BIOMEDICAL COMPUTATION @ STANFORD 2001

SYMPOSIUM PROCEEDINGS

BCATS 2001 SYMPOSIUM PROCEEDINGS

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BIOMEDICAL COMPUTATION AT STANFORD 2001

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ACKNOWLEDGEMENTS

This symposium would not have been possible without the support of many individuals and several organizations.

The organizing committee would like to thank the Biomedical Information Technology at Stanford (BITS) faculty. The BITS faculty had the vision and initiative to create a symposium that brings together young, innovative Stanford researchers who will become tomorrow's leaders in biomedical computation.

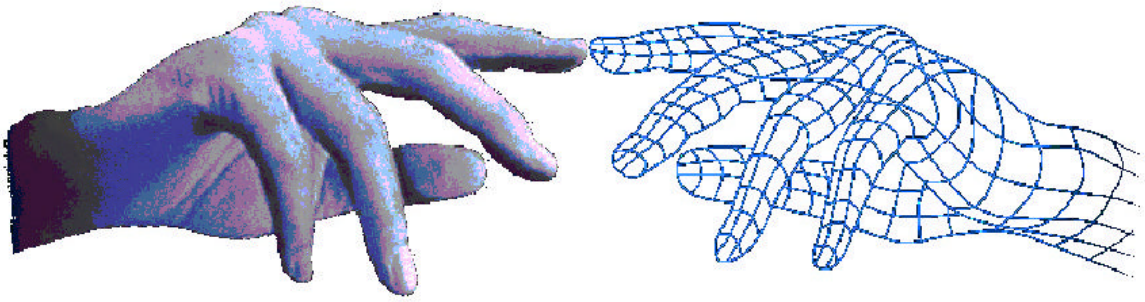
We would like to thank Dr. Christopher Johnson and Dr. William C. Swope, two of today's leaders in biomedical computation, for sharing their visions of the field's exciting future with us.

We would like to acknowledge the generous financial support of the National Library of Medicine through a Medical Informatics Training Grant. This year we are pleased to have the additional collaboration of the Bio-X initiative at Stanford.

We are also grateful to the following corporate sponsors for their financial support and for promoting biomedical computation beyond the walls of academia: Alloy Ventures, DoubleTwist, Incyte Genomics, Roche Bioscience, Sun Microsystems, Honda, the Northern California Pharmaceutical Discussion Group, Structural GenomiX, and SurroMed. In addition, we would like to thank the people at those organizations whose efforts made the sponsorships possible.

We recognize the tremendous effort put forth by the BCATS 2000 committee – Jonathan Dugan, David Paik, Brooke Steele and Olga Troyanskaya. These individuals paved the way for us by organizing the first annual BCATS symposium.

Finally, the organizing committee wishes to thank the many volunteers and department administrators for their tireless assistance with every aspect of this year's symposium.



BIOMEDICAL INFORMATION TECHNOLOGY @ STANFORD

ABOUT BITS

The Biomedical Information Technology at Stanford (BITS) faculty group is the key supporter of BCATS.

BITS is an inter-connected, cross-disciplinary group of researchers who develop, share, and utilize computer graphics, scientific computing, medical imaging, and modeling applications in biology, bioengineering, and medicine. Our mission is to establish a world-class biomedical computing and visualization center at Stanford that will support joint initiatives between the Schools of Engineering, Medicine and Humanities and Sciences.

Participating labs promote the efficient development of new courses, programs, computational models, and tools that can be used in classrooms, clinical practice, and the biomedical research community. Our goal is to become be an international resource for partners in the biotechnology, biomedical device, computing, medical imaging, and software industries.

BITS faculty support teaching and training in the biomedical computing sciences and the creation of interdisciplinary biocomputational courses at the undergraduate, graduate, and post-graduate levels, both on-campus and at remote sites.

More information can be found at:
http://bits.stanford.edu

Symposium Schedule and Map

Saturday, October 20, 2001

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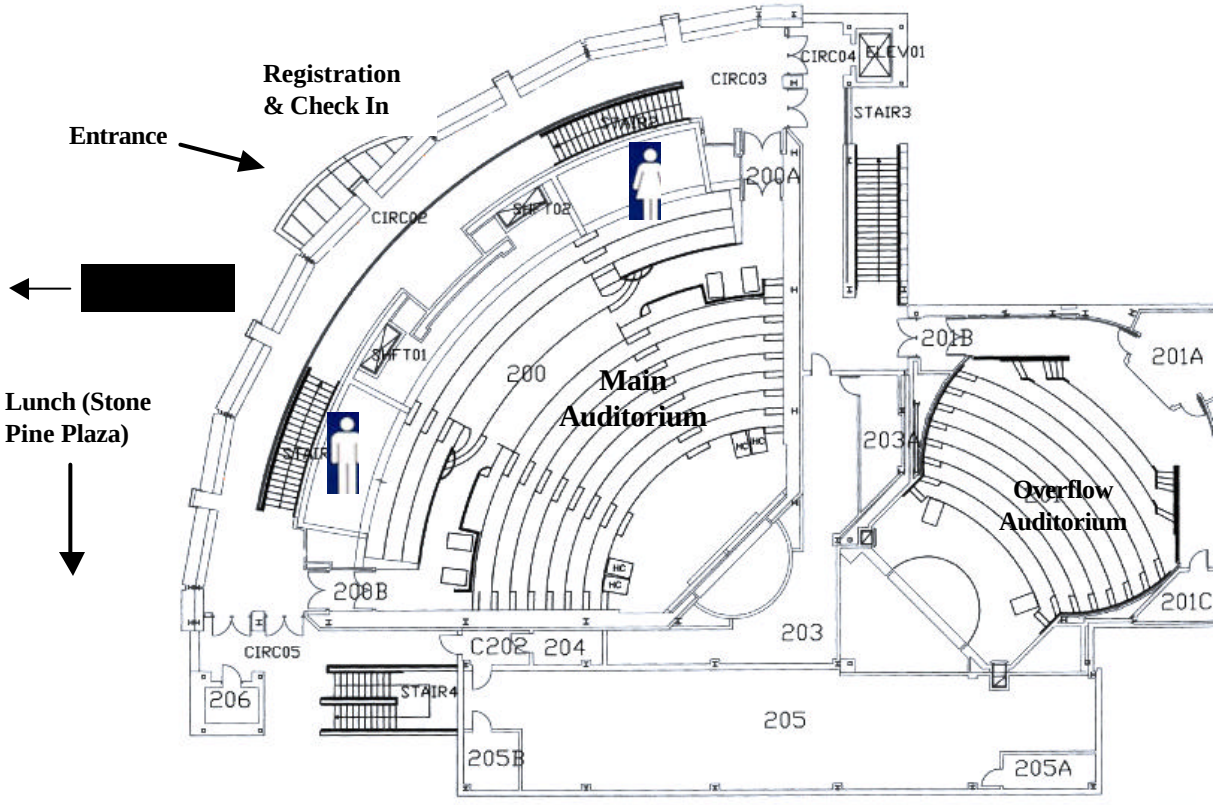

KEYNOTE SPEAKERS

William C. Swope, Ph.D.

IBM Research Division
Almaden Research Center

THE IBM BLUEGENE PROJECT: PROTEIN FOLDING AND PARALLEL COMPUTER DESIGN

In late 1999 IBM announced plans to begin a five year research program to develop a very large parallel computer system capable of nearly petaFLOPS (10**15 floating point operations per second) levels of performance that could be used to perform biomolecular simulations. The goal is to use this capability to study biological processes at a molecular level, and, in particular, to help improve the understanding of the phenomenon of protein folding. This ambitious project will also push the state of the art in large scale computer design and in the software tools that will be needed to fully exploit the associated hardware architecture.

The IBM BlueGene team is working with members of the computational chemistry and biology communities in academia and government to outline meaningful research programs that can make effective use of the Blue Gene resource. This talk will give a status report on some of the biological science aspects of this research program. Some early scientific results will also be presented.

Dr. Swope is a research staff member currently helping with the Blue Gene Protein Science project. He started his career in IBM at IBM Instruments, Inc., an IBM subsidiary that developed scientific instrumentation, where he worked in an advanced processor design group. He also worked for six years at the IBM Scientific Center in Palo Alto, California, where he helped IBM customers develop software for numerically intensive scientific applications. In 1992 Dr. Swope joined the IBM Research Division at Almaden, where he has been involved in software development for computational chemistry applications and in technical data management for petroleum and life sciences applications. He obtained his undergraduate degree in chemistry and physics from Harvard University and his Ph.D. degree in quantum chemistry from the University of California at Berkeley. He then performed postdoctoral research on the statistical mechanics of condensed phases in the chemistry department at Stanford University. He maintains a number of scientific relationships and collaborations with academic and commercial scientists involved in the life sciences and, in particular, drug development.

Christopher Johnson, Ph.D.

Director,
Scientific Computing and Imaging Institute
University of Utah

INTERACTIVE SIMULATION AND VISUALIZATION IN MEDICINE: APPLICATIONS TO CARDIOLOGY, NEUROSCIENCE, AND MEDICAL IMAGING

In this talk I will present recent research results in computational neuroscience, imaging, and cardiology within the context of an interactive problem solving environment (BioPSE) for biomedical applications. As opposed to the typical "off-line" simulation mode - in which the scientist manually sets input parameters, computes results, visualizes the results via a separate visualization package, then starts again at the beginning - SCIRun "closes the loop" and allows interactive steering of the design, computation, and visualization phases of the simulation. I will provide examples of several driving applications of steering and interactive visualization in cardiology (defibrillation simulation and device design), neuroscience (new inverse source localization techniques and surgical planning), and imaging (new methods for interactive visualization of large-scale 3D MRI and CT volumes, and introduce new methods for diffusion tensor imaging).

Professor Johnson directs the Scientific Computing and Imaging Institute at the University of Utah where he is a Professor of Computer Science and holds faculty appointments in the Departments of Physics, and Bioengineering. His research interests are in the area of scientific computing. Particular interests include inverse and imaging problems, adaptive methods, problem solving environments, large scale computational problems in medicine, and scientific visualization. Professor Johnson was awarded a Young Investigator's (FIRST) Award from the NIH in 1992, the NSF National Young Investigator (NYI) Award in 1994, and the NSF Presidential Faculty Fellow (PFF) award from President Clinton in 1995. In 1996 he received a DOE Computational Science Award and in 1997 received the Par Excellence Award from the University of Utah Alumni Association and the Presidential Teaching Scholar Award. In 1999, Professor Johnson was Awarded the Governor's Medal for Science and Technology.

ABSTRACT LIST

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SCIENTIFIC TALKS SESSION I

QUANTIFIABLE REAL-TIME 3D ULTRASOUND DATA ACQUISITION AND VISUALIZATION

Jacqueline Nerney Welch, Jeremy A. Johnson, Michael R. Bax, Samuel K. S. So, Thomas M. Krummel and Ramin Shahidi

Purpose

Surgeons are increasingly turning to 3D imaging to enhance their understanding of anatomical relationships, increase efficiency and accuracy, and improve surgical outcomes. The advantages of ultrasound include relatively low cost, real-time interaction, a lack of ionizing radiation, and operation near metallic objects. Most volume-rendering systems must render offline, which is inadequate for real-time surgical applications. The Image Guidance Laboratories at Stanford have developed a near real-time, freehand 3D ultrasound visualization system for image-guided surgical applications such as liver resection, tumor ablation, and breast biopsy.

Material and Methods

The ultrasound data is scanned using a Sonosite 180 handheld ultrasound system with a 5 MHz linear transducer. Ultrasound probe position and orientation measurements are acquired using an Image Guided Technologies optical tracking system. The software has been developed on a Silicon Graphics 320 workstation with an integrated video frame grabber.

Our system maps the series of 2D ultrasound scans to 3D volume space through a series of system transformations. The transformation from the ultrasound probe's tracking sensor coordinate space to the slice coordinate space requires spatial calibration. In order to determine the calibration parameters, the positions of the features in world coordinates are correlated to their positions in image coordinates through ultrasound imaging of a phantom with known geometry.

With its position and orientation information, each slice is properly inserted into the volume. The volume is updated and maintained through the use of computationally efficient algorithms. A volume-rendering engine simultaneously displays the updated volume image.

Results

Spatial accuracy is comparable to other published methods, with an average absolute error of below 1 mm. The system acquires ultrasound data at up to 15 frames per second and renders an updated volume every second on a Pentium II PC.

Conclusion

Our system design emphasizes ease of use and acceptance in the surgical environment. The system relies on conventional ultrasound technology, which does not expose the patients or physicians to ionizing radiation. Hospitals will benefit from the cost-effective transformation of existing ultrasound machines into 3D systems. In addition, it is compatible with metallic surgical instruments and machinery, since it relies on optical rather than magnetic tracking technology. Furthermore, current surgical procedures will need minimal modification to incorporate the new 3D protocols, as the physician will still have freehand control over the position of the probe.

References

1. Welch JN, Johnson JA, Bax MR, Badr R, Shahidi R. A Real-time Freehand 3D Ultrasound System for Image-Guided Surgery. *2000 IEEE Ultrasonics Symposium Proceedings*. 2:1601-04, 2000.

STOCHASTIC ROADMAP SIMULATION: EFFICIENT REPRESENTATION AND ALGORITHMS FOR THE ANALYSIS OF MOLECULAR MOTION

Serkan Apaydin, Carlos Guestrin, David Hsu, Douglas Brutlag and Jean-Claude Latombe

Purpose

Many interesting properties of molecular motion are best characterized statistically by considering an ensemble of motion pathways rather than an individual one. Proteins are thought to fold in a multi-dimensional funnel by following a myriad of paths. Unfortunately, classical simulation techniques such as Monte Carlo (MC) and molecular dynamics (MD) generate individual paths and are inefficient if applied in a brute-force fashion to deal with many pathways. In this talk, we introduce Stochastic Roadmap Simulation (SRS), a new technique for exploring the kinetics of molecular motion by examining multiple pathways simultaneously.

Material and Methods

In SRS, we compactly encode many paths by a graph, or roadmap. Every path in the roadmap is a potential motion pathway for the molecule, with associated probability indicating the likelihood that a molecule may follow that path. By analyzing all paths represented in the roadmap, we can efficiently obtain kinetic information on the motion of molecules over the entire energy landscape. Furthermore, we formally prove that SRS converges to the same distribution as MC simulation.

Our compact representation can be applied to the computation of the probability of folding (Pfold): an important order parameter, indicating how far a conformation is from the native structure. Current approaches for computing Pfold require a large number of MC or MD simulations for each conformation. In contrast, our approach efficiently computes Pfold for all conformations in the roadmap simultaneously.

Results

For validation, we compared the Pfold computed by our approach to MC results. We observe that the accuracy of the SRS estimates improves as the roadmap size increases and, more interestingly, as number of MC simulations per starting conformation increases, the correlation increases. Thus, indicating that SRS estimates Pfold more accurately than MC. Furthermore, computing Pfold for all 10,000 conformations in a roadmap requires ~800s, while less accurate MC estimates for only 100 conformations require ~8000s.

Conclusion

In conclusion, we will present a new representation for analyzing molecular motion. Our roadmap representation encodes many possible MC simulation paths into a compact graph structure. Such structure allows us to perform biologically relevant queries very efficiently. Furthermore, we formally proved that our roadmap approach converges to the same distribution as MC simulation. We apply our method to the computation of the probability of folding, an important order parameter in protein folding. We obtain more accurate Pfold estimates than ones obtained by a conventional method, with a speed-up of many orders of magnitude. We are currently applying these concepts to the problem of ligand-protein docking.

Web Page

http://robotics.stanford.edu/~guestrin/Research/Protein/BCATS2001/

AUTOMATED CREATION OF RADIOLOGY TEACHING MODULES: DEMONSTRATION OF PACS INTEGRATION, CONVERSION AND DISTRIBUTION

Bhargav Raman, Raghav Raman, Lalithakala Raman, Yaseen Samara, Danny Lau, Garry Gold and Chris Beaulieu

Purpose
The creation of teaching modules has historically required manual processing that acts as a barrier to producing and maintaining an adequately large and updated teaching database. We demonstrate a system that provides a standard DICOM interface to an automated teaching file database. Our system is capable of seamlessly integrating with commercial PACS systems to produce enterprise radiology teaching modules without user input.

Material and Methods
We evaluated the feasibility of our system using a pilot database integrated with the PACS system deployed at our institution (GE Medical Systems, Milwaukee, WI). Our teaching file database server was deployed on a networked Windows workstation (Microsoft, Redmond, Ca) running SQL Server 2000, which was registered on our PACS system as a DICOM receiver. Our system requires minimal additional configuration of enterprise PACS systems.

Results
Teaching files were specified at clinical workstations and any desired annotation and cataloguing instructions were added using standard annotation tools. Standard DICOM network transfer was used to push studies to the dedicated teaching file server. All anonymizing, annotation and cataloguing was done automatically by the teaching file server using DICOM Header information. The system is capable of accepting institution-specific information from HIS/RIS systems as private DICOM header fields that specify additional and optional data and instructions for automatic annotation and cataloguing. In our institution this was accomplished with the cooperation of our PACS engineers. Teaching files were then stored in a Teaching Module database. A web interface to the teaching file database was provided to allow browsing and searching as well as adminstration of the database. Images were available to users in DICOM and JPEG format to download for inclusion in personal teaching syllabi.

