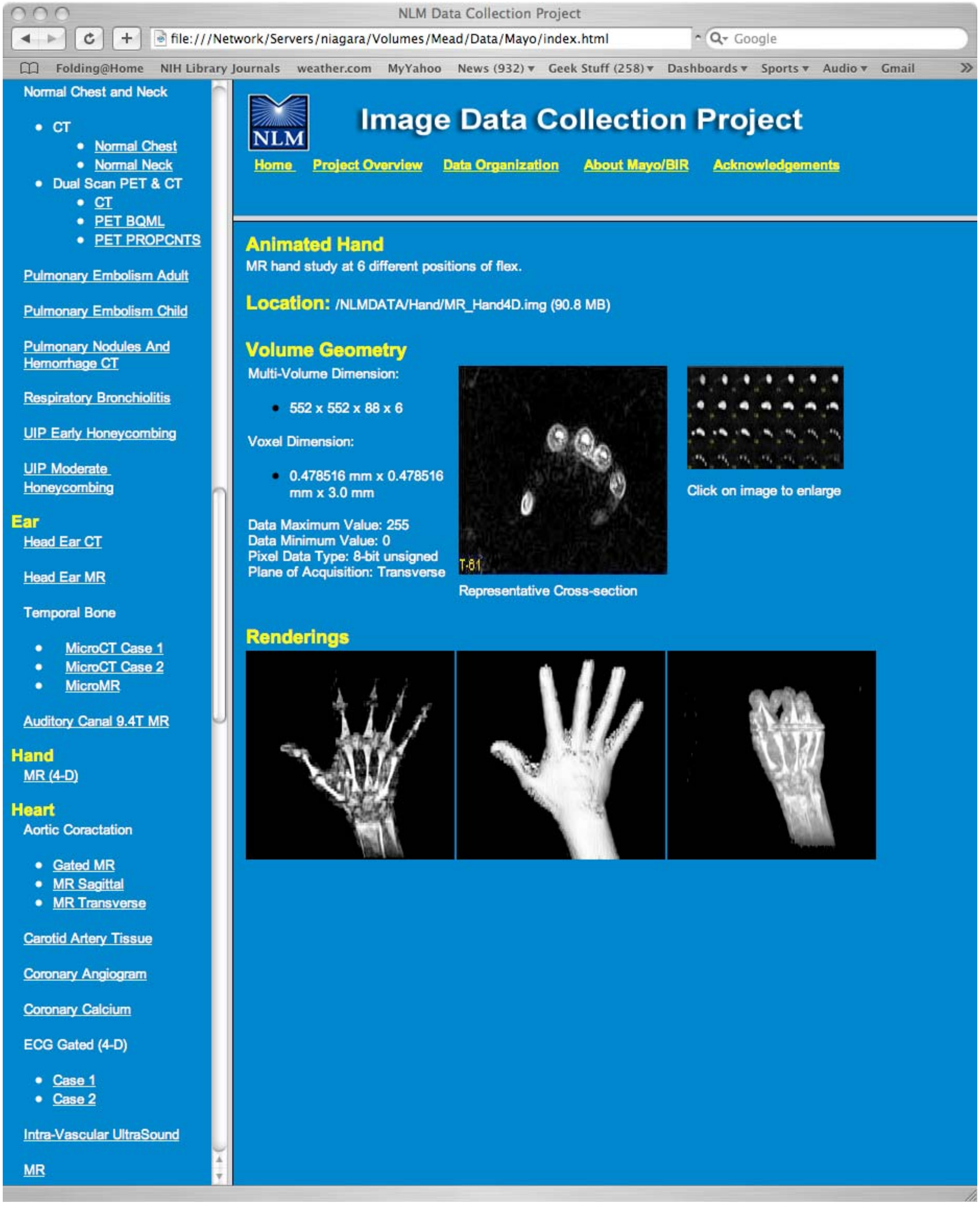


Figure 4. Screen shot of the Mayo Clinic collection, acquired for distribution by the Three-D Informatics Group of the NLM HPCC Office. The collection includes over 100 datasets representing dozens of animal and clinical cases, including micro-CT data of a human temporal bone and auditory system, a 4D canine cardiac sequence, and a 4D MRI of a human hand shown above.

