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Optomagnetic Imaging Spectroscopy (OMIS) for in situ detection of bacteria in blood – feasibility study

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Abstract – *Introduction*: Sepsis is one of the leading causes of death in military and civilian hospitals. Rapid identification of involved pathogens is a key step for appropriate diagnosis, treatment and ultimately survival. Current diagnostics tools are either very bulky and not deployment ready, or require a long time to provide results. Given these obstacles, new solutions are urgently needed. Optomagnetic Imaging Spectroscopy (OMIS) is novel technology successfully used for the detection of cancer cells and viruses. OMIS has high sensitivity due to recording the unpaired and paired electrons of sample material. Furthermore, machine learning that uses the algorithms random forest (RF) classifier and artificial neural network (ANN) is integrated into the technology to enhance detection. Here we evaluated the feasibility of OMIS for the detection of bacteria in blood. *Methods*: We used commercially available human blood spiked with a defined concentration multidrug resistant *Staphylococcus aureus* derived from a clinical isolate. Final concentrations of bacteria of 1×10^6, 1×10^5 and 1×10^4 CFU/mL corresponding to High (H), Medium (M) and Low (L) concentrations respectively. A total of 240 samples (60 samples per concentration as well as 60 samples of sterile blood (N)) was imaged, and the data were analyzed using random forest classifier and artificial neural network. Images for the training set and validation sets were separately obtained and used for comparison against true positive values (confirmatory plating on the nutrient agar). *Results*: The average score of classification samples in the correct category (N, L, M, H) one-by-one was 94% for the ANN algorithm, while for the RF algorithm accuracy was 93% (average means that three times different 40 samples (of 240 samples) were chosen, and each prediction test had different sample mixtures). The closeness of the two values of accuracy strongly indicates that the input data (interaction of light with paired and unpaired electrons) and output data (classification N, L, M, H concentration of bacteria) are correlated.

Keywords: Sepsis bloodstream infections, Optomagnetic imaging spectroscopy *in situ* detection, *S. aureus*, Human blood

Introduction

Sepsis is a life-threatening condition due to a dysregulated host response to infections [1]. It is a global problem and risk for patients irrespective of economic status. In a large study that reviewed literature from 1997 to 2015, the authors estimated 31.5 million sepsis and 19.4 million severe sepsis cases occurred, with potentially 5.3 million deaths per annum globally [2]. In the military, past experience shows that infections, including sepsis, pose an enormous threat to injured soldiers [3]. Early application of appropriate treatment which can be successfully achieved with improved detection/identification of bacteria is a key step in the suppression of sepsis mortality [4, 5]. In a large study of 35,000 patients the median time to first antibiotic treatment was 2.1 h "*each hour of delay in administering the appropriate antibiotic lowers survivability by ~ 9%*" [6]. With this in mind, physicians are forced to initiate treatment with a broad spectrum of antibiotics relying on

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experience and clinical judgment. This empirical approach leads to misuse and overuse of antibiotics that may be harmful. The Center for Disease Control (CDC) observed that 20–50% of antibiotics received by patients are unnecessary or inadequate and 80% of patients are not treated with the right antibiotic [7]. In addition to the enormous cost in lives claimed by sepsis, it is the most expensive hospital-treated condition in the United States, representing $20.3 billion in healthcare costs ($55.6 million/day). These costs are primarily driven by the extended hospitalization of patients generally involving on average 15 days in the Intensive Care Units.

Despite advances in medical technology, blood culture (BC) remains a gold standard and the only approved method in clinical practice to detect and identify infectious agents. The guidelines that describe the principles and practices of BC, which identifies/conforms an infectious etiology of disease, have been well established [8]. Several automated blood culture detection systems have been developed that allow for quicker time to detection. However, they still require up to 38 h depending on the species with anaerobic pathogens taking longer times [9]. Development of optical techniques such as infrared, Raman and fluorescence spectroscopy has the potential for a quicker detection of blood-stream infectious agents [10]. However, optical technologies often require expensive, large foot-print instruments with high electrical needs, maintenance and personnel with specialized training and therefore, can be limited for a widespread clinical use. One optical platform that has a potential to overcome these logistical limitations and contribute to the rapid diagnosis of bacteria in blood is optomagnetic imaging spectroscopy (OMIS) due to the small size of the instrument (~1.5 lb), fast detection (less than 4 min), low energy requirements (about 4 W/sample scan, or 80 W/h) and ease of use as it does not require specialized training.