Conclusion
We present a system which integrates the creation of online teaching files into the daily clinical workflow, allowing clinicians to immediately publish interesting cases online without moving from their clinical workstation. Our system uses standard protocols and requires minimal configuration to integrate with existing PACS systems, enabling a low-cost, expandable and platform and vendor independent solution.

Web Page
http://bigred.stanford.edu/bcatsteaching/default.asp

MODELING BIOLOGICAL PROCESSES USING WORKFLOW AND PETRI NET MODELS

Mor Peleg, Iwei Yeh and Russ Altman

Purpose

With the increasing volume of genomic data, it has become clear that biologists need computational methods for organization and analysis. We are developing a knowledge-based environment for organizing the data into computer-interpretable and human-browsable formats. Our focus is on bridging the gap between high-level physiological processes and molecular-level functions.

Material and Methods

We defined a set of properties that should characterize a biological process model: (1) intuitive, graphical representation, (2) formal semantics that enables verification of the correctness of the model and reasoning about biological processes and the relationships among processes and their participants, (3) modeling the structure, function, and dynamics of a biological system, (4) hierarchical structure to manage the complexity of the representation, and (5) inclusion of a biological ontology.

We assessed eleven models that were developed in the fields of software engineering, business, and biology, with respect to these properties. We found the most appropriate model to be a Workflow model. It supports almost all of the desired properties, except for the inclusion of a biological ontology and reasoning that is dependent on it. The Workflow model maps to Petri Nets, allowing verification of properties such as reachability, boundedness, and soundness.

Results

Our framework for modeling biological processes is based on the Workflow model and incorporates the TAMBIS ontology as a biological controlled vocabulary. We added other elements that are relevant to biological systems: cellular location information for process participants and the types of evidence that support facts in the knowledge base. We augmented the Workflow model with elements taken from Object-Process Methodology, to create a graphical representation of four relationship types that occur between a process and the structural components that participate in it (i.e., catalysts, substrates, products, and inhibitors).

We implemented our framework using the Protégé-2000 tool and tested it by representing Malaria parasites invading host erythrocytes. Using Protégé's axiom language, we composed queries that can aid discovering relationships among processes and structural components. We used reachability analysis to answer queries that relate to dynamic aspects.

Conclusion

We developed a formal yet intuitive knowledge model of biological processes and functions that is graphical, for human comprehension, and machine-interpretable, to allow reasoning. The model enables verification of safety and soundness, and querying information that can assist in discovering relationships among processes and structural components that participate in them.

EFFECT OF RELEASE OF FLEXOR POLLICIS LONGUS' A1 PULLEY ON THE MUSCLE'S THUMB-TIP FORCE: A COMPUTER SIMULATION

Joseph Towles, Wendy Murray and Felix Zajac

Purpose

The magnitude of a typical pinch force of a person with cervical spinal cord injury is small and, thus, limits the person's ability to perform important everyday activities. Reconstructive surgery of the thumb after tetraplegia is designed to restore the ability to use the thumb to produce pinch forces whose magnitudes are sufficiently large and purposefully directed to carry out activities of daily living. One such surgery—specifically designed to increase the magnitude of a muscle's endpoint force—is the release of the first annular (A1) pulley of the flexor pollicis longus (FPL), a muscle which plays an important role as the thumb generates pinch forces. Currently, it is unclear if, indeed, this release has the desired effect and only that effect. This work is intended to investigate the endpoint force effect of releasing FPL's A1 pulley. We hypothesized that the release would influence both the magnitude and direction of the endpoint force.

Material and Methods

This study involved the development of a static, two-dimensional, moment-driven model of the human thumb to simulate the release of FPL's A1 pulley at the metacarpophalangeal joint (MPJ) and to determine its influence on the muscle's endpoint force (see Fig. 1A). We applied joint moments based on 10 N of FPL force and its moment arms (Smutz et al., 1998, see Fig. 1A) and we calculated the ensuing endpoint force based on point-contact between the thumb-tip and a rough surface (see Fig. 1B, 1C). We simulated the pulley release by increasing the MPJ moment arm by 30% and, thus, increased the MPJ flexion moment by 30% and compared the change in force pre- and post-release.

Results

Both the magnitude and direction of FPL's endpoint force changed after release of the A1 pulley. Before the release, the nominal endpoint force was 1.6 N pointing 30 degrees with respect to the palmar axis (see Fig. 2A). After the release, which increased FPL's moment arm by 30%, the magnitude of the endpoint force increased by 68% and the orientation was less palmarly directed by 20 degrees (see Fig. 2B).

Conclusion

This study illustrates that when FPL's A1 pulley is released, the endpoint force increases in magnitude and becomes less palmarly directed. The functional consequence of this can only be interpreted in the context of meeting the force requirements for an everyday activity, for example, holding a fork or a hair brush. In general, such activities will require endpoint forces directed primarily in the palmar direction with some freedom to produce proximally and distally directed forces depending on the frictional properties at the contact between the thumb and object being grasped.

References

1. Smutz WP et al. Mechanical advantage of the thumb muscles. *Journal of Biomechanics* 31:565- 70, 1998.

Web page

http://www.stanford.edu/~towles/Image1.jpg, http://www.stanford.edu/~towles/Image3.jpg

QUANTITATIVE STRUCTURAL ANALYSIS METHODS FOR ELECTRON MICROSCOPE TOMOGRAPHY

Mark L. Harlow, David Ress, Robert M. Marshall and U. J. McMahan

Purpose

Transmission electron microscopes can reveal fine structural details of biological samples not obtainable by any other means. Electron microscopes are now capable of collecting a series of 2D projections collected at 1° (or 2°) intervals to angles of ±80° (fig. 1). Tomographic methods can be used to reconstruct a 3D volume from this series of projections with a final spatial resolution of 2-3 nm.

To analyze the complex organization present in tissue volumes, we have developed novel quantitative segmentation, rendering and analysis schemes. We refer to our image alignment, reconstruction, filtering, segmentation and rendering package as "EM3D". We have applied EM3D to the structural analysis of the frog's neuromuscular junction (Harlow et al. Nature [article] 409:479-484 (2001)).

Methods

Structures were segmented from the reconstructed volume using a combination of manual and automatic methods applied to a series of two-dimensional slices. Each segmentation defined the boundaries of a volume of interest (VOI), a subset of the entire volume. For heavily stained structures with a simple geometry, a semi-automatic scheme was used in which the operator needed only to mark an anchor path on a single volume slice. For structures with complex geometry and light to moderate stain, VOIs were defined by manually marking a closed path on a series of slices. For all segmentation, the angular orientation of the slice plane was completely adjustable to maximize contrast boundary discrimination of the stained structure under study, and boundaries were slightly larger than the stained structures that they enclosed to allow for accurate and complete isodensity surface calculations for rendering. To observe the stained structures within each VOI, a surface was calculated on the basis of a particular stain-density (gray) value. Initially, the isodensity value for each VOI was chosen to correspond to the 60% population value on the gray-scale cumulative distribution function; in some cases the value was subsequently adjusted slightly by the operator to correct for local inhomogeneities in stain density.

Results

We applied EM3D to the structural analysis of aggregates of proteins, known as active zone material (AZM), in motor axon terminals at the frog's neuromuscular junction, see fig. 2. Our results indicate that the AZM helps dock synaptic vesicles at the presynaptic membrane and anchor calcium channels within the membrane, and that the architecture of AZM provides a particular spatial relationship and structural linkage between them.

Conclusions

The computational methods of EM3D allow for effective segmentation, visualization and quantitative analysis of the fine structure present electron microscope tissue volumes.

Webpage

http://www.stanford.edu/~aruba/bcats.html

SCIENTIFIC TALKS SESSION II

SNPs And Protein Function: Structural Modeling of Disease Associated Mutation

Sean Mooney and Teri E. Klein

Single Nucleotide Polymorphisms (SNPs) are the most common type of genetic variation between individuals. There are a number of commercial and public projects collecting genetic variation data to provide an understanding of how genotype is associated with diseases, drug responses, and normal phenotypic variation. Typically, this data associates specific mutations with their observed phenotype. Unfortunately, phenotypic annotations alone do not adequately characterize the underlying structural and functional causes for observed pathologies. The goal of my research is to build computational protocols for automatic prediction and annotation of the effects of SNPs. To achieve this goal, these methods will be used to understand how polymorphism is distributed in genomes and whether this distribution holds functional information. We are approaching this problem by assessing the underlying molecular basis of specific disease-associated mutations and their distribution within a gene.

Molecular modeling methods, such as molecular simulation and homology modeling, have the potential to characterize disease-associated polymorphisms. I am using the collagenous disease Osteogenesis Imperfecta, androgen associated prostate cancer and Lesch-Nyhan syndrome as models for disease-associated mutations. Our model of collagenous disease reproduces both experimental structures as well as denaturation free energy differences between wildtype and mutant peptides. We have found that disease-associated mutations in collagen are structurally distinct from their wildtype forms and have a significantly disrupted triple helix. We also find that these peptides have different interactions with solvent than the corresponding wildtype forms, suggesting at how mutations compensate for lost stability. Mutations in the HPRT1 gene is associated with Lesch-Nyhan syndrome and hypoxanthine guanine phosphoribosyltransferase deficiency. The locations of these mutations within the structure of the HPRT enzyme suggest at which positions are genetically variable within the population and which positions are likely to be important for the function of the enzyme. Finally, we are using the androgen receptor as a model for observing differences in binding. Our quantitative computational studies are being performed to correlate changes in binding preferences with observed disease-associated mutations.

These three genes represent a fibrillar protein, a globular enzyme and a nuclear receptor. We find that the underlying principles guiding function are similar between them, but a broad analysis may not be sufficient for building computational screening protocols for analyzing disease-associated mutations at a molecular level.

A FAST AND ROBUST APPROACH FOR DEFORMABLE MODELING IN SURGERY SIMULATION

Matthias Teschner and Sabine Girod

Purpose

The success of craniofacial surgical procedures is critically dependent on careful planning. The planning process is aimed at the restoration of functionality and at the improvement of the patient's aesthetics. We present interactive, 3-D methods for the simulation of surgical procedures that can be used to improve the planning process. All methods are integrated in a PC-based software that can support medical training. The system handles real patient data sets and can be presented.

Material, Methods, and Results

The simulation system is based on a model of a patient's skull derived from a CT scan and on a 3-D, photorealistic model of the patient's preoperative appearance obtained by a laser range scanner.

Patient-individual soft tissue is discretized into mass points which are connected using springs. The mass-spring model allows the representation of a variable number of soft-tissue layers with arbitrary thickness. In addition to features like skin turgor and gravity the model takes the nonlinear stress-strain relationship of soft tissue into account. Furthermore, volume preservation is considered.

Instead of simulating the dynamic behavior of soft tissue, an optimization approach is applied to directly estimate global, nonlinear soft-tissue deformation due to external forces. The optimization approach is very robust and extremely efficient with regard to computational costs.
The approach to soft-tissue deformation is part of an integrated system for surgery simulation. The system can be used to simulate bone cutting and realigning. The bone structure can be split using a cutting plane which can be placed arbitrarily. Realistic simulation of realigning bone structures can be performed interactively due to integrated collision detection and collision avoidance. The software has been tested with several individual patient data sets. The system not only predicts resulting soft-tissue changes due to bone realignment. Additionally, it allows to simulate soft-tissue deformation and soft-tissue cutting due to surgical instruments.

Conclusion

Due to the fact that postoperative facial aesthetics largely depend on facial expressions, ongoing work focusses on the integration of a subset of facial muscles into the 3-D soft-tissue model that would allow the simulation of facial expressions. Furthermore, it is intended to perform clinical studies to estimate appropriate parameters for the introduced soft-tissue model, such as number, thickness and elasto-mechanical properties of soft-tissue layers. Postoperative surface scans of a patient's face, which are registered with the preoperative surface scan, are used to compare the simulated soft-tissue deformation and the actual surgical result.

Web Page

http://www.stanford.edu/~teschner/

USING SURFACE ENVELOPES IN 3D STRUCTURE MODELING

Jonathan M. Dugan, Glenn A. Williams and Russ B. Altman

Modeling the 3D structure of biomolecules assists in the understanding of diseases and normal biological processes, and in the discovery of novel pharmaceuticals. Current crystallographic methods for the determination of these structures have been very successful, but are not applicable for all cases. Fortunately, other experimental methods can provide useful evidence regarding biomolecular structure, although typically these data are noisy and sparse. For example, we can derive surface envelope (SE) data from cryo-electron microscopy, binding or affinity measurements, predictions, or homology modeling. Inter-atomic distances are derived from NMR and other biochemical and biophysical experiments. Our research has focused on the development of unified data structures and algorithms that are highly flexible and applicable to a variety of different data types -- with the goal of combining these heterogeneous data sources to maximize their utility in modeling macromolecular structures.

This talk outlines the development and implementation of algorithms capable of integrating both inter-atomic distance data and SE data into the 3D structure modeling process. We present a set of novel methods that apply nonlinear constrained global optimization to create high resolution biomolecule structures. We present the application of this optimization process using experimentally measurable data sources, such as distances and SE data, as constraints on molecular structure.

Our evaluation of the modeling system involves modeling the structure of several artificial structures and solved structures from the Protein Data Bank (PDB). In each modeling run, the input includes the residue sequence, inter-atomic distance data, and SE data. The results include quantitative evaluations of the RMSD and residual errors in resulting models, and a qualitative assessment of numerical convergence and local minimal behavior. For each test structure, the value of adding shape information from the SE is assessed by a direct comparison of modeling results with and without using SE data during modeling.

COMPUTER-ASSISTED BEAM ORIENTATION SELECTION FOR IMRT

Andrei B. Pugachev and Lei Xing

Purpose

The selection of beam orientations for intensity-modulated radiation therapy (IMRT) treatment is complicated and time-consuming task. Often, several trial-and-error attempts are required to determine an acceptable set of beam orientations. In conventional radiation therapy, the most developed and recognized technique is the beam's-eye-view (BEV) tool. However, BEV method becomes less useful in IMRT treatment planning because it does not account for intensity modulation. In this report, we present a BEV dosimetrics (BEVD) technique for beam orientation selection designed for IMRT.

Method

In our method, each possible beam orientation was evaluated from the standpoint of the deliverable target dose. In addition to the prescribed dose, each structure or normal tissue was assigned a tolerance dose. For each beamlet crossing the target, we calculated the maximum intensity that could be used without exceeding the tolerance of the OARs and generic normal tissue, such as muscle or bone, located on the path of the beamlet. By performing this procedure for each beamlet of a beam, we arrive to the "maximum" beam intensity profile, in which intensity of any beamlet cannot be further increased without violating the tolerance of some structure. After the dose distribution corresponding to the "maximum" intensity profile was computed, the beam was ranked using an empirical score function.

For a given patient, the BEVD technique is used to scan all possible beam directions to identify the "good" and "bad" beam orientations. However, one should note that the BEVD score is obtained under the assumption that there is only one incident beam. Therefore, the decision on placing the beams should be made by combining the BEVD score and the principle of maximum beam separation.

Results

In this study, five 15 MV photon beams were used for the treatment of a paraspinal tumor. The BEVD-selected beam configuration improved the target coverage and OAR sparing: the minimum dose to the target was increased from 71% to 84% of the prescribed dose, while the maximum dose was reduced to 114% from 119% of the prescription. At the same time, dramatic improvement of kidney sparing and significant reduction of the liver dose was achieved.

Conclusion

In this report, we have established a BEVD framework for the beam orientation selection in IMRT. Compared to other techniques, e.g. beam orientation selection based on different optimization algorithms, neural network or knowledge-based system, the BEVD is computationally efficient and does not require extensive knowledge base. The tool is especially valuable for complicated clinical cases possibly requiring the use of non-coplanar beams.

MICROARRAY CLUSTER EVALUATION: EASY AS 1-2-3

Joshua M Stuart, Laura C Lazzeroni, Art B Owen, Moni Kiraly, James Lund and Stuart K Kim.

Purpose

Beyond finding meaningful clusters, biologists using clustering methods on microarray results are faced with the additional challenge of assessing the significance of any discovered relationships. Approximating the likelihood of uncovering a single biologically meaningful group (biogroup) is difficult, but even more difficult is assessing the likelihood of how well an entire set of clusters capture prior biological knowledge. I present three methods we employ in our analysis of C. elegans microarray data for assessing how well a clustering result matches anticipated biogroups.

Material and Methods

Each approach takes as input a matrix of p-values *P* computed using the hypergeometric distribution. Each *Pij* holds the probability of getting the same number of overlaps or greater between cluster *i* and biogroup *j*. The first method constructs sensitivity versus specificity plots in the ROC style. The second approach applies a second cluster analysis to the derived *P* matrix. The third approach searches for biogroups that are correlated across clusters as measured by these p-values.

Results

The p-value matrices computed from cluster results on *C. elegans* microarray data reveal many significant overlaps with biogroups. Simulation studies confirm the presence of far more significant overlaps with biogroups than would be expected by chance. The ROC curves computed from *P* are also informative as judged by simulation. Inspection of clusters from the second clustering revealed meaningful relationships among the biogroups. For example, kinases and phosphatases, which have opposite enzymatic activities have correlated p-values. This seemingly counterintuitive result may reflect the fact that these enzymes participate in the same pathways.