The reconfigured and equipped Collab has been essential to the prosecution of the initiatives described in this report. This resource makes possible the participation of summer faculty, associates, fellows and interns by providing space and unique computing equipment for visiting researchers and students. With the creation of successful initiatives and the establishment of effective development spaces, our program has met its research and development goals.

5.4 The Insight Toolkit

NLM and the National Institute for Dental and Craniofacial Research sponsored a joint planning workshop in 1997 to explore new directions for the Visible Human Project. One of the recommendations of the subsequent report: Summary Report, Virtual Head and Neck Anatomy Workshop, February 25, 1998, was the creation of a software initiative for a medical image segmentation and registration suitable for use on the Visible Human Project data.

As a result of this recommendation, 3D Informatics staff in the HPCC Office conceived of a research program in image processing software development. This program was intended to serve as a foundation for a broad spectrum of academic medical imaging research. We proposed that the entire program be executed in the public domain as open-source software, one of the first such projects ever executed by any agency at NIH. We also created the focus on image segmentation and registration, and to promote portability, we required that the software run on multiple platforms from a single set of source code. We also excluded any funding for visualization development, encouraging the integration of the segmentation and registration tools into existing image processing workstations. This emphasis would later ensure the portability and usability of the code.

Armed with these basic principles, OHPCC began assembling a software team to develop public image processing tools. We decided early in the process to create a consortium of academic and commercial developers, recognizing that in order to create a large community, we needed to start with a group project and not a single viewpoint on image analysis [Yoo 2000a]. OHPCC remained firmly in control of all phases of the software development, directing the quarterly design meetings of the software developers and serving as the final arbiters for any deadlocked vote among the principal investigators. OHPCC also arranged the collaborative funding for the tool development project, drawing resources from across NIH (including the National Institute for Dental and Craniofacial Research, the National Eye Institute, the National Institute on Mental Health, the National Institute of Neural Disorders and Stroke, the National Institute on Deafness and other Communication Disorders, and the National Cancer Institute), as well as across agencies including the National Science Foundation and the Department of Defense – Telemedicine and Advanced Technology Research Center (See Figure 5).

In November 1999, the HPCC Office called the first developers meeting of the Insight Software Consortium, assembling the six contractors and four initial subcontractors to begin development of the Insight Tool Kit (See Figure 6). NLM subsequently ran 14 meetings of the developers consortium, including meetings at Columbia Medical School on algorithm validation [Yoo 2000b, 2001]. All work on the project was coordinated and specified by NLM through a series of work assignments, and all invoices were individually approved by OHPCC project staff [Yoo 2002].

Figure 5. Sponsors of the Visible Human Project: From Data to Knowledge - The National Library of Medicine (NLM), in partnership with the National Institute for Dental and Craniofacial Research (NIDCR), the National Eye Institute (NEI), the National Science Foundation (NSF), the National Institute for Neurological Disorders and Stroke (NINDS), the National Institute on Deafness and other Communication Disorders (NIDCD), the National Cancer Institute (NCI), and the U.S. Army, Telemedicine and Advanced Technology Research Center (TATRC).

The Insight Software Consortium has completed design and development of a public medical image segmentation and registration toolkit known as the Insight Tool Kit (ITK). The goal was to create an application programmer's interface (API) that can be used by developers in medical programs and software products wherever the problems of image or volume segmentation and registration exist. Unlike previous NIH software development efforts, the goal is specifically not to create a single monolithic program where the software is owned by the developer. Rather, we are pursuing a open-source public software foundation from which a broad range of programs can be supported. The ITK API has undergone continuous review and modification by the expert developers on the programming team. GE Corporate R&D along with Kitware, Inc. serve as the lead design groups, with GE CRD handling issues of testing and quality control during development and Kitware serving as system integrators for the project. Other teams from across the consortium are contributing new implementations of complex medical image processing algorithms, helping to refine the software architecture as the toolkit grows in complexity and mathematical sophistication [Yoo 2005b].

