Государственное образовательное учреждение
высшего профессионального образования
**«Томский государственный университет
систем управления и радиоэлектроники»**

ТЕМАТИЧЕСКИЙ РЕФЕРАТИВНЫЙ СБОРНИК № 3-1

“Cancer Diagnostics”
(«Диагностика рака»)

Журнальные публикации

Источник: *Digital Library IEEEXplore*
Язык: *английский*
Глубина поиска: *2001 – 2011 гг.*
Дата формирования: *март 2011 г.*
Составитель: *В.И. Карнышев*

Томск – 2011

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"Predicting Breast Screening Attendance Using Machine Learning Techniques"

Machine learning-based prediction has been effectively applied for many healthcare applications. Predicting breast screening attendance using machine learning (prior to the actual mammogram) is a new field. This paper presents new predictor attributes for such an algorithm. It describes a new hybrid algorithm that relies on back-propagation and radial basis function-based neural networks for prediction. The algorithm has been developed in an open source-based environment. The algorithm was tested on a 13-year dataset (1995-2008). This paper compares the algorithm and validates its accuracy and efficiency with different platforms. Nearly 80% accuracy and 88% positive predictive value and sensitivity were recorded for the algorithm. The results were encouraging; 40-50% of negative predictive value and specificity warrant further work. Preliminary results were promising and provided ample amount of reasons for testing the algorithm on a larger scale. [J1]

"An Optimal Transportation Approach for Nuclear Structure-Based Pathology"

Nuclear morphology and structure as visualized from histopathology microscopy images can yield important diagnostic clues in some benign and malignant tissue lesions. Precise quantitative information about nuclear structure and morphology, however, is currently not available for many diagnostic challenges. This is due, in part, to the lack of methods to quantify these differences from image data. We describe a method to characterize and contrast the distribution of nuclear structure in different tissue classes (normal, benign, cancer, etc.). The approach is based on quantifying chromatin morphology in different groups of cells using the optimal transportation (Kantorovich-Wasserstein) metric in combination with the Fisher discriminant analysis and multidimensional scaling techniques. We show that the optimal transportation metric is able to measure relevant biological information as it enables automatic determination of the class (e.g., normal versus cancer) of a set of nuclei. We show that the classification accuracies obtained using this metric are, on average, as good or better than those obtained utilizing a set of previously described numerical features. We apply our methods to two diagnostic challenges for surgical pathology: one in the liver and one in the thyroid. Results automatically computed using this technique show potentially biologically relevant differences in nuclear structure in liver and thyroid cancers. [J2]

"Optofluidic Intracavity Spectroscopy of Canine Hemangiosarcoma"

The label-free technique of optofluidic intracavity spectroscopy (OFIS) uses light transmitted through a cellular body in a microfluidic optical resonator to distinguish different types of cells by their optical properties. The OFIS technique has differentiated canine hemangiosarcoma (HSA) cells from monocytes in peripheral blood mononuclear cells based on their distinctive transmission spectra. A single characteristic parameter indicative of strong multi-transverse-mode resonances was determined for each cell by forming a linear combination of the mean and standard deviation of the transmission spectra over one free spectral range, excluding the peaks of passive Fabry-Pйrot cavities without cells. The difference in the characteristic parameters of HSA and monocyte samples was statistically highly significant with a p-value as low as 10^{-6}. The same method shows that the characteristic parameters of canine lymphoma and lymphocytes are distinct with $p < 0.005$. A receiver operating-characteristic curve constructed from t-distributions fit to the HSA and monocyte data indicates that 95% sensitivity and 98% specificity can be simultaneously achieved. [J3]

"Domain-Specific Image Analysis for Cervical Neoplasia Detection Based on Conditional Random Fields"

This paper presents a domain-specific automated image analysis framework for the detection of pre-cancerous and cancerous lesions of the uterine cervix. Our proposed framework departs from previous methods in that we include domain-specific diagnostic features in a probabilistic manner using conditional random fields. Likewise, we provide a novel window-based performance assessment scheme for 2D image analysis which addresses the intrinsic problem of image misalignment. Image regions corresponding to different tissue types are indentified for

the extraction of domain-specific anatomical features. The unique optical properties of each tissue type and the diagnostic relationships between neighboring regions are incorporated in the proposed conditional random field model. The validity of our method is examined using clinical data from 48 patients, and its diagnostic potential is demonstrated by a performance comparison with expert colposcopy annotations, using histopathology as the ground truth. The proposed automated diagnostic approach can support or potentially replace conventional colposcopy, allow tissue specimen sampling to be performed in a more objective manner, and lower the number of cervical cancer cases in developing countries by providing a cost effective screening solution in low-resource settings. [J4]

"A cDNA Microarray Gene Expression Data Classifier for Clinical Diagnostics Based on Graph Theory"

Despite great advances in discovering cancer molecular profiles, the proper application of microarray technology to routine clinical diagnostics is still a challenge. Current practices in the classification of microarrays' data show two main limitations: the reliability of the training data sets used to build the classifiers, and the classifiers' performances, especially when the sample to be classified does not belong to any of the available classes. In this case, state-of-the-art algorithms usually produce a high rate of false positives that, in real diagnostic applications, are unacceptable. To address this problem, this paper presents a new cDNA microarray data classification algorithm based on graph theory and is able to overcome most of the limitations of known classification methodologies. The classifier works by analyzing gene expression data organized in an innovative data structure based on graphs, where vertices correspond to genes and edges to gene expression relationships. To demonstrate the novelty of the proposed approach, the authors present an experimental performance comparison between the proposed classifier and several state-of-the-art classification algorithms. [J5]

"Evidence for Cancer Biomarkers in Exhaled Breath"

A Review: Cancer cell growth releases molecular biomarkers into blood that can be useful in diagnostic tests, e.g., serum biomarkers. The use of serum biomarkers involves an invasive sample collection procedure. Human exhaled breath is potentially a noninvasive source of cancer biomarker compounds. A few breath analysis studies have reported sensitivities > 90% and specificities > 80% using a suite of exhaled breath biomarkers to differentiate cancer subjects from controls. A significant challenge for establishing breath analysis as a feasible cancer diagnostic procedure is the lack of validated diagnostic procedure. We found over 2000 breath-related studies published since circa1900 reporting on a wide variety of breath chemical analysis methods and diagnostic findings; only a small fraction of these studies were directly related to cancer molecular biomarkers in breath. Compared to other detectors and separation techniques, mass spectrometry and gas chromatography are most suitable techniques for breath analysis. Compounds detectable in exhaled breath, with potential diagnostic utility in cancer detection, include small gaseous molecules, volatile organic compounds, proteins, and DNA. The types of cancers previously investigated using chemical analysis of exhaled breath was breast, colon, liver, lung, ovarian, and stomach cancers. Lack of multiple studies using the same breath analysis method(s) precluded meta-analysis. Our review covers the reported methods on breath analysis and assumed exhaled biomarkers. This review makes available to other researchers a catalog of published data on breath analysis for cancer detection. We make recommendations to standardize methods for more accurate breath tests in cancer detection. [J6]

"CancerSpace: A Simulation-Based Game for Improving Cancer-Screening Rates"

Can playing a video game help save lives? It might seem unlikely, especially if the first image that comes to mind at the word "gamer" is that of an overstimulated, underdeveloped teenager who desperately needs a suntan and a girlfriend. However, like many of today's gamers, video games are moving out of their parents' basement and into the real world. Video games are maturing and facing adaptation to serious applications. Such serious games are seeing use in a variety of fields, from the military to corporate management, and are finally being employed in healthcare. One of the biggest, most challenging areas is modeling simulations for medical training, particularly for managing chronic illness and providing system-level population-based care. [J7]

"Sensitivity of Time-Resolved Fluorescence Analysis Methods for Disease Detection"

Time-resolved fluorescence (TRF) measurements of biological tissue provide chemical and structural information useful for detecting subtle disease processes, including cancers originating in mucosal tissues. A number of techniques for analyzing such TRF measurements exist, but they have not yet been compared to determine which of them can provide the greatest sensitivity to differences between a TRF measurement from nondiseased tissue and one from diseased tissue. We have evaluated four TRF analysis methods in this study: biexponential curve fitting, monoexponential curve fitting, Laguerre function representation, and computing the area under the

decay curve (AUDC). We performed this study on a large dataset of computer-generated TRF decay curves based on colonic mucosa and typical measurement instrumentation. We statistically determined the minimum detectable change (MDC) in the relative contribution of each mucosal layer to the total TRF signal with each analysis method. We also determined the MDC in fluorescence lifetime of the upper mucosal layer. These two types of changes are due to the structural and biochemical changes expected in mucosa with onset of neoplasia. Under a wide range of baseline conditions, the monoexponential, AUDC, and Laguerre analysis methods all yield dramatically superior sensitivity and robustness over the standard biexponential method, with several caveats. [J8]

"Toward Carbon-Nanotube-Based Theranostic Agents for Microwave Detection and Treatment of Breast Cancer: Enhanced Dielectric and Heating Response of Tissue-Mimicking Materials"

The experimental results reported in this paper suggest that single-walled carbon nanotubes (SWCNTs) have the potential to enhance dielectric contrast between malignant and normal tissue for microwave detection of breast cancer and facilitate selective heating of malignant tissue for microwave hyperthermia treatment of breast cancer. In this study, we constructed tissue-mimicking materials with varying concentrations of SWCNTs and characterized their dielectric properties and heating response. At SWCNT concentrations of less than 0.5% by weight, we observed significant increases in the relative permittivity and effective conductivity. In microwave heating experiments, we observed significantly greater temperature increases in mixtures containing SWCNTs. These temperature increases scaled linearly with the effective conductivity of the mixtures. This work is a first step towards the development of functionalized, tumor-targeting SWCNTs as theranostic (integrated therapeutic and diagnostic) agents for microwave breast cancer detection and treatment. [J9]

"Optical Characterization of a 1-D Nanostructure by Dark-Field Microscopy and Surface Plasmon Resonance to Determine Biomolecular Interactions"

This paper presents a multifunctional imaging system that combines dark-field microscopy (DFM) with spectroscopy to image nanostructures and identify their optical properties from absorption spectra. The optical resolving power of this system is determined using a 1-D nanostructure with pitches of 120, 390, and 770 nm with four formats of optical disks. These pattern sizes are verified by atomic force microscopy (AFM) first. The results demonstrate that the resolving power of current system setup can down to 86 nm. The resultant DFM images appear to be slightly larger than the AFM images. A 50-nm-thick gold film was then deposited on top of these nanostructures, and their absorption spectra were obtained to elucidate its optical properties, enhanced by surface plasmon resonance. The immobilization of streptavidin on the surface of gold-coated nanostructure causes the absorption spectra to shift from 600 to 610 nm. A protein nanoarray with a dot size of 50 nm was also imaged by DFM, and can be implemented as a potential biochemical diagnostic system on an optical disk format. Specimens of adenocarcinoma cells and ovary cancer cells were also imaged using this DFM system, and the nuclei structure and some cellular organs can be recognized using a 100Г‘В— objective oil lens. [J10]

"Automated coregistered imaging using a hand-held probe-based optical imager"

Near-infrared optical imaging holds a promise as a noninvasive technology toward cancer diagnostics and other tissue imaging applications. In recent years, hand-held based imagers are of great interest toward the clinical translation of the technology. However hand-held imagers developed to date are typically designed to obtain surface images and not tomography information due to lack of coregistration facilities. Herein, a recently developed hand-held probe-based optical imager in our Optical Imaging Laboratory has been implemented with novel coregistration facilities toward real-time and tomographic imaging of tissue phantoms. Continuous-wave fluorescence-enhanced optical imaging studies were performed using an intensified charge coupled device camera based imaging system in order to demonstrate the feasibility of automated coregistered imaging of flat phantom surfaces, using a flexible probe that can also contour to curvatures. Three-dimensional fluorescence tomographic reconstructions were also demonstrated using coregistered frequency-domain measurements obtained using the hand-held based optical imager. It was also observed from preliminary studies on cubical phantoms that multiple coregistered scans differentiated deeper targets (3cm)from artifacts that were not feasible from a single coregistered scan, demonstrating the possibility of improved target depth detectability in the future. [J11]

"Repeated Imaging of Lung Cancer Development Using PIXSCAN, a Low Dose Micro-CT Scanner Based on XPAD Hybrid Pixel Detectors"

PIXSCAN is the first micro-CT prototype based on XPAD hybrid pixel detectors whose properties (high signal to noise ratio and detection efficiency) theoretically allow imaging at low irradiation dose. We have tested the impact of repeated imaging sessions with PIXSCAN on living mice. Mice were subjected on average to 10

imaging sessions over two weeks without any detectable sign of X-ray injuries as assessed by spontaneous activity in the cage, examination of hair and skin, or comparison of lung absorbing properties for X-rays. PIXSCAN was therefore used to detect and non-invasively monitor the progression of lung metastasis in a murine model of cancer. Aim was two-fold: i) to provide imaging assistance to decide timing of animal sacrifice for subsequent histological characterization; ii) to optimize imaging protocol to allow direct evaluation of new therapeutic agents to stop cancer progression. Comparing in vivo tomographic reconstruction of freely breathing mice with post mortem examination of their lungs, we have shown that identification and localization of millimetric tumors was compatible with X-ray imaging protocol delivering only 10 mGy per exam. [J12]

"Diagnostic Models Based on Personalized Analysis of Trends (PAT)"

Many changes have taken place in medicine over the last century. In the first-half of the 20th century physicians were faced with the challenge of making diagnoses with too little information, often resorting to exploratory surgery to confirm the presence or absence of a condition. Due to rapid technological advances during the second-half of the 20th century, and continuing to this day, the position of the physician has now shifted from an information-poor environment to an environment with too much information, often exceeding the limits of human decision-making capabilities. To take full advantage of all available information, a new approach based on refined automated decision support methods is needed to assist the physician in the decision-making process. Medical decision support systems need to evolve from stand-alone systems to cooperative systems in which the physician becomes the decision maker, but relies on the decision support system to sift through information to determine relevant trends. In this paper, a decision support system that combines a number of methodologies for trend analysis is described, along with examples in cardiology. The methods have also been used in applications in neurology as well as cancer diagnosis and prognosis. [J13]

"On Combining Morphological Component Analysis and Concentric Morphology Model for Mammographic Mass Detection"

Mammographic mass detection is an important task for the early diagnosis of breast cancer. However, it is difficult to distinguish masses from normal regions because of their abundant morphological characteristics and ambiguous margins. To improve the mass detection performance, it is essential to effectively preprocess mammogram to preserve both the intensity distribution and morphological characteristics of regions. In this paper, morphological component analysis is first introduced to decompose a mammogram into a piecewise-smooth component and a texture component. The former is utilized in our detection scheme as it effectively suppresses both structural noises and effects of blood vessels. Then, we propose two novel concentric layer criteria to detect different types of suspicious regions in a mammogram. The combination is evaluated based on the Digital Database for Screening Mammography, where 100 malignant cases and 50 benign cases are utilized. The sensitivity of the proposed scheme is 99% in malignant, 88% in benign, and 95.3% in all types of cases. The results show that the proposed detection scheme achieves satisfactory detection performance and preferable compromises between sensitivity and false positive rates. [J14]

"Quasi-Multistatic MIST Beamforming for the Early Detection of Breast Cancer"

Microwave imaging via space-time (MIST) beamforming has been shown to be one of the most promising imaging modalities for detecting small malignant breast tumors. This paper outlines two modifications to the MIST system developed by Hagness for the early detection of breast cancer, resulting in a quasi-multistatic MIST beamformer (multi-MIST). Multistatic MIST beamforming involves illuminating the breast with an ultrawideband (UWB) signal from one antenna while collecting the reflections at an array of antennas, as opposed to traditional monostatic MIST beamforming where only the transmitting antenna records the reflections from the breast. In order to process the multistatic data, traditional data-adaptive artifact removal algorithms have to be modified to accommodate signals from all antennas. Also, the MIST beamforming algorithm, which spatially focuses the signal and compensates for frequency-dependent propagation effects, has to be modified. The algorithms are tested on a 2-D anatomically accurate finite-difference time-domain model of the breast. The multi-MIST beamformer described here is shown to offer an improved signal to clutter ratio when compared to the traditional monostatic MIST beamformer. [J15]

"Ensemble Rough Hypercuboid Approach for Classifying Cancers"

Cancer classification is the critical basis for patient-tailored therapy. Conventional histological analysis tends to be unreliable because different tumors may have similar appearance. The advances in microarray technology make individualized therapy possible. Various machine learning methods can be employed to classify cancer tissue samples based on microarray data. However, few methods can be elegantly adopted for generating accurate and reliable as well as biologically interpretable rules. In this paper, we introduce an approach for

classifying cancers based on the principle of minimal rough fringe. For training rough hypercuboid classifiers from gene expression data sets, the method dynamically evaluates all available genes and sifts the genes with the smallest implicit regions as the dimensions of implicit hypercuboids. An unseen object is predicted to be a certain class if it falls within the corresponding class hypercuboid. Based upon the method, ensemble rough hypercuboid classifiers are subsequently constructed. Experimental results on some open cancer gene expression data sets show that the proposed method is capable of generating accurate and interpretable rules compared with some other machine learning methods. Hence, it is a feasible way of classifying cancer tissues in biomedical applications. [J16]

"Exploratory Consensus of Hierarchical Clusterings for Melanoma and Breast Cancer"

Finding subtypes of heterogeneous diseases is the biggest challenge in the area of biology. Often, clustering is used to provide a hypothesis for the subtypes of a heterogeneous disease. However, there are usually discrepancies between the clusterings produced by different algorithms. This work introduces a simple method which provides the most consistent clusters across three different clustering algorithms for a melanoma and a breast cancer data set. The method is validated by showing that the Silhouette, Dunne's and Davies-Bouldin's cluster validation indices are better for the proposed algorithm than those obtained by k-means and another consensus clustering algorithm. The hypotheses of the consensus clusters on both the data sets are corroborated by clear genetic markers and 100 percent classification accuracy. In Bittner et al.'s melanoma data set, a previously hypothesized primary cluster is recognized as the largest consensus cluster and a new partition of this cluster into two subclusters is proposed. In van't Veer et al.'s breast cancer data set, previously proposed "basal?? and "luminal A?? subtypes are clearly recognized as the two predominant clusters. Furthermore, a new hypothesis is provided about the existence of two subgroups within the "basal?? subtype in this data set. The clusters of van't Veer's data set is also validated by high classification accuracy obtained in the data set of van de Vijver et al. [J17]

"Potential and Challenges for Mid-Infrared Sensors in Breath Diagnostics"

Exhaled breath contains more than 1000 constituents at trace level concentrations, with a wide variety of these compounds potentially serving as biomarkers for specific diseases, physiologic status, or therapeutic progress. Some of the compounds in exhaled breath (EB) are well studied, and their relationship with disease pathologies is well established. However, molecularly specific analysis of such biomarkers in EB at clinically relevant levels remains an analytical and practical challenge due to the low levels of such biomarkers frequently below the ppb (v/v) range in EB. In this contribution, mid-infrared (MIR) spectroscopic sensing techniques are reviewed for potential application in breath diagnostics. While the spectral regime from 3-20 Г‚Вїm has already been utilized for fundamental studies on breath analysis, significant further improvements are in demand for substantiating MIR spectroscopy and sensing techniques as a suitable candidate for clinically deployable breath analyzers. Several advantageous features including inherent molecular selectivity, real-time monitoring capability, comparable ease of operation, potentially low costs, and a compact device footprint promise reliable optical diagnostics in the MIR. Hence, while the application of MIR spectroscopy and sensing systems to breath analysis yet appear in their infancy, recent progress on advanced MIR light sources, waveguides, and device concepts forecasts next-generation optical sensing platforms suitable for addressing the challenges of in situbreath diagnostics. [J18]

"Alternative Transrectal Prostate Imaging: A Diffuse Optical Tomography Method"

This paper presents a transrectal dual-modality near-infrared (NIR) diffuse optical tomography technique coupled with ultrasonography that provides an integrated method for detecting prostate cancer (PCa). The study that provides an alternative transrectal prostate imaging system stems from the perceived inadequacy of conventional transrectal ultrasound (TRUS) in PCa imaging. The transrectally applied diffuse optical tomography aims to characterize the spatially resolved optical properties of the intactprostate that are known to have intraorgan and intersubject heterogeneities. A canine model of PCa using canine transmissible venereal tumor was used to demonstrate the utility of this technology in detecting PCa. Tumors in the pelvic canal, including tumors in the prostate, were found to be detectable at 2-week postinjection based upon the NIR absorption contrast, which was detected a few weeks earlier than using NIR-reduced scattering and effective attenuation contrasts, as well as TRUS. Transrectal optical tomography detection of cancerous tissues in vivoin intactcanine prostate based upon NIR contrasts may prove useful for diagnostic imaging of PCa and potentially aid in pretreatment planning for phototherapy applications. [J19]

"A Multiple-Filter-Multiple-Wrapper Approach to Gene Selection and Microarray Data Classification"

Filters and wrappers are two prevailing approaches for gene selection in microarray data analysis. Filters make

use of statistical properties of each gene to represent its discriminating power between different classes. The computation is fast but the predictions are inaccurate. Wrappers make use of a chosen classifier to select genes by maximizing classification accuracy, but the computation burden is formidable. Filters and wrappers have been combined in previous studies to maximize the classification accuracy for a chosen classifier with respect to a filtered set of genes. The drawback of this single-filter-single-wrapper (SFSW) approach is that the classification accuracy is dependent on the choice of specific filter and wrapper. In this paper, a multiple-filter-multiple-wrapper (MFMW) approach is proposed that makes use of multiple filters and multiple wrappers to improve the accuracy and robustness of the classification, and to identify potential biomarker genes. Experiments based on six benchmark data sets show that the MFMW approach outperforms SFSW models (generated by all combinations of filters and wrappers used in the corresponding MFMW model) in all cases and for all six data sets. Some of MFMW-selected genes have been confirmed to be biomarkers or contribute to the development of particular cancers by other studies. [J20]

"A Wireless Narrowband Imaging Chip for Capsule Endoscope"

This paper presents a dual-mode capsule gastrointestinal endoscope device. An endoscope combined with a narrowband image (NBI), has been shown to be a superior diagnostic tool for early stage tissue neoplasms detection. Nevertheless, a wireless capsule endoscope with the narrowband imaging technology has not been presented in the market up to now. The narrowband image acquisition and power dissipation reduction are the main challenges of NBI capsule endoscope. In this paper, we present the first narrowband imaging capsule endoscope that can assist clinical doctors to effectively diagnose early gastrointestinal cancers, profited from our dedicated dual-mode complementary metal-oxide semiconductor (CMOS) sensor. The dedicated dual-mode CMOS sensor can offer white-light and narrowband images. Implementation results show that the proposed 512 Ч 512 CMOS sensor consumes only 2 mA at a 3-V power supply. The average current of the NBI capsule with an 8-Mb/s RF transmitter is nearly 7 ~ 8 mA that can continuously work for 6 ~ 8 h with two 1.5-V 80-mAh button batteries while the frame rate is 2 fps. Experimental results on backside mucosa of a human tongue and pig's small intestine showed that the wireless NBI capsule endoscope can significantly improve the image quality, compared with a commercial-of-the-shelf capsule endoscope for gastrointestinal tract diagnosis. [J21]

"Parametric imaging for characterizing focal liver lesions in contrast-enhanced ultrasound"

The differentiation between benign and malignant focal liver lesions plays an important role in diagnosis of liver disease and therapeutic planning of local or general disease. This differentiation, based on characterization, relies on the observation of the dynamic vascular patterns (DVP) of lesions with respect to adjacent parenchyma, and may be assessed during contrast-enhanced ultrasound imaging after a bolus injection. For instance, hemangiomas (i.e., benign lesions) exhibit hyper-enhanced signatures over time, whereas metastases (i.e., malignant lesions) frequently present hyper-enhanced foci during the arterial phase and always become hypo-enhanced afterwards. The objective of this work was to develop a new parametric imaging technique, aimed at mapping the DVP signatures into a single image called a DVP parametric image, conceived as a diagnostic aid tool for characterizing lesion types. The methodology consisted in processing a time sequence of images (DICOM video data) using four consecutive steps: (1) pre-processing combining image motion correction and linearization to derive an echo-power signal, in each pixel, proportional to local contrast agent concentration over time; (2) signal modeling, by means of a curve-fitting optimization, to compute a difference signal in each pixel, as the subtraction of adjacent parenchyma kinetic from the echo-power signal; (3) classification of difference signals; and (4) parametric image rendering to represent classified pixels as a support for diagnosis. DVP parametric imaging was the object of a clinical assessment on a total of 146 lesions, imaged using different medical ultrasound systems. The resulting sensitivity and specificity were 97% and 91%, respectively, which compare favorably with scores of 81 to 95% and 80 to 95% reported in medical literature for sensitivity and specificity, respectively. [J22]

"An imaging proton spectrometer for short-pulse laser plasma experiments"

The ultraintense short pulse laser pulses incident on solid targets can generate energetic protons. In addition to their potentially important applications such as in cancer treatments and proton fast ignition, these protons are essential to understand the complex physics of intense laser plasma interaction. To better characterize these laser-produced protons, we designed and constructed a novel spectrometer that will not only measure proton energy distribution with high resolution but also provide its angular characteristics. The information obtained from this spectrometer compliments those from commonly used diagnostics including radiochromic film packs, CR39 nuclear track detectors, and nonimaging magnetic spectrometers. The basic characterizations and sample data from this instrument are presented. [J23]

"Microfluidics-assisted photo nanoimprint lithography for the formation of cellular bioimprints"

Morphology and surface features provide important markers for cell development and reaction to external stimuli. Bioimprint offers a technique for the permanent capture of these features into an UV-curing, biocompatible, methacrylate biopolymer. This material shows excellent replication fidelity and fast setting times. However, the minimum reproducible feature size depends on the skillful application of the liquid prepolymer. To enable the repeatable formation of high-resolution, structurally bioactive cellular bioimprints, a modified process based on the use of microfluidics for integrated cell culture and polymer delivery has been developed. In this article, the authors introduce the process and demonstrate its use for the culture and imaging of Ishikawa endometrial cancer cells. Transfer of a 100 nm thick Cr test pattern with micrometer-scale features into the biopolymer is demonstrated. Replication and atomic force microscopy imaging of imprinted cellular surface features with sub-50 nm resolution is shown. The process has applications in disease diagnostics, in drug discovery, and for the creation of biomimetic cell culture scaffolds. [J24]

"Strain Imaging of the Breast by Compression Microwave Imaging"

A method that uses microwave pulses to achieve strain imaging of the breast is presented. In the proposed method, the breast is inserted in an enclosure that defines the boundary conditions for the breast deformation under the influence of external pressure. The upper plate of the enclosure, which also includes an antenna array, is attached to a compression tool, whereas the lower and the front plates are fixed. The breast is allowed to extend in the lateral direction when pressed by the top plate. Each of the antennas at the top plate is used to send an ultrawideband pulse to penetrate the breast and measure the backscattered pulse. Two sets of measurements are taken: one pre- and another post-compression of the breast. A sliding window of cross correlation is then performed on the two sets of data to establish the time delay of each segment of the scattered pulse due to compression. That time delay is then employed to get a three-dimensional strain image of the breast. As lesion tissue is typically much stiffer than normal breast tissue, then regions of low or zero strain indicate areas in need of further diagnostic checks. Full-wave simulations are used to validate the presented imaging method. [J25]

"Reconstructing the human ribcage in 3d with x-rays and geometric models"

To avoid lung disease, regular preemptive screenings are an absolute necessity. This article describes a technique that creates a 3D reconstruction of the ribcage without expensive scanners. One of the major uses of this 3D reconstruction software would be as a medical visualization tool that would show the real shape of a ribcage. This 3D reconstruction method could be combined with diagnosis software to help detect lung cancer, to generate 3D size estimates, and to improve visualization of affected regions. [J26]

"Radiofrequency field absorption by carbon nanotubes embedded in a conductive host"

Understanding the electromagnetic response of carbon nanotubes (CNTs) in the radio frequency range is very important for experimental development of therapeutic and diagnostic CNT applications, including selective thermolysis of cancer cells and thermoacoustic imaging. In this study, we present the theory of electromagnetic wave scattering by several finite length CNT configurations, including singlewall CNT's having a surfactant coating, CNT bundles, and multiwall CNTs. Absorption cross-sections of these structures in a conductive host region are theoretically studied in the radio frequency range. Strong local field enhancement due to edge effects is predicted to be inherent to metallic singlewall CNTs in the near-field zone, providing an additional mechanism of energy dissipation in a conductive host. Due to the screening effect the application of singlewall CNTs for the enhancement of energy dissipation is more effective than the application of multiwall CNTs or CNT bundles at the same mass fraction of CNT inclusions. The presence of a lossy dielectric (surfactant) coating can significantly increase the absorption cross section of singlewall CNTs. [J27]

"In It to WIN It"

Nanotechnology and its applications are poised for explosive growth in the years ahead. The Waterloo Institute for Nanotechnology (WIN), with a new state-of-theart Quantum Nano Centre, a young and dynamic research faculty, and home to hundreds of Canada's best nanotechnology engineering students, is positioned to contribute to that growth as one of the foremost centers for nanoresearch and innovation in the world. From developments in advanced lithium-ion battery technologies, next-generation solar photovoltaic cells, and thermoelectric conversion materials to hybrid bionanocomposite materials and nanocatalysts, advances in fundamental understanding of materials design will lead to real-world applications. WIN anticipates major progress in organic electronic devices, large-area displays, and miniaturized CNTs or graphene-based X-ray sources. Single-electron and single-photon quantum devices enabled by nanotechnology will be fabricated and employed in quantum information processing. Handheld lab-on-a-chip diagnostic devices with microfluidic flow in channels controlled by electric fields will become a reality for disease and pathogen diagnosis, replacing more bulky and

expensive analytical instrumentation. Drugs encapsulated in nanoparticles delivering therapies directly to a cancerous tissue will be in clinical trials for early adoption, and new, innovative nanotools for imaging and measurement will be introduced. These are only a few of the exciting results researchers expect to see from the next ten years of research at WIN. [J28]

"A Spatio-Temporal Deconvolution Method to Improve Perfusion CT Quantification"

Perfusion imaging is a useful adjunct to anatomic imaging in numerous diagnostic and therapy-monitoring settings. One approach to perfusion imaging is to assume a convolution relationship between a local arterial input function and the tissue enhancement profile of the region of interest via a ??residue function?? and subsequently solve for this residue function. This ill-posed problem is generally solved using singular-value decomposition based approaches, and the hemodynamic parameters are solved for each voxel independently. In this paper, we present a formulation which incorporates both spatial and temporal correlations, and show through simulations that this new formulation yields higher accuracy and greater robustness with respect to image noise. We also show using rectal cancer tumor images that this new formulation results in better segregation of normal and cancerous voxels. [J29]

"Biomedical Nanomagnetics: A Spin Through Possibilities in Imaging, Diagnostics, and Therapy"

Biomedical nanomagnetics is a multidisciplinary area of research in science, engineering and medicine with broad applications in imaging, diagnostics and therapy. Recent developments offer exciting possibilities in personalized medicine provided a truly integrated approach, combining chemistry, materials science, physics, engineering, biology and medicine, is implemented. Emphasizing this perspective, here we address important issues for the rapid development of the field, i.e., magnetic behavior at the nanoscale with emphasis on the relaxation dynamics, synthesis and surface functionalization of nanoparticles and core-shell structures, biocompatibility and toxicity studies, biological constraints and opportunities, and in vivo and in vitro applications. Specifically, we discuss targeted drug delivery and triggered release, novel contrast agents for magnetic resonance imaging, cancer therapy using magnetic fluid hyperthermia, in vitro diagnostics and the emerging magnetic particle imaging technique, that is quantitative and sensitive enough to compete with established imaging methods. In addition, the physics of self-assembly, which is fundamental to both biology and the future development of nanoscience, is illustrated with magnetic nanoparticles. It is shown that various competing energies associated with self-assembly converge on the nanometer length scale and different assemblies can be tailored by varying particle size and size distribution. Throughout this paper, while we discuss our recent research in the broad context of the multidisciplinary literature, we hope to bridge the gap between related work in physics/chemistry/engineering and biology/medicine and, at the same time, present the essential concepts in the individual disciplines. This approach is essential as biomedical nanomagnetics moves into the next phase of innovative translational research with emphasis on development of quantitative in vivo imaging, targeted and triggered drug release, and imag--e guided therapy including validation of delivery and therapy response. [J30]

"Virtual Biopsy [JPoint of View]"

