Compact Microscopy for Telemedicine Applications

Anthony Nguyen
UCLA, 2609 B Carnegie Lane, Redondo Beach, CA, 90278
anthony.c.nguyen@ucla.edu

Abstract: The growing field of telemedicine offers the potential to spread healthcare in the world. In this review, I synthesize information to describe how a smartphone can be combined with different compact microscopes in order to bring diagnosis to patients in remote locations. The Fletcher Lab used as their method, attaching a Nokia phone with camera to a Edmund Optics microscope lenses to conduct brightfield and fluorescence imaging [1]. The group demonstrated that their configuration got images with ~1.2 µm resolution, which was enough to diagnose malaria, sickle cell anemia, and TB. This discussion of the CellScope acted for the group as a proof of principle; follow up field studies are being done in India, Vietnam, and other countries.
OCIS codes: (000.0000) General; (000.0000) General [8-pt. type. For codes, see www.opticsinfobase.org/submit/ocis.]

1. Introduction: Telemedicine and the Great Demand

Since the beginning of medicine, new fields have developed together with contemporary technology. Today's technology has enabled another new field of medicine: telemedicine. Telemedicine refers to medical technology where IT and telecommunications networks are used to provide healthcare at a distance from hospitals and clinics [2]. Three branches of telemedicine are remote monitoring, store and forward, and real-time services [3]. An example of store and forward will be discussed with the compact microscopy technology here. This technology is important because access to healthcare is a problem. Telemedicine is made possible by today's cell phone networks. Today, there are 8 billion people in the world. 7 of these 8 billion people are within the range of cellular networks [4]. They could all potentially be reached by telemedicine devices. It has been shown that even in the US, rural areas are lacking in healthcare compared to urban areas. According to a presentation at Stanford's Rural West Conference, "rural physicians make up 9 percent of the physician population, amidst 20 percent of the population." [5]. In other countries the disparity is even worse.

Considering specifically compact microscopy applications, we can consider some diseases that are diagnosed with a microscope. In many developing countries, malaria is "the leading cause of death and disease." In 2010, an estimated 216 million people had malaria, and half the world population were at risk [6]. Similarly, in 2011, 9 million people became sick with tuberculosis, 1/3 of the world population is infected with TB, which is the leading cause of death for people with HIV [7]. These are both diseases that better diagnosis would help against.

There is a quantifiable demand for telemedicine. BCC Research reports that the current value of the market is $11.6 billion, and that it will have a $27 billion global market value in 2016 [8]. The report broke up the 2011 number into two sub-markets as telehospitals and clinics, which make up $8 billion and telehome, which makes up $3.5 billion. Further expanded information can be found in a report by Broadband Expanded, which discusses how faster connectivity and health regulations make a favorable environment for telemedicine in the US [9]. Together these financial and patient statistics show that there are economic and social reasons for developing telemedicine applications.

There are several groups currently researching applications of microscopy in telemedicine. The Ozcan Research Group has developed LUCAS, which is a holography based solution [10]. At the University of Illinois, Urbana-Champaign, there is work being done to use a cellphone as a spectrophotometer for detection [11]. This paper reviews the CellScope, a portable microscopy solution from The Fletcher Lab at UC Berkeley. All of the mentioned examples involve examination of samples through different kinds of microscopes. These microscopes are necessarily cheap, compact, and easy to use, to meet the demand for these devices in rural areas, where training, facilities, and funds are all lacking. Hopefully in the future, these or other applications can successfully save millions more lives.

2. Mobile Phone Based Clinical Microscopy for Global Health Applications (CellScope) [1]

In 2008, The Fletecher Lab published this paper in which they discuss a device they developed which they call the CellScope. This research did not develop new microscopy technologies, nor did it use any new cell phone technology. By using contemporarily available materials, the *purpose* of this research is was to "demonstrate the feasibility of creating an entirely integrated and portable mobile phone microscopy system." They illustrate this

application by using light microscopy test for diagnosing three diseases: tuberculosis (TB), malaria, and sickle cell disease.

This describes the *materials and methods* used. All of the parts of the CellScope system were found to be inexpensive and standard. The system uses a Nokia N73 camera phone, which comes standard with a "3.2 MP (2048x1536 pixel) CMOS camera with a 5.6 x 4.2 mm sensor, yielding ~2.7 µm spacing". The imaging system that was attached to the phone comes from Edmund Optics. It features a 20X wide field microscope eyepiece, and it is located 160 mm from the microscope objective, which had "60X 0.85 NA DIN Achromat objective." For the fluorescent imaging tests, a Luxeon III 455 nm LED, with 5° spot lens, biconvex lens 11 cm from the spot lens, excitation filter (D460/D0X, Chroma) was used. The excitation intensity at the sample was 2.0mW/mm^2. See Figure 1, the image labeled B, to see what the complete setup looked like.