The OMIS-20ML is a prototype instrument that utilizes quantum mechanics and machine learning (ML) to detect, at the nano level, interactions between light (electromagnetic phenomenon) and valence electrons within the sample (covalent bonds, hydrogen bonds, ion-electron interaction, and van der Waals interactions). OMIS is a spectroscopy method that measures the ratio of unpaired and paired electrons of as sample by leveraging the known aspects of light-matter interactions [15]. Light, as an electromagnetic phenomenon, consists of electric and magnetic waves. When a sample is illuminated under a specific angle, the reflected light is polarized. The specific angle at which this occurs is known as Brewster's angle; each material has a unique Brewster's angle value. When using OMIS, light from a diffused light source is reflected by a sample and recorded by the sensor, as indicated in Figure 1. Subsequently, diffuse white light from a second light source placed at the Brewster's angle of the material is reflected by the sample and recorded by the sensor. The reflected polarized light detected by the sensor contains predominantly an electrical component of light-matter interaction. By subtracting the reflected polarized light (electrical properties) from the reflected white diffuse light (electro-magnetic properties), the result provides information about the magnetic properties of matter based on light-matter interaction (Fig. 1) [15]. A pair of digital images is acquired under white diffuse light, and white diffuse light under Brewster's angle will result in three spectra – blue, red and green – for each image. When blue, green or red spectra for the image of the sample taken under Brewster's angle are subtracted from the blue, green or red spectra for the image of the sample taken under diffuse light, the resultant composite spectrum will represent an opto-magnetic spectrum of the sample.

For processing (classification) of samples, machine learning is integrated to use the Artificial Neural Network (ANN) algorithm to create a model that can distinguish between different classes of samples. This differentiation is further confirmed by the Random Forest (RF) algorithm. The limit of detection is directly related to algorithm training and efficiency and the capabilities of the charge-coupled device (CCD). The more data provided to the algorithm, the more efficient the algorithm for detection becomes, and in turn, the detection becomes more sensitive and specific at differentiation of samples.

The measuring repeatability of the OMIS-20ML for the same sample is: 98.8 ± 1.2%, 97.8 ± 2.2% and 96.9 ± 3.1%, for solid state matter, viscoelastic matter (tissues) and liquids, respectively. OMIS-20ML has been successfully used as diagnostic tool for several cancers [11–14] and detection of viruses in plasma [15] with very high accuracy and sensitivity.

Here we present results of the proof-of-principle study using OMIS for the rapid detection of bacteria in blood.

Material and methods

Bacterial strain and growth conditions

Glycerol stocks of each bacterial species used in this project originated from the diversity sets in possession of the Wound Infections Department at Walter Reed Army Institute of Research (WRAIR). Diversity sets consist of clinical isolates collected from the wounded service members. Overnight bacterial cultures were sub-cultured on the day of the experiments in LB broth (37 °C, 250 rpm) and grown to optical density 0.5 (OD_{600} = 0.5). The solution of bacteria with this optical density corresponds to the known number of bacteria which was used for final dilutions prepared by mixing appropriate volume of bacterial suspension with fresh human blood (Human Whole Blood K3EDTA-treated, pooled gender blood was used as control (Lot#BRH1574334) BioIVT, USA) and used for experiments.