Biopsy is a medical procedure involving the surgical removal of tissue for close examination. As a rule, a biopsy is performed on suspected cancerous tissue in order to determine the appearance of cancer cells and the cancer stage. Obtaining accurate evaluation of the suspected tissue requires high-resolution optical imaging that allows a clear view of the cell structure. This requires chemical treatment in some cases, freezing, dying, thinly slicing, and examining the tissue under a high-magnification microscope. The downside of the biopsy is that it is an invasive surgical procedure, there could be serious surgical complications such as bleeding and/or infection, and it can take several days to weeks before the final pathological report is ready to be presented to the patient. These limitations have motivated researchers to develop ways to achieve a high-resolution internal cellular imaging of the cancerous tissue noninvasively and in real time. From the advent of noninvasive three-dimensional (3D) imaging techniques such as ultrasound and magnetic resonance imaging (MRI) for more than 50 and 30 years, respectively, there have been extensive efforts by many researchers to attain "virtual biopsy." Some techniques have been shown and proven to be highly effective diagnostic tools for different cancer types. However, none is being effectively developed as a screening tool that can replace traditional biopsy. Consequently, many people in the field are asking and wondering if virtual biopsy is a realistic screening tool for the future. A proper screening of the cancerous tissue requires highly magnified images of an internal cellular structure. In order to perform subsurface imaging, 3D imaging modalities such as computed tomography (CT) scan, MRI, ultrasound, optical coherence tomography (OCT), and confocal microscope could be used and could be candidates for "virtual biopsy." This paper will discuss some of the proposed techniques for virtual biopsy. [J31]

"Computer-Aided Diagnosis With Temporal Analysis to Improve Radiologists' Interpretation of

Mammographic Mass Lesions"

The purpose of this study was to evaluate the effect of independent reading with computer-aided diagnosis (CAD) and independent double reading on radiologists' performance to characterize mass lesions on serial mammograms. Six radiologists rated 198 cases, 99 benign and 99 malignant. For each case, the mammograms from two consecutive screening rounds were available. The mass was visible on the prior view in 40% of the cases. Independently, a CAD programe also rated each mass lesion making use of information from prior and current views. The following reading situations were compared: single reading, independent reading with CAD, and independent double reading. Independent reading with CAD was implemented by averaging the scaled ratings from each radiologist and the scaled CAD scores. We implemented independent double reading by averaging the scaled scores from two radiologists. Results were evaluated using receiver-operating characteristic (ROC) methodology and multiple reader multiple case analysis. The average performance, measured as the area under the ROC curve (Azvalue), was 0.80 for the single-reading mode. For independent double reading, the average performance improved to 0.81. This improvement was not significant. For independent interpretation with CAD, the average performance significantly increased to 0.83 ($P < 0.05$). We conclude that CAD technology with temporal analysis has the potential to help radiologists with the task of discriminating between benign and malignant masses. [J32]

"Real-Time Viewer for Positron Emission Mammography Guided Biopsy"

PEM-guided biopsy is successful in localizing sub-centimeter lesions that cannot be seen by other modalities. To help the physician quickly visualize the position of an interventional device in relation to a lesion, we have developed a method to view PEM images in near real time, allowing visualization of lesion displacement within 30 seconds. Phantom and patient data were collected on a commercially available high-resolution, organ-specific PET scanner. The real-time display is realized by showing only one imaging plane and calculating the intersection point of each line of response through a plane where the lesion was targeted based on a prior diagnostic-quality scan. A variety of refresh and persistence times from 2 to 30 seconds were evaluated. In a phantom study both point source and line source movements were successfully visualized in real-time with a refresh time of two seconds and a persistence time of 10 to 15 seconds. Simulation based on real clinical data shows that the localization of lesions can be obtained almost real-time and even relatively faint lesions with a lesion to background ratio of 2:1 can be localized in 10 seconds. [J33]

"Assessment of a Breast Mass Identification Procedure Using an Iris Detector"

Breast cancer is the main cause of cancer deaths among women in the world. About one million new cases appear every year, and about 25% of them lead to the death of the patient. The best solution is the early detection of suspicious tumoral signs through an effective mammographic screening program. Unfortunately, this kind of images is very difficult to interpret by the radiologists because of its very low contrast, so proper image-processing procedures could help them to achieve better diagnoses. This paper improves and assesses an algorithm, already proposed by the authors, that suggests to doctors the suspicious regions that could contain tumoral masses. The procedure succeeds also in the case of very low contrast because it depends only on the orientation of the gradient vectors in the image but not on their amplitude. [J34]

"Snakules: A Model-Based Active Contour Algorithm for the Annotation of Spicules on Mammography"

We have developed a novel, model-based active contour algorithm, termed "snakules", for the annotation of spicules on mammography. At each suspect spiculated mass location that has been identified by either a radiologist or a computer-aided detection (CADe) algorithm, we deploy snakules that are converging open-ended active contours also known as snakes. The set of convergent snakules have the ability to deform, grow and adapt to the true spicules in the image, by an attractive process of curve evolution and motion that optimizes the local matching energy. Starting from a natural set of automatically detected candidate points, snakules are deployed in the region around a suspect spiculated mass location. Statistics of prior physical measurements of spiculated masses on mammography are used in the process of detecting the set of candidate points. Observer studies with experienced radiologists to evaluate the performance of snakules demonstrate the potential of the algorithm as an image analysis technique to improve the specificity of CADe algorithms and as a CADe prompting tool. [J35]

"Introduction to the Issue on Digital Image Processing Techniques for Oncology"

The 17 papers in this special issue focus on digital image processing techniques for oncology. The papers are distributed among cancer detection and diagnosis, image processing, pattern analysis, machine learning, diagnostic decision making and other related areas. [J36]

"Breast Tumor Analysis in Dynamic Contrast Enhanced MRI Using Texture Features and Wavelet Transform"

Dynamic contrast enhanced MRI (DCE-MRI) is an emerging imaging protocol in locating, identifying and characterizing breast cancer. However, due to image artifacts in MR, pixel intensity alone cannot accurately characterize the tissue properties. We propose a robust method based on the temporal sequence of textural change and wavelet transform for pixel-by-pixel classification. We first segment the breast region using an active contour model. We then compute textural change on pixel blocks. We apply a three-scale discrete wavelet transform on the texture temporal sequence to further extract frequency features. We employ a progressive feature selection scheme and a committee of support vector machines for the classification. We trained the system on ten cases and tested it on eight independent test cases. Receiver-operating characteristics (ROC) analysis shows that the texture temporal sequence (Az: 0.966 and 0.949 in training and test) is much more effective than the intensity sequence (Az: 0.871 and 0.868 in training and test). The wavelet transform further improves the classification performance (Az: 0.989 and 0.984 in training and test). [J37]

"Design and Development of a New Multi-Projection X-Ray System for Chest Imaging"

Overlapping anatomical structures may confound the detection of abnormal pathology, including lung nodules, in conventional single-projection chest radiography. To minimize this fundamental limiting factor, a dedicated digital multi-projection system for chest imaging was recently developed at the Radiology Department of Duke University. We are reporting the design of the multi-projection imaging system and its initial performance in an ongoing clinical trial. The system is capable of acquiring multiple full-field projections of the same patient along both the horizontal and vertical axes at variable speeds and acquisition frame rates. These images acquired in rapid succession from slightly different angles about the posterior-anterior (PA) orientation can be correlated to minimize the influence of overlying anatomy. The developed system has been tested for repeatability and motion blur artifacts to investigate its robustness for clinical trials. Excellent geometrical consistency was found in the tube motion, with positional errors for clinical settings within 1%. The effect of tube-motion on the image quality measured in terms of impact on the modulation transfer function (MTF) was found to be minimal. The system was deemed clinic-ready and a clinical trial was subsequently launched. The flexibility of image acquisition built into the system provides a unique opportunity to easily modify it for different clinical applications, including tomosynthesis, correlation imaging (CI), and stereoscopic imaging. [J38]

"A Unified Model-Based Image Analysis Framework for Automated Detection of Precancerous Lesions in Digitized Uterine Cervix Images"

A unified framework for a fully automated diagnostic system for cervical intraepithelial neoplasia (CIN) is proposed. CIN is a detectable and treatable precursor pathology of cancer of the uterine cervix. Algorithms based on mathematical morphology, and clustering based on Gaussian mixture modeling (GMM) in a joint color and geometric feature space, are used to segment macro regions. A non-parametric technique, based on the transformation and analysis of the D(R) (distortion-rate) curve is proposed to assess the model order. This technique provides good starting points to infer the GMM parameters via the expectation-maximization (EM) algorithm, reducing the segmentation time and the chances of getting trapped in local optima. The classification of vascular abnormalities in CIN, such as mosaicism and punctations, is modeled as a texture classification problem, and a solution is attempted by characterizing the neighborhood gray-tone dependences and co-occurrence statistics of the textures. The model presented in this paper provides a sequential framework for translating digital images of the cervix into a complete diagnostic tool, with minimal human intervention. In its current form, the research presented in this work may be used to aid physicians to locate abnormalities due to CIN and assess the best areas for a biopsy. [J39]

"Assisted Diagnosis of Cervical Intraepithelial Neoplasia (CIN)"

This paper introduces an automated computer- assisted system for the diagnosis of cervical intraepithelial neoplasia (CIN) using ultra-large cervical histological digital slides. The system contains two parts: the segmentation of squamous epithelium and the diagnosis of CIN. For the segmentation, to reduce processing time, a multiresolution method is developed. The squamous epithelium layer is first segmented at a low (2X) resolution. The boundaries are further fine tuned at a higher (20X) resolution. The block-based segmentation method uses robust texture feature vectors in combination with support vector machines (SVMs) to perform classification. Medical rules are finally applied. In testing, segmentation using 31 digital slides achieves 94.25% accuracy. For the diagnosis of CIN, changes in nuclei structure and morphology along lines perpendicular to the main axis of the squamous epithelium are quantified and classified. Using multi-category SVM, perpendicular lines are classified into Normal, CIN I, CIN II, and CIN III. The robustness of the system in term of regional

diagnosis is measured against pathologists' diagnoses and inter-observer variability between two pathologists is considered. Initial results suggest that the system has potential as a tool both to assist in pathologists' diagnoses, and in training. [J40]

"Learning of Perceptual Similarity From Expert Readers for Mammogram Retrieval"

Content-based image retrieval relies critically on the use of a computerized measure of the similarity (i.e., relevance) of a query image to other images in a database. In this work, we explore a superivised learning approach for retrieval of mammogram images, of which the goal is to serve as a diagnostic aid for breast cancer. We propose that the most meaningful measure is one that is designed specifically to match that perceived by the radiologists in their interpretation of mammogram lesions. In our approach, we model the notion of similarity as an unknown function of the image features characterizing the lesions, and use modern machine-learning algorithms to learn this function from similarity scores collected from radiologists in reader studies. This approach is evaluated using data collected from an observer study with a set of clinical mammograms. Our results demonstrate that the proposed machine learning approach can be used to model the notion of similarity as judged by expert readers in their interpretation of mammogram images and that it can outperform alternative similarity measures derived from unsupervised learning. [J41]

"Noise-Enhanced Detection of Micro-Calcifications in Digital Mammograms"

The appearance of micro-calcifications in mammograms is a crucial early sign of breast cancer. Automatic micro-calcification detection techniques play an important role in cancer diagnosis and treatment. This, however, still remains a challenging task. This paper presents novel algorithms for the detection of micro-calcifications using stochastic resonance (SR) noise. In these algorithms, a suitable dose of noise is added to the abnormal mammograms such that the performance of a suboptimal lesion detector is improved without altering the detector's parameters. First, a SR noise-based detection approach is presented to improve some suboptimal detectors which suffer from model mismatch due to the Gaussian assumption. Furthermore, a SR noise-based detection enhancement framework is presented to deal with more general model mismatch cases. Our algorithms and the framework are tested on a set of 75 representative abnormal mammograms. They yield superior performance when compared with several classification and detection approaches developed in our work as well as those available in the literature. [J42]

"Image Feature Extraction in the Last Screening Mammograms Prior to Detection of Breast Cancer"

Image feature extraction was utilized to retrospectively analyze screening mammograms taken prior to the detection of a malignant mass for early detection of breast cancer. The mammograms of 58 biopsy proven breast cancer patients were collected. In each case, the mammograms taken 10 to 18 months prior to cancer detection were evaluated. For each of the two mammographic projections of the abnormal breast, two regions were marked: 1) region one, which corresponded to the site where the malignant mass subsequently developed and 2) a region which appeared similar to region one on the same mammogram. On each projection of the normal breast a third region which corresponds to region one but on the opposite breast was also marked (mirror-image site). Sixty-two texture and photometric image features were then calculated for all of the marked areas. A stepwise discriminant analysis showed that six of these features could be used to best distinguish between the normal and abnormal regions. The best linear classification function resulted in a 72% average classification. At its current stage, the system can be used by a radiologist to examine any pattern in a mammogram. The regions which are flagged by the system have a 72% chance of developing a malignant mass by the time of the next screening. Therefore, further evaluation of these patients (e.g., a screening examination sooner than the normal one year interval) could result in earlier detection of breast cancer. The ultimate goal is to run the system automatically over the whole mammogram and flag any suspicious area. [J43]

"A Direct Image Contrast Enhancement Algorithm in the Wavelet Domain for Screening Mammograms"

In breast cancer diagnosis, the radiologists mainly use their eyes to discern cancer when they screen the mammograms. However, in many cases, cancer is not easily detected by the eyes because of the bad imaging conditions. In order to improve the correct diagnosis rate of cancer, image-enhancement technology is often used to enhance the image and aid the radiologists. In this paper, we develop a new image-enhancement technology in the wavelet domain for radiologists to screen mammograms. The new image-enhancement algorithm has several advantages. First, the proposed image-enhancement technology modifies a multiscale measure which matches the human vision system and thus the enhanced images have better visual quality; second, the image enhancement is accomplished in the wavelet domain and thus it can save time if the image is

compressed by wavelet transform based methods; third, the end users can adjust the enhancement by manipulating a single parameter. Experiments were performed on mammograms and the results are progressive. [J44]

"Comparison and Evaluation of Methods for Liver Segmentation From CT Datasets"

This paper presents a comparison study between 10 automatic and six interactive methods for liver segmentation from contrast-enhanced CT images. It is based on results from the "MICCAI 2007 Grand Challenge" workshop, where 16 teams evaluated their algorithms on a common database. A collection of 20 clinical images with reference segmentations was provided to train and tune algorithms in advance. Participants were also allowed to use additional proprietary training data for that purpose. All teams then had to apply their methods to 10 test datasets and submit the obtained results. Employed algorithms include statistical shape models, atlas registration, level-sets, graph-cuts and rule-based systems. All results were compared to reference segmentations five error measures that highlight different aspects of segmentation accuracy. All measures were combined according to a specific scoring system relating the obtained values to human expert variability. In general, interactive methods reached higher average scores than automatic approaches and featured a better consistency of segmentation quality. However, the best automatic methods (mainly based on statistical shape models with some additional free deformation) could compete well on the majority of test images. The study provides an insight in performance of different segmentation approaches under real-world conditions and highlights achievements and limitations of current image analysis techniques. [J45]

"Network-Based Inference of Cancer Progression from Microarray Data"

Cancer cells exhibit a common phenotype of uncontrolled cell growth, but this phenotype may arise from many different combinations of mutations. By inferring how cells evolve in individual tumors, a process called cancer progression, we may be able to identify important mutational events for different tumor types, potentially leading to new therapeutics and diagnostics. Prior work has shown that it is possible to infer frequent progression pathways by using gene expression profiles to estimate ldquodistancesrdquo between tumors. Here, we apply gene network models to improve these estimates of evolutionary distance by controlling for correlations among coregulated genes. We test three variants of this approach: one using an optimized best-fit network, another using sampling to infer a high-confidence subnetwork, and one using a modular network inferred from clusters of similarly expressed genes. Application to lung cancer and breast cancer microarray data sets shows small improvements in phylogenies when correcting from the optimized network and more substantial improvements when correcting from the sampled or modular networks. Our results suggest that a network correction approach improves estimates of tumor similarity, but sophisticated network models are needed to control for the large hypothesis space and sparse data currently available. [J46]

"Effect of Oblique X-ray Incidence in Flat-Panel Computed Tomography of the Breast"

We quantify the variation in resolution due to anisotropy caused by oblique X-ray incidence in indirect flat-panel detectors for computed tomography breast imaging systems. We consider a geometry and detector type utilized in breast computed tomography (CT) systems currently being developed. Our methods rely on MANTIS, a combined X-ray, electron, and optical Monte Carlo transport open source code. The physics models are the most accurate available in general-purpose Monte Carlo packages in the diagnostic energy range. We consider maximum-obliquity angles of 10deg and 13deg at the centers of the 30 and 40 cm detector edges, respectively, and 16deg at the corner of the detector. Our results indicate that blur is asymmetric and that the resolution properties vary significantly with the angle (or location) of incidence. Our results suggest that the asymmetry can be as high as a factor of 2.6 between orthogonal directions. Anisotropy maps predicted by MANTIS provide an understanding of the effect that such variations have on the imaging system and allow more accurate modeling and optimization of breast CT systems. These maps of anisotropy across the detector could lead to improved reconstruction and help motivate physics-based strategies for computer detection of breast lesions. [J47]

"Measuring Objective Quality of Colonoscopy"

Advances in video technology are being incorporated into today's healthcare practices. Colonoscopy is regarded as one of the most important diagnostic tools for colorectal cancer. Indeed, colonoscopy has contributed to a decline in the number of colorectal-cancer-related deaths. Although colonoscopy has become the preferred screening modality for prevention of colorectal cancer, recent data suggest that there is a significant miss rate for the detection of large polyps and cancers, and methods to investigate why this occurs are needed. To address this problem, we present a new computer-based method that analyzes a digitized video file of a colonoscopic procedure and produces a number of metrics that likely reflect the quality of the procedure. The method consists of a set of novel image-processing algorithms designed to address new technical challenges due to uncommon

characteristics of videos captured during colonoscopy. As these measurements can be obtained automatically, our method enables future quality control in large-scale day-to-day medical practice, which is currently not feasible. In addition, our method can be adapted to other endoscopic procedures such as upper gastrointestinal endoscopy, enteroscopy, and bronchoscopy. Last but not least, our method may be useful to assess progress during colonoscopy training. [J48]

"Automated Method for Improving System Performance of Computer-Aided Diagnosis in Breast Ultrasound"

The purpose of this research was to demonstrate the feasibility of a computerized auto-assessment method in which a computer-aided diagnosis (CADx) system itself provides a level of confidence for its estimate for the probability of malignancy for each radiologist-identified lesion. The computer performance was assessed within a leave-one-case-out protocol using a database of sonographic images from 542 patients (19% cancer prevalence). We investigated the potential of computer-derived confidence levels both as 1) an output aid to radiologists and 2) as an automated method to improve the computer classification performance-in the task of differentiating between cancerous and benign lesions for the entiredatabase. For the former, the CADxclassification performance was assessed within ranges of confidence levels. For the latter, the computer-derived confidence levels were used in the determination of the computer-estimated probability of malignancy for each actual lesion based on probabilities obtained from different views. The use of this auto-assessment method resulted in the modest but statistically significant increase in the area under the receiver operating characteristic (ROC) curve (AUC value) of 0.01 with respect to the performance obtained using the ldquotraditionalrdquo CADxapproach, increasing the AUC value from 0.89 to 0.90 (p-value 0.03). We believe that computer-provided confidence levels may be helpful to radiologists who are using CADxoutput in diagnostic image interpretation as well as for automated improvement of the CADxclassification for cancer. [J49]

"-Information Measures for Efficient Selection of Discriminative Genes From Microarray Data"

Among the great amount of genes presented in microarray gene expression data, only a small fraction is effective for performing a certain diagnostic test. In this regard, mutual information has been shown to be successful for selecting a set of relevant and nonredundant genes from microarray data. However, information theory offers many more measures such as the f-information measures that may be suitable for selection of genes from microarray gene expression data. This paper presents different f-information measures as the evaluation criteria for gene selection problem. To compute the gene-gene redundancy (respectively, gene-class relevance), these information measures calculate the divergence of the joint distribution of two genes' expression values (respectively, the expression values of a gene and the class labels of samples) from the joint distribution when two genes (respectively, the gene and class label) are considered to be completely independent. The performance of different f-information measures is compared with that of the mutual information based on the predictive accuracy of naive Bayes classifier, K-nearest neighbor rule, and support vector machine. An important finding is that some f-information measures are shown to be effective for selecting relevant and nonredundant genes from microarray data. The effectiveness of different f-information measures, along with a comparison with mutual information, is demonstrated on breast cancer, leukemia, and colon cancer datasets. While some f-information measures provide 100% prediction accuracy for all three microarray datasets, mutual information attains this accuracy only for breast cancer dataset, and 98.6% and 93.6% for leukemia and colon cancer datasets, respectively. [J50]

"The Design and Evaluation of a Computerized and Physical Simulator for Training Clinical Prostate Exams"

The most effective screening for prostate cancer combines the prostate specific antigen blood test with the digital rectal examination (DRE). In performing a DRE, two sequential tasks are completed: (taska) palpating the prostate to identify abnormalities and (taskb) linking identified abnormalities to a disease diagnosis. At present, clinicians find too few abnormalities and have variable rates of detection, due in part to the inadequacy of training simulators. The Virginia Prostate Examination Simulator (VPES) was designed, built, and tested to address the inadequacies of current simulators by incorporating the design requirements of the basic elements of accurate anatomy, multiple and reconfigurable scenarios of graded difficulty, and technique and performance feedback. We compared the training effectiveness of the VPES with two commercial simulators in an experiment of 36 medical and nurse practitioner students. Results indicate each type of training simulator-improved abilities, in general. Upon closer analysis, however, the following key patterns emerge: 1) Across all types of training, more deficiencies lie in skill-based rather than rule-based decision making, which improves only for VPES trainees; 2) only VPES training transfers both to other simulators and previously unencountered scenarios; 3) visual feedback may increase the number of abnormalities reported yet hinder the ability to discriminate; and 4) applied finger pressure did not correlate with the ability to identify abnormalities. [J51]

"Computer-Aided Detection and Diagnosis of Breast Cancer With Mammography: Recent Advances"

Breast cancer is the second-most common and leading cause of cancer death among women. It has become a major health issue in the world over the past 50 years, and its incidence has increased in recent years. Early detection is an effective way to diagnose and manage breast cancer. Computer-aided detection or diagnosis (CAD) systems can play a key role in the early detection of breast cancer and can reduce the death rate among women with breast cancer. The purpose of this paper is to provide an overview of recent advances in the development of CAD systems and related techniques. We begin with a brief introduction to some basic concepts related to breast cancer detection and diagnosis. We then focus on key CAD techniques developed recently for breast cancer, including detection of calcifications, detection of masses, detection of architectural distortion, detection of bilateral asymmetry, image enhancement, and image retrieval. [J52]

"Segmentation of Lung Lobes in High-Resolution Isotropic CT Images"

Modern multislice computed tomography (CT) scanners produce isotropic CT images with a thickness of 0.6 mm. These CT images offer detailed information of lung cavities, which could be used for better surgical planning of treating lung cancer. The major challenge for developing a surgical planning system is the automatic segmentation of lung lobes by identifying the lobar fissures. This paper presents a lobe segmentation algorithm that uses a two-stage approach: (1) adaptive fissure sweeping to find fissure regions and (2) wavelet transform to identify the fissure locations and curvatures within these regions. Tested on isotropic CT image stacks from nine anonymous patients with pathological lungs, the algorithm yielded an accuracy of 76.7%-94.8% with strict evaluation criteria. In comparison, surgeons obtain an accuracy of 80% for localizing the fissure regions in clinical CT images with a thickness of 2.5-7.0 mm. As well, this paper describes a procedure for visualizing lung lobes in three dimensions using software-amira-and the segmentation algorithm. The procedure, including the segmentation, needed about 5 min for each patient. These results provide promising potential for developing an automatic algorithm to segment lung lobes for surgical planning of treating lung cancer. [J53]

"PathMiner: A Web-Based Tool for Computer-Assisted Diagnostics in Pathology"

Large-scale, multisite collaboration has become indispensable for a wide range of research and clinical activities that rely on the capacity of individuals to dynamically acquire, share, and assess images and correlated data. In this paper, we report the development of a Web-based system, PathMiner, for interactive telemedicine, intelligent archiving, and automated decision support in pathology. The PathMiner system supports network-based submission of queries and can automatically locate and retrieve digitized pathology specimens along with correlated molecular studies of cases from ldquoground-truthrdquo databases that exhibit spectral and spatial profiles consistent with a given query image. The statistically most probable diagnosis is provided to the individual who is seeking decision support. To test the system under real-case scenarios, a pipeline infrastructure was developed and a network-based test laboratory was established at strategic sites at the University of Medicine and Dentistry of New Jersey-Robert Wood Johnson Medical School, Robert Wood Johnson University Hospital, the University of Pennsylvania School of Medicine, Hospital of the University of Pennsylvania, The Cancer Institute of New Jersey, and Rutgers University. The average five-class classification accuracy of the system was 93.18% based on a tenfold cross validation on a close dataset containing 3691 imaged specimens. We also conducted prospective performance studies with the PathMiner system in real applications in which the specimens exhibited large variations in staining characters compared with the training data. The average five-class classification accuracy in this open-set experiment was 87.22%. We also provide the comparative results with the previous literature and the PathMiner system shows superior performance. [J54]

"An Extended Markov Blanket Approach to Proteomic Biomarker Detection From High-Resolution Mass Spectrometry Data"

High-resolution matrix-assisted laser desorption/ionization time-of-flight mass spectrometry has recently shown promise as a screening tool for detecting discriminatory peptide/protein patterns. The major computational obstacle in finding such patterns is the large number of mass/charge peaks (features, biomarkers, data points) in a spectrum. To tackle this problem, we have developed methods for data preprocessing and biomarker selection. The preprocessing consists of binning, baseline correction, and normalization. An algorithm, extended Markov blanket, is developed for biomarker detection, which combines redundant feature removal and discriminant feature selection. The biomarker selection couples with support vector machine to achieve sample prediction from high-resolution proteomic profiles. Our algorithm is applied to recurrent ovarian cancer study that contains platinum-sensitive and platinum-resistant samples after treatment. Experiments show that the proposed method performs better than other feature selection algorithms. In particular, our algorithm yields good performance in

terms of both sensitivity and specificity as compared to other methods. [J55]

"Ultrasound-mediated drug delivery"

Although ultrasound-based drug delivery has only seen limited clinical use for transdermal drug delivery, there has been considerable momentum in research aimed at using ultrasound for a wide variety of medical applications. Ultrasound-mediated gene therapy using sonoporation and targeted delivery has progressed from in vitro proof-of-concept studies to produce biological effects in angiogenesis and diabetes studies. These techniques have also been used for cancer therapy, thrombolysis, and disruption of the blood-brain barrier in animal models. It is also worth noting that ultrasound can facilitate targeted drug delivery through thermal means, in addition to the mechanisms associated with cavitation. Ultrasound hyperthermia can be used to target thermally sensitive drug-carrying liposomes or to induce gene expression through localized heat shock response. [J56]

"X-ray elastography: Modification of x-ray phase contrast images using ultrasonic radiation pressure"

The high resolution characteristic of in-line x-ray phase contrast imaging can be used in conjunction with directed ultrasound to detect small displacements in soft tissue generated by differential acoustic radiation pressure. The imaging method is based on subtraction of two x-ray images, the first image taken with, and the second taken without the presence of ultrasound. The subtraction enhances phase contrast features and, to a large extent, removes absorption contrast so that differential movement of tissues with different acoustic impedances or relative ultrasonic absorption is highlighted in the image. Interfacial features of objects with differing densities are delineated in the image as a result of both the displacement introduced by the ultrasound and the inherent sensitivity of x-ray phase contrast imaging to density variations. Experiments with ex vivo murine tumors and human tumor phantoms point out a diagnostic capability of the method for identifying tumors. [J57]

"Guest Editorial: Introduction to the Special Section on Biomedical Informatics"

The five papers in this special section provide a snapshot of emerging technologies in biomedical informatics. The selected papers were originally presented at the International Special Topic Conference on Information Technology in Biomedicine, held in October 2006, in Ioannina, Epirus, Greece. [J58]

"The tissue diagnostic instrument"

Tissue mechanical properties reflect extracellular matrix composition and organization, and as such, their changes can be a signature of disease. Examples of such diseases include intervertebral disk degeneration, cancer, atherosclerosis, osteoarthritis, osteoporosis, and tooth decay. Here we introduce the tissue diagnostic instrument (TDI), a device designed to probe the mechanical properties of normal and diseased soft and hard tissues not only in the laboratory but also in patients. The TDI can distinguish between the nucleus and the annulus of spinal disks, between young and degenerated cartilage, and between normal and cancerous mammary glands. It can quantify the elastic modulus and hardness of the wet dentin left in a cavity after excavation. It can perform an indentation test of bone tissue, quantifying the indentation depth increase and other mechanical parameters. With local anesthesia and disposable, sterile, probe assemblies, there has been neither pain nor complications in tests on patients. We anticipate that this unique device will facilitate research on many tissue systems in living organisms, including plants, leading to new insights into disease mechanisms and methods for their early detection. [J59]

"Development of microfluidic device and system for breast cancer cell fluorescence detection"

A biomicrofluidic device and a compact cellular testing system were developed to be used in cancer diagnostics. The device was fabricated by lithography-based microfabrication techniques, followed by two-step etching of deep reactive ion etching, and channels were formed by anodic bonding of Si and Pyrex. The device is based on the capture of cells inside a new meandering weir-type filter design, followed by detection and characterization using specific fluorescent labeling. Breast cancer cells MCF-7 and control cells MCF-10A were flowed through the microfluidic channels, and captured by meandering weir-type filters. 17beta -Estradiaol(E2)-BSA (bovine serum albumin)-FITC (fluorescein isothiocyanate) macromolecular complex was found to selectively label MCF-7, potentially serving as a cancer cell detection marker. MCF-7 cells were detected with specific and strong FITC signals after only 4minof contact with the stain. The signals were about seven times stronger than that of a labeling performed on conventional glass slides. These results strongly suggest that this novel design has a potential application to detect cancer cells or other diseased cells without compromising the advantage of high sensitivity of the microfluidic approach. [J60]

"A multimodal spectroscopy system for real-time disease diagnosis"

The combination of reflectance, fluorescence, and Raman spectroscopy-termed multimodal spectroscopy (MMS)-provides complementary and depth-sensitive information about tissue composition. As such, MMS is a promising tool for disease diagnosis, particularly in atherosclerosis and breast cancer. We have developed an integrated MMS instrument and optical fiber spectral probe for simultaneous collection of all three modalities in a clinical setting. The MMS instrument multiplexes three excitation sources, a xenon flash lamp (370-740 nm), a nitrogen laser (337 nm), and a diode laser (830 nm), through the MMS probe to excite tissue and collect the spectra. The spectra are recorded on two spectrograph/charge-coupled device modules, one optimized for visible wavelengths (reflectance and fluorescence) and the other for the near-infrared (Raman), and processed to provide diagnostic parameters. We also describe the design and calibration of a unitary MMS optical fiber probe 2 mm in outer diameter, containing a single appropriately filtered excitation fiber and a ring of 15 collection fibers, with separate groups of appropriately filtered fibers for efficiently collecting reflectance, fluorescence, and Raman spectra from the same tissue location. A probe with this excitation/collection geometry has not been used previously to collect reflectance and fluorescence spectra, and thus physical tissue models ("phantoms") are used to characterize the probe's spectroscopic response. This calibration provides probe-specific modeling parameters that enable accurate extraction of spectral parameters. This clinical MMS system has been used recently to analyze artery and breast tissue in vivo and ex vivo. [J61]

"Prostate Brachytherapy Seed Reconstruction With Gaussian Blurring and Optimal Coverage Cost"

Intraoperative dosimetry in prostate brachytherapy requires localization of the implanted radioactive seeds. A tomosynthesis-based seed reconstruction method is proposed. A three-dimensional volume is reconstructed from Gaussian-blurred projection images and candidate seed locations are computed from the reconstructed volume. A false positive seed removal process, formulated as an optimal coverage problem, iteratively removes ldquoghostrdquo seeds that are created by tomosynthesis reconstruction. In an effort to minimize pose errors that are common in conventional C-arms, initial pose parameter estimates are iteratively corrected by using the detected candidate seeds as fiducials, which automatically ldquofocusesrdquo the collected images and improves successive reconstructed volumes. Simulation results imply that the implanted seed locations can be estimated with a detection rate of ges97.9% and ges99.3% from three and four images, respectively, when the C-arm is calibrated and the pose of the C-arm is known. The algorithm was also validated on phantom data sets successfully localizing the implanted seeds from four or five images. In a Phase-1 clinical trial, we were able to localize the implanted seeds from five intraoperative fluoroscopy images with 98.8% (STD=1.6) overall detection rate. [J62]

"Electrical detection of proteins and DNA using bioactivated microfluidic channels: Theoretical and experimental considerations"