Figure 1: Device and Imaging Results, 10 µm scale bars

The cost was said to be roughly $75, and this paper was published in 2009. The brightfield pictures were taken with ambient light, and "default camera settings, with the flash disabled." The fluorescent images were taken in "Night" mode, with flash disabled. The illumination for the fluorescence was a "high-power blue LED, emitting within the excitation range of the fluorescent Auramine O stain commonly used for detection of TB bacilli." The pictures were JPEG pictures with compression. ImageJ was used for automated counting of samples. The malaria and sickle cell samples were from patients that were already confirmed to have those diseases, and the TB samples were confirmed in culture. In later studies they could use samples that are unconfirmed and then check using the CellScope and then compare with other diagnostic measures.

The paper had many *major results*, which were discussed for imaging for all three diseases. Two modes of illumination, brightfield and fluorescence, were discussed. The system was determined to have ~ 1.2 µm resolution, as measured by FWHM. In Figure 1, image C, the beads that they used appear clearly. The same image from Figure 1 was resolved using the LED Fluorescence illumination, and the same resolution observed in image labeled D. The brightfield imaging was used for malaria and sickle cell anemia, and the fluorescent imaging was used with TB. Imaging for malaria initially uses a "thick" blood smear, and then follow-up work uses a "thin" blood smear. Two figures, not included here, showed brightfield images of thick and thin smears of malaria infected blood, as captured by the CellScope system. The authors commented that a higher NA objective could improve the images. Likewise, in the same figure, the system showed enough contrast between cells to identify sickle cell anemia sickled cells, without using other techniques.

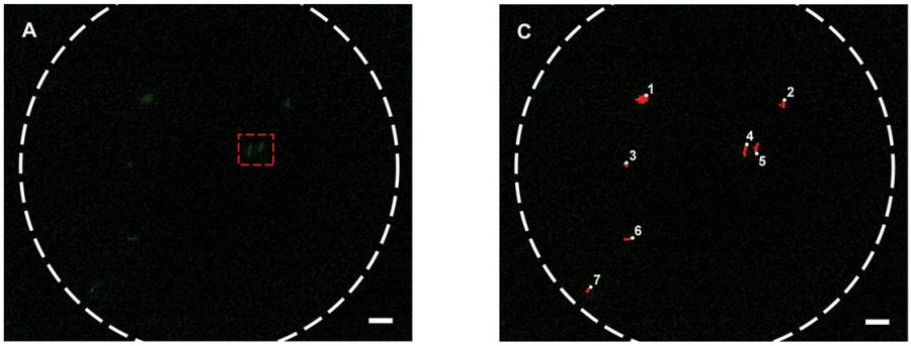

Figure 2: TB Detection and Counting, 10 µm scale bars

For fluorescent imaging of tuberculosis, Auramine O was used to stain smears. The resolution "was high enough to allow easy identification of individual TB bacteria in the sample, as well as to observe the standard rod-shaped

morphology." This can be seen in Figure 2, image A. Compared with the current standard Ziehl-Neelsen stain, which requires screening of over 100 fields of view of ~ 180 µm, use of the fluorescence imaging have improved ease of reading, possibly increased accuracy, less toxic production, and 25 times less images are needed. The study also performed automated counting for TB using this system, as seen in Figure 2, image C. In this research the automatic counting was done on a computer, but there is no reason why this could not be done on the phone itself.

The paper's *conclusions* were optimistic. They gave an example regarding TB, suggesting that this technology could be adapted to adhere to current standards, and portably as well, in order to be quickly adopted, since "sample evaluation could potentially be performed in real time while a patient is still in the presence of a healthcare worker, rather than requiring days or weeks." Other improvements that would go along with this system include "digital record keeping, automated sample analysis, expert diagnosticians, and epidemiological monitoring." Finally, to resolve the issue of minimally trained health workers in the rural areas, one suggestion was "automated sample preparation."