Conclusion

These approaches yield useful information both for assessing microarray results and for understanding biological relationships. Correlation analysis reveals some expected and some unexpected results about the relationships between some biogroups. The empirical results suggest the overlap p-values tend to increase with larger cluster size and so we are still developing these methods in an attempt to compensate for this tendency.

References

1. Kim SK, Lund J, Kiraly M, Duke K, Jiang M, Stuart JM, Eizinger A, Wylie BN, Davidson GS A gene expression map for Caenorhabditis elegans. *Science* 293:2087-92, 2001.
2. Lazzeroni L, Owen AB Plaid Models for Gene Expression Data. *Stanford Technical Report*. 2000.

Web Page

http://cmgm.stanford.edu/~kimlab

COMPUTER AIDED DETECTION OF LUNG NODULES AND COLONIC POLYPS FROM VOLUMETRIC CT IMAGES

David S. Paik, Geoffrey D. Rubin, Christopher F. Beaulieu, Judy Yee, R. Brooke Jeffrey, Jr., Curtis H. Coulam, David Naidich and Sandy Napel

Purpose

Lung cancer and colon cancer are the first and second leading causes of cancer death in the United States. Early diagnosis using volumetric imaging techniques is very promising. However, the amount of image data per imaging exam is overwhelming. Computer aided detection has the potential to make interpretation more accurate and more efficient. The purpose of this study was to develop and evaluate an automated method for detecting both lung nodules and colonic polyps.

Material and Methods

We have developed a novel CAD algorithm, which is based on the Hough transform for spheres. Our method improves the robustness for detecting nodules and polyps that are non-spherical while distinguishing from potential false positive structures. For evaluating lung nodule detection, we obtained the CT scan consisting of 304 images reconstructed at 1 mm intervals, of a 54-year-old man with metastatic renal cell carcinoma (32 nodules > 6 mm, 17 nodules 3-6 mm). The gold standard was the consensus of 3 radiologists. For evaluating colonic polyp detection, we obtained CT scans for 51 patients who underwent bowel cleansing prior to scanning. There were a total of 14 significant polyps (> 8.5 mm) in 9 patients. The rest of the patients had no lesions larger than 8.5 mm for an overall prevalence of 18%. Fiberoptic colonoscopy was used as the gold standard..

Results

For lung nodule detection, the algorithm was able to achieve 100% sensitivity with 1 FP/dataset for nodules > 6 mm. It achieved 94% sensitivity with 18 FP/dataset for nodules 3-6 mm. For polyp detection, the algorithm achieved 92.9% sensitivity with 7.9 FP/dataset.

Conclusion

Our CAD algorithm is able to detect clinically significant lung nodules and colonic polyps reliably with a low false positive rate. This suggests a practical role for our CAD algorithm in aiding radiologist interpretation. The algorithm might be used as a second reader where the radiologist uses the CAD results to make sure no lesions were overlooked after reviewing the entire exam. Alternatively, the algorithm might be used as a first reader where the radiologist only reviews potential lesions detected by the algorithm.

POSTER SESSIONS

SURVEILLANCE SYSTEMS IN BIOLOGICAL SCIENCES

Shuo Liu, Teri E. Klein and Russ B. Altman

Abstract
The development of high throughput techniques and large-scale studies in biological sciences has given rise to an explosive growth in the volume and types of data available to a researcher. A surveillance system that monitors the data repositories and reports changes to a researcher based on his or her interests provides a researcher much needed assistance managing the data overload. In addition, such a system could act as a feedback loop to confirm the data submission to the repositories initiated by a researcher. We developed a dbSNP surveillance system that performs surveillance on the dbSNP database and confirms data submissions to dbSNP. In order to perform its function, the surveillance system needs to retrieve data from several data repositories: PharmGKB, Locus Link, Genbank, and dbSNP. Data Warehouse approach to data integration was chosen to integrate the data because of the need to timestamp and save derived results and performance, scalability, and reliability considerations. A common object model that encompasses Gene and SNP is created and data from the diverse databases is mapped to the object model. A data access layer is created that provides the mechanism to support the storage and retrieval of the data from a variety of storage systems such as RDBMS, ODBMS, KBMS, XML file, and flat file. The data access layer works directly with objects for data storage and retrieval. The existence of the data access layer allows flexibility and portability of the system with regard to storage backend.

Web Page
http://www.pharmgkb.org/PharmGKB/surveillance/genelist.jsp

BIOCOMPUTATION OF TECHNICAL SKILLS PERFORMANCE

Chantal L. Rawn, Carla M. Pugh,
Wm. LeRoy Heinrichs and Thomas M. Krummel

Purpose
In medical training, vast efforts have been made to objectively assess clinical cognitive skills, however, objective evaluation of technical skills has proven difficult. The purpose of this study was to determine whether a simulator can be used to detect specific, objective differences in clinical female pelvic examination skills between experienced clinicians and medical students.

Material and Methods
This study used the e-Pelvis, an electronic mannequin which allows students and instructors to visualize on a computer screen the location and intensity of touch applied during simulated pelvic examinations. While examiners perform clinical assessments on the simulator, performance data is collected and stored in an electronic data file.

Performance data were collected from fifty-three Stanford medical students randomly assigned to either a lecture and demonstration (n=23) or mannequin group (n=30), and twenty fully trained obstetrics and gynecology clinicians. Each group performed complete bimanual pelvic exams on three different simulators for a total of 219 exams. During the exams, electronic data were collected and participants documented their clinical findings on assessment forms.

Assessment of significant differences in clinical skills performances was completed using analyses of variance (ANOVA). Performance measures from the simulator data included: 1) length of time required to perform complete exam, 2) number of sensors or pressure points touched during the exam, 3) frequency, or total number of times a given pressure point was touched, and 4) the maximum amount of pressure used while touching each point. An accuracy variable was created from scoring the written clinical assessments.

Results
Performance score analyses revealed significant differences between students and clinicians for the accuracy, frequency, and time scores, $p<.05$. There were no significant differences in the number of pressure points touched or maximum pressures used during the exam when comparing students and clinicians. Clinicians were more accurate in their clinical assessment of the size, shape and position of pelvic organs and achieved this result while palpating the same critical anatomic areas as medical students with significantly less frequency and utilizing significantly less exam time, $p<.05$.

Conclusion
Objective assessment of technical skill is often impossible as clinician observation and evaluation are predisposed to subjective interpretation. This is the first study to report, specific, objective differences in clinical pelvic examination skill when comparing medical students and clinicians. While this study supports the use of simulator for objective skills assessment, there are not standard means of analyzing the electronic performance data. Our initial efforts at defining innovative computation methods have been successful however, more studies need to be performed.

Web Page
http://epelvis.com

INFORMATION GAIN AND LOSS IN 4 PROSTATE CANCER MICROARRAY RESEARCH

Zhenbin Fan

Purpose

Microarray research on cancer has been used so popular, but still has some problem to consider. I compared the differences of the information gain and loss in three popular processing methods.

Material and Methods

Using 6500 gene chip (Affymetrix), I studied 4 primary prostate cancer in three different approaches. The first (named T1) was to reverse transcript total RNA of 5 ug from the cancer tissue to cDNA, then amplified and labeled with biotin via T7 transcription kit. After fragmentation, biotin-labeled cRNA conjugated with fluorescein, and hybridized to the chip and generated the data. The second (named T2) was to process as above while the total RNA used < 0.2 ug and cRNA not labeled in first amplification; cRNA was reverse transcript into new round cDNA, which was done as in T1. The third (named LCM) was to process as the second approach while the total RNA came from cancer cells only via laser capture microdissection.

Data analysis: 1. According to the chip maker's recommendation, any gene expression outside of 20-10,000 was cleaned up. 2. Counted the gene numbers in each case and divided into 7 category (Table 1). 3. Without significant difference between 4 cases, we pooled them together and calculated the average percentile of each category. 4.The gain or loss of gene expression information between three methods were compared (Table 2).

Results

I found that majority of genes (83.7%) were detectable in all methods. T1 and T2 lost the gene numbers low (5.8% and 4.9%), while LCM lost high (10.2%). It may due to LCM excluded stromal cells information. Information gains were all very low(2.1%, 1.6% and 0.8%).

Conclusion

This study confirmed the reliability of our methodology and system. Information gain (false positive) or loss (false negative) still have, though not much but should be carefully considered in the gene analysis. LCM is really able to make improvement in cancer study.

References

1. Chee M, Yang R, Hubbell E, et al. Accessing genetic information with high-density DNA arrays. *Science*, 274:610-614, 1996.
2. Sirivatanauksorn Y, Drury R, Crnogorac-Jurcevic T, et al. Laser-assisted microdissection: applications in molecular pathology. *J. Pathology*, 189:150-154, 1999.

Web Page

http://www.stanford.edu/~zbfan/Tables.gif

THE EFFICACY AND ACCURACY OF TWO-DIMENSIONAL VIRTUAL FLUOROSCOPIC NAVIGATION IN INTRADISCAL PROCEDURE

Yung C. Chen and Sang-heon Lee

Purpose

To investigate the efficacy and accuracy of two-dimensional fluoroscopic navigation during intradiscal procedures.

Material and Methods

A virtual fluoroscopy system (The ION™ FluoroNav; Medtronic Surgical Navigation Technologies, Broomfield, CO) was used. Fluoroscopic images of the lumbar spine of an intact, unembalmed cadaver were obtained and the three fluoroscopic images were calibrated, and saved to an image-guided surgery system (StealthStation; Medtronic Sofamor-Danek, Memphis, TN).

The trajectory of a "virtual tool" corresponding to the tracked tool was overlaid onto the saved fluoroscopic views in real time. Live fluoroscopic images of the inserted spinal disc probe were then obtained. Distances between the tips of the virtual and fluoroscopically displayed probes were quantified using the image-guided computer's measurement tool. Trajectory angle differences were measured using a standard goniometer and printed copies of the workstation computer display.

The time of surgeon's radiation exposure was obtained. The satisfaction of 62 interventional spine physicians from Stanford Interventional Spine Cadaver course were surveyed. The duration of procedure time is measure.

Results

Excellent correlation between the virtual fluoroscopic images and live fluoroscopy was observed. Mean probe tip error was 0.97 +/- 0.40 mm. Mean trajectory angle difference between the virtual and fluoroscopically displayed probes was 2.7[degrees] +/- 0.6[degrees]. Survey from 62 interventional spine physicians revealed 98% satisfaction and expressed interests utilizing virtual fluoroscopy in intradiscal procedures. The average time of probe insertion to the disc is 8.2 seconds.

Conclusion

Virtual fluoroscopy offers several advantages over conventional fluoroscopy while providing acceptable targeting accuracy and speedy percutaneous disc procedures. It also dramatically reduces radiation exposure to the patient and surgical team by eliminating the need for repetitive fluoroscopic imaging for tool placement. This technology enables physicians for easy targeting, planning, and intra-operative disc aiming. In summary, Percutaneous disc procedure is simple, fast, accurate and radiation free under virtual fluoroscopy. Further registratable flexible spinal needles, catheter, or probe and simple attachable fiducial markers need to be developed for interventional spinal procedures.

References

Spetzger U, Laborde G, Gilsbach JM Frameless neuronavigation in modern neurosurgery. *Minim Invasive Neurosurg.* 1995 Dec;38(4):163-6.

STATISTICAL EVALUATION OF BRAIN WAVE RECOGNITION OF SENTENCES

Dik Kin Wong, Marcos Perreau Guimaraes and Patrick Suppes

Purpose

In our previous experiments, EEG recordings of brain waves were made under several different experimental conditions. The analysis here focused on visual condition, in which EEG signals were labeled according to the sentence trigger presented on a monitor. Results show that substantial information is present in the EEG in order to achieve significant classification rate.

Material and Methods

As in our earlier work, the analysis consisted of averaging over trials to create prototypes and test samples, each of which was filtered by a bandpass filter characterized with low frequency and width. The filtered time domain signals were classified using a least square criterion over a temporal interval. All these results are evaluated against both our probabilistic models of chance level and the empirical distribution of the rates obtained after random permutations of labels.[1]

We present three analyses here. First, we show the current best results of the new 100-sentence experiment using the filtering method mentioned above. Second, we address the criticism considering the arbitrary 2-element partitions in our previous analyses, of which a 90% recognition rate was achieved using five subjects to build the average prototype and the other four subjects to build the average test samples in the 48-sentence experiment.[2] We exhaustively ran all the possible 510 2-element partitions of the nine subjects to verify the results. Finally, we tried to classify individual trials instead of averaging the test samples. Five sets of test samples, for a total of 120 individual trials, were run.

Results

First, in the new 100-sentence experiment, 93 out of the 100 averaged samples of the best subjects were correctly classified. Second, 506 of the 510 2-element partitions of the 48-sentence experiment yield significant results. We will show two histograms to demonstrate the distributions of the different partitions. Finally, 95 out of the 120 recognition task of the 24-sentence experiment was correctly classified.

Conclusion

These results extend our analyses in three directions. First, the current method is shown to be able to tackle a classification problem with a significant number of trigger types. Second, a single set of brain wave prototypes, which can be used for different subjects, may be possible to be constructed. Finally, classifying individual trials for some subjects is plausible.

References

1. Feller W. An Introduction to Probability Theory and its Application. Vol. I. 1950 Wiley, New York.
2. Suppes P, Han B., Epelboim J., Lu ZL. Invariance between subjects of brain wave representations of language. *Proc. Natl. Acad. Sci. USA.* 1996: 12953-12958.

CURVATURE COLOR SHADING OF AORTA AND ITS BRANCHES

Haobo Xu

Purpose

Arterial curvature has been qualitatively identified as a cause of complication relating to endovascular treatment. Knowledge of curvature beforehand could be helpful for planning the route and method of endovascular repair and access. So far, clinical techniques for aortoiliac measurements have been typically based on 2D representations of a 3D structure, which could lead to misrepresentation and inaccuracy. Here, we propose a method of color shading the curvature of aorta and both iliac arteries to reduce the subjectivity and view dependence inherent in the 2D image interpretation.

Material and Methods

3D CT volume data were processed and visualized in a SGI workstation. The work related to curvature color shading was based on the research software PathPlan (developed by David Paik.) First, an isotropic volume was created with a linear interpolation. Then, the aorta and its branches were extracted from the surroundings by means of 3D region growing, from which 2 median paths (from the aorta to the left/right iliac) were calculated. 3D Curvature along these 2 paths was also calculated. The paths were then rendered as color shaded curves with color encoded as curvature. With a reasonable color table, this allows the observer to read the quantitative value of curvature at any point along the paths by perceiving its color instead of the shape of the curve. The arterial wall was also reconstructed using the marching cube algorithm and rendered as a translucent surface. This allows the observer to view both the color-coded median paths and the morphology of aortic arteries.

Results

Figure 1 shows two renderings of the same patient data from different viewing directions. Figure 2 shows the color table used in this study. A and B are 2 sets of corresponding points in different renderings. Notice that point A would seem to have a low curvature value in the left rendering and that point B would seem to have a low curvature value in the right rendering, if only the path shape were available. Thus, the color of the path provides a viewing clue of the curvature value along the path.

Figure 1: Two renderings of the same volume data

Figure 2: Color table. Curvature (cm-1) vs. Color

Conclusion

This preliminary study shows that curvature color shading has the potential to eliminate viewing dependence in 2D image interpretation. Further investigation into the best choice of color map is desired. Additionally, the work could be extended to also color encode cross sectional area measurements to further assist diagnosis and treatment planning.

LEXICAL METHODS INCREASE PRECISION IN FINDING GENE/DRUG RELATIONSHIPS

Jeffrey Chang and Russ Altman

Biology is a data-intensive field in which much data is disseminated by publishing in scholarly journals. Having data in electronic format yields benefits such as the ability to query it, communicate it efficiently, and run computational algorithms such as data mining. Automatic methods to translate text into a structured text format suitable for computation remains a challenge. Pharmacogenomics, in particular, will benefit from having methods to automatically detect gene/drug relationships that appear in MEDLINE abstracts. In this poster, we use cooccurrence (genes and drugs that appear in the same sentence) to identify putative relationships, and then use lexical methods to refine the results.

MODELING LIVER MOTION AND DEFORMATION DURING THE RESPIRATORY CYCLE USING INTENSITY-BASED FREE-FORM REGISTRATION OF GATED MR IMAGES

Torsten Rohlfing, Calvin R. Maurer, Jr.,
Walter G. O'Dell and Jianhui Zhong

Purpose

Stereotactic radiosurgery has been used to treat cranial lesions for more than a decade, exploiting the fact that the brain inside a closed cranium is approximately rigid. We are interested in treating extracranial lesions such as metastases and primary tumors in the liver which typically move 10-30 mm during relaxed respiration. One approach is to draw a large margin around the lesion to account for position uncertainty during respiration. Tissue motion tracking and respiratory gating of radiotherapy can potentially allow for increased radiation dose to the tumor while minimizing the dose to healthy tissue. We are interested in using kinematic models of motion to determine an appropriate gating window during which the position of the target is known within a specified excursion. In this paper, we demonstrate a technique for modeling liver motion during the respiratory cycle using intensity-based free-form deformation registration of gated MR images.

