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The Medical Image Display & Analysis Group at the University of North Carolina: Reminiscences and Philosophy

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The UNC Medical Image Display & Analysis Group (MIDAG) traces its history to Steve Pizer's PhD work in restoration of scintigrams at Massachusetts General Hospital in the middle 1960s. Indeed, the word "scintigram" did not appear in his dissertation and had not yet come into common usage at that time. These nuclear medicine images were the first targets of medical image computing simply because their 32 × 32 or 64 × 64 size made them the only medical images that could fit into the memories of the computers of the time. Done at roughly the same time as Robert Nathan's work at the Jet Propulsion Lab and Richard Robb's work at the University of Utah, the image processing system Pizer built on a PDP-7 in 1966-7 was one of the earliest pieces of medical image processing software; we are interested in hearing of earlier ones. Steve's dissertation research, done in collaboration with Henri Vetter, combined image processing and human vision research, a practice continued in MIDAG. The initial reason for involving human vision research was that the resulting images were to be viewed by humans, but later we also realized that understanding how humans analyzed images could give important hints at how to get computers to analyze them.

MIDAG has also promoted the fusion of image processing and statistics. This emphasis began in 1971, while Pizer was jointly at UNC and at MGH, still working on scintigraphic image restoration. He was invited to join the 2^{nd} conference in what later came to be called IPMI: International Conference on Information Processing in Medical Imaging. The invitation to present a paper there provided an opportunity to present and publish a method that Steve and Charles Metz, at the University of Chicago, were developing together, an idea that they thought, as it indeed turned out, would be quite useful for image processing. That IPMI paper (still in our files), CE Metz & SM Pizer, "Nonstationary and Nonlinear Scintigram Processing" described essentially what today is called the "EM algorithm", some years before the paper by Dempster et al. [1977] normally credited with that algorithm, although our paper did not have the strong probabilistic basis provided by Dempster et al. Unfortunately, the untimely death of the IPMI 2 organizer, Eberhard Jahns, led to the promised Proceedings of IPMI 2 never appearing and thus the Metz & Pizer paper never being published.

Another result of the IPMI invitation was an agreement between Steve Pizer and Andrew Todd-Pokropek that Steve would take a sabbatical in 1973-4 with Andrew at University College Hospital in London. Based on evaluation experiments led by Andrew, Steve had realized that the restoration improvements that were being obtained were largely washed out in the weak display approaches of the day. During his sabbatical he switched his research direction from restoration to medical image display, a decision leading to the initial directions of MIDAG.

When Steve returned to UNC in 1974, interdepartmental collaboration in medical image display led to what we now call the formation of MIDAG. Gene Johnston and Ed Staab had joined the UNC Radiology Department, coming from Vanderbilt. Their collaboration reflected what we take to be a central requirement of research in medical image computing: multidisciplinary collaborations between scientific and medical faculty and among a broad spectrum of disciplines in each. Within medicine the research needs contributions from the image acquisition, diagnostic, and therapeutic fields. Thus Radiology, Radiation Oncology, and Surgery, and more recently Psychiatry and Neurology have been central departments in MIDAG. Among the sciences the theories of physics, the theoretical underpinnings provided by mathematics and statistics, the experimental designs and tests of effectiveness provided by biostatistics, and the engineering and methodological approaches provided by computer science and biomedical engineering all form critical components. In MIDAG perceptual psychophysics has historically been an important discipline, as well.

Bringing scientists from all these disciplines together requires specific attention to easy interaction. Indeed in our case, this principle has been applied not only across disciplines but also between the nearby universities of UNC and Duke. Duke University faculty have been part of the MIDAG team for its whole life, providing expertise in neuroradiology, in the formation of ultrasound and MR images, and in statistics. Obtaining and keeping this spirit of cross-disciplinary collaboration has been a matter of constant awareness and action for the MIDAG leader. Having departments committed to cross-disciplinary collaboration and sharing of research budgets is a sine qua non. We have been blessed with chairmen especially of Computer Science, Radiology, and Radiation Oncology who have hewed to this philosophy. In Computer Science we have benefited from and adhered to the philosophy promulgated by its founding chairman, Fred Brooks, that the computer scientist is a toolsmith who is measured by the success of the users of his or her tools.

The period of MIDAG so far is 1974-2002: more than 27 years. We began with a focus on 2D display: contrast enhancement, display scale choice, and display device standardization. We co-invented adaptive histogram equalization and later improved it to Contrast-Limited AHE, and we were perhaps the first to show that adaptive contrast enhancement, i.e., care in the mapping between recorded and displayed intensity and variation of that mapping with the local properties of the image, could significantly affect diagnostic or therapeutic decisions: Julian Rosenman, Robert Cromartie, and Steve Pizer [1993] showed that with respect to portal images in radiation oncology, and Etta Pisano, Gene Johnston, Brad Hemminger, Steve Pizer, and Stephen Aylward [Hemminger 2001] showed that with respect to mammograms.

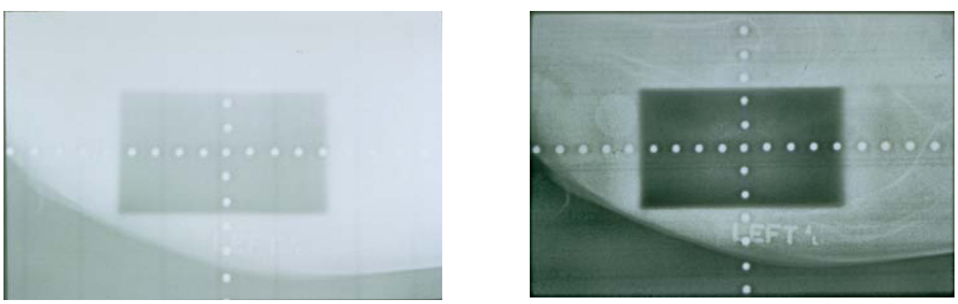

Fig. 1. An early clinical result of contrast enhancement [Rosenman 1993]: the fact that the penny taped to the patient during planning had inadvertently not been removed at the time of the first radiation treatment was not obvious in this portal image until the image underwent CLAHE.