In order to detect diseases such as cancer at an early stage while it still may be curable, it is necessary to develop a diagnostic technique which can rapidly and inexpensively detect protein and nucleic acid biomarkers, without making any sacrifice in the sensitivity. The authors have developed a technique, based on the use of bioactivated microfluidic channels integrated with electrodes for electrical sensing, which can be used to detect protein biomarkers, target cells, and DNA hybridization. In this article, they discuss the theoretical detection limits of this kind of sensor and also discuss various experimental considerations in the electrical characterization of our device. In particular, they discuss the temperature dependence, the impedance drift, the noise sources, and various methods for optimizing the signal to noise ratio. [J63]

"Atomic force microscopic study of folate receptors in live cells with functionalized tips"

Membrane associated folate receptors (FR) is gaining importance in cancer research. Understanding the FR density, distribution, and the strength of its interaction with ligands is crucial in cancer diagnostics and therapeutics. Here we reported the enhanced phase contrast image of FR by scanning with properly functionalized atomic force microscope (AFM) tips over live cell lines. The choice of the ligand was made for better interaction of tip with FR, expressed in the cell lines. The selectively enhanced force of interaction at the receptor molecule produced a considerable enhancement in the phase contrast between a receptor site and a nonreceptor site. [J64]

"Potential of Computer-Aided Diagnosis to Improve CT Lung Cancer Screening"

The development of low-dose spiral computed tomography (CT) has rekindled hope that effective lung cancer screening might yet be found. Screening is justified when there is evidence that it will extend lives at reasonable

cost and acceptable levels of risk. A screening test should detect all extant cancers while avoiding unnecessary workups. Thus optimal screening modalities have both high sensitivity and specificity. Due to the present state of technology, radiologists must opt to increase sensitivity and rely on follow-up diagnostic procedures to rule out the incurred false positives. There is evidence in published reports that computer-aided diagnosis technology may help radiologists alter the benefit-cost calculus of CT sensitivity and specificity in lung cancer screening protocols. This review will provide insight into the current discussion of the effectiveness of lung cancer screening and assesses the potential of state-of-the-art computer-aided design developments. [J65]

"MEMS-Based Selective Preconcentration of Trace Level Breath Analytes"

This paper presents high-performance micropreconcentrators (muPCs) aimed at breath analysis and a method for eliminating unwanted species from breath samples by using a two-step preconcentration procedure. The muPC consists of embedded high aspect-ratio three-dimensional (3-D) micro pillars coated with an adsorbent polymer. The silicon-glass die has outer dimensions of 7 mm times 7 mm, total inner surface area of ~ 10 m2, and a total inner volume of ~ 6.5 muL. The muPC has on-chip thermal desorption capability and comprises more than 3500 micro pillars with dimensions of 30 mum times 120 mum times 240 mum. The preconcentration factor of the presented muPCs was measured to be above 10 000. Results showed the possibility of selective preconcentration by cascading multiple muPCs with temperature and flow control. The work presented here has profound implications for handheld point-of-care breath analysis instrumentation by first concentrating trace levels of VOCs found in human breath undergoing anesthesia such as n-decane (C10), n-dodecane (C12), 2,6-diisopropylphenol (Propofol), n-tetradecane (C14), and n-hexadecane (C16). Second, it succeeded in eliminating water-like solvent (1-propanol) from the sample to be analyzed. Third, it selectively preconcentrated target compound such as Propofol which is used for medical procedures. The relative concentration of Propofol to C14was changed from 50% (with one muPC) to 99.8% (with cascaded muPC). The water-like solvent was also eliminated by 99.9%. [J66]

"Microcalcification border characterization"

Breast cancer is a disease that can be treated if detected in its early stages. Microcalcifications are high-frequency components on digital images. A transform that deals with frequency components can be used in trying to detect these objects on the breast image. We used the wavelet transform on the proposed work to detect these elements and to classify the nature of their borders, being smooth or rugged. [J67]

"Acoustic imaging of thick biological tissue"

Up to now, biomedical imaging with ultrasound for observing a cellular tissue structure has been limited to very thinly sliced tissue at very high ultrasonic frequencies, i.e., 1 GHz. In this paper, we present the results of a systematic study to use a 150 to 200 MHz frequency range for thickly sliced biological tissue. A mechanical scanning reflection acoustic microscope (SAM) was used for obtaining horizontal cross-sectional images (C-scans) showing cellular structures. In the study, sectioned specimens of human breast cancer and tissues from the small intestine were prepared and examined. Some accessories for biomedical application were integrated into our SAM (Sonix HS-1000 and Olympus UH-3), which operated in pulse-wave and tone-burst wave modes, respectively. We found that the frequency 100 to 200 MHz provides optimal balance between resolution and penetration depth for examining the thickly sliced specimens. The images obtained with the lens focused at different depths revealed cellular structures whose morphology was very similar to that seen in the thinly sectioned specimens with optical and scanning acoustic microscopy. The SAM operation in the pulse-echo mode permits the imaging of tissue structure at the surface, and it also opens up the potential for attenuation imaging representing reflection from the substrate behind the thick specimen. We present such images of breast cancer proving the method's applicability to overall tumor detection. SAM with a high-frequency tone-burst ultrasonic wave reveals details of tissue structure, and both methods may serve as additional diagnostic tools in a hospital environment. [J68]

"Numerical FEM Models for the Planning of Magnetic Induction Hyperthermia Treatments With Nanoparticles"

A numerical FEM model of a magnetic fluid hyperthermia (MFH) treatment on an hepatocellular carcinoma (HCC) metastasis has been simulated. Starting from actual CT images of the patient, a 3-D geometry of the anatomical district has been reconstructed and a coupled electromagnetic and thermal transient analysis has been performed, in order to predict the temperature distribution during the treatment. The invivoeffect of blood perfusion has also been implemented through the Pennes's model. Various simulations have been carried out, based on different particle sizes and concentrations, as well as different exciting field intensities. [J69]

"Tumor Clustering Using Nonnegative Matrix Factorization With Gene Selection"

Tumor clustering is becoming a powerful method in cancer class discovery. Nonnegative matrix factorization (NMF) has shown advantages over other conventional clustering techniques. Nonetheless, there is still considerable room for improving the performance of NMF. To this end, in this paper, gene selection and explicitly enforcing sparseness are introduced into the factorization process. Particularly, independent component analysis is employed to select a subset of genes so that the effect of irrelevant or noisy genes can be reduced. The NMF and its extensions, sparse NMF and NMF with sparseness constraint, are then used for tumor clustering on the selected genes. A series of elaborate experiments are performed by varying the number of clusters and the number of selected genes to evaluate the cooperation between different gene selection settings and NMF-based clustering. Finally, the experiments on three representative gene expression datasets demonstrated that the proposed scheme can achieve better clustering results. [J70]

"Phase-Adaptive Superresolution of Mammographic Images Using Complex Wavelets"

This correspondence describes a new superresolution approach for enhancing the resolution of mammographic images using complex wavelet frequency information. This method allows regions of interest of a mammographic image to be viewed in enhanced resolution while reducing the patient exposure to radiation. The proposed method exploits the structural characteristics of breast tissues being imaged and produces higher resolution mammographic images with sufficient visual fidelity that fine image details can be discriminated more easily. In our approach, the superresolution problem is formulated as a constrained optimization problem using a third-order Markov prior model and adapts the priors based on the phase variations of the low-resolution mammographic images. Experimental results indicate the proposed method is more effective at preserving the visual information when compared with existing resolution enhancement methods. [J71]

"Nanoscintillators for Microscopic Diagnostics of Biological and Medical Objects and Medical Therapy"

The main focus of this paper is the description of qualitatively new facilities for diagnostics of biological and medical objects and medical therapy obtained by applications of nanocrystalline scintillators. These facilities are based on abilities of nanoscintillators to selective conjugation with various biomolecular objects and noticeable variations of their atomic structures, X-ray diffraction (XRD) patterns, and light-emission characteristics induced by modifications of conditions on their external surfaces. Experimental results presented in this paper provide development of detection invivojust inside a living organism of various viruses, cancer cells, and other pathological macromolecules by means of scanning X-ray diffractometry of nanoparticles introduced into the body. These data are produced by selective adsorption of pathological bioobjects by these nanoparticles and subsequent modifications of their XRD patterns. Application of narrow collimated X-ray beams and new types of X-ray detector matrices providing microscopic spatial resolution due to usage of nanoscintillators enables determination of the regions where these pathologies are localized with high accuracy. The procedure of detection of pathological organelles by this method improves possibilities for effective destruction of these pathologies by low-dose X-ray irradiation of the places of their localization. High effectiveness of this X-ray destruction is provided by concentrated absorption of X-ray quanta by the nanoscintillators and direct transfer of the absorbed energy to the pathological objects that are attached to the absorbing particles. Constructions of 3-D radiation detector matrices providing necessary microscopic spatial and angular resolutions of X-ray imaging are described on the basis of nanoscintillators, fiber light guides, and microcapillary matrices. [J72]

"Fluorescence Spectroscopy: An Adjunct Diagnostic Tool to Image-Guided Core Needle Biopsy of the Breast"

We explored the use of a fiber-optic probe for invivofluorescence spectroscopy of breast tissues during percutaneous image-guided breast biopsy. A total of 121 biopsy samples with accompanying histological diagnosis were obtained clinically and investigated in this study. The tissue spectra were analyzed using partial least-squares analysis and represented using a set of principal components (PCs) with dramatically reduced data dimension. For nonmalignant tissue samples, a set of PCs that account for the largest amount of variance in the spectra displayed correlation with the percent tissue composition. For all tissue samples, a set of PCs was identified using a Wilcoxon rank-sum test as showing statistically significant differences between: 1) malignant and fibrous/benign; 2) malignant and adipose; and 3) malignant and nonmalignant breast samples. These PCs were used to distinguish malignant from other nonmalignant tissue types using a binary classification scheme based on both linear and nonlinear support vector machine (SVM) and logistic regression (LR). For the sample set investigated in this study, the SVM classifier provided a cross-validated sensitivity and specificity of up to 81% and 87%, respectively, for discrimination between malignant and fibrous/benign samples, and up to 81% and 81%, respectively, for discriminating between malignant and adipose samples. Classification based on LR

was used to generate receiver operator curves with an area under the curve (AUC) of 0.87 for discriminating malignant versus fibrous/benign tissues, and an AUC of 0.84 for discriminating malignant from adipose tissue samples. This study demonstrates the feasibility of performing fluorescence spectroscopy during clinical core needle breast biopsy, and the potential of this technique for identifying breast malignancy invivo. [J73]

"Imaging System for XRF Microtomography at LNLS-Brazil"

An X-ray transmission microtomography (CT) system combined with an X-ray fluorescence microtomography (XRFCT) system was implemented in the Brazilian Synchrotron Light Laboratory (LNLS), Campinas, Brazil. The main of this work is to determine the elemental distribution map in reference samples and breast tissue samples in order to verify the concentration of some elements correlated with characteristics and pathology of each tissue observed by the transmission CT. The experiments were performed at the X-Ray Fluorescence beamline (D09B-XRF) of the Brazilian Synchrotron Light Laboratory, Campinas, Brazil. A quasi-monochromatic beam produced by a multilayer monochromator was used as an incident beam. The sample was placed on a high precision goniometer and translation stages that allow rotating as well as translating it perpendicularly to the beam. The fluorescence photons were collected with an energy dispersive HPGe detector placed at 90degto the incident beam, while transmitted photons were detected with a fast Na(Tl) scintillation counter placed behind the sample on the beam direction. The CT images were reconstructed using a filtered-back projection algorithm and the XRFCT were reconstructed using a filtered-back projection algorithm with absorption corrections. [J74]

"Overview of Advanced Computer Vision Systems for Skin Lesions Characterization"

During the last years, computer-vision-based diagnosis systems have been used in several hospitals and dermatology clinics, aiming mostly at the early detection of skin cancer, and more specifically, the recognition of malignant melanoma tumour. In this paper, we review the state of the art in such systems by first presenting the installation, the visual features used for skin lesion classification, and the methods for defining them. Then, we describe how to extract these features through digital image processing methods, i.e., segmentation, border detection, and color and texture processing, and we present the most prominent techniques for skin lesion classification. The paper reports the statistics and the results of the most important implementations that exist in the literature, while it compares the performance of several classifiers on the specific skin lesion diagnostic problem and discusses the corresponding findings. [J75]

"Registration Method for the Detection of Tumors in Lung and Liver Using Multimodal Small Animal Imaging"

Small animal PET scanning with 18F-FDG has been increasingly used in the studies using murine tumor models. The aim of this study was to obtain multimodal tumor images with the use of small animal PET and clinical CT by using hardware guidance and a registration method. PET imaging studies were performed with a dedicated small animal PET scanner. Static PET images of mice with liver and lung tumors were scanned for 20 minute by the use of hardware guidance with 1% activity of the injected dose. The CT images obtained with the use of a clinical CT scanner can be used to improve the anatomical localization of uptake in PET images. 124I - FIAU-PET was obtained from mice containing an orthotopic hepatocellular carcinoma (HCC). Contrast enhanced CT images were obtained at three hours after injection of contrast agent. The PET and CT images were fused using hardware fiducial markers that were manually identified in both data sets. The PET and CT images were precisely registered by the use of a small animal contour point in both data sets to perform a point-based rigid registration. The registered images in the HCC model and a lung metastatic tumor model showed good agreement of tumor region on the both PET and CT images. The use of PET and contrast enhanced CT allowed a precise and improved detection of tumors in liver and lung models. Multimodal imaging with small animal PET and clinical CT images was useful in the detection of metastatic tumors and this multimodal imaging registration method can improve the quantitative accuracy and interpretation of tracer. [J76]

"CMOS RF Biosensor Utilizing Nuclear Magnetic Resonance"

We report on a CMOS RF transceiver designed for detection of biological objects such as cancer marker proteins. Its main function is to manipulate and monitor RF dynamics of protons in water via nuclear magnetic resonance (NMR). Target objects alter the proton dynamics, which is the basis for our biosensing. The RF transceiver has a measured receiver noise figure of 0.7 dB. This high sensitivity enabled construction of an entire NMR system around the RF transceiver in a 2-kg portable platform, which is 60 times lighter, 40 times smaller, yet 60 times more mass sensitive than a state-of-the-art commercial benchtop system. Sensing 20 fmol and 1.4 ng of avidin (protein) in a 5 muL sample volume, our system represents a circuit designer's approach to pursue low-cost diagnostics in a portable platform. [J77]

"Review Paper: Materials and Techniques for In Vivo pH Monitoring"

Advances in semiconductor sensor technology, medical diagnostics, and health care needs a rapid boost in research into novel miniaturized pH sensors, which can be used in vivo for continuous patient monitoring. Requirements for thein vivo sensor are materials biocompatibility, high measurement precision, a response time of an order of less than seconds, and the possibility of continuous 24-h monitoring. Monitoring of the pH values is important in the study of tissue metabolism, in neurophysiology, cancer diagnostics, and so forth. Muscle pH can be used to triage and help treat trauma victims as well as to indicate poor peripheral blood flow in diabetic patients. Clearly, to avoid infection and spread of diseases, all in vivo monitoring devices should be single-use/disposable, which puts strict requirement on their price. This paper reviews the wide range of methods and materials used for in vivo measurement of pH levels, such as using the optical fibers, pH-sensitive polymers, ion-sensitive field effect transistors, near infrared spectroscopy, nuclear magnetic resonance, and fluorescent pH indicators. [J78]

"An Association Rule-Based Method to Support Medical Image Diagnosis With Efficiency"

In this paper, we propose a method based on association rule-mining to enhance the diagnosis of medical images (mammograms). It combines low-level features automatically extracted from images and high-level knowledge from specialists to search for patterns. Our method analyzes medical images and automatically generates suggestions of diagnoses employing mining of association rules. The suggestions of diagnosis are used to accelerate the image analysis performed by specialists as well as to provide them an alternative to work on. The proposed method uses two new algorithms, PreSAGe and HiCARe. The PreSAGe algorithm combines, in a single step, feature selection and discretization, and reduces the mining complexity. Experiments performed on PreSAGe show that this algorithm is highly suitable to perform feature selection and discretization in medical images. HiCARe is a new associative classifier. The HiCARe algorithm has an important property that makes it unique: it assigns multiple keywords per image to suggest a diagnosis with high values of accuracy. Our method was applied to real datasets, and the results show high sensitivity (up to 95%) and accuracy (up to 92%), allowing us to claim that the use of association rules is a powerful means to assist in the diagnosing task. [J79]

"Multimodality Biomolecular Imaging"

Molecular imaging represents the next phase in the evolution of medical imaging and this issue describes many aspects of imaging technologies that can be combined to efficiently enhance diagnostic performance. [J80]

"Tethered Capsule Endoscopy, A Low-Cost and High-Performance Alternative Technology for the Screening of Esophageal Cancer and Barrett's Esophagus"

Esophageal cancer is currently the fastest growing cancer in the United States. To help combat the recent rise in morbidity, our laboratory has developed a low-cost tethered capsule endoscope system (TCE) aimed at improving early detection of esophageal cancer. The TCE contains a resonant fiberoptic laser scanner (1.6 mm O.D.) which fits into 6.4-mm easy-to-swallow capsule at the distal tip. The tethered portion contains a single mode optical fiber multiplexed to three laser diodes at the proximal end. This design offers two main advantages over current endoscope technology. First, because of its small size, the TCE can be swallowed with minimal patient discomfort, thereby obviating sedation. Second, by imaging via directed laser light, the TCE is strategically positioned to employ several burgeoning laser-based diagnostic technologies, such as narrow-band, hyperspectral, and fluorescence imaging. It is believed that the combination of such imaging techniques with novel biomarkers of dysplasia will greatly assist in identifying precancerous conditions such as Barrett's esophagus (BE). As the probe is swallowed, the fiber scanner captures high resolution, wide-field color images of the gastroesophageal junction (500 lines at 0.05-mm resolution) currently at 15-Hz frame rate. Video images are recorded as the capsule is slowly retracted by its tether. Accompanying software generates panoramic images from the video output by mosaicing individual frames to aid in pattern recognition. This initial report describes the rationale for the unique TCE system design, results from preliminary testing in vitro and in vivo, and discussion on the merits of this new platform technology as a basis for developing a low-cost screening program for esophageal cancer. [J81]

"A Multidimensional Classification Approach for the Automated Analysis of Flow Cytometry Data"

We describe an automated multidimensional approach for the analysis of flow cytometry data based on pattern classification. Flow cytometry is a widely used technique both for research and clinical purposes where it has become essential for the diagnosis and follow up of a wide spectrum of diseases, such as HIV-infection and neoplastic disorders. Flow cytometry data sets are composed of quite a large number of observations that can be viewed as elements of a -dimensional space. The aim of the analysis of such data files is typically to classify

groups of cellular events as specific populations with biological meaning. Despite significant improvements in data acquisition capabilities of flow cytometers, data analysis is still based on bi-dimensional strategies which were defined a long time ago. These are strongly dependent on the expertise of an expert operator, this approach being relatively subjective and potentially leading to unreliable results. Automated analysis of flow cytometry data is an essential step to improve reproducibility of the results. The proposed automated analysis was implemented on peripherial blood lymphocyte subsets from 307 samples stained and prepared in an identical way and it was capable of identifying all cell subsets present in each sample studied that could also be detected in the same data files by an expert operator. A highly significant correlation was found between the results obtained by an expert operator using a conventional manual method of analysis and those obtained using the implemented automated approach. [J82]

"Endoscopic OCT Approaches Toward Cancer Diagnosis"

A majority of human cancers originate in the epithelial tissues of the body. These include cancers in the oral cavity and pharynx, the digestive system, the respiratory system, the genital system, and the urinary system. It has been shown that early detection of these cancers can significantly improve the prognosis of affected patients. These cancers are currently diagnosed using endoscopic methods during which video imaging systems are inserted to visualize the tissue surface and guide tissue biopsies. Endoscopic optical coherence tomography (EOCT) has the potential to improve the early detection of epithelial cancers by providing high resolution, subsurface images of epithelial tissues. These subsurface images can assist the surgeon in selecting biopsy locations, and may also provide diagnostic information including the presence of cancerous and precancerous conditions in these tissues. This paper reviews current EOCT approaches toward imaging and evaluating internal epithelial tissues for various pathologies. [J83]

"Registered 3-D Ultrasound and Digital Stereotactic Mammography for Breast Biopsy Guidance"

Large core needle biopsy is a common procedure used to obtain histological samples when cancer is suspected in diagnostic breast images. The procedure is typically performed under image guidance, with freehand ultrasound and stereotactic mammography (SM) being the most common modalities used. To utilize the advantages of both modalities, a biopsy device combining three-dimensional ultrasound (3DUS) and digital SM imaging with computer-aided needle guidance was developed. An implementation of a stereo camera method was applied to SM calibration, providing a target localization error of 0.35 mm. The 3D transformation between the two imaging modalities was then derived, with a target registration error of 0.52 mm. Finally, the needle guidance error of the device was evaluated using tissue-mimicking phantoms, showing a sample mean and standard deviation of and 0.49 plusmn 0.27 mm for targets planned from 3DUS and SM images, respectively. These results suggest that a biopsy procedure guided using this device would successfully sample breast lesions at a size greater than or equal to the smallest typically detected in mammographic screening (~2mm). [J84]

"Extracting Dynamics from Static Cancer Expression Data"

Static expression experiments analyze samples from many individuals. These samples are often snapshots of the progression of a certain disease such as cancer. This raises an intriguing question: Can we determine a temporal order for these samples? Such an ordering can lead to better understanding of the dynamics of the disease and to the identification of genes associated with its progression. In this paper, we formally prove, for the first time, that under a model for the dynamics of the expression levels of a single gene, it is indeed possible to recover the correct ordering of the static expression data sets by solving an instance of the traveling salesman problem (TSP). In addition, we devise an algorithm that combines a TSP heuristic and probabilistic modeling for inferring the underlying temporal order of the microarray experiments. This algorithm constructs probabilistic continuous curves to represent expression profiles and can thus account for noise and for individual background expression differences leading to accurate temporal reconstruction for human data. Applying our method to cancer expression data, we show that the ordering derived agrees well with survival duration. A classifier that utilizes this ordering improves upon other classifiers suggested for this task. The set of genes displaying consistent behavior for the determined ordering is enriched for genes associated with cancer progression. [J85]

"Quantification of Thyroid Volume Using 3-D Ultrasound Imaging"

Ultrasound (US) is among the most popular diagnostic techniques today. It is non-invasive, fast, comparably cheap, and does not require ionizing radiation. US is commonly used to examine the size, and structure of the thyroid gland. In clinical routine, thyroid imaging is usually performed by means of 2-D US. Conventional approaches for measuring the volume of the thyroid gland or its nodules may therefore be inaccurate due to the lack of 3-D information. This work reports a semi-automatic segmentation approach for the classification, and

analysis of the thyroid gland based on 3-D US data. The images are scanned in 3-D, pre-processed, and segmented. Several pre-processing methods, and an extension of a commonly used geodesic active contour level set formulation are discussed in detail. The results obtained by this approach are compared to manual interactive segmentations by a medical expert in five representative patients. Our work proposes a novel framework for the volumetric quantification of thyroid gland lobes, which may also be expanded to other parenchymatous organs. [J86]

"A Novel Breast Tissue Density Classification Methodology"

It has been shown that the accuracy of mammographic abnormality detection methods is strongly dependent on the breast tissue characteristics, where a dense breast drastically reduces detection sensitivity. In addition, breast tissue density is widely accepted to be an important risk indicator for the development of breast cancer. Here, we describe the development of an automatic breast tissue classification methodology, which can be summarized in a number of distinct steps: 1) the segmentation of the breast area into fatty versus dense mammographic tissue; 2) the extraction of morphological and texture features from the segmented breast areas; and 3) the use of a Bayesian combination of a number of classifiers. The evaluation, based on a large number of cases from two different mammographic data sets, shows a strong correlation (and 0.67 for the two data sets) between automatic and expert-based Breast Imaging Reporting and Data System mammographic density assessment. [J87]

"Polygonal Modeling of Contours of Breast Tumors With the Preservation of Spicules"

Malignant breast tumors typically appear in mammograms with rough, spiculated, or microlobulated contours, whereas most benign masses have smooth, round, oval, or macrolobulated contours. Several studies have shown that shape factors that incorporate differences as above can provide high accuracies in distinguishing between malignant tumors and benign masses based upon their contours only. However, global measures of roughness, such as compactness, are less effective than specially designed features based upon spicularity and concavity. We propose a method to derive polygonal models of contours that preserve spicules and details of diagnostic importance. We show that an index of spiculation derived from the turning functions of the polygonal models obtained by the proposed method yields better classification accuracy than a similar measure derived using a previously published method. The methods were tested with a set of 111 contours of 65 benign masses and 46 malignant tumors. A high classification accuracy of 0.94 in terms of the area under the receiver operating characteristics curve was obtained. [J88]

"Multiple-Instance Learning Algorithms for Computer-Aided Detection"

Many computer-aided diagnosis (CAD) problems can be best modelled as a multiple-instance learning (MIL) problem with unbalanced data, i.e., the training data typically consists of a few positive bags, and a very large number of negative instances. Existing MIL algorithms are much too computationally expensive for these datasets. We describe CH, a framework for learning a convex hull representation of multiple instances that is significantly faster than existing MIL algorithms. Our CH framework applies to any standard hyperplane-based learning algorithm, and for some algorithms, is guaranteed to find the global optimal solution. Experimental studies on two different CAD applications further demonstrate that the proposed algorithm significantly improves diagnostic accuracy when compared to both MIL and traditional classifiers. Although not designed for standard MIL problems (which have both positive and negative bags and relatively balanced datasets), comparisons against other MIL methods on benchmark problems also indicate that the proposed method is competitive with the state-of-the-art. [J89]

"Nonlinear Support Vector Machine Visualization for Risk Factor Analysis Using Nomograms and Localized Radial Basis Function Kernels"

Nonlinear classifiers, e.g., support vector machines (SVMs) with radial basis function (RBF) kernels, have been used widely for automatic diagnosis of diseases because of their high accuracies. However, it is difficult to visualize the classifiers, and thus difficult to provide intuitive interpretation of results to physicians. We developed a new nonlinear kernel, the localized radial basis function (LRBF) kernel, and new visualization system visualization for risk factor analysis (VRIFA) that applies a nomogram and LRBF kernel to visualize the results of nonlinear SVMs and improve the interpretability of results while maintaining high prediction accuracy. Three representative medical datasets from the University of California, Irvine repository and Statlog dataset-breast cancer, diabetes, and heart disease datasets-were used to evaluate the system. The results showed that the classification performance of the LRBF is comparable with that of the RBF, and the LRBF is easy to visualize via a nomogram. Our study also showed that the LRBF kernel is less sensitive to noise features than the RBF kernel, whereas the LRBF kernel degrades the prediction accuracy more when important features are

eliminated. We demonstrated the VRIFA system, which visualizes the results of linear and nonlinear SVMs with LRBF kernels, on the three datasets. [J90]

"Modeling the Visibility of Breast Malignancy by a Microwave Radiometer"

A breast tumor is visible by a passive microwave radiometer if it changes the radiometric output of a healthy breast to an extent that overcomes the radiometric resolution for the given sensing antenna and integration time. We modeled breast temperature by the standard Pennes equation using thermal parameters found in the literature for normal and cancerous breast tissue. An apparent thermal volume and its dependence on blood perfusion have been estimated. The radiometric weighting function has been evaluated as a function of the size of a contacting antenna modeled as an aperture antenna. For comparison with the radiometric resolution, the difference signal between the outputs in the presence of a lesion and in its absence has been evaluated for different tumor sizes and depths. The results of the numerical analysis show that this difference signal depends on the average over-temperature in the lesion times the heating efficiency, given by the fraction of power delivered to the tumor when the antenna radiates onto the breast in active modality. A tumor of 6 mm (10 mm) diameter is visible by a 0.1 K radiometer and a 3 cm aperture antenna when it is not deeper than 1.2 cm (2.8 cm) under the assumption of ideal radiometer and antenna. [J91]

"A Computational Investigation of Microwave Breast Imaging Using Deformable Reflector"

In recent years, active microwave breast imaging is increasingly being viewed as a promising complementary imaging modality for cancer detection. In this paper, we present a novel deformable reflector microwave tomography technique for noninvasive characterization of the breast tissue. In contrast to conventional multitransceiver designs, the proposed technique utilizes a continuously deformable reflector with metallic coating to acquire field measurements for imaging. Computational feasibility of the proposed technique to image heterogeneous dielectric tissue property is evaluated using simplified 2-D breast models. The robustness of the deformable reflector-based tomography technique in imaging the spatial distribution of the tissue dielectric property in the presence of measurement noise is investigated using first-order Tikhonov regularization. Preliminary results obtained for the 2-D breast models appear promising and indicate further investigation of the new microwave tomography technique for breast imaging. [J92]

"Predicting Tumor Location by Modeling the Deformation of the Breast"

Breast cancer is one of the biggest killers in the western world, and early diagnosis is essential for improved prognosis. The shape of the breast varies hugely between the scenarios of magnetic resonance (MR) imaging (patient lies prone, breast hanging down under gravity), X-ray mammography (breast strongly compressed) and ultrasound or biopsy/surgery (patient lies supine), rendering image fusion an extremely difficult task. This paper is concerned with the use of the finite-element method and nonlinear elasticity to build a 3-D, patient-specific, anatomically accurate model of the breast. The model is constructed from MR images and can be deformed to simulate breast shape and predict tumor location during mammography or biopsy/surgery. Two extensions of the standard elasticity problem need to be solved: an inverse elasticity problem (arising from the fact that only a deformed, stressed, state is known initially), and the contact problem of modeling compression. The model is used for craniocaudal mediolateral oblique mammographic image matching, and a number of numerical experiments are performed. [J93]

"Energy-Based Diagnostic and Treatment Techniques"

In this article, our previous research on the application of thermal energy transfer for tumor treatment and early diagnosis has been briefly reviewed. The work encompasses some mechanistic studies of the thermal effects on the breast cancer cells and microvascular networks. Accordingly, a new thermal system was designed for more effective thermal therapy and targeted drug delivery. It was clearly demonstrated that the thermal-physical treatment could be effectively applied to tumor therapy, and the therapeutic effect could be enhanced through rapid cooling and heating alternations in the tissue. [J94]

"Biomedical Engineering in China"

Biomedical engineering has had a remarkable growth in the past decade in China. With the significant increase in research funding in the past several years, our Chinese colleagues have enjoyed good times for biomedical engineering research and development. This special issue includes a collection of articles contributed by groups, which cover the broad spectrum of biomedical engineering research, including molecular imaging, cancer detection and treatment, health information technology, neural engineering, electrophysiology, and biomedical imaging. [J95]

"Size-based Transfer Functions: A New Volume Exploration Technique"

The visualization of complex 3D images remains a challenge, a fact that is magnified by the difficulty to classify or segment volume data. In this paper, we introduce size-based transfer functions, which map the local scale of features to color and opacity. Features in a data set with similar or identical scalar values can be classified based on their relative size. We achieve this with the use of scale fields, which are 3D fields that represent the relative size of the local feature at each voxel. We present a mechanism for obtaining these scale fields at interactive rates, through a continuous scale-space analysis and a set of detection filters. Through a number of examples, we show that size-based transfer functions can improve classification and enhance volume rendering techniques, such as maximum intensity projection. The ability to classify objects based on local size at interactive rates proves to be a powerful method for complex data exploration. [J96]

"From photovoltaics to medical imaging: Applications of thin-film CdTe in x-ray detection"

Recent developments in photovoltaics created a commercially viable technology of large area uniform thin-film structures, potentially extendable to the field of medical imaging, where the capability of producing large area x-ray detectors is essential for the successful diagnosis and treatment of cancer. We propose a large area thin-film CdTe structure suitable for radiation detection and discuss its main characteristics under x-ray beams used in radiation therapy. While based on the same principle, the details of its operations are very dissimilar from that of photovoltaics. [J97]

"Electron cyclotron resonance ion source experience at the Heidelberg Ion Beam Therapy Center"

Radiotherapy with heavy ions is an upcoming cancer treatment method with to date unparalleled precision. It associates higher control rates particularly for radiation resistant tumor species with reduced adverse effects compared to conventional photon therapy. The accelerator beam lines and structures of the Heidelberg Ion Beam Therapy Center (HIT) have been designed under the leadership of GSI, Darmstadt with contributions of the IAP Frankfurt. Currently, the accelerator is under commissioning, while the injector linac has been completed. When the patient treatment begins in 2008, HIT will be the first medical heavy ion accelerator in Europe. This presentation will provide an overview about the project, with special attention given to the 14.5GHzelectron cyclotron resonance (ECR) ion sources in operation with carbon, hydrogen, helium, and oxygen, and the experience of one year of continuous operation. It also displays examples for beam emittances, measured in the low energy beam transport. In addition to the outlook of further developments at the ECR ion sources for a continuously stable operation, this paper focuses on some of the technical processings of the past year. [J98]