Material and Methods

We acquired 3-D MR images of the abdomen of several volunteers at end-inhalation, end-exhalation, and five time points in between using respiratory gating. We computed the deformation field between the inhalation and exhalation images using intensity-based affine and non-rigid registration algorithms that optimize normalized mutual information. The non-rigid transformation is a free-form deformation with B-spline interpolation between uniformly-spaced (typically 20 mm spacing) control points. The transformations between inhalation and exhalation were visually inspected using various image fusion techniques.

Results

The liver moves by up to 25 mm. Thus unregistered images are clearly misaligned. In our volunteers, much of the liver motion is cranial-caudal translation, and the affine transformation captures much of the motion. But there is still substantial residual deformation that the affine transformation does not account for. The free-form transformation produces a deformation field that appears on visual inspection to be very accurate. This is true for the liver surface, internal liver structures such as the vascular tree, and the external skin surface.

Conclusion

We have demonstrated that abdominal organ motion due to respiration can be satisfactorily modeled using an intensity-based non-rigid image registration approach. This allows for an easier and potentially more accurate and patient-specific deformation field computation than physics-based models using assumed tissue properties. We believe that this work is the first effort to predict abdominal organ motion and deformation due to respiration from volumetric image data using intensity-based non-rigid image registration rather than using explicit mechanical models.

FRAME-BASED REPRESENTATION OF BIOLOGICAL EXPERIMENTAL DATA AND ITS APPLICATIONS

Mike Bada, Michelle Whirl Carillo and Russ Altman

Purpose

The biomedical community has witnessed the power of structured representation of biological data in the successes of databases such as GenBank and PDB. These conventional relational databases have weaknesses, though: As there is no controlled vocabulary, different terms are sometimes used to represent the same concept, and even worse, the same term is sometimes used to represent different concepts. Furthermore, there are no formalized relationships between many of the terms, which reduces the ability to draw meaningful inferences. To address these concerns, we have built a frame-based knowledge base of biological experimental data; more specifically, we have chosen experimental data that provide structural information for the *E. coli* ribosome as our domain of interest. We have also built RiboWeb and Ask Sophia, two applications that showcase the power of the high degree of structure of the ontology-based knowledge base.

Material and Methods

Experimental data relevant to the structure of the *E. coli* ribosome were extracted from approximately 200 biological journal articles and manually entered into Sophia, a basic frame-based knowledge-representation system built by members of the Altman lab. RiboWeb consists of the ribosomal knowledge base, computational modules that operate on data selected by users, a session manager that maintains sessions started by users, and an interface through which users interact with the system. Ask Sophia is a Web-based application written as a series of Perl-based CGI scripts that gathers query information from the user at each step.

Results

The ribosomal knowledge base includes not only the modeling of the experimental data but also of relevant entities such as macromolecules, small molecules, complexes and parts of these molecules, organisms, measurements, units, and reference information. It currently contains over 150 classes, 200 relations, and 19,000 instances. It is a core component of RiboWeb, a tool that aids biological researchers in the construction of new models of the ribosome, in part or in whole, and in the evaluation of these models. This is done substantially through the selection of specific experimental-data sets from the knowledge base and the conversion of these data into quantitative distance constraints. The ribosomal knowledge base has also been used as a test knowledge base for Ask Sophia, an application that is designed to be usable by domain experts but also capable of guiding the user in the construction of complex queries of knowledge bases stored in Sophia.

Conclusion

The controlled vocabulary, along with their definitions and interrelationships, allow for a much clearer semantics, as compared to conventional relational databases. This in turn permits precise querying of (*i.e.*, extraction of specific data from) the knowledge base—something upon which virtually all database-based applications depend.

References

1. Bada, MA, Altman, RB. Computational modeling of structural experimental data. *Methods Enzymol.* 317:470-91, 2000.
2. Altman, RB, Bada, M, Chai, XJ, Carillo, MW, Chen, RO, Abernethy, NF. Riboweb: An Ontology-Based System for Collaborative Molecular Biology. *IEEE Intelligent Systems.* 14:68-76, 1999.

RELATIVE MOTION OF THE RECTUS FEMORIS AND VASTUS INTERMEDIUS DURING KNEE EXTENSION

Deanna Asakawa, Silvia Blemker, Garry Gold and Scott Delp

Purpose

The goal of our work is to understand the function of the rectus femoris muscle after surgical transfer of its distal tendon. In this surgery, the tendon of the rectus femoris (RF) is detached from the patella and reattached behind the knee. The surgery is performed in persons with cerebral palsy who walk with stiff-knee gait, and is thought to convert the muscle from a knee extensor to a knee flexor [1]. However, stimulation of the muscle after surgery revealed that it does not generate a knee flexion moment [2]. Scar tissue may form after surgery adhering the RF to the vastus intermedius (VI) and restricting independent motion of the two muscles. We hypothesized that RF will move in the same direction as VI in control subjects, and in the opposite direction of VI in rectus femoris transfer subjects. We tested these hypotheses by measuring the displacements of the RF and the VI muscles during knee extension using dynamic MRI.

Material and Methods

We used cine phase-contrast (cine-PC) MRI to capture muscle tissue velocity *in vivo* [3,4]. One magnitude image and three velocity images are acquired for each of 24 time frames in a cine-PC MRI movie. Sagittal plane cine-PC MR images of the thigh were acquired from 10 control subjects and 3 subjects after RF transfer with a 1.5T GE scanner. Subjects were imaged as they moved their knee through repeated cycles of extension/flexion from 65? of flexion to near full extension at a rate of 35 cycles/min. Images were also acquired as the investigator moved the subject's relaxed leg. The displacement of regions in the mid-thigh portion of the RF and the VI muscles (Fig. 1) were calculated by integrating the velocity image data [5].

Results

In control subjects, the RF and VI displaced in the same direction, as hypothesized, and displacements were greater in the RF than in the VI (Fig. 2). In subjects after RF transfer, the RF displaced in the same direction as the VI, a knee extensor, but in contrast to the control subjects, the RF displaced less than the VI (Fig. 3-5).

Conclusion

This study demonstrates that we can quantitatively assess the motions of muscles *in vivo* using dynamic MR imaging. We showed that RF displaces more than VI in control subjects, but does not move in the direction of the knee flexors after tendon transfer. This indicates that the transferred muscle does not function as a knee flexor after surgery.

References

1. Perry, J (1987). *Dev Med Child Neurol*, 29, 153-8.
2. Riewald, SR, Delp, SL (1997). *Dev Med Child Neurol*, 39, 99-105.
3. Pelc, NJ et al. (1991). *Mag Res Quarterly*, 7, 227-54.
4. Pappas, GP (2001). Ph.D. Dissertation, Stanford University.
5. Zhu, Y et al. (1996). *Magn Res Med*, 35, 471-80.

Web Page

http://www.stanford.edu/people/djasakawa/bcats2001.html
http://www.stanford.edu/group/nmbl/

MECHANOBIOLOGY OF DEVELOPMENTAL DYSPLASIA OF THE HIP

Sandra J. Shefelbine and Dennis R. Carter

Purpose

Developmental dysplasia of the hip (DDH) occurs in utero when the head of the femur is displaced from the acetabular socket. During normal growth the growth front is flat in the diaphysis and becomes convex around the metaphysis. In the proximal femur of a child with DDH, the growth front progresses more on the medial side than on the proximal side, resulting in coxa valga, or a large neck-shaft angle.

Previous studies have proposed that endochondral growth and ossification is promoted by intermittent octahedral shear stress and inhibited by intermittent hydrostatic compression[1]. Using a finite element model of the proximal femur, we examined the stresses that resulted from both normal and DDH loading conditions. From mechanobiological principles we calculated growth rates in the developing cartilage and compared the predicted growth front morphologies to histologies of normal and DDH proximal femurs.

Material and Methods

Loads were applied to a 3D finite element model of the proximal femur to simulate hip joint loading for both the normal and DDH loading conditions. The specific growth rate was determined as the sum of biological growth ($d?_b/dt$) and mechanobiological influences ($d?_m/dt$):

$$d?/dt = d?_b/dt + d?_m/dt = d?_b/dt + aMax?_s + bMin?_h,$$

with $?_s$ and $?_h$ as the octahedral and hydrostatic stress respectively. Growth front morphology was predicted based on the calculated growth rates at the growth front.

Results

The predicted growth front for the normal load history grew the most in the middle resulting in a convex morphology. In the DDH load history, the growth front progressed much more on the medial side of the femur than on the lateral side, resulting in a large neck-shaft angle.

Conclusion

The growth front morphology predictions compare well to clinical and histological observations. The results from this study demonstrate that mechanobiological principles can predict the formation of coxa valga in DDH. Abnormal loading conditions on the developing bone alter the stresses in the bone and cartilage. These stresses regulate the local growth rate and progression of the growth front and ultimately determine the morphology of the bone. These findings may help in understanding the etiology and pathology of other developmental bone deformities.

References

1. Carter, D. R. and G. S. Beaupré. *Skeletal Function and Form.* Cambridge, UK: Cambridge University Press, 2000.

FAST BRAIN FLATTENING

Alex Wade, Robert F. Dougherty and Brian A. Wandell

Purpose

The gray matter of the cerebral cortex approximately has the topology of a large sheet. In its natural state, the cortex is folded, so that it is difficult to appreciate the sheet in a single view. For some applications, it is useful to view the activity along the cortical sheet in a single view.

We have developed methods of generating such flattened representations of the cortical surface in order to visualize functional brain imaging data.

Material and Methods

A 3D model of the cortical sheet is generated by identifying and marking regions corresponding to white and gray matter in anatomical MR scans of the brain. This model is converted into a triangulated mesh using a standard volume visualization routine (the "marching cubes" algorithm). The 3D mesh points are mapped to a 2D plane by solving a large, sparse system of linear equations that maps each point to the average location of all its neighbors [1]. Functional data obtained in separate scans can then be mapped from the 3D cortical surface to the 2D representation.

Results

The unfolding routine is extremely efficient: Because the process occurs in a single step, every node in the cortical mesh can be included in the calculation thereby improving the accuracy of the final flat map compared to previous methods that relied on interpolation. The topographical properties of the flat map are known and can be controlled by modifying a weighting function in the 2D parameterization equation. For example, a modification to this weighting function ensures that the resulting parameterization minimizes the error between edge lengths in the 2D and 3D representations.

Conclusion

Visualizing 3D cortical activation patterns in 2D is essential to understanding the spatial relationships of different functional cortical areas. This flattening procedure allows us to flatten areas of cortex quickly and accurately. It also provides a way of controlling and quantifying the distortions inherent in such a mapping procedure.

References

1. M.S. Floater, “Parameterization and smooth approximation of surface triangulations”, Comp. Aided Geom. Design 14 (1997), 231-250.

Web Page

http://white.stanford.edu/~brian/segmentUnfold.htm

COMPUTATIONAL INVESTIGATION OF THE BIOMECHANICAL RESPONSE OF THE CORNEA TO LAMELLAR PROCEDURES

F.A. Guarnieri, P.M. Pinsky and J. Shimmick

Purpose

To investigate the biomechanical response of the cornea to ALK, PRK and LASIK using a computational modeling approach. The model provides data on the deformations of the stromal bed and may be used to predict the refractive outcome of surgery.

Material and Methods

We have created a nonlinear finite element program for analyzing the cornea that is based on a new model for the biomechanics of the stroma. This model consists of treating an individual lamella as a system of interlinked collagen fibers within a mucopolysacaride matrix. A homogenization technique is used to obtain the stromal tissue model that exhibits isotropy in the corneal plane. The parameters of the constitutive model were calibrated by simulating experimental data from inflation tests on enucleated eyes. For LASIK and PRK, Munnerlynn's equations were used to define the ablation geometry. For ALK we compare the results of the model with nomograms of clinical data.

Results

Several axisymmetric studies of ALK, PRK and LASIK were performed. In ALK, the spherical equivalent refraction (SER) for a flap thickness of 300 ?m and diameter of 6.6 mm was 1.25 ± 0.45 D with a nomogram value of 1.0 D and for a flap thickness of 375 ?m and diameter of 5.6 mm was 5.65 ±0.95 D with a nomogram value of 5.0 D. In PRK, the SER for an ablation depth of 50 ?m and a diameter of 7 mm was close the value predicted by Munnerlynn's equation. LASIK studies were based on a flap diameter of 7 mm, flap thickness of 150 ?m and apical corneal thickness of 500 ?m. A series of ablation depths, ranging from 50 ?m to 150 ?m, were analyzed and the resulting SER was compared to values predicted by Munnerlynn's equation. The results indicate an undercorrection that increases with ablation depth.

Conclusion

The SER in ALK simulation was comparable to clinical data for a range of flap thicknesses. The SER in PRK confirmed that the mechanical response is minimal for this procedure. The SER in LASIK was consistent with the observation that mechanical deformation increases for higher corrections. The computational model is able to quantify the instantaneous biomechanical component in lamellar procedures.

MEDIAL AXIS REGISTRATION OF SUPINE AND PRONE CT COLONOGRAPHY DATA

Ping Li, Burak Acar, Sandy Napel, David S. Paik, Judy Yee, R. Brooke Jeffrey, Jr. and Christopher F. Beaulieu

Purpose

The primary goal of Computed Tomographic Colonography (CTC) is to detect colonic polyps. Typically, two scan data sets for each patient are acquired in supine and prone positions. We have developed a heuristic, fully automatic algorithm for anatomically registering the supine and prone CTC data. The preliminary evaluation in 24 patients shows this algorithm is promising.

Material and Methods

Initial data processing involves colon segmentation and automatic determination of central colonic path from rectum to cecum. The path is then decomposed into the *X* (coronal), *Y* (Sagittal) and *Z* (Axial) axis components, which are interpreted as three coupled functions of path length *d*. The morphological similarity between supine and prone paths can be simplified as a similarity between the local extrema, i.e. the zero derivative (with respect to *d*) points.

The locations and types (local maxima or local minima) of the zero-derivative points are computed for all *X, Y,* and *Z* components of both supine and prone paths. These points serve as the landmarks for matching using a heuristic decision algorithm that takes account of their types and the closeness in terms of their coordinate values and locations along the paths. Once two landmarks (one from each path) are chosen as marking the same anatomical location, the paths are linearly stretched/shrunk in terms of *d*, to align these two selected landmarks. The algorithm works in a recursive manner, starting from the pair of landmarks with the highest matching likelihood, thus the resultant deformation function is non-linear with piecewise linearity. The three axes are matched iteratively in the order of *Z, X, Y.*

Results

To evaluate this algorithm, a data set of 24 CTC cases (mean age 62, 20 males) with both supine and prone data was used. For each case, a radiologist manually determined 5 pairs of identical anatomical points on supine and prone paths, that included sessile polyps, unique diverticulae, folds, or ileocecal valves. They served as the gold standard. The mean misalignment distance (MMD) was used as the measure to evaluate the effect of the path registration on each case.

Using our registration algorithm, the average MMD over all 24 cases was reduced from 47.1 mm to 12.7mm, i.e. by 73%. Only for two cases the algorithm did not improve registration: one was increased from 6.0mm to 14.9mm and another one from 7.4mm to 12.9mm.

Conclusion

The initial results over a data set of 24 cases suggest that the morphological similarity of colon medial axis coordinates, interpreted as three coupled functions, is relevant registration of supine and prone CTC data. Such an algorithm can be adapted to facilitate simultaneous examination of two data sets.

EVALUATION OF SOFT-TISSUE MODEL PARAMETERS

Matthias Teschner and Sabine Girod

Purpose

Computer-based techniques for the simulation of craniofacial surgical procedures and for the prediction of the surgical outcome have been shown to be very useful. However, the assessment of the accuracy of the simulated surgical result and the parametrization of the employed deformable model are difficult. We describe a technique which allows to compare the simulated surgical outcome and the actual result. This technique can be used to adapt the parameters of the deformable model which is used to predict the surgical outcome.

Material, Methods, and Results

For the simulation of craniofacial surgical procedures we employ a system which can handle patient-individual data sets. The system is able to simulate bone cutting and bone realignment. It can be used to compute the corresponding soft-tissue changes. The system is based on a CT scan of the patient's head and on a surface scan of the patient's face.

In order to assess the quality of the simulated surgical outcome the simulated postoperative patient's appearance is compared to a second surface scan which is obtained postoperatively. The pre- and postoperative surface scans, which are different due to the surgery, are registered employing a robust variant of the Iterative Closest Point (ICP) algorithm. This algorithm iteratively computes corresponding points and estimates a transformation between both scans by minimizing the median of Euclidean distances of corresponding points. The registration method is able to detect differences of both scans. This is essential, since areas of the face which have been affected by surgical procedures could falsify the registration result and have to be excluded in following iterations of the registration algorithm.

Since the preoperative surface scan is taken to perform the surgery simulation, the registration of the actual pre- and postoperative surface scans enables the comparison of the simulated and the actual postoperative surface of a patient's face. This allows to assess the quality of the simulated facial soft-tissue deformation. In case of differences the parameters of the soft-tissue model, which is used for the surgical simulation process, can be adapted with respect to minimized differences of corresponding points of the simulated and the actual postoperative surface of a patient's face.

