Toward Development of a Portable System for 3D Fluorescence Lymphography

Alexander W. Dixon, *Member, IEEE*, Samuel P. Richardson, Hiroo Suami, Thiranja P. Babarenda Gamage, Poul M.F. Nielsen, *Member, IEEE*, and Hayley M. Reynolds

***Abstract*— Lymphoedema is a debilitating disease that results in chronic swelling of a body region due to a dysfunctional lymphatic system. Since a cure is yet to be identified for this disease, management is currently the best option for preventing disease progression and improving patient outcomes. Fluorescence lymphography is a popular approach for mapping the lymphatic vessels to provide information about the underlying lymphatic dysfunction. However, current clinical fluorescence lymphography tools do not enable the creation of comprehensive 3D maps of lymphatics throughout affected limbs. This work presents the development toward multi-camera 3D reconstruction with fluorescence imaging to overcome the current limitations in clinical tools. Pilot studies have been performed that identify suitable instrumentation for this multi-camera approach and techniques for creating a 3D fluorescence lymphography device are discussed.**

***Clinical Relevance*— This paper presents development toward new low-cost and portable clinical tools for lymphoedema diagnosis and to facilitate personalised treatment and self-management of this disease.**

I. Introduction

Lymphoedema is debilitating chronic swelling in a region of the body that develops when lymph fluid is unable to drain properly through the lymphatic system [1]. It can be a congenital disease with no underlying cause (primary lymphoedema) or a result of damage to the lymphatics (secondary lymphoedema) often from cancer treatment such as lymph node dissection surgery or radiation therapy. Studies have estimated that secondary lymphoedema will occur in 20% of patients following treatment for breast, genitourinary, gynaecological, and melanoma cancers and in 5% to 8% of patients following a sentinel lymph node biopsy [2]. Since medical research has yet to identify a cure, effective diagnosis, and management in early stages of the disease is the current option for preventing disease progression and improving patient outcomes.

The most common metric for disease assessment and monitoring in patients with arm or leg lymphoedema is limb volume. Limb volume is typically measured manually by tape but can also be measured with perometers. However, these are expensive and patients with leg lymphoedema can struggle to separate their legs to provide an accurate measurement. Such limitations have motivated research into portable 3D imaging devices using depth cameras for estimating limb volume [3]–[5]. While such devices provide useful information for assessing limb volume and shorten procedure times, they do not provide any information about the underlying lymphatic dysfunction.

Real-time fluorescent imaging, specifically indocyanine green (ICG) fluorescence lymphography, is a popular approach to map the lymphatic vessels [6], [7]. It operates in the near infrared (NIR) spectrum, where tissues are much more translucent than in visual wavelengths. During lymphography for lymphoedema, ICG dye is injected into the skin and a camera sensitive to NIR is used to map the movement of dye through lymphatic vessels up to a 20 mm depth from the skin surface. This enables dynamic visualisation of patent lymphatic vessels, areas of dermal backflow (where lymph congestion causes refluxes of lymph to the skin) and altered drainage pathways [8]. Disease severity is assessed by MD Anderson Cancer Centre (MDACC) ICG staging [9], [10] and results are used to personalise treatment and give important visual feedback to patients so they can understand and learn how to self-manage their condition.

Whilst fluorescence lymphography provides dynamic lymphatic mapping that is highly sensitive and reproducible, devices are expensive and there are technical and practical challenges which limit its widespread use as a standard diagnostic tool. For example, current devices only obtain images in 2D for a small field of view (e.g. 200 mm × 200 mm with PDE, Hamamatsu K.K. Japan). These limitations have forced clinicians to manually stitch fluorescence images together for clinical reporting and manually mark lymphatic vessels and areas of dermal backflow directly onto patients' limbs during imaging [8]. Therefore, current fluorescence imaging can be challenging and clinical reporting time consuming.

A possible approach to overcoming such limitations is to use multi-camera imaging systems with suitable illumination and spectral filtering for fluorescence imaging. This approach could provide 3D mapping of the lymphatic vessels as well a measure of limb volume. Stereo imaging systems can be made low-cost and portable for clinical use. In this paper, we present the development of a low-cost portable device for mapping lymphatics in human limbs, and preliminary results from pilot studies to demonstrate efficacy of this technology. This system will enable the development of clinical tools for lymphoedema diagnosis to facilitate personalised treatment and self-management.

