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Diagnostic Imaging with Light, and Beyond

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Summary: In this report we consider the merits of optical methods for use as a nonionizing diagnostic imaging tool in relation to current imaging methods, and discuss critical issues needing further development. Of added promise is the potential for developing a range of optical contrast agents sensitive to different metabolic states, and for extending the utility of optical methods beyond diagnosis to create new strategies for rational therapeutic intervention.

Introduction: The red glow produced by pressing a flashlight to the palm of a hand or inside the mouth demonstrates that red light is penetrating in tissue. At near infrared wavelengths (700-1300 nm), multi-centimeter penetration is possible. As long ago as 1929, investigators recognized the potential of optical measurements for the study of tissues [1]. The first impression of many, though, is that thick tissue imaging with light is simply not possible. At optical wavelengths, tissues appear opaque because propagating photons experience intense scattering due to the localized variations in refractive index that are a result of differences in the size and composition of cellular components. Conventional wisdom would hold that if there is no well-defined path for the signal propagating from a source to a detector, there is no possibility of recovering an image. This position is not without intuitive merit: the mythological Theseus was able to find his way out of the Labyrinth by following a piece of string he'd laid down while entering it, but it is easy to see that the "strings" corresponding to individual NIR photon trajectories in thick tissues are thoroughly tied in knots. Nevertheless, qualitatively and quantitatively accurate images of the absorption and scattering properties of various target media having optical properties similar to a breast have already been obtained experimentally [2,3], and similar results have been obtained with numerical data derived from anatomically accurate priors of the breast [4,5] and brain [6,7]. Presently, an aggressive worldwide effort is underway to develop practical NIR imaging systems. In the scientific literature, this field of study has come to be known as *photon migration imaging*. Below we elaborate on the merits of optical imaging, not only as economical, non-ionizing imaging tool, but also as one that holds great promise to become a highly versatile and sensitive metabolic imaging method.

Tools for Clinical Diagnosis: An ideal diagnostic tool would have both high sensitivity and high specificity to a broad range of disease states. Targets for analysis include collected specimens and sites evaluated *in situ*. The field of laboratory medicine is concerned with examining collected specimens, while imaging methods are useful for *in situ* evaluation. Early on in a disease process, metabolic derangements precede morphologic changes. These derangements result in excess or reduced production of enzymatic or structural components of cells, or of factors regulating their production or of metabolic intermediates. It follows that early detection of disease states will require use of methods sensitive to the various constituents of cellular metabolism. One approach is to analyze markers released into physiologic fluids. While this is effective, it frequently is moderately invasive and is subject to the variable accessibility of systemic fluid compartments (*e.g.*, vascular space) to different humoral sites. Not infrequently, anatomic barriers exist that prevent release of these markers and hence prevent early detection. An alternative methodology would be to directly probe the suspect tissue using some form of penetrating energy. The ideal method here would be one that employs nonionizing sources, has high temporal and spatial resolution, is sensitive to local tissue environments, and employs economical, compact instrumentation that can be made portable. In the following we discuss the capacity of optical methods to currently satisfy many of these criteria and their potential to meet all.

Energy Sources for Imaging Studies: A broad range of energy sources is currently employed in diagnostic imaging studies. These vary in site of origin, type, energy level, and mechanism of interaction with underlying tissues. Examples include sources of acoustic energy, electromagnetic radiation, magnetic fields, and electric fields. Endogenous sources include the electrical and magnetic fields produced as a result of synaptic propagation of the chemical signals generated in nerve and muscle tissues. Electroencephalo-graphic (EEG) and magnetoencephalographic (MEG) imaging methods are based on measurement of these signals. Exogenous sources

represent a larger class and include those invasively introduced into tissue and, more typically, those applied externally. Representative of the former are radioscintigraphic imaging methods such as single photon emission computed tomography (SPECT) and positron emission tomography (PET), while among the methods in the latter category are magnetic resonance imaging (MRI), x-ray CT, ultrasound imaging and impedance tomography.