In order to accommodate the requirements set forth by OHPCC, ITK developers undertook a new approach to software engineering adapting the emerging discipline of *extreme programming.* These concepts include community source code control, rapid and continual testing of the software, and collaborative development of all programming with oversight of each individual line of code shared by at least two programmers. A common software style was adopted, and a commitment to testing was impressed upon all programmers [Schroeder 2004]. Most importantly, new software engineering tools were approved and funded by NLM. These tools include: CMake, an open-source cross platform build tool [Martin 2003]; Dart, a framework for rapid regression testing of community software; and CABLE, an automated language wrapping tool for providing multiple

Figure 6. The Insight Tool Kit (ITK) developer team. ITK was built by a consortium of developers across industry and academia, including engineering schools, medical schools, small business, and large corporations.

language bindings for a software library [Martin 2002][King 2003]. NLM has provided leadership in new approaches to engineering for public open-source software.

Status of ITK

At the time of this writing, The Insight Toolkit (ITK) is available online (see the URL: http://www.itk.org) in its latest release 3.4 [Ibanez 2005]. The ITK software has been downloaded over 8,000 times, and the user's mailing list has over fifteen hundred (1,500) subscribers in as many as 40 countries. Dozens of methods are represented in ITK including algorithms for segmentation and registration of clinical data [Yoo 2004]. Validation studies are published with the software, testing a set of the software tools on a variety of data including MRI data from Alzheimer's patients, cases involving Multiple Sclerosis, ultrasound data, and volume studies for brain tumors. Current users include not only academic medical research groups, but also include commercial ventures including at least one company using ITK for handwriting recognition. At least six new software applications and/or research programs are directly enabled through the adoption of ITK [Bitter 2007].

Hundreds of papers are either based on ITK methods or rely on the software resource for comparative algorithms. A survey of 102 ITK users by one developer in 2006 showed that 73% of those users have cited ITK in at least one publication, 40% of the users have put ITK in grant proposals, 75% of the users have used ITK to generate preliminary data for a grant proposal, and 90% of the users proposed to use ITK in their grant. For more details see the public wiki page at: http://www.itk.org/Wiki/2006_Survey_Summary.

The Georgetown University Imaging Science and Information Systems (ISIS) Center is one of these users. ITK is a central part of their initiative to build the Image-Guided Surgery Toolkit

(IGSTK). This program is an open source C++ software library for robotic and image-guided surgery, seeking FDA approval for their devices employing IGSTK (and consequently using ITK). The NIH National Institute for Biomedical Imaging and Bioengineering has provided grant as funding for IGSTK, with additional funding from the U.S. Army through the Telemedicine and Advanced Technology Research Center. IGSTK developers not only adopted ITK, but they also adopted the entire software engineering approach including the use of CMake and Dart [Cleary 2007]

The most noteworthy user of ITK is the National Alliance for Medical Image Computing (NA-MIC) headed by Harvard Medical School's Surgical Planning Laboratory. Founded in 2004, NA-MIC is a consortium of over 14 universities and companies committed to research in medical image analysis. As one of the NIH Roadmap National Centers for Biomedical Computing, NA-MIC is dedicated to developing public computing tools for medicine. They have chosen to base their $4 million/year in schizophrenia research projects on ITK as their software foundation in medical image analysis, adopting not only the code from ITK, but all of the software engineering practices developed by NLM for the Insight Software Consortium. While it may be an overstatement to say that NA-MIC would not be possible without ITK, it is clear that other NIH research concerns are benefiting from NLM's investment in public software tools and our approach to open-source software development. For more information on NA-MIC, see: http://na-mic.org.

5.5 ITK Related Programs

From 2002 to 2007, Approximately 20 purchase orders were awarded for reference data sets and enhanced algorithms to support the further development of ITK. This initiative known as the VHP ITK Algorithm, Adapters, and Data Distribution (A2D2) program was developed to directly test the software architecture of ITK as well as the design of the API. This effort supported the integration of ITK into research platforms such as the Analyze from the Mayo Clinic, SCIRun from the University of Utah's Scientific Computing and Imaging Institute, and the development of a new release of VolView, free software for medical volume image viewing and analysis to see if the ITK API was suitable for use in a spectrum of application programs. New algorithms and methods have also been included to test the versatility and adaptability of the software architecture of ITK to accommodate new techniques.

The results of these programs and the initial ITK effort have had a widespread impact across the research domain. We mention a few derivative projects and their importance to the community.