A. W. Dixon*, S. P. Richardson, T. P. Babarenda Gamage, P. M. F. Nielsen, and H. M. Reynolds are with the Auckland Bioengineering Institute, University of Auckland, Auckland 1010, New Zealand (*corresponding author e-mail: alex.dixon@auckland.ac.nz).

P. M. F. Nielsen is also with the Department of Engineering Science, University of Auckland, Auckland 1010, New Zealand.

H. Suami is with Australian Lymphatic Education, Research and Treatment (ALERT) and Macquarie University, Sydney, Australia.

II. ICG Fluorescence Lymphography

Experiments were performed to test suitable illumination and spectral filtering for ICG lymphography in limbs. Participants with upper limb or lower limb lymphoedema were recruited and imaged following a standard clinical ICG lymphography imaging examination at the Macquarie Health ALERT (Australian Lymphoedema, Education, Research and Treatment) Clinic. All participants provided their written informed consent, and the study protocols were approved by the Macquarie University Human Research Ethics Committee (Reference #520221214841722). The protocol for a standard ICG examination has been described in detail previously for both upper and lower limb lymphoedema [8], [11]. Briefly, the protocol involved four injections of ICG dye administered into each limb. In the upper limb, ICG was injected into the dorsal hand just proximal to the first and fourth web spaces, radial aspect of the anterior distal wrist, and ulnar aspect of the anterior distal wrist. Manual lymphatic drainage massage was undertaken by a lymphoedema therapist during the ICG lymphography imaging to facilitate ICG transit via the lymphatics.

Following standard ICG lymphography, participants were imaged with a custom NIR ICG lymphography imaging instrument. This instrument consisted of a 20-megapixel monochrome camera (FLIR, BFS-U3-200S6M-C) and lens with 12 mm focal length (computar, V1226-MPZ). A long-pass filter with cut-on wavelength of 830 nm (Edmund Optics, 66106) was mounted to the front of the lens. Excitation illumination of the injected ICG was provided by two custom high-power LED lighting modules of 734 nm peak wavelength (Osram, LZ1-00R302). Scattered light from the excitation illumination was absorbed by the long-pass filter, whilst fluorescence of the ICG was passed and detected on the camera sensor.

Fig. 1 shows an example ICG fluorescence image acquired with the custom setup of a patient with MDACC Stage 2 lymphoedema in the upper limb. These experiments indicated that the illumination wavelength and power, long-pass filter, and camera chosen for our custom NIR ICG imaging device was suitable for visualising lymphatics in the whole upper limb.

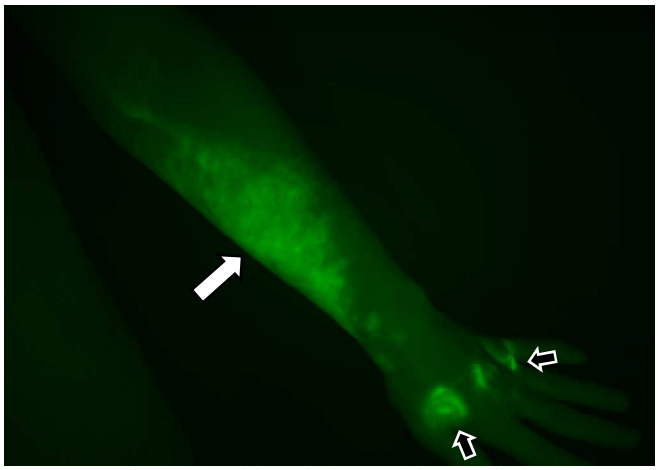

Figure 1. ICG fluorescence false-color image of the upper limb in patient with MDACC Stage 2 lymphoedema. ICG injection sites (black arrows) and a region of dermal backflow (white arrow) is visible in the posterior forearm.

III. 3D Imaging

Experiments were performed to test suitable illumination and multi-camera configuration for 3D reconstruction of the upper limb. Our custom 3D imaging system consisted of two 20-megapixel monochrome cameras (FLIR, BFS-U3-200S6M-C) and lenses with 12 mm focal length (computar, V1226-MPZ). The cameras were mounted with a baseline (spacing) of 60 mm with sensors aligned in the same plane. The cameras were controlled using custom software written in LabVIEW (National Instruments, 2020). The two cameras were calibrated using the stereo camera calibration toolbox in MATLAB (MathWorks, R2021b) with an A3-sized checkerboard calibration target bonded to an acrylic board. The focus and iris controls of the camera lenses were fixed following calibration for all subsequent experiments.

