Terra Incognita: Potential Uses of Optical Spectroscopy for Combat Casualty Care

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ABSTRACT

Conventional medical imaging modalities currently revolve around magnetic resonance imaging (MRI), ultrasound or radiographic techniques. While each of these has added significant value to healthcare today, none of these techniques singlehandedly reveals the complete details regarding a patients' physiological status or injury. Secondly, these techniques do not easily lend themselves to use in remote areas or the battlefield. This can be due to a combination of power requirements, durability and size/weight. Techniques such as ultrasound represent a significant alternative, but also come with tradeoffs, such as sensitivity to artifacts and decreased spatial resolution as compared to computed tomography or MRI.

With respect to combat casualty care there is a strong need to develop a new generation of tools that matches or betters the spatial resolution of CT/MRI while retaining the portability and higher durability of ultrasound devices. Methods using photons in the range of wavelengths between 200 and 16,000 nanometers may offer a favourable combination of attributes to detect and diagnose morbidities associated with the battlefield. These techniques are particularly good at surface imaging and therefore applicable to burns and infections. This paper will describe relevant methods that use these photons for biomedical applications, discuss roadblocks for translation out of the clinic, and describe the potential future of these techniques with respect to combat casualty care on and off the battlefield.

This will be a review of most of the current relevant literature for optical spectroscopy within the context of currently identified military needs that are addressable by this group of techniques.

Optical imaging presents significant assets to support ongoing medical operations on and off the battlefield. New technologies and methods of data processing and analysis could lead to applications ranging from burn assessment to the monitoring of skin infections. There are also a host of secondary applications that could benefit the rehabilitation of wounded servicemembers.

1.0 INTRODUCTION

Medical imaging techniques such as magnetic resonance imaging (MRI), computed tomography (CT) and ultrasonography (US) have improved medical outcomes for cancers, neurodegenerative diseases, and trauma.

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14. ABSTRACT

Conventional medical imaging modalities currently revolve around magnetic resonance imaging (MRI), ultrasound or radiographic techniques. While each of these has added significant value to healthcare today, none of these techniques singlehandedly reveals the complete details regarding a patients physiological status or injury. Secondly, these techniques do not easily lend themselves to use in remote areas or the battlefield. This can be due to a combination of power requirements, durability and size/weight. Techniques such as ultrasound represent a significant alternative, but also come with tradeoffs, such as sensitivity to artifacts and decreased spatial resolution as compared to computed tomography or MRI. With respect to combat casualty care there is a strong need to develop a new generation of tools that matches or betters the spatial resolution of CT/MRI while retaining the portability and higher durability of ultrasound devices. Methods using photons in the range of wavelengths between 200 and 16,000 nanometers may offer a favourable combination of attributes to detect and diagnose morbidities associated with the battlefield. These techniques are particularly good at surface imaging and therefore applicable to burns and infections. This paper will describe relevant methods that use these photons for biomedical applications, discuss roadblocks for translation out of the clinic, and describe the potential future of these techniques with respect to combat casualty care on and off the battlefield. This will be a review of most of the current relevant literature for optical spectroscopy within the context of currently identified military needs that are addressable by this group of techniques. Optical imaging presents significant assets to support ongoing medical operations on and off the battlefield. New technologies and methods of data processing and analysis could lead to applications ranging from burn assessment to the monitoring of skin infections. There are also a host of secondary applications that could benefit the rehabilitation of wounded servicemembers.

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These imaging modalities are also used routinely in the hospital to aid in the prevention, detection and treatment of disease and injury. The techniques offer assessments of tumor volumes, early indications of tissue pathology associated with trauma and response to surgical or pharmaceutical intervention. Medical imaging also offers the capabilities to evaluate the early stages and longitudinal progression of disease through functional imaging techniques such as positron emission tomography (PET) (1).

