Multimodality Biomolecular Imaging

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Discoveries in the field of molecular biology over the past two decades have radically altered how bioengineers approach biological and diagnostic imaging. The genetic and biochemical mechanisms underlying cancer, for example, provide new opportunities for detection, classification, and treatment of multiform, complex disease processes. Cancer is a principal application of molecular imaging, as we see from papers in this issue, for good reason—oncology represents 37% of all clinical imaging in the United States.

Medical imaging was originally developed a century ago as a tool for viewing gross anatomy noninvasively; the applications were diagnosis and surgical planning. As technology improved, the number of medical imaging modalities expanded to meet the growing need for more detailed diagnostic information with greater sensitivity and improving spatial resolution. For the past several decades, it has been possible to image functional properties of the body such as cardiac dynamics, blood volume and flow, metabolic activity, and biochemical features. Medicine now utilizes a broad range of modalities to generate image contrast for the specific information required to accurately diagnose diseases in patients with variable physiological characteristics. Recently, imaging scientists have sought to combine diverse data from simultaneous imaging acquisitions to more accurately blend the anatomical and functional information; to improve quantitative estimation of substrate uptake, blood flow, and like features; or to use data from one modality to improve the image reconstruction of another.

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.

Molecular imaging represents the next phase in the evolution of medical imaging. It incorporates genomic and proteomic advances into existing multimodality imaging approaches. The premise offered by molecular biology through the systems-biology perspective on disease management is that the phenotype of cells, and indeed whole organisms, can be predicted when they are considered products of genes interacting with their environment. Thus, a greater understanding of how cells react to and control environmental factors is possible with *in vivo* imaging tools. Molecular imaging allows us to see the interactions of signaling molecules with sites on cell membranes and extracellular matrix that characterize normal and pathological biological processes.

One goal in cancer molecular imaging is to visualize the dynamics of genetic mutations and secondary changes in gene expression that predict tumor growth and metastatic potential. Such information would enable earlier detection in patients and the design of more individualized treatment strategies. However, cancer has also been viewed as an inappropriate response of cells to their environment. Thus, despite its genetic etiology, environmental factors promoting tumor progression also are targeted by molecular imaging techniques. Accordingly, molecular imaging is valued as an in situ tool for basic research and drug discovery as much as it is for clinically diagnosis.

Many approaches to molecular imaging are designed around *exogenous* molecular probes (targeted contrast agents) that bind preferentially to macromolecules or cell membrane structures, or they are transported into the cell, all in response to specific biological stimuli. Probes introduced into the blood stream accumulate at

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sites targeted for imaging. *Molecular probes* often have two components. The biologically active *carrier* is a small molecule, peptide, or antibody selected for its high affinity for ligands, receptors, and other disease-specific molecules. Chemically bound to carriers are *reporters* that radiate internal energy or reflect external sources; for example, radionuclides, fluorophores, gas microbubbles, and magnetic particles are used with positron emission tomography (PET), optical, ultrasonic, and magnetic resonance imaging (MRI) methods, respectively. Sites frequently targeted for molecular imaging describe cellular proliferation, angiogenesis, apoptosis, hypoxia, cell trafficking, adhesion molecule expression, and pharmacokinetics—applications generally related to cancer and cardiovascular diseases. Exogenous probes promise the possibility of imaging very sparse biomarkers to detect early processes associated with disease.

Another approach exploits *endogenous* sources of contrast such as biochemical signatures (e.g., magnetic resonance spectroscopy, mid- and near-infrared spectroscopic imaging) and biomechanical features (e.g., elasticity imaging). These methods aim to describe the cellular microenvironment that initiates or stimulates molecular signals. Unlike exogenous probes, the ability to detect endogenous-contrast targets related to molecular signaling requires larger ensemble events. Those events may indicate that conditions are right for malignant cell transformations; metabolic and genetic instabilities from changes in local pH; responses to injury such as edema, fibrosis, and desmoplasia; or characteristic changes in protein conformations.