The controlled studies of the effectiveness of certain contrast enhancement methods begun by John Zimmerman and continued by the just mentioned teams were perhaps the first to measure scientifically the effects of contrast enhancement (Figs. 1, 2). They were early exemplars of what we and the field now take to be critical components of research in medical image computing: evaluation of the techniques. These studies brought biostatistician Keith Muller into our team in 1989, and he has been an important cog ever since. Not only has he designed and supervised the analysis of the data from an enormous number of observer experiments analyzing the methods that we have developed, but he has also carried out important research in the statistical analysis of experiments with repeated variables, and he has supervised the research of many research assistants working on MIDAG-related projects.

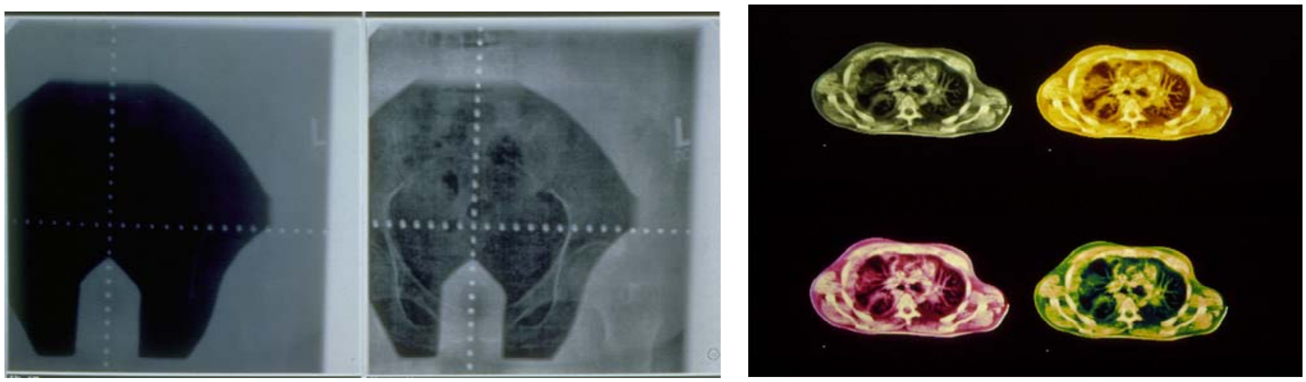

Fig. 2. Left: A pelvic portal image before and after CLAHE. This image was used in our experiment validating contrast enhancement [Rosenman 1993]. Right: presentations used in study of pseudocolor scales.

The display device standardization research has led to ACR-NEMA standards promulgated through the work of Brad Hemminger [DICOM 1998]. It was based heavily on the work in human vision that we carried out. Our Radiology Department may have been the first to have a “black room” for vision experiments (Fig. 3). Diane Rogers joined us after her UNC PhD in perceptual psychology, and our focus on visual psychophysics research continued for years, including Steve Pizer’s two sabbaticals with Jan Koenderink in Utrecht and his collaboration with Christina Burbeck [1994a] on medial models for the vision of objects (Fig. 4). These observer experiment techniques were also used in our multiyear study of the hypothesis that pseudocolor could produce display scales that would provide important increases in sensitivity to changes in medical image intensities. We believe that our negative result [Pizer 1995], that pseudocolor scales (Fig. 2) provided only small sensitivity improvements in controlled test image studies and no measurable improvements with real medical images was an important result for the field, albeit one still not learned by one and all.

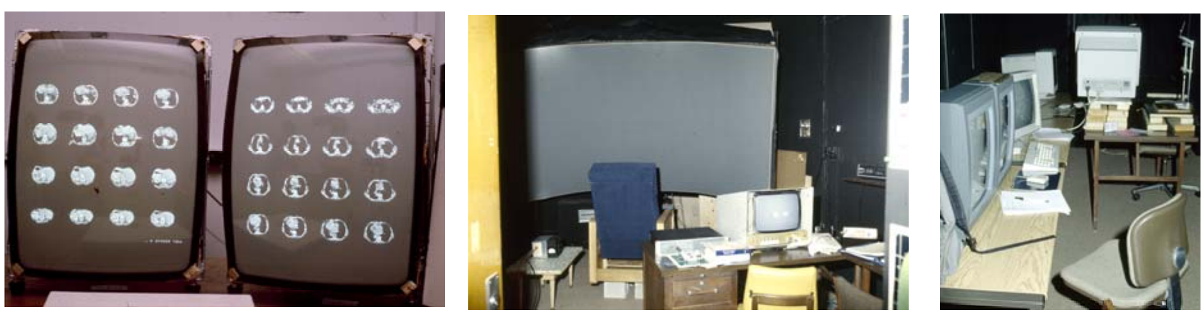

Fig. 3. Human vision apparatus used in early observer studies, from left to right: experimental 2K × 2K monitors we evaluated, the Radiology black room ganzfeld environment for observer studies, computer monitors for multi-monitor observer studies

Another example of the combination of vision research with medical image objectives was in Victoria Interrante’s dissertation study [1997] of how and whether to use texturing of transparent surfaces (Fig. 4) to understand the geometric relations between the two interpenetrating surfaces of a tumor and a radiation isodose locus. Also, our focus on medial models for the representation of objects, discussed more below, was heavily affected by our human vision studies that, together with the results of other visual scientists, convinced us that human perception of objects had a figural component (in 3D, figures are slabs or tubes).

