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Review Articles

Recent Advances in Point of Care Diagnostic Tools: A Review

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Abstract: Globally, there is a great need for portable, inexpensive diagnostic tools that can provide quick, accurate results using relatively small sample volumes. Point-Of-Care (POC) measurements of human saliva, sweat and/or blood capable of detecting glucose levels, foreign pathogens such as bacteria, fungi and many different viruses (HIV, Ebola, Influenza, etc.) that use microfluidics and optofluidics are close to commercial availability. These diagnostic tools use both optical and electrical methods for the detection and analysis of single biomolecules. The applications extend beyond healthcare and can be used for pathogen detection in aquatic environments such as drinking water. Additional research in handheld Optical Coherence Tomography (OCT) offers the possibility for inexpensive diagnosis and treatment of tissue like middle ear infection and breast cancer. Finally, microscopes are also getting smaller and cheaper, with an inexpensive plastic florescence microscope that can quantify white blood cell levels and a suitcase sized microscope that can look at a single drop of blood for a million biomarkers, searching for signs of sepsis and infectious disease. POC devices such as these will provide medical care to poor, remote areas that can be administered by junior physicians or even used for self-diagnosis. In this study, a review of advances in POC devices reported in recent literature is conducted, in order to provide the reader with a thorough description of new diagnostic techniques that have taken place in the last couple of years.

Keywords: Viral Detection, Point of Care, Diagnostics, Biomolecules

Introduction

Recent years have seen exciting advances in diagnostic tools that aim to bring higher quality health care to poor or isolated communities which lack the resources necessary to provide quality results in a timely manner. With the bird flu, Ebola and other pathogens that can spread rapidly on a global scale, there is a great need for portable, inexpensive diagnostic tools that can provide quick, accurate results using relatively small sample volumes. Point-Of-Care (POC) devices capable of detecting glucose levels, quantifying foreign pathogens such as bacteria, fungi and many different viruses, imagining tissue and performing white blood cell counts, are close to commercial availability (Henderson, 2015; OS, 2016). Many different groups of researchers have found ways to classify and count various strains of Influenza. Some devices are as simple as placing a drop of sample on paper. Others make use of microfluidics, optofluidics and electrical methods, to detect, identify and quantify biomolecules (Lei *et al*., 2015). Recently the discovery of synthetic antibodies known as aptamers, which allows for specific binding of Influenza A, B, *Escherichia coli* (*E. coli*) and certain nucleic acids, have resulted in several diagnostic tools (Chung *et al*., 2015; Lai *et al*., 2014; Wang *et al*., 2016). Once target biomolecules are bound by aptamers, they can be quantified using different techniques, such as spectral analysis (Ozcelik *et al*., 2015), emission intensity and electrical signals (Liu *et al*., 2014). The applications extend beyond healthcare and can be used for pathogen detection in aquatic environments such as drinking water (Yu *et al*., 2014).

In addition to POC devices that screen for pathogens, new optical devices are making portable lab analysis and diagnosis possible in rural areas. These devices can be administered by junior physicians or used for self-diagnosis. One method that has several biomedical applications is Optical Coherence Tomography (OCT). OCT is a non-invasive imaging technique that can see

into human tissue, looking past the eardrum into the middle ear, checking for infections or used after surgical procedures for the detection of breast cancer remnants (Pande *et al*., 2016).

Finally, microscopes are also getting smaller and cheaper. An inexpensive plastic florescence microscope that can printed with a 3D printer and fitted with aspheric lenses, can quantify white blood cell levels (Forcucci *et al*., 2015). A suitcase sized microscope can simultaneously detect a million biomarkers, searching for signs of sepsis and infectious disease within a single drop of blood (Shorr *et al*., 2007).

