Report of MIT Laboratory Tour

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Overview

This report describes MIT laboratory tour on Mar. 25-29, 2015. We visited three laboratories in this tour, laboratories of Prof. So, Prof. Jamison and Prof. Jensen. Among student participants, only I participated in laboratory tour of Prof. So. Therefore I focus on describing this laboratory tour.

About Laboratory

On Mar. 26, we visited Laser Biomedical Research Center in Massachusetts Institute of Technology. Laser Biomedical Research Center is managed by Dr. So as a principal investigator (PI) and Dr. Bawendi, and Dr. Dasari as cooperative PIs. Dr. So is a well-known researcher in fluorescence microscopy for medical applications [1]. Dr. Bawendi has studied nanocrystal sensors for quantum dots bio-imaging [2]. Dr. Dasari has investigated spectroscopic imaging and tomography using Raman and phase microscopy [3]. The laboratory aim to obtain basic scientific understanding and new techniques required for clinical applications. There were so many spectroscopic instruments in this laboratory and we saw many researchers constructing frontier measuring system to monitor human body and tissues. At first, we presented government decision in Japan and newly established program in Kyoto University called pre-Super Global University Program. After that, some researcher in this laboratory introduced us their recent research and showed us some instruments in the laboratory. In this report, I summarize their research and related paper.

Presentation by Dr. Spegazzini

First speaker was Dr. Nicolas Spegazzini. He belonged to Dr. Ozaki's lab. in Kwansei Gakuin University before he came to MIT. He has been investigating spectroscopic-based indirect implicit calibration using derivative double two-dimensional correlation spectroscopy [4] and improved concentration independent calibration (iCONIC) approach [5]. In medical diagnosis, concentration levels of analytes have been desired to be monitored continuously. Especially in the case of diabetic patients, glucose concentrations in blood are difficult to measure without pain because conventional method such as oral glucose tolerance test requires drawing blood many times and it can't be applied to patients whose glucose concentrations are high. In his research, non-invasive glucose monitoring was developed using Raman scattering and iCONIC. Fig.1 illustrates measurement of interstitial fluid (ISF) using Raman scattering. Raman bands were subtly changed by glucose concentration. However, ISF glucose concentration is different from blood glucose concentration (BG). Therefore glucose concentration estimated by

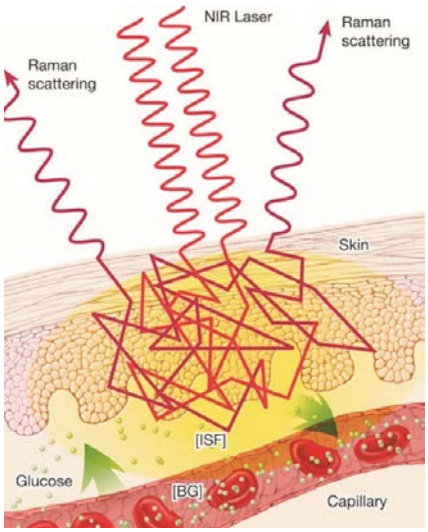

Figure 1 A schematic illustration of Raman spectroscopic measurement process for *in vivo* continuous glucose monitoring [5].

conventional calibration methods (Partial least squares with leave-one out cross validation) didn't agree with measured glucose concentration of drawn blood.

To solve this problem, glucose concentration of ISF was estimated by Raman spectroscopy and then transformed to BG using physiological dynamics model from their previous research [6]. Mass conservation of glucose is simply explained by linear equation model shown in Eq. (1). In this case, kinetics parameters are fitting parameters from Raman-based calibration. Compared to conventional methods, singular value decomposed matrix of spectra (**U**) and regularization parameter (λ) were introduced to objective function ($\mathbf{Q}_{reg}$) for the improvement in reducing baseline fluctuation and robustness in convergence (see Eq. (2)).

$$\frac{d}{dt}\left(c_{ISF}\right) = k_1 c_{ISF} - k_2 c_{BG} \qquad \text{Eq. (1)}$$

$$\mathbf{Q}_{reg} = \left\|(\mathbf{I} - \mathbf{U}\mathbf{U}^{T})\hat{\mathbf{c}}_{ISF}\right\|^2 + \lambda\left\|\mathbf{k}\right\|^2 \qquad \text{Eq. (2)}$$

Optimal computed kinetic parameters (**k**) were determined by minimizing objective function with Newton-Gauss-Levenberg/Marquardt method. From their results, estimated BG profile coincided with measured glucose concentration by drawn blood. Especially their method showed good agreement at the time when glucose concentration reached at the highest value after the oral glucose taking of patients. PLS methods couldn't estimate when to decrease glucose concentration. This problem is crucial for diagnosing patients. This concept of mass-conservation and SVD based method has wide application possibility such as chemistry, agriculture, and medicine.