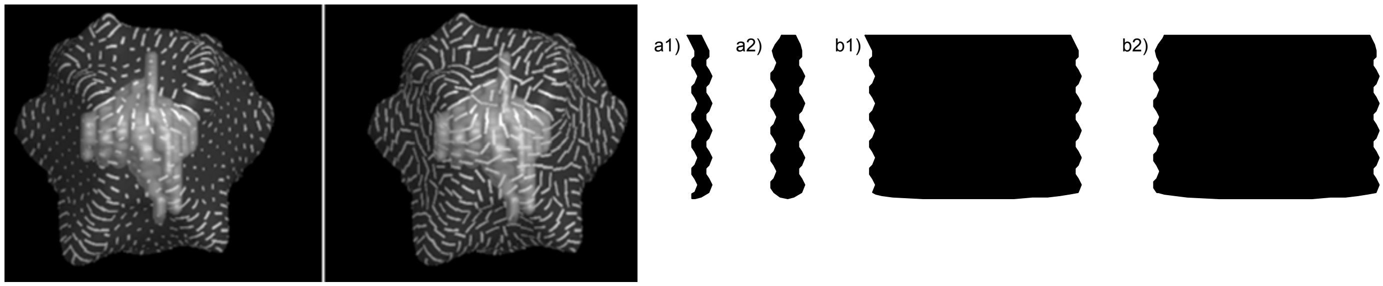

Fig. 4. Human vision figs: Left: test patterns used by Vicki Interrante to study understanding intersurface relations using textured transparent surfaces. Right: stimuli used by Burbeck & Pizer [1994b] to study effect of width on object perception.

Henry Fuchs's arrival at UNC Computer Science in 1978 brought us a new display focus: 3D. He, Steve Pizer, and Duke neuroradiologist Ralph Heinz began by investigating the usefulness of varifocal mirror display (Fig. 5) for images of the carotid artery and found 3D visualization to have merits but found that displays that failed to have occlusion produce too much visual clutter to be frequently useful. We also helped in evaluating 3D stereo display through polarizing plates (Fig. 5). We began working on rendered images (Fig. 6). Through the pivotal contributions of Marc Levoy, then a MIDAG doctoral student, new methods of rendering through ray casting (Fig. 6) were invented and began to be applied to radiation treatment planning, under the leadership of Julian Rosenman in Radiation Oncology. Radiation Oncology had split from Radiology, and from its very beginning, through the leadership of Ed Chaney, it had committed its research to a collaboration with Computer Science. This commitment was made real by decisions to buy common computer and display equipment; the Ikonas graphics systems that both Computer Science and Radiation Oncology installed were one the earliest raster graphics systems used in medicine. Together we adopted the principle suggested by Fred Brooks – using computers for *IA*: Intelligence Amplification was more fruitful than using it for *AI*: artificial intelligence.

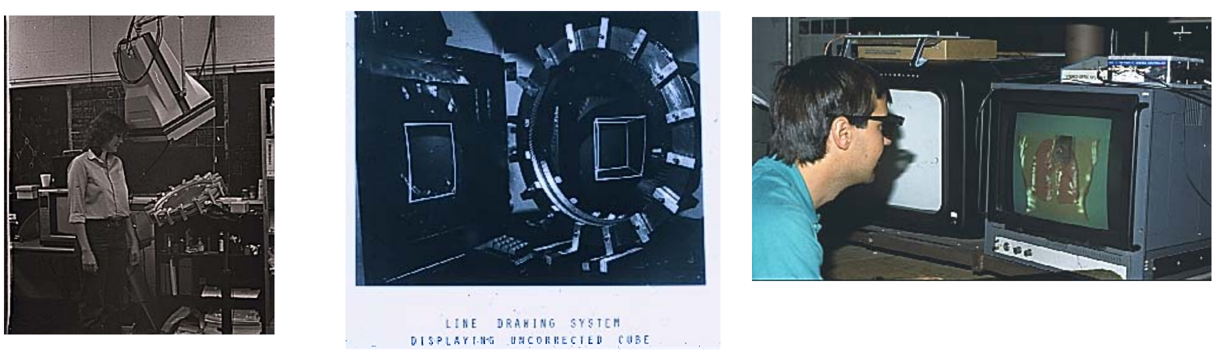

Fig. 5. Varifocal mirror (with Marcia Hunt) and stereo display (with John Gauch)

The "computorium" that grew from this commitment in Radiation Oncology became an important incubator for other medical image display and analysis work centered at the UNC Hospitals. In particular, neurosurgeon Liz Bullitt's entry into that field and association with our group was nurtured at the Radiation Oncology computorium. Our multidisciplinary style has benefited from the fact that at UNC the hospital is a 10-minute walk from the Computer Science/Mathematics/Statistics building complex, but we have also come to realize the great importance of having laboratory facilities in the medical school where physician users can walk in and thereby bring the needs of their driving problems to the attention of the scientists and engineers. In addition some of our methods installed at the computorium were used by Bill Oliver at the Armed Forces Institute of Pathology to show that Rodney King was indeed beaten. Also, the computorium, the graphics and image lab at Computer Science, and the Microelectronics Center of North Carolina's supercomputer were the nodes of VISTAnet (Fig. 6), an early experiment in distributed computing for radiation treatment delivery led by Julian Rosenman, Henry Fuchs, and Vernon Chi.