CMake (the ITK cross-platform build environment)

Building software from a single set of source code across multiple platforms (from Windows 2000 and Windows Vista to Unix-based systems such as Linux, Sun Solaris, and Apple OSX) is a problem that is not unique to ITK. CMake, the build tool created by the ITK developers, has repeated proven itself to be an adaptable software engineering tool for many different software groups. CMake has its own following and it has become an essential element of open-source initiatives [Martin 2003, Hoffman 2003].

In particular, the world's largest open-source software development project measured by lines of source code, the K Desktop Environment (KDE), was seeking a solution to their cross-platform build issues for many years. The existing infrastructure of scripts and makefiles was not suitable for the heterogeneous programming environment encountered by their contributors. After evaluating and discarding multiple proposed solutions, the KDE group adopted CMake as their build configuration tool. We see this event as an affirmation that NLM has made contributions not only in medical image analysis research, but is influencing computer science directly at its foundations of programming and software engineering.

Dart – regression testing for open source software development

Dart, the online ITK regression testing tool is an essential piece to managing a geographically distributed software development team. The server runs at a central location while clients continually download the source code from the central repository, compile the latest versions, and upload the results and warnings from the compile-tests to a web-based dashboard. Clients for ITK run on almost every combination of compiler and operating system imaginable, creating coverage for ITK across numerous architectures and programming environments. Developers who do not have access to rare or old hardware configurations can nevertheless test their changes through the ITK regression-testing mechanism. Researchers worldwide have volunteered their machines and their time to contribute to this effort, making ITK a truly collaborative public software development project.

The ease and importance of managing software projects with Dart has not gone unnoticed. Dart has been adopted by many programming teams, most only remotely interested in image processing. Dart is at the heart of quality assurance and program management in the ITK project, and it is rapidly being assimilated by other teams in other disciplines. Groups mentioned before such as the NA-MIC team and the IGSTK developers use Dart, and are even extending its capabilities. The NIH Clinical Center Diagnostic Radiology Department has begun configuring Dart dashboards for their own projects, demonstrating that OHPCC efforts are not only affecting outside research but teams within NIH as well. (See http://public.kitware.com/Dart/HTML/Index.shtml).

The Insight Journal

In 2004, NLM endorsed an experiment in interactive publication where open peer-reviewed articles on image analysis algorithms are linked with working source code. This online publication, called the Insight Journal, is an exploration that combines open access journalism with open-source software, promoting reproducible computer science. Computer programmers communicate largely through programs, not through text. By publishing both the article and the programming that underlies the results, the Insight Journal seeks to accelerate discovery in computer science.

The Insight Journal continues to thrive. Over 150 articles have been published since December 2005 when the Insight Journal began accepting combined articles with linked source code. New ideas can be submitted to the journal as well as deliverables for NIH-funded research contracts and grants, preserving the contribution not only as a peer-review manuscript, but also as the original programming that accompanies it. The Insight Software Consortium has adopted the Insight Journal as the gatekeeper and arbiter of new contributions to the toolkit. All proposed additions to ITK must first be submitted to the Insight Journal, and only the top 10 methods each period are ported and committed to the ITK source code repository for inclusion in the next release. The Insight Journal is proving to be a valuable experiment in open access publishing as well as a vital clearinghouse for medical image processing algorithms. (See http://insight-journal.org).

VolView

The ITK A2D2 program encouraged the integration of ITK into existing image analysis workstations to test the ability of the API to support a variety of research platforms. One notable project was the integration of ITK into VolView, a volume visualization tool produced by Kitware, Inc. The result was VolView release 2.0, a flexible volume rendering console which is able to call ITK filtering methods as well as its segmentation and registration algorithms. VolView 2.0 includes by agreement with NLM a free license which is distributed with every copy of the software. The availability of an inexpensive volume rendering workstation has promoted new research as well as fledgling efforts in interactive publication of online journals where articles are merged with volume data and the results tied together with free visualization tools. Thus, NLM-supported projects are continuing to promote open science through open data and open source. (See http://kitware.com/products/volview.html).