The ability to identify injured regions of interest through imagery provides essential indicators for intervention planning. Radiological techniques are key to assessing injuries to extremities sustained in combat (2). In addition to characterizing injuries to the trunk and extremities, there has been much recent emphasis in the neuroscience community to use medical imaging to assess the psychological, cognitive and motor deficits produced by traumatic brain injury (TBI) or posttraumatic stress disorder (PTSD) that are sustained in recent combat. The relationship between PTSD and TBI is unclear; however similar frequencies are reported for both PTSD and mild TBI (3). While correlation between the two is not implied, imaging techniques, such as diffusion tensor imaging (DTI) are envisioned as part of the roadmap for the detection and treatment of each (4).

The use of these aforementioned techniques in the far-forward environment is limited by size, weight and power requirements. PET, CT and MRI have the additional requirements for tracers and contrast agents. These requirements have precluded techniques such as MRI and PET from use in the forward environment. While CT can be found in the forward environment, it is not always available due to power and maintainability constraints. Additionally, conventional imaging technologies such as US require in-depth training in image acquisition, post-processing and image interpretation. Lastly, cost limits the widespread availability of most of these tools.

Optical imaging is an alternative modality that may complement battlefield medical assessments. While initially confined to the laboratory, the discipline has begun to focus on biologically-relevant problems. This is particularly true for cancer research (5). Advances in signal processing over the past two decades have finally permitted the deconvolution of complex datasets which stem from the molecular signatures of tissues and cells.

A number of optical tools have shown promise to detect the molecular signatures of cancer and are in clinical trials. Photons ranging from between 200 and 16,000 nanometers interact with tissues in numerous ways, including absorption, scattering, fluorescence and phosphorescence. These physical interactions offer a potential combination of high spatial resolution, in conjunction with high specificity and sensitivity to aberrations in tissue morphology and even cellular metabolism without the use of dyes or fluorescent proteins.

This article identifies several uses for optical spectroscopy for combat casualty care. These were identified by means of literature search. This publication is a distillation of several promising optical techniques relevant to dermal wound healing, burn characterization, and neuroimaging. The paper is written from a pathological perspective and outlines research conducted in relevant optical techniques for each of these pathologies. While not exhaustive in nature, this paper provides an overview of optical techniques relevant to commonly found combat-related injuries. As part of the evaluations of these techniques, this paper will also discuss some current roadblocks for each technique that prevent translation into the battlefield for combat casualty care.

2.0 NEUROIMAGING WITH OPTICAL SPECTROSCOPY

Many groups are exploring non-invasive optical brain imaging, despite the complex optical properties of the skull, brain and associated tissues. This paper highlights some current efforts with functional near infrared spectroscopy (fNIRS) for imaging of the cortex with respect to simple motor tests and cognition. A review article written by Arenth et al. (6) provides a comprehensive overview. The review notes several notable advantages for using this technique in the clinic. These included portability, cost, non-invasiveness and real-time monitoring of task performance. Several examples of imaging with respect to the visual and motor cortices of the brain were described. The work was primarily driven due to the localizations of function, which are well established for these regions of the cortex. Many of the studies provided apparently good correlation with functional MRI and PET data. One study highlighted in this review (Francescini et al. (7)) provided a comparison of active versus passive motor movement using fNIRS imaging. The study compared active movement (via finger opposition task) with passive tactile stimulation (via touch by investigator) and electrical stimulation of the hand. Hemodynamic response, as monitored by MRI and PET was observed in the sensorimotor cortex contralateral to the stimulated hand. This was also observed using fNIRS. Stronger hemodynamic response was associated with the active voluntary task. Arenth et al. noted that this difference between active and mock task performance was identified in another study (8). Also cited in this review were several studies relating to cognition. Unfortunately, a lack of common methodology has prevented a comparison. While the measurements were generally consistent with functional MRI, further study is required to substantiate this tool for use in cognition monitoring and testing.