Presentation by Dr. Pandey

Second speaker was Dr. Rishikesh Pandey. He has been investigating chemical imaging of middle ear for the application of pathology. Chemical imaging of disease in middle ear could be visualized by fluorescence otoscope and Raman spectroscopy. Paper about fluorescence otoscope [7] has already been published. In vivo diagnosis of middle ear requires visualization in the ear. However, current otoscope using white light reflection has low resolution so that many patients have been overtreated under the assumption of worst cases. To solve this problem, fluorescence otoscope was constructed (shown in Fig. 2). This instrument was applied to visualize congenital cholesteatoma, a disease derived from micro calcification in middle ear. From the results, cholesteatoma could successfully be detected among normal patients and patients having congenital cholesteatoma using autofluorescence with 405 and 450 nm excitations. In their current research, Raman spectroscopy was introduced for further investigation of chemical structure in middle ear. From the Raman spectra with principal component analysis, images of cholesteatoma and myringosclerosis could be separately constructed. The difference in cholesteatoma and myringosclerosis might be attributed to C=O bond. Real-time imaging of middle ear using

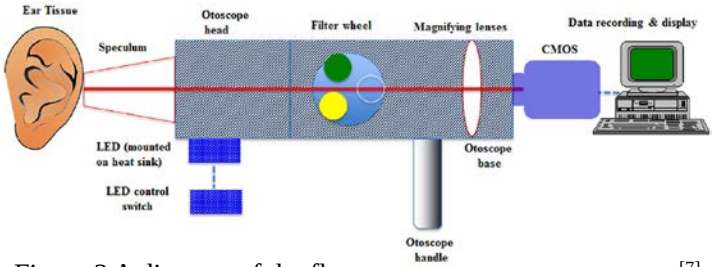

Figure 2 A diagram of the fluorescence otoscope prototype [7].

constructed otoscope could enable complete removal of affected part of ear with minimal surgical procedure and risk of treatment.

Presentation by Mr. Hosseini

Third speaker was Mr. Pooya Hosseini. He is graduate student in MIT now and has studied visualizing sickle cell disease. He would like to trace the change in shape of sickle cell to investigate one of the sickle cell diseases. To visualize the shape of sickle cell, phase microscopies were applied [8-9]. Phase microscopy is a measuring technique that converts phase shift of light derived from refractive index to thickness of optical path length. Fig. 3 shows one of the results of his work. Applying tomographic technique, three dimensional shape of a sickle cell could be constructed like Fig. 4. These methods could also apply to tiny polymer particles and cancer cells [9]. Therefore these methods could apply variable biomedical application in future.

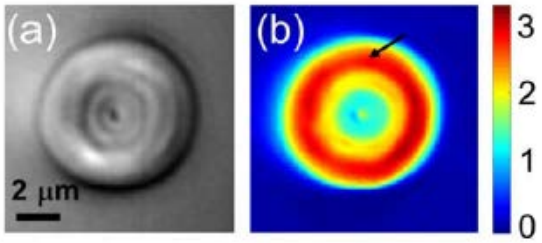

Figure 3 Double transmission images of a sickle cell for (a) amplitude and (b) phase [8].

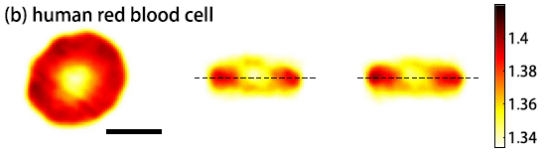

Figure 4 Cross-sectional slices of reconstructed refractive index of a sickle cell (dotted line indicates focal plane, and scale bar corresponds to 5 μm) [9].

Conclusion

In this tour of Laser Biomedical Research Center in MIT, we could get much understanding about spectroscopic and other optical techniques. Raman spectroscopy, fluorescence and phase microscopy could be useful in a variety of biomedical applications.

Acknowledgement

I would like to appreciate the people in Laser Biomedical Research Center for welcoming us, and Prof. Ohshima, Prof. Hasebe and Dr. Kim. I also appreciate financial support by JGP program.

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