The proposed registration method has been applied to numerous individual patient data sets.

Conclusion

The introduced registration method can be used to assess the quality of surgical simulation and to evaluate soft-tissue model parameters. Furthermore, the method has been applied to compute the volume of swellings.

Web Page

http://www.stanford.edu/~teschner/

ANALYSIS OF BIOCHEMICAL PROXIMITY EXPERIMENTS: THE RIBOSOME CASE

Michelle Whirl Carrillo, Irene S. Gabashvili, Michael Bada, D. Rey Banatao and Russ B. Altman

Purpose

The study of the complex, often elusive, interactions between cellular components plays a key role in understanding biological function. Experimental techniques developed for this purpose have been applied to the ribosome, a large ribonucleoprotein aggregate. Many techniques generate data that reflect proximity between parts of the ribosome. Modelers used this information to predict the ribosomal structure before crystal structures were solved. Now that the structures have been solved, many biologists and modelers ask: how accurate was the proximity information? This question is vital as these experimental techniques continue to generate proximity information for use in modeling other macro-molecular complexes. Biochemists are eager to learn in retrospect which techniques yielded precise, reproducible results in order to continue to perform valuable experiments. Modelers wish to understand how these experimental results can be appropriately interpreted and integrated into accurate molecular models. In this poster we present a limited analysis of proximity measurements generated by three types of techniques: cross-linking, footprinting and cleavage analysis.

Material and Methods

We selected published experimental results from our ribosomal knowledge based system, RiboWeb[1]. For each piece of proximity data, we calculated the distance between atoms as reported in the crystal structures[2,3] using RiboWeb tools.

Results

Most proximity measurements reflected distances less than 20 to 30Å, but the distance distribution stretched over 130Å. RNA cross links displayed a vague correlation between distance and experimental analysis. Protein-protein cross links for the 30S subunit displayed a much tighter range of distances than those for the 50S; inter-subunit cross links represented erroneously large distances. Footprinting and cleavage experiments represented a tighter range of distances than cross links, but a larger range than was typically expected.

Conclusion

According to our evaluation of the data set, modelers should be able to consistently rely on proximity data generated from cleavage and footprinting experiments, as long as they are aware of the larger than previously expected range of molecular distances. Cross linking experiments can be more detailed and specific, perhaps giving clues to conformational changes. However, that specificity can make the experiments very complex, leaving more room for error than in other types of techniques.

References

1. Chen, R.O. et al. 1997. Proc. Int. Conf. Intell. Syst. Mol. Biol. *5*:84-7.
2. Cate, J.H. et al. 1999. Science *285*:2095-104.
3. Wimberly, B.T. et al. 2000. Nature *407*:327-39.

OF SCREENSAVERS AND PROTEINS: SIMULATING FOLDING OF BETA HAIRPIN USING DISTRIBUTED COMPUTING

Bojan Zagrovic, Eric Sorin and Vijay Pande

Purpose

We have used distributed computing techniques and a supercluster of thousands of computer processors to analyze folding of a beta hairpin segment from protein G in atomistic detail. The beta hairpin from protein G is the system of choice for studying the formation of beta structures in isolation, both experimentally and computationally, and it has been studied extensively. This, however, is the first computational study where the hairpin molecule has been fully folded starting from an unfolded state.

Material and Methods

Using Langevin dynamics and an implicit solvent model, we have obtained 38 microseconds of simulated time which is more than an order of magnitude more than has ever been reported using a similar model. More importantly, we have in fact simulated the folding of this protein *multiple* times, obtaining 8 complete folding trajectories starting from the fully extended state.

Results

The wealth of simulated data has allowed us to analyze the mechanism of folding of the molecule in great detail. Folding begins with hydrophobic collapse which brings the strands of the hairpin together. This is followed by the formation of interstrand hydrogen bonds and the completion of the hydrophobic core. The final structures exhibit a significant diversity of hydrogen bonding patterns and we show that this is consistent with the available experimental data. Finally, we have estimated the folding rate of the molecule based on our simulations (4.8 microseconds) and the agreement with the experimentally measured value (6 microseconds) is excellent.

Conclusion

In addition to having significant biological implications, this study has demonstrated the power of using distributed computing techniques to study protein folding and dynamics. In addition, it has shed light on the quality of the GBSA implicit solvent model and the OPLS force field in general.

References

1. Zagrovic, B., Sorin, E. and Pande, V. Beta Hairpin Folding Simulations Using an Implicit Solvent Model. Journal of Molecular Biology (accepted for publication).

Web Page

http://folding.stanford.edu

GENERATION OF TRAVELING WAVES OF *MYXOCOCCUS XANTHUS* CELLS

Roy D. Welch, Oleg Igoshin, George Oster and Dale Kaiser

Purpose

A population of the bacteria *Myxococcus xanthus*, when grown in liquid culture and then spotted onto a nutrient-limited agar surface, will move in a coordinated fashion to form a series of dome-shaped structures called fruiting bodies. Each fruiting body contains approximately $1X10^5$ cells, and the subset of cells located at the interior of the fruiting body eventually differentiates into environmentally resistant spores. It is important to note that the initial population consists of identical cells, and that the initial orientation of these cells is random. The transition to fruiting bodies with ordered structures and spatially and temporally coordinated cell differentiation takes as little as 12 hours and involves multiple dynamic stages of self-organization.

One of the first stages in development is called rippling, when traveling waves form on the surface of an *M. xanthus* population. The crest of each wave is a dense ridge of cells moving at constant velocity. The purpose of this work is to determine how these cells coordinate their movement to produce multicellular patterns.

Experiments

Culture conditions have been developed wherein a small number of cells (approximately $1X10^6$) develops in a stable environment under constant observation. Using fluorescence microscopy, a sub-population of GFP-expressing cells mixed into a largely non-fluorescent population have been observed and tracked for several hours. The movement of these cells in rippling and pre-rippling populations has been analyzed, and a set of behaviors has been identified that are characteristic of rippling cells.

Results and Conclusion

These data, as well as accumulated data on *M. xanthus* behavioral genetics, are used to reconstruct the process of rippling. The model is based on the biochemistry of C-signal, a non-diffusible cell contact mediated signal that is the product of the *csg*A gene. All of the behaviors described for individual cells in a rippling population are reproduced in the model, thereby illustrating how collective behavior can arise from intracellular dynamics, contact-mediated intercellular communication, and cell motility. This model of *M. xanthus* wave formation represents a new mode of biological pattern formation that depends on cell contact interactions, rather than reaction-diffusion.

References

1. Sager B, Kaiser D. Intercellular C-signaling and the traveling waves of Myxococcus. *Genes Dev.* 8(23):2793-804 1994.

Web Page

http://nature.berkeley.edu/~oleg/movies.html

SIMULATIONS OF A DESIGNED BETA-BETA-ALPHA FOLD

Christopher D. Snow and Vijay S. Pande

Purpose

A full understanding of the relationship between protein sequence and structure requires a detailed explanation of the mechanism of protein folding. Simulation methods competent to reproduce experimental results while providing detailed molecular trajectories would find broad application in the molecular biosciences including pharmacology and medicine. Despite four decades of effort in this direction, it is a prevaling view that molecular dynamics cannot successfully find the native state at the global free-energy minimum due to limitations on simulation time-scale and the accuracy of the force field. Here we employ distributed computing techniques to simulate many thousands of short (10 nanosecond) independent molecular dynamics trajectories in an attempt to bypass the former limitation.

Material and Methods

The polypeptide of interest is a fast-folding designed beta-beta-alpha fold of 23 residues, BBAW, created and characterized in the Gruebele laboratory. Our molecular dynamics calculations treat the 274 heavy atoms and polar hydrogens explicitly (using the OPLS parameter set) and the solvent implicitly (using the generalized-born-surface-area method).

Results

After only a nanosecond, the nucleation of secondary structure at preferred sites is apparent. After 10 nanoseconds of simulation at 278K, a significant fraction of the ensemble has formed the expected secondary structure; 262 have a type II' beta turn at positions 4 and 5, 4207 contain at least one turn of alpha helix, and 157 have both elements of secondary structure. Moreover, 39 trajectories find a tertiary structure similar to BBA5 (alpha carbon RMSD < 3.5) a highly homologous fold, with 21 of 23 residues identical.

Conclusion

For the small fast-folding protein BBAW, thousands of short molecular dynamics trajectories using an established solvation model and force field provide sufficient sampling to reach native-like conformations. Furthermore, the fast formation of secondary structure is likely responsible for the rapid folding kinetics of BBAW.

GABRIEL: A MACHINE LEARNING SYSTEM FOR THE ANALYSIS OF DNA MICROARRAYS AND OTHER GENETIC DATASETS

Kuang-Hung Pan, Chih-Jian Lih and Stanley N. Cohen

Purpose

The ability to concurrently analyze the transcription of thousands of genes using DNA microarrays offers both major scientific opportunities and significant bioinformatics challenges. Currently-used analytical approaches for extracting biological information from microarray data generally employ non-supervised algorithms that group genes showing quantitative similarities in transcription; the expertise of individual users is then applied to interpret these groupings. Here we describe GABRIEL, a machine-learning system that incorporates expert knowledge into rules.

Material and Methods

In Gabriel, each rule includes premises that must be satisfied for a specified conclusion to be reached. This knowledge is then applied uniformly and consistently to the analysis of microarry results. GABRIEL's problem-solving rules direct stereotypical tasks, while domain knowledge pertains to gene functions or to experimental conditions. GABRIEL subsystems explain the logic that underlies conclusions and provide a graphic interface for the acquisition of new knowledge. The knowledge contained in GABRIEL's rules also allows inferences to be made about the significance of changes in gene expression, the mechanisms underlying these changes, and genetic regulatory relationships? enabling conclusions that extend beyond gene classification. Gabriel also can identify patterns among profiles that have been pre-ordered by a non-supervised learning algorithm such as hierarchical clustering or by the chromosomal location. In addition, Gabriel can learn rules from the dataset through genetic algorithms, which identify patterns able to best fit the data obtained.

Results

We compare GABRIEL's output with published findings in which expert knowledge has been applied post-hoc to microarray groupings generated by hierarchical clustering of serum addition dataset (Iyer *et al.* 1999). An event-response pattern-based rule defined in GABRIEL successfully identified genes whose expression was progressively elevated immediately following the addition of serum. Immediate-early response genes were also identified by a proband-based rule. We showed that GABRIEL could also learn both of these rules de novo from the dataset using a continuity/gap rule and a genetic algorithm-based pattern search rule.

Conclusion

Gabriel is a platform for incorporating knowledge into the analysis of microarray data. It is distinct from existing microarray data analysis methods in its explicit and systematic use of knowledge in the exploration and analysis of data. It is potentially applicable to the analysis of other genome-scale data.

References

1. Iyer, V., et al., *Science*. 283(5398):83-87, 1999.

MODELING MOLECULAR FUNCTION AND FAILURE: MISREADING OF GENETIC CODE BY THE RIBOSOME

Irene S. Gabashvili, Mor Peleg and Russ B. Altman

Purpose

In engineering, specifying mechanical and electronic systems and finding sources of their failure can be very complicated. It requires representing the structure and behavior at multiple levels of abstraction. In biology, the complexity is exceedingly increasing due to our far more imperfect knowledge. Troubleshooting of bio-devices and living systems is mostly non-formal and requires creative "what if" thinking. Knowledge of the structure at the atomic level greatly facilitates understanding of biological function and malfunction. However, the large number of working parts and communication pathways calls for the application of effective knowledge engineering tools and models able to reason about all relations and interactions between the biochemical and biophysical components. The purpose of this study is to develop such a knowledge representation model of molecular bio-machines. The ribosome, a complex of about 10,000 molecular blocks, amino acids and nucleotides, arranged in more than 50 proteins and at least three RNA molecules, an organelle that intervenes in the major cellular functions by making proteins for every vital purpose, is an excellent example for this research.

Material and Methods

We are building a model that integrates the structural (inter-atomic distances), behavioral (conformational dynamics) and functional (every potential role of each molecular part) aspects of ribosomal life cycle and the ontology of underlying biological concepts and their relationships. We use a Workflow model to describe the management of molecular activities and events by the ribosome. The model is further mapped into Petri nets. The ontology is developed in the Protégé-2000 environment. The Protégé constraint language is employed for specifying possible queries about the system.

Results

Using our framework, we can represent experimental data on changes in translational fidelity (the ability to read the RNA message by selecting cognate tRNAs) due to various mutations, interfering antibiotics or other functional defects. It is also possible to check internal inconsistencies in available information and perform behavioral simulations.

Conclusion

The initial results show promise and support the further development of the system towards evaluation of functional consequences of various structural modifications in the ribosome. This would be important for finding potential targets in bacterial invasion and viral attack and help to cure human diseases associated with ribosomal malfunction.

EFFICIENT INCREMENTAL COLLISION DETECTION FOR LARGE MOLECULAR MODELS

Itay Lotan and Fabian Schwarzer

Purpose

Applications in Computational Biochemistry such as Monte Carlo simulation of proteins, geometry-based approaches to protein folding, interactive manipulation of macro molecules, decoy generation and many others require a geometric representation of macro molecules. The prevalent representation is a collection of spheres linked by bonds, thus forming a kinematic chain. Efficient operations on such a structure are of great importance since most applications perform a huge number of them or require interactive performance.

In particular, we need to avoid steric clashes and compute internal energy while changes are being applied to the degrees of freedom of the molecular structure. Both tasks require an efficient method of detecting self collisions. Current approaches such as indexing into a grid or hierarchies of bounding volumes fail to utilize the chain topology in two respects: (1) local changes have global effects all the way to the end of the chain. This forces a complete reconstruction after every update of at least one half of the chain. (2) All parts of the chain become suspect for collisions after changing only a few bonds, even though large pieces of the chain are internally unaffected and need not be tested for self-collisions.

Material and Methods

We introduce a novel hierarchical representation of a kinematic chain that exploits the topology of the chain. Based on this representation we superimpose a hierarchy of oriented bounding boxes over the molecular structure that can be updated incrementally in O(log N) time per update operation. Although our representation requires O(N) time in the worst case for finding collisions it can be expected to do much better on the average. The rationale is that we avoid testing for self-collisions in parts of the chain that were not affected by the most recent changes.

Results

We have finished implementing a prototype of our algorithm and tested it against a grid based algorithm and a standard hierarchical data structure approach. On pseudo molecular chains of up to 10000 spheres our algorithm provides a better than 10 time speed up over the other approaches [See attached web page].

Conclusion

The project is still in its early stages but our results are very promising. It is clear that incremental updates allow for faster operations than complete recomputation of the structure. We are planning to further evaluate our approach with real proteins in folded and intermediate states. Future work will also include evaluating different bounding volume types. Our results are relevant to applications in other fields as well (e.g. robot manipulator arm collision testing).

Web Page

http://robotics.stanford.edu/~itayl/collisions/chaintree.htm

THOROUGHLY SEARCHING SEQUENCE SPACE: LARGE-SCALE PROTEIN DESIGN OF STRUCTURAL ENSEMBLES

Stefan M. Larson, Jeremy L. England, John R. Desjarlais and Vijay S. Pande

Purpose

Computational protein design seeks to predict amino acid sequences which will stably fold into specific three-dimensional protein structures. Incorporating backbone flexibility into computational protein design not only captures the behaviour of real proteins, but is also a prerequisite for the accurate exploration of a structure's vast sequence space, which is in itself of great theoretical (e.g. the inverse folding problem) and practical (e.g. directed protein evolution) importance. Unfortunately, including backbone flexibility in the design process inevitably greatly increases the computational complexity of the problem.

We present here a simple novel method for widely exploring sequence space through computational protein design to a structural ensemble. Although this method is computationally intensive, a distributed computing architecture (Genome@home) has allowed us to use 10,000 processors to generate hundreds of diverse designed sequences each, for a set of 253 proteins.

Results

Designing to a *single fixed* backbone using our method produces results very similar to other recently published studies. Designing to a structural ensemble, however, produces a much greater diversity of sequences. Homology searches against natural sequence databases show that the relevance and quality of the designed sequences is not diminished. In fact, the number of accurate PSI-BLAST hits increases when designed sequence libraries are used as queries. The diversity of the designed sequences increases asymptotically as the structural ensemble grows, and the average identity to the native target sequence decreases when designing to a structural ensemble.

The entropies of the designed sequence sets for very similar structures (in the same fold) tend to cluster together very tightly, whereas the sequence entropies across individual residue positions within a fold do not show significant correlations. In all cases, the designed sequence sets have greater overall sequence entropy than the natural sequence alignments, but no correlations were seen between the diversity of natural sequence alignments and the diversity of the corresponding sets of designed sequences. The relatively tight clustering of sequence entropies within a fold and the separation of sequence entropy distributions for different folds suggests a) that the diversity of the designed sequence set for a structure is primarily determined by its overall fold and b) that the designability principle postulated from studies of simple models may hold in real proteins.

Conclusions

The utilization of a distributed computing architecture has enabled exploration of protein sequence space with all-atom detailed structural ensembles. Initial characterizations of realistic sequence space agree with predictions from simple model studies.