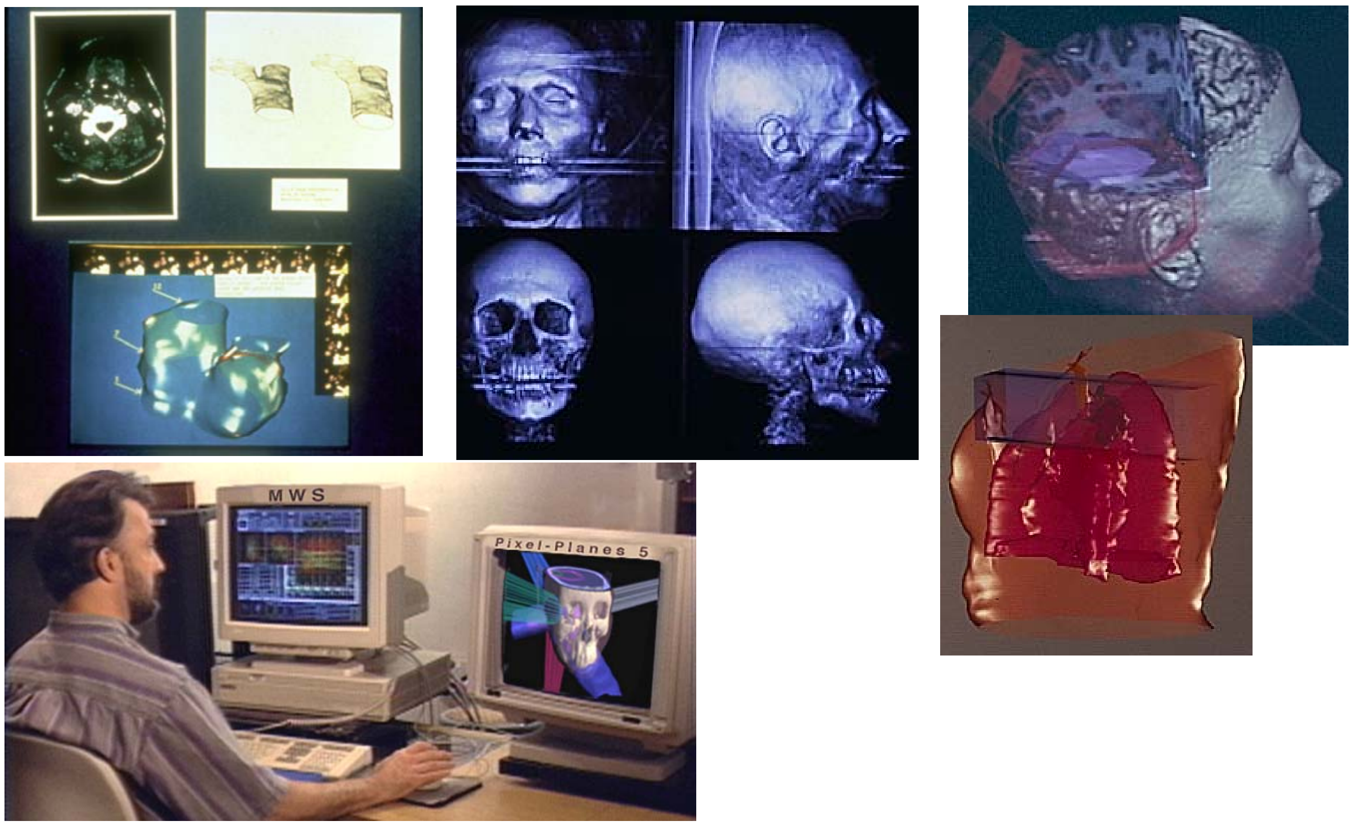

Fig. 6. 3D rendering: Top left: early studies on the carotid artery. Top center & right: early results from Levoy volume rendering. Top right: radiation treatment visualizations. Bottom left: Jim Symon at VISTAnet station

The other major collaboration represented by our work on rendering of 3D objects from medical images is with, indeed as a part of, the graphics research team in our Department of Computer Science. The fact that two of the major three means of 3D rendering, namely ray casting [Levoy 1990] and splatting [Westover 1989], were invented within the UNC Computer Science team, and MIDAG's work in this area being among the earliest in medicine, makes us feel that we have had a serious effect on the major use of 3D display in medicine today. Indeed, our persevering in our research despite the controversy in the early days as to whether 3D display would be medically useful is one of a number of experiences pointing to the importance of understanding the medical need and working toward it but not accepting the straitjackets imposed by the medical practices of the day. Our work in 3D rendering goes on today, most recently via research by Liz Bullitt on fast volume rendering allowing viewing of original data in regions about segmented objects.

Another extension of our work on 3D display is a major program for carrying out biopsy and surgery through augmented reality (Figs. 7 & 8) under the leadership of Henry Fuchs in Computer Science, Etta Pisano in Radiology, and Anthony Meyer in Surgery. Both patients and computer science students, staff, and faculty are surprised when breast biopsies are carried out in the Graphics & Image Lab at Computer Science to experimentally evaluate these visualization techniques.

Fig. 7. Early appearance of single and multiple ultrasound slices of the fetus in utero in the augmented reality headmount. That early headmount is seen in the rightmost picture.

