Form 1

2019 Report Form for Collaboration with Research Center for Biomedical Engineering

Year/month/date	
Number	P–2068

Date /Month/Year
date: 25/03/2020

To Chairman, Board of Directors, Research Center for Biomedical Engineering

Applicant

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Report Form for Collaboration Research

Research Theme	（和） 迅速な非接触外傷評価のための臨床用カメラの設計 （English） Clinical Imager Design for Rapid, Non-contact Wound Assessment
Research Area	1. Biomaterials **2. Bioengineering** 3. Functional molecules 4. Chemistry/Electrical Engineering/Mechanical Engineering/Materials Science
Research Period	From: Date/month/Year 01/ 06/2019 To: Date/month/Year 31/ 03/2020

Applicant Organization			
Name	Department	Title	Role
Rolf B Saager	Biomedical Engineering, Linkoping Univ. Sweden	Asst. Professor	Project mgmt. Spectral analysis
Nandan K Das	Biomedical Engineering, Linkoping Univ. Sweden	Post-Doctoral Scholar	Integration, System testing
Collaboration Partners in the Research Center	Keiichiro Kagawa (Associate Professor, Research Institute of Electronics, Shizuoka University)		

Research Results (Including Purpose, Results, Figures, etc.)

Purpose: The purpose of this project in the 1-st year is the fabrication of a spectrally optimized compact Spatial Frequency Domain Imaging (SFDI) device that will enable the rapid, wide-field quantification of multiple physiologic parameters in depth, critical to addressing unmet needs in burn severity assessment and wound healing. A compact compound eye camera developed at Shizuoka University is utilized as a key device. The primary method of determining burn severity is subjective visual assessment. Its accuracy, even by experts in the field, is only 60–80%. SFDI has the potential to non-invasively segment tissue, based on both functional and structural tissue parameters specific to burn physiology; thereby establish a noncontact method for quantifying clinical burn depth. Spatial Frequency Domain Spectroscopy (SFDS), and adaptation of SFDI, was invented and developed at UCI by the PI to enable high spectral resolution, depth-specific, quantitative tissue spectroscopy. The most significant limitation of our current SFDS system is that it can only measure tissue at a single location at a time. Whereas this “point-spectroscopy” SFDS system has demonstrated depth sensitive quantification of in vivo optical properties, both burns and their subsequent wound healing will also present differential responses in lateral spatial extent.

Method: Figure 1a shows the two primary optical components of the proposed compact burn assessment device: a projector and a multi-spectral compound eye camera with 9 bandpass filters that will enable simultaneous spectral imaging over the same field of view. An optimized multi-spectral compound eye camera (Shizuoka University) will detect remitted light. As this compound eye design affords us the opportunity to customize the spectral bands and their widths through the selection of either commercially available interference filters or through custom bandpass filter designs, the key element for success is the method by which this selection is made. Figure 1b shows the physical layout of this compact device, with the compound eye camera positioned above the compact micro-projector unit. The hand holding this system gives a reference to the compact size of this integrated device.

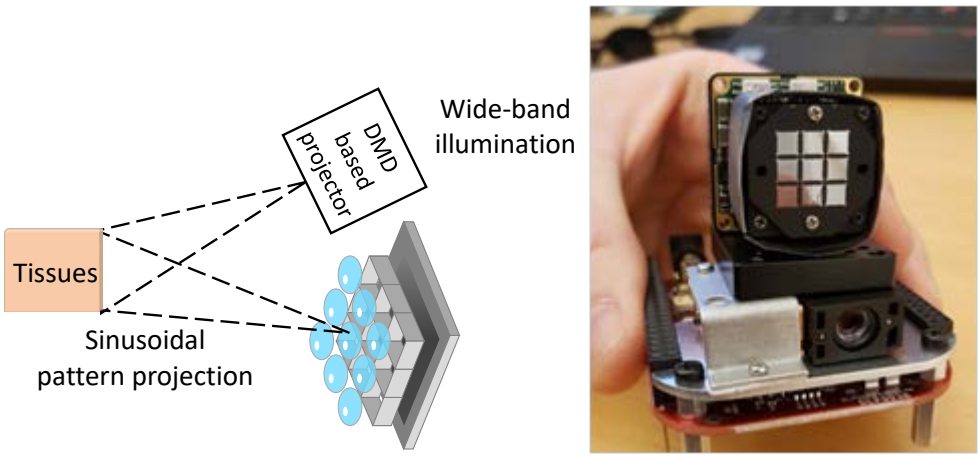

Fig. 1. Concept of compact SFDI device.