Imaging procedure

A total volume of 50 µL of blood/blood spiked with bacteria was used for imaging. Blood was placed on the glass slide and covered with glass cover slips creating a thin layer of blood. Slides were inserted in the slide holder of the OMIS-20ML instrument (Fig. 2). The probe was placed

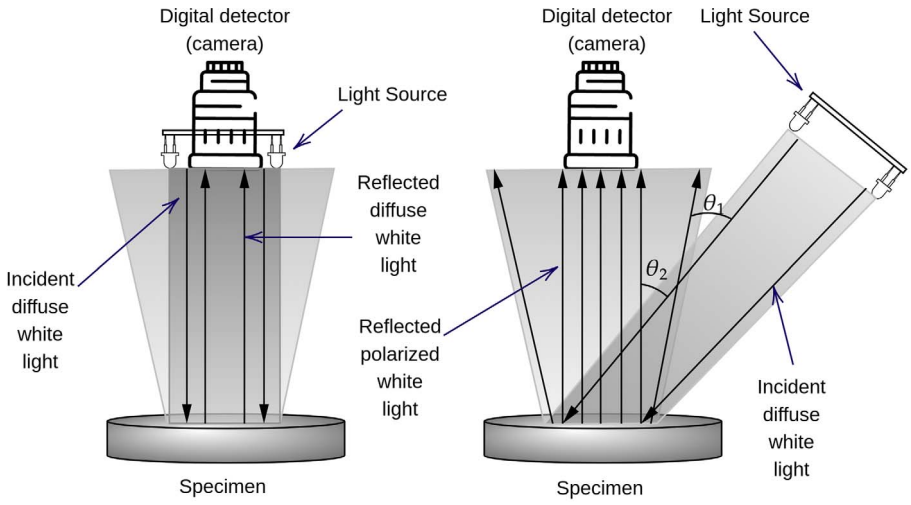

Figure 1. Schematic representation of conventional imaging spectroscopy using diffuse light (left) and special imaging spectroscopy using polarized light (right). The relative positions of light sources for the two imaging spectroscopies are indicated. Reflected diffuse white light arises from the Light source (6 light-emitting diodes arranged in the circle) perpendicular to the sample and reflected polarized light (right) arises from the light source positioned at Brewster's angle (for biological tissues, approximately 530 degrees). The degree of light polarization is 95.4%, while angular diffusion of the light source is ± 1:6 (the difference between the angles θ_1 and θ_2), which through convolution spectra gives Opto-magnetic Imaging Spectroscopy.

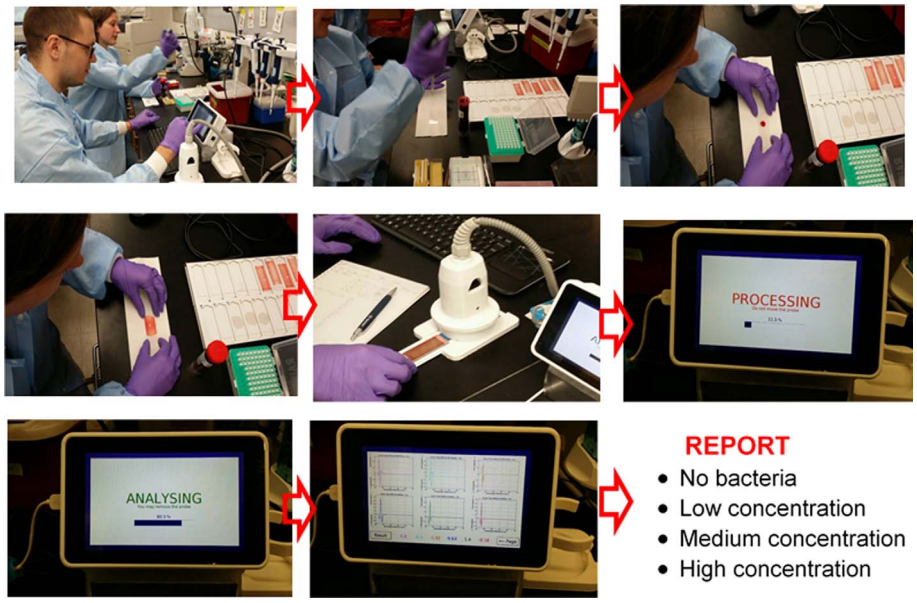

Figure 2. Workflow of the OMIS imaging and data analysis. Step 1 – set up experiment in laboratory; Step 2 – sampling blood; Step 3 – placement of 50 µL of blood on glass slide; Step 4 – cover the blood using glass cover slip; Step 5 – positioning of the slide in the OMIS20-ML slide