If imaging methods are to have diagnostic utility, it is necessary to establish correlations between tissue properties and the physical quantities that are actually displayed in the images. Among the factors that will limit the ability to do this are the spatial and temporal image contrast and resolution. In relation to the preceding discussion, the ideal imaging method should, in addition to having good contrast and resolution, also exhibit sensitivity to metabolic states. While the distinction between morphologic and physiologic/metabolic imaging methods is becoming increasingly blurred with ongoing development, certain general principles are likely to remain in place. Among these is the necessity for a method that is sensitive to metabolic states to employ a form of energy that in some fashion is influenced by the *electronic* state of the material through which it propagates. It follows that acoustic imaging, which measures differential compressibility of tissue, is unlikely to become a useful tool for detection of metabolic states[1]. A similar conclusion pertains to x-ray imaging, as the photoelectric and Compton effects, which are the principal interactions of x-rays with tissue, depend very weakly upon the material's electronic state. It also follows that radioscintigraphic imaging methods, notwithstanding certain applications of PET, will have limited applicability in this area, as the emissivity of a radioisotope is for all practical purposes insensitive to variations in its immediate chemical environment.

Apart from these considerations, practical issues are receiving increasing weight in definitions of the utility of imaging methods. Among these are their cost, required facilities and portability. Most of the primary imaging technologies (*i.e.*, x-ray CT, MRI, SPECT, PET) involve large, costly, fixed installations. These descriptions, for the most part, do not apply to optical technologies. Intense but non-damaging light sources are increasingly becoming available in the NIR region in the form of laser diodes. These devices are very compact, inexpensive and require little input power. In addition, a range of detection systems are available that also are relatively inexpensive and compact, and have high sensitivity. Further, the availability of optical fibers serves to extend the range of applications of optical studies. In all, optical technologies have progressed to an advanced state and can be regarded as highly reliable, sensitive, compact and economical.

These developments in optical technology have occurred at the same time that interest in using light as a tool for studying tissue metabolism has been growing rapidly, and to some extent they have been driven by it. There is a sound theoretical basis for believing that optical methods can be sensitive probes of metabolic states. Many compounds, some naturally occurring in tissue, have electronic or vibrational energy level intervals that allow absorption of photons at optical wavelengths. Among these are species that participate in reversible reactions that are important in many metabolic processes, and in which compounds fluctuate between distinct chemical (*e.g.*, Hb $\leftrightarrow$ Hb-O_2, $NAD^+ \leftrightarrow$ NADH) or electronic [*e.g.*, cyt-c(Fe^{2+}) $\leftrightarrow$ cyt-c(Fe^{3+})] states. Structurally, these are molecular and complex-ionic species consisting of low-atomic-number atoms and a small but significant number of period-4 transition metal ions. Many contain π molecular orbital systems in which the electrons are delocalized over many atoms (*e.g.*, porphyrin structures). It is the π molecular orbitals and the *d* orbitals of the transition metal ions whose energy levels change most extensively during the metabolic reactions, and electrons in these orbitals frequently can absorb photons at optical wavelengths. This is the microscopic-level basis for the sensitivity of optical methods to metabolic states. Analogous examination of the mechanism(s) of interaction of radiation in other parts of the electromagnetic spectrum, and of acoustic energy, with tissue indicates that these could not be expected to have such sensitivity.

A feature that MRI and optical methods, especially fluorescence, have in common is their sensitivity to local chemical environments. While this sensitivity enables high resolution imaging for MRI, it is well known that only species present in relatively high concentration are detectable by MR. This is due mainly to the fact that the net signal is produced only by the small difference between the numbers of hydrogen atoms in the low- and high-energy magnetization states. By contrast, high sensitivity for optical measurements *is* possible, in part because every target molecule contributes to the acquired signal. In principle, MR can provide a wealth of information regarding metabolic states. However, its low sensitivity limits practical efforts to provide imaging data about a particular species. Functional imaging of hemoglobin by MRI is gaining increasing attention [8], but even here it would seem that of all the compounds that one might wish to study, hemoglobin may be the only one present in sufficient concentration to exert an appreciable effect on the acquired signal. The range of naturally occurring species that are measurable at NIR wavelengths is also limited, and of these

[1]This conclusion does not hold for photoacoustic measurements. Here, however, while acoustic signals are measured, the spectroscopic information obtained is a result of photon absorption.