"3-D-Microwave Breast Tumor Detection: Study of System Performance"

This paper presents a study of performance for a 3-D breast tumor detection system. The system is based on processing the scattered signals when a narrow pulse is transmitted from a set of antennas placed surrounding the breast. The 3-D system performance is evaluated by placing the tumor at any breast position, even at locations near the breast muscle where detection is more difficult. Results are obtained for different sizes and positions of the abnormalities that are defined as spherical and bunch-shaped geometries, which approach the well-known breast tumors morphology. These results show that the array distribution considered will have a high impact on detection. [J99]

"Mechanical Imaging of the Breast"

In this paper, we analyze the physical basis for elasticity imaging of the breast by measuring breast skin stress patterns that result from a force sensor array pressed against the breast tissue. Temporal and spatial changes in the stress pattern allow detection of internal structures with different elastic properties and assessment of geometrical and mechanical parameters of these structures. The method entitled mechanical imaging is implemented in the breast mechanical imager (BMI), a compact device consisting of a hand held probe equipped with a pressure sensor array, a compact electronic unit, and a touchscreen laptop computer. Data acquired by the BMI allows calculation of size, shape, consistency/hardness, and mobility of detected lesions. The BMI prototype has been validated in laboratory experiments on tissue models and in an ongoing clinical study. The obtained results prove that the BMI has potential to become a screening and diagnostic tool that could largely supplant clinical breast examination through its higher sensitivity, quantitative record storage, ease-of-use, and inherent low cost. [J100]

"Investigating the Efficacy of Nonlinear Dimensionality Reduction Schemes in Classifying Gene and Protein Expression Studies"

The recent explosion in procurement and availability of high-dimensional gene and protein expression profile data

sets for cancer diagnostics has necessitated the development of sophisticated machine learning tools with which to analyze them. While some investigators are focused on identifying informative genes and proteins that play a role in specific diseases, other researchers have attempted instead to use patients based on their expression profiles to prognosticate disease status. A major limitation in the ability to accurately classify these high-dimensional data sets stems from the "curse of dimensionality," occurring in situations where the number of genes or peptides significantly exceeds the total number of patient samples. Previous attempts at dealing with this issue have mostly centered on the use of a dimensionality reduction (DR) scheme, principal component analysis (PCA), to obtain a low-dimensional projection of the high-dimensional data. However, linear PCA and other linear DR methods, which rely on euclidean distances to estimate object similarity, do not account for the inherent underlying nonlinear structure associated with most biomedical data. While some researchers have begun to explore nonlinear DR methods for computer vision problems such as face detection and recognition, to the best of our knowledge, few such attempts have been made for classification and visualization of high-dimensional biomedical data. The motivation behind this work is to identify the appropriate DR methods for analysis of high-dimensional gene and protein expression studies. Toward this end, we empirically and rigorously compare three nonlinear (Isomap, Locally Linear Embedding, and Laplacian Eigenmaps) and three linear DR schemes (PCA, Linear Discriminant Analysis, and Multidimensional Scaling) with the intent of determining a reduced subspace representation in which the individual object classes are more easily discriminable. Owing to the inherent nonlinear structure--of gene and protein expression studies, our claim is that the nonlinear DR methods provide a more truthful low-dimensional representation of the data compared to the linear DR schemes. Evaluation of the DR schemes was done by 1) assessing the discriminability of two supervised classifiers (Support Vector Machine and C4.5 Decision Trees) in the different low- dimensional data embeddings and 2) five cluster validity measures to evaluate the size, distance, and tightness of object aggregates in the low-dimensional space. For each of the seven evaluation measures considered, statistically significant improvement in the quality of the embeddings across 10 cancer data sets via the use of three nonlinear DR schemes over three linear DR techniques was observed. Similar trends were observed when linear and nonlinear DR was applied to the high-dimensional data following feature pruning to isolate the most informative features. Qualitative evaluation of the low-dimensional data embedding obtained via the six DR methods further suggests that the nonlinear schemes are better able to identify potential novel classes (e.g., cancer subtypes) within the data. [J101]

"Optofluidic Intracavity Spectroscopy of Canine Lymphoma and Lymphocytes"

Multiple transverse mode, intracavity spectra of canine lymphoma cells in a passive Fabry-Perot cavity are distinct from single-mode spectra of normal lymphocytes. Two-dimensional effective-index modal calculations provide insight into the nuclear size versus refractive index relationship and clarify the impact of lateral optical confinement on modal shift. [J102]

"Mammographic Images Enhancement and Denoising for Breast Cancer Detection Using Dyadic Wavelet Processing"

Mammography is the most effective method for the early detection of breast diseases. However, the typical diagnostic signs such as microcalcifications and masses are difficult to detect because mammograms are low-contrast and noisy images. In this paper, a novel algorithm for image denoising and enhancement based on dyadic wavelet processing is proposed. The denoising phase is based on a local iterative noise variance estimation. Moreover, in the case of microcalcifications, we propose an adaptive tuning of enhancement degree at different wavelet scales, whereas in the case of mass detection, we developed a new segmentation method combining dyadic wavelet information with mathematical morphology. The innovative approach consists of using the same algorithmic core for processing images to detect both microcalcifications and masses. The proposed algorithm has been tested on a large number of clinical images, comparing the results with those obtained by several other algorithms proposed in the literature through both analytical indexes and the opinions of radiologists. Through preliminary tests, the method seems to meaningfully improve the diagnosis in the early breast cancer detection with respect to other approaches. [J103]

"Comparing Mammographic Images"

The main motivation in using intensity attributes to analyze and compare the technologies of mammography images acquisition is that such images are intrinsically of low contrast, which hinders the lesions detection and interpretation. Considering the viewing conditions, the study is under development to validate the influence of the contrast variation of many types of equipment on the radiologist's diagnosis. However, for the image processing, the contrast variation can be considered a problem affecting the detection of important structures. A large-intensity variation in a digitized image can be manipulated by image-processing techniques and aid in lesion detection. However, low-intensity variation, as observed in the images of full-field digital mammography systems,

can impede the detection of some lesions types, as masses are structures of low contrast. Therefore, the new technologies should be tested and validated for an adequate calibration according to the procedures adjacent to the image acquisition itself. [J104]

"Robust Linearized Image Reconstruction for Multifrequency EIT of the Breast"

Electrical impedance tomography (EIT) is a developing imaging modality that is beginning to show promise for detecting and characterizing tumors in the breast. At Rensselaer Polytechnic Institute, we have developed a combined EIT-tomosynthesis system that allows for the coregistered and simultaneous analysis of the breast using EIT and X-ray imaging. A significant challenge in EIT is the design of computationally efficient image reconstruction algorithms which are robust to various forms of model mismatch. Specifically, we have implemented a scaling procedure that is robust to the presence of a thin highly-resistive layer of skin at the boundary of the breast and we have developed an algorithm to detect and exclude from the image reconstruction electrodes that are in poor contact with the breast. In our initial clinical studies, it has been difficult to ensure that all electrodes make adequate contact with the breast, and thus procedures for the use of data sets containing poorly contacting electrodes are particularly important. We also present a novel, efficient method to compute the Jacobian matrix for our linearized image reconstruction algorithm by reducing the computation of the sensitivity for each voxel to a quadratic form. Initial clinical results are presented, showing the potential of our algorithms to detect and localize breast tumors. [J105]

"Sequential Activation of a Segmented Ground Pad Reduces Skin Heating During Radiofrequency Tumor Ablation: Optimization via Computational Models"

Radiofrequency (RF) ablation has become an accepted treatment modality for unresectable tumors. The need for larger ablation zones has resulted in increased RF generator power. Skin burns due to ground pad heating are increasingly limiting further increases in generator power, and thus, ablation zone size. We investigated a method for reducing ground pad heating in which a commercial ground pad is segmented into multiple ground electrodes, with sequential activation of ground electrode subsets. We created finite-element method computer models of a commercial ground pad (14 times 23 cm) and compared normal operation of a standard pad to sequential activation of a segmented pad (two to five separate ground electrode segments). A constant current of 1 A was applied for 12 min in all simulations. Time periods during sequential activation simulations were adjusted to keep the leading edge temperatures at each ground electrode equal. The maximum temperature using standard activation of the commercial pad was 41.7degC. For sequential activation of a segmented pad, the maximum temperature ranged from 39.3degC (five segments) to 40.9degC (two segments). Sequential activation of a segmented ground pad resulted in lower tissue temperatures. This method may reduce the incidence of ground pad burns and enable the use of higher power generators during RF tumor ablation. [J106]

"Advances in Giant Magnetoresistance Biosensors With Magnetic Nanoparticle Tags: Review and Outlook"

We present a review of giant magnetoresistance (GMR) spin valve sensors designed for detection of magnetic nanoparticles as biomolecular labels (nanotags) in magneto-nano biodetection technology. We discuss the intricacy of magneto-nano biosensor design and show that as few as approximately 14 monodisperse 16-nm superparamagnetic nanoparticles can be detected by submicron spin valve sensors at room temperature without resorting to lock-in (narrow band) detection. GMR biosensors and biochips have been successfully applied to the detection of biological events in the form of both protein and DNA assays with great speed, sensitivity, selectivity, and economy. The limit of molecular detection is well below 10 pM in concentration, and the protein or DNA assay time can be under two hours. The technology is highly scalable to deep multiplex detection of biomarkers in a complex disease, and amenable to integration of microfluidics and CMOS electronics for portable applications. On-chip CMOS circuitry makes a sensor density of 0.1-1 million sensors per square centimeter feasible and affordable. The theoretical and experimental results thus far suggest that magneto-nano biochip-based GMR sensor arrays and nanotags hold great promise in biomedicine, particularly for point-of-care molecular diagnostics of cancer, infectious diseases, radiation injury, cardiac diseases, and other diseases. [J107]

"Accurate Cancer Classification Using Expressions of Very Few Genes"

We aim at finding the smallest set of genes that can ensure highly accurate classification of cancers from microarray data by using supervised machine learning algorithms. The significance of finding the minimum gene subsets is three-fold: 1) it greatly reduces the computational burden and "noise" arising from irrelevant genes. In the examples studied in this paper, finding the minimum gene subsets even allows for extraction of simple diagnostic rules which lead to accurate diagnosis without the need for any classifiers, 2) it simplifies gene expression tests to include only a very small number of genes rather than thousands of genes, which can bring

down the cost for cancer testing significantly, 3) it calls for further investigation into the possible biological relationship between these small numbers of genes and cancer development and treatment. Our simple yet very effective method involves two steps. In the first step, we choose some important genes using a feature importance ranking scheme. In the second step, we test the classification capability of all simple combinations of those important genes by using a good classifier. For three "small" and "simple" data sets with two, three, and four cancer (sub)types, our approach obtained very high accuracy with only two or three genes. For a "large" and "complex" data set with 14 cancer types, we divided the whole problem into a group of binary classification problems and applied the 2-step approach to each of these binary classification problems. Through this "divide-and-conquer" approach, we obtained accuracy comparable to previously reported results but with only 28 genes rather than 16,063 genes. In general, our method can significantly reduce the number of genes required for highly reliable diagnosis [J108]

"Lesion Quantification in Dual-Modality Mammotomography"

This paper describes a novel x-ray/SPECT dual modality breast imaging system that provides 3D structural and functional information. While only a limited number of views on one side of the breast can be acquired due to mechanical and time constraints, we developed a technique to compensate for the limited angle artifact in reconstruction images and accurately estimate both the lesion size and radioactivity concentration. Various angular sampling strategies were evaluated using both simulated and experimental data. It was demonstrated that quantification of lesion size to an accuracy of 10% and quantification of radioactivity to an accuracy of 20% are feasible from limited-angle data acquired with clinically practical dosage and acquisition time [J109]

"Multiclass Cancer Classification Using Semisupervised Ellipsoid ARTMAP and Particle Swarm Optimization with Gene Expression Data"

It is crucial for cancer diagnosis and treatment to accurately identify the site of origin of a tumor. With the emergence and rapid advancement of DNA microarray technologies, constructing gene expression profiles for different cancer types has already become a promising means for cancer classification. In addition to research on binary classification such as normal versus tumor samples, which attracts numerous efforts from a variety of disciplines, the discrimination of multiple tumor types is also important. Meanwhile, the selection of genes which are relevant to a certain cancer type not only improves the performance of the classifiers, but also provides molecular insights for treatment and drug development. Here, we use semisupervised ellipsoid ARTMAP (ssEAM) for multiclass cancer discrimination and particle swarm optimization for informative gene selection. ssEAM is a neural network architecture rooted in adaptive resonance theory and suitable for classification tasks. ssEAM features fast, stable, and finite learning and creates hyperellipsoidal clusters, inducing complex nonlinear decision boundaries. PSO is an evolutionary algorithm-based technique for global optimization. A discrete binary version of PSO is employed to indicate whether genes are chosen or not. The effectiveness of ssEAM/PSO for multiclass cancer diagnosis is demonstrated by testing it on three publicly available multiple-class cancer data sets. ssEAM/PSO achieves competitive performance on all these data sets, with results comparable to or better than those obtained by other classifiers [J110]

"A Reconstruction Algorithm for Breast Cancer Imaging With Electrical Impedance Tomography in Mammography Geometry"

The conductivity and permittivity of breast tumors are known to differ significantly from those of normal breast tissues, and electrical impedance tomography (EIT) is being studied as a modality for breast cancer imaging to exploit these differences. At present, X-ray mammography is the primary standard imaging modality used for breast cancer screening in clinical practice, so it is desirable to study EIT in the geometry of mammography. This paper presents a forward model of a simplified mammography geometry and a reconstruction algorithm for breast tumor imaging using EIT techniques. The mammography geometry is modeled as a rectangular box with electrode arrays on the top and bottom planes. A forward model for the electrical impedance imaging problem is derived for a homogeneous conductivity distribution and is validated by experiment using a phantom tank. A reconstruction algorithm for breast tumor imaging based on a linearization approach and the proposed forward model is presented. It is found that the proposed reconstruction algorithm performs well in the phantom experiment, and that the locations of a 5-mm-cube metal target and a 6-mm-cube agar target could be recovered at a target depth of 15 mm using a 32 electrode system [J111]

"Architecture and Performance of a Grid-Enabled Lookup-Based Biomedical Optimization Application: Light Scattering Spectroscopy"

This paper presents a case study of a Grid-enabled implementation of light scattering spectroscopy (LSS). The LSS technique allows noninvasive detection of precancerous changes in human epithelium, differentiating from

traditional biopsies by allowing in vivo diagnosis of tissue samples and quantitative analyses of parameters related to cancerous changes via numerical techniques. This paper describes the architecture of GridLSS and its integration with a Web-based Grid computing portal. GridLSS solves an optimization problem of determining the light scattering spectrum that best fits experimental spectral data among a large set of spectra computed analytically using rigorous Mie theory. The novel approach taken in this paper is based on the precomputation and storage of Mie theory spectra in lookup databases that are queried during the minimization process. The paper makes three important contributions: 1) it presents a novel parallel application for LSS analysis that delivers high performance in wide-area distributed computing environment; 2) it evaluates and analyzes the performance of this application in cluster-based high-performance computing environments that are typical of Grid deployments; and 3) it shows that the performance of GridLSS benefits significantly from the use of on-demand Grid data transfers based on virtualized distributed file systems and from user-level caches for remote file system data [J112]

"Terahertz imaging diagnostics of cancer tissues with a chemometrics technique"

Terahertz spectroscopic images of paraffin-embedded cancer tissues have been measured by a terahertz time domain spectrometer. For the systematic identification of cancer tumors, the principal component analysis and the clustering analysis were applied. In three of the four samples, the cancer tissue was recognized as an aggregate of the data points in the principal component plots. By the agglomerative hierarchical clustering, the data points were well categorized into cancer and the other tissues. This method can be also applied to various kinds of automatic discrimination of plural components by terahertz spectroscopic imaging. [J113]

"Identification and Imaging of the Nerves Responsible for Erectile Function in Rat Prostate, In Vivo, Using Optical Nerve Stimulation and Optical Coherence Tomography"

The cavernous nerves on the prostate surface are responsible for erectile function. Optical diagnostic tools such as optical coherence tomography and laser nerve stimulation may assist in the identification, imaging, and preservation of these microscopic nerves during prostate cancer surgery, and thus, help preserve sexual function after surgery. The feasibility of noncontact laser stimulation of the cavernous nerves is demonstrated in an in vivo rat prostate model with comparison to conventional electrical nerve stimulation. High-resolution optical coherence tomographic images of the nerves are also obtained and compared with histology. These optical technologies may be suitable as surgical guidance tools during laparoscopic and robotic nerve-sparing prostate cancer surgery. [J114]

"Elastic Scattering Spectroscopy as a Diagnostic Tool for Apoptosis in Cell Cultures"

Apoptosis, ldquoprogrammed cell death,rdquo is a cellular process exhibiting distinct biochemical and morphological changes. There is much interest regarding the role of apoptosis in cancer and the response to cancer treatment. Although apoptosis can occur spontaneously in malignant tumors and often significantly retards their growth, the initial response to successful cancer treatment is often massive apoptosis. In typical in vitro studies, current apoptosis detection methods require cell culture disruption via fixation, trypsinization, and/or staining. Our aim is to develop a nondisruptive optical method of detecting and tracking apoptosis in living cells and tissues, initially focusing on cell cultures. Such a method would allow for real-time evaluation of apoptotic progression of the same cell culture over time without perturbation or alteration. We report initial studies on the use of in vitro elastic scattering spectroscopy (ESS) to monitor changes in light-scattering properties of cells due to apoptotic morphology changes. For a sequence of times post treatment, we have measured the angle-dependent scattering at a single wavelength and also the wavelength-dependent scattering at discrete angles, of treated and control cell cultures. A novel polar nephelometer, developed in our laboratory, was used to obtain the angle-dependent scattering for the range of 90-145. Wavelength-dependent ESS measurements were made with a spectrometer, for several discrete near-forward angles. The results indicate that light scattering measurements can reliably discriminate between treated and control cells, correlating well with benchmark assays for apoptosis. [J115]

"Argumentation-Based Inference and Decision Making--A Medical Perspective"

The argumentation services platform with integrated components (Aspic) project aims to provide advanced argumentation-based computational capabilities. Argumentation is a potentially important paradigm for developing commercial and public services that are flexible and easily understood by human users. [J116]

"Broadband Dielectric Characterization of Tumorous and Nontumorous Breast Tissues"

The broadband dielectric properties of tumorous and nontumorous tissues were analyzed at the millimeter-wave and terahertz frequencies. Ex-vivomeasurements were obtained using the backward-wave oscillator-based free-

space quasi-optical spectroscopy and dispersive Fourier transform spectroscopy methods. Both techniques were modified to yield the real and imaginary parts of permittivity, absorption coefficient, refractive index, and transmission data over an extended frequency range from 30 to 900 GHz. Results reveal characteristic signatures of breast tissues and display a significant difference in the electromagnetic response of tumorous and nontumorous tissues. The techniques employed in this study provide prospects for extending ex-vivomeasurements to in-vivo breast cancer detection and diagnostics. [J117]

"Guest Editors' Introduction: Argumentation Technology"

This introduction to the special issue on argumentation technology discusses argumentation's role in modern computing. It also identifies the challenges that the community must meet before it can achieve widespread deployment of argumentation technologies. [J118]

"Neuroimaging for the Diagnosis and Study of Psychiatric Disorders [JLife Sciences]"

This paper summarizes the neuroimaging methods in the diagnostic assessment process that have been applied to neuropsychiatric studies. Here, we outline the signal processing challenges in structural and functional neuroimaging methods and discuss the specific difficulties in multisite data analysis for the diagnosis of neuropsychiatric disorders. Currently, fMRI and other brain imaging methods are used to aid in diagnosis primarily by revealing various types of pathology; e.g., evidence of brain tumors or multiple strokes. Significant research efforts have been directed toward understanding, analyzing, and diagnosing neuropsychiatric disorders. [J119]

"Effective Gene Selection Method With Small Sample Sets Using Gradient-Based and Point Injection Techniques"

Microarray gene expression data usually consist of a large amount of genes. Among these genes, only a small fraction are informative for performing a cancer diagnostic test. This paper focuses on effective identification of informative genes. We analyze gene selection models from the perspective of optimization theory. As a result, a new strategy is designed to modify conventional search engines. Also, as overfitting is likely to occur in microarray data because of their small sample set, a point injection technique is developed to address the problem of overfitting. The proposed strategies have been evaluated on three kinds of cancer diagnosis. Our results show that the proposed strategies can improve the performance of gene selection substantially. The experimental results also indicate that the proposed methods are very robust under all of the investigated cases. [J120]

"Implantable cardioverter-defibrillators and hospice care [JIssues in Ethics]"

Discusses the issues that arise with patients who have implantable cardioverter-defibrillators (ICDs) and are under end-of-life care. [J121]

"Integrating Diagnostic B -Mode Ultrasonography Into CT-Based Radiation Treatment Planning"

This paper presents methods and a clinical procedure for integrating B-mode ultrasound images tagged with position information with a planning computed tomography (CT) scan for radiotherapy. A workflow is described that allows the integration of these modalities into the clinic. A surface mapping approach provides a preregistration of the ultrasound image borders onto the patient's skin. Successively, a set of individual ultrasound images from a freehand sweep is chosen by the physician. These images are automatically registered with the planning CT scan using novel intensity-based methods. We put a particular focus on deriving an appropriate similarity measure based on the physical properties and artifacts of ultrasound. A combination of a weighted mutual information term, edge correlation, clamping to the skin surface, and occlusion detection is able to assess the alignment of structures in ultrasound images and information reconstructed from the CT data. We demonstrate the practicality of our methods on five patients with head and neck tumors and cervical lymph node metastases and provide a detailed report on the conducted experiments, including the setup, calibration, acquisition, and verification of our algorithms. The mean target registration error on nine data sets is 3.9 mm. Thus, the additional information about intranodal architecture and fulfillment of malignancy criteria derived from a high-resolution ultrasonography of lymph nodes can be localized and visualized in the CT scan coordinate space and is made available for further radiation treatment planning. [J122]

"Temporal Change Analysis for Characterization of Mass Lesions in Mammography"

In this paper, we present a fully automated computer-aided diagnosis (CAD) program to detect temporal changes in mammographic masses between two consecutive screening rounds. The goal of this work was to

improve the characterization of mass lesions by adding information about the tumor behavior over time. Towards this goal we previously developed a regional registration technique that finds for each mass lesion on the current view a location on the prior view where the mass was most likely to develop. For the task of interval change analysis, we designed two kinds of temporal features: difference features and similarity features. Difference features indicate the (relative) change in feature values determined on prior and current views. These features may be especially useful for lesions that are visible on both views. Similarity features measure whether two regions are comparable in appearance and may be useful for lesions that are visible on the prior view as well as for newly developing lesions. We evaluated the classification performance with and without the use of temporal features on a dataset consisting of 465 temporal mammogram pairs, 238 benign, and 227 malignant. We used cross validation to partition the dataset into a training set and a test set. The training set was used to train a support vector machine classifier and the test set to evaluate the classifier. The average Azvalue (area under the receiver operating characteristic curve) for classifying each lesion was 0.74 without temporal features and 0.77 with the use of temporal features. The improvement obtained by adding temporal features was statistically significant (P = 0.005). In particular, similarity features contributed to this improvement. Furthermore, we found that the improvement was comparable for masses that were visible and for masses that were not visible on the prior view. These results show that the use of temporal features is an effective approach to improve the characteriz--ation of masses. [J123]

"Multicategory Classification Using An Extreme Learning Machine for Microarray Gene Expression Cancer Diagnosis"

In this paper, the recently developed Extreme Learning Machine (ELM) is used for directing multicategory classification problems in the cancer diagnosis area. ELM avoids problems like local minima, improper learning rate and overfitting commonly faced by iterative learning methods and completes the training very fast. We have evaluated the multicategory classification performance of ELM on three benchmark microarray data sets for cancer diagnosis, namely, the GCM data set, the Lung data set, and the Lymphoma data set. The results indicate that ELM produces comparable or better classification accuracies with reduced training time and implementation complexity compared to artificial neural networks methods like conventional back-propagation ANN, Linder's SANN, and Support Vector Machine methods like SVM-OVO and Ramaswamy's SVM-OVA. ELM also achieves better accuracies for classification of individual categories. [J124]

"A Concentric Morphology Model for the Detection of Masses in Mammography"

We propose a technique for the automated detection of malignant masses in screening mammography. The technique is based on the presence of concentric layers surrounding a focal area with suspicious morphological characteristics and low relative incidence in the breast region. Mammographic locations with high concentration of concentric layers with progressively lower average intensity are considered suspicious deviations from normal parenchyma. The multiple concentric layers (MCLs) technique was trained and tested using the craniocaudal views of 270 mammographic cases with biopsy proven malignant masses from the digital database of screening mammography. One-half of the available cases were used for optimizing the parameters of the detection algorithm. The remaining cases were used for testing. During testing, malignant masses were detected with 92%, 88%, and 81% sensitivity at 5.4, 2.4, and 0.6 false positive marks per image. Testing on 82 normal screening mammograms showed a false positive rate of 5.0, 1.7, and 0.2 marks per image at the previously reported operating points. Furthermore, additional evaluation on 135 benign cases produced a significantly lower detection rate for benign masses (61.6%, 58.3%, and 43.7% at 5.1, 2.8, and 1.2 false positives per image, respectively). Overall, MCL is a promising computer-assisted detection strategy for screening mammograms to identify malignant masses while maintaining the detection rate of benign masses considerably lower. [J125]

"FISH and chips: chromosomal analysis on microfluidic platforms"

Interphase fluorescence in situ hybridisation (FISH) is a sensitive diagnostic tool used for the detection of alterations in the genome on cell-by-cell basis. However, the cost-per-test and the technical complexity of current FISH protocols have slowed its widespread utilisation in clinical settings. For many cancers, the lack of a cost-effective and informative diagnostic method has compromised the quality of life for patients. We present the first demonstration of a microchip-based FISH protocol, coupled with a novel method to immobilise peripheral blood mononuclear cells inside microfluidic channels. These first on-chip implementations of FISH allow several chromosomal abnormalities associated with multiple myeloma to be detected with a ten-fold higher throughput and 1/10-th the reagent consumption of the traditional slide-based method. Moreover, the chip test is performed within hours whereas the conventional protocol required days. In addition, two on-chip methods to enhance the hybridisation aspects of FISH have been examined: mechanical and electrokinetic pumping. Similar agitation methods have led to significant improvements in hybridisation efficiency with DNA microarray work, but with this cell-based method the benefits were moderate. On-chip FISH technology holds promise for sophisticated and

cost-effective screening of cancer patients at every clinic visit [J126]

"Fuzzy Receiver Operating Characteristic Curve: An Option to Evaluate Diagnostic Tests"

Traditional receiver operating characteristic (ROC) analysis is widely utilized to evaluate diagnostic tests but it is restricted to dichotomous results. The aim of this study is to develop the "fuzzy receiver operating characteristic" methodology combining the fuzzy sets theory and the traditional ROC methodology, and to utilize this new tool to evaluate a diagnostic test. We review traditional ROC analysis in mathematical language that utilizes crisp sets and rewrites it based on fuzzy sets. Fuzzy ROC analysis is used to evaluate a fuzzy-rule-based system (FRBS) developed to predict the pathological stage of a prostate cancer in its ability to discriminate between two states: organ-confined and non-confined. Traditional ROC analysis is insufficient to evaluate this system because the result is given in possibilistic terms. The methodology developed in this work is a generalization of the dichotomous ROC analysis, and appears to better represent the performance of diagnostic tests that include a degree of uncertainty similar to the one presented here [J127]

"Variable Background Active Contour Model for Computer-Aided Delineation of Nodules in Thyroid Ultrasound Images"

This paper presents a computer-aided approach for nodule delineation in thyroid ultrasound (US) images. The developed algorithm is based on a novel active contour model, named variable background active contour (VBAC), and incorporates the advantages of the level set region-based active contour without edges (ACWE) model, offering noise robustness and the ability to delineate multiple nodules. Unlike the classic active contour models that are sensitive in the presence of intensity inhomogeneities, the proposed VBAC model considers information of variable background regions. VBAC has been evaluated on synthetic images, as well as on real thyroid US images. From the quantification of the results, two major impacts have been derived: 1) higher average accuracy in the delineation of hypoechoic thyroid nodules, which exceeds 91%; and 2) faster convergence when compared with the ACWE model. [J128]

"Improve Computer-Aided Diagnosis With Machine Learning Techniques Using Undiagnosed Samples"

In computer-aided diagnosis (CAD), machine learning techniques have been widely applied to learn a hypothesis from diagnosed samples to assist the medical experts in making a diagnosis. To learn a well-performed hypothesis, a large amount of diagnosed samples are required. Although the samples can be easily collected from routine medical examinations, it is usually impossible for medical experts to make a diagnosis for each of the collected samples. If a hypothesis could be learned in the presence of a large amount of undiagnosed samples, the heavy burden on the medical experts could be released. In this paper, a new semisupervised learning algorithm named Co-Forest is proposed. It extends the co-training paradigm by using a well-known ensemble method named Random Forest, which enables Co-Forest to estimate the labeling confidence of undiagnosed samples and easily produce the final hypothesis. Experiments on benchmark data sets verify the effectiveness of the proposed algorithm. Case studies on three medical data sets and a successful application to microcalcification detection for breast cancer diagnosis show that undiagnosed samples are helpful in building CAD systems, and Co-Forest is able to enhance the performance of the hypothesis that is learned on only a small amount of diagnosed samples by utilizing the available undiagnosed samples. [J129]

"Locomotion techniques for robotic colonoscopy"

Colonoscopy has become a routine procedure in many hospitals all over the world for colon cancer diagnosis. This review article discusses the work done by researchers in the quest to automate the colonoscopy procedure. In vitro and in vivo experimentation have been carried out to prove the possibilities of a robot crawling along a patient's colon, treating polyps as they are encountered. Locomotion is an essential part of robotic colonoscopy. The robot must be able to propel itself from the anus right up to the cecum without damaging the colon walls. The challenge is to design a robust locomotion technique that is able to advance through the stretchable, slippery, and mobile colon, which is always in its collapsed stage, in three-dimensional orientation. The authors believe that in the future, conventional colonoscopy will be revolutionized, giving way to robotics to assist doctors in colonoscope manipulation and performing therapeutic procedures and leaving doctors to concentrate on the diagnostic aspect of the procedure, which would encourage mass screening as more patients can be evaluated per session. [J130]

"A hybrid system for detecting masses in mammographic images"

This paper discusses the hybrid system for detecting masses in mammographic images. The proposed approach

analyzes mammograms in three major steps. First, a global segmentation method is applied to find regions of interest. This step uses texture features, decision trees, and a multiresolution Markov random field model. The second stage works on the output of the previous algorithm. Here, a combination of three different local segmentation methods is used, and then, some relevant features are extracted. Some of them refer to the shape of the object; others are texture parameters. The final decision is made using a linear combination of these features [J131]

"An efficient semi-unsupervised gene selection method via spectral biclustering"

Gene selection is an important issue in microarray data processing. In this paper, we propose an efficient method for selecting relevant genes. First, we use spectral biclustering to obtain the best two eigenvectors for class partition. Then gene combinations are selected based on the similarity between the genes and the best eigenvectors. We demonstrate our semi-unsupervised gene selection method using two microarray cancer data sets, i.e., the lymphoma and the liver cancer data sets, where our method is able to identify a single gene or a two-gene combinations which can lead to predictions with very high accuracy. [J132]

"Co-Occurrence Analysis for Discovery of Novel Breast Cancer Pathology Patterns"

To discover novel patterns in pathology co-occurrence, we have developed algorithms to analyze and visualize pathology co-occurrence. With access to a database of pathology reports, collected under a single protocol and reviewed by a single pathologist, we can conduct an analysis greater in its scope than previous studies looking at breast pathology co-occurrence. Because this data set is unique, specialized methods for pathology co-occurrence analysis and visualization are developed. Primary analysis is through a co-occurrence score based on the Jaccard coefficient. Density maps are used to visualize global co-occurrence. When our co-occurrence analysis is applied to a population stratified by menopausal status, we can successfully identify statistically significant differences in pathology co-occurrence patterns between premenopausal and postmenopausal women. Genomic and proteomic experiments are planned to discover biological mechanisms that may underpin differences seen in pathology patterns between populations [J133]

"MRI-guided focused ultrasound: methodology and applications"