over the glass slide and imaged for 90 s. Analysis was performed over a duration of approximately 60 s. Set up (approximately 30 s) and analysis lasted for total of 180 s (Fig. 2).

Experimental design

A total of 240 samples (60 samples per concentration with 60 samples of sterile blood) were imaged and data were analyzed. About 1×10^6, 1×10^5 and 1×10^4 CFU/mL corresponded to High (H), Medium (M) and Low (L) concentrations respectively. In the validation phase, personnel performing the data acquisition and analysis were blinded for group/number of bacteria in the sample.

Data analysis and statistical analysis

We used machine learning to classify samples. Machine learning overcomes some limitations of the conventional statistical methods by making use of a more diverse type

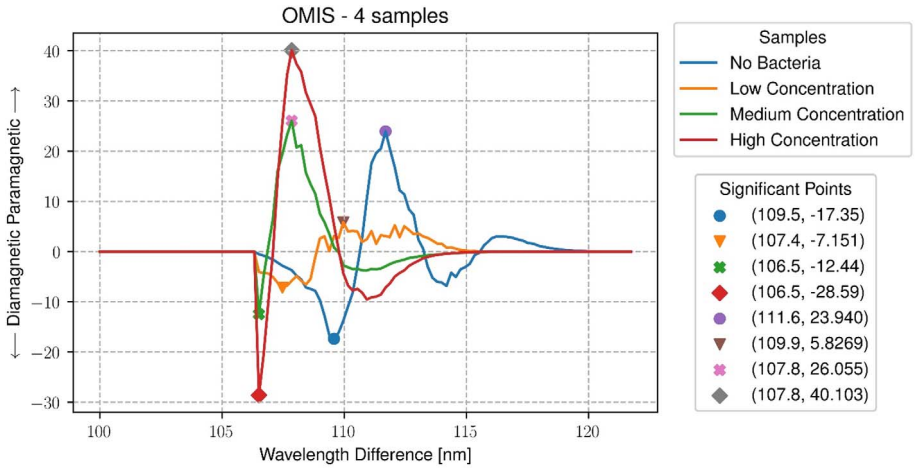

Figure 3. Representative diagram of results for all classes of samples analyzed with significant wavelengths used for differentiation of samples.

of input data, as well as giving us a more generalized mathematical model for classifying data. For machine learning no prior knowledge about the data is needed. The analytical method used to collect the data needs to provide features that the algorithm can use to create a model that can distinguish between different classes. In the case of OMIS, these features are the ratio between unpaired electrons (paramagnetic) and paired electrons (diamagnetic) of the sample.

We used two approaches, Random Forest Classifier (RFC) and ANN to classify data into predetermined categories. The type and architecture of an ANN is based on the task it needs to perform, after which it is conjured by using a class-labelled dataset so that, when it is presented with unknown data of the same type, it can determine to which class it belongs. We used Multilayer Perceptron, a feedforward artificial neural network with four output neurons competing with each other that takes in the entire nonzero portion of the OMIS spectrum. Prior to the model's configuration, the dataset was split into two parts, a set of class-labelled data used to configure the model, and the data used to test the prediction capability of the new model configuration. Next, we performed training of the ANN through an iterative process of configuring the ANN with labelled data, and testing the models accuracy and efficacy on the unknown data (validations), until the desired accuracy was reached.