3D reconstruction measurements were performed on a healthy participant in a dark room with no ambient light. The participant held their upper limb at an angle of 30 deg with anterior surface facing towards the cameras. The upper limb was illuminated with three different wavelengths using custom high-power LED lighting modules of 528 nm, 734 nm, and 850 nm peak wavelength (Osram, LZ1-00G102, LZ1-00R302, and LZ1-00R602, respectively). During each illumination wavelength, images were captured from both cameras.

Fig. 2 shows the images captured from one of the cameras for each of the illumination wavelengths. The visible wavelength illumination (526 nm) provided rich texture on the skin whereas the NIR wavelength illuminations (734 nm and 850 nm) gave relatively featureless texture, particularly on the upper arm. This is likely due to reduced melanin absorption at longer wavelengths in the NIR window.

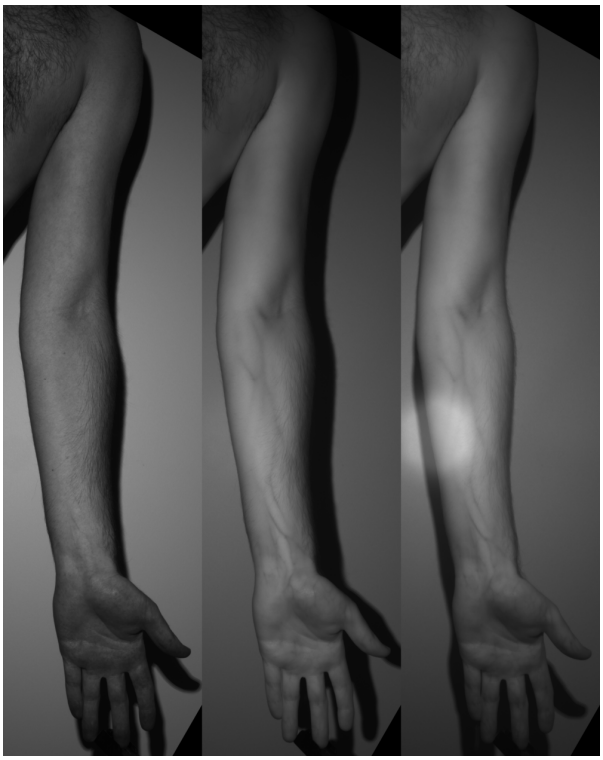

Figure 2. Images of healthy upper limb from one of the two cameras in the system with illumination wavelengths of 526 nm, 734 nm, and 850 nm (left to right) demonstrating variation of recorded skin texture.

3D reconstruction was performed for each image pair using the stereo camera calibration. This process consisted of rectification, disparity estimation using semi-global matching (uniqueness threshold: 20), and scene reconstruction. Estimated depth maps from 3D reconstruction are shown in Fig. 3 for each of the illumination wavelengths.

Reconstruction performed well for the visible wavelength illumination (526 nm) with high completion of the whole upper limb. Reconstruction generally performed poorly for the NIR wavelength illuminations (734 nm and 850 nm). There was partial reconstruction of the forearm and hand with NIR illuminations, however this is likely to be from the texture provided by the hair and blood vessels in this region. As patients will have differing amounts of hair on their limbs, this is an unreliable source of texture for 3D reconstruction and use in clinical practice.

The 3D reconstruction of the upper limb for the 526 nm illumination is shown in Fig. 4 as a dense point cloud. Intensity values from the reference (left) camera images are mapped onto the point cloud color.

IV. Discussion

Results indicated that uniform NIR illumination does not provide sufficient texture on the skin for camera-based 3D reconstruction using standard computer vision approaches (OpenCV), whereas visible illumination wavelengths are more suitable. Considering visible illumination is a more reliable source of texture for 3D reconstruction, designing a camera-based 3D lymphography system that uses fixed wavelength filters for imaging ICG NIR fluorescence is technically challenging.

An approach could be to use non-uniform NIR illumination, in the pass band of the ICG filters, to project texture or structured light to assist with 3D reconstruction. Such an approach is taken in systems using commercial depth cameras [12]. However, as the NIR illumination would likely interfere with the ICG fluorescence signal, such an approach may require the acquisition of images at multiple time steps where the active illumination is switched on and off sequentially. A snapshot 3D imaging system is more desirable as it would enable recording of dynamic scenes and better handle any patient movement during the imaging procedure.