Results: As we have data on burn wounds in a preclinical study of 30 animals, collected by SFDS, we have the basis from which to determine the 9 most significant spectral bands related to burn wound assessment and design the senor around these application specific needs. In the design of compound eye camera prototype, commercially available filters were used, which limited the overall performance. However, this scheme was cost-efficient. Figure 2 shows a prototype multi-spectral camera (without filters in the photo) and filter assignment. A global-shutter CMOS image sensor with enhanced near-infrared (NIR) light sensitivity was utilized to capture because NIR wavelengths provide deep tissue information. Figure 3 shows the measured relative spectral response of the prototype camera.

710nm	850nm	970nm
560nm	590nm	620nm
470nm	490nm	520nm

(a) (b)

Fig. 2. (a) Multi-spectral compound eye camera (without filters) and (b) wavelength assignment.

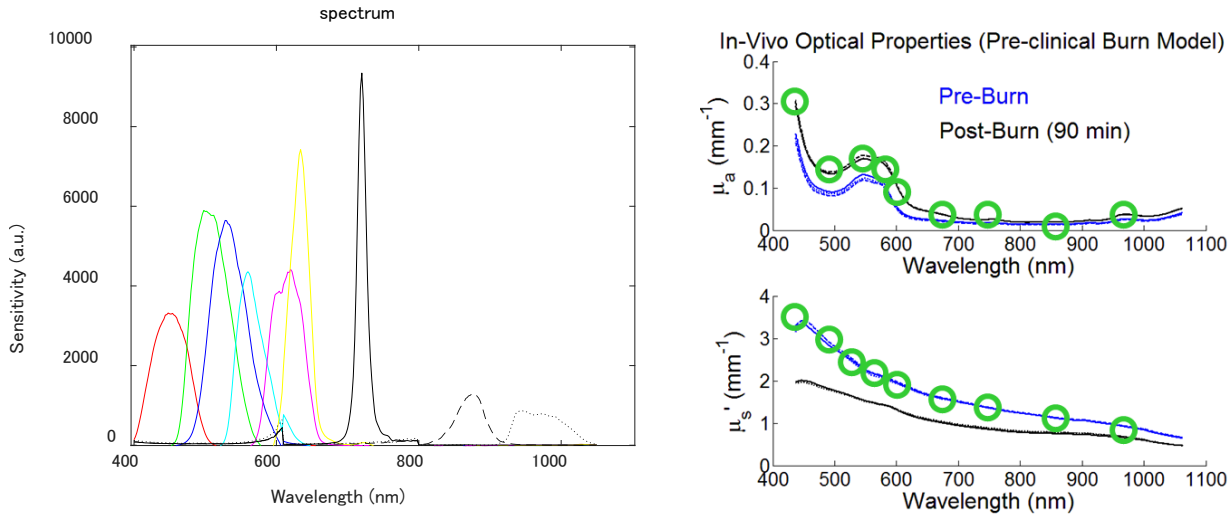

Fig. 3. Measured total spectral response of all 9 channels of the camera and the emulated spectral measurements from burn tissue response (derived from SFDS measurements in the previous preclinical study)

System Integration: Though the micro-projector is a commercially available component, it is not fully suited for this application and requires some modification. In terms of the hardware, this projector only uses Red, Green and Blue LEDs as its light source, however for this application; we require illumination that spans both visible and near infrared regimes. This modification was simply achieved by replacing the LEDs with a Quartz-Tungsten-Halogen bulb. This bulb is battery powered, giving superior intensity stability and this modification also allows acquisition speeds to be up to 3x faster as the LED approach would illuminate the tissue serially.