Literature Review

Advances in Imaging

Optical Coherence Tomography (OCT) utilizes low coherence interferometry to perform optical imaging. Because OCT is noninvasive and can result in high resolution, depth-resolved, cross-sectional images of biological samples, it has many wide-spread applications in biomedicine. In the past, one of the limitations for handheld OCT systems, has been the motion artifacts created during manual scanning due to variations in the scan velocity of the imaging probe. By replacing the OCT's galvanometer- or Micro-Electromechanical Systems (MEMS)-scanning mirrors with sensor-based methods the problem of motion artifacts can be eliminated. As the handheld OCT is moved across tissue the trigger rate is adaptively altered based on the instantaneous scan velocity. Using a computational approach that utilizes both amplitude and phase data to reconstruct images, the lateral Fields-Of-View (FOV) can be increased from a few mm in conventional galvanometer- or MEMS-scanning mirrors systems to a few cm's in the sensor-based systems. Pande *et al*. (2016) at the University in Illinois has created a sensor-based manual scanning technique that uses real-time feedback from an optical motion sensor which is triggered during data acquisition. The handheld OCT has a maximum scanning speed of 2.5 cm/s, which is satisfactory for most freehand scanning applications (Pande *et al*., 2016). Boppart expects the commercialization of their scanners to happen in the next five years. Diagnostics Photonics, Inc. has recently obtained FDA approval for this handheld system to image breast tissue, with the aim of removing tumor cells around the border of surgically removed tissue, which can sometimes be missed with the naked eye. Another company PhotoniCare Inc. will use a similar device to image tissue behind the eardrum for better diagnosis and treatment of issues like middle ear infection (Coffey, 2016). A variant of OCT is Real Time Optical Coherence Imaging (OCI) which uses semiconductor quantum wells as dynamical holographic films to provide two dimensional images from different coherence-gated depths of a turbid object. A recent development uses the Phase Coherent Photorefractive (PCP) effect in ZnSe quantum wells to enable holographic imaging in two complementary high depth-resolution modes. For depth-resolved OCI these films use the coherence of excitons for time-gating which provides depth information of an object from the brightness profile of its holographic image with a resolution of a few micrometers. By using two colors with a technique called Contrast-Enhanced Holographic Imaging (CEHI), high-speed three-Dimensional (3D) imaging through skin becomes possible. A group of researchers at UC have imaged a concealed 95 μm thick wire behind a thin layer of chicken skin. The technique may make it possible to one day access the quality of implants without surgery or exposure to x-ray radiation (Dongol *et al*., 2015).

Tissue, blood and other organic matter, have been imaged with microscopes since the late 17th century. Microscopes are getting smaller, cheaper and more powerful every day. It is now possible to assemble a fluorescence microscope with a 3D printer and some carefully chosen lens. Researchers at Rice University have developed a miniature, achromatic microscope with magnification of -4.5 x and a 1.2 mm diameter Field of View (FOV). The custom-designed microscope requires no manual adjustment between samples and with mass production will cost about $600 and only a few cents per sample. They have used this microscope to count white blood cells. An increased or decreased total White Blood Cell count (WBC) may indicate abnormal bone marrow pathology or the presence of a microbial or viral infection like Dengue fever. Three-part WBC differentials identify and quantify lymphocytes, monocytes and granulocytes. Commercially available Point Of Care (POC) devices for clinical use in the United States are currently available and cost around $1,000 per unit and $3 per sample. These devices use impedance cell counting and spectrophotometric measurement of hemoglobin concentration. They do a good job of counting for lymphocytes and granulocytes but do not accurately count monocytes. With a 1.2 mm diameter FOV, the 3D printed microscope allows for at least 130 cells to be present in each field of the three-part WBC differential. This FOV is necessary for statistical significance when quantifying three-part WBC differential. By mixing a drop of whole blood with the fluorescent staining compound acridine orange, health care workers can identify these three types of white blood cells. Acridine orange fluoresces when bound to DNA or RNA. When bound to double stranded DNA (dsDNA), its emission maximum is 525 nm. When bound to RNA and single stranded DNA (ssDNA), its emission maximum is 650 nm. Each cell's red-to-green ratio is recorded resulting in two distinct groups of cells: Lymphocytes (lowest red-to-green ratios) or