Both approaches have strengths and weaknesses. The interest in novel diagnostic imaging probes increases significantly when the same probe can be utilized to deliver therapeutic agents (e.g., drugs or genes). These drugs can be designed to enhance conventional therapies and also provide physicians with tools to monitor patient responses. However, targeted probes and therapeutics can be very expensive, and the high rate of mutations in oncogenes for common cancers increases the diversity of epitopes that probes must target to uniquely identify a condition. The most effective and economical imaging strategies extract all of the diagnostic information available from each exam. This is a major goal of multimodality imaging.

This special issue of the PROCEEDINGS OF THE IEEE on "Multimodality Biomolecular Imaging" is an update to the 2005 issue on "Molecular Imaging." Each paper describes an aspect of imaging technologies that can be combined to efficiently enhance diagnostic performance. You will notice that the approaches to multimodality imaging vary widely, making it difficult to draw boundaries around those techniques that qualify. Nevertheless, they share a basic struggle with technology, often pushing forward the frontiers of instrumentation, signal analysis, and chemical synthesis to achieve their unique biomedical goals. Papers in this issue address the engineering behind implementation of novel multimodality methods in the context of challenging biological and medical problems.

The first paper is "Elucidating Structure and Function *In Vivo* with Hybrid Fluorescence and Magnetic Resonance Imaging" by Niedre and Ntziachristos. They review hybrid optical MRI techniques in the context of cancer and vascular imaging. Two approaches are described. When two modalities share an acquisition geometry, differences in their endogenous contrast increase the diagnostic content of the study. However, the technical challenges of simultaneous acquisition or spatial registration for sequential acquisitions can be reduced using exogenous hybrid probes that generate complimentary diagnostic information with a shared object geometry. Also discussed are the uses of MRI data to regularize diffuse optical tomography reconstructions and interventional imaging of tissue structure and function on disparate scales.

The second paper is "Perfluorocarbon Nanoparticles for Molecular Imaging and Targeted Therapeutics" by Hughes *et al.* The authors describe advancements on the use of nanoparticles containing liquid perfluorocarbon as a versatile stage for launching probe development in the diagnosis, treatment, and therapeutic monitoring of cardiovascular diseases and cancer. The probe technology pioneered by these authors is extending the range of targeted molecular imaging beyond PET and single photon emission computed tomography tracers to include MRI, ultrasound, and optical modalities on a single probe platform. They show how perfluorocarbon nanoparticles generate target-specific contrast and thus enable sensing of very sparse concentrations of biomarkers.

The third paper is "The Integration of Positron Emission Tomography with Magnetic Resonance Imaging" by Cherry *et al.* The authors provide a detailed accounting of the development of PET and MRI systems that emphasizes instrumentation, molecular probe design strategies, and results of preclinical applications. The high sensitivity of PET for targeted probes and the high intrinsic soft-tissue contrast of MRI are combined to image subtle signaling and metabolic processes. Nanoparticle probes have been introduced to include optical reporters that validate PET/MRI studies and eventually could enable biopsy guidance. Dual technologies with simultaneous acquisitions are emphasized to image time-dependent gene expression, prodrug activity, cell trafficking, and therapeutic response of tumors.

The fourth paper is "New Imaging Technologies to Enhance the Molecular Sensitivity of Positron Emission Tomography" by Levin. This paper details the challenges and emerging solutions facing investigators attempting to use PET imaging near the limits

of current technology. Cancer imaging in particular demands systems with greater molecular probe sensitivity to provide more accurate spatial maps of isotope activity. The author explains the most promising innovations in instrumentation and reconstruction algorithms aimed at improving spatial resolution, detector sensitivity, signal-to-noise ratio (SNR), energy resolution, and coincidence-time resolution.

The fifth paper is "Design, Performance, and Applications of a Hybrid X-Ray/MR System for Interventional Guidance" by Fahrig *et al.* Dual-modality X-ray fluoroscopy/MRI (XMR) systems are described for applications in image-guided minimally invasive surgical procedures. The authors begin by detailing their experience building and testing an open-magnet MR system with a static-anode fluoroscopy system. Each component technology was reconsidered for the hybrid system where classic solutions perform suboptimally or not at all. They overcame difficulties associated with generating and imaging X-rays in strong magnetic fields by modifying chamber geometry and applying novel instrumentation. Clinical applications in the abdomen are described that combine the high temporal/spatial resolutions of fluoroscopy with the superior soft-tissue contrast of MR. This paper closes with designs for a new closed-bore XMR system with rotating anode currently under development that promise significantly superior clinical performance if the new technical challenges are met.