6 The Planning Process

A panel of experts in the fields of anatomy, radiology, forensic medicine, algorithms, and computer graphics and visualization was convened at National Library of Medicine (NLM) on January 16 and 17, 2007 to discuss future opportunities for the NLM to pursue under the Visible Human Project (VHP). The charge to the panel read:

> "The purpose of this panel is to explore some major branches of a possible program. We would like to consider scaling our current VHP efforts, including: (A) a possible broadening of the data collection toward clinically relevant, driving biological problems; (B) an exploration of multi-scale issues between gross anatomy at the organ level to micro anatomy at cellular resolutions; (C) an investigation of whether existing software systems scale with the data collections and an assessment of strategies for software validation; and (D) a program of pilot biomedical visualization partnerships to promote new collaborations between biomedical domain experts and computer scientists. In addition, we hope to achieve a consensus on certain requirements such as an insistence on open source and open access to data and algorithms alike.
>
> "We are especially interested in discussing likely opportunities, benefits, costs, commitments, risks, and the possible impact of possible projects."

By the end of their deliberations the panel members found consensus around four themes:

- Human anatomical variation;
- Validation framework;
- Web-anatomy 2.0; and
- Multi-scale anatomical modeling.

6.1 Human Anatomical Variation

Although we speak of the Visible Human male and female cadavers as "typical," there really is no such thing as a typical human being. The Visible Human cadavers are two individuals, not the every-man and every-woman as we would like to think of them. Over the years it has been suggested that NLM expand the number of cadavers in the Visible Human collection in order to have examples of the range of human anatomical variability. This appears to be a very impractical solution. It would take thousands of cadavers to capture the full range of human anatomical variability.

The anatomical community has been telling us for many years that the statistical information which defines the range of variability for each anatomical object is already presented in the anatomical literature of the later 19^{th} century and earlier 20^{th} century. The information can be extracted and a statistical database created. But each of the statistical variables is not independent from each other. For the sake of an example, a change in bone length may cause a statistically known shift in the statistically normal range of bone diameter. This information is said to be in the literature as well. What we are really talking about then is better characterized as a knowledge base rather than a database. This represents at least an order of magnitude increase in the complexity of the data indexing and retrieval problems.

6.2 Validation Framework - A resource for anatomical imaging

If one had a database containing the statistical information describing human anatomical variation, the content needs to be validated. The most obvious way is to collect more data and then to see if the data in the database is in agreement with or able to predict the new observations. In as few as five years ago, this would have been a problem worthy of at least a modified Visible Human data effort. But the members of the panel who were knowledgeable about the imaging technology used in the practice of radiology stated that the imaging techniques being used clinically today were capable of providing images with a resolution comparable to the original Visible Human data sets. Patient information is not needed as long as the subject's gender was known, the subject was between 20 and 60 years old, and it was agreed that the anatomy being studied was normal. Images obtained from whole body scanner studies would be ideal but whole body studies would not be absolutely necessary. The source of test images could therefore be any routine higher resolution clinical image.

In addition the use of images derived from virtopsies was considered. A virtopsy is a virtual autopsy. A detailed whole body CAT scan is taken of the cadaver in lieu of performing a physical autopsy. The U.S. military performs a virtopsy on every member that dies while on active duty. Although parts of the cadaver may not be suitable for our purpose, it was suggested that the majority of each cadaver will be. In additions these images, being cadaver images, would be subject to high ethical standards, but would not be subject to most patient privacy constraints.

6.3 Web Anatomy 2.0 - A Community Annotation and Software Framework

Although the release of the Mosaic browser and the subsequent popularization of the World Wide Web happened about 15 years ago, the web is said to be experiencing a second coming - Web 2.0.

Web 2.0 is a phrase coined by O'Reilly Media in 2003 in reference to, at the time, a perceived second generation of web-based communities and hosted services - such as social-networking sites, wikis and folksonomies - which facilitate collaboration and sharing between users.