A direct comparison of BOLD to fNIRS was recently completed studying activation in the human primary visual cortex (9). This work is unique in that the statistical analyses used were common to both imaging modalities. Webb et al. transformed the fNIRS data into Talairach space, converted to ANALYZE format, and analyzed using the same software tools as the BOLD data. The authors noted that the statistical significance of fNIRS data was much lower than that of the functional MRI data. This was attributed to the low signal-to-noise of the fNIRS measurements. The authors cite high inter-subject variability in their measurements as the source of the poorer signal-to-noise ratio for the fNIRS data. The authors also note that a better understanding of the complex optical properties of the skull and brain will indeed boost the signal-to-noise ratio for these measurements. The authors provide several recommendations on how to achieve this available in the full paper.

Aside from potentially providing useful data regarding cognitive, psychological and motor status, fNIRS is under evaluation for monitoring trauma, such as hematoma or intracranial hemorrhage. Irani et al. point to early work which showed that the technique could detect the formation of hematoma (10). This work was conducted with patients admitted to hospitals that sustained head trauma. A total of 40 patients were studied. The intracranial hematomas were classified as subdural, epidural or intracerebral using CT. In all 40 cases, fNIRS demonstrated greater absorption of light at 760 nm over the affected hemisphere with hematoma. An attempt to classify CT outcomes with hematoma classification did not achieve statistical significance. The review also described efforts for the detection of primary and secondary responses, such as increase in intracranial pressure, to brain injury in adults and children. The authors conclude that while the technique shows promise, the issues cited by Webb et al. require rectification for the technique to advance towards standard of care for brain injuries.

It is undoubtable that innovations in the field will raise the signal-to-noise ratio for the fNIRS measurements. The work will continue to benefit from better photon modelling, innovations in hardware and signal processing. The primary task for now seems to be accurate modelling of the optical path for fNIRS, along with better understanding of both the absorptive and scattering properties of the cortex, skull and surrounding milieu. It will also likely take on the nature of a hyperspectral approach, since tissue properties can be assessed using visible photons as alluded to in the exposed cortex work. Accurate modelling will likely be a composite of empirical work, with an understanding that variability between measurents must be controlled for as well. It is clear that work has begun to take advantage of the empirical data available for all studies using fNIRS.

3.0 ASSESSMENT OF WOUND HEALING

Human skin is a multilayered structure, primarily divided into the dermis and epidermis. The epidermis is composed of four stratified layers ranging between 50–1500 μm thick. The dermis is primarily composed of the structural proteins collagen and elastin. This layer typically ranges between 100–500 μm thick and contains hair follicles, glands and other larger scale structures. The thickness of all layers varies with body location (9). Understanding the absorptive, emissive and scattering properties of each layer presents a series of challenging problems for optical imaging. Recent advances in optical imaging such as the development of robust and cost-effective femtosecond lasers now allow for preliminary optical characterizations of these layers using techniques such as multiphoton microscopy (MPM). This section highlights recent advances in the optical imaging of wound healing and burn characterization.

MPM comprises a series of optical techniques including second harmonic generation (SHG), coherent anti-Stokes Raman (CARS) and autofluorescence (9). These techniques use non-linear excitation and are also referred to as nonlinear optical microscopy (NLOM), since they use multiple photons for excitation. Since they use endogenous chromophores, they largely reveal information on structure and structural integrity within the skin. Work with dyes is an emerging sub-discipline of NLOM; however it adds extra layers of complexity in terms of obtaining measurements. Bardeen et al. did identify a study with SHG which could successfully differentiate normal, precancerous, and cancerous squamous epithelial tissues using an animal model of this disease. The authors report several other successes in this area but also highlight the need for more research, especially with relation to building comprehensive libraries of skin tumor molecular signatures for MPM. Additional applications are alluded to and include wound healing, but are limited to studies related to tumor destruction.