hemoglobin is the dominant one. However, unlike MR, a wealth of optical contrast agents sensitive to various aspects of metabolism either presently exist or could easily be developed. For example, of particular interest to us are fluorescent probes that produce characteristic signals at concentrations orders of magnitude lower than would be required in MR studies. This enhanced sensitivity, coupled with the newly developed method of optical tomography, affords the potential to evaluate, for the first time, the overwhelming majority of constituents of biological systems whose concentrations are too low for detection by MR and are not measurable by other imaging modalities. Thus, it would seem that optical methods hold the greatest intrinsic potential to yield information regarding the metabolic state of tissue with high sensitivity.

Tomographic Imaging of Tissue with Light

The physical measurement: The approach to tomographic imaging of tissue using optical sources is similar to schemes employed in other imaging modalities (*e.g.*, x-ray CT). Data collection involves performing a set of optical measurements about a target, usually at multiple source positions. Measurements can either be limited to the steady state or can include temporal measurements performed in the time or frequency domain. Time-resolved measurements contain the greatest information about the target medium, but presently require costly and delicate instrumentation. Equivalent information can be obtained in the frequency domain by performing measurements at multiple frequencies. While a limited number of frequency measurements are practical, frequency chirping remains an expensive alternative. Most cost-effective, and easily employed, are steady-state measurements.

An open question is whether equivalent image quality can be obtained from each of the mentioned source conditions. In principle, one would expect time-resolved measurements to yield the highest resolution images. For thin scattering media this is certainly correct. However, for thick media, (*e.g.*, the breast) reduced signal-to-noise levels in the data can be expected to partially offset the enhanced spatial resolution contained in the temporal data. For a particular source condition, many combinations of source-detector configurations could be employed. Which is best will likely depend on the particular aspect of the anatomy being examined. For example, for studies of the breast, a planar compression geometry could be adopted with sources on one side and detectors on the other. For studies of the brain of an adult, it will be necessary to work with mainly backscatter measurements, as the expected signal strength for a transmission measurement is very weak. Regarding other aspects of the anatomy, the signal strength expected on the basis of known attenuation values suggests that for adults, transmission measurements will be limited to structures <15 cm thick and backscatter measurements to a maximum depth of ~4 cm. This would enable interrogation of nearly the entire volume of an infant and most of the volume of an adult with the exception of interior regions of the torso, particularly for obese individuals.

Another unanswered question is whether noncontact measurements, such as those employed in CT imaging, are feasible. The advantage here is that nearly any target geometry can be evaluated. Contact measurements would impose greater requirements on the construction of detector heads, but these added constraints could be justified by the expected significant enhancement in signal levels and reduced impact of motion artifacts. Presently, numerous groups, including ourselves, are developing and testing different system configurations primarily for breast and brain imaging. Our bias is to adopt contact measurements using a geometrically adaptive detector head, as we believe tolerance to motion artifacts will be very limited.

A particularly attractive feature of optical measurements is their capacity for fast data acquisition. The temporal resolution of optical detectors greatly exceeds that of any physiological event, and thus the potential to monitor time-varying processes will be limited only by expected signal strengths or other factors not related to properties of the detector.

Data Analysis:

i. Modeling Schemes: Our original contribution to the field of photon migration imaging was to demonstrate that *intensity* data acquired at the surface of dense scattering media contain sufficient information to enable recovery of accurate images of internal structures [9,10]. Prior to these reports, all previous studies on scattering media involved measurement and analysis of the scattered *field*. The significance of our work was two-fold. First, it provided a direct connection between the types of physical measurements typically performed using optical detectors and the required analysis. Second, the analysis scheme itself was computationally tractable. The basic approach we described, which has been subsequently adopted and modified by many, was to treat propagating photons as particles rather than as waves. This formulation, described by the well-known Boltzmann transport equation [11], is correct provided that the net scattered fields are uncorrelated, a condition satisfied in almost all cases of thick tissues illuminated by NIR light. This equation relates the combined effects of localized absorption, scattering, intensity gradients and source strength to the net change in angular intensity at a point with time. The physical quantities derivable include the absorption and scattering cross sections (μ_a and μ_s, respectively). These have units of inverse length