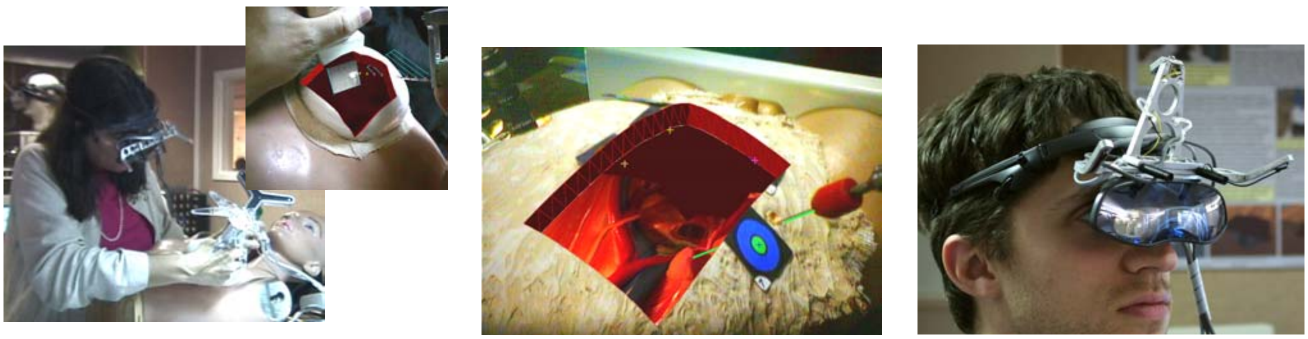

Fig. 8. Recent appearance of breast biopsy augmented reality experiments by Etta Pisano and of abdominal laparoscopy on phantoms. Jeremy Ackerman is shown on the right with a late, open view headmount.

The education of doctoral and masters students has been a central goal of MIDAG, and their contributions have been essential. We number MIDAG PhDs as about 60 across a variety of disciplines: computer science, biomedical engineering, statistics, biostatistics, mathematics, and psychology, and at both UNC and Duke. Many of our graduates have stayed in the medical image analysis field, including at many major universities, at the Armed Forces Institute of Pathology, at various institutes of the National Institutes of Health, and in industry. At the last IPMI we were excited to encounter a professional great grandchild of the MIDAG faculty. At the last MICCAI there were 10 PhD or MD participants who were or once had been at UNC.

MIDAG prides itself in having affected medical practice and thus the lives of patients. Despite the fact that bringing research from conception to actual medical use is a process sometimes taking a decade, the largest fraction, perhaps all, of our graduate students and faculty are attracted to these applications of computers by this altruism. Areas in which MIDAG research has come to this fruition are the uses of color display in nuclear medicine, the standardization of CRT display and the realization of how many bits of intensity are needed, and the use of tested contrast enhancement methods in areas of medical image use where subtle changes must be detected. Medical areas where we have had an effect are mammography, a major target area for both the standardization and contrast enhancement ends, and portal imaging in radiotherapy, a target area for contrast enhancement. Indeed our method of adaptive histogram equalization and its variants seem to have so thoroughly penetrated the tools available in commercially available image display packages that their source in our lab is frequently not recognized. That's just fine by us – again quoting Fred Brooks, "Scientists who have the most ideas stolen win."

Another area where MIDAG has had a serious effect on medical care is in the building of the 3D radiation treatment planning system, *PlanUNC*, [Sailer 1992, 1996], which is in clinical use at UNC and in research use in quite a number of sites across the United States and Europe. This system, for which major credit should be given to Ed Chaney, Julian Rosenman, George Sherouse, and Tim Cullip, was built on the 3D display capabilities that we had developed within MIDAG, as well as manual image segmentation and registration tools that we had developed. A related contribution built into PlanUNC and developed under the direction of Julian Rosenman was a tool for display-guided 3D/3D rigid registration [Rosenman 1998].

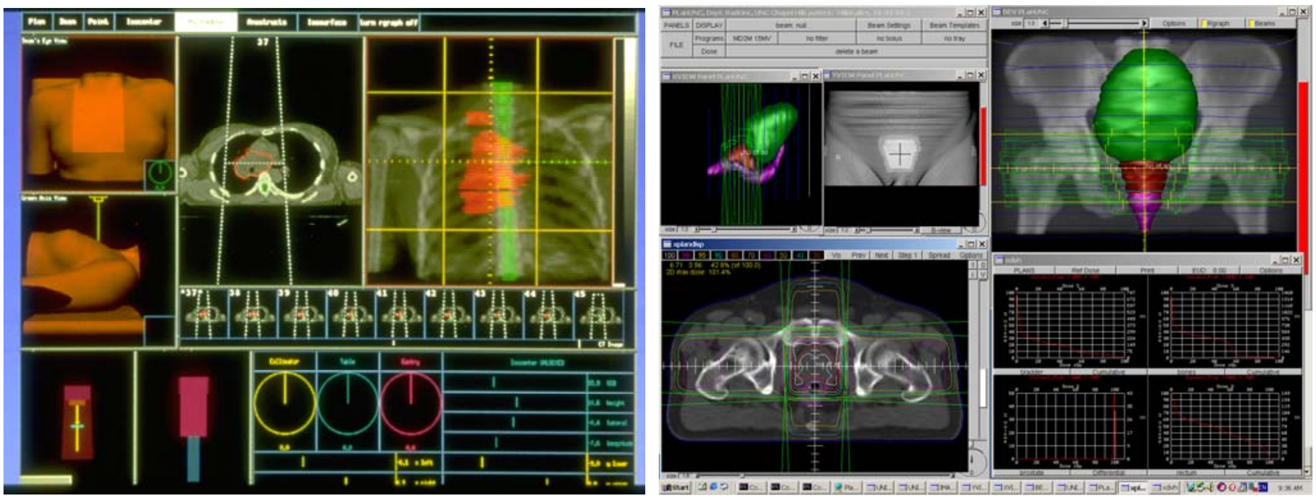

Fig. 9. PlanUNC screen shots: historical and now

In the 1980s some of MIDAG's attention moved to image analysis. We are now recognized as a center for representing objects by medial geometry; then doctoral student Lee Nackman's dissertation work [Nackman 1985] started us in this direction. While we began our work towards extracting medial loci from images, i.e., describing images, we came to realize that a more fruitful goal was to represent the anatomic objects in the real world medially, using a structure we call m-reps (Fig. 10), and to see images as evidence for the particular medial values describing a particular patient. In this way we followed [Pizer 1999] the posterior optimization approach that has been sweeping the image analysis world.