granulocytes (highest red-to-green ratios). Monocytes (cells with red-to-green ratios that fall in the middle of the other two groups) are the most difficult to identify. (Forcucci *et al*., 2015; Ruth, 2015) Monocytes are the white blood cells that can sense foreign antigens. They use transmembrane proteins that can distinguish between dangerous pathogens like bacteria, fungi and viruses. These transmembrane proteins are called Toll-Like Receptors (TLRs). When TLRs bind with a specific pathogen's antigen, inflammatory cytokines are secreted. The cytokines produced are specific to the pathogen detected. For example, the cytokine tumor necrosis factor-α is an indicator of autoimmune diseases, like rheumatoid arthritis and cancer. Drug developers and disease investigators rely on the detection of these cytokines to assess immune competency. A reconfigurable microfluidic device has been designed that can profile cytokines from human monocytes. The platform consists of a two-layer PDMS device mounted on top of antibody spots imprinted on the substrate. The two layers permit toggling between serial and parallel flow of solution. Sets of antibody arrays are made up of cytokine capture spots with antibodies against 3 specific cytokines and two controls. The arrays were printed between cell capture bands, to increase overall surface area for cell capture. By developing a microfluidic device that can profile these cytokines, researchers at UC-Davis hope to reduce the amount of blood needed by more traditional detection methods, allowing animals involved in longitudinal studies to remain alive and to create a tool in pediatric populations where only a small volume of blood is available (Vu *et al*., 2015).

As impressive as a 3D printed microscope is, perhaps even more incredible is a microscope that can detect over a million biomarkers in just 30 min. At ICFO-The Institute of Photonic Sciences in Barcelona, Spain, researchers in the 'Scalable point-of-care and label free microarray platform for rapid detection of Sepsis'(RAIS) project have developed a portable microscope the size of a book. Polarized beams of light are sent through birefringent crystals and a cartridge with a small blood sample. The interaction of light with the bacteria or proteins is captured by an array of receptors. Then the intensity of the transmission image is analyzed for more than one million biomarkers (Terborg *et al*., 2016). Biomarkers such as micro-ribonucleic acids (microRNAs) and interleukins, amongst others, are associated with Sepsis, a potentially fatal inflammation of tissues that accompanies infection. Current tests take as long as one day to perform but this microscope will complete the work in just 30 min. Since early diagnosis is necessary to properly manage sepsis, this new POC device has the potential to save many lives (Dubay, 2016). For example in a 2008 study, it was estimated that if the U.S. achieved earlier sepsis identification and treatment, there would be 92,000 fewer deaths annually and reductions in hospital expenditures of over $1.5 billion (Shorr *et al*., 2007).

Advances in Ease of Use POC Devices

When it comes to POC devices, the use of paper for the development of diagnostic devices has many advantages. It is lightweight, easy to use and inexpensive. A group in Taiwan has developed a paper-based immunoassay for rapid screening in POC applications. The colorimetric paper-based sandwich immunoassay successfully detects and subtypes both influenza A H1N1 and H3N2 viruses. Currently, the most reliable diagnostic of influenza virus is based on real-time Reverse-Transcriptase Polymerase-Chain-Reaction (RT-PCR), which takes 6 h and requires a laboratory. The paper assay can be performed with less sample and reagent volumes in around 1 h. The paper was fabricated by wax-printing and features an array of circular test zones for running multiple assays in parallel. The internal structural protein (NP) of influenza virus is captured via anti-NP antibody, then outer surface glycoproteins (H1 and H3) of influenza virus are used to subtype the influenza A H1N1 and H3N2 viruses via anti-H1 and anti- H3 antibodies. The design can be extended to detect entire subtypes of influenza viruses (Lei *et al*., 2015).

Overall the biggest advances in POC devices come from microfluidic and optofluidic research, were small sample volumes, low cost and portability make them ideal for wide-spread applications in biomedicine. Microfluidic platforms are the size of a postage stamp and can automate multistep sample preparation in an enclosed environment, protecting samples from contamination. Optofluidic platforms are also small and can integrate both biological sample handling and optical readout into a single system. Glucose meters have been around for a while, allowing diabetes patients to self-diagnose and self-treat hyperglycemia and insulin deficiency. However, these devices require invasive finger-pricking, multiple times a day. Glucosense Diagnostics Ltd., a University of Leeds spin-off company, offers an alternative to finger pricking that can effectively communicate with glucose molecules through skin. The optical glucose sensor is made of an intermediate glass material which features an active layer of ions that fluoresce under a low power Near-Infrared (NIR) laser diode. The surface engineering of the glass is a novel process called ultrafast laser plasma implantation. Glucose absorbs and scatters the light causing a decay in the fluorescence signal that allows glucose levels to be determined within 30 seconds. This wearable device can continuously monitor glucose levels allowing people to self-regulate and minimize emergency hospital treatment (Henderson, 2015). A