Focused ultrasound is very well suited for inducing noninvasive local hyperthermia. Since magnetic resonance imaging (MRI) may be employed to obtain real-time temperature maps noninvasively the combination of these two technologies offers great advantages specifically aimed toward oncological studies. Real-time identification of the target region and accurate control of the temperature evolution during the treatment has now become possible. Thermal ablation of pathological tissue, local drug delivery using thermosensitive micro-carriers and controlled transgene expression using thermosensitive promoters have recently been demonstrated with this unique technology. Based on these experiments combined focused ultrasound and MRI thermometry holds promise for future oncological diagnostics and treatment. In this paper, we review some of the recent methodological developments as well as experimental and first clinical studies using this approach [J134]

"Computer analysis of computed tomography scans of the lung: a survey"

Current computed tomography (CT) technology allows for near isotropic, submillimeter resolution acquisition of the complete chest in a single breath hold. These thin-slice chest scans have become indispensable in thoracic radiology, but have also substantially increased the data load for radiologists. Automating the analysis of such data is, therefore, a necessity and this has created a rapidly developing research area in medical imaging. This paper presents a review of the literature on computer analysis of the lungs in CT scans and addresses segmentation of various pulmonary structures, registration of chest scans, and applications aimed at detection, classification and quantification of chest abnormalities. In addition, research trends and challenges are identified and directions for future research are discussed. [J135]

"Computer-aided diagnosis scheme using a filter bank for detection of microcalcification clusters in mammograms"

Mammography is considered the most effective method for early detection of breast cancers. However, it is difficult for radiologists to detect microcalcification clusters. Therefore, we have developed a computerized scheme for detecting early-stage microcalcification clusters in mammograms. We first developed a novel filter bank based on the concept of the Hessian matrix for classifying nodular structures and linear structures. The mammogram images were decomposed into several subimages for second difference at scales from 1 to 4 by this filter bank. The subimages for the nodular component (NC) and the subimages for the nodular and linear component (NLC) were then obtained from analysis of the Hessian matrix. Many regions of interest (ROIs) were selected from the mammogram image. In each ROI, eight features were determined from the subimages for NC

at scales from 1 to 4 and the subimages for NLC at scales from 1 to 4. The Bayes discriminant function was employed for distinguishing among abnormal ROIs with a microcalcification cluster and two different types of normal ROIs without a microcalcification cluster. We evaluated the detection performance by using 600 mammograms. Our computerized scheme was shown to have the potential to detect microcalcification clusters with a clinically acceptable sensitivity and low false positives. [J136]

"Morphological segmentation and partial volume analysis for volumetry of solid pulmonary lesions in thoracic CT scans"

Volumetric growth assessment of pulmonary lesions is crucial to both lung cancer screening and oncological therapy monitoring. While several methods for small pulmonary nodules have previously been presented, the segmentation of larger tumors that appear frequently in oncological patients and are more likely to be complexly interconnected with lung morphology has not yet received much attention. We present a fast, automated segmentation method that is based on morphological processing and is suitable for both small and large lesions. In addition, the proposed approach addresses clinical challenges to volume assessment such as variations in imaging protocol or inspiration state by introducing a method of segmentation-based partial volume analysis (SPVA) that follows on the segmentation procedure. Accuracy and reproducibility studies were performed to evaluate the new algorithms. In vivo interobserver and interscan studies on low-dose data from eight clinical metastasis patients revealed that clinically significant volume change can be detected reliably and with negligible computation time by the presented methods. In addition, phantom studies were conducted. Based on the segmentation performed with the proposed method, the performance of the SPVA volumetry method was compared with the conventional technique on a phantom that was scanned with different dosages and reconstructed with varying parameters. Both systematic and absolute errors were shown to be reduced substantially by the SPVA method. The method was especially successful in accounting for slice thickness and reconstruction kernel variations, where the median error was more than halved in comparison to the conventional approach. [J137]

"Maximizing sensitivity in medical diagnosis using biased minimax probability Machine"

The challenging task of medical diagnosis based on machine learning techniques requires an inherent bias, i.e., the diagnosis should favor the "ill" class over the "healthy" class, since misdiagnosing a patient as a healthy person may delay the therapy and aggravate the illness. Therefore,the objective in this task is not to improve the overall accuracy of the classification,but to focus on improving the sensitivity (the accuracy of the "ill" class) while maintaining an acceptable specificity (the accuracy of the "healthy" class). Some current methods adopt roundabout ways to impose a certain bias toward the important class, i.e., they try to utilize some intermediate factors to influence the classification. However, it remains uncertain whether these methods can improve the classification performance systematically. In this paper, by engaging a novel learning tool, the biased minimax probability machine(BMPM), we deal with the issue in a more elegant way and directly achieve the objective of appropriate medical diagnosis. More specifically, the BMPM directly controls the worst case accuracies to incorporate a bias toward the "ill" class. Moreover, in a distribution-free way, the BMPM derives the decision rule in such a way as to maximize the worst case sensitivity while maintaining an acceptable worst case specificity. By directly controlling the accuracies,the BMPM provides a more rigorous way to handle medical diagnosis; by deriving a distribution-free decision rule, the BMPM distinguishes itself from a large family of classifiers, namely, the generative classifiers, where an assumption on the data distribution is necessary. We evaluate the performance of the model and compare it with three traditional classifiers: the k-nearest neighbor, the naive Bayesian, and the C4.5. The test results on two medical datasets, the breast-cancer dataset and the heart disease dataset, show that the BMPM outperforms the other three models [J138]

"An alternate line erasure and readout (ALER) method for implementing slot-scan imaging technique with a flat-panel detector-initial experiences"

This paper describes and demonstrates an electronic collimation method, referred to as the alternate line erasure and readout (ALER) technique, for implementing slot-scan digital radiography technique with an amorphous silicon (a-Si) thin-film transistor (TFT) array based flat-panel detector. An amorphus selenium (a-Se) flat-panel detector was modified to implement the ALER technique for slot-scan imaging. A stepping-motor driven fore-collimator was mounted in front of an X-ray tube to generate a scanning X-ray fan beam. The scanning speed and magnification were adjusted to synchronize the fan beam motion with the image line readout rate. The image lines on the leading and trailing edges of the fan beam were tracked and alternately reset and read out, respectively. The former operation resulted in the erasure of the scatter signals accumulated in the leading edge image line prior to the arrival of the fan beam. The latter operation resulted in the acquisition of fan beam exposure data integrated in the trailing edge image line right after the fan beam passed. To demonstrate the scatter rejection capability of this technique, an anthropomorphic chest phantom was placed in PA position and

scanned at a speed of 576 lines (8.0 cm)/s at 117 kVp and 32 mA. A tungsten bar is placed at the entrance side of the chest phantom to measure the scatter-to-primary ratio (SPR), scatter reduction factor (SRF), and contrast-to-noise ratio degradation factor (CNRDF) in the slot-scan images to evaluate the effectiveness of scatter rejection and the resultant improvement of image quality. SPR and CNRDF in the open-field images were also measured and used as the reference for comparison. A scatter reduction by 86.4 to 95.4% across lower lung and heart regions has been observed with slot-scan imaging. The CNRs have been found to be improved by a factor of 2 in the mediastinum areas over the open-field image as well. [J139]

"Multifusion Multispectral Lightwave Polarimetric Detection Principles and Systems"

The objective of this paper is to present novel detection principles based on all active multispectral polarimetric subtraction imaging principles of targets embedded in scattering media. The novelty of this contribution consists in the formation of multispectral Stokes' parameter image differences, degree of linear polarization image differences, and Mueller-matrix image differences. As a result, high-contrast high-specificity images can be obtained by removing the background from the target. Further contrast enhancement of the target with light beam steering capabilities can be obtained by doping the background surrounding the target or the target itself with high-index-of-refraction polar molecules/nanoparticles. The presented optical principles can be successfully applied to a variety of applications, such as cancer detection and treatment, molecular imaging, and development of photonics and nanophotonic devices, for a widespread group of applications, such as defense and advanced medical diagnostic and analytical devices [J140]

"Medical Image Computing and Computer-Aided Medical Interventions Applied to Soft Tissues: Work in Progress in Urology"

Until recently, computer-aided medical interventions (CAMI) and medical robotics have focused on rigid and nondeformable anatomical structures. Nowadays, special attention is paid to soft tissues, raising complex issues due to their mobility and deformation. Mini-invasive digestive surgery was probably one of the first fields where soft tissues were handled through the development of simulators, tracking of anatomical structures and specific assistance robots. However, other clinical domains, for instance urology, are concerned. Indeed, laparoscopic surgery, new tumour destruction techniques (e.g., HIFU, radiofrequency, or cryoablation), increasingly early detection of cancer, and use of interventional and diagnostic imaging modalities, recently opened new challenges to the urologist and scientists involved in CAMI. This resulted in the last five years in a very significant increase of research and developments of computer-aided urology systems. In this paper, we propose a description of the main problems related to computer-aided diagnostic and therapy of soft tissues and give a survey of the different types of assistance offered to the urologist: robotization, image fusion, surgical navigation. Both research projects and operational industrial systems are discussed [J141]

"Lines of Curvature for Polyp Detection in Virtual Colonoscopy"

Computer-aided diagnosis (CAD) is a helpful addition to laborious visual inspection for preselection of suspected colonic polyps in virtual colonoscopy. Most of the previous work on automatic polyp detection makes use of indicators based on the scalar curvature of the colon wall and can result in many false-positive detections. Our work tries to reduce the number of false-positive detections in the preselection of polyp candidates. Polyp surface shape can be characterized and visualized using lines of curvature. In this paper, we describe techniques for generating and rendering lines of curvature on surfaces and we show that these lines can be used as part of a polyp detection approach. We have adapted existing approaches on explicit triangular surface meshes, and developed a new algorithm on implicit surfaces embedded in 3D volume data. The visualization of shaded colonic surfaces can be enhanced by rendering the derived lines of curvature on these surfaces. Features strongly correlated with true-positive detections were calculated on lines of curvature and used for the polyp candidate selection. We studied the performance of these features on 5 data sets that included 331 pre-detected candidates, of which 50 sites were true polyps. The winding angle had a significant discriminating power for true-positive detections, which was demonstrated by a Wilcoxon rank sum test with $p<0.001$. The median winding angle and inter-quartile range (IQR) for true polyps were 7.817 and 6.770-9.288 compared to 2.954 and 1.995-3.749 for false-positive detections [J142]

"A Fully Automated Method for Lung Nodule Detection From Postero-Anterior Chest Radiographs"

In the past decades, a great deal of research work has been devoted to the development of systems that could improve radiologists' accuracy in detecting lung nodules. Despite the great efforts, the problem is still open. In this paper, we present a fully automated system processing digital postero-anterior (PA) chest radiographs, that starts by producing an accurate segmentation of the lung field area. The segmented lung area includes even those parts of the lungs hidden behind the heart, the spine, and the diaphragm, which are usually excluded from

the methods presented in the literature. This decision is motivated by the fact that lung nodules may be found also in these areas. The segmented area is processed with a simple multiscale method that enhances the visibility of the nodules, and an extraction scheme is then applied to select potential nodules. To reduce the high number of false positives extracted, cost-sensitive support vector machines (SVMs) are trained to recognize the true nodules. Different learning experiments were performed on two different data sets, created by means of feature selection, and employing Gaussian and polynomial SVMs trained with different parameters; the results are reported and compared. With the best SVM models, we obtain about 1.5 false positives per image (fp/image) when sensitivity is approximately equal to 0.71; this number increases to about 2.5 and 4 fp/image when sensitivity is ap0.78 and ap0.85, respectively. For the highest sensitivity (ap0.92 and 1.0), we get 7 or 8 fp/image [J143]

"Synthesizing Biofunctionalized Nanoparticles to Image Cell Signaling Pathways"

This minireview outlines the synthetic efforts, from our research group, to produce nanomaterials for use as imaging agents to study cell signaling pathways. An overview of our approach to the synthesis and biofunctionalization of metal, semiconductor, and ceramic nanomaterials is presented. The probes investigated include coinage metals, Cd-based, Gedeg, naturally occurring fluorescent (NOF) minerals, and Ln-based nanoparticles which were synthesized from novel metal alkoxide, amide, and alkyl precursors. We illustrate the applications of some of these materials as imaging probes to detect signaling pathway components and cellular responses to signals (apoptosis and degranulation) in inflammatory and cancer cells [J144]

"Comparison of the Performance of Linear Multivariate Analysis Methods for Normal and Dyplasia Tissues Differentiation Using Autofluorescence Spectroscopy"

We compared the performance of three widely used linear multivariate methods for autofluorescence spectroscopic tissues differentiation. Principal component analysis (PCA), partial least squares (PLS), and multivariate linear regression (MVLR) were compared for differentiating at normal, tubular adenoma/epithelial dysplasia and cancer in colorectal and oral tissues. The methods' performances were evaluated by cross-validation analysis. The group-averaged predictive diagnostic accuracies were 85% (PCA), 90% (PLS), and 89% (MVLR) for colorectal tissues; 89% (PCA), 90% (PLS), and 90% (MVLR) for oral tissues. This study found that both PLS and MVLR achieved higher diagnostic results than did PCA [J145]

"Microwave reflectometry as a novel diagnostic tool for detection of skin cancers"

More than 1 000 000 people are diagnosed with skin cancer each year in the United States, and more than 10 000 people die from the disease. Methods such as visual inspection and dermoscopy are available for early detection of skin cancers, but improvement in accuracy is needed. This paper investigates the use of microwave reflectometry as a potential diagnostic tool for detection of skin cancers. Open-ended coaxial probes were used to measure microwave properties of skin. The influences of measurement parameters such as probe application pressure, power level, and variation in reflection properties of skin with location and hydration were investigated. Using an available electromagnetic formulation, providing for the reflection properties of a layered dielectric structure irradiated by a coaxial probe, measurement and simulation results were compared. The results of the measurements and simulations for normal and moistened skin show that the water content of normal skin and benign and malignant lesions may cause significant differences among their reflection properties and subsequently render a malignant lesion detectable. The results of microwave measurements performed on human subjects are also presented, which show the potential of this technique to distinguish between cancerous and benign lesions. [J146]

"Feature Subset Selection for Improving the Performance of False Positive Reduction in Lung Nodule CAD"

We propose a feature subset selection method based on genetic algorithms to improve the performance of false positive reduction in lung nodule computer-aided detection (CAD). It is coupled with a classifier based on support vector machines. The proposed approach determines automatically the optimal size of the feature set, and chooses the most relevant features from a feature pool. Its performance was tested using a lung nodule database (52 true nodules and 443 false ones) acquired by multislice CT scans. From 23 features calculated for each detected structure, the suggested method determined ten to be the optimal feature subset size, and selected the most relevant ten features. A support vector machine classifier trained with the optimal feature subset resulted in 100% sensitivity and 56.4% specificity using an independent validation set. Experiments show significant improvement achieved by a system incorporating the proposed method over a system without it. This approach can be also applied to other machine learning problems; e.g. computer-aided diagnosis of lung nodules [J147]

"Utilization of Miniprobes in Modern Endoscopic Ultrasonography"

This paper is devoted to a modern diagnostic method called the endoscopic ultrasonography (EUS). In many countries, the diagnostic attributes of the EUS still need to be more widely spread among physicians and clinical engineers in health-care fields. This method is based on two-imaging techniques: videoendoscopy and ultrasonography (USG), making a possible effective aiding of diagnostics as well as evaluating possibilities of performing a radical surgical therapy. Rotating the USG probes enables acquiring images vertical to an axis for the round angle area. Small diameters and adequate frequencies of these miniprobes make it possible for their deep penetration into such difficult sites as the biliary and pancreatic ducts. In this paper, the EUS advantages and limitations are discussed on the basis of several examples of real interventions practiced by the authors. All images reported in this paper are concerned in using the EUS to assist the minimally invasive diagnostics and surgery processes made on the upper parts of the intestinal tract. Real interventions were assisted by the EUS, which were performed with a rotating minihead inserted through the endoscopic operating channel. Improving a combined imaging of the operation site allowed evaluating the degree to which the cancer formation has spread beyond the tract wall and detecting lesions as small as 1 to 3 mm. Utilization of the EUS has allowed precise diagnostics without disturbances occurring at the conventional ultrasound imaging [J148]

"Prostate mechanical imaging: 3-D image composition and feature calculations"

We have developed a method and a device entitled prostate mechanical imager (PMI) for the real-time imaging of prostate using a transrectal probe equipped with a pressure sensor array and position tracking sensor. PMI operation is based on measurement of the stress pattern on the rectal wall when the probe is pressed against the prostate. Temporal and spatial changes in the stress pattern provide information on the elastic structure of the gland and allow two-dimensional (2-D) and three-dimensional (3-D) reconstruction of prostate anatomy and assessment of prostate mechanical properties. The data acquired allow the calculation of prostate features such as size, shape, nodularity, consistency/hardness, and mobility. The PMI prototype has been validated in laboratory experiments on prostate phantoms and in a clinical study. The results obtained on model systems and in vivo images from patients prove that PMI has potential to become a diagnostic tool that could largely supplant DRE through its higher sensitivity, quantitative record storage, ease-of-use and inherent low cost [J149]

"Extended Kalman Filtering for the Modeling and Analysis of ICG Pharmacokinetics in Cancerous Tumors Using NIR Optical Methods"

Compartmental modeling of indocyanine green (ICG) pharmacokinetics, as measured by near infrared (NIR) techniques, has the potential to provide diagnostic information for tumor differentiation. In this paper, we present three different compartmental models to model the pharmacokinetics of ICG in cancerous tumors. We introduce a systematic and robust approach to model and analyze ICG pharmacokinetics based on the extended Kalman filtering (EKF) framework. The proposed EKF framework effectively models multiple-compartment and multiple-measurement systems in the presence of measurement noise and uncertainties in model dynamics. It provides simultaneous estimation of pharmacokinetic parameters and ICG concentrations in each compartment. Moreover, the recursive nature of the Kalman filter estimator potentially allows real-time monitoring of time varying pharmacokinetic rates and concentration changes in different compartments. Additionally, we introduce an information theoretic criteria for the best compartmental model order selection, and residual analysis for the statistical validation of the estimates. We tested our approach using the ICG concentration data acquired from four Fischer rats carrying adenocarcinoma tumor cells. Our study indicates that, in addition to the pharmacokinetic rates, the EKF model may provide parameters that may be useful for tumor differentiation [J150]

"A registration framework for the comparison of mammogram sequences"

In this paper, we present a two-stage algorithm for mammogram registration, the geometrical alignment of mammogram sequences. The rationale behind this paper stems from the intrinsic difficulties in comparing mammogram sequences. Mammogram comparison is a valuable tool in national breast screening programs as well as in frequent monitoring and hormone replacement therapy (HRT). The method presented in this paper aims to improve mammogram comparison by estimating the underlying geometric transformation for any mammogram sequence. It takes into consideration the various temporal changes that may occur between successive scans of the same woman and is designed to overcome the inconsistencies of mammogram image formation. [J151]

"Use of magnetic nanoparticle heating in the treatment of breast cancer"

Magnetic nanoparticles are promising tools for the minimal invasive elimination of small tumours in the breast

using magnetically-induced heating. The approach complies with the increasing demand for breast conserving therapies and has the advantage of offering a selective and refined tuning of the degree of energy deposition allowing an adequate temperature control at the target. The biophysical basis of the approach, the magnetic and structural properties of magnetic nanoparticles are reviewed. Results with model targets and in vivo experiments in laboratory animals are reported. [J152]

"Dimension reduction-based penalized logistic regression for cancer classification using microarray data"

The use of penalized logistic regression for cancer classification using microarray expression data is presented. Two dimension reduction methods are respectively combined with the penalized logistic regression so that both the classification accuracy and computational speed are enhanced. Two other machine-learning methods, support vector machines and least-squares regression, have been chosen for comparison. It is shown that our methods have achieved at least equal or better results. They also have the advantage that the output probability can be explicitly given and the regression coefficients are easier to interpret. Several other aspects, such as the selection of penalty parameters and components, pertinent to the application of our methods for cancer classification are also discussed. [J153]

"Mining Text for Expert Witnesses"

Text mining is a relatively new research area associated with the creation of novel information resources from electronic text repositories. An expert-witness database based on text from legal, medical, and news documents demonstrates the successful application of text-mining techniques. [J154]

"Using AI to detect breast cancer"

Scientists are marshalling AI tools in the fight against the leading cause of cancer among women. Using digital information from traditional breast cancer detection techniques as well as newer detection methods, new applications of data mining and neural networks are helping doctors detect cancers sooner. The AI tools can also reduce the number of biopsies required in the diagnostic process. Neural networks and AI methods of pattern recognition can help indicate the presence of breast cancers. [J155]

"A comparison of human and model observers in multislice LROC studies"

Model and human observers have been compared in a series of localization receiver operating characteristic (LROC) studies involving single-slice and multislice image displays. The task was detection of Ga-avid lymphomas within single photon emission computed tomography (SPECT)-reconstructed transverse slices of a mathematical phantom, and the studies involved four reconstruction strategies: the filtered-backprojection (FBP) and ordered-subset expectation-maximization (OSEM) algorithms with two- and three-dimensional postreconstruction filtering. The human-observer data was drawn from studies performed by Wells et al. (2000), while multiclass versions of the nonprewhitening (NPW), channelized nonprewhitening (CNPW), and channelized Hotelling (CH) model observers, each capable of performing the tumor search task, were applied. The channelized observers were evaluated with multiple square-channel models and both with and without internal noise. For the multislice studies, two different capacities for integrating the slice information were also tested. The CH observer gave good quantitative agreement with the human data from both image-display studies when the internal-noise model was used. The CNPW observer performed similarly with the iterative strategies. Wells et al. had shown that human observers are imperfect integrators of multislice information, and this is characterized as increased internal noise with the model observers. [J156]

"Nanoparticles for biotechnology applications"

Rabbit. [J157]

"Detection performance theory for ultrasound imaging systems"

A rigorous statistical theory for characterizing the performance of medical ultrasound systems for lesion detection tasks is developed. A design strategy for optimizing ultrasound systems should be to adjust parameters for maximum information content, which is obtained by maximizing the ideal observer performance. Then, given the radio-frequency data, image and signal processing algorithms are designed to extract as much diagnostically relevant information as possible. In this paper, closed-form and low-contrast approximations of ideal observer performance are derived for signal known statistically detection tasks. The accuracy of the approximations are tested by comparing with Monte Carlo techniques. A metric borrowed and modified from photon imaging, Generalized Noise Equivalent Quanta, is shown to be a useful and measurable target-independent figure of merit

when adapted for ultrasound systems. This theory provides the potential to optimize design tradeoffs for detection tasks. For example it may help us understand how to push the limits of specific features, such as spatial resolution, without significantly compromising overall detection performance. [J158]

"Data mining for case-based reasoning in high-dimensional biological domains"

Case-based reasoning (CBR) is a suitable paradigm for class discovery in molecular biology, where the rules that define the domain knowledge are difficult to obtain and the number and the complexity of the rules affecting the problem are too large for formal knowledge representation. To extend the capabilities of CBR, we propose the mixture of experts for case-based reasoning (MOE4CBR), a method that combines an ensemble of CBR classifiers with spectral clustering and logistic regression. Our approach not only achieves higher prediction accuracy, but also leads to the selection of a subset of features that have meaningful relationships with their class labels. We evaluate MOE4CBR by applying the method to a CBR system called TA3-a computational framework for CBR systems. For two ovarian mass spectrometry data sets, the prediction accuracy improves from 80 percent to 93 percent and from 90 percent to 98.4 percent, respectively. We also apply the method to leukemia and lung microarray data sets with prediction accuracy improving from 65 percent to 74 percent and from 60 percent to 70 percent, respectively. Finally, we compare our list of discovered biomarkers with the lists of selected biomarkers from other studies for the mass spectrometry data sets. [J159]

"Advances in oral cancer detection using optical coherence tomography"

Optical coherence tomography (OCT) is a new modality capable of cross sectional imaging of biological tissue. Due to its many technical advantages such as high image resolution, fast acquisition time, and noninvasive capabilities, OCT is potentially useful in various medical applications. Because OCT systems can function with a fiber optic probe, they are applicable to almost any anatomic structures accessible either directly, or by endoscopy. OCT has the potential to provide a fast and noninvasive means for early clinical detection, diagnosis, screening, and monitoring of precancer and cancer. With an imaging depth range of 2-3 mm, OCT diagnostics are particularly suitable for the oral mucosa. Currently, it is difficult to detect premalignant and malignant oral lesions due to their often multifocal nature and need for repeated biopsies. The goal of this study was to evaluate the feasibility of OCT for the diagnosis of multiple stages of oral cancer progression. In this paper, we present not only conventional 2-D OCT images, but also 3-D volume images of normal and precancerous lesions. Our results demonstrate that OCT is a potential tool for cancer detection with comprehensive diagnostic images. [J160]

"Investigation of near-infrared autofluorescence imaging for the detection of breast cancer"

Detection of breast cancer in fresh tissue obtained from surgery is investigated using near-infrared autofluorescence imaging under laser excitation at 532 and 632.8 nm. The differences in intensity between the three main components of breast tissue (cancer, fibrous, and adipose) are estimated and compared to those obtained from cross-polarized light scattering images recorded under polarized illumination at 700 nm. The optical spectroscopic images for each tissue sample were subsequently compared with the histopathology slides. The experimental results indicate that the intensity of the near-infrared emission is considerably different in breast cancer compared to that of the adjacent nonneoplastic tissues (adipose and fibrous tissue). The experimental results suggest that 632.8-nm excitation offers key advantages compared to 532 nm excitation. [J161]

"Improved prostate cancer imaging with SPECT/CT and MRI/MRSI"

We propose a combined imaging technique for prostate cancer using 111In-ProstaScint SPECT/CT and MRI/MRSI. When used alone, either SPECT/CT or MRI/MRSI has limitations in assessing the patient undergoing clinical prostate cancer management. However, combined imaging can use MRI/MRSI to assess the prostate gland while SPECT/CT 111In-ProstaScint imaging can evaluate nearby and distant lymph nodes for metastases. The combined imaging study thereby provides complementary information useful for the cancer management. 111In-ProstaScint SPECT data are reconstructed using an iterative algorithm that includes CT-derived attenuation correction and depth-dependent collimator blurring compensation. 3D MR spectra are overlaid on the T2-weighted MR image. Image data from 3 patient studies demonstrate the potential role of combined 111In-ProstaScint SPECT/CT and MRI/MRSI imaging of prostate cancer. In the first, SPECT/CT revealed increased uptake of 111In-ProstaScint, but that occurred beyond the sensitive region of MRSI. Images from a second patient sequentially received 111In-ProstaScint SPECT/CT and MRI/MRSI in one and half months and were correlative and complementary to each other. Images from a third patient who had undergone androgen deprivation therapy show that MRI improved anatomical definition in comparison to CT, with 111In-ProstaScint indicating disease where MRSI was either equivocal or indicated atrophy. Overall, MRI/MRSI generally provided

better specificity for the cancer detection within the prostate in the absence of androgen deprivation therapy, and better anatomic details of the prostate than 111In-ProstaScint SPECT/CT. Yet, 111In-ProstaScint SPECT/CT improves sensitivity for detection of distant lymph node metastases, and also is more sensitive when the patient is undergoing androgen deprivation therapy and thereby provides useful diagnostic information that complements the MRI/MRSI study alone. [J162]

"Restrictions on the three-class ideal observer's decision boundary lines"

We are attempting to develop expressions for the coordinates of points on the three-class ideal observer's receiver operating characteristic (ROC) hypersurface as functions of the set of decision criteria used by the ideal observer. This is considerably more difficult than in the two-class classification task, because the conditional probabilities in question are not simply related to the cumulative distribution functions of the decision variables, and because the slopes and intercepts of the decision boundary lines are not independent; given the locations of two of the lines, the location of the third will be constrained depending on the other two. In this paper, we attempt to characterize those constraining relationships among the three-class ideal observer's decision boundary lines. As a result, we show that the relationship between the decision criteria and the misclassification probabilities is not one-to-one, as it is for the two-class ideal observer. [J163]

"Counting moles automatically from back images"

Density of moles is a strong predictor of malignant melanoma, therefore, enumeration of moles is often an integral part of many studies that look at malignant melanoma. An automatic method of segmenting and counting moles would help standardize studies, compared with manual counting. We have developed an unsupervised algorithm for segmenting and counting moles from two-dimensional color images of the back torso region, as part of a study to evaluate the effectiveness of sunscreen. The method consists of a new variant of mean shift filtering that forms clusters in the image and removes noise, a region growing procedure to select candidates, and a rule-based classifier to identify moles. When this algorithm was compared to an assessment by an expert dermatologist, the algorithm showed a sensitivity rate of 91% and diagnostic accuracy of 90% on the test set, for moles larger than 1.5 mm in diameter. [J164]

"Toward automated segmentation of the pathological lung in CT"

Conventional methods of lung segmentation rely on a large gray value contrast between lung fields and surrounding tissues. These methods fail on scans with lungs that contain dense pathologies, and such scans occur frequently in clinical practice. We propose a segmentation-by-registration scheme in which a scan with normal lungs is elastically registered to a scan containing pathology. When the resulting transformation is applied to a mask of the normal lungs, a segmentation is found for the pathological lungs. As a mask of the normal lungs, a probabilistic segmentation built up out of the segmentations of 15 registered normal scans is used. To refine the segmentation, voxel classification is applied to a certain volume around the borders of the transformed probabilistic mask. Performance of this scheme is compared to that of three other algorithms: a conventional, a user-interactive and a voxel classification method. The algorithms are tested on 10 three-dimensional thin-slice computed tomography volumes containing high-density pathology. The resulting segmentations are evaluated by comparing them to manual segmentations in terms of volumetric overlap and border positioning measures. The conventional and user-interactive methods that start off with thresholding techniques fail to segment the pathologies and are outperformed by both voxel classification and the refined segmentation-by-registration. The refined registration scheme enjoys the additional benefit that it does not require pathological (hand-segmented) training data. [J165]

"Evaluation of fully 3-D emission mammotomography with a compact cadmium zinc telluride detector"

A compact, dedicated cadmium zinc telluride (CZT) gamma camera coupled with a fully three-dimensional (3-D) acquisition system may serve as a secondary diagnostic tool for volumetric molecular imaging of breast cancers, particularly in cases when mammographic findings are inconclusive. The developed emission mammotomography system comprises a medium field-of-view, quantized CZT detector and 3-D positioning gantry. The intrinsic energy resolution, sensitivity and spatial resolution of the detector are evaluated with Tc-99m (140 keV) filled flood sources, capillary line sources, and a 3-D frequency-resolution phantom. To mimic realistic human pendant, uncompressed breast imaging, two different phantom shapes of an average sized breast, and three different lesion diameters are imaged to evaluate the system for 3-D mammotomography. Acquisition orbits not possible with conventional emission, or transmission, systems are designed to optimize the viewable breast volume while improving sampling of the breast and anterior chest wall. Complications in camera positioning about the patient necessitate a compromise in these two orbit design criteria. Image quality is evaluated with

signal-to-noise ratios and contrasts of the lesions, both with and without additional torso phantom background. Reconstructed results indicate that 3-D mammotomography, incorporating a compact CZT detector, is a promising, dedicated breast imaging technique for visualization of tumors [J166]

"Computer-aided diagnostic scheme for distinction between benign and malignant nodules in thoracic low-dose CT by use of massive training artificial neural network"

Low-dose helical computed tomography (LDCT) is being applied as a modality for lung cancer screening. It may be difficult, however, for radiologists to distinguish malignant from benign nodules in LDCT. Our purpose in this study was to develop a computer-aided diagnostic (CAD) scheme for distinction between benign and malignant nodules in LDCT scans by use of a massive training artificial neural network (MTANN). The MTANN is a trainable, highly nonlinear filter based on an artificial neural network. To distinguish malignant nodules from six different types of benign nodules, we developed multiple MTANNs (multi-MTANN) consisting of six expert MTANNs that are arranged in parallel. Each of the MTANNs was trained by use of input CT images and teaching images containing the estimate of the distribution for the "likelihood of being a malignant nodule", i.e., the teaching image for a malignant nodule contains a two-dimensional Gaussian distribution and that for a benign nodule contains zero. Each MTANN was trained independently with ten typical malignant nodules and ten benign nodules from each of the six types. The outputs of the six MTANNs were combined by use of an integration ANN such that the six types of benign nodules could be distinguished from malignant nodules. After training of the integration ANN, our scheme provided a value related to the "likelihood of malignancy" of a nodule, i.e., a higher value indicates a malignant nodule, and a lower value indicates a benign nodule. Our database consisted of 76 primary lung cancers in 73 patients and 413 benign nodules in 342 patients, which were obtained from a lung cancer screening program on 7847 screenees with LDCT for three years in Nagano, Japan. The performance of our scheme for distinction between benign and malignant nodules was evaluated by use of receiver operating characteristic (ROC) analysis. Our scheme achieved an Az (area under the ROC curve) value of 0.882 in a round-robin test. Our scheme correctly iden--tified 100% (76/76) of malignant nodules as malignant, whereas 48% (200/413) of benign nodules were identified correctly as benign. Therefore, our scheme may be useful in assisting radiologists in the diagnosis of lung nodules in LDCT. [J167]