Results

After signals are analyzed, OMIS-20ML provides a graphical output of the spectra with appropriate categorization of the sample (Fig. 3). It is important to note that the OMIS-20ML analyzes diamagnetic and paramagnetic properties of each sample across the entire spectrum of wavelengths and analyze them. Significant points described in Figure 3 are some of the most obvious differences demonstrated for the user; however, the result is provided based on the entire spectrum.

Using OMIS, we successfully differentiated between sterile versus not sterile blood. In first set of experiments, we tested the ability of OMIS to can detect the presence of bacteria in blood samples and to provide binary, sterile blood versus blood with bacteria irrespective of the number. We achieved 91.3% accuracy in detecting bacteria in blood. We then proceeded to test whether OMIS can classify the samples semi-quantitatively into one of four categories based on the final concentration of bacteria in ml of blood. A 1×10^6, 1×10^5 and 1×10^4 CFU/mL corresponded to High (H), Medium (M) and Low (L) concentration, respectively. A total of 240 samples (60 samples per High, Medium, and Low as well as 60 samples of sterile blood) was imaged, and the data was analyzed. The average score of classification of samples in the correct category (N, L, M, H) one-by-one was 94.16 ± 2.95%. Sensitivity, specificity, positive and negative predictive values have been calculated, and their values for ANN and Random Forest Classifier (RFC) are presented in Table 1. By achieving high accuracy with both ANN and RFC, we proved that differentiating features exist between the samples with various concentrations of bacteria.

Discussion

A rapid detection of the presence of bacteria in the blood, their identification and the ability to quantify them is the key for successful application of appropriate antibiotics, and ultimately the key step for survival of patients with sepsis. In the present study, we provide proof-of-principle data for OMIS to detect the presence of clinical isolate of *Staphylococcus aureus* (*S. aureus*) directly in human blood without sample processing, staining and need for isolation of the pathogen. We were able to achieve 91.3% accuracy in identifying presence of bacteria in blood and the average score of classification samples in the right category (N, L, M, H) one-by-one was 94.16 ± 2.95% for the NN algorithm, while for the RF algorithm accuracy was 93.33 ± 4.10%.

Table 1. Results of the OMIS-20ML evaluation based on 3 independent validation experiments. Results are presented as mean ± standard deviation for ANN and RFC. Since those two values of accuracy are very close our results strongly indicate that input data (interaction of light with paired and unpaired electrons) and output data (classification into sterile versus non-sterile blood (irrespective of the concentration of bacteria) is valid.

	ANN		RFC	
	Mean	SD	Mean	SD
Sensitivity	0.9663	0.0005	0.9222	0.0629
Specificity	0.9333	0.0943	1.0000	0
Positive predictive value	0.9785	0.0304	1.0000	0
Negative predictive value	0.9024	0.0095	0.8253	0.1122
Accuracy	0.9581	0.02	0.9415	0.05

The "gold standard" clinical microbiological techniques such as plating, various stainings (i.e. Gram staining), and various biochemical tests, in combination with modern techniques such as whole genome sequencing, are very robust and can provide a myriad of information ranging from identification of specific strains, identification of antibiotic resistance genes, and even whole genome sequences. However, these procedures are lengthy, ranging from several hours to several of days, to yield clinically applicable results. The use of matrix assisted laser desorption ionization-time of flight mass spectrometry (MALDI-TOF), rapid diagnostic tests, and whole genome sequencing, which are increasingly implemented in routine care, have yet to lead to clinically impactful results [16, 17]. One of the reasons for this is that despite the rapid diagnostic protocols in pathogen identification takes close to 48 h post-sample collection. Discussion of these techniques and their clinical impact have been presented elsewhere and are beyond the scope of this publication (please refer to Lamy et al., 2020 [18]). Interestingly, the use of artificial intelligence has resulted in an alternative approach for the detection of bacteria in blood. Instead of the identification of bacteria, these approaches are evaluating the host's response to infectious agents and by mining host's "omics" data can identify causative agents (i.e. bacteria vs. virus vs. fungi) [19–21]. Development of artificial intelligence and machine learning have allowed the emergence of the several spectroscopy-based approaches for direct detection of pathogens *in situ*. Infrared and Raman spectroscopy are currently being developed for this purpose [22–26]. While promising, both of these approaches are yet to be fully integrated in routine care, and face some of the same challenges discussed above for the military applicability.