different group at the Hong Kong Polytechnic University and Zhejiang University has developed an optofluidic glucose meter with ultrasensitive detection. It can detect glucose oxidation concentrations as low as 1nM, using only a drop of sweat. The researchers have integrated a fiber optic glucose sensor into a microfluidic chip, thus eliminating the electromagnetic interference that often appears in electrochemical sensors. Like the detector under development by Glucosense Diagnostics Ltd., this lab-on-a-chip is fast, with a response time of only 70 s (Yin *et al*., 2016; OS, 2016).

Advances in Viral Detection

Viruses pose a huge threat to public health, thus detection and quantification of virus particles using POC devices that are smaller, cheaper and faster, is a major goal for many research groups. Both optical and electrical methods for the detection and analysis of single biomolecules have been developed. By combining these detection methods, researchers have developed a lab-on-a-chip device that can detect influenza virions. Using a 157 nanopore gate, an 80-120 nm virion can be identified within a complex, heterogeneous mixture using different combinations of optical and electrical parameters (fluorescence intensity, wavelength, current blockade depth and dwell time). First a patch-clamp amplifier applies voltage across the nanopore. Then a pair of lasers excite the molecules. Next, the optical signal is spectrally filtered and collected by two avalanche photodiodes. In general, larger particles are brighter compared with the smaller ones. However, there is a brightness region in which the particle subpopulations cannot be resolved using the optical signal alone. The electrical signal from the nanopore allows for the identification of particle size by the depth of the current blockade. By combining the optical brightness, spectral identification and amplitude for each detected particle, identification of a virus subpopulation from a nanoparticle mixture can be made (Liu *et al*., 2014). A different group at Brown University uses oil and paramagnetic particles to isolate nucleic acids, such as Influenza RNA, within a closed microfluidic system. First Influenza RNA is extracted from a nasal swab. The sample is then mixed with silica Paramagnetic Particles (PMPs) and lysis/binding solution. Next the PMPs are pulled through an oil-filled microchannel and into a well containing elution buffer. Specifically, the microfluidic device consists of three wells: The Lysate Well (LW) where cells are broken down and their internal compounds can be analyzed, the Elusion Well (EW) where material is extracted via a low salt solution and an Oil Reservoir (OR) which acts as a filter pinching off the PMPs from the rest of the lysate when PMPs coalesce at the oil water interface. The PMP/lysate is moved between wells via a permanent neodymium magnet as shown in Fig. 1. This whole process can be completed in under 2 min (Cui *et al*., 2016). Another optofluidic device for detecting and identifying biomarkers uses the Wavelength Division Multiplexing (WDM) principle to create color-dependent excitation spot patterns from a single integrated waveguide structure. An optofluidic platform that combines both solid-core and liquid-core Antiresonant Reflecting Optical Waveguides (ARROWs) is used for chip-based biomedical analysis. Optical wavelengths resulting from the fluorescence excitation of biological particles in the visible and NIR are carried by a single Multimode Interference (MMI) solid-core optical waveguide to an intersecting fluidic channel. The waveguide produces wavelength-dependent spatial patterns in the fluidic channel. As the light waves travel with different propagation constants, they interfere with each other. Spot patterns are created at propagation distances where the relative phases of these modes match up correctly. The spatial encoding of spectral information allows for direct identification of multiple labeled biological particles with extremely high accuracy. The chip diagnostics were tested by directly identifying and counting individual virus particles from three different influenza A subtypes (H1N1, H2N2 and H3N2). (Ozcelik *et al*., 2015) A similar approach is used for the detection of Ebola virus.