"Multiple SVM-RFE for gene selection in cancer classification with expression data"

This paper proposes a new feature selection method that uses a backward elimination procedure similar to that implemented in support vector machine recursive feature elimination (SVM-RFE). Unlike the SVM-RFE method, at each step, the proposed approach computes the feature ranking score from a statistical analysis of weight vectors of multiple linear SVMs trained on subsamples of the original training data. We tested the proposed method on four gene expression datasets for cancer classification. The results show that the proposed feature selection method selects better gene subsets than the original SVM-RFE and improves the classification accuracy. A Gene Ontology-based similarity assessment indicates that the selected subsets are functionally diverse, further validating our gene selection method. This investigation also suggests that, for gene expression-based cancer classification, average test error from multiple partitions of training and test sets can be recommended as a reference of performance quality. [J168]

"A prototype for unsupervised analysis of tissue microarrays for cancer research and diagnostics"

The tissue microarray (TMA) technique enables researchers to extract small cylinders of tissue from histological sections and arrange them in a matrix configuration on a recipient paraffin block such that hundreds can be analyzed simultaneously. TMA offers several advantages over traditional specimen preparation by maximizing limited tissue resources and providing a highly efficient means for visualizing molecular targets. By enabling researchers to reliably determine the protein expression profile for specific types of cancer, it may be possible to elucidate the mechanism by which healthy tissues are transformed into malignancies. Currently, the primary methods used to evaluate arrays involve the interactive review of TMA samples while they are viewed under a microscope, subjectively evaluated, and scored by a technician. This process is extremely slow, tedious, and prone to error. In order to facilitate large-scale, multi-institutional studies, a more automated and reliable means for analyzing TMAs is needed. We report here a web-based prototype which features automated imaging, registration, and distributed archiving of TMAs in multiuser network environments. The system utilizes a principal color decomposition approach to identify and characterize the predominant staining signatures of specimens in color space. This strategy was shown to be reliable for detecting and quantifying the immunohistochemical expression levels for TMAs. [J169]

"Thickness correction of mammographic images by means of a global parameter model of the compressed breast"

Peripheral enhancement and tilt correction of unprocessed digital mammograms was achieved with a new reversible algorithm. This method has two major advantages for image visualization. First, the display dynamic range can be relatively small, and second, adjustment of the overall luminance to inspect details is not required in most cases. The correction is useful for preprocessing in computer-aided detection/diagnosis algorithms. The method is based on knowledge of the three-dimensional compressed breast shape to equalize thickness by adding virtual tissue, which results in intensity equalization for the mammographic image. Previously described methods implicitly estimate the contribution of thickness variations to image intensity, usually by nonparametric methods. The proposed method employs a global parametric breast shape model, which is advantageous for visualization and CAD. [J170]

"The Goodman-Kruskal coefficient and its applications in genetic diagnosis of cancer"

Increasing interest in new pattern recognition methods has been motivated by bioinformatics research. The analysis of gene expression data originated from microarrays constitutes an important application area for classification algorithms and illustrates the need for identifying important predictors. We show that the Goodman-Kruskal coefficient can be used for constructing minimal classifiers for tabular data, and we give an algorithm that can construct such classifiers. [J171]

"Dielectrophoresis-based sample handling in general-purpose programmable diagnostic instruments"

As the molecular origins of disease are better understood, the need for affordable, rapid, and automated technologies that enable microscale molecular diagnostics has become apparent. Widespread use of microsystems that perform sample preparation and molecular analysis could ensure that the benefits of new biomedical discoveries are realized by a maximum number of people, even those in environments lacking any infrastructure. While progress has been made in developing miniaturized diagnostic systems, samples are generally processed off-device using labor-intensive and time-consuming traditional sample preparation methods. We present the concept of an integrated programmable general-purpose sample analysis processor (GSAP) architecture where raw samples are routed to separation and analysis functional blocks contained within a single device. Several dielectrophoresis-based methods that could serve as the foundation for building GSAP functional blocks are reviewed including methods for cell and particle sorting, cell focusing, cell ac impedance analysis, cell lysis, and the manipulation of molecules and reagent droplets. [J172]

"Detection of basal cell carcinoma using electrical impedance and neural networks"

Variations in electrical impedance over frequency might be used to distinguish basal cell carcinoma (BCC) from benign skin lesions, although the patterns that separate the two are nonobvious. Artificial neural networks (ANNs) may be good pattern classifiers for this application. A preliminary study to show the potential of neural networks to distinguish benign from malignant skin lesions using electrical impedance is presented. Electrical impedance was measured in vivo from 1 kHz to 1 MHz at five virtual depths on 18 BCC and 16 benign or premalignant lesions. A feed-forward neural network was trained using back propagation to classify these lesions. Two methods of preprocessing were used to account for the impedance of normal skin and the size of the lesion, one based on estimating the impedance of the lesion relative to adjacent normal skin and one based on estimating the impedance of the lesion independent of size or surrounding normal skin. Neural networks were able to classify measurements in a test set with 100% accuracy for the first preprocessing technique and 85% accuracy for the second. These results indicate electrical impedance may be a promising clinical diagnostic tool for basal cell carcinoma or other forms of skin cancer. [J173]

"Local contralateral subtraction based on bilateral symmetry of lung for reduction of false positives in computerized detection of pulmonary nodules"

A novel method called local contralateral subtraction has been developed for the removal of normal anatomic structures in chest radiographs based on the symmetry between the left and right lung regions. The method was oriented to the reduction of false positives reported by a computer-aided diagnosis (CAD) scheme for detection of lung nodules in chest radiographs. In our method, two regions of interest (ROIs) are extracted, one from the position where a nodule candidate is located, and the other from the anatomically corresponding location in the opposite lung, which contains similar normal structures. A wavelet-based, multiresolution image registration method is employed for matching the two ROIs, and subtraction is performed. If no structure remains in the subtracted ROI, then the original ROI is identified as negative (i.e., it contains only normal structures); otherwise, it is regarded as positive (i.e., it contains a nodule). A measure that quantifies the remaining structures was developed to distinguish between nodules and false positives. Application of the method to clinical chest radiographs showed that it was effective in eliminating normal anatomic structures and reducing the number of

false detections in the CAD scheme for detection of lung nodules. [J174]

"Three-dimensional nonlinear image reconstruction for microwave biomedical imaging"

Active microwave imaging has attracted significant interests in biomedical applications, in particular for breast imaging. However, the high electrical contrasts in breast tissue also increases the difficulty of forming an accurate image because of the increased multiple scattering. To model such strong three-dimensional (3-D) multiple scattering effects in biomedical imaging applications, we develop a full 3-D inverse scattering algorithm based on the combination of the contrast source inversion and the fast Fourier transform algorithm. Numerical results show that our algorithm can accurately invert for the high-contrast media in breast tissue. [J175]

"Skin cancer identification using multifrequency electrical impedance-a potential screening tool"

Electrical bio-impedance can be used to assess skin cancers and other cutaneous lesions. The aim of this study was to distinguish skin cancer from benign nevi using multifrequency impedance spectra. Electrical impedance spectra of about 100 skin cancers and 511 benign nevi were measured. Impedance of reference skin was measured ipsi-laterally to the lesions. The impedance relation between lesion and reference skin was used to distinguish the cancers from the nevi. It was found that it is possible to separate malignant melanoma from benign nevi with 75% specificity at 100% sensitivity, and to distinguish nonmelanoma skin cancer from benign nevi with 87% specificity at 100% sensitivity. The power of skin cancer detection using electrical impedance is as good as, or better than, conventional visual screening made by general practitioners. [J176]

"Spacecraft converge on Mars"

The mystery of whether there is or has been life on Mars may be clarified or even resolved soon, with four new spacecraft-two from the European Space Agency and two from NASA-arriving at the planet. They join two NASA probes already in orbit, though one of them-Odyssey-had a radiation sensor knocked out by the unusually intense solar storms in October. [J177]

"Using uncorrelated discriminant analysis for tissue classification with gene expression data"

The classification of tissue samples based on gene expression data is an important problem in medical diagnosis of diseases such as cancer. In gene expression data, the number of genes is usually very high (in the thousands) compared to the number of data samples (in the tens or low hundreds); that is, the data dimension is large compared to the number of data points (such data is said to be undersampled). To cope with performance and accuracy problems associated with high dimensionality, it is commonplace to apply a preprocessing step that transforms the data to a space of significantly lower dimension with limited loss of the information present in the original data. Linear discriminant analysis (LDA) is a well-known technique for dimension reduction and feature extraction, but it is not applicable for undersampled data due to singularity problems associated with the matrices in the underlying representation. This paper presents a dimension reduction and feature extraction scheme, called uncorrelated linear discriminant analysis (ULDA), for undersampled problems and illustrates its utility on gene expression data. ULDA employs the generalized singular value decomposition method to handle undersampled data and the features that it produces in the transformed space are uncorrelated, which makes it attractive for gene expression data. The properties of ULDA are established rigorously and extensive experimental results on gene expression data are presented to illustrate its effectiveness in classifying tissue samples. These results provide a comparative study of various state-of-the-art classification methods on well-known gene expression data sets [J178]

"Nonnegative matrix factorization for rapid recovery of constituent spectra in magnetic resonance chemical shift imaging of the brain"

We present an algorithm for blindly recovering constituent source spectra from magnetic resonance (MR) chemical shift imaging (CSI) of the human brain. The algorithm, which we call constrained nonnegative matrix factorization (cNMF), does not enforce independence or sparsity, instead only requiring the source and mixing matrices to be nonnegative. It is based on the nonnegative matrix factorization (NMF) algorithm, extending it to include a constraint on the positivity of the amplitudes of the recovered spectra. This constraint enables recovery of physically meaningful spectra even in the presence of noise that causes a significant number of the observation amplitudes to be negative. We demonstrate and characterize the algorithm's performance using 31P volumetric brain data, comparing the results with two different blind source separation methods: Bayesian spectral decomposition (BSD) and nonnegative sparse coding (NNSC). We then incorporate the cNMF algorithm into a hierarchical decomposition framework, showing that it can be used to recover tissue-specific spectra given a processing hierarchy that proceeds coarse-to-fine. We demonstrate the hierarchical procedure on 1H brain data and conclude that the computational efficiency of the algorithm makes it well-suited for use in diagnostic

work-up. [J179]

"Pulmonary nodule distribution modeling as a diagnostic tool for HRCT image analysis"

In an attempt to improve pulmonary CT scan reading, a computerized model of lung has first been elaborated. The secondary lobule was used as structuring lung element. The entire organ was composed of several lobule layers and of broncho-vascular trees. As pulmonary nodule distribution modes may turn the diagnostic onto specific pathology type, it is very important to define them as precisely as possible. Seven nodule distributions have been modeled: homogenous, peripheral, centrolobular, pleural, lymphatic, and broncho-vascular. A software tool was developed which allows the radiologist to spread nodules either in the whole lung or in anatomical lung areas, using one or more defined distribution modes until the simulated images mimic the CT scans under analysis. First results show a good agreement between scans and synthesized slices. The software tool described here help the physician to determine the true underlying nodule distribution involved in the pulmonary CT under analysis and lead then to a more precise diagnosis. Moreover, it can be used for radiologist education and training. [J180]

"Finger doses received during 18 FDG injections calculated with Monte Carlo Simulations"

The main objective of this paper is to evaluate the absorbed doses, derived from the administration of 18FDG, in the fingers of PET physicians using the GEANT3 Monte Carlo code. A comparison is made with data obtained with thermoluminescent dosimeters. Considering a workload of 10 patients per week and per medical doctor, each physician receives doses five times lower than the weekly skin dose limit when the fingers are around the active volume and 20 times lower if they are at the rear end of the syringe. In the calculations, a typical administered activity of 0.370 GBq was assumed with a finger-syringe contact time of 5 s. Monte Carlo calculations were performed for different kinds of syringes and different injected volumes. Finger doses as a function of the syringe wall thickness for three kinds of wall materials are also calculated. Results show a slight dose reduction when the polypropylene syringe is replaced with a Pyrex one. They also allow deriving guidelines for the handling of syringes containing the most used PET radiopharmaceuticals. [J181]

"Automatic pectoral muscle segmentation on mediolateral oblique view mammograms"

Mammograms are X-ray images of the breast which are used to detect breast cancer. When mammograms are analyzed by computer, the pectoral muscle should preferably be excluded from processing intended for the breast tissue. For this and other reasons, it is important to identify and segment out the pectoral muscle. In this paper, a new, adaptive algorithm is proposed to automatically extract the pectoral muscle on digitized mammograms; it uses knowledge about the position and shape of the pectoral muscle on mediolateral oblique views. The pectoral edge is first estimated by a straight line which is validated for correctness of location and orientation. This estimate is then refined using iterative "cliff detection" to delineate the pectoral margin more accurately. Finally, an enclosed region, representing the pectoral muscle, is generated as a segmentation mask. The algorithm was found to be robust to the large variations in appearance of pectoral edges, to dense overlapping glandular tissue, and to artifacts like sticky tape. The algorithm has been applied to the entire Mammographic Image Analysis Society (MIAS) database of 322 images. The segmentation results were evaluated by two expert mammographic radiologists, who rated 83.9% of the curve segmentations to be adequate or better. [J182]

"Noninvasive quantification of the differential portal and arterial contribution to the liver blood supply from PET measurements using the 11 C-acetate kinetic model"

Our recent research has demonstrated that 11C-acetate could be a complementary tracer to 18F-fluorodeoxyglucose (FDG) in positron emission tomography (PET) imaging of hepatocellular carcinoma (HCC). In our previous modeling study, a three-compartment four-parameter model with a fixed contribution ratio of the liver's two blood supplies was proposed to characterize the kinetic behavior of 11C-acetate in liver. However, in real pathology, both tumor and nontumor liver tissue can be heterogeneous in the distribution and proportion of the two blood supplies. To further improve the accuracy of quantitative analysis, the actual proportion of the hepatic artery and portal vein (PV) in different regions of interest (ROIs) was investigated in this study. An extra parameter avwas included in the model input function to describe the contribution of PV to the liver. Ten ROIs extracted from six patients were used to test the models with fixed/nonfixed weighted dual-input function. The weighted nonlinear least squares algorithm was used to estimate all of the parameters. Evaluation of the adequacy of the two models was conducted and the computer simulation was performed to test the estimation accuracy of the new model. The forward clearance K was also estimated by the linear Patlak method. The results show that the model with parameter avin the input function was more suitable for mapping the tracer time activity curves. Moreover, the estimated avvalue fits the practical physiological and pathological conditions well

and could be a potential candidate to provide useful additional diagnostic information for the early detection of hepatic metastases. [J183]

"Multiwavelet grading of pathological images of prostate"

Histological grading of pathological images is used to determine the level of malignancy of cancerous tissues. This is a very important task in prostate cancer prognosis, since it is used for treatment planning. If infection of cancer is not rejected by noninvasive diagnostic techniques like magnetic resonance imaging, computed tomography scan, and ultrasound, then biopsy specimens of tissue are tested. For prostate, biopsied tissue is stained by hematoxyline and eosine method and viewed by pathologists under a microscope to determine its histological grade. Human grading is very subjective due to interobserver and intraobserver variations and in some cases difficult and time-consuming. Thus, an automatic and repeatable technique is needed for grading. The Gleason grading system is the most common method for histological grading of prostate tissue samples. According to this system, each cancerous specimen is assigned one of five grades. Although some automatic systems have been developed for analysis of pathological images, Gleason grading has not yet been automated; the goal of this research is to automate it. To this end, we calculate energy and entropy features of multiwavelet coefficients of the image. Then, we select most discriminative features by simulated annealing and use a k-nearest neighbor classifier to classify each image to appropriate grade (class). The leaving-one-out technique is used for error rate estimation. We also obtain the results using features extracted by wavelet packets and co-occurrence matrices and compare them with the multiwavelet method. Experimental results show the superiority of the multiwavelet transforms compared with other techniques. For multiwavelets, critically sampled preprocessing outperforms repeated-row preprocessing and has less sensitivity to noise for second level of decomposition. The first level of decomposition is very sensitive to noise and, thus, should not be used for feature extraction. The best multiwavelet me--thod grades prostate pathological images correctly 97% of the time. [J184]

"An adaptive resource-allocating network for automated detection, segmentation, and classification of breast cancer nuclei topic area: image processing and recognition"

This paper presents a unified image analysis approach for automated detection, segmentation, and classification of breast cancer nuclei using a neural network, which learns to cluster shapes and to classify nuclei. The proposed neural network is incrementally grown by creating a new cluster whenever a previously unseen shape is presented. Each hidden node represents a cluster used as a template to provide faster and more accurate nuclei detection and segmentation. Online learning gives the system improved performance with continued use. The effectiveness of the resulting system is demonstrated on a task of cytological image analysis, with classification of individual nuclei used to diagnose the sample. This demonstrates the potential effectiveness of such a system on diagnostic tasks that require the classification of individual cells. [J185]

"A fuzzy logic based-method for prognostic decision making in breast and prostate cancers"

Accurate and reliable decision making in oncological prognosis can help in the planning of suitable surgery and therapy, and generally, improve patient management through the different stages of the disease. In recent years, several prognostic markers have been used as indicators of disease progression in oncology. However, the rapid increase in the discovery of novel prognostic markers resulting from the development in medical technology, has dictated the need for developing reliable methods for extracting clinically significant markers where complex and nonlinear interactions between these markers naturally exist. The aim of this paper is to investigate the fuzzy k-nearest neighbor (FK-NN) classifier as a fuzzy logic method that provides a certainty degree for prognostic decision and assessment of the markers, and to compare it with: 1) logistic regression as a statistical method and 2) multilayer feedforward backpropagation neural networks an artificial neural-network tool, the latter two techniques having been widely used for oncological prognosis. In order to achieve this aim, breast and prostate cancer data sets are considered as benchmarks for this analysis. The overall results obtained indicate that the FK-NN-based method yields the highest predictive accuracy, and that it has produced a more reliable prognostic marker model than both the statistical and artificial neural-network-based methods. [J186]

"A HOTLink/networked PC data acquisition and image reconstruction system for a high-resolution whole-body PET with respiratory or ECG-gated performance"

An ultrahigh-resolution positron emission tomography (PET) camera in whole-body scanning or gated imaging study needs super computer-processing power for creating a huge sinogram as well as doing image reconstruction. A fast HOTLink serial bus attached to networked cluster personal computers (PC) has been developed for this special purpose. In general, the coincidence data from a PET camera is unidirectional; therefore, an additional daisy-chain bus using high-speed HOTLink (400 Mb/s, Cypress Semiconductor, inc.)

transmitters and receivers is designed to carry the coincidence data to the entire networked (LAN) computers (PCs), the data from HOTLink are interfaced to a PC through a fast PCI I/O board (80 Mbyte/s). The overall architecture for the image acquisition and reconstruction computing system for a whole-body PET scanning is a pipeline design. One PC will acquire sinogram data for one bed position, and after completion of data acquisition that PC will begin to reconstruct the image. Meanwhile, another PC in the network will start data acquisition for the next bed position. The image results from the previous PC will be sent to a master computer for final tabulation and storage through the standard network, and then it will be free for processing a new bed position. [J187]

"Inexpensive position sensitive detector block for dedicated PET cameras using 40-mm diameter PMT in quadrant sharing configuration"

Recent approvals by CMS (HCFA) for reimbursement of positron emission tomography (PET) scans fuels the rapid grow of the PET market, thus creating the need for more affordable dedicated PET scanners. The objective of the work presented here was the development of a BGO position-sensitive block with similar detector area (40 mm Ч 40 mm) and same number of crystals (8 Ч 8) as the block of a commercial BGO PET, using the less expensive photomultiplier quadrant sharing (PQS) technique. This block is coupled to four single-anode 40-mm diameter photomultipliers (PMT) instead of the 19-mm PMT used in a popular commercial BGO PET, and each PMT is shared by four adjacent detector blocks. Potentially, this design needs only 25% of the number of PMT used in the commercial BGO PET. In order not to waste the unused half-row of PMT at the edges of a detector panel/module when the module is made up solely of square blocks, an extended rectangular block has to be developed for the edge-blocks in the module, which maximized the use of the PMT and minimized the gap between modules. Only the extended block needs to be developed to derive the design for all the blocks in the module because the symmetric square block uses the same light-distributing partitions as those along the short side of the extended rectangular block. White-paint masks applied with accurate templates and airbrush were fine-tuned for every pair of adjacent crystals. The experimental block developed in this study provided good crystal-decoding. The composite energy spectrum of all 64 crystals showed a prominent photopeak. The worst crystal sitting in the air space between 4 round PMTs still has 60% of the signal pulse height as the best crystal. The average energy resolution was 21.8% for 511 keV gamma (range 17%-28.7%) that compared well with the 22%-44% measured with GE and CTI blocks. The image resolution provided by the PQS blocks is expected to be comparable to that of commercial BGO PETs as similar size crystals were decoded. [J188]

"Signal characteristics of individual crystals in high resolution BGO detector designs using PMT-quadrant sharing"

The PMT-quadrant sharing (PQS) detector design allows very high resolution detectors to be built with 70% fewer PMTs and lower cost. A common concern for the design is that there is a big gap (photo-insensitive area) between four circular PMTs and the photoelectron signal (pulse height) may be much lower for the central crystals. The concern increases with the use of smaller PMTs for high-resolution designs because small PMTs have relatively thicker walls and relatively larger tolerance spaces between them. The authors measured the pulse heights and energy resolution for each crystal in three different types of PQS blocks for 19 mm PMT. For a square 7 Ч 7 block detector (2.66 mm Ч 2.66 mm Ч 18 mm BGO needles), the maximum photopeak signals occurred at the corner crystal of the block. The signals for the worst central five crystals (sitting on space with no PMT connection) had pulse heights 0.87 as high as that of the corner crystals. The 12 crystals (outside the central five) with coupling only to the glass wall but not to the photocathode had a relative pulse height of 0.92. The eight crystals with partial exposure to photocathodes had a 0.94 relative pulse height. The energy resolution for individual crystals was 22%-30% with an average of 26%. Asymmetric photopeaks, especially for the corner crystals, were observed, and these were found to be the result of the depth-of-interaction effect. In the latest PQS design, extended blocks with asymmetric light distributions were used on the four edges and four corners of a large detector module so that the previously unused (wasted) half-row of peripheral PMT could be covered by crystals. An asymmetric block, single-extended (7 Ч 8 crystals) was also tested. The pulse-height ratio between the worst and best group of crystals in the single-extended block was 0.72 and that of the double-extended block was also 0.72. In a more demanding, higher spatial resolution 8 Ч 8 array (2.3 mm Ч 2.3 mm Ч 10 mm BGO) for mouse PET with shallower crystals, the pulse-height ratio was 0.73 with an average energy resolution of 20%. This study demonstrated that pulse height uniformity for the PQS design using circular PMT was excellent, better than the typical 3/1-pulse-height ratio in conventional block detectors. [J189]

"A novel spectral microscope system: application in quantitative pathology"

A novel spectral microscope system is presented together with a method for the quantitative assessment of the uptake by histologic samples of stains used in pathology to label tissue features of diagnostic importance. The

critical component of the microscope is a variable interference filter-based monochromator. The system is capable of performing real-time spectral imaging in a plurality of spectral bands and micro-spectroscopy in any image pixel, in the spectral range 400-1000 nm. The wavelength-tuning step is 2.4-2.6 nm, while the full-width at half maximum in each step is about 1.5% of the operating central wavelength. The developed system integrates algorithms and calibration procedures for the calculation of the stain-uptake by the tissue. The acquired spectra from both stained tissue and calibration stain solutions enable the calculation of the concentration maps of the stains, even if the latter are multiple and overlap spatially and spectrally. The system was used for the quantitative mapping of the expression of estrogen and progesterone receptors in breast cancer cells. In this particular case, model validation shows that although two stains are employed, capturing of their transmittance at more than ten wavelengths is required in order to obtain an acceptable accuracy. These findings highlight the need for the development and implementation of spectral microscopy in pathology and its potential to introduce novel more reliable diagnostic criteria. [J190]

"High-resolution X-ray imaging based on curved Bragg mirrors: first results"

Small animal cancer imaging has drawn increased attention over the last few years due to greater availability of genetically modified mice, permitting the study of human diseases in animal models. Submillimeter resolution would be of great value to provide the fine detail needed in the imaging of small tumors traced by radio-labeled agents. Despite extensive research and improvements in instrumentation and imaging reconstruction, until now, there has been no efficient technology for this task. The limitations of scintillation cameras with pinhole collimators, currently the highest resolution devices, are fundamental in nature. They include image blurring through edge effects, scattering at the pinhole, and inelastic Compton scattering. Furthermore, such devices often yield low efficiency. In this paper, a new approach to high-resolution imaging of radio-labeled agents is introduced and first results are shown. The technique is based on curved perfect-crystal X-ray mirrors applied in a one-to-one focusing geometry. Such Bragg diffraction optics yields high reflectivity and excellent energy resolution and it has been applied in X-ray spectroscopy for many years. Today large perfect-crystal mirrors are commercially available and efficient devices covering a substantial solid angle can be envisioned. The potential advantage over conventional pinhole cameras is twofold. First, focusing diffraction optics provides a "virtual" pinhole, which can effectively be inside the object under investigation and does not suffer from edge effects. Second, Bragg optics has an energy resolution of a few eV and discriminates against Compton scattering. The fundamentals of Bragg optics are discussed and first results using 55Fe and 95mTc phantoms are presented. Our data show spatial resolutions of less than 1 and 2 mm, respectively. Current limitations of this new technique and possible future designs are discussed. [J191]

"ROC analysis of ordered subset expectation maximization and filtered back projection technique for FDG-PET in lung cancer"

The purpose of this study was to evaluate the image quality and discriminative ability of fluoro-deoxy-D-glucose positron emission tomography (FDG-PET) images reconstructed by conventional filtered back projection (FBP) and ordered subset expectation maximization (OSEM) in patients with lung cancer. Thirty-six subjects including normal controls and lung cancer patients underwent whole body PET scan (emission 3 min, transmission 1 min) using a GE Advance Scanner after the administration of approximately 370 MBq of FDG. The raw data were then reconstructed by conventional FBP and OSEM. The PET images were interpreted by two observers with random exposure of normal and diseased cases for transverse and coronal sections. The results were evaluated using receiver operating characteristic (ROC) curve analysis. The image quality of 36 subjects including normal controls and lung cancer patients reconstructed by OSEM was generally superior to FBP in terms of visual analysis. FBP without attenuation correction had better image contrast than OSEM, although it had poor image quality. ROC analysis indicated that for this limited set of studies OSEM with attenuation correction out-performed conventional FBP in terms of its discriminative ability of lung cancer with FDG-PET. The results indicated that OSEM provides better image quality and superior discriminative ability than conventional FBP for diagnosis of lung cancer by whole body FDG-PET. [J192]

"Integrated wavelets for enhancement of microcalcifications in digital mammography"

This paper presents a new algorithm for enhancement of microcalcifications in mammograms. The main novelty is the application of techniques we have developed for construction of filterbanks derived from the continuous wavelet transform. These discrete wavelet decompositions, called integrated wavelets, are optimally designed for enhancement of multiscale structures in images. Furthermore, we use a model based approach to refine existing methods for general enhancement of mammograms resulting in a more specific enhancement of microcalcifications. We present results of our method and compare them with known algorithms. Finally, we want to indicate how these techniques can also be applied to the detection of microcalcifications. Our algorithm was positively evaluated in a clinical study. It has been implemented in a mammography workstation designed for

soft-copy reading of digital mammograms developed by IMAGETOOL, Germany. [J193]

"ROC analysis of ultrasound tissue characterization classifiers for breast cancer diagnosis"

Breast cancer diagnosis through ultrasound tissue characterization was studied using receiver operating characteristic (ROC) analysis of combinations of acoustic features, patient age, and radiological findings. A feature fusion method was devised that operates even if only partial diagnostic data are available. The ROC methodology uses ordinal dominance theory and bootstrap resampling to evaluate Azand confidence intervals in simple as well as paired data analyses. The combined diagnostic feature had an Azof 0.96 with a confidence interval of [0.93, 0.99] at a significance level of 0.05. The combined features show statistically significant improvement over prebiopsy radiological findings. These results indicate that ultrasound tissue characterization, in combination with patient record and clinical findings, may greatly reduce the need to perform biopsies of benign breast lesions. [J194]

"Medical diagnosis with C4.5 rule preceded by artificial neural network ensemble"

Comprehensibility is very important when machine learning techniques are used in computer-aided medical diagnosis. Since an artificial neural network ensemble is composed of multiple artificial neural networks, its comprehensibility is worse than that of a single artificial neural network. In this paper, C4.5 Rule-PANE, which combines an artificial neural network ensemble with rule induction by regarding the former as a preprocess of the latter, is proposed. At first, an artificial neural network ensemble is trained. Then, a new training data set is generated by feeding the feature vectors of original training instances to the trained ensemble and replacing the expected class labels of original training instances with the class labels output from the ensemble. Additional training data may also be appended by randomly generating feature vectors and combining them with their corresponding class labels output from the ensemble. Finally, a specific rule induction approach, i.e., C4.5 Rule, is used to learn rules from the new training data set. Case studies on diabetes, hepatitis, and breast cancer show that C4.5 Rule-PANE could generate rules with strong generalization ability, which benefits from an artificial neural network ensemble, and strong comprehensibility, which benefits from rule induction. [J195]

"The effects of compensation for scatter, lead X-rays, and high-energy contamination on tumor detectability and activity estimation in Ga-67 imaging"

Compton scatter, lead X-rays, and high-energy contamination are major factors affecting image quality in Ga-67 imaging. Scattered photons detected in one photopeak window include photons exiting the patient at energies within the photopeak, as well as higher energy photons which have interacted in the collimator and crystal and lost energy. Furthermore, lead X-rays can be detected in the main energy photopeak (93 keV). We have previously developed two energy-based methods, based on artificial neural networks (ANN) and on a generalized spectral (GS) approach to compensate for scatter, high-energy contamination, and lead X-rays in Ga-67 imaging. For comparison, we considered also the projections that would be acquired in the clinic using the optimal energy windows (WIN) we have reported previously for tumor detection and estimation tasks for the 93, 185, and 300 keV photopeaks. The aim of the present study is to evaluate under realistic conditions the impact of these phenomena and their compensation on tumor detection and estimation tasks in Ga-67 imaging. ANN and GS were compared on the basis of performance of a three-channel Hotelling observer (CHO), in detecting the presence of a spherical tumor of unknown size embedded in an anatomic background as well as on the basis of estimation of tumor activity. Projection datasets of spherical tumors ranging from 2 to 6 cm in diameter, located at several sites in an anthropomorphic torso phantom, were simulated using a Monte Carlo program that modeled all photon interactions in the patient as well as in the collimator and the detector for all decays between 91 and 888 keV. One hundred realistic noise realizations were generated from each very-low-noise simulated projection dataset. The presence of scatter degraded both CHO signal-to-noise ratio (SNR) and estimation accuracy. On average, the presence of scatter led to a 12% reduction in CHO SNR. Correcting for scatter further diminished CHO SNR but to a lesser extent with ANN (5% reduction) than with GS (12%). Both scatter corrections improved performance in activity estimation. ANN yielded better precision (1.8% relative standard deviation) than did GS (4%) but greater average bias (5.1% with ANN, 3.6% with GS). [J196]

"Comparison of multiexcitation fluorescence and diffuse reflectance spectroscopy for the diagnosis of breast cancer (March 2003)"

Nonmalignant (n = 36) and malignant (n = 20) tissue samples were obtained from breast cancer and breast reduction surgeries. These tissues were characterized using multiple excitation wavelength fluorescence spectroscopy and diffuse reflectance spectroscopy in the ultraviolet-visible wavelength range, immediately after excision. Spectra were then analyzed using principal component analysis (PCA) as a data reduction technique. PCA was performed on each fluorescence spectrum, as well as on the diffuse reflectance spectrum individually,

to establish a set of principal components for each spectrum. A Wilcoxon rank-sum test was used to determine which principal components show statistically significant differences between malignant and nonmalignant tissues. Finally, a support vector machine (SVM) algorithm was utilized to classify the samples based on the diagnostically useful principal components. Cross-validation of this nonparametric algorithm was carried out to determine its classification accuracy in an unbiased manner. Multiexcitation fluorescence spectroscopy was successful in discriminating malignant and nonmalignant tissues, with a sensitivity and specificity of 70% and 92%, respectively. The sensitivity (30%) and specificity (78%) of diffuse reflectance spectroscopy alone was significantly lower. Combining fluorescence and diffuse reflectance spectra did not improve the classification accuracy of an algorithm based on fluorescence spectra alone. The fluorescence excitation-emission wavelengths identified as being diagnostic from the PCA-SVM algorithm suggest that the important fluorophores for breast cancer diagnosis are most likely tryptophan, NAD(P)H and flavoproteins. [J197]