An alternative approach to enable snapshot 3D ICG imaging may be to use additional cameras, where two cameras capture visible light images for 3D reconstruction simultaneously, with at least one additional camera for capturing ICG fluorescence images.

V. Conclusion

The results presented in this paper will inform the development toward a new 3D fluorescence lymphography imaging system. This system will enable the creation of a comprehensive 3D map of the lymphatics in the whole affected limb, from which the patent lymphatic vessels can be demarcated, and regions of dermal backflow can be quantified. Our goal is to use this system to facilitate more personalised lymphoedema treatment and self-management.

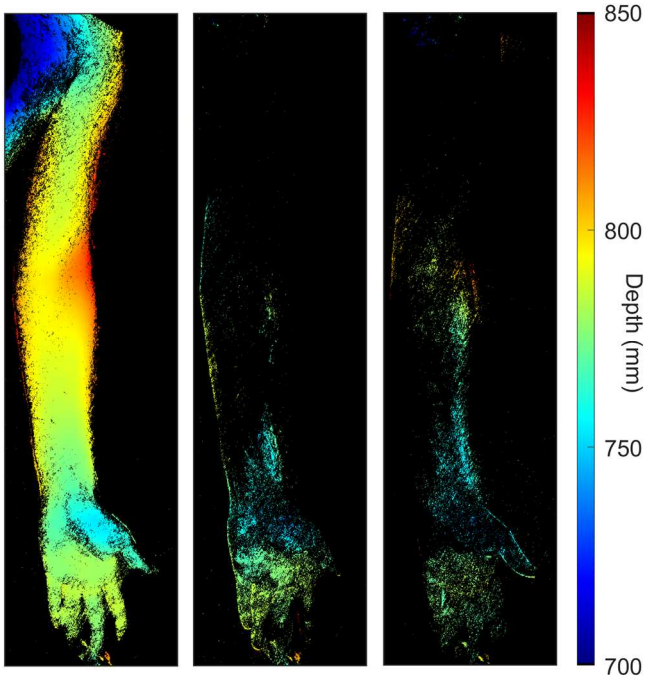

Figure 3. Estimated depth from 3D reconstruction of the upper limb for illumination wavelengths of 526 nm, 734 nm, and 850 nm (left to right). Visible wavelength illumination (526 nm) resulted in a more complete reconstruction.

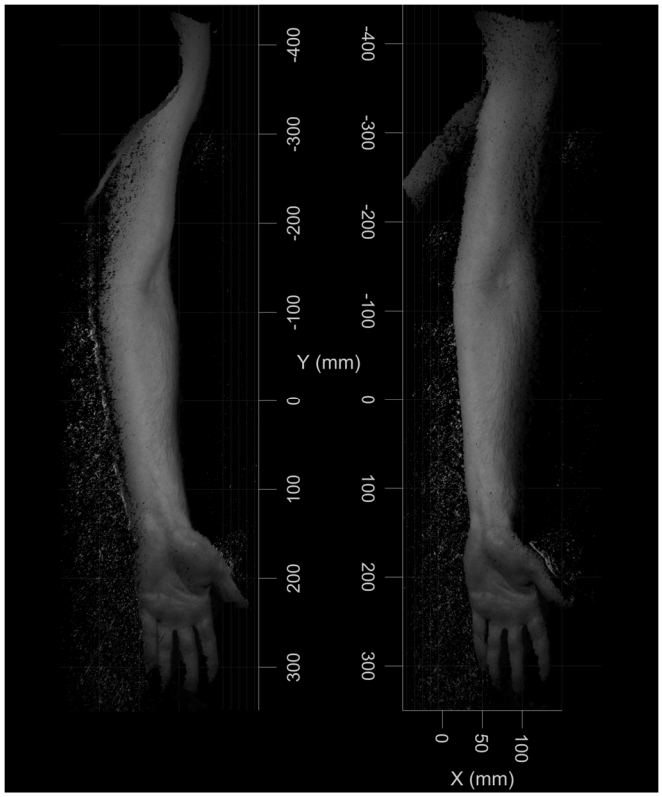

Figure 4. 3D model of the upper limb with visible light (526 nm) illumination from two different viewpoints.

ACKNOWLEDGMENT

The authors would like to acknowledge Katrina Gaitatzis, Dr Louise Koelmeyer, and Dr Helen Mackie at ALERT for their contributions to the ICG lymphography clinical study. Additionally, Llewellyn Sims Johns for contribution to design and manufacturing of the lighting modules used in this work.