This is a proof-of-principle study performed to test feasibility of using OMIS to detect pathogens in blood; several important questions remain unanswered. First, we evaluated OMIS for only on one bacterial species. Therefore, it is unknown at this time how effectively OMIS differentiates between different species of Gram-positive and Gram-negative bacteria or how OMIS performs in the context of polymicrobial infections. We are currently planning studies that will address these questions with a focus on the ESKAPEE pathogens (*Enterococcus faecium*, *S. aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, *Enterobacter* species, and *Escherichia coli*) that are emerging as medical emergency due to their increasing antibiotic resistance using our large collection of multi-drug resistant (MDR) pathogens. Secondly, we have not determined the lower limit of detection, which is currently being investigated. Presently, 5–1000 CFU/mL of blood is the recommended cutoff for sepsis classification. We believe that the enhanced sensitivity of OMIS due to detection of unpaired and paired electrons of sample by light waves can be applied to identify bacterial samples in clinically relevant range. Additionally, unlike some other methods, OMIS does not damage the biological sample, and we plan to capitalize on this feature to determine the lower detection limit by plating the samples following imaging to generate a true positive control for construction of the receiver operating characteristic (ROC) curve. Finally, one of the major benefits of using the artificial intelligence (AI) is that with enough training samples, software can be trained to "become expert" in any given categorization and CCD camera resolution restriction will derive limits of detection. The use of AI for mining the OMIS spectra, particularly ANN and RFC, which improves accuracy as the database of the analyzed spectra increases suggest that this is an achievable goal. There is a major limitation even for advanced optical technologies to detect directly in the blood when the concentration of bacteria is very low (5–1000 cells/mL of blood). For comparison, there are around 5 billion erythrocytes, 135–317 million platelets and 3–10 million white blood cells per ml of human adult blood. Sample processing to deplete blood cells (i.e. depletion of the red blood cell which have paramagnetic properties) may increase OMIS sensitivity and decrease the lower detection limit threshold. Moreover, combining OMIS with blood culturing to increase number of bacteria to a detectable level may be necessary. Similar approaches have been reportedly successful with other detection techniques. For example, the use of selective blood cell lysis, concentration of bacteria by centrifugation, and culturing microorganisms in broth resulted in increased sensitivity using surface-enhanced Raman spectroscopy (SERS) [22]. In this study, 17 blood clinical isolates were detected within 7 h [22]. At 2 CFU/mL all tested microorganisms had mean recoveries of 55%, but this increased to 72% when CFU was increased to 11 per mL. The priority of our ongoing efforts is to determine the lower limit of detection of bacteria in human blood, and based on these results, we may improve the method.

Conclusion

Our proof-of-concept study demonstrated that the OMIS can detect small number of bacteria in blood. The intended use of OMIS is to provide a rapid diagnostic tool

for triage of patients with suspected bacteremia/sepsis and support antimicrobial stewardship early in the course of treatment, while providers are waiting for results from clinical microbiology laboratories.

Nomenclature of abbreviations

AI	Artificial intelligence
ANN	Artificial neural network
BC	Blood culture
CCD	Charged-coupled device
CDC	Center for Disease Control
CFU/mL	Colony Forming Units per Milliliter
ESKAPEE	acronym For *Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa, Enterobacter* spp., and *Escherichia coli*, comprising high to critical drug-resistant, World Health Organization Critical Priority I and II pathogens
H	High
L	Low
M	Medium
MALDI-TOF-MS	Matrix Assisted Laser Desorption Ionization – Time of Flight Mass Spectrometry
ML	Machine learning
OMIS	Optomagnetic imaging spectroscopy
RFC	Random forest classifier
WRAIR	Walter Reed Army Institute of Research

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