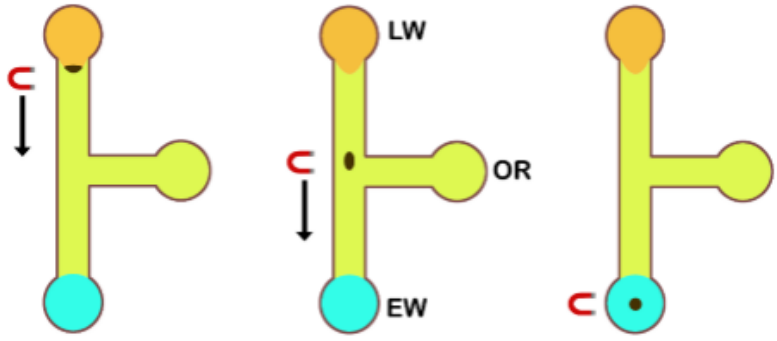

Fig. 1. Channel design and operation. The sample is pipetted into the LW then PMPs are transported past the oil-water interface to the EW (Cui *et al*., 2016)

Given recent outbreaks in Africa, Ebola has emerged as reminder that in our globally connected world, infectious diseases can be difficult to contain and therefore pose a threat to the entire global population. To detect Ebola, the chip is made up of a microfluidic and an optofluidic layer. The microfluidic layer is for sample preparation. It is automated by an array of lifting gate microvalves. Fluid is transported between microvalves by a pneumatic layer below. The outlets from this chip are connected to the optofluidic layer which is used for detection. It has a rectangular channel with metal reservoirs at each end to control the introduction of biological samples and flow. The metal reservoirs interface with the microfluidic layer which guides light through liquids (i.e., it is the liquid-core) using ARROWs. The sides and top of the channel are covered by a thin film which can be patterned into solid-core ridge waveguides directing light to and from the Liquid Core (LC). The intersection of solid (SC) and LC ARROWs at the center of the chip enable single molecule detection. Fluorescence signals from molecules flowing past this point are collected by the LC ARROW and routed to the edge of the chip. Single nucleic acids are identified by individual fluorescence peaks much like in single-photon counting. When tested, the chip successfully detected Ebola at expected concentrations. Sudan virus and Lake Victoria Marburg virus were successfully used as negative selections, meaning they were not counted when incorporated into the sample. The detection levels were comparable to PCR, a standard procedure for amplifying DNA (Cai *et al*., 2015). Human Immunodeficiency Virus (HIV-1) is also a massive threat to public health and safety. There has already been a good review paper on HIV detection using microfluidic platforms (Desai *et al*., 2011). Instead this review focused on recent developments over the last two years for POC viral detection that may or may not include HIV.

