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MOBILE & WIRELESS HEALTH

Rapid Low-Cost Microfluidic Detection in Point of Care Diagnostics

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Abstract
Clinical diagnostics is a challenge in resource poor areas. Accessibility to diagnostic laboratories is severely curtailed in areas where resources and infrastructure are limited. There is a need to develop low cost and portable devices to promote healthcare services in such places. The development of low cost paper-based microfluidic devices (μPADS) and thread-based devices have the potential to revolutionize point of care diagnostics in poverty-ridden areas. In this report, we describe how frugal technologies can be used for the detection of biological fluids, and the need for developing low cost wireless and wearable technologies to be deployed in resource poor settings.

Keywords Microfluidics · Frugal science · Point of care diagnostics

Introduction

In areas where resources and infrastructure are limited, there is an increased awareness to enhance point of care diagnostics. Thousands of villages in developing countries do not have access to electricity or primary healthcare. In developing countries, laboratories are sparsely distributed and often have limited access to a large proportion of the population [1]. Furthermore, it has been reported that lack of proper diagnosis and treatment as well as access to health care centers are the reasons for more than 95% of deaths due to infectious diseases [2]. One recent study found that less than two-thirds of hospitals providing surgical care in several low and middle-income countries had a reliable water source [3]. Even in developed countries, remote areas with limited access to health care require innovative cost-effective technologies in health screening and disease prevention. Affordability and accessibility of diagnostic tools are major problems in resource poor and remote neighborhoods. Portable, simple, and low-cost stand-alone devices can advance much needed healthcare in these areas. Therefore, development of frugal, but reliable, techniques to monitor health in underprivileged neighborhoods is being increasingly recognized.

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Low-cost paper and thread-based microfluidic techniques

Microfluidics is revolutionizing molecular analytics in clinical diagnostics, environmental testing, and food quality testing. Microfluidics is the technology of manipulation and analysis of fluids at the microscale. This technology reduces the size of complex analytical systems significantly, and it is also important in research where the reduction of fluid volume facilitates the study of an increasing number of parameters such as in molecular diagnostics using biospecimens. Microfluidics also has an emerging vital role in the development of wearable technologies as in the detection of analytes in the sweat or in the monitoring of wound healing.

The studies in microfluidic technologies have been growing rapidly since the late 2000s. Using microfluidics, most laboratory tests can be performed using a very small amount of biological samples. The samples that require centrifugation, such as separation of plasma from blood cells, can be achieved by allowing the sample to go through layers in the platform. Mixing of the samples and reagents, as well as preparation of samples, can be done by fabricating the platforms appropriately.

About 10 years ago, the Whitesides laboratory in Harvard University reported the development of a prototype of paper-

based microfluidics [4, 5]. Since then, a number of studies demonstrated a promising trend in paper-based microfluidics. Though the initial report involved the detection of glucose and protein in urine, the technique has been improvised to test blood typing, environmental analysis, and food chemistry. Paper as a channel substrate has several advantages including easy availability, low cost, porosity and capillarity, printability, and compatibility with many biochemical applications. According to the World Health Organization, microfluidic paper-based analytical devices (μPADs) will have a leading role in point of care diagnostics in resource-poor settings [4]. The technique using paper harnesses the capillary effect due to porosity, however the fluid migrates in all directions. In order to provide directional movement of the fluid in paper, channels are created by embedding hydrophobic materials outside the channel areas in the paper. This is achieved in two ways: (1) making the entire paper substrate hydrophobic by techniques such as waxing, and removing the hydrophobic materials (e.g. treatment to remove wax) in selected areas to create fluid migration channels, or (2) printing wax outside of predefined channel areas so that the channels will remain clear for fluid migration [6]. In order to make uniform channels on paper in microdimensions, techniques such as photolithography are used. These complex modifications are circumvented when wicking threads are used as channels [7, 8].

Fluid wicking threads have been in use for centuries, for example, in the use of oil lamps. The space between fibers in the thread allow capillary flow of fluids – this can be easily demonstrated when you taut a wet thread as droplets begin dripping from the thread. This is a demonstration of the need for capillary spaces for wicking. Though threads made of a variety of materials such hemp, nylon, and polyester can be used, cotton thread is an easily available source. It has also been shown that mercerized cotton does not require any preprocessing. Mercerization is done to increase the luster of the thread, and it is a process in which cotton is treated with sodium hydroxide and neutralized by acid. However, mercerization also improves the mechanical strength and wettability of the thread. Therefore, unlike paper, threads allow directional migration of fluids without the need for patterning. Threads may also be twisted or woven without destroying the capillary function. A thread may also be woven through the inner surface of a skin patch to the outer side enabling migration of fluids from the lower side to the outer side for detection in a wearable device. Recently, a thread based microfluidic network, integrating biological tissues coupled with physical and chemical sensors, was developed for real time data collection to be used as a wearable medical device [9]. These "smart threads" have limitless possibilities in diagnostics and wearable devices.