Also beginning in the 1980s we began to make some contributions to the notions of scale space description of images. This work, as well as work on object shape, was stimulated by Steve Pizer's sabbatical with Jan Koenderink in 1983-4. An early contribution from MIDAG was Larry Lifshitz's often referenced dissertation result [Lifshitz 1990] on segmentation failures induced by following annihilations of intensity saddle / maximum pairs through scale via intensity level curves. In the early '90s we had moved onto scale spaces through nonlinear geometry-limited diffusion in work led by PhD student Ross Whitaker [1993], and we were pleased to have contributed to the international multi-center collaboration that yielded the influential book BM ter Haar Romeny: *Geometry-Driven Diffusion in Computer Vision* (Kluwer, 1994). That work on geometry-limited diffusion continued in a collaboration of Ross Whitaker with Guido Gerig at ETH, Zürich after Ross left with his PhD, and after Guido joined MIDAG in 1998, that work, in turn, continued into Guido's present work with Sean Ho [2002] on tumor extraction by such techniques (Fig. 11). MIDAG's collaborations with quite a few laboratories both in Europe and in North America have been an important source of inspiration, and the many student interns and other visitors from these laboratories have been very useful to our team.

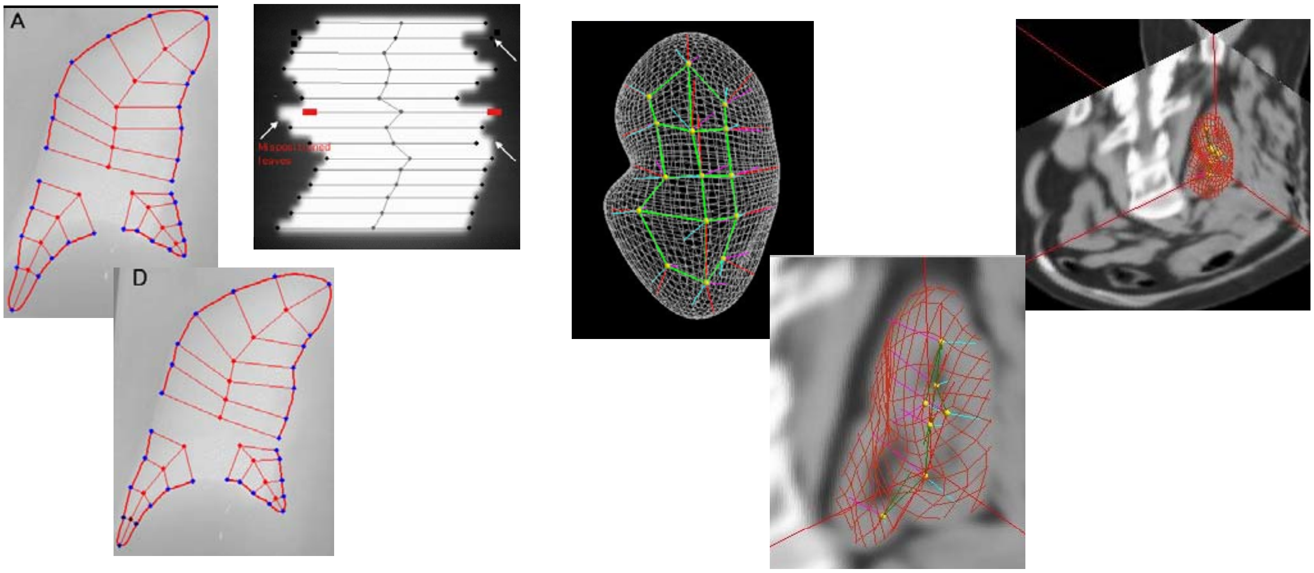

Fig. 10. M-reps. Left three: 2D, right three: 3D. Leftmost [Willis 2002]: Willis et al's deformation of model from planning (simulation) radiograph onto lung portal image: A: initial position, D: segmented result and model (model, initial placement, after warp into image). Next right: Chaney et al's detection of misplaced leaves in multileaf collimator [Chaney 2001]. Right three: above: kidney model and location after optimal movement; below: after optimal warp of m-rep.

Fig. 11. Left two: The Whitaker blob, which has served as a test object for many students, and ridges computed from this image in Whitaker's dissertation. Right: Tumor segmented by Ho & Gerig by competitive geodesic snakes

Neurosurgeon Liz Bullitt joined MIDAG in the early '90s, doing some of her early medical image analysis research on the construction of 3D blood vessel trees from biplane angiograms [Bullitt 1997]. Liz amazed many of us by her practice of doing surgery in the daytime and writing topnotch C++ code in the wee hours of the morning, and computer science grad students are still impressed by having a neurosurgeon, indeed one now with an Adjunct Professorship in Computer Science, wandering the corridors of the Computer Science building. Alan Liu did dissertation work in blood vessel segmentation and 2D/3D registration via blood vessels [Liu 1998], and Stephen Aylward, following his leading work on medial approaches to the extraction of 3D tubes and most especially blood vessels from 3D images [Aylward 2002], and Liz Bullitt developed methods for the formation of the trees from the tubes, and Liz and Stephen combined their methods to produce a strong, commercially available software system for producing patient-specific vascular geometric representations from various types of angiographic images. More recently Stephen has developed means of 3D/3D multimodality registration based on blood vessels that appears to have an enormous potential and range of applicability.