Recently, aptamers have emerged as promising candidates for diagnostic assays. Aptamers are novel nucleic acid-based affinity reagents (sometimes called artificial anti-bodies) that have several advantages over antibodies. They can bind to a specific target molecule (including small molecules, peptides, proteins and whole pathogens/cells). They can be screened from a pool of random nucleic acid sequences allowing for the selection of their bound targets. But most importantly they can be synthesized by chemical methods making them accurate, cheap and, not reliant on an animal's immune response, which is not always uniform (Lai *et al*., 2014). DNA aptamers can bind specific molecular targets and may change their shape under different operating conditions (Wang *et al*., 2016). For example Aptamer-conjugated Fluorescent Nanoparticles (A-FNPs) will selectively bind to the surface of target bacteria such as *E. coli* and label them so that target bacteria can be counted in an optofluidic particle-sensor (Chung *et al*., 2015). Groups from Taiwan and Korea are using aptamers for rapid disease diagnosis and to test for water contamination. A microfluidic chip composed primarily of microchambers includes a single universal aptamer-coated beads chamber, a washing buffer chamber, a fluorescently-labeled single universal aptamer chamber, a sample loading chamber and two sets of identical reaction chambers (Fig. 2) to detect three different influenza viruses (influenza AH1N1, H3N2 and influenza B) at the same time. The entire diagnostic process is performed automatically in 20 min with minimal human intervention (Lai *et al*., 2014). Another microfluidic device that screens for virus uses a magnetic-bead assay to screen for influenza A (H1N1), which is a biomarker for an influenza infection. The screening process is known as Systematic Evolution of Ligands and Exponential Enrichment (SELEX). The microchip is made of two PDMS layers and one glass substrate, but the key devices are a suction-type micropump and a micromixer. Positive and negative selections are used as alternate processes to screen for Influenza A (H1N1). The positive selection uses magnetic beads that capture specific Influenza A/H1N1-ssDNA complexes amplified by using on-chip PCR. Negative selection uses magnetic beads that capture specific Influenza B-ssDNA complexes, which are removed from solution. The positive and negative selection processes were repeated alternately. Compared to traditional SELEX methods, this integrated microfluidic device is smaller in size, takes less than half the time of conventional methods and consumes less sample and reagents. Also because the entire process is automatic, it is less labor-intensive and reduces the risk of contaminated results and operator infections (Wang *et al*., 2016). In general, optofluidic systems are widely applicable for the fast and continuous detection of microbial cells. Another pathogen that can be selected for using aptamers is the bacteria *E. coli*. When water becomes contaminated, it poses a serious health risk to the public. *E. coli* is an important indicator for monitoring microbial contamination in drinking water. A-FNP bound *E. coli* are injected into a microfluidic platform along with a sheath fluid (Phosphate buffered saline) which focuses the sample flow into the center of the microchannel. An optical fiber directs 532 nm light onto the fluorescent nanoparticles which emit light at 560 nm. A multi-pixel photon counter detects fluorescence from the A-FNP-bound target microbes. This optofluidic system allows for continuous, real-time detection of microbes that corresponds well with results obtained using the conventional culture-based detection protocol (Chung *et al*., 2015).

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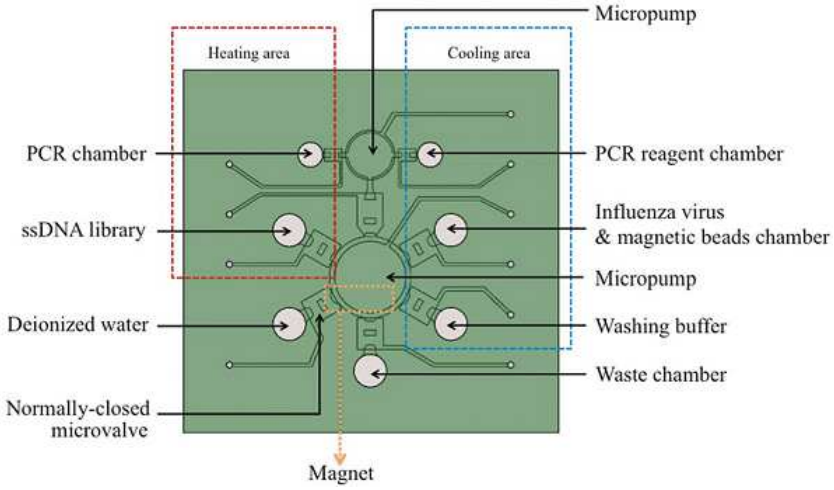
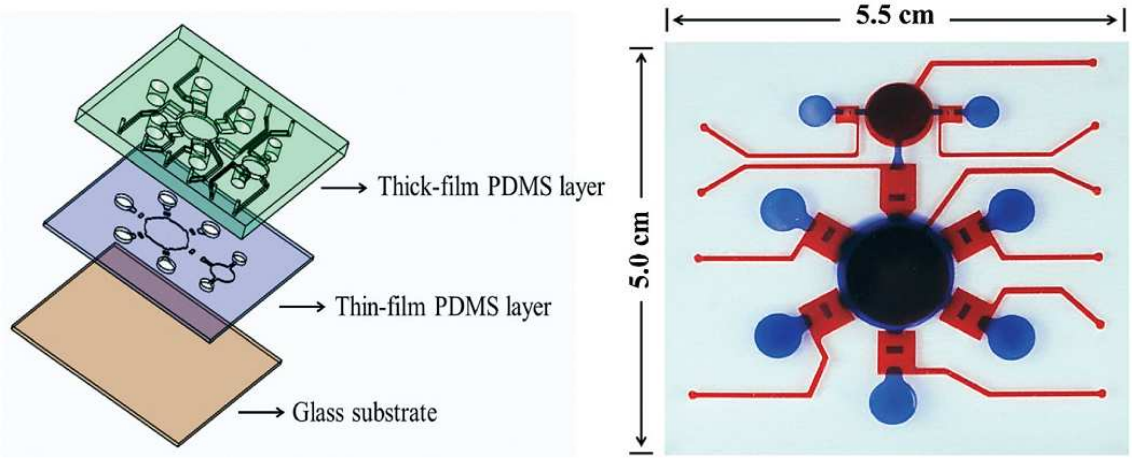