Other optical methods are already transitioning from cancer into studies of wound healing. Kollias et al. (10) have used NIRS for imaging of cutaneous edema. The authors note a variety of sources for this condition, including both cancer and trauma. Conventional imaging for edema is a robust field, but requires imaging modalities such as CT or PET and a trained physician to review the images. Kollias et al. evaluated the sensitivity and specificity of NIRS to detect histamine-induced edema in a total of eight patients. Using characteristic absorption bands of water and hemoglobin, the investigators were able to demonstrate functional imaging of an edema reaction following histamine exposure via iontophoresis. The investigators illustrate these observations by showing histamine concentration-dependent increases in oxyhemoglobin and water, while deoxyhemoglobin concentration remained constant. Tissue scattering properties were altered as well and the investigators presented a light-scattering intensity map, which summarized this phenomenon. The authors grossly addressed the change in tissue scattering in terms of an optical ‘‘dilution’’ of collagen fibers which resulted from extracellular water accumulation in the histamine-exposed areas.

An alternative technique, Optical Coherence Tomography (OCT) has been evaluated for wound healing (13). This method was tested in vivo using a porcine model. The authors cite that assessment of wound healing is largely subjective as it is accomplished largely by researcher or clinician. Wounds were set at a depth of 600 μm, which were estimated to require three to six days to completely re-epithelialize. Due to animal size, the wounds were excised, but a portable system was suggested for use in future experiments. Subsequent OCT and histological analyses were completed. The correlation between percent re-epithelialization using OCT and histology was good (0.66; $p < 0.001$). Interobserver correlation was very strong (0.88; $p < 0.001$) and strongly supports the correlation between histology report and OCT.

4.0 ASSESSMENT OF BURN

Re-epithelialization is also a critical part of the burn healing response. Many superficial burns are capable of healing by rapid re-epithelialization. More serious burns however require surgical intervention. Tools such as clinical evaluation, biopsy and histology are available to verify degree and depth of burn; however, these methods are invasive and subjective. Optical methods offer the potential for objective and non-invasive monitoring to improve standard-of-care for burns. Several techniques are available, including thermal imaging, laser doppler imaging (LDI) and NIRS. Monstrey et al. identified these techniques and this section supplements this review (14).

Thermal imaging has shown some potential for imaging burns (15). In a preliminary study, Renkielska et al. studied burns using a porcine skin model to investigate an advanced form of static thermal imaging (STI). Active dynamic IR thermal imaging (ADT) offers a method by which to quantitatively assess the mean values of skin temperature for the burn wound area and the unaffected reference skin area, which has proven challenging to accomplish with STI. ADT assesses thermal tissue properties instead of changes in temperature distribution. This is accomplished by measuring the steady-state temperature distribution of a given surface followed by mild thermal excitation. The resulting thermal transients are captured, yielding a thermal time constant, τ. The investigators were able to build a library of burns that were either less than or greater than 60% of the dermis thickness at the measurement site (dtms). Wounds that were less than 60% dtms were expected to heal within 3 weeks, while wounds greater than this value were not expected to heal. The mean value of the thermal time constant for burns shallower than 60% of the dtms (those healing within 3 weeks) was greater (τ = 12.08 +/- 1.94 s) than for the ‘‘nonhealing’’ wounds (τ = 9.07 +/- 0.68 s). The difference was statistically significant ($p < 0.05$). The future of this research will likely include burn depth assessment and volumetric studies. Monstrey et al. did note that while the technique shows promise, evaporative and ambient heat losses need to be more readily accounted for (14).

LDI has also been assessed as a tool for burn measurements. It works under the principle that laser light directed at moving blood cells will produce a frequency change that is proportional to the amount of perfusion in the tissue. With respect to burn, it is a widely studied imaging modality for burn assessment and has preliminarily shown efficacy in some human studies for accurately detecting burn depth (14). These reports neatly summarize the evolution, strengths and challenges for this technique to assess burn. Early measurements required direct contact with the skin and have now evolved to distance scanning. Monstrey et al. (14) also noted two reports that detailed superior accuracy in terms of predicting both depth and outcome when compared to clinical inspection. In a prospective study of 76 intermediate depth burns, an accuracy of 97% was obtained for LDI in terms of depth prediction (16). This was compared to visual inspection which typically yields accuracies of 60-80% for burn depth. Indeed, the authors measured an accuracy of 70%. Monstrey et al. also cited another study with children. In a study of more than 50 children, Holland et al. showed that clinical examination correctly determined 66% of patients with deep partial or full thickness burns, while LDI correctly determined burn depth in 90% of the patients (17). In addition to high sensitivity, specificity for burn was equally good.