"The perception of breast cancers-a spatial frequency analysis of what differentiates missed from reported cancers"

The primary detector of breast cancer is the human eye. Radiologists read mammograms by mapping exogenous and endogenous factors, which are based on the image and observer, respectively, into observer-based decisions. These decisions rely on an internal schema that contains a representation of possible malignant and benign findings. Thus, to understand the hits and misses made by the radiologists, it is important to model the interactions between the measurable image-based elements contained in the mammogram and the decisions made. The image-based elements can be of two types, i.e., areas that attracted the visual attention of the radiologist, but did not yield a report, and areas where the radiologist indicated the presence of an abnormal finding. In this way, overt and covert decisions are made when reading a mammogram. In order to model this decision-making process, we use a system that is based upon the processing done by the human visual system, which decomposes the areas under scrutiny in elements of different sizes and orientations. In our system, this decomposition is done using wavelet packets (WPs). Nonlinear features are then extracted from the WP coefficients, and an artificial neural network is trained to recognize the patterns of decisions made by each radiologist. Afterwards, the system is used to predict how the radiologist will respond to visually selected areas in new mammogram cases. [J198]

"Determination of epithelial tissue scattering coefficient using confocal microscopy"

Most models of light propagation through tissue assume the scattering properties of the various tissue layers are the same. The authors present evidence that the scattering coefficient of normal cervical epithelium is significantly lower than values previously reported for bulk epithelial tissue. They estimated the scattering coefficient of normal and precancerous cervical epithelium using measurements of the reflectance as a function of depth from confocal images. Reflectance measurements were taken from ex vivo cervical biopsies and fit to an exponential function based upon Beer's law attenuation. The mean scattering coefficients derived were 22 cm-1for normal tissue and 69 cm-1for precancerous tissue. These values are significantly lower than previously reported for bulk epithelial tissues and suggest that scattering of bulk tissue is dominated by the stroma. They also suggest that computational models to describe light propagation in epithelial tissue must incorporate different scattering coefficients for the epithelium and stroma. Further, the lower scattering of the epithelium suggests greater probing depths for fiber optic probes used by optical diagnostic devices which measure reflectance and fluorescence in epithelial tissue. The difference in scattering between normal and precancerous tissue is attributed to increased nuclear size, optical density, and chromatin texture. The scattering coefficients measured here are consistent with predictions of numerical solutions to Maxwell's equations for epithelial cell scattering. [J199]

"Neural networks for computer-aided diagnosis: detection of lung nodules in chest radiograms"

The paper describes a neural-network-based system for the computer aided detection of lung nodules in chest radiograms. Our approach is based on multiscale processing and artificial neural networks (ANNs). The problem of nodule detection is faced by using a two-stage architecture including: 1) an attention focusing subsystem that processes whole radiographs to locate possible nodular regions ensuring high sensitivity; 2) a validation subsystem that processes regions of interest to evaluate the likelihood of the presence of a nodule, so as to reduce false alarms and increase detection specificity. Biologically inspired filters (both LoG and Gabor kernels) are used to enhance salient image features. ANNs of the feedforward type are employed, which allow an efficient use of a priori knowledge about the shape of nodules, and the background structure. The images from the public JSRT database, including 247 radiograms, were used to build and test the system. We performed a further test by using a second private database with 65 radiograms collected and annotated at the Radiology Department of the University of Florence. Both data sets include nodule and nonnodule radiographs. The use of a public data set along with independent testing with a different image set makes the comparison with other systems easier

and allows a deeper understanding of system behavior. Experimental results are described by ROC/FROC analysis. For the JSRT database, we observed that by varying sensitivity from 60 to 75% the number of false alarms per image lies in the range 4-10, while accuracy is in the range 95.7-98.0%. When the second data set was used comparable results were obtained. The observed system performances support the undertaking of system validation in clinical settings. [J200]

"Magnetic resonance and light microscopy investigation of a dextran coated magnetic fluid"

A dextran-coated magnetite-based magnetic fluid (MF) sample (DexMF) was developed for cancer diagnostic and therapeutic purposes. In order to perform biological studies DexMF samples were endovenously injected into female Swiss mice. Magnetic resonance (MR) spectra showed a broad line around g=2,typical of magnetic nanoparticles (MNPs) suspended in a nonmagnetic matrix. The MR data showed that MNPs essentially spread in liver, spleen, and bone marrow. MNPs in blood stream were found up to 60 min after injection. Histological analysis also showed MNP agglomeration in liver, spleen, and bone marrow, from 1 h up to 28 days. No damaged cells or any other kind of alteration were observed in the investigated tissues. The data suggested that DexMF sample is biocompatible and adequate for biomedical applications. copyright 2003 American Institute of Physics. [J201]

"Three-dimensional segmentation and growth-rate estimation of small pulmonary nodules in helical CT images"

Small pulmonary nodules are a common radiographic finding that presents an important diagnostic challenge in contemporary medicine. While pulmonary nodules are the major radiographic indicator of lung cancer, they may also be signs of a variety of benign conditions. Measurement of nodule growth rate over time has been shown to be the most promising tool in distinguishing malignant from nonmalignant pulmonary nodules. In this paper, we describe three-dimensional (3-D) methods for the segmentation, analysis, and characterization of small pulmonary nodules imaged using computed tomography (CT). Methods for the isotropic resampling of anisotropic CT data are discussed. 3-D intensity and morphology-based segmentation algorithms are discussed for several classes of nodules. New models and methods for volumetric growth characterization based on longitudinal CT studies are developed. The results of segmentation and growth characterization methods based on in vivo studies are described. The methods presented are promising in their ability to distinguish malignant from nonmalignant pulmonary nodules and represent the first such system in clinical use. [J202]

"Differentiation among basal cell carcinoma, benign lesions, and normal skin using electric impedance"

This paper presents a preliminary study showing the diagnostic potential of electrical impedance to detect basal cell carcinoma (BCC). Electrical impedance was measured in vivo from 1 kHz to 1 MHz on 24 human subjects over BCC (19 lesions), over benign tumors (11 lesions), and over normal skin (all 24 patients). Lesions ranged from 2-15 mm in diameter. Indexes based on the magnitude (MIX), phase (PIX), real-part (RIX) and imaginary-part (IMIX) of impedance were calculated for each measurement. Significant differences were found between measurements over BCC, benign lesions and normal skin for indexes MIX, PIX, and IMIX (P = 0.04 to P = 7 Ч 10-7). Indexes were generally smaller for measurements of BCC than for benign lesions or normal skin. Differences were not a result of differences in the patient's age or the measurement location. The large size of our measurement electrode (10 mm) probably limited our ability to differentiate lesions because significant amounts of normal skin were included in each lesion measurement. A linear regression fit of data with tumor size suggests that a smaller probe or more sophisticated analysis techniques may improve differentiation. Results suggest that electrical impedance could be used to provide rapid and noninvasive differentiation of BCC from similar looking benign lesions. [J203]

"Method for quantifying volumetric lesion change in interval liver CT examinations"

We propose a method of using a relatively low degree of freedom (DOF) warping to accurately measure the interval change of lesions having homogeneous contrast. The setting presented here presupposes the use of interval computed tomography (CT) liver exams. After a 3 Ч 24 DOF warping of the later examination to match the liver's pose in the earlier exam of the interval pair is performed, the lesion's volume change is estimated using the computed difference volume of the two data sets via a novel method that counts partial volume contributions and is insensitive to slight misregistration. A mathematically generated phantom is used to quantify accuracy in the presence of noise. We also quantify the accuracy of our CT liver registrations using microcoils implanted for chemotherapy. A probabilistic liver atlas is used to support automatic masking and liver-focused registration. [J204]

"Uncertainty in the output of artificial neural networks"

Analysis of the performance of artificial neural networks (ANNs) is usually based on aggregate results on a population of cases. In this paper, we analyze ANN output corresponding to the individual case. We show variability in the outputs of multiple ANNs that are trained and "optimized" from a common set of training cases. We predict this variability from a theoretical standpoint on the basis that multiple ANNs can be optimized to achieve similar overall performance on a population of cases, but produce different outputs for the same individual case because the ANNs use different weights. We use simulations to show that the average standard deviation in the ANN output can be two orders of magnitude higher than the standard deviation in the ANN overall performance measured by the Azvalue. We further show this variability using an example in mammography where the ANNs are used to classify clustered microcalcifications as malignant or benign based on image features extracted from mammograms. This variability in the ANN output is generally not recognized because a trained individual ANN becomes a deterministic model. Recognition of this variability and the deterministic view of the ANN present a fundamental contradiction. The implication of this variability to the classification task warrants additional study. [J205]

"Study of hole-type gas multiplication structures for portal imaging and other high count rate applications"

We performed studies in the operation of various hole-type gaseous multiplication structures (GEM, capillary plates, and others) at very high fluxes of X-rays (5-106Hz/mm2; in the case of gammas it reached levels of up to 109Hz/mm2during the pulses. In most measurements, the entire area of the detector was exposed to these extremely high fluxes. Results obtained so far indicate that the GEM and the hydrogen-treated capillary plates could be successfully used in medical imaging applications. [J206]

"Combined numerical and linguistic knowledge representation and its application to medical diagnosis"

In this paper, we propose a novel hybrid intelligent system (HIS) which provides a unified integration of numerical and linguistic knowledge representations. The proposed HIS is a hierarchical integration of an incremental learning fuzzy neural network (ILFN) and a linguistic model, i.e., fuzzy expert system (FES), optimized via the genetic algorithm (GA). The ILFN is a self-organizing network. The linguistic model is constructed based on knowledge embedded in the trained ILFN or provided by the domain expert. The knowledge captured from the low-level ILFN can be mapped to the higher level linguistic model and vice versa. The GA is applied to optimize the linguistic model to maintain high accuracy, comprehensibility, completeness, compactness, and consistency. The resulted HIS is capable of dealing with low-level numerical computation and higher level linguistic computation. After the system is completely constructed, it can incrementally learn new information in both numerical and linguistic forms. To evaluate the system's performance, the well-known benchmark Wisconsin breast cancer data set was studied for an application to medical diagnosis. The simulation results have shown that the proposed HIS performs better than the individual standalone systems. The comparison results show that the linguistic rules extracted are competitive with or even superior to some well-known methods. Our interest is not only on improving the accuracy of the system, but also enhancing the comprehensibility of the resulted knowledge representation. [J207]

"Optimal excitation wavelengths for discrimination of cervical neoplasia"

Fluorescence spectroscopy has shown promise for the in vivo, real-time detection of cervical neoplasia. However, selection of excitation wavelength has in the past been based on in vitro studies and the availability of light sources. The goal of this study was to determine optimal excitation wavelengths for in vivo detection of cervical neoplasia. Fluorescence excitation-emission matrices (EEMs) were measured in vivo from 351 sites in 146 patients. Data were analyzed in pairs of diagnostic classes to determine which combination of excitation wavelengths yields classification algorithms with the greatest sensitivity and specificity. We find that 330-340-, 350-380-, and 400-450-nm excitation yield the best performance. The sensitivity and specificity for discrimination of squamous normal tissue and high-grade squamous intraepithelial lesion (HGSIL) were 71 % and 77 % on cross validation using three excitation wavelengths. These results are comparable with those found in earlier in vivo studies; however, in this study we find that the proportion of samples which are HGSIL influences performance. Furthermore stratification of samples within low-grade squamous intraepithelial lesion and HGSIL also appears to influence diagnostic performance. Future diagnostic studies should be carried out at these excitation wavelengths in larger groups so that data can be stratified by diagnostic subcategory, age and menopausal status. Similarly, large studies should be done in screening populations. [J208]

"Novel EIS postprocessing algorithm for breast cancer diagnosis"

A new postprocessing algorithm was developed for the diagnosis of breast cancer using electrical impedance scanning. This algorithm automatically recognizes bright focal spots in the conductivity map of the breast. Moreover, this algorithm discriminates between malignant and benign/normal tissues using two main predictors: phase at 5 kHz and crossover frequency, the frequency at which the imaginary part of the admittance is at its maximum. The thresholds for these predictors were adjusted using a learning group consisting of 83 carcinomas and 378 benign cases. In addition, the algorithm was verified on an independent test group including 87 carcinomas, 153 benign cases and 356 asymptomatic cases. Biopsy was used as gold standard for determining pathology in the symptomatic cases. A sensitivity of 84% and a specificity of 52% were obtained for the test group. [J209]

"Electrical impedance spectroscopy (EIS) in the urinary bladder: the effect of inflammation and edema on identification of malignancy"

Previous studies have shown that tetrapolar electrical impedance spectroscopy measurements can identify cervical interstitial neoplasia with the same sensitivity and specificity as cervical smears. In the urinary bladder, the same technique yields significant differences (p [J210]

"Health economics and technology reimbursement-Product reimbursement and APCs: why all the fuss?"

First Page of the Article [J211]

"Development of a dual-detector system based on a-Si:H arrays and multi-element silicon detectors for diffraction-enhanced breast imaging"

X-ray diffraction analysis of normal and diseased breast tissue specimens as well as cell lines proved that there are significant differences in measured spectra, if cancer is present, enabling us to quantify the various clinical conditions enhancing diagnosis. It was also demonstrated that the stereoscopic presentation of images of breast samples obtained by an a-Si:H-based digital imaging system provides important additional information and has potential benefits over the more traditional two-dimensional (2-D) data. Work is currently under way to build a prototype stereoscopic digital dual-sensor breast imaging system to evaluate the potential of diffraction-enhanced imaging approach and the likely increased detectability offered by this technique in comparison with current breast imaging modalities. [J212]

"Not your mother's mammography [Jbreast cancer detection]"

Breast cancer accounts for nearly one of every three cancers diagnosed in US women. While great strides have been made in early detection, the conventional method of mammography is not failproof it has trouble imaging dense tissue, it may show suspicious areas where no malignancy exists, and radiologists interpreting the images can miss up to 15 percent of cancers. It's also uncomfortable, requiring each breast to be compressed between plastic plates, which can lead to bruising. Susan Hagness wants to change all that. An assistant professor of electrical engineering at the University of Wisconsin-Madison, she is pioneering a novel detection technique that uses ultrawideband microwaves to image even the tiniest malignant tumors in the breast. Breast tumors and normal tissue show much more contrast at microwave frequencies than at the X-ray frequencies used for mammograms. Microwaves are also nonionizing, and the technique requires no breast compression. In Susan Hagness' search for a better way to detect breast cancer, she gets her students involved, too. Such efforts have paid off: her courses consistently receive high marks on student evaluations. [J213]

"Electrical impedance endo-tomography: imaging tissue from inside"

This paper describes a new method for scanning the conductivity of a tissue or an organ using a multielectrode impedance probe placed at the center of the region of interest. The long-term objective of the study is the evaluation, using an urethral impedance probe, of the lesion produced by ultrasound ablathermy of localized prostate cancer. The probe consists of electrodes placed at the surface of an insulating cylinder. The injected current passes around the cylinder and spreads in the medium surrounding the probe. This paper presents the theoretical bases of this method, the calculated sensitivity distributions of electrode configurations involving a pair of diametrically opposed electrodes and an application in vitro. The experimental set-up consisted of a water tank and a 16-electrode prototype probe 50 mm in diameter. Data sets were collected in the presence of conductivity perturbations produced by small size insulators or conductors and a 7.5% constant perturbation model. The presented images, although reconstructed using a simple retro-projection algorithm, demonstrate the feasibility of the method. Improvements in data collection and image reconstruction are possible. [J214]

"Applications of RF/microwaves in medicine"

Medical applications of RF/microwaves are highlighted in this paper. The emphasis is placed on newer emerging diagnostic and therapeutic applications, such as microwave breast cancer detection, and treatment with localized high power used in ablation of the heart, and liver, benign prostate hypertrophy, angioplasty, and others. A very brief outline of biological effects of RF/microwaves and associated issues is given as background to the applications [J215]

"Microwave medical devices"

This article describes several new microwave medical devices that either were or are being developed at MMTC, Inc. in cooperation with the following institutions: Celsion Corporation, Columbia, Maryland (microwave balloon catheters); Montefiore Medical Center (MMC), Bronx, New York (microwave balloon catheters, dual microwave antennas, and microwave poration); and the University of California at San Francisco (conformal array antennas). The individuals who developed these devices have previously published patents and articles that contain most of the material presented here. All of the medical devices described depend on the ability of microwaves to deeply penetrate into living tissues. The depth to which microwaves can penetrate tissues is primarily a function of the dielectric properties of the tissues and of the frequency of the microwaves. In general, the lower the water content of the tissue, the deeper a wave at a given frequency can penetrate. Also, at the frequencies of interest, the lower the frequency, the deeper is the depth of penetration into tissues with given water content [J216]

"A multiple circular path convolution neural network system for detection of mammographic masses"

A multiple circular path convolution neural network (MCPCNN) architecture specifically designed for the analysis of tumor and tumor-like structures has been constructed. We first divided each suspected tumor area into sectors and computed the defined mass features for each sector independently. These sector features were used on the input layer and were coordinated by convolution kernels of different sizes that propagated signals to the second layer in the neural network system. The convolution kernels were trained, as required, by presenting the training cases to the neural network. In this study, randomly selected mammograms were processed by a dual morphological enhancement technique. Radiodense areas were isolated and were delineated using a region growing algorithm. The boundary of each region of interest was then divided into 36 sectors using 36 equi-angular dividers radiated from the center of the region. A total of 144 Breast Imaging-Reporting and Data System-based features (i.e., four features per sector for 36 sectors) were computed as input values for the evaluation of this newly invented neural network system. The overall performance was 0.78-0.80 for the areas (Az) under the receiver operating characteristic curves using the conventional feed-forward neural network in the detection of mammographic masses. The performance was markedly improved with Azvalues ranging from 0.84 to 0.89 using the MCPCNN. This paper does not intend to claim the best mass detection system. Instead it reports a potentially better neural network structure for analyzing a set of the mass features defined by an investigator. [J217]

"A direct reconstruction algorithm for electrical impedance tomography"

A direct (noniterative) reconstruction algorithm for electrical impedance tomography in the two-dimensional (2-D), cross-sectional geometry is reviewed. New results of a reconstruction of a numerically simulated phantom chest are presented. The algorithm is based on the mathematical uniqueness proof by A.I. Nachman [1996] for the 2-D inverse conductivity problem. In this geometry, several of the clinical applications include monitoring heart and lung function, diagnosis of pulmonary embolus, diagnosis of pulmonary edema, monitoring for internal bleeding, and the early detection of breast cancer. [J218]

"Analysis and development of locomotion devices for the gastrointestinal tract"

The authors are developing devices for semi-autonomous or autonomous locomotion in the gastrointestinal (GI) tract. In this paper, they illustrate the systematic approach to the problem of "effective" locomotion in the GI tract and the critical analysis of "inchworm" locomotion devices, based on extensor and clamper mechanisms. The fundamentals of locomotion and the practical problems encountered during the development and the testing (in vitro and in vivo) of these devices are discussed. A mini device capable of propelling itself in the colon and suitable to perform, at least, rectum-sigmoidoscopy (the tract where approximately 60% of all colon cancers are found) is presented. This paper introduces preliminary, but useful, concepts for understanding, modeling and improving the performance of virtually any existing and novel devices for endoscopy of the GI tract. [J219]

"Vibro-acoustic tissue mammography"

A novel method for detection and imaging of microcalcifications in breast tissue is presented. The method, called vibro-acoustography, uses the radiation force of ultrasound to vibrate tissue at low (kHz) frequency and utilizes the resulting response to produce images that are related to the hardness of the tissue. The method is tested on human breast tissues. The resulting vibro-acoustographic images are in agreement with corresponding X-ray mammography images of the specimens. The existence of microcalcifications in locations indicated by vibro-acoustography is confirmed by histology. Microcalcifications as small as 110 \μm in diameter are detected by this method. Resulting vibro-acoustographic images show microcalcifications with high contrast with respect to the background soft tissue. Structures such as dense sclerotic tissue do not seem to interfere with detection of microcalcifications. [J220]

"Septa design study for volumetric imaging in positron emission tomography"

Positron emission tomography (PET) has become an essential imaging tool to localize tumors in diagnostic radiology and to monitor the size of a lesion before and during the treatment in oncology. Currently, commercial PET cameras operate only in two extreme modes: i) no-septa: three-dimensional (3-D) acquisition mode, also called volumetric imaging; and ii) all-septa-in: two-dimensional (2-D) acquisition mode, also called multislice imaging. In this paper, intermediate septa designs in the brain mode have been sought to minimize the scatter and accidental coincidences with acceptable sensitivity loss. To achieve this goal, Monte Carlo simulations were performed to evaluate possible septa designs. Information about septal penetration, absorption and scattering components from simulations guided us to modify the thickness and total number of septa in the new configurations. Count rate performances of three septa configurations were measured on our experimental high resolution PET camera with 3.85-cm axial field-of-view (AFOV); the measurements were compared with the simulation results. No-septa configuration had lower noise equivalent count (NEC) compared the other two configurations because of small AFOV Monte Carlo simulations were performed to predict the count rate performances of seven septa configurations for 13.1-cm AFOV. In the large AFOV, because of increased number of line of responses, NEC rate for no-septa case peaked rapidly at 0.07 μCi/cc. No-septa configuration is not recommended for high count rate studies. In this case where activity density is 0.3 μCi/cc or more, 10-septa and 15-septa configurations performed better than the other configurations. Intermediate 5-septa designs with variable septum length performed better between 0.07-μCi/cc and 0.3-μCi/cc range which represents the clinical activity level for 18F-FDG brain studies. [J221]

"Technological developments in hadron therapy (plenary)"

Hadron therapy, which is taken here to exclude neutrons but include ions, has its roots in a paper by Robert R. Wilson in [Radiology 47, 487 (1946)]. His paper spoke mainly of protons and the advantages of their Bragg peak behavior, but it also had the foresight to mention carbon ions. Pioneering work with different ion species was started at LBL in 1975 and continued for about 15 years. Today, there is a small number of working centers and many project proposals that present between them a bewildering range of particles, accelerators, extraction techniques, delivery mechanisms, and diagnostics for the treatment of deep-seated cancers. Recent advances in the understanding of the radio-biological effect of different ions and in accelerator design, reviewed in this article, suggest that there are optimum combinations and that these combinations should be matched to specific cancer types. The deeper the knowledge, the more demanding the requirements have become for the operation and control of the accelerator complex from the ion source down to the patient. The intensity, emittance and purity of the ion species from the source are the first parameters in this chain and the reliability and reproducibility are of paramount importance for the operation. It is the medical community that will compare and ultimately choose between the various accelerator options being developed, but it is the responsibility of the accelerator community to provide the very best tools. copyright 2002 American Institute of Physics. [J222]

"Targeting breast cancer detection with military technology"

Discusses the applicability of automated target recognition technology (ATR) to early screening for breast cancer. An overview of ATR technology is given and parallels to the cancer screening problem are given. Recommendations for future investigation are given. [J223]

"From tanks to tumors"

This article summarizes proceedings of the "Tanks to Tumors" workshop that was held in Arlington, Virginia, 4-5 December 2001. The workshop was co-sponsored by the Office of the Director, Defense Research and Engineering, Space and Sensor Technology Directorate; the Deputy Assistant Secretary of the Army for Environment, Safety and Occupational Health; the Defense Advanced Research Projects Agency; and the Army

Research Office. The purpose was to explore means for exploiting the technological opportunities in the integration of image processing, Web-based database management and development, and infrared sensor technology for the early detection of breast cancer. A second objective was to provide guidance to a program sponsored by the Army, with help from the Office of Naval Research (ONR) and Office of the Secretary of Defense (OSD). Significant military advances in thermal imaging and automatic target recognition coupled with the medical understanding of abnormal vascularity (angiogenesis) offer the prospect of automated detection from one to two years earlier than other, more costly and invasive screening methods. Applications of infrared imaging and automatic target recognition image processing for early detection of breast cancer. [J224]

"Infrared imaging: making progress in fulfilling its medical promise"

Discusses past, present, and future applications of infrared imaging in medicine. The topics mentioned include: breast cancer; helmet-mounted infrared for battlefield medical application; burns; image analysis and algorithm development. [J225]

"Automatic centerline extraction for virtual colonoscopy"

In this paper, we introduce a concise and concrete definition of an accurate colon centerline and provide an efficient automatic means to extract the centerline and its associated branches (caused by a forceful touching of colon and small bowel or a deep fold in twisted colon lumen). We further discuss its applications on fly-through path planning and endoscopic simulation, as well as its potential to solve the challenging touching and colon collapse problems in virtual colonoscopy. Experimental results demonstrated its centeredness, robustness, and efficiency. [J226]

"Edge displacement field-based classification for improved detection of polyps in CT colonography"

Colorectal cancer can easily be prevented provided that the precursors to tumors, small colonic polyps, are detected and removed. Currently, the only definitive examination of the colon is fiber-optic colonoscopy, which is invasive and expensive. Computed tomographic colonography (CTC) is potentially a less costly and less invasive alternative to FOC. It would be desirable to have computer-aided detection (CAD) algorithms to examine the large amount of data CTC provides. Most current CAD algorithms have high false positive rates at the required sensitivity levels. We developed and evaluated a postprocessing algorithm to decrease the false positive rate of such a CAD method without sacrificing sensitivity. Our method attempts to model the way a radiologist recognizes a polyp while scrolling a cross-sectional plane through three-dimensional computed tomography data by classification of the changes in the location of the edges in the two-dimensional plane. We performed a tenfold cross-validation study to assess its performance using sensitivity/specificity analysis on data from 48 patients. The mean specificity over all experiments increased from 0.19 (0.35) to 0.47 (0.56) for a sensitivity of 1.00 (0.95). [J227]

"Immunofluorescence imaging as a tool for studying the pharmacokinetics of a human monoclonal single chain fragment antibody"

We have used immunofluorescence imaging to study binding of a monoclonal antibody fragment to subcutaneously implanted human melanoma cells in nude mice. The data acquired using this nontraditional approach was then analyzed using standard pharmacokinetic methods to produce estimates of ke(0.06 h-1), t12/ (16 h), mean residency time (23.4 h) and percent exposure of the antibody to the tumor (40%). To our knowledge this is the first time standard pharmacokinetic analyzes have been conducted on immunofluorescence imaging data. The combination of this novel imaging technique and standard pharmacokinetic analytical methods should prove to be a useful tool for comparing the properties of antibody fragments in animal models. [J228]

"Computed microtomography (μCT) with unmonochromatized synchrotron X-rays for cancerous human breast tissue and mouse vertebra"

The use of X-ray computed microtomography (PCT) has increased in biomedical research and industrial applications. The inherited high quality of synchrotron radiation (SR) X-rays including high flux, collimation, and coherence, has been used recently to produce radiographic images with high spatial resolution and contrast. A simple and stable imaging system using an unmonochromatized SR source based on the principle of phase contrast X-ray imaging consists of a charge-coupled device (CCD) detector coupled with an optical lens system at the Pohang Light Source (PLS) 5C1 beamline. The spatial resolution of the imaging system was determined using the modulation transfer function (MTF), which was measured by step-by step calculations obtained from sharp edge images. Projection image data were obtained at 250 steps over 180 degrees of rotation with an acquisition time, depending on the imaged object materials, of 30 to 150 ms per projection image. The

tomographic images were reconstructed using a simple filtered backprojection algorithm to reconstruct two-dimensional (2-D) images using projection data which may include characteristics of beam collimation and phase contrast. Although the use of a monochromatic X-ray beam has previously demonstrated to provide high resolution and enhanced contrast, our approach uses an unmonochromatized SR X-ray beam and shows similar image capability, without the needs for sophisticated X-ray optics, in an exposure time which is significantly less, by two orders of magnitude, than that for the monochromatic SR system. The current PLS 5C1 SR imaging system can produce projection images at a spatial resolution of 8.3 μm over a field of view of about 5 mm at an exposure time of 30 ms per projection image for 1.5 Ч optical magnification. This study presents the results of SR μCT images of cancerous human breast tissue containing microcalcifications, mouse lumbar vertebra, and mouse coccygeal vertebra. The unmonochromatized SR μCT imaging system provides an effective means of evaluating microstructures, not only in biomedical specimens but also in inorganic samples. [J229]

"Small field of view scintimammography gamma camera integrated to a stereotactic core biopsy digital X-ray system"

A small field of view gamma camera has been developed for integration with a commercial stereotactic core biopsy system. The goal is to develop and implement a dual-modality imaging system utilizing scintimammography and digital radiography to evaluate the reliability of scintimammography in predicting the malignancy of suspected breast lesions from conventional X-ray mammography. The scintimammography gamma camera is a custom-built mini gamma camera with an active area of 5.3 cm Ч 5.3 cm and is based on a 2 Ч 2 array of Hamamatsu R7600-C8 position-sensitive photomultiplier tubes. The spatial resolution of the gamma camera at the collimator surface is [J230]

"Scintillating fiber dosimeter for radiation therapy accelerator"

Radiation therapy accelerators require highly accurate dose deposition and the output must be monitored frequently and regularly. Ionization chambers are the primary tool for this control, but their size and fragility make them unsuitable for use during patient treatment. In collaboration with a French center for cancer treatment in Caen, we describe the development and testing of a low-cost radiotherapy dosimeter (SDM) based on scintillating fibers and signal processing to reduce the effect of Cerenkov radiation background. The employment of photodiodes for light collection reduces the cost relative to systems using photomultipliers (PMTs). However, we have also developed a highly sensitive system that uses PMTs for very low-dose deposition for Brachytherapy. Comparison with standard ionization chambers shows about a 1% difference over a range of 6- to 25-MV photons. This dosimeter is 1 mm in diameter and can be placed where ever required including inside the body. Its small size and flexibility make it useful for delimiting critical regions, where organs may be very radiation sensitive. [J231]

"ATMTN: a telemammography network architecture"

One of the goals of the National Cancer Institute (NCI) to reach more than 80% of eligible women in mammography screening by the year 2000 yet remains as a challenge. In fact, a recent medical report reveals that while other types of cancer are experiencing negative growth, breast cancer has been the only one with a positive growth rate over the last few years. This is primarily due to the fact that 1) examination process is a complex and lengthy one and 2) it is not available to the majority of women who live in remote sites. Currently for mammography screening, women have to go to doctors or cancer centers/hospitals annually while high-risk patients may have to visit more often. One way to resolve these problems is by the use of advanced networking technologies and signal processing algorithms. On one hand, software modules can help detect, with high precision, true negatives (TN), while marking true positives (TP) for further investigation. Unavoidably, in this process some false negatives (FN) will be generated that are potentially life threatening; however, inclusion of the detection software improves the TP detection and, hence, reduces FNs drastically. Since TNs are the majority of examinations on a randomly selected population, this first step reduces the load on radiologists by a tremendous amount. On the other hand, high-speed networking equipment can accelerate the required clinic-lab connection and make detection, segmentation, and image enhancement algorithms readily available to the radiologists. This will bring the breast cancer care, caregiver, and the facilities to the patients and expand diagnostics and treatment to the remote sites. This research describes asynchronous transfer mode telemammography network (ATMTN) architecture for real-time, online screening, detection and diagnosis of breast cancer. ATMTN is a unique high-speed network integrated with automatic robust computer-assisted diagnosis-detection/digital signal processing (CAD/DSP) metho--ds for mass detection, region of interest (ROI) compression algorithms using Digital Imaging and Communications in Medicine (DICOM) 3.0 medical image standard. While ATMTN has the advantage of higher penetration into the women for cancer screening, it provides the diagnosis with higher efficiency, better accuracy and potentially lower cost. This paper presents the development of the infrastructure and algorithm design for ATMTN-based telemammography. The research goals

involved: 1) networking stations for telemammography to demonstrate, evaluate, and validate technologies and methods for delivering mammography screening services via high-speed (155 MB/s) links, performing real-time network-transmitted, high-resolution mammograms for immediate diagnosis as a "second opinion" strategy; 2) development of object-oriented compression methods for storage, retrieval and transmission of mammograms; 3) inclusion and optimization of detection algorithms for identification of normal images in different resolutions to increase the speed and effectiveness of telemammography as a "second opinion" strategy; 4) resolving the compatibility issues between images from different equipment (DICOM standards); and 5) optimization of an integrated ATMTN with adaptive CAD/DSP methods that are robust for large image databases and input sources. [J232]

"Binary rule generation via Hamming Clustering"

The generation of a set of rules underlying a classification problem is performed by applying a new algorithm called Hamming Clustering (HC). It reconstructs the AND-OR expression associated with any Boolean function from a training set of samples. The basic kernel of the method is the generation of clusters of input patterns that belong to the same class and are close to each other according to the Hamming distance. Inputs which do not influence the final output are identified, thus automatically reducing the complexity of the final set of rules. The performance of HC has been evaluated through a variety of artificial and real-world benchmarks. In particular, its application in the diagnosis of breast cancer has led to the derivation of a reduced set of rules solving the associated classification problem. [J233]