3. Conclusions

After the publication of this paper, there has been further news regarding developments with the CellScope. One unexpected result was that it is being used to teach kids at the San Francisco Friends School [12]. The device found an educational application that complements the medical application; further support and publicity for the educational development of the technology could potentially help the medical uses. Furthermore, there are ongoing studies with the device right now. A 1 year study in Vietnam is studying "diagnosis efficacy of tuberculosis" [13]. There is also a study by the World Health Partners in India right now, partnered with many telemedicine clinics [14]. A similar study in held in Uganda also showed that the cell phone networks there, as well as staff with minimal training, were able to use a similar system [15]. Hopefully among the various different compact microscopy methodologies, one or more of them is able to make a significant impact on malaria, TB, and other diseases around the world.

4. References

[1] D. N. Breslauer, R. N. Maamari, N. A. Switz, W. A. Lam and D. A. Fletcher, "Mobile Phone Based Clinical Microscopy for Global Health Applications," *PLOS One*, vol. 4, no. 7, 2009.

[2] ATA, "What is Telemedicine?," The American Telemedicine Association, [Online]. Available: http://www.americantelemed.org/learn. [Accessed 14 June 2013].

[3] News-Medical.Net, "Types of Telemedicine," News-Medical.Net, [Online]. Available: http://www.news-medical.net/health/Types-of-Telemedicine.aspx. [Accessed 14 June 2013].

[4] Y. Wang, "More People Have Cell Phones Than Toilets, U.N. Study Shows," Time, 25 March 2013. [Online]. Available: http://newsfeed.time.com/2013/03/25/more-people-have-cell-phones-than-toilets-u-n-study-shows/. [Accessed 14 June 2013].

[5] Stanford University, "Health Care in the Rural West: Persistent Problems, Glimmers of Hope," The Bill Lane Center for the American West, Stanford University, 5 July 2011. [Online]. Available: http://www.stanford.edu/group/ruralwest/cgi-bin/drupal/content/rural-health-care. [Accessed 14 June 2013].

[6] CDC, "CDC - Malaria - Maleria WorldWide - Impact of Malaria," CDC, 9 November 2012. [Online]. Available: http://www.cdc.gov/malaria/malaria_worldwide/impact.html. [Accessed 14 June 2013].

[7] CDC, "CDC - Global Tuberculosis - TB," CDC, 3 January 2013. [Online]. Available: http://www.cdc.gov/tb/topic/globaltb/default.htm. [Accessed 14 June 2013].

[8] BCC Research, "Global Telemedicine Market to Reach $27.3 Billion in 2017," BCC Research, 09 March 2012. [Online]. Available: http://www.bccresearch.com/pressroom/report/code/HLC014E. [Accessed 14 June 2013].

[9] Broadband Expanded, "Broadband & Telemedicine," Broadband Expanded, January 2012. [Online]. Available: http://www.broadbandexpanded.com/policymakerfiles/telemedicine/Telemedicine_Stats&Data.pdf. [Accessed 14 June 2013].

[10] W. Bishara, O. Mudanyali, I. Sencan, T.-W. Su, D. Tseng, O. Yaglidere, U. Sikora and A. Ozcan, "Lensfree On-Chip Microscopy and Tomography for Biomedical Applications," *IEEE JOURNAL OF SELECTED TOPICS IN QUANTUM ELECTRONICS*, vol. 18, no. 3, pp. 1059-1072, 2012.

[11] D. Gallegos, K. D. Long, H. Yu, P. P. Clark, Y. Lin, S. George, P. Nath and B. T. Cunningham, "Label-free biodetection using a smartphone," *Lab on a Chip*, vol. 13, no. 11, pp. 2124-2132, 2013.

[12] M. McCrea, "The CellScope: Not Just for James Bond Any More," Healthline, 06 February 2013. [Online]. Available: http://www.healthline.com/health-news/cellscopes-introduced-in-the-classroom-121712. [Accessed 14 June 2013].

[13] Blum Center, "Cellscope | Blum Center," Blum Center, 2013. [Online]. Available: http://blumcenter.berkeley.edu/pathway/cellscope/. [Accessed 14 June 2013].

[14] GOOD, "Can the CellScope Cell Phone Microscope Revolutionize Rural Health Care?," GOOD, 15 February 2011. [Online]. Available: http://www.good.is/posts/can-the-cellscope-cell-phone-microscope-revolutionize-rural-health-care. [Accessed 14 June 2013].

[15] C. J. Tuijn, B. J. Hoefman, H. van Beijma, L. Oskam and N. Chevrollier, "Data and Image Transfer Using Mobile Phones to Strengthen Microscopy-Based Diagnostic Services in Low and Middle Income Country Laboratories," *PLOS One*, vol. 6, no. 12, 2011.