The sixth paper is "Simultaneous Molecular and Hypoxia Imaging of Brain Tumors *In Vivo* Using Spectroscopic Photoacoustic Tomography" by Li *et al.* The authors describe preclinical trials of optical imaging for assessing brain metabolism, hemodynamics, and expression of glioblastoma-tumor-specific biomarkers. Near-infrared (NIR) wavelengths sense endogenous contrast indicating regional changes in hypoxia and blood flow, whereas exogenous contrast media modulate NIR absorption and fluorescence for biomarker detection. This one imaging modality provides several types of information about brain tumors and their surrounding cellular environments. However, the scattering-dominated interactions of light photons at NIR wavelengths limit spatial resolution of the method. To improve resolution, the shock wave from locally absorbed NIR light (photoacoustic effect) is used to localize the source. Thus spectroscopic photoacoustic tomography combines the high object contrast of NIR absorption with the high spatial resolution of ultrasonic tomography to enhance performance. Anatomical, functional, and metabolic images of brain tumors are obtained along with images of biomarkers related to angiogenesis.

The seventh paper is "Potential of MRI and Ultrasound Radiation Force in Elastography: Applications to Diagnosis and Therapy" by Sinkus *et al.* The authors combine MRI and ultrasonic methods to image viscoelastic features of soft tissues. Mechanical properties of stromal breast tissue are strongly influenced by malignant processes. MR signals sensing shear waves introduced into breast tissue are processed to image the complex mechanical shear modulus. The authors found a significant improvement in diagnostic specificity when modulus images were added to other features of the BIRADS classification. They also describe novel acoustic radiation force methods to induce a cone of shear waves into the body for imaging the shear modulus with greater SNR. This method has advantages over current MRI/high-intensity focused ultrasound techniques for tracking spatial patterns of temperature increases during heat ablation treatments of tumors.

The eighth paper is "A Task-Based Approach to Adaptive and Multimodality Imaging" by Clarkson *et al.* Building on their substantial body of work on the analysis of imaging system performance, this group outlines a framework for assessing multimodality imaging systems. They begin by broadly classifying imaging tasks as detection or estimation. They then consider object variability, describe computational observers for comparison with or to represent expert humans, and define figures of merit for observer performance assessment. Examples illustrate how the analysis can be applied in many of the situations found in other papers of the issue. Included are situations where modalities provide distinct physical/biological information about objects (e.g., hybrid X-ray/MR systems) and different aspects of the same object (e.g., dual-modality targeted probes). Also considered are situations where data from one measurement are used to determine acquisition parameters of another for the same modality (e.g., MRI scout images); where images from one modality acquisition are used to enable quantitation in another modality [e.g., computed tomography (CT) image defines spatial regions for isotope activity estimation]; and where one modality is used to assist with the image reconstruction of another (e.g., CT attenuation maps used for PET reconstructions). Similarities between multimodality and adaptive imaging system analysis are also illustrated.

The ninth paper is "State of the Art in Information Extraction and Quantitative Analysis for Multimodality Biomolecular Imaging" by Ahmed *et al.* The authors describe how advances in two-and three-dimensional fluorescence microscopy and *in vivo* small-animal imaging are leading advances in molecular biology and medicine. However, the enormous volume of data resulting from multispectral, multiprobe imaging studies requires a tasked-based approach to spatiotemporal registration, segmentation, and noise reduction. Combining innovative methods for feature reduction and tissue classification with the appropriate validation, these imaging studies are able to deepen our understanding of biomolecular processes. ■

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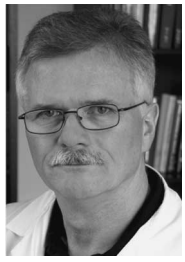

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