Web Page

http://gah.stanford.edu/

REGULATORY NETWORKS REVEALED BY TRANSCRIPTIONAL PROFILING IN THE YEAST

Wei Wang, J. Michael Cherry, Hao Li and David Botstein

Purpose, Material and Methods

Transcriptional regulation is achieved by transcription factors that can recognize specific DNA segments, called regulatory elements, in the gene promoter regions. We apply a new method recently proposed by Buchermann et al.[1] to identify regulatory elements responsive to various conditions, as a first step towards deciphering the transcriptional networks. Further analysis of this data can provide many insights about the transcriptional regulation: A) Analyzing expression of a gene under different conditions and occurrences of different regulatory elements in its promoter region can suggest how different factors regulate the gene's expression in a combinatorial way; B) The occurrences of a regulatory element under different conditions suggest that the corresponding transcription factor is activated under these conditions. A global view of different elements appearing under many different conditions will give us insight into cross talks between different pathways.

Results and Conclusion

We have identified about 250 motifs from about 220 microarray experiments using Bussemaker el al. algorithm[1]. These 220 microarray experiments include environmental stress response[2], sporulation[3], cell cycle[4], and phosphate metabolism[5]. We observed several motifs, such as general stress response element agggg/cccct, appear in most experiments while some motifs, such as the regulatory element recognized by GCN4, only appear in certain conditions. Specific appearances of regulatory elements under certain conditions imply that the corresponding transcription factors are activated only in specific pathways. Analysis of the global appearance profile for each gene can shed light on cross talks between different regulatory pathways.

References

1. Bussemaker HJ, Li H, Siggia ED. 2001. Regulatory element detection using correlation with expression. *Nature Genetics* 27: 167
2. Gasch AP, Spellman PT, Kao CM, Carmel-Harel O, Eisen MB, et al. 2000. Genomic expression programs in the response of yeast cells to environmental changes. *Molecular Biology of the Cell* 11: 4241
3. Chu S, DeRisi J, Eisen M, Mulholland J, Botstein D, et al. 1998. The transcriptional program of sporulation in budding yeast. *Science* 282: 699
4. Spellman PT, Sherlock G, Zhang MQ, Iyer VR, Anders K, et al. 1998. Comprehensive identification of cell cycle-regulated genes of the yeast Saccharomyces cerevisiae by microarray hybridization. *Molecular Biology of the Cell* 9: 3273
5. Ogawa N, DeRisi J, Brown PO. 2000. New components of a system for phosphate accumulation and polyphosphate metabolism in Saccharomyces cerevisiae revealed by genomic expression analysis. *Molecular Biology of the Cell* 11: 4309

SMALL LIBRARIES OF PROTEIN FRAGMENTS ACCURATELY MODEL NATIVE PROTEIN STRUCTURES

Rachel Kolodny, Patrice Koehl, Leo Guibas and Michael Levitt

Purpose

We investigate the geometry of small contiguous sub-units of protein backbones, referred to as protein fragments, in order to gain insight on structural properties of local environments in protein structure. We aim to build optimal, finite libraries of such fragments that provide accurate representations of all proteins in structure space. These libraries can be further employed in construction of better discrete approximation spaces of protein structure.

Material and Methods

We consider four data sets of protein fragments, each corresponding to a fixed length (from 4 to 7 residues). These fragments are extracted from reliable protein structures from the Protein Data Bank (PDB). The data sets are clustered using a combination of simulated annealing and k-means, and the representative fragments (one per cluster), are stored in libraries. The libraries are characterized by their size (i.e. the number of clusters considered), and the length of the fragments they contain.

The libraries of fragments are used to construct discrete 3D approximation spaces. Structures in these spaces are constructed from fragments from the libraries that are added sequentially to a chain. Chain buildup proceeds by superimposing the first three residues of the fragment to be added on the last three residues of the existing chain. With this method, fragments of 4, 5, 6 and 7 residues add 1, 2, 3 and 4 residues to the existing chain, respectively. We find approximations to known protein structures from these spaces using a greedy algorithm.

Results

We investigate the effect of the length of the fragments in the libraries on the quality of protein models constructed with this method. We associate with each model a complexity measure that measures the size of the approximation space. Referring to a test set of 145 protein structures, we observed that we found more accurate approximations to these proteins in approximation spaces of a given size that are constructed from longer fragments. Using longer fragments in the construction of an approximation space implies that the structures in that space also account for correlations of conformations of neighboring residues. Using a library of fragments of size 5 with a complexity of 12 states per residues, we are able to construct model structures with an average cRMS of 1 angstrom from the native structure.

Conclusion

These results reveal the importance of the correlation of the conformations of neighboring residues in proteins. In particular, better discrete approximation spaces of protein structure can be built by exploiting these correlations.

IDENTIFICATION OF CLINICALLY RELEVANT GENES IN LUNG TUMOR EXPRESSION DATA

Olga G. Troyanskaya, Mitchell E. Garber, Russ B. Altman and David Botstein

The advent of DNA expression microarrays provided scientists a unique opportunity to create a snap shot of a cell, with the ability to gather information about the behavior of thousands of genes at a time. A major biomedical question in microarray studies is selecting genes associated with specific clinical parameters, for example patient survival. Identification of such markers, or groups of genes, may lead to clinical outcomes prediction and treatment guidance. Additionally, analysis of gene expression data associated with clinical data may allow molecular-level tumor classification. These tumor subtypes, which may appear histologically similar, are molecularly distinct and lead to differences in clinical outcomes such as patient survival, drug response, and metastatic status. Methods for automated analysis of gene expression data associated with clinical data are therefore needed.

Our work is focused on developing and evaluating methods for detecting clinically relevant genes in the context of lung cancer gene expression data. We use a non-parametric t-test based method for identification of genes associated with specific tumor types. This method was applied to lung tumor data to distinguish between subtypes of lung adenocarcinomas which are not histologically distinct. We also describe a correlation-based method for identification of genes correlated with patient survival. The method identifies genes whose expression can be best used to classify tumors in terms of 'good' and 'bad' survival outcomes for patients with lung adenocarcinomas.

AUTOMATED FUNCTIONAL ANNOTATION OF PROTEIN STRUCTURES

Mike Hsin-Ping Liang, Russ B. Altman and Doug L. Brutlag

Purpose

Following the sequencing of the human genome, structural genomics initiatives are rapidly determining structures of many gene products without knowledge of their function. Methods to assist in the functional annotation of these structures are increasingly important. In order to discover the biological functions of large proteomes and structural databases we need methods that can search for function with both high specificity and high sensitivity simultaneously.

An automated method for prediction of functional sites on protein structures is presented. The method leverages existing sequence-function motif databases by automatically constructing structural models that represent the function associated with the sequence motif.

Material and Methods

Statistical models of functional sites can be constructed by studying the conserved physical and chemical properties surrounding the site [Wei and Altman]. FEATURE is a system that can build these models given a set of protein structures, the exact location of sites with similar function, and sites that lack the function. These structural motifs can be used to detect functional sites on protein structures with high sensitivity. Unfortunately creating the training sets to build a library of models for various function is difficult and time-consuming. Conserved residues in protein sequences that share similar function can also be used to detect functional sites. The *e*MOTIF database contains consensus sequences that can identify functional sites in protein sequences with varying specificity [Nevill-Manning, Wu, Brutlag]. Sequence motifs, however, ignore structural information that can improve sensitivity in detecting functional sites. By using FEATURE to build structural motifs from *e*MOTIFs, we can use the conserved physicochemical properties surrounding the consensus sequence to improve functional site detection. Our new method, SeqFEATURE, automatically generates training sets for FEATURE from the *e*MOTIFs. The occurrence of the consensus sequence is located in the protein structure and the site is determined by taking the geometric centroid of the occurrence. Nonsites are selected by randomly sampling points in the structure outside the sites but with similar atom density.

Results and Conclusion

We compare motifs based on conserved biophysical properties of a calcium binding site with structural motifs determined from the consensus sequence. We also compare the performance of consensus sequences with that of structural motifs built from the consensus sequences. We will present evidence that structural motifs built from *e*MOTIFS can improve sensitivity while preserving precision in identifying functional sites.

References

1. Wei L, Altman RB. Recognizing Protein Binding Sites Using Statistical Descriptions of their 3D Environments. *Pac Symp Biocomput.* 1998;:497-508.
2. Nevill-Manning CG, Wu TD, Brutlag DL. Highly specific protein sequence motifs for genome analysis. *Proc Natl Acad Sci U S A*. 1998 May 26;95(11):5865-71.

HOW DOES SOLEUS STRENGTH AFFECT GAIT CHARACTERISTICS?

Jill S. Higginson, Richard R. Neptune, Felix E. Zajac and Steve A. Kautz

Purpose

Walking is a complex motor task which involves coordination of multiple muscles. Clinicians have debated the role of ankle plantarflexors during normal walking, but recent forward dynamic simulations[1] have clarified that the soleus (SOL) and gastrocnemius (GAS) have distinct roles for forward progression and vertical support of the trunk. However, it is unclear how a change in muscle properties (e.g. maximal isometric force) affects the resulting motion of the musculoskeletal system. Thus, the goal of this study was to quantify the effect of reduced bilateral SOL strength on (1) joint kinematics, (2) muscle induced accelerations of the hip and knee joints, and (3) the contribution of SOL to trunk support and forward progression during walking.

Methods

A 9 DOF, 11 segment musculoskeletal model was built using SIMM[2] to represent the trunk and lower limbs of a male subject[1]. Forces due to muscles, passive joint resistance, gravity and ground contact were included. The equations of motion were derived using SD/FAST[3] and were decomposed to find the contributions of each muscle to joint acceleration[4]. A forward dynamic simulation was produced by Dynamics Pipeline[2]. Experimental data[5] were tracked to find optimal muscle excitation patterns. The maximal soleus isometric force was reduced by 50% and the first gait cycle was compared with the nominal simulation.

Results

With decreased SOL force, time to complete one gait cycle was reduced and stride length was shortened resulting in a decline in gait speed. Right hip, knee, and ankle angles also became more flexed than normal (see Fig. 1). Decreased SOL force produced a smaller ankle plantarflexion moment and offered less support at the ankle. SOL normally induces acceleration of the knee and hip into extension during stance[1]; a weak SOL had a lesser effect and rotation of these joints was reduced. Induced linear and angular acceleration of the trunk by SOL were also diminished (see Fig. 2). Altered system kinematics due to the weak SOL had an impact on the length and forces of GAS, which also contributed to changes in acceleration of the trunk.

Conclusion

Decreased SOL strength reduced trunk support and forward acceleration, causing shortened stride length and slower gait speed. Our results may help explain why older adults with decreased muscle strength walk slowly. Future work will address how specific patient populations compensate for reductions in muscle strength.

References

1. Neptune et al., 2001.
2. Musculographics, Inc.
3. Symbolic Dynamics, Inc.
4. Fregly and Zajac, 1996.
5. Andriacchi et al., 1997.

Web Page

http://www.stanford.edu/~jstartz/BCATS/Higginson.htm

AUTOMATED AORTIC FLOW-CHANNEL SEGMENTATION: METHOD AND COMPARISON WITH MANUAL SEGMENTATION

Feng Zhuge, Sandy Napel, Smadar Shiffman and Geoffrey D. Rubin

Purpose

To develop and validate a semi-automatic system for precise segmentation of the human aortic flow channel from CT angiography (CTA) scans.

Material and Methods

Our method consists of two components: the "locator" and the boundary "outliner". The locator finds the approximate area of the flow channel; and the outliner decides the final position of edge voxels within the area provided by the former. For the locator, the user provides a single seed point per patient inside the aorta. The output of the locator is obtained via 3D region growing constrained by intensity and variance, followed by binary image operations. Next, the outliner finds edge candidates based on gradient magnitude, direction and neighboring intensity information. Finally, an edge tracing technique is applied to the candidates to outline the lumen. In the absence of a gold standard for the boundaries of human aortas in vivo, we compared consistency, defined as the overlapped area of a pair of segmentations divided by the average area of the two, between computerized and human expert results. We processed 16 patient CTA volumes with our method, and randomly selected 30 CT images to be used as the test dataset. 5 radiologists independently performed manual editing on these images using an Advantage Windows Workstation (G.E. Medical Systems, Milwaukee, WI) with the available tools. We applied a test of equivalency to reject the null hypothesis (H_0) that the expected difference between consistency amongst radiologist-pairs and computer-radiologist pairs is > ?, where ? = 3% of the average consistency measurement. H_0 can be rejected with ? =0.05 and ? =0.08 if the equivalency statistic is less than –1.96.

Results

The mean ± s.d. of the inter-radiologist consistency was 0.970 ± 0.029; and that of computer-radiologist was 0.959 ± 0.024. These result in an equivalency statistic of –2.54, which rejects H_0 with a two-sided p of 0.01 based upon the normal distribution. Manual editing required a mean operator time of 32.5 s/image while our method required negligible operator time (a single "click" per volume) and 3.9 s/image of processing time on Octane-2 (SGI, Mountain View, CA) with 2 360 MHz processors.

Conclusion

Our method performs comparably to expert humans using existing tools for manual segmentation of the aortic flow channel in CTA scans, but requires significantly less time and effort. It is likely to be applicable to other blood vessels and to volume data from other modalities, such as MRA and ultrasound.

MOVE TO A CURE

Lorenzo Torresani, Danny B. Yang,
Eugene J. Alexander, Christoph Bregler and Helen Bronte-Stewart

Purpose

Dystonia is an involuntary movement disorder, characterized by uncontrollable writhing and fixed abnormal movements. Deep Brain Stimulation (DBS) has proven an effective tool in reducing the symptoms of dystonia. The patient undergoes a surgical procedure in which neurosurgeons strategically place an electrode deep inside the brain. When turned on, the electrode delivers a continuous electrical impulse that can silence errant cells in the brain responsible for the symptoms of the disease. The challenge is to determine which neurons to target without harming nearby structures. To achieve this goal requires technologies capable of recording and reporting the firing patterns of single neurons synchronously with 3D kinematic information on limb movements. Our contribution to this project is the design of a multi-camera high-speed human motion capture system that can be used as an aid for kinematic analysis in a surgical setting. The proposed solution is a marker-less vision based algorithm capable of recovering the motion of deforming objects without prior knowledge of their 3D shape. From the apparent motion of the pixels, the optical flow, computed with this technique the non-rigid 3D structure is derived using a reconstruction algorithm developed by the authors.

Material and Methods

This work addresses the problem of 3D tracking and model acquisition of non-rigid human motion in video sequences. Standard low-level tracking schemes usually fail due to local ambiguities and noise. Most recent approaches overcome this problem with the use of a model, for instance an approximate kinematic chain. These models lose many details and consequently have difficulty in correctly estimating the motion of non-rigid torsos, deforming shoes, and in general any type of deformable body motion. We are interested in these cases where the existing models are too restricted and would not be able to recover all subtleties. The input to our technique is a single-view video recording of an arbitrary deforming object and the output is the 3D motion AND a 3D shape model parameterized by its modes of non-rigid deformation. Our solution exploits the assumption that a non-rigid 3D object undergoing rotation and deformation can be effectively approximated using a linear combination of 3D basis shapes. This puts a bound on the rank of the tracking matrix. The rank constraint is used to achieve robust and precise low-level optical flow as well as to recover the 3D non-rigid structure.

Results

The tracking and 3D reconstruction systems have been tested on a variety of video sequences. Results can be found on the project web page. In the near future we are planning to apply the algorithm to recordings of patients with dystonia.

Web Page

http://movement.stanford.edu/nonrig

AN AUTOMATED METHOD TO QUANTIFY AIR TRAPPING IN OBSTRUCTIVE PULMONARY DISEASE

Zhu June Hongyun, Michael L. Goris and Terry E. Robinson

Purpose

There are reasons to believe that some forms of obstructive pulmonary disease may progress early locally with later effects on global pulmonary function tests. One expression of the disease is the presence of air trapping distally of bronchial branches too small to be evaluated directly. In CT images regions with air trapping appear as regions of low density. The detection of this is an easy visual task for a radiologist, but not its reproducible quantification of it. Our aim is to develop a quantitative and operator independent method to evaluate air trapping and to demonstrate that the measure is more sensitive than global pulmonary function tests.

Material and Methods

The method utilizes high resolution CT images. Six closely corresponding slices acquired in full inspiration and expiration are analyzed for each patient. The analysis consists of an automated segmentation of the lungs, and then, within the lungs, the identification of contiguous low-density regions. Low density is defined on the basis of the distribution of densities in the expanded lung. Contiguity is defined on the basis of a median filter. The analysis yields the quantity of air trapping expressed as a percentage of the expanded or compressed lung volume.

Results

In a set of 15 patients and 5 controls, the percentage of air trapping volume correlated with global pulmonary function loosely, but more precisely discriminated between affected and unaffected patients. In none of the cases did lung segmentation or air trapping definition fail.

Conclusion

Our method of analysis would be well suited to evaluate early disease and small evolution in disease in an objective manner.

MECHANOBIOLOGY OF SOFT SKELETAL TISSUE REGENERATION: A MATHEMATICAL APPROACH FOR DESCRIBING MATERIAL PROPERTY CHANGES DURING SOFT SKELETAL TISSUE FORMATION

Loboa Polefka EG, Wren TAL, Beaupré GS and Carter DR

Introduction

Mesenchymal tissue is capable of differentiating into a variety of soft skeletal tissues. It is known that mechanical stresses play a role in this process, however, the mechanobiological mechanisms affecting material property adaptations during differentiation are not completely understood. We implement a fiber-network reinforced, poroelastic model[1] of mesenchymal tissue to introduce an analytical model describing the differentiation of mesenchymal tissue in response to simulated applications of tensile stress and fluid pressure.