(a)



(b) (c)

Fig. 2. (a) A schematic of the microfluidic chip. (b) An exploded view of the chip. (c) A photograph of an assembled integrated microfluidic SELEX chip (Lai *et al*., 2014)

Since many viruses are pathogenic to humans, a platform that can identify multiple viruses has broad diagnostic applications in food safety, homeland security and infectious disease diagnosis. A POC assay for viral load measurement has been developed that can detect and quantify multiple Human Immunodeficiency Virus (HIV) subtypes (A, B, C, D, E, G and panel), Epstein-Barr Virus (EBV) and Kaposi's Sarcoma-associated Herpes Virus (KSHV) using small sample sizes of either blood or saliva. The printed flexible plastic microchip with screen-printed electrodes uses electrical sensing of viral lysate (a solution containing lysed cell or viral material). First viruses are captured by antibodies attached to magnetic beads, then they are washed with a low-electrically conductive solution and lysed. The release of charged molecules into the buffer solution changes the bulk electrical properties of the buffer. The viral load is determined by the change in magnitude of the capacitance. This microchip is also capable of capturing and detecting *E. coli* (Shafiee *et al*., 2015).

Keeping viral infection rates down, depends not only on early detection in the population but also in our environment. Researchers in Singapore have developed a droplet optofluidic system to monitor drinking water quality that uses refractive index changes in the microdroplet to detect *E. coli*. Bacteriophage is a virus that infects bacterial cells. The concentration of bacteriophages is strongly correlated with virus concentrations in water samples, therefore it is good indicator of drinking water quality. The microfluidic device starts with two inlets, a water sample containing bacteriophage and a sample containing *E. coli* in culture medium. Each sample is split into uniform microdroplets by the microfluidic structure. When the microchannels merge a microdroplet from each sample is mixed

together. The host cell growth condition in the microdroplet is reduced by the presence of the bacteriophage. This host cell growth condition is detected with an optical detection system. Specifically, the scattering pattern of the microdroplet carrier is determined by the final concentration of the host cell. A scattering pattern from a reduced host cell population (0-1 cells per droplet) will have a different diffraction pattern compared to a healthy cell population (100 cells per droplet). The concentration of cells in the microdroplet can be measured by the disorder in the scattering pattern of the microdroplet resulting from reflection and refraction of the incident light on the microdroplet. This optofluidic system is a fast and reliable detector for the bacteriophage, that does not require labeling. (Yu *et al*., 2014)

Conclusion

Advances in microfluidics and optofluidics are making POC diagnostics more portable and cheaper every day. Antibodies, along with the newly discovered aptamers, are used to detect pathogens in water and bodily fluids. As mentioned, they have been used to bind biomolecules to magnetic beads for transport, or to paper for quick identification. Microfluidics and optofluidics that have also been used to detect glucose levels are very close to commercialization. It is hoped that the methods mentioned in this paper will soon move from the research lab to the field, assisting in viral detection and classification. The POC devices reviewed will one day replace large laboratories in performing white blood cell differentials and in the detection of cytokines produced by monocytes. Lastly, OCT is becoming portable, by producing a handheld OCT device for self-diagnosis, patients may be able to avoid a trip to the doctor altogether.

Author's Contributions

Laura Wessels: Conducted the literature review and wrote the manuscript.

Haider Raad: Provided guidance, fact-checking and technical insight.

Ethics

The authors have no conflicts of interest or existing collaborations with the groups cited in this review.

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