The panel members predicted a huge and expensive problem caused by the volume of data which will be required to be segmented into the appropriate anatomical objects. The appropriate measurements will then need to be made on each of the objects in order to validate or correct the Knowledge Base of Human Anatomical Variation. It was pointed out that the problem does not have to be solved manually. Automatic or user controlled software like NLM's Insight Tool Kit (ITK) might represent appropriate automated software solutions. NLM might not able to afford to mount the effort that this would require but Web Anatomy 2.0 could. Just like Wikipedia enlisted the community to create and continues to refine and update an online encyclopedia, NLM could create a Web site, equipped with the appropriate tools, for the community to provide or help to process the information necessary for validating or increasing the accuracy of the Knowledge Base of Human Anatomical Variation. It was recognized that quality control would be a critical problem. But this is part of the challenge of harnessing the potential power of Web 2.0.

6.4 Multi-scale Anatomical Modeling

The Visible Human Project was designed to explore and has been focusing on gross anatomy. It is clear that each of the anatomical objects and spaces which are visible in the Visible Human data sets is made up of microscopic anatomy. The microscopic anatomy includes a physically smaller chemical anatomy. And that chemical anatomy is ultimately defined by a genetic anatomy. Each level of anatomy represents a change in several orders of magnitude in scale to the next level of anatomy. By way of example, the smallest difference at the genetic level, a single protein, can have easily observable effects at the gross anatomical level. Being able to accurately visualize and model anatomic structures across so many orders of magnitude of size is the ultimate goal of multi-scale modeling efforts. The first three themes represent an extension of the Visible Human Project in the dimension of anatomical variability. This fourth theme represents an extension in the dimension of anatomical scale.

7 The VHP3 Program

The reason for convening a planning panel was to discuss what might be the future opportunities for the NLM which could be accomplished under the Visible Human Project while building our expertise in 3D Informatics. The result was four themes from which a program could be molded. Through several discussions with NLM leadership it was clear that each of the four themes were related and taken together described an exciting multi-year, multi-phase project which had the potential to be both budget and time scalable. We had a sense of the big picture goal. We needed a starting point.

Further discussion made it clear that the program could be started at any of the four themes and could be directed to ultimately reach the end goal. We needed a starting point that made the most sense in keeping with the immediate functions of the NLM in a time of shrinking budgets. The answer was unanimous - Human Anatomical Variation.

7.1 Human Anatomical Variation

The Human Anatomical Variation approach starts in a library with a librarian. We were advised that all the statistical anatomy data that we would need to build a database of human anatomical variation is already in the literature. Unfortunately that literature was probably written between 1850 and 1950 and is therefore not in the current Medline. A hand search of the literature would have to be undertaken. An initial study was undertaken by NLM's Library Operation Division (LO) to determine how long it would take to collect this literature for a single anatomical object - the lung. The study suggested that it would take about 14 weeks. One can only guess the time needed if this finding is extrapolated to include all the anatomical objects in the entire body. It would either be a very slow process for a single team or a very expensive process if the job were divided up between multiple teams. It was time for reassessment.

The Visible Human Project has traditionally been aimed at the needs of the teaching community. Past experience has shown that the orthopedic community, both clinicians and engineers, are also extensive user and might be interested in a database of human anatomical variation. LO was asked to undertake a second study, to estimate the time it would take to collect the appropriate literature describing the bones and joints of the human arm, including the shoulder. The study suggested that it would take about 7 weeks. Therefore collecting the data relevant to every bone and joint in the body may take about a year. This represents a feasible pilot project. As an immediate library service, each article from the literature which was found would be scanned and a PDF file would be created. Most, if not all of this literature is beyond copyright and the PDF files could be indexed and made available on the web.

7.2 From Database to Knowledge Base

It is at this point the pilot database needs to be restructured as a knowledge base. The purpose of building a database of human anatomical variation is not just to present what is already in the literature in a convenient and compact format but to interpolate that data and extrapolate it in order to predict what is not explicitly in the original data and to explore how different data elements interact with each other. For example, if the *radius* bone is longer and has a greater diameter than the data in the database, what can be expected in the dimensionality of the *ulna* bone and the *elbow* joint?

Several LHC staff members have had previous experience with building knowledge bases based on artificial intelligence principles. A graphical interface to this data would be ideal and LHC staff has also had experience with image analysis, processing and visualization. Advisory panel members representing the visualization community indicated that computers are now fast enough and graphical engines are now sophisticated enough that such a real time graphical interface, including the morphing images based on statistical variables from the Visible Human data sets, is possible. Not only is it possible to retrieve the original anatomy and display it, it is possible to specify the parameters of the desired anatomy anywhere along a normal continuum and display images which are morphed from the available Visible Human images within the teachable moment.