"Factor analysis in prostate cancer: delineation of organ structures and automatic generation of in- and output functions"

Factor analysis (FA) is used for extracting the properties of dynamic datasets. Objective: FA was applied to dynamic studies using positron emission topography (PET) to create factor images and factor curves from which input and output functions could be derived for kinetic modeling. This noninvasive automated and image-based analysis should permit routine application of quantitative PET in cancer patients. Methods: In nine men with prostate cancer, dynamic PET studies were performed on an ECAT HR+ system. After administration of 13.5 mCi of 11C-labeled acetate, data were acquired for 20 min. Images were reconstructed with iterative algorithms, a maximum a posteriori (MAP) for transmission scans, and ordered subset expectation maximization (OSEM) for emission scans. The body contour was determined with thresholding of the transmission images. All voxels included in the body contour were used for processing. FA extracted the shape of the pure time activity curves (TACs). The factors were used to create functional images, from which a region-of-interest (ROI) could be generated with thresholding techniques. These ROIs were used to create image-based TACs. Results: The automated procedure was successful in eight out of nine patients. Minimal intervention generated reliable factors in the remaining patient. Factors are normalized; their magnitude was adjusted by a scale factor using: (1) reversed normalization and (2) image-based parameters. In principle, the input factor generated by FA has no spillover and produces a pure vascular image and curve. Factor images provided diagnostic information on tumors. The method is operator independent and reproducible. Conclusion: The automated procedure generated factors from dynamic PET data corresponding to vessels and tumor. FA can noninvasively generate input and output functions. This processing tool facilitates PET as a reproducible quantification method in routine oncological applications. [J234]

"Optimal filter-based detection of microcalcifications"

Deals with the problem of texture feature extraction in digital mammograms. The authors use the extracted features to discriminate between texture representing clusters of microcalcifications and texture representing normal tissue. Having a two-class problem, the authors suggest a texture feature extraction method based on a single filter optimized with respect to the Fisher criterion. The advantage of this criterion is that it uses both the feature mean and the feature variance to achieve good feature separation. Image compression is desirable to facilitate electronic transmission and storage of digitized mammograms. In this paper, the authors also explore the effects of data compression on the performance of their proposed detection scheme. The mammograms in their test set were compressed at different ratios using the Joint Photographic Experts Group compression method. Results from an experimental study indicate that the authors' scheme is very well suited for detecting clustered microcalcifications in both uncompressed and compressed mammograms. For the uncompressed mammograms, at a rate of 1.5 false positive clusters/image the authors' method reaches a true positive rate of about 95%, which is comparable to the best results achieved so far. The detection performance for images compressed by a factor of about four is very similar to the performance for uncompressed images. [J235]

"Fuzzy CoCo: a cooperative-coevolutionary approach to fuzzy modeling"

Co-evolutionary algorithms have received increased attention in the past few years within the domain of evolutionary computation. In this paper, we combine the search power of co-evolutionary computation with the expressive power of fuzzy systems, and introduce a novel algorithm, called Fuzzy CoCo (fuzzy cooperative coevolution). We demonstrate the efficacy of Fuzzy CoCo by applying it to a hard, real-world problem-breast cancer diagnosis, obtaining the best results to date while expending less computational effort than previous processes. Analyzing our results, we derive guidelines for setting the algorithm parameters given a (hard) problem to solve. We hope Fuzzy CoCo proves to be a powerful tool in the fuzzy modeler toolkit [J236]

"Dielectrophoretic detection of molecular bindings"

The specificity of molecular binding between the "target" and the "probe" molecule, for example, between antigen and antibody or between two complementary deoxyribonucleic acid (DNA) sequences, is the principle of affinity assays. In the assay, the target is mixed with the fluorescence-labeled probe, so that the probe binds to the target to form a target-probe complex. Then, the bound complex is separated from the free (unbound) probe somehow (bound/free (BF) separation), and the fluorescence emission from the separated complex is measured to obtain the target concentration in the original sample. In this paper, the authors propose and experimentally demonstrate the use of dielectrophoresis (DEP) for such B/F separations. Using DEP chromatography, DEP characteristics of various biomolecules are measured, and: (1) separation of A-DNA (48.5 kbp) and oligonucleotide (22base); and (2) quantitative detection of antigen-antibody bindings, are demonstrated. Using the triple complex formation to facilitate DEP separation, a method is developed to detect B/F binding by a direct observation of the separation pattern on the microelectrode system. Et is applied for: (1) quantitative detection of alpha-fetoprotein, the diagnostic marker of liver cancer, through antigen-antibody reaction; and (2) the detection of DNA sequence through hybridization. The methods developed here are compatible with with micro fabrication, and suitable for affinity assays in micro-total analysis systems [J237]

"A digital phantom of the axilla based on the Visible Human Project data set"

In this paper, we describe the development of a new digital phantom designed for Monte Carlo simulations of breast cancer and particularly positron emission tomography (PET) imaging of the axillary lymph nodes. The phantom was based on data from the Visible Human Project female data set. The phantom covers the head-to-diaphragm regions; 17 major tissue types were segmented and 66 individual lymph nodes were identified. The authors have used the phantom in Monte Carlo simulations to model a reduced field-of-view PET imager based on two flat plate arrays placed on either side of the shoulder. Images used a simple single angle set of projections. The authors have conducted two preliminary studies: one modeling a single-frame PET acquisition 60 min after FDG injection and the other modeling a dynamic PET acquisition simulating four time frames after FDG injection. The dynamic results were processed into parametric images using the Patlak method and show the advantage to be gained by including the temporal information for legion detection. The authors' preliminary results indicate that the performance of such an imager forming projection images is not sufficient for axillary node PET imaging [J238]

"Optimization of PET system design for lesion detection"

Traditionally, the figures of merit used in designing a positron emission tomography (PET) scanner are spatial resolution, noise equivalent count rate, noise equivalent sensitivity, etc. These measures, however, do not directly reflect the lesion detectability using the PET scanner. Here the author proposes to optimize PET scanner design directly for lesion detection. The signal-to-noise ratio (SNR) of lesion detection can be easily computed using the theoretical expressions that the author has previously derived. Because no time-consuming Monte Carlo simulation is needed, the theoretical expressions allow evaluation of a large range of parameters. The PET system parameters can then be chosen to achieve the maximum SNR for lesion detection. The simulation study shown in this paper was focused on a single ring PET scanner without depth of interaction measurement. It can be extended to multiring (two- or three-dimensional) PET scanners and detectors with depth of interaction measurement [J239]

"Deblurring subject to nonnegativity constraints when known functions are present with application to object-constrained computerized tomography"

The reconstruction of tomographic images is often treated as a linear deblurring problem. When a high-density, man-made metal object is present somewhere in the image field, it is a deblurring problem in which the unknown function has a component that is known except for some location and orientation parameters. The authors first address general linear deblurring problems in which a known function having unknown parameters is present. They then show how the resulting iterative solution can be applied to tomographic imaging in the presence of man-made foreign objects, and they apply the result, in particular, to X-ray computed tomography

imaging used in support of brachytherapy treatment of advanced cervical cancer. [J240]

"Guest editorial computer-aided diagnosis in medical imaging"

First Page of the Article [J241]

"Computer-aided characterization of mammographic masses: accuracy of mass segmentation and its effects on characterization"

Mass segmentation is used as the first step in many computer-aided diagnosis (CAD) systems for classification of breast masses as malignant or benign. The goal of this paper was to study the accuracy of an automated mass segmentation method developed in our laboratory, and to investigate the effect of the segmentation stage on the overall classification accuracy. The automated segmentation method was quantitatively compared with manual segmentation by two expert radiologists (R1 and R2) using three similarity or distance measures on a data set of 100 masses. The area overlap measures between R1 and R2, the computer and R1, and the computer and R2 were 0.76\±0.13,0.74 \±0.11, and 0.74\±0.13, respectively. The interobserver difference in these measures between the two radiologists was compared with the corresponding differences between the computer and the radiologists. Using three similarity measures and data from two radiologists, a total of six statistical tests were performed. The difference between the computer and the radiologist segmentation was significantly larger than the interobserver variability in only one test. Two sets of texture, morphological, and spiculation features, one based on the computer segmentation, and the other based on radiologist segmentation, were extracted from a data set of 249 films from 102 patients. A classifier based on stepwise feature selection and linear discriminant analysis was trained and tested using the two feature sets. The leave-one-case-out method was used for data sampling. For case-based classification, the area Azunder the receiver operating characteristic (ROC) curve was 0.89 and 0.88 for the feature sets based on the radiologist segmentation and computer segmentation, respectively. The difference between the two ROC curves was not statistically significant. [J242]

"Computerized analysis of multiple-mammographic views: potential usefulness of special view mammograms in computer-aided diagnosis"

Purpose: To investigate the potential usefulness of special view mammograms in the computer-aided diagnosis of mammographic breast lesions. Materials and Methods: Previously, we developed a computerized method for the classification of mammographic mass lesions on standard-view mammograms, i.e., mediolateral oblique (MLO) view and/or cranial caudal (CC) views. In this study, we evaluate the performance of our computerized classification method on an independent database consisting of 70 cases (33 malignant and 37 benign cases), each having CC, MLO, and special view mammograms (spot compression or spot compression magnification views). The mass lesion identified in each of the three mammographic views was analyzed using our previously developed and trained computerized classification method. Performance in the task of distinguishing between malignant and benign lesions was evaluated using receiver operating characteristic analysis. On this independent database, we compared the performance of individual computer-extracted mammographic features, as well as the computer-estimated likelihood of malignancy, for the standard and special views. Results: Computerized analysis of special view mammograms alone in the task of distinguishing between malignant and benign lesions yielded an Azof 0.95, which is significantly higher (p zvalues of 0.78 and 0.75, respectively). Use of only the special views correctly classified 19 of 33 benign cases (a specificity of 58%) at 100% sensitivity, whereas use of the CC and MLO views alone correctly classified 4 and 8 of 33 benign cases (specificities of 12% and 24%, respectively). In addition, we found that the average computer output of the three views (Azof 0.95) yielded a significantly better performance than did the maximum computer output from the mammographic views. Conclusions: Computerized analysis of special view mammograms provides an improved prediction--of the benign versus malignant status of mammographic mass lesions. [J243]

"Feature extraction and classification of dynamic contrast-enhanced T2*-weighted breast image data"

The relatively low specificity of dynamic contrast-enhanced T1-weighted magnetic resonance imaging (MR) imaging of breast cancer has lead several groups to investigate different approaches to data acquisition, one of them being the use of rapid T2*-weighted imaging. Analyses of such data are difficult due to susceptibility artifacts and breathing motion. One-hundred-twenty-seven patients with breast tumors underwent MR examination with rapid, single-slice T2*-weighted imaging of the tumor. Different methods for classifying the image data set using leave-one-out cross validation were tested. Furthermore, a semi-automatic region of interest (ROI) definition tool was presented and compared with manual ROI definitions from a previous study. Finally, pixel-by-pixel analysis was done and compared with ROI analysis. The analyses were done with and

without noise reduction. The minimum enhancement parameter was the most robust and accurate of the parameters tested. The semi-automatic ROI definition method was fast and produced similar results as the manually defined ROIs. Noise reduction improved both sensitivity and specificity, but the improvement was not statistically significant. The pixel-based analysis methods used in the present study did not improve classification results. In conclusion, analysis of T2*-weighted breast images can be done in a rapid and robust manner by using semi-automatic ROI definition tools in combination with noise reduction. Minimum enhancement gives an indication of malignancy in T2*-weighted imaging. [J244]

"Patient-specific models for lung nodule detection and surveillance in CT images"

The purpose of this work is to develop patient-specific models for automatically detecting lung nodules in computed tomography (CT) images. It is motivated by significant developments in CT scanner technology and the burden that lung cancer screening and surveillance imposes on radiologists. We propose a new method that uses a patient's baseline image data to assist in the segmentation of subsequent images so that changes in size and/or shape of nodules can be measured automatically. The system uses a generic, a priori model to detect candidate nodules on the baseline scan of a previously unseen patient. A user then confirms or rejects nodule candidates to establish baseline results. For analysis of follow-up scans of that particular patient, a patient-specific model is derived from these baseline results. This model describes expected features (location, volume and shape) of previously segmented nodules so that the system can relocalize them automatically on follow-up. On the baseline scans of 17 subjects, a radiologist identified a total of 36 nodules, of which 31 (86%) were detected automatically by the system with an average of 11 false positives (FPs) per case. In follow-up scans 27 of the 31 nodules were still present and, using patient-specific models, 22 (81%) were correctly relocalized by the system. The system automatically detected 16 out of a possible 20 (80%) of new nodules on follow-up scans with ten FPs per case. [J245]

"A statistical 3-D pattern processing method for computer-aided detection of polyps in CT colonography"

Adenomatous polyps in the colon are believed to be the precursor to colorectal carcinoma, the second leading cause of cancer deaths in United States. In this paper, we propose a new method for computer-aided detection of polyps in computed tomography (CT) colonography (virtual colonoscopy), a technique in which polyps are imaged along the wall of the air-inflated, cleansed colon with X-ray CT. Initial work with computer aided detection has shown high sensitivity, but at a cost of too many false positives. We present a statistical approach that uses support vector machines to distinguish the differentiating characteristics of polyps and healthy tissue, and uses this information for the classification of the new cases. One of the main contributions of the paper is the new three-dimensional pattern processing approach, called random orthogonal shape sections method, which combines the information from many random images to generate reliable signatures of shape. The input to the proposed system is a collection of volume data from candidate polyps obtained by a high-sensitivity, low-specificity system that we developed previously. The results of our tenfold cross-validation experiments show that, on the average, the system increases the specificity from 0.19 (0.35) to 0.69 (0.74) at a sensitivity level of 1.0 (0.95). [J246]

"Three-dimensional computer-aided diagnosis scheme for detection of colonic polyps"

We have developed a three-dimensional (3-D) computer-aided diagnosis scheme for automated detection of colonic polyps in computed tomography (CT) colonographic data sets, and assessed its performance based on colonoscopy as the gold standard. In this scheme, a thick region encompassing the entire colonic wall is extracted from an isotropic volume reconstructed from the CT images in CT colonography. Polyp candidates are detected by first computing of 3-D geometric features that characterize polyps, folds, and colonic walls at each voxel in the extracted colon, and then segmenting of connected components corresponding to suspicious regions by hysteresis thresholding based on these geometric features. We apply fuzzy clustering to these connected components to obtain the polyp candidates. False-positive (FP) detections are then reduced by computation of several 3-D volumetric features characterizing the internal structures of the polyp candidates, followed by the application of discriminant analysis to the feature space generated by these volumetric features. The locations of the polyps detected by our computerized method were compared to the gold standard of conventional colonoscopy. The performance was evaluated based on 43 clinical cases, including 12 polyps determined by colonoscopy. Our computerized scheme was shown to have the potential to detect polyps in CT colonography with a clinically acceptable high sensitivity and a low FP rate. [J247]

"Detection of cancerous breasts by dynamic area telethermometry"

This study demonstrated the following 3 new important concepts. 1) Dynamic imaging can yield meaningful

clinical diagnostic information objectively, without need for human expertise. The same methodology can be applicable to any quantitative pathophysiological assessment. 2) Using classical FFT and elementary statistics (Student's t tests and z-value statistics, or alpha and beta statistics), the authors have shown how to reduce thousands of observations to a single quantitative clinical diagnostic parameter. This approach should be applicable to any multiparametric diagnostic technique. 3) After 3 decades of controversial reports on the use of thermal imaging in the diagnosis of breast cancer, the authors have shown that dynamic infrared imaging (in contrast to static thermal imaging), using a plausible pathophysiological model and up-to-date infrared equipment, can distinguish between noncancerous and cancerous breasts with a highly impressive sensitivity and specificity. [J248]

"Multiresolution detection of spiculated lesions in digital mammograms"

We present a novel multiresolution scheme for the detection of spiculated lesions in digital mammograms. First, a multiresolution representation of the original mammogram is obtained using a linear phase nonseparable two-dimensional (2-D) wavelet transform. A set of features is then extracted at each resolution in the wavelet pyramid for every pixel. This approach addresses the difficulty of predetermining the neighborhood size for feature extraction to characterize objects that may appear in different sizes. Detection is performed from the coarsest resolution to the finest resolution using a binary tree classifier. This top-down approach requires less computation by starting with the least amount of data and propagating detection results to finer resolutions. Experimental results using the MIAS image database have shown that this algorithm is capable of detecting spiculated lesions of very different sizes at low false positive rates [J249]

"A new algorithm for autoreconstruction of catheters in computed tomography-based brachytherapy treatment planning"

Describes innovative software for automatic reconstruction, which the authors term autoreconstruction, of plastic and metallic brachytherapy catheters using computed tomography (CT) data. No such automatic facility has previously existed in any treatment planning software. The patient data consists of a set of past-implantation CT images with the catheters in situ in their final positions. This new software solves those difficulties which arise when the catheters are intersecting or when loop techniques are used. With the software algorithms, catheter reconstruction time is significantly reduced and accuracy is also improved when compared with that achieved using the classical manual method of CT-slice-by-CT-slice reconstruction. [J250]

"An artificial intelligent algorithm for tumor detection in screening mammogram"

Cancerous tumor mass is one of the major types of breast cancer. When cancerous masses are embedded in and camouflaged by varying densities of parenchymal tissue structures, they are very difficult to be visually detected on mammograms. This paper presents an algorithm that combines several artificial intelligent techniques with the discrete wavelet transform (DWT) for detection of masses in mammograms. The AI techniques include fractal dimension analysis, multiresolution Markov random field, dogs-and-rabbits algorithm, and others. The fractal dimension analysis serves as a preprocessor to determine the approximate locations of the regions suspicious for cancer in the mammogram. The dogs-and-rabbits clustering algorithm is used to initiate the segmentation at the LL subband of a three-level DWT decomposition of the mammogram. A tree-type classification strategy is applied at the end to determine whether a given region is suspicious for cancer. The authors have verified the algorithm with 322 mammograms in the Mammographic Image Analysis Society Database. The verification results show that the proposed algorithm has a sensitivity of 97.3% and the number of false positives per image is 3.92. [J251]

"Three-dimensional reconstruction of microcalcification clusters from two mammographic views"

Classification of benign/malignant microcalcification clusters is a major diagnostic challenge for radiologists. Clinical studies have revealed that the shape of the cluster, and the spatial distribution of individual microcalcifications within it, are important indicators of its malignancy. However, mammographic images of clustered microcalcifications confound their three-dimensional (3-D) distribution with image projection and breast compression. This paper presents a novel model-based method for reconstructing microcalcification clusters in 3-D from two mammographic views (cranio-caudal and medio-lateral oblique-"shoulder to the opposite hip" or lateral-medio). The authors develop a 3-D breast representation and a parameterised breast compression model which constraints geometrically the possible 3-D positions of a calcification in a two-dimensional image. Corresponding calcifications in the two views are matched using an estimate of the calcification volume. Both the geometric constraint and the matching criterion are utilized in the final reconstruction step to build the 3-D reconstructed clusters. Validation experiments are described using 30 clusters to verify the individual steps of the model, and results consistent with known ground truth are obtained. Some of the approximations in the model

and future work are discussed in the concluding section. [J252]

"Telemedicine system using computed tomography van of high-speed telecommunication vehicle"

The current medical system provides medical services to patients who visit hospitals. However, medical services can be provided at or close to the home of the patient using fully-equipped mobile telemedicine systems. Such a system can identify diseases at an early stage, improve the patient's quality of life and prognosis through early diagnosis and treatment, and reduce the cost of the medical service. Furthermore, the unit can provide mass screenings of the population, as well as a full medical service to remote areas. The Telecommunications Advanced Organization of Japan and Shinshu University Hospital established a research center for a unique telemedicine project using a mobile system. The mobile unit consists of a van that houses a spiral computed tomography (CT) machine and various telecommunications equipment. The unit allows medical examinations, CT scanning, and online two-way transfer of image data/teleconferencing to a medical center for consultation with various specialists. We have used the system thus far for the early detection of lung cancer through mass screenings over a four-year period in 29 administrative districts. Mass screenings of 19,117 residents resulted in the identification of 75 cases of early lung cancer in patients who were later treated by partial pneumonectomy. We have also used the system to provide medical services and telemedicine support to remote areas, winter-time telemedicine support to an international sports competition, and various medical services to a home-care facility. [J253]

"A novel optical imaging method for the early detection, quantitative grading, and mapping of cancerous and precancerous lesions of cervix"

Describes a novel optical imaging method for the in vivo early detection, quantitative staging, and mapping of cervical cancer and precancer. A multispectral imaging system was developed, which is capable of performing time-resolved imaging spectroscopy. The system was used in order to assess quantitatively the alterations in the light scattering properties of the cervix, induced selectively and reversibly in cervical neoplasias, after the application of acetic acid solution. Spectral imaging and analysis of cervix show that the maximum contrast between acetic acid responsive and nonresponsive areas is obtained at 525\±15 nm, which is further enhanced by cutting off the regular component of tissue reflection, with the aid of two linear cross polarizers. Successive snapshot imaging at this spectral band enables the quantitative assessment of the temporal alterations in the intensity of the backscattered light, in any spatial location of the examined area. Initial clinical trials show that optical contrast enhancement results in a notable improvement of the sensitivity in detecting incipient lesions. It was also shown that the measured temporal characteristics of the phenomenon contain specific information, which enables the differentiation between neoplastic and nonneoplastic lesions, as well as between neoplasias of different grade. The demonstrated improved sensitivity and specificity highlight the potential of the method in both clinical research and noninvasive diagnosis. [J254]

"A computational neural approach to support the discovery of gene function and classes of cancer"

Advances in molecular classification of tumours may play a central role in cancer treatment. Here, a novel approach to genome expression pattern interpretation is described and applied to the recognition of B-cell malignancies as a test set. Using cDNA microarrays data generated by a previous study, a neural network model known as simplified fuzzy ARTMAP is able to identify normal and diffuse large B-cell lymphoma (DLBCL) patients, Furthermore, it discovers the distinction between patients with molecularly distinct forms of DLBCL without previous knowledge of those subtypes. [J255]

"A telematic system for oncology based on electronic health and patient records"

The NHS in the UK recognizes six levels of IT adoption in healthcare systems. Most current healthcare systems are at Level 1 (clinical administrative data), with some notable specialized exceptions. The telematic system for oncology is at Level 6 (advanced multimedia and telematics). Oncology is a particularly complicated area, as it draws on most of the other diagnostic systems and also has a number of different treatment regimes, each of which may have their own system. Relevant information is extracted from the underlying systems on a regular basis and stored on a server that can be accessed by various parties. Regarding the electronic health record (EHR), a centralized national directory would need to be in place to show the locations of individual electronic patient records (EPRs). In order to clearly capture and specify the requirements of the telematic system for oncology, it was decided that a framework based on Ariadne, especially designed for describing computer-supported cooperative work (CSCW) should be used. The use of such a framework captures the workflow, clearly showing the tasks of each actor within the processes, as well as the resources needed by each actor. The Ariadne framework was developed as part of a European ESPRIT research project (No. 6225) which studied computational notations for representing CSCW. Ariadne can be considered as a notation for defining a multi-

agent architecture for supporting articulation work among cooperating actors. [J256]

"Automated detection of pulmonary nodules in helical CT images based on an improved template-matching technique"

The purpose of this study is to develop a technique for computer-aided diagnosis (CAD) systems to detect lung nodules in helical X-ray pulmonary computed tomography (CT) images. The authors propose a novel template-matching technique based on a genetic algorithm (GA) template matching (GATM) for detecting nodules existing within the lung area; the GA was used to determine the target position in the observed image efficiently and to select an adequate template image from several reference patterns for quick template matching. In addition, a conventional template matching was employed to detect nodules existing on the lung wall area, lung wall template matching (LWTM), where semicircular models were used as reference patterns; the semicircular models were rotated according to the angle of the target point on the contour of the lung wall. After initial detecting candidates using the two template-matching methods, the authors extracted a total of 13 feature values and used them to eliminate false-positive findings. Twenty clinical cases involving a total of 557 sectional images were used in this study. 71 nodules out of 98 were correctly detected by the authors' scheme (i.e., a detection rate of about 72%), with the number of false positives at approximately 1.1/sectional image. The authors' present results show that their scheme can be regarded as a technique for CAD systems to detect nodules in helical CT pulmonary images. [J257]

"Computational modeling of three-dimensional microwave tomography of breast cancer"

The microwave tomographic approach is proposed to detect and image breast cancers. Taking into account the big difference in dielectrical properties between normal and malignant tissues, the authors have proposed using the microwave tomographic method to image a human breast. Because of the anatomical features of the objects, this case has to be referred to the tomography with a limited angle of observation. As a result of computer experiments the authors have established that multiview cylindrical configurations are able to provide microwave tomograms of the breast with a small size tumor inside. Using the gradient method, the authors have developed a computer code to create images of the three-dimensional objects in dielectrical properties on microwave frequencies. [J258]

"Fast and noninvasive fluorescence imaging of biological tissues in vivo using a flying-spot scanner"

The authors have developed a flying-spot scanner (FSS), for fluorescence imaging of tissues in vivo. The FSS is based on the principles of single-pixel illumination and detection via a raster scanning technique. The principal components of the scanner are a laser light source, a pair of horizontal and vertical scanning mirrors to deflect the laser light in these respective directions on the tissue surface, and a photo multiplier tube (PMT) detector. This paper characterizes the performance of the FSS for fluorescence imaging of tissues in vivo. First, a signal-to-noise ratio (SNR) analysis is presented. This is followed by characterization of the experimental SNR, linearity and spatial resolution of the FSS. Finally, the feasibility of tissue fluorescence imaging is demonstrated using an animal model. In summary, the performance of the FSS is comparable to that of fluorescence-imaging systems based on multipixel illumination and detection. The primary advantage of the FSS is the order-of-magnitude reduction in the cost of the light source and detector. However, the primary disadvantage of the FSS its significantly slower frame rate (1 Hz). In applications where high frame rates are not critical, the FSS will represent a low-cost alternative to multichannel fluorescence imaging-systems. [J259]

"Analysis of asymmetry in mammograms via directional filtering with Gabor wavelets"

This paper presents a procedure for the analysis of left-right (bilateral) asymmetry in mammograms. The procedure is based upon the detection of linear directional components by using a multiresolution representation based upon Gabor wavelets. A particular wavelet scheme with two-dimensional Gabor filters as elementary functions with varying tuning frequency and orientation, specifically designed in order to reduce the redundancy in the wavelet-based representation, is applied to the given image. The filter responses for different scales and orientation are analyzed by using the Karhunen-Loeve (KL) transform and Otsu's method of thresholding. The KL transform is applied to select the principal components of the filter responses, preserving only the most relevant directional elements appearing at all scales. The selected principal components, thresholded by using Otsu's method, are used to obtain the magnitude and phase of the directional components of the image. Rose diagrams computed from the phase images and statistical measures computed thereof are used for quantitative and qualitative analysis of the oriented patterns. A total of 80 images from 20 normal cases, 14 asymmetric cases, and six architectural distortion cases from the Mini-MIAS (Mammographic Image Analysis Society, London, U.K.) database were used to evaluate the scheme using the leave-one-out methodology. Average classification

accuracy rates of up to 74.4% were achieved. [J260]

"A constrained modulus reconstruction technique for breast cancer assessment"

A reconstruction technique for breast tissue elasticity modulus is described. This technique assumes that the geometry of normal and suspicious tissues is available from a contrast-enhanced magnetic resonance image. Furthermore, it is assumed that the modulus is constant throughout each tissue volume. The technique, which uses quasi-static strain data, is iterative where each iteration involves modulus updating followed by stress calculation. Breast mechanical stimulation is assumed to be done by two compressional rigid plates. As a result, stress is calculated using the finite element method based on the well-controlled boundary conditions of the compression plates. Using the calculated stress and the measured strain, modulus updating is done element-by-element based on Hooke's law. Breast tissue modulus reconstruction using simulated data and phantom modulus reconstruction using experimental data indicate that the technique is robust. [J261]

"Development of a quasi-monochromatic CT system for breast cancer study with combined emission-transmission tomography"

A combined SPECT-CT tomographic imager for breast cancer study is being developed as a large research program of Italian universities. The basic idea is to integrate the SPECT technique with a CT scanner in order to fuse the functional with the morphological information by using a high-resolution and compact gamma camera and a quasi-monochromatic X-ray system. These two dedicated systems will be assembled as a unique ring prototype, which will enable the authors to perform both the scintimammography and the X-ray tomography in the same geometrical conditions. High-intensity and tunable quasi-monochromatic X-ray beams have already been produced for mammography applications. The authors' aim is to investigate the use of this novel source for tomographic imaging of the breast [J262]

"Breast tissue density quantification via digitized mammograms"

Studies reported in the literature indicate that breast cancer risk is associated with mammographic densities. An objective, repeatable, and a quantitative measure of risk derived from mammographic densities will be of considerable use in recommending alternative screening paradigms and/or preventive measures. However, image processing efforts toward this goal seem to be sparse in the literature, and automatic and efficient methods do not seem to exist. Here, the authors describe and validate an automatic and reproducible method to segment dense tissue regions from fat within breasts from digitized mammograms using scale-based fuzzy connectivity methods. Different measures for characterizing mammographic density are computed from the segmented regions and their robustness in terms of their linear correlation across two different projections-cranio-caudal and medio-lateral-oblique-are studied. The accuracy of the method is studied by computing the area of mismatch of segmented dense regions using the proposed method and using manual outlining. A comparison between the mammographic density parameter taking into account the original intensities and that just considering the segmented area indicates that the former may have some advantages over the latter. [J263]

"maxPET, a dedicated mammary and axillary region PET imaging system for breast cancer"

Presents initial measurements from a high-performance prototype dedicated PET camera (maxPET) designed for mammary and axillary region imaging. The system consists of two 15Ч15 cm2planar scintillation detector plates operating in coincidence, with each plate composed of 25 modular detectors. The modular detectors are comprised of a 9Ч9 array of 3Ч3Ч20 mm3lutetium oxyorthosilicate (LSO) detector elements, read out by a position-sensitive photomultiplier tube (PS-PMT). A multiplexing readout scheme is used to reduce the number of readout channels from 200 (4X and 4Y readouts per PS-PMT) to 8 channels per plate. The detectors have a measured intrinsic spatial resolution of 2.3 mm. Over 95% of the 4050 crystals in the system can be identified in flood histograms of the detector plates. The coincidence timing resolution for the entire system is 8.1 ns. A line source phantom was scanned with the system and images reconstructed using focal plane tomography. The estimated resolution in projection images is 4 mm based on profiles taken through the line source phantom images. The goal of the maxPET system will be to aid in breast cancer patient management by assisting in imaging women with dense fibro-glandular breasts, detecting axillary lymph node metastases without surgery, and monitoring chemotherapy effectiveness. Future research on the maxPET system will focus on changes to the electronics to improve count rate performance and timing resolution and the mounting of the detectors on a rotating gantry for tomographic studies [J264]

"High-resolution absolute SPECT quantitation for I-131 distributions used in the treatment of lymphoma: a phantom study"

Clinical lymphoma I-131 radioimmunotherapy (RIT) studies are underway at the authors' institution. The effectiveness of treatment can be evaluated through accurate time-dependent three-dimensional (3-D) dosimetry calculations based on SPECT images. The authors compared the absolute quantitative SPECT performance of a high-resolution rotating parallel-hole collimator (RPHC) designed to minimize septal penetration with that of a traditional medium-energy parallel-hole collimator (MEPHC). The authors scanned a phantom consisting of four spheres having inner diameters of 2.2 and 2.8 cm and whose activity concentration ratios with respect to the surrounding medium were between 5:1 and 17:1. Images were reconstructed using the OSEM algorithm (10 subsets, 20 iterations) with spatial resolution modeling. Quantitation of the MEPHC SPECT images yielded a large over-estimation of the surrounding activity concentration (50%) due to septal penetration. Quantitation of the RPHC SPECT image yielded a surrounding medium activity concentration within 8% of the expected value, and the activity within the spheres was estimated to within 20% of their absolute expected values for the RPHC. The authors also investigated the effect of out of field-of-view (FOV) uncollimated gamma rays on SPECT quantitation. It is concluded that for the present quantitation application, the benefits of septal penetration suppression by the RPHC outweigh the increased image noise due to low count rate. These results point to the feasibility of using a large-FOV collimator based on the imaging principles of the RPHC for accurate clinical SPECT quantitation of I-131 RIT [J265]

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Тематический реферативный сборник сгенерирован в атоматическом режиме
с использованием специализированного программного модуля (ПИО ТУСУР)