Methods

Using a time-dependent algorithm (Fig. 1), we simulate changes in three material properties of differentiating mesenchymal tissue: tensile elastic modulus (E_t), compressive aggregate modulus (H_A), and permeability (k). In this approach, fluid pressure and tensile strain regulate changes in k, H_A, and E_t in differentiating tissue through their effects on proteoglycan synthesis and collagen fibrillogenesis. Fluid pressure causes an increase in both proteoglycan and type II collagen synthesis, resulting in a decrease in k and increase in H_A due to the hydrophilic nature and large size of the aggregating proteoglycans. It further causes a slight increase in E_t due to the formation of type II collagen and increased aggregate modulus. Tensile strain increases collagen formation, resulting in an increase in E_t due to the elevated number, size, and cross-linking of collagen fibers and a decrease in k due to the increased flow path length..

Results (Table I)

The simulations predicted the largest increases in tensile elastic modulus during differentiation into fibrous tissue and the smallest with differentiation into articular cartilage. Final permeabilities exhibited a reverse trend from tensile elastic moduli results with articular cartilage having the highest permeability and fibrous tissue the lowest. The aggregate modulus exhibited no change during differentiation into fibrous tissue but attained its maximum value during differentiation into articular and fibrocartilage.

Conclusion

We have presented a computational approach for simulating the effect of mechanics on material property adaptations during mesenchymal tissue differentiation. Our algorithm calculates final values of tensile elastic modulus, aggregate modulus, and permeability for articular cartilage, fibrocartilage, and fibrous tissue that are consistent with what has been observed in experimental studies. Our time-dependent model provides a framework for describing material property adaptations during the full process of mesenchymal tissue differentiation and provides principles to help explain the formation of different types of soft skeletal tissue during this process.

References

1. Li et al (1999) Clin Biomech 673-682.

Web Page

http://guide.stanford.edu/People/loboa/BCATS2001/

MEDICAL IMAGING USING CAPACITIVE MICROMACHINED ULTRASONIC TRANSDUCER ARRAYS

Jeremy Johnson, Ömer Oralkan, Utkan Demirci, Sanli Ergun, Mustafa Karaman and Pierre Khuri-Yakub

Purpose

We are investigating the use of capacitive micromachined ultrasonic transducers (cMUT's) for use in medical imaging. A proposed probe architecture is designed to provide real-time volumetric ultrasound imaging from within an endoscope channel to assist minimally-invasive surgery. We present our current work towards this effort.

Material and Methods

An experimental system has been constructed to acquire RF A-scans of phantoms using cMUT arrays. The data acquisition system consists of four circuit boards: array fan-out, DC bias, RF switching and ADC. The array fan-out board contains the connections from the cMUT array to the DC-bias board on which the DC biasing of the cMUT cells is handled. The RF-switching board performs transmit/receive switching, multiplexing of transducer channels, and signal pre-amplification. The ADC board is a 4-channel data acquisition PCI card that digitizes RF signals from 4 parallel channels at 20 MHz with 12-bit resolution. Custom software running on a PC controls the overall acquisition process. A single element can be selected for transmission and four elements for reception, allowing 4 A-scans to be acquired simultaneously. A complete data set is formed by collecting A-scans from all possible transmit/receive element combinations. The acquired RF echo signals are stored for offline digital processing.

Beamforming and image formation algorithms that aim to reduce the complexity of data acquisition hardware are tested via numerical simulations and using real data acquired from our system.

Results

The received A-scans are used to test the bandwidth and sensitivity of the cMUT arrays. To emulate digital imaging systems with cMUT arrays, we have reconstructed B-scan images of a wire phantom using the raw RF data sets. The images provide a qualitative basis for evaluating the general performance of the system. Quantitative measurements are also made from the images, including point and contrast resolution, and image SNR. These measurements are compared for classical full-phased array and for a method called multi-element synthetic aperture.

Conclusion

As part of our effort to build a miniature volumetric ultrasound imaging device, we have constructed an experimental system for testing the imaging ability of cMUT's. Transducer characteristic measurements show that cMUT's have a wide bandwidth and high sensitivity. Images have been reconstructed from transducer pulse-echo data, and image characteristics such as the point and constract resolution have been measured. The measurements show that cMUT arrays are promising for real-time volumetric medical ultrasound imaging.

AN ADVANCED VISUALIZATION TOOL FOR GENE EXPRESSION

Tuan Pham, Amit Kaushal, Eran Segal, Nir Friedman and Daphne Koller

DNA microarray technology is currently producing a wealth of gene expression data on genome-wide scale. Much work has focused on clustering genes and experiments with similar expression level. Most methods perform clustering of genes and experiments separately and then combine the results. Recently, there has been growing interest in "two-sided clustering" methods that are able to cluster genes and experiments simultaneously, thereby revealing relationships that exist between genes only over subset of the experiments. In addition, there is also growing interest in methods that can incorporate other sources of information into the analysis such as sequence data, functional information about genes, experimental parameters and more. Computational tools and algorithms that address these challenges are rapidly being developed.

For a computational tool to be useful, it must present the analysis in a format easy to understand and manipulate. We developed a visualization tool for gene expression that supports two sided clustering as well as visualization of additional gene and experiment specific attributes that may have been used in the analysis, allowing researchers to effectively focus on the relevant aspects of the computational analysis. To make the tool broadly applicable, the input is in XML format and can readily display clustering results from many types of algorithms. The program offers three different views of the clustering algorithmic output. Interaction with any of the views updates all views to the correct context, providing the relevant data in all views concurrently.

The first view is a tree browser like view, allowing the user to view the clustering in a hierarchal fashion, which is among the most popular displays of expression analysis to date. The nodes of the tree offer information on clustering splits as well as the path that was followed to arrive at the specific node. The second view is a global image of the clustering hierarchy. This view provides an overall picture of the clusters that were formed by the algorithm. The third view is a zoomed-in view of the currently selected cluster. This view provides information regarding which genes & experiments belong to the particular chosen cluster. Moreover, gene and experiment attribute annotations and their values are displayed next to the expression data. Emphasis was put on controls that allow the user to customize display settings such as image size, fonts, colors, expression intensity thresholds and more. Snapshots of the software can be viewed at:
http://robotics.stanford.edu/~erans/tsc_files/frame.htm

SEMI-AUTOMATIC IDENTIFICATION OF RETINOTOPIC VISUAL AREAS

R.F. Dougherty, V.M. Koch, A.R. Wade, B. Fischer and B.A. Wandell

Purpose

Viewing certain periodic visual stimuli (such as a rotating textured wedge or expanding ring) creates traveling waves of neural activity in the visual cortex that can be measured with fMRI. These measurements, which can be acquired in a half-hour session using a standard MRI scanner, can be used to identify the retinotopic visual areas in an individual subject's brain. The traveling waves are much easier to visualize on a flattened representation of the cerebral cortex than other standard representations, such as slices or 3-dimensional reconstructions. Therefore, 2-dimensional images representing computationally flattened cortex are used to identify the retinotopic visual areas. These areas are typically identified by subjective visual inspection of the data.

Material and Methods

We have developed and implemented a general approach for fitting a pair of two-dimensional parameterized models (the atlases) to the measured fMRI signals. The atlases represent the expected patterns of activity found in visual cortex of subjects viewing the expanding ring and rotating wedge stimuli. The 'ring' atlas models the central-to-peripheral organization of the cortical retinotopic map and the 'wedge' atlas models the polar angle organization of this map. To identify the retinotopic visual areas, these two atlases are coarsely aligned with the measured signal by hand. Then, the atlases are simultaneously elastically deformed to fit the measured data by minimizing both the difference between each atlas and its associated measurement image and the strain energy of the deformation field[1].

Results

Once the best-fitting atlases are computed, we can overlay the visual areas from the deformed atlases onto the measurements. Thus, the retinotopic visual areas can be objectively and automatically identified based on the traveling wave data. The visual areas found by the program are similar to those generated by an experienced human operator.

Conclusion

We have developed a set of tools to identify retinotopic visual areas in a simple, automatic, and objective way from functional Magnetic Resonance Imaging (fMRI) data.

References

1. Fischer, B. and Modersitzki, J. (1999) Fast Inversion of Matrices Arising in Image Processing. *Numerical Algorithms 22*; 1-11.

Web Page

http://white.stanford.edu/projects/mrFindBorders/

PROGENETIX.NET: STORAGE AND VISUALIZATION OF GENOMIC ABERRATION DATA IN HUMAN MALIGNANCIES AS STARTING POINT FOR DATA MINING PROCEDURES

Michael Baudis

Purpose

Publications in the field of (molecular-)cytogenetics are notorious for their variation in the format of the communicated data, although standards had been set by the ISCN (1). Up to now, no online source for CGH (Comparative Genomic Hybridization) data with a standardized format suitable for data mining procedures has been made available for public access. Although previously genetic hotspots had been pinpointed through CGH experiments, such a data repository could be valuably in identifying genetic aberration patterns with linkage to specific disease entities, and provide additional information for filtering data from expression array experiments.

A case and band specific aberration matrix was selected as most suitable format for the mining of CGH data. Data acquisition and transformation for the [progenetix.net] repository (2) consist of several steps, which are briefly described in their current implementation.

Material and Methods

1. PubMed is searched for publications applying CGH to the analysis of malignant tumors. Articles are selected according to their online availability and the description of genomic imbalances on a per case basis.
2. Chromosomal aberration data are transformed from the various styles communicated in the publications to a common format adherent to ISCN 1995 recommendations. In some instances, data is provided by the authors or transcribed from ideograms.
3. Currently, the primary data is stored in a dedicated "off-line" database. Besides case identifier and ISCN adapted chromosomal imbalance data, tumor classification and source information including the PubMed identifier is recorded. Disease entities are reclassified to ICD-O-3 codes.
4. For the generation of the case and band specific aberration matrix, a dedicated text pattern comparison model was developed using Perl. A matrix with 324 band resolution is generated, annotating chromosomal gains with "1" and losses with "-1".
5. Band specific graphical overviews of chromosomal imbalances as well as chromosome specific pages are generated for each registered project as well as for each ICD-O-3 entity and for several subsets (e.g. all lymphoid neoplasias, breast carcinoma cases); the according aberration matrices are linked for download.

Results

In the current implementation, two main purposes are being served. First, access to the band specific pattern of chromosomal imbalances allows the instantaneous identification of genomic "hotspots". Second, the band specific aberration matrices can be included in data mining efforts. As an example, the clustering off all informative cases from the current (September 2001) dataset can be found under www.progenetix.net/bcats/clustered.png.

References

1. Mitelman, F. (1995). ISCN (1995): An international system for human cytogenetic nomenclature. Basel, Karger.
2. Baudis M and Cleary M. Progenetix.net – An online repository for molecular cytogenetic aberration data. *Bioinformatics* (in press).

CORRECTION OF MOTION ARTIFACTS IN THREE-DIMENSIONAL CT-DSA USING CONSTRAINED ADAPTIVE MULTI-LEVEL FREE-FORM REGISTRATION

Torsten Rohlfing and Calvin R. Maurer, Jr.

Purpose

Digital subtraction angiography (DSA), the subtraction of pre- and post-contrast images, has been a valuable tool in vascular diagnosis for years. One problem with the technique is its susceptibility to patient motion, especially when applied to 3D data such as CT. High intensity gradients such as skin-air and bone-soft tissue interfaces cause severe artifacts after even minor patient movement. Rigid registration can improve results, but more powerful methods are required in highly deformable anatomical regions such as the neck or abdomen.

Material and Methods

We have developed a non-rigid registration algorithm based on mutual information. Tissue motion is described by a free-form deformation using B-spline interpolation between uniformly spaced control points. We incorporated several improvements over related methods: Using multilevel B-splines our method is capable of capturing both large and small deformations. Second, the deformation is constrained by a volume-preservation criterion based on the Jacobian determinant of the transformation. Its purpose is to protect vessels from being shrinking during non-rigid registration, as contrast uptake between pre- and post-contrast images represents the kind inconsistency that intensity-based registration algorithms are designed to eliminate. To assess the usefulness of our method, it was applied to clinical CT images. Subtraction images were generated after both rigid and non-rigid registration and rendered in 3D by maximum intensity projection.

Results

Subtraction images showed spectacular improvements by our method as compared to rigid registration. The deformation constraint successfully prevented contrast-enhanced structures from shrinking. The ability of the deformation to compensate for motion artifacts was not reduced. The constraint was found to be insensitive to the choice of its weight relative to image similarity. Computation times were sufficiently small to allow routine application of our method (about 1 hour on a Sun UltraSparc at 400 MHz for two 512x512x50 images).

Conclusion

We have developed a fast and robust intensity-based non-rigid registration algorithm that leads to a dramatic reduction of motion artifacts in CT-DSA. The incompressibility constraint eliminates the problem of contrast-enhanced structures collapsing during non-rigid registration. Our method is the first that employs the Jacobian determinant during the registration process. It enforces tissue incompressibility without constraining the shape of deformed structures. This allows a potentially more realistic registration of soft tissue. Our method is fully non-interactive and efficient on standard workstations and is therefore suitable for routine clinical application.

GENOME INTERSECTION ANALYSIS: A NEW MEANS OF IDENTIFYING BIOLOGICAL PATHWAYS

Theodor Hanekamp, Iwei Yeh and Russ Altman

Purpose

Facilitating experimental research, extracting new knowledge from genome databases, identifying potential drug targets and gaining new insights on the evolution of pathways are the main purposes of this analysis. (1) Currently identification of new biological pathways is exclusively in the hands of experimental scientists. The methods applied to identify pathways are generally labor-intensive and often require a series of relatively expensive biochemical or genetic experiments that may take months or years, before a pathway is completely analyzed. Numerous pathways have been partially characterized and identification of missing components can be exponentially difficult. (2) Whole genome analyses allow the assignment of protein functions based on sequence similarities. However, a large number of these homologs cannot be placed in any biological pathways. Furthermore, several pathways have been completely characterized biochemically, and the complete genomic sequence is available. Nevertheless, in some cases genes encoding these components could not be identified. (3) Among other criteria good drug targets constitute components in sensitive pathways that are essential for the survival and unique to that pathogen. (4) While molecular evolution of individual proteins is a well-established research area, little is known about evolution of entire pathways.

Material and Methods

Genome Intersection Analysis (GIA) is a relatively fast computational approach that combines whole genome protein sequence comparisons and clustering techniques to group proteins into units that may constitute protein complexes, metabolic or non-metabolic pathways. Currently we are using existing clustering methods, such as Cleaver (http://classify.stanford.edu/k-means.html) to analyze our data sets. We are in the process of developing an algorithm based on nested sorting to identify protein clusters that will facilitate the identification of pathways.

Results

We have used annotated gene products of the incomplete *Plasmodium falciparum* genome to identify protein homologs in 48 completely sequenced genomes. The largest genome intersections are shared between *P. falciparum* and other eucaryotes, while archaebacteria share the least number of proteins with *Plasmodium.* Although potential new biological pathways have been identified, we are currently focused on the identification of already characterized pathways to test the validity of our approach.

Conclusion

This project is still in its initial phase, yet we can make several conclusions. First, an added benefit of our approach is the identification of potential gene duplications in *Plasmodium*, as the encoded gene products end up in the same protein clusters. Second, the number of eucaryotic genomes is too small to generate genome intersections that are small enough to form protein clusters that may represent individual pathways.

References

1. Raychaudhuri S, Sutphin PD, Chang JT, Altman RB. Basic microarray analysis: grouping and feature reduction. *Trends in Biotechnology*. 19:189-193, 2001.

CURVED THIN SLAB MAXIMUM INTENSITY PROJECTIONS (CTS-MIP): METHOD AND EVALUATION FOR CT ANGIOGRAPHY

Raghav Raman, Sandy Napel and Geoffrey D. Rubin

Purpose

The Maximum Intensity Projection (MIP) algorithm is commonly used as a 3D postprocessing method to depict vascular anatomy. As the thickness of the projected volume increases, contrast is lost due to the inclusion of excessive soft tissue. We aimed to develop and validate a new method of producing optimal high contrast MIPs by automatically specifying a curved thin slab (CTS-MIP) enclosing only vessels of interest while maximally excluding extraneous tissue.

Material and Methods

Following user selection of vessel start and endpoints, CTS-MIP computes their median centerlines and produces MIPs using a curved branching slab that parallels the centerlines, with thickness adaptively adjusted to enclose the vessels of interest. To evaluate our algorithm, we transferred CTAs from 4 consecutive patients (3 male, mean age 64 yrs) with abdominal aortic aneurysms to our offline workstation, and selected six arteries (celiac, superior mesenteric, bilateral renal and bilateral aortoiliac arteries) from each patient. Standard clinical thin slab (TS) MIPs were produced through each vessel for these patients by 3D technologists and CTS-MIPs were produced at orientations identical to those for TS-MIPs. In addition, composite CTS-MIPs including multiple vessels were produced for each patient.