7.3 Validation Framework

Validation is generally recognized as the most frustrating if not most difficult part of any project. Our advisory panel suggested that we validate the Knowledge Base of Human Anatomical Variation by obtaining additional anatomical dimensionality data and testing how well the new data was predicted by the data already in the knowledge base. The addition of this additional data to the knowledge base should increase the accuracy of its predictions. The new data would come from appropriate radiological data sets or from virtopsy images. 3D Informatics staff has discussed acquiring and hosting research image data sets for open community use in the mode of the original Visible Human data sets. The image data sets obtained for the Knowledge Base of Human Anatomical Variation could also serve that purpose.

To support the VHP3 Program, the appropriate statistical data would have to be extracted from the images in the data sets and entered into the knowledge base. The 3D Informatics team developed Insight Tool Kit (ITK) is appropriate to the task of data extraction. The planning panel suggested that this would be an opportunity for NLM to explore the usability of the Web 2.0 environment. Mounting such an effort in the tradition manner would be a massive and very expensive effort. The planning panel suggested launching Web Anatomy 2.0.

7.4 Web Anatomy 2.0

Web Anatomy 2.0 provides an opportunity for NLM to experiment in the Web 2.0 environment. Normally NLM would call together or contract with groups of experts who would extract the required statistical data elements from the available image data sets. NLM could still do this. But NLM could also enlist the community to do the data extraction and reporting. This raises many questions in qualifying the people doing the extraction and assuring the proper level of quality control. There are examples of successfully using the Web 2.0 environment. The experiment needs to be tried for this type of work. This means that NLM needs to provide the rules and the tools to maintain order and ultimate quality.

3D Informatics staff and various members of the NLM community have much of the needed expertise. We have expertise in building different kind of databases. We have experience in designing a user friendly input stream and management usable audit stream. We know how to enlist the needed expertise from the anatomical and orthopedic communities. Web 2.0 communities are not unlike the open source software community with which LHC has had several successes.

7.5 From Pilot to Project

A plan to produce a pilot Knowledge Base of Human Anatomical Variation has been described. The resulting knowledge base will only contain skeletal system information. The plan is scalable in time and with respect to yearly cost. Its success will give us valuable experience and insight into how to build, and the value in building, a complete Knowledge Base of Human Anatomical Variation. With this experience a decision can be made on building a complete Knowledge Base of Human Anatomical Variation.

Such a complete knowledge base of anatomical variation is a natural connection between the gross anatomy of phenotypic expression and the genetic anatomy genomic structure. This leads us into the last theme advocated by our advisory panel - Multi-scale anatomical modeling.

7.6 Multi-scale Anatomical Modeling

Moving from gross anatomy to micro anatomy to chemical anatomy to genetic anatomy will require a greater understanding of the mathematics of multi-scale modeling. We will need to accurately visualize and model anatomic structures across many orders of magnitude of size. Somewhere between gross anatomy and genetic anatomy, physiology must be modeled as it has a profound and dynamic effect. DARPA's Virtual Soldier program proved the feasibility of this approach. The 3D Informatics staff is positioned for the challenge.

8 Summary

The research area we call 3D Informatics is a synthesis of medical image processing, computer graphics, modeling, and data storage and retrieval. It is an underserved and underrepresented research area that deserves investment. We have proposed and delivered a comprehensive research program for the Lister Hill Center. This concept is built up of multiple strengths or research pillars, and like a table with three legs, will stand stably only with the strength and support of all three. We believe that a program that is *not* comprehensive, that does not integrate the breadth of volume data analysis, modeling, and representation will focus too tightly on the narrow confines of their mathematics and techniques, and so be incapable of adequately supporting the practice and research endeavors of medicine. We believe that we have grown a program with this vision, supplying the Lister Hill Center with a new opportunity to lead in the medical community.

Our future plans include an innovative array of projects designed to reinforce one another, building from shared mathematics and statistics foundations. The plan is designed to elevate our program across the range of our supporting research columns, increasing our prominence in this and related fields. The ultimate goal is to create for the Lister Hill Center one of the premier national laboratories in medical imaging.