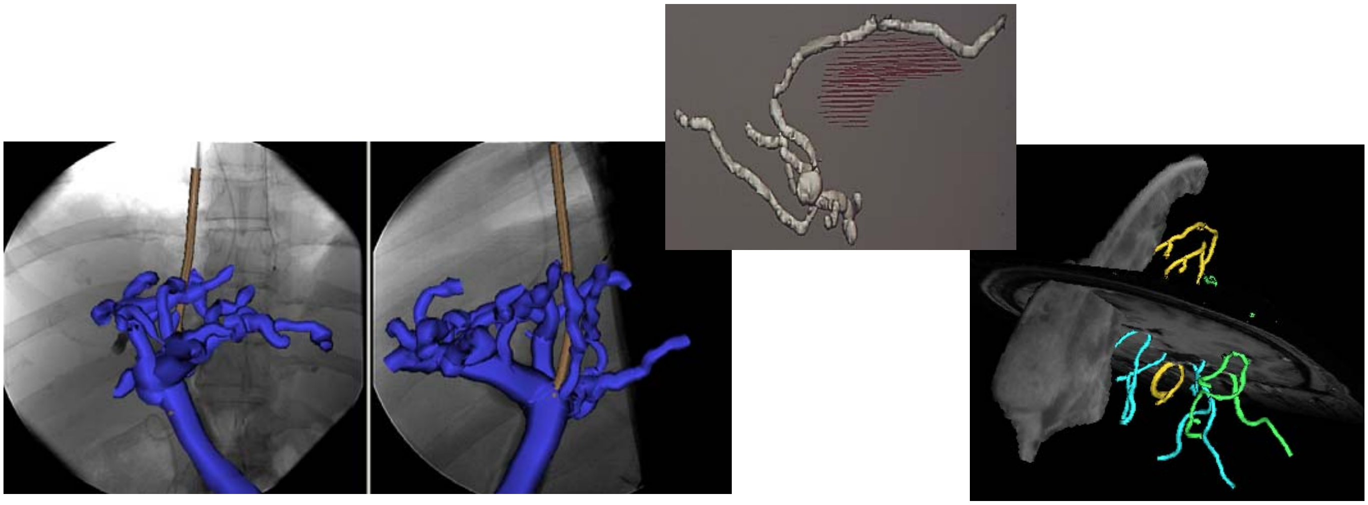

Fig. 12. Top: Aylward's early extraction of blood vessels and aneurysm from MRA (with hand-contoured cerebral ventricles). Bottom, left two: a venous vessel tree in blue, segmented from CT by Aylward, is registered with a pair of DSA views by Bullitt and shown with a planned catheter entering the portal system; right: blood vessels from MRI colored by source vessel vs. tumor it supplies and greyscale slice.

In 1998 Guido Gerig joined MIDAG from ETH in Switzerland, having already himself worked on medial representations for shape in medical images. Guido, whose professorial appointment is equally split between Computer Science and Psychiatry, formed a new lab in the hospital for MIDAG, the Neuroimage Analysis Lab. This lab is now bustling with medical students and faculty and computer science students and faculty hard at work on research towards the diagnosis and comprehension of psychiatric diseases such as schizophrenia and autism. In this research he is part of the large research group led by psychiatrist Jeffrey Lieberman. Guido has particularly led research in methods for and studies of statistical geometric characterization of populations of brain structures, such as the hippocampi and the cerebral ventricles [Gerig 2001a, 2001b]. In this work he has collaborated closely not only with his doctoral advisee, Martin Styner, and Steve Pizer, but also with Sarang Joshi, who joined Radiation Oncology and Biomedical Engineering in 1999 and who had preceded UNC research on shape statistics by an analysis of hippocampal shape via diffeomorphisms, in collaboration with John Csernansky [1998] at Washington University, which formed one of the earliest published shape statistics studies.

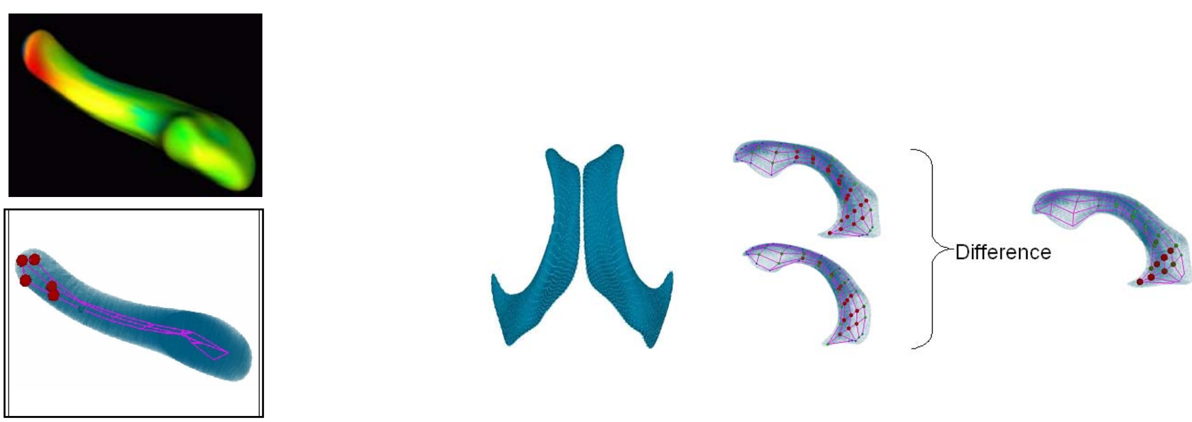

Fig. 13. Hippocampus shape and cerebral ventricle shape in schizophrenia in a study by Styner et al. [Styner 2002]. Left: shape location and type of variation of the hippocampus. Right: inter-twin width differences by location in the cerebral ventricle.