As this is a commercial mirco-projector, we do not have direct access to the onboard DMD. Here, the video projections do not display images linearly across the dynamic range of the DMD. Monitors and projectors are tailored to the nonlinear response of human perception and hence convolve any input image with a gamma function, before projecting it. In this case, if a purely sinusoidal intensity image were to be used as an input to the projector, the intensity distribution projected on to tissue would no longer be sinusoidal. We have characterized the intensity throughput function (gamma correction) for this specific projector by measuring the intensity of a series of grayscale planar images reflected from a known reflectance standard (SRT-99-100, Labsphere, North Sutton NH) and used this to precondition every spatial frequency image used, ensuring that the resulting intensity pattern projected onto tissue will represent a pure sinusoid.

The current systems development and integration is run off of a laptop as both camera and

projector are USB compatible. It can also be run off of a micro-board computer, such as a Beagle Bone Black or Raspberry PI. By making this a self-contained unit, it would greatly enhance its clinical utility by not requiring the unit to be tethered to a separate computer. This effort to make the integrated device fully handheld and cable-free is in parallel development.

Burn Wound Tissue Simulating Phantom advancements for use in system testing and evaluation: Based on our initial investigations of partial thickness burns, we have been developing a suite of tissue simulating phantoms that mimic burns and wound healing. While these phantoms can mimic some optical properties encountered in burn wounds, there remain a number of limitations in their fabrication methods and materials. These hinder full emulation across both visible and near infrared spectral regimes. Novel fabrication methods have now been developed to address these issues, establishing a new phantom paradigm that can replicate burn wound severity in both visible and near infrared regimes. These issues specifically address: 1) incorporation of stabilized hemoglobin in hydrophobic media (PDMS) and 2) characterization of several scattering agents that can replicate sub- and extra-cellular changes both in effected and underlying burn tissue. This work is currently in preparation for publication.

List of Publications Related to the Collaboration Research

None

List of Presentations (Conference, Meeting, etc)

1. Keiichiro Kagawa, Izumi Nishidate, Rolf Saager, Norimichi Tsumura, Jun Tanida, "Measurement of absorption and scattering spectra with TOMBO-based multi-band spatial frequency domain imaging: comparison with inverse Monte-Carlo simulation," in Proc. Optics & Photonics Japan 2019, 2pF1 (Osaka University, Dec. 2-5, 2019).

List of Awards

Registration of research-theme continuation for next year Prior consent from the collaboration partner in the Research Center is necessary.	**Yes**	No

Research plan for the next year (from April 1, 2020 to March 31, 2021), if the collaboration research is continued.

Next year, we will quantify key biomarkers for rapid burn wound assessment and tissue response/recovery, such as: *1)* ***burn depth***, as well as, depth-specific *2)* ***structural tissue damage***, *3)* ***hemoglobin (tissue viability)*** *and 4)* ***water (edema, inflammation)*** without perturbing tissue.

Validation using layered tissue-simulating media: Based on our initial investigations of partial thickness burns, we have developed a suite of tissue simulating phantoms that mimic the differential sources of optical contrast, in depth, observed in burns and wound healing. These are multi-layer phantoms where we can control the concentrations of hemoglobin and water absorption surrogates, as well as scattering spectra that

mimic structural changes in burns (e.g. collagen denaturation) and wound healing (tissue remodeling). We have reported several recent developments and refinements in our methods to fabricate complex phantoms that can replicate both scattering changes as well as functional changes observed from in vivo measurements[15-18]. These new and advanced phantoms will provide better emulation of physiologic tissue properties (in terms of both spectral response and tissue structure) and a quantitative, traceable proxy that will validate the performance and accuracy of proposed SFDS instrument in the context of graded burn severities and wound healing, prior to its application in any preclinical study.

Outcomes: This step will establish the imager's ability to determine burn depth and depth-specific physiology *a priori*, ensuring future investigational deployment of this device (beyond the scope of this application) will result in compelling preliminary data results while only utilizing a minimal *in vivo* population size.

	Quarter #1	Quarter #2	Quarter #3	Quarter #4
Aim: Validation using tissue simulating phantoms a) Phantom fabrication b) Dynamic (spectral) range testing c) Sensitivity to differentiation of graded burns