The original goal of the Visible Human was "to transparently link the print library of functional-physiological knowledge with the image library of structural-anatomical knowledge into one unified resource of medical information." This Knowledge Base of Human Anatomical Variation pilot project is but a small step in the direction of bringing this vision into reality.

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CURRICULUM VITAE

Name: Michael J. Ackerman, Ph.D.

Position Title: Assistant Director of High Performance Computing and Communications

Education and Training:

Institution	Degree	Years	Field of Study
Hofstra University	B.A.	1962 - 1966	Biology
Clark University/Worcester Polytechnic Institute	M.A.	1966 - 1968	Biomedical Engineering
University of North Carolina at Chapel Hill	Ph.D.	1968 - 1971	Biomedical Mathematics & Engineering

Research and Professional Experience:

Supervise intramural research program

- Algorithms for 3D medical image segmentation and interactive modeling
- Network quality of service (QoS) requirements
- Use of collaboratory tools for telemedicine and distance learning
- Novel Medline search methods
- Outreach to major medical societies including demonstrations and classes

Plan, develop and implement NLM's Next Generation Network (NGN) program

- Coordinate NGN planning, research and development activities with the federal National Coordination Office for Information Technology Research and Development, and the academic UCAID/Internet2 organization
- NLM liaison to scientific organizations and all levels of government - state, national, and international - to plan and implement research in NGN technologies
- Develop programs and guide management of 11 current NGN contracts

Project Officer and initiator of the concept of the Visible Human Project

- Provide long range vision and guidance
- Develop consensus among sponsoring NIH Institutes
- Implementation within policy and budget guidelines
- Oversee tracking of over 2,400 user licenses from 43 countries
- Chaired three biannual conferences with Proceedings published on CD-

ROM and web

- Senior Science Advisor to “The Human Body” IMAX film.

Lead Science Officer - NIH Roadmap National Center for Biomedical Computing (NCBC) Program

- Member of the NCBC Project Team
- Provide scientific guidance to the National Alliance for Medical Imaging Computing (NAMIC)
- NIH liaison to the NAMIC external advisory committee

Honors:

2006 Senior Member, Institute of Electrical and Electronic Engineers
2006 American Telemedicine Association Dedicated Service Award
2004 American Medical Informatics Association Dedicated Service Award
1998 National Institutes of Health Award of Merit for service to BECON
1998 Johns Hopkins University Ranice W. Crosby Distinguished Achievement Award
1997 Government Technology Leadership Award
1996 National Institutes of Health Director's Award
1996 Friends of the National Library of Medicine Public Service Award
1996 Smithsonian Finalist Award for Information Technology
1996 Satava Award for Medical Applications of Virtual Reality
1995 Public Health Service Special Recognition Award
1992 Founding Fellow, American Institute for Medical and Biological Engineering (AIMBE)
1985 Fellow, American College of Medical Informatics (ACMI)

Recent Publications:

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CURRICULUM VITAE

Name: Terry S. Yoo **Position Title:** Computer Scientist

Education and Training:

Institution	Degree	Year	Field of Study
Harvard University	A.B.	1985	Biology
Univ. of North Carolina at Chapel Hill	M.S.	1990	Computer Science
Univ. of North Carolina at Chapel Hill	Ph.D.	1996	Computer Science

Research and Professional Experience:

1998 - Present **Computer Scientist**
Lister Hill National Center for Biomedical Communications, Bethesda, MD

1995 – 1998 **Assistant Professor of Radiology**
University of Mississippi Medical Center, Jackson, MS

Research Assistant Professor of Engineering (joint appointment)
University of Mississippi, Oxford, MS

1990 – 1995 **Senior Research Associate**
Department of Computer Science
University of North Carolina at Chapel Hill, Chapel Hill, NC

1987 – 1990 **Member Technical Staff**
Microelectronics Center of North Carolina, Research Triangle Park, NC

1986 – 1987 **Information Systems Designer**
AT&T Technologies, Burlington, NC

1985 – 1986 **Scientist**
BBN Laboratories, Incorporated, Cambridge, MA

Selected Publications:

Books and Book Chapters

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