Statistical pattern recognition (SPR) has long been an important technique in the armamentarium of MIDAG. Research on SPR methods was led for years by James Coggins, and Stephen Aylward, while a dissertation advisee of James Coggins and Stephen Pizer, produced an interesting medial application in feature space for statistical analysis. Tumor segmentation work led by Gerig, Moon, Joshi, and Bullitt makes important use of SPR, as well.

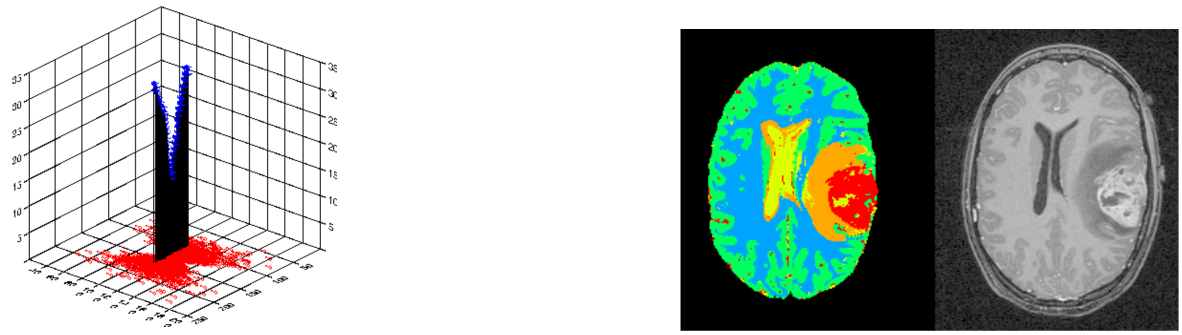

Fig. 15. Left: Aylward's continuous mixture modeling via medial loci of Gaussian goodness of fit [Aylward 1997]. Right: Moon and Gerig's SPR segmentation of tumor from pre- & post-gadolinium MRIs based on atlas modified to accommodate tumor [Moon & Gerig].

Any lab working on medical image processing methods must be concerned with its software environment and its computer hardware infrastructure. Graham Gash has led in these areas for years and indeed has provided our corporate memory for our software. More recently, Stephen Aylward has also led in this area, and with Luis Ibañez and Graham Gash, has contributed to the architecture and library of the ITK (Insight Tool Kit) software. ITK is being developed under the leadership of our PhD alumnus, Terry Yoo at the National Library of Medicine to provide a web-resident library (www.itk.org), to which all can contribute, for the international community using and developing 3D medical image analysis methods.

With all of our emphasis on the development of segmentation by deformable models and our aforementioned principle that validation is a critical part of research developing image analysis and display methods, we have begun to seriously face the issues of how to validate segmentation and how to choose the parameters of a segmentation method. Our experimental design and analysis techniques involve a variety of new methods for repeated variables designs developed by Keith Muller, who also leads our data analysis team. Guido Gerig has led the development of measurement and visualization tools for comparing segmentations by different individuals or computer based techniques. To counter the problem that for many years groups working on segmentation methods, including us, validated them, if at all, on a very small number of cases, Ed Chaney, Steve Pizer, and Sarang Joshi, and doctoral student James Chen are leading the development of an approach to develop arbitrarily large sets of 3D test images with known segmentation truth, based on the statistical analysis of geometry methods mentioned earlier.

Important future directions that we see for ourselves and for the field are the following. We are already embarked on many of them.

- The fiducial structures on which to base deformable intra-patient multimodality or temporal registration can extremely usefully involve blood vessel trees, we think, since these structures appear everywhere in the body and are well imaged by a variety of imaging modalities, including the 3D real-time modality of 3D ultrasound. Stephen Aylward has developed this idea and plans to develop it much further.

- The statistical characterization and discrimination of object geometry will, we think, lead to clues to the organic processes of growth and disease and as well provide priors for segmentation, registration, and other methods of image understanding. Guido Gerig, Steve Pizer, and Sarang Joshi, and postdoc Conglin Lu are working in this direction. These methods extend to multi-object geometry and thus to the description of the variability of atlases and thus to the teaching of anatomy.
- Providing not just spatial object descriptions but also spatiotemporal object descriptions will become an important direction, one in which Sarang Joshi and Guido Gerig are already working. Clinical analyses related to heart and respiratory motion abound, as do those of normal and pathological growth and response to therapy.
- While our segmentation work based on the geometric description of classes of anatomic structures in normal patients and in certain pathological classes has a long way to go and must be extended to topological and not just geometric differences across patients, it still does not seriously apply to tumor segmentation. We have begun research on tumor segmentation by restricting ourselves to non-infiltrating tumors with smooth boundaries, but we anticipate work towards the segmentation of the larger class of tumors whose boundary and interior topology will need to be more statistically described or which intermingle with the tissue of the anatomic structures within whose tissue they are formed.
- We interpret our results to indicate that augmented reality has serious potential for improving image-guided medical interventions but that the degree of this improvement continues to depend on the technical limitations of the interaction and display devices such as tetherless motion trackers and see-through head-mounted displays. Thus we plan to work simultaneously on three fronts: measuring where these technical limitations are, improving the hardware to reduce these limitations, and developing and testing challenging and clinically important medical uses of augmented reality.
- New methods of validation of image analysis techniques will for a time be a growing activity. New paradigms and metrics for comparing and evaluating medical image analysis tools require the blending of the clinical trials world view of the medical scientist, the image or geometric metrics of the image analyst, and the prototype testing approach of an engineer.
- Finally, while we have always believed that connections of image display and analysis research to acquisition research was fruitful, we plan to make this plan real in regard to improvements in MRI acquisition, given the addition a couple of years ago of Weili Lin to our Radiology Department's faculty.

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