and are inversely proportional to the mean free pathlengths for absorption and scattering, respectively. In most tissues, the ratio μ_s/μ_a is >>1. Under these conditions the transport equation can be simplified to the diffusion equation by truncating the spherical harmonics expansion of the angular intensity after the linear terms and asserting that flux is related to intensity by Fick's law. Many groups have sought to adopt the diffusion formulation instead of transport because of its reduced computational burden. As fast codes do exist for solution to the transport equation, it may prove unwise at this point to conclude that the diffusion-based schemes are adequate in the absence of a careful side-by-side comparison. In fact, in the case of the brain, recent results from our group would suggest that diffusion solutions cannot accurately describe photon propagation [12].

Numerical Methods for Image Recovery. The numerical methods used for image recovery are in many cases very similar to those employed in other imaging modalities. The approach we have adopted is to compute solutions to a linear perturbation equation. This is a standard scheme that has been successfully used to solve many types of inverse problems. A range of numerical methods is available to solve this equation including Newton-type iterative algebraic solvers [13,14]. Many of the reports that have appeared thus far have been restricted to computing 2-D images of cylindrically symmetric objects or to composing a set of 2D slices to constitute a 3D image [15]. For most practical applications, 3D solutions will be needed, particularly if iterative updates are required. Under these conditions, choice of numerical method is important as the computational burden can quickly become overwhelming. Appreciation of this has prompted several groups to explore development of fast solvers [16-19]. Invariably, most are derived from the diffusion equation. Should this governing equation prove sufficiently accurate then these methods might well prove adequate. Much additional development and testing is needed in this area, particularly using data collected on complex phantom structures using well-engineered prototypes.

Image Quality: A large number of reports have focused primarily on determining the quality of reconstructed images obtained from numerical and experimental studies of simply-structured phantom media [15] and, more recently, on anatomical maps derived from MRI data [4-7]. Serious clinical studies are only just beginning. The corresponding thickness of target media examined has typically varied from 6-10 cm. Overall, the quality of reconstructed images has been much better than one might expect given the extensive homogenizing effect of the background scattering medium. Images obtained frequently correctly locate the added inclusion(s) and in some cases quantitatively recover simultaneous perturbations in absorption and scattering properties in the presence of added noise. While most studies have involved phantoms containing strong discontinuities, more recent reports have obtained qualitatively good images of low-contrast inclusions [20-22]. Resolution limits have not been well defined, but most agree that objects having a size on the order of 0.5 cm are readily discernible. Qualitatively similar results have been obtained on studies of anatomical maps [4-7].

Tomographic scanning systems: A number of groups in academic and industrial settings, including ours, have active instrument development programs. This field has caught the attention of the leading medical imaging manufacturers and nearly all have active programs. At the time of this writing (May 1997) there are no tomographic systems commercially available. Construction of prototype instruments suitable for investigation of laboratory phantoms is easy accomplished at modest cost. A similar effort suitable for evaluation of volunteers is significantly more challenging. Unresolved design issues include the desirability/feasibility of contact *vs.* non-contact measurements, influence of boundary conditions, and effects of motion artifacts. Notably lacking has been the availability of a defined deformable phantom with complex internal structure. In its absence, verification of the suitability of a specified measurement/analysis scheme remains incomplete.

Tomographic Imaging of Fluorescence: Consideration of the influence that localized variations in the absorption and scattering properties of tissue have on the response of detectors located at the surface indicates that an upper limit of sensitivity will quickly be reached even for a totally absorbing object. For any particular region of interest (ROI), it is useful to consider two classes of photons: those that interact with the ROI (class I) and those that do not, but ultimately reach the detector (class II). In many situations the ratio of class I to class II photons is <<1. Because class II photons carry no information about the ROI, they can effectively be treated as noise. As a result, the "signal-to-noise-ratio" corresponding to many targets of interest (*e.g.*, small tumors) could be very low. It follows that infusion of an absorbing species into the ROI will be of limited benefit. Far better would be to identify a strategy whereby the intensity of class II photons could be *selectively* reduced. Fluorescence provides this capability. In the presence of a suitable blocking filter and restriction of fluorescent material to a ROI, the only signal detectable here would be those photons born in the ROI. Under these conditions, the corresponding "signal-to-noise-ratio" is infinite. In practice, it can be expected that an infused fluorescent probe, even one linked to a specific biotargeting vehicle (*e.g.*, monoclonal antibody, hormone, *etc.*) would also be present in the background tissue. This would reduce the "signal-to-noise-ratio" in a nonlinear fashion depending on the location of the source and detector in relation to the