In a simple point of care detection, one end of the thread may be treated with the testing reagent, and an analyte solution may be applied to the other end (Fig. 1A). Branching

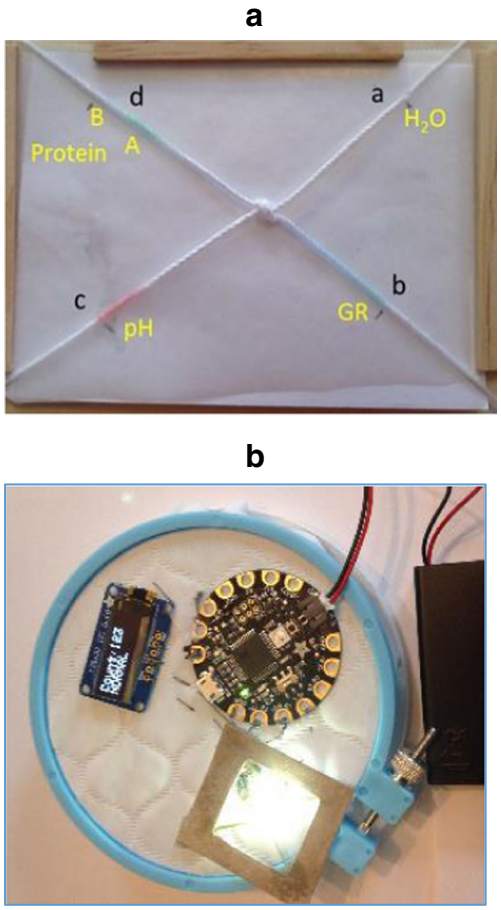

Fig. 1 A. A frugal analyte detection device. A homemade flow device demonstrating the feasibility of low cost analyte detection. GR = Glucose Reagent. Glucose reagent, protein and pH reagents were added to distal ends of the thread and analyte solution was applied to the center knot. Protein detection reagent consisted of two constituents, A and B. Each arm of the multichannel device is labelled a, b, c and d. **B**. Color detection: An Arduino based prototype that allows the detection and quantitation of the color developed on the thread. The channel is placed above the light source in the detection device

designs as shown in the Fig. 1A can be used for simultaneous detection of multiple analytes using small sample volumes. By reducing the thickness of the thread, the sample volume can be reduced to 50 μl or less. It is also possible to laminate a thread so that migrating fluids do not get exposed to the environment. Electronic devices can be coupled with thread-based microfluidics to facilitate quantitation of analytes (Fig. 1B) and used as wireless devices. The paper and thread-based low-cost point of care techniques are being successfully tested in more complex problems: for example, researchers have recently demonstrated the feasibility of a paper-based multiplexed transaminase test for rapid, semi-quantitative measurement of aspartate and alanine transaminases (AST and ALT) in finger-prick blood for liver function [10–13]. In summary, thread based microfluidics allow the development of low-volume, low-cost, and semiquantitative methods in point of care diagnostics in resource-poor areas.

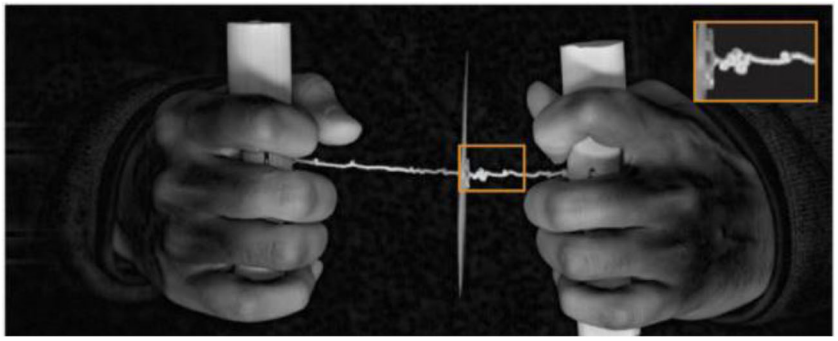

Fig. 2 The paperfuge. A paperfuge as developed by Dr. Prakash and colleagues. This device can separate plasma from small volumes of blood in 90 min without the need for electrical devices (Nat. Biomed. Eng. 2007: 1, 0009; adapted with permission)

Another challenge to healthcare diagnostics is sample preparation in the field. Though biological fluids such as urine can be directly applied on these devices, fluids such as blood may be better tested for analytes when the cells are separated. More specifically, red blood cells may not only interfere with redox reactions, they may also interfere in colorimetric detection. Centrifugation of biological specimens in the field has been a major challenge and people have tried several low cost methods (egg beaters, salad spinners, etc.) that do not depend on electricity, but with limitations including low rotational speeds (less than 300 g) [14]. In order to overcome these problems, Manu Prakash and colleagues at Stanford recently described a hand held whirligig centrifuge which can achieve up to 125,000 rpm (Fig. 2). The paperfuge, a centrifuge made out of a paper disc, was based on the ancient hand powered whirligig, also known as buzzer toy. They demonstrated separation of plasma from red blood cells with very high reproducibility and speed; a complete separation of 20 μl of human blood was achieved in 90 s. The hematocrit values obtained were comparable to that obtained using standard centrifugation. By performing a 15 min centrifugation, they were able to successfully separate the buffy coat from human blood.

Future directions

The frugal sample preparation techniques, paper or thread based channels, reaction substrates, and low cost optical (e.g. Arduino-based) detection systems have the potential to be used at home or by community health workers to improve healthcare in resource poor settings. These stand-alone units can be enabled wirelessly and operated with smart phones by integrating application interfaces. The vast majority of challenges in this area of research center around the development of simple medical systems that yield reproducible and quantifiable results with the needed sensitivity. With adequate technical training and educational initiatives it is possible to produce these simple medical systems locally. The advantages of implementing these methods in low income neighborhoods include bringing affordable clinical testing to the patient, increasing health awareness among the poor, and local empowerment in healthcare.

The emergence of novel paper and thread based techniques are set to revolutionize point of care diagnostics that can empower individuals to perform health care diagnostics for preventative measures and to complement telemedicine consultations. These techniques are expected to play a prominent role in personalized medicine within the decade.

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