Jaskille et al. (18) recently published a critical review of LDI. While the cited examples above highlight the successes of LDI, this review identifies several critical parameters that prevent LDI from widespread use in the clinic across diverse patient populations. Examples included room temperature, patient positioning and respiratory rate. Ambient temperature was shown to affect sensitivity and specificity of these measurements. Additionally, while room temperature was controlled in several studies, it was noted that wound temperature was not studied and likely plays a role in terms of accurately estimating burn depth since temperature would undoubtedly affect the perfusion rate within the wound. As part of the patient positioning issue, Jaskille et al.

questioned what the correct distance from the wound should be and noted variability from 20 to 70 centimetres. Concerns regarding the use of variable angles of measurement were also raised. Jaskille et al. make a persuasive case for providing a better standardization of measurement conditions. They also make the point that the perfusion rate varies with location and this must be factored into burn depth modelling for LDI.

NIRS is also applicable to burn and appears to be an emerging technique for burn research (14). In a study of 16 patients, Cross et al. (19) used NIRS to assess hemodynamic information from burns. They used a combination of point and camera imaging. Point imaging was accomplished by means of a custom-built multifiber optic bundle. As stated, previously NIRS offers an assessment of hemodynamics upon which a comparison of superficial versus full thickness burns was made. Superficial burns showed increases in oxygen saturation and total hemoglobin when compared to control areas. Full-thickness burns showed decreases in these parameters. However, it should be cautioned that this effort was preliminary, considered a variety of anatomical sites with varying thickness and only superficially controlled for wound healing over time of measurement.

Other methods such as orthogonal polarization spectral imaging (OPSI) (20) are emerging as well. A recent 2010 publication by Goertz et al. detailed a study using OPSI to evaluate 81 tissue burns between 1 and 4 days postburn. The study showed that OPSI was slightly less than par for accurate determination of burn depth when compared to clinical evaluation.

5.0 CONCLUSION

Over the past few decades, optical spectroscopy has made great strides towards translating into the clinic for medical applications. Literature search identified wound healing, burn assessment and neuroimaging as potential uses for these technologies. Size and cost of all the technologies reviewed here are significantly than techniques such as CT and MRI, and require no tracer agents are required as compared to modalities such as PET and CT. For each of the trauma conditions discussed in the article, it is clear that standard methodologies need to be developed before the techniques reach widespread use.

This is in addition to better modelling of optical tissue properties in terms of absorption and scattering. Better modelling of the substructures of the dermis and accounting for variability in thickness, temperature heterogeneities (at the wound site and in the room), and perfusivity at different body sites will undoubtedly standardize optical methods for assessing burn volume regardless of chosen optical modality. There is a similar problem for imaging of brain trauma, in which the optical properties of brain tissue, skull, skin and the dura must be better understood before high resolution imaging of injury can be detected and diagnosed.

It is worth noting that optical spectroscopy has the potential for suitability in other aspects of trauma. For example the early stage detection of infection. One example provided by Naumann et al. demonstrated a bacterial classification system based on bacterial spectra obtained using Fourier-transform infrared spectroscopy (FTIR) (21). As part of this project, a database of Staphylococcus, Streptococcus, Clostridium, Legionella and Escherichia coli spectra was developed. The database contained 139 bacterial reference spectra and could identify unknown species, as tested with clinically isolated cultures. This work was accomplished in vitro, but points to the potential of optical spectroscopy to quickly identify bacterial species.

It is hoped that both innovation in research and standardization of technique will lead to the translation of optical methods into the clinic and perhaps the battlefield.

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