fluorescent ROI. The tenor of this scheme is very similar to current strategies used in radioscintigraphic imaging. Here, instead of a fluorescent probe, a radioisotope is infused (*e.g.*,Tc^{99m}), usually bound to some chelating agent. The presence of isotope in the background serves to limit the achievable contrast. While various wash-out strategies in one form or another exist to reduce the signal originating from the background, their effectiveness is limited. Beyond this, as mentioned, for all practical purposes, the emissivity of radioisotopes is completely insensitive to their chemical environment.

Recently we [23,24] and others [25,26] have described detailed imaging schemes that are capable of obtaining images of fluorescence yield and fluorescence lifetime. Interest in fluorescence is very high because of the possibility of employing probes whose emission properties are sensitive to local chemical environments. It is well known that fluorescence techniques are among the most sensitive, and even single molecule detection is possible. As described below, we have recognized the added advantages of using probes that exhibit fluorescence enhancement as opposed to quenching in certain environments.

Selectively Activated Fluorescence Emission (SAFE) Imaging: By taking advantage of the property of sensitivity to local chemical environments, the problem of background emission for fluorescence can be addressed in ways not possible with radioisotopes. The approach we have adopted is to employ probes that exhibit selective activation of fluorescence emission (hence SAFE) in certain chemical environments. The advantages gained in sensitivity can be considerable. If properly designed, fluorescent probes of the indocyanine class can exhibit enhancement of fluorescence by as much as 50 fold upon reduction from pH 7 to pH 5 [G. Patonay, personal communication], where the latter is an environment often found in solid tumors. Assuming a target:background ratio of 10:1 in a ROI, this results in a 500-fold enhancement in detectability over the surrounding region. This magnitude of enhancement, while significant, is, by no means, the achievable upper limit. Through careful design of probes whose fluorescence emission overlaps with the excitation spectrum of another SAFE probe (*e.g.*, one sensitive to Ca^{2+}), *multiplicative* enhancement of sensitivity should be achievable. This technique, known as fluorescence energy transfer, can be extended to situations whereby energy transfer is accomplished between two or more probes upon their becoming juxtaposed due to conformational changes induced by specific binding to various macromolecules. As the existence of high affinity binding in biological systems is omnipresent, it would seem that detection strategies sensitive to any structural component of a cell (including complementary regions of DNA) or metabolic intermediate could be devised. In addition, as numerous SAFE probes could be employed, it also seems that there should be no upper limit to its potential diagnostic specificity. No doubt, development of appropriate probes having acceptable toxicity and biocompatibility features is a nontrivial task. This, however, this is a technical challenge. More important, fundamentally it would seem that fluorescence optical imaging techniques, in the form of SAFE imaging, hold the potential for devising new imaging strategies having unparalleled diagnostic sensitivity and specificity.

SAFE Therapy: The previously described technique, in effect, allows for the production of fluorescent photons in defined chemical environments. It has occurred to us that this capability may also afford the potential to improve upon the existing technique of photodynamic therapy (PDT) in ways that might provide a basis for specifying rational treatment modalities optimized to the individual. The goal would be to restrict the activation of PDT agents to specific chemical environments shown to exist by SAFE imaging. In principle, this could also be accomplished by fluorescence energy transfer techniques, for which the last link in the chain is the PDT agent. In this fashion, only when the correct pH, oxygen level, Ca^{2+} concentration, *etc.*, exist, as determined by SAFE imaging, would it possible to produce the activating fluorescent photon. As with SAFE imaging, accomplishment of this task no doubt would constitute a daunting challenge. Nevertheless, it would seem that this technique represents a fundamentally new approach to devising individualized rational treatment modalities. In all, it would seem that the prospects for expanded applicability of optical techniques in clinical medicine is indeed bright.

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