This study has been supported by a Faculty Research and Development Fund at the University of Auckland and the Ministry of Business, Innovation and Employment Te Titoki Mataora MedTech Research Translator Concept Seeding and 12 Labours funds.

REFERENCES

[1] "The diagnosis and treatment of peripheral lymphedema: 2020 Consensus Document of the International Society of Lymphology.," *Lymphology*, vol. 53, no. 1, pp. 3–19, 2020.

[2] S. A. McLaughlin, C. L. Brunelle, and A. Taghian, "Breast Cancer–Related Lymphedema: Risk Factors, Screening, Management, and the Impact of Locoregional Treatment," *Journal of Clinical Oncology*, vol. 38, no. 20, pp. 2341–2350, 2020, doi: 10.1200/JCO.19.02896.

[3] K. Karakashian, L. Shaban, C. Pike, and R. van Loon, "Investigation of Shape with Patients Suffering from Unilateral Lymphoedema," *Ann Biomed Eng*, vol. 46, no. 1, pp. 108–121, 2018, doi: 10.1007/s10439-017-1929-y.

[4] I. M. Lu and J. Brandon Dixon, "Assessment of Upper Extremity Swelling among Breast Cancer Survivors with a Commercial Infrared Sensor," *Lymphat Res Biol*, vol. 17, no. 4, pp. 424–433, 2019, doi: 10.1089/lrb.2018.0010.

[5] I. M. Lu, M. J. Weiler, N. D. Frank, J. Jordi, and J. Brandon Dixon, "Monitoring Leg Lymphedema over the Course of Therapy Using an Infrared System," *Lymphat Res Biol*, vol. 18, no. 4, pp. 333–339, 2020, doi: 10.1089/lrb.2019.0036.

[6] N. Unno *et al.*, "Preliminary experience with a novel fluorescence lymphography using indocyanine green in patients with secondary lymphedema," *J Vasc Surg*, vol. 45, no. 5, pp. 1016–1021, 2007, doi: 10.1016/j.jvs.2007.01.023.

[7] T. F. O'Donnell, J. C. Rasmussen, and E. M. Sevick-Muraca, "New diagnostic modalities in the evaluation of lymphedema," *J Vasc Surg Venous Lymphat Disord*, vol. 5, no. 2, pp. 261–273, 2017, doi: 10.1016/j.jvsv.2016.10.083.

[8] H. Suami, A. Heydon-White, H. Mackie, S. Czerniec, L. Koelmeyer, and J. Boyages, "A new indocyanine green fluorescence lymphography protocol for identification of the lymphatic drainage pathway for patients with breast cancer-related lymphoedema," *BMC Cancer*, vol. 19, no. 1, pp. 1–7, 2019, doi: 10.1186/s12885-019-6192-1.

[9] D. W. Chang, H. Suami, and R. Skoracki, "A prospective analysis of 100 consecutive lymphovenous bypass cases for treatment of extremity lymphedema," *Plast Reconstr Surg*, vol. 132, no. 5, pp. 1305–1314, 2013, doi: 10.1097/PRS.0b013e3182a4d626.

[10] A. T. Nguyen, H. Suami, M. M. Hanasono, V. A. Womack, F. C. Wong, and E. I. Chang, "Long-term outcomes of the minimally invasive free vascularized omental lymphatic flap for the treatment of lymphedema," *J Surg Oncol*, vol. 115, no. 1, pp. 84–89, 2017, doi: 10.1002/jso.24379.

[11] H. Suami *et al.*, "A new indocyanine green fluorescence lymphography protocol for diagnostic assessment of lower limb lymphoedema," *Journal of Plastic, Reconstructive & Aesthetic Surgery*, vol. 75, no. 11, pp. 3946–3955, Nov. 2022, doi: 10.1016/j.bjps.2022.08.017.

[12] J. C. Rasmussen, M. B. Aldrich, E. M. Sevick-Muraca, C. Gutiérrez, R. J. Karni, and S. F. Shaitelman, "Towards 3D Quantification of Dermal Lymphatic Backflow as an Indicator of Lymphatic Disease," in *Biophotonics Congress: Biomedical Optics 2022 (Translational, Microscopy, OCT, OTS, BRAIN)*, 2022. doi: 10.1364/TRANSLATIONAL.2022.JTu3A.40.