The time required to produce images by both means was recorded. Arterial contrast was quantified by comparing pixel intensity along the central axis of the vessel to the intensity of background pixels 0.5 mm from vessel edges. The full vessel width at half maximum intensity was measured for both CTS- and TS-MIP. Measurements were compared using two-tailed paired t tests.

Results

CTS-MIP excluded 87% of the soft tissue present in standard TS-MIP ($p<0.0001$). While central vessel intensity was identical, background intensity in CTS-MIPs was decreased by 0 - 680 HU (mean 62.4 HU, $p<0.0001$), improving mean arterial contrast to 216.1 HU from 153.7 HU (Fig. 1). Vessel width in TS-MIP was reduced by 0.12-1.09 mm with a mean decrease of 0.47 mm (95% CI 0.44,0.50, $p<0.0001$). Following extraction of the median centerline, specification of the curved slabs required 9 ± 3 s per patient, compared to 150 ± 24 s required by technologists to produce TS-MIPs. To display all vessels, 7 TS-MIPs were required per patient compared with 3 composite CTS-MIPs (Fig. 2).

Conclusion

CTS-MIP has increased contrast compared to TS-MIP due to reduced background intensity. A corresponding reduction in vessel narrowing may reduce overestimation of stenoses, common in MIP images. Our method enables multiple vessels to be included in each image without including excessive soft tissue and high attenuation bone. This method has the potential to reduce the time required to assess CT angiograms with MIPs.

Web Page

http://bigred.stanford.edu/bcatsmip/default.asp

WAVELET CENSORING FOR STATISTICAL ANALYSES OF BRAIN WAVES

Marcos Perreau Guimaraes, Patrick Suppes and Dik Kin Wong

Purpose

In previous papers [1] we have presented optimal filtering methods to classify language related EEG events. To improve the classification results we propose a censoring of the EEG signal using a wavelet transform.

Material and Methods

In an experiment using mandarin words with four subjects we presented 800 trials of 8 words to each subject. Each mandarin word is represented 100 times in a random order to build the 800 trials. The experiment is repeated three times with different modalities of presentations of the words: visual images, visual words and auditory words. EEG signals are recorded on 22 channels during each experiment.

Here a quarter of the data is taken to build the prototype data, which is used to classify the other 3/4 of the data, the test data, split in 3 equal sized bins. The classification rate, the number of words correctly classified, is then a number ranging from 0 to 24. Classifications are done within a modality (prototype and test trials belong to the same modality) and across modalities (prototype and test trials belong to different modalities).

In the classical censoring means and standard deviations across the trials are computed for each triple (word, channel, observation). All observations out of A standard deviations from the mean are excluded before the classification. The best parameter A is estimated by running a grid.

In the wavelet censoring method each trial is transformed by an orthogonal wavelet transform [2]. Means and standard deviations of the wavelet coefficients are computed for each quadruple (word, channel, scale, shift). For each trial, wavelet coefficients are excluded with the rule defined above. Then an inverse wavelet transformation gives back a regularized signal, which is classified. The censoring is performed for both prototype and test data.

Results

The results with the standard method for intra modality adding all the subjects are: 20/24 for visual images, 10/24 for visual words and 22/24 for auditory words. The best result for cross modality is 13/24 for visual words versus auditory words. With the classical observation censoring results improve to 21/24, 14/24, 24/24 and 17/24 in the same order as above. The results are consistently higher with the wavelet censoring, always better or equal, with 24/24, 15/24, 24/24 and 18/24.

Conclusion

These results show that wavelet transforms combined with classical statistical tools help in our classification problem.

References

1. Suppes P., Han B., Epelboim J., Lu Z. L. Invariance between subjects of brain wave representations of language. PNAS. Vol 96. No 22. Oct. 1999.
2. Mallat S. a wavelet tour of signal processing. Academic press. 1997.

HANDHELD ACCESS TO RADIOLOGY TEACHING FILES: AN AUTOMATED SYSTEM FOR FORMAT CONVERSION AND CONTENT CREATION

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Purpose

Handheld computers (PDAs) have enjoyed an ever increasing penetration into the medical arena. Current PDAs are capable of image display and are ideal for the distribution of radiology teaching files, but existing medical images are often stored in varying formats and locations. We have developed a suite of tools that allows the creation of annotated radiology teaching files in handheld format from existing repositories of medical images in DICOM and other image formats.

Material and Methods

Our toolkit incorporated a desktop application, a web conversion server and viewer software for commercial handheld devices running the Palm (Palm Inc, Santa Clara, CA) and Windows CE (Microsoft Corp., Redmond, CA) operating systems. Our toolkit was deployed on a networked Windows workstation that was registered on our hospital medical image database (PACS) system as a DICOM receiver. Our conversion server allowed network access to the functionality of the desktop application and our custom viewer provided radiology–specific functionality including image library organization, window/level manipulation and viewing of information specific to images. We evaluated our system by obtaining 40 DICOM images (20 magnetic resonance (MR) and 20 computed tomography (CT) images) from the hospital PACS system and our preexisting teaching file database. An annotated subset of test images was processed and converted into handheld format teaching files and then transferred to commercially obtainable handheld devices to provide proof of concept and demonstrate functionality.

Results

The only parameter required for desktop and server processing was the target handheld device. Image processing was automatically customized for each type of medical image and each handheld device. DICOM source images were processed by optimizing the window/level settings to maximize contrast resolution. Patient information was anonymized. Selected information from the header was included in annotations and images were automatically organized into handheld teaching files. Our server application could produce teaching files from web clients running the Windows, Macintosh or Unix operating systems. Teaching files were then transferred to handheld devices using wired and wireless transfer and compatible expansion media, and were then available categorized by content.

Conclusion

We present a usable and simple set of tools to merge disparate repositories of radiological teaching file content to produce organized teaching file packages that can be viewed on handheld devices. The incorporation of a web interface allows platform-independent access. The distribution of handheld-compatible radiology teaching files has the potential to increase the availability and effectiveness of radiology teaching.

Web Page

http://bigred.stanford.edu/bcatspalm/default.asp

AN INTERACTIVE APPROACH TO INDIVIDUALIZING GENERIC MEDICAL DECISION MODELS

George C. Scott and Ross D. Shachter

Purpose

Complex decision models in an expert system often contain utilities and probabilities for entire populations or demographic subgroups. In order to apply a generic decision model to an individual, the model should be customized to the individual's specific quantities. Quantities, such as personal probabilities and preferences, cannot be observed and can only be estimated using formal assessment techniques. This process can be unreasonable and inconvenient for practical decisions. In addition, although we barter goods and services for money every day, we rarely make decisions between length and quality of life. This makes information that we do obtain noisy and erroneous.

Methods

We propose an interactive approach for efficiently improving our knowledge about quantities for specific individuals given a prior joint distribution of their quantities and a decision model. The quantities are maintained as log-odds of the assessed values in a multivariate Gaussian distribution. We define the concept of value of elicitation and use it to determine dynamically the optimal sequence of elicitations for a given individual. After each elicitation, we determine the next most valuable assessment to make taking into account both the value of the assessment and its assigned cost. We continue to elicit information from the patient until the net expected benefit is less than its expected cost.

Results

We evaluated the algorithm using a decision model for treatment of benign prostatic hyperplasia (Cher & Lenert, JAMIA, 1994). We simulated six groups of 1000 patients each. The simulated populations were assigned parameter values randomly sampled from the population priors used to develop the model. Each assessment was assumed to have a variance of 0.02. There were eleven possible quantities that could be assessed for each patient. We establish a threshold for stopping to be 0.01 quality-adjusted life months. The number of assessments needed ranged from 1 to 7 (1.68±0.99). Quantities were assessed anywhere from 0 to 4 times resulting in a final value of elicitation of 0 to 0.01 (0.0031±0.0034) quality-adjusted life months.

Conclusions

We believe that the study results indicate that it is possible to individualize a generic decision model to a given patient in an efficient manner by dynamically ordering the assessment of quantities according to the net benefit an additional elicitation is expected to provide. By intelligently selecting the order of assessments, and possibly re-assessing quantities, based on their net value of elicitation, it might be possible to make the use of generic decision models practical on a patient-by-patient basis.

SKOLAR CARDS - MOBILE ACCESS TO HIGH QUALITY CLINICAL INFORMATION

Jeremy C. Durack, Todd Grappone, Scott Kush and Al Nevarez.

Purpose

Stanford SKOLAR™, Lane Medical Library, and the Stanford School of Medicine Palm Project team have joined in a collaborative effort to improve access to high-quality clinical information at the point of patient care. We have developed an application that enables Stanford clinicians and medical students to upload personally selected pieces of medical information found as a result of using Stanford SKOLAR MD's online medical knowledge system. Our goal is to study the type and extent of use, as well as the potential clinical benefit of the "SKOLAR Cards" application within the Stanford medical community.

Material and Methods

The "SKOLAR Cards" application allows any user of the SKOLAR Internet browser-based content delivery system to quickly and easily upload medical information to their PDA device. Dynamically generated web pages are displayed on a Personal Digital Assistant (PDA) using the AvantGo PDA browser platform.

A physician or medical trainee first utilizes Stanford SKOLAR's integrated knowledge search engine to retrieve medical information on a desktop computer. Customized selections of text can quickly instantiate a new SKOLAR Card. Cards are organized on the PDA device in a fashion consistent with the SKOLAR search result interface (Textbooks, Drug information, Medline, Journals, Evidence Based Medicine, Guidelines, Patient Education). SKOLAR Card content will be delivered to the PDA on a subsequent data synchronization with a desktop computer.

Results

The concept of providing personalized, mobile access to high quality digital information demonstrated by the SKOLAR Cards application is currently in prototype phase at the Stanford School of Medicine.

Conclusion

Our study is ongoing, but initial reactions to the utility of the service are very positive. Combining the relevance and comprehensive nature of Stanford SKOLAR resources with the portability of a PDA empowers the physician and medical student with medical knowledge that may be used in the context of patient care. The content delivered to the PDA is anticipated for future reference. Other medical PDA applications are often built upon limited information resources. These applications are useful for confined knowledge areas, such as drug information, but cannot bring the breadth and depth of SKOLAR's comprehensive medical knowledge base to the bedside.

USING BINNING TO MAINTAIN CONFIDENTIALITY IN PHARMACOGENOMIC DATABASES

Zhen Lin, Michael Hewett and Russ Altman

Privacy and confidentiality of medically related databases have been always a serious concern because of the fact that various parties can misuse information from these databases. Pharmacogenomic databases are particularly problematic since they contain not only a patient's clinical manifestations but also his genomic information, indicating his existing and future health status as well as health information about his relatives. We are interested in making available pharmacogenomic information online, while being sensitive to privacy and confidentiality issues. Our approach is to anonymize patients' de-identified data so that no patients may be uniquely identified from the database. We developed specific binning algorithms to generalize numerical as well as symbolic data from the database. The preliminary binning results show that it is possible to provide patients' information at different granularity, yet potentially be beneficial to research.

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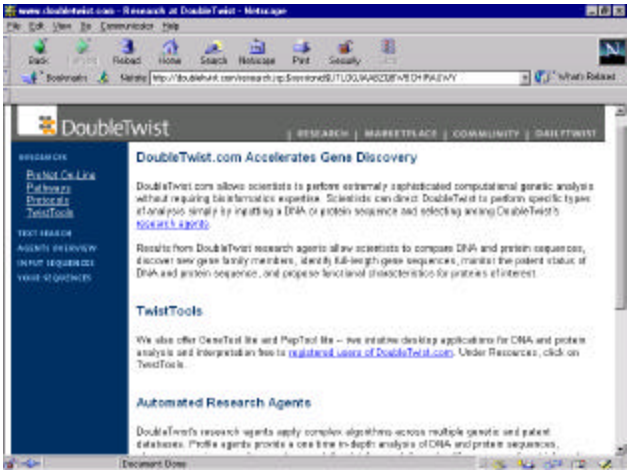

Incyte Genomics, Inc. has developed the leading integrated platform of genomic technologies designed to aid in the understanding of the molecular basis of disease. Incyte develops and markets genomic databases and partnership programs, genomic data management software, microarray-based gene expression services, related reagents and services. These products, programs and services assist pharmaceutical and biotechnology researchers with all phases of drug discovery and development including gene discovery, understanding disease pathways, identifying new disease targets and the discovery and correlation of gene sequence variation to disease. In addition, Incyte has the largest portfolio of issued United States patents covering human full-length genes and the proteins they encode and is leveraging its intellectual property position to be a leader in therapeutic discoveries.

The employees of Incyte, our greatest asset, provide the tremendous energy, talent and expertise that will enable us to help revolutionize health. We are looking for individuals who share our vision and want to play a role in defining the future. We offer competitive salaries, an outstanding benefits package including: 20 days PTO, matching 401K plan, domestic partnership coverage, full medical insurance, onsite cafeteria and fitness center to name a few as well as significant opportunities for professional growth. Incyte Genomics Inc. values the talents of our diverse workforce and is proud to be an Equal Opportunity Employer. EOE. F/M/V.

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Northern California Pharmaceutical Discussion Group

Since 1983 the NCPDG has provided a forum for the Bay Area pharmaceutical/biotechnology industry for development of the community and discussion of topics important to our industry. The NCPDG holds monthly dinner meetings that are attended by individuals representing every aspect of industry life and from nearly every pharmaceutical/biotechnology company in the Bay Area to hear talks on subjects ranging from genomics to contract manufacturing to financing company operations. Our unique combination of fellowship and education provides several material benefits to our members.

?? Opportunities for effective networking
?? Increased understanding of industry issues
?? Expanded knowledge of various pharmaceutical/biotechnology businesses
?? Self-Improvement and education

Your company can also take advantage of NCPDG involvement. Our membership spans the width and breadth of the pharmaceutical/biotechnology industry in the Bay Area and we regularly have presentors and attendees from as far away as Europe and Japan. By becoming a NCPDG Sponsor your company can gain increased visibility in the Bay Area and beyond while helping to support individual professional development. Benefits of sponsorship include:

?? Name exposure on our printed materials, web site and e-mail distributions
?? Tailored sponsorship opportunities
?? Distribution of job announcements and other materials at NCPDG meetings
?? Another way to help your employees develop professional and social skills

For more information on the NCPDG visit our web site, e-mail us at RSVP@NCPDG.ORG, or contact Ben Borson at (415) 362-3800, Eric Schuur at (650) 224-4178, or Helen Wang at (415) 922-3868.

WWW.NCPDG.ORG

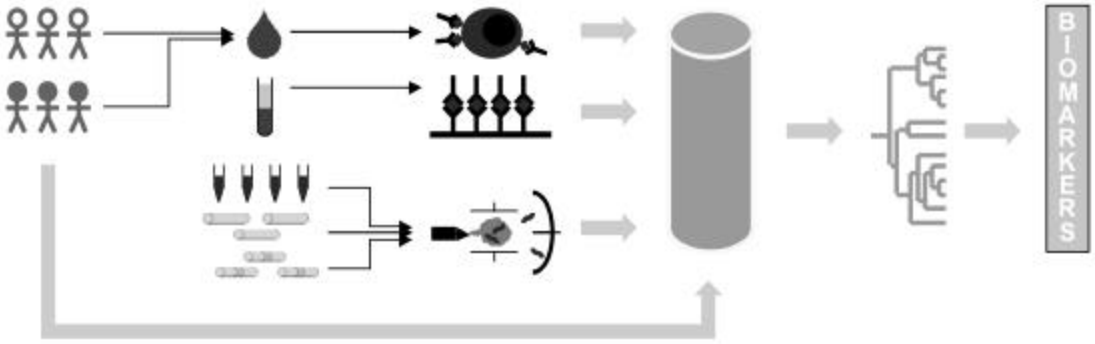
SurroMed

Comprehensive Phenotypic Analysis
Biological Marker Discovery
Integrative Biology

SurroMed, a privately-held, well-funded biotechnology company, is applying its integrated phenotyping and biological marker discovery platform to better understand the root causes of disease and the factors underlying patient-to-patient variations in disease presentation, progression and response to therapy. Discoveries arising from its research will enable the improved, cost-efficient discovery and development of therapeutic and diagnostic products. SurroMed's phenotyping and biological marker discovery platform incorporates advanced proprietary technologies for profiling and analysis of hundreds of immune cell populations, proteins and low molecular weight biomolecules in small volumes of blood and/or other biological samples. SurroMed captures and analyzes an enormous amount of clinical and biological information in a massively parallel fashion to identify useful biological markers. This integrative approach to disease phenotyping and biological marker discovery will enable the precise diagnosis and personalized treatment of disease.

SurroMed's strategy for discovering novel biological markers is to conduct comprehensive phenotyping studies in well-defined patient populations with specific diseases. The objective of these phenotyping studies is to capture comprehensive patient clinical data as well as bioanalytical information that can be analyzed and mined to identify novel biological markers and patterns.

SurroMed Informatics is responsible for the software, algorithms and databases used to capture, process, analyze, store and mine the data we collect in our clinical studies.



SurroMed captures comprehensive phenotypic information from patients at the molecular level - proteins and low molecular weight species - the cellular level - cell populations and cell surface antigens - as well as detailed clinical information. Data analysis and data mining tools are used to identify biological markers

SurroMed currently has positions available in its Informatics Department and in other research areas. Please visit our website for details.

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