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PAPER

nanoLAB: An ultraportable, handheld diagnostic laboratory for global health†

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Driven by scientific progress and economic stimulus, medical diagnostics will move to a stage in which straightforward medical diagnoses are independent of physician visits and large centralized laboratories. The future of basic diagnostic medicine will lie in the hands of private individuals. We have taken significant strides towards achieving this goal by developing an autoassembly assay for disease biomarker detection which obviates the need for washing steps and is run on a handheld sensing platform. By coupling magnetic nanotechnology with an array of magnetically responsive nanosensors, we demonstrate a rapid, multiplex immunoassay that eliminates the need for trained technicians to run molecular diagnostic tests. Furthermore, the platform is battery-powered and ultraportable, allowing the assay to be run anywhere in the world by any individual.

Introduction

With increases in healthcare costs, a constantly expanding population, and a limited supply of physicians,[1,2] radical changes must be made in order for the healthcare system to remain sustainable. A compelling solution to this pressing need is to alleviate some of the burden on the healthcare system and on physicians by equipping the general population with the tools to make their own diagnoses.[3] While there will always be a need for physicians to treat complicated diseases, manage multifaceted treatment regimens, and perform surgical procedures, there are several aspects of the current healthcare system that can be streamlined. Some researchers have taken steps in this direction by introducing point-of-care (POC) testing into the community; however, many of these technologies to date rely on medical professionals to run the assays.[4,5,6,7] By and large, easy to use POC devices for individuals are still limited to simple scenarios like pregnancy testing and glucose monitoring. By introducing more versatile molecular diagnostic tools to the general public that individuals can use on their own, they will be able to manage many unique aspects of their own healthcare and bypass costly and time consuming clinic visits in many circumstances.

In this report, we present a method of protein and virus detection using a magnetic nanosensor-based technology that makes it feasible to bring the same diagnostic potential of centralized laboratories to developing countries, remote field settings, airports, waiting rooms, or to the patient's home. By developing a rapid protein assay that obviates the need for washing steps and does not require training prior to implementation, all individuals will be capable of diagnosing him or herself with respect to a variety of disease states or monitoring response to therapy. In addition, by miniaturizing the detection platform into a handheld and battery powered device, the diagnostic tool, coined the "nanoLAB", can be transported anywhere, removing necessary ties to a hospital or laboratory setting. Just as miniaturization of computers, which once filled large rooms, into the microprocessor revolutionized the computer industry,[8] miniaturization of medical diagnostic tools has the potential to restructure our healthcare system in a similar fashion. By moving away from costly and complex biomolecular detection platforms that are constrained to centralized laboratories, we set out to design a medical diagnostic tool which is both cost effective and will allow individuals to take an active part in their own health care. In addition, applications in the developing world, where access to modern medical laboratories and trained personnel are often nonexistent, will make an impact on the quality of life and health care.

The recent proliferation of research in nanotechnology has led to the development of several innovative biosensing modalities.[9,10,11,12,13] Accordingly, over the past several years, the sensitivity, dynamic range, and multiplex capability of each platform has been pushed to new limits. Laboratories around the world have begun to see the benefits of this research as these

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devices transition from academia into practice. However, many technologies have not been able to fully surmount the POC barrier due to issues related to the complexity of the assay or microfluidic integration,[14] expense of the technology, or inherent lack of portability. For a technology to be used on-site by non-technical end-users, it must be compact (ideally battery powered), simple to setup and operate, highly sensitive, quick, and reliable. With the nanoLAB, all of these requirements have been accomplished in a platform that is more sensitive than the current gold standard in protein detection, the enzyme linked immunosorbent assay (ELISA).

Materials and methods

Fabrication of the disposable nanoLAB stick

The disposable stick contains a silicon die, with 64 giant magnetoresistive (GMR) spin-valve sensors (fabricated according to Osterfeld *et al.*[12]), that was glued to a printed circuit board (PCB) with two part epoxy. Nine of the sensors were wirebonded directly to pads on the PCB. The sensors were arranged in a half Wheatstone bridge with one shared reference sensor. The reaction well was made by bonding Tygon tubing (Tygon® tubing, ¼″ ID x ¾ ″ OD, 5 mm in length) to the chip with a two component epoxy. A dual in-line package (DIP) header was soldered on to the stick as a connector.

Surface functionalization

The GMR sensor surface was first cleaned with acetone, methanol and isopropanol and dried with nitrogen air. Next, a ten minute exposure of the chips to oxygen plasma (PDC-32G Basic Plasma Cleaner, Harrick Plasma) was implemented in order to remove organic materials. Subsequently, a 2% solution of polyethylenimine (PEI, CAS 9002-98-6, Sigma Aldrich) in deionized water was added to the chip. After 3 min incubation, the chips were rinsed with deionized water and then baked for 15 min at 150 °C. Next, 120 nL drops of each capture probe (anti-p24, anti-HCV, anti-CEA, anti-EpCAM, and/or anti-VEGF) were placed over at least two sensors at a concentration of approximately 1 mg mL^{-1}. In addition, control sensors were covered with 1% bovine serum albumin (BSA) in phosphate buffered saline (PBS). A reference sensor was deposited with a two component epoxy. The capture probes were incubated for 1 h at room temperature at 90% relative humidity. The reaction well on each stick was subsequently washed with a washing buffer (0.1% BSA and 0.5% Tween 20 in PBS) and then blocked with 50 μL of 1% BSA in PBS for 30 min.

Wash-free protein detection assay

20 μL of sample (either p24, HCV capsid protein, CEA, EpCAM, and/or VEGF spiked into PBS) was added to the reaction well. After at least 5 min incubation of the sample, 20 μL of magnetic nanoparticle tags, functionalized with streptavidin, (MACS 130-048-102, Miltenyi Biotec, Auburn, CA) were added to the reaction well followed by 10 μL of biotinylated detection antibodies complementary to the proteins of interest at a concentration of 10 μg mL^{-1}. The user then seals the reaction well and hits "start" on the handheld device. After 15 min, the assay is complete and the protein concentration is displayed to the user *via* a panel of light emitting diodes (LEDs).

Fabrication of the circuit boards

The nanoLAB platform is composed of three circuit boards: a disposable stick, a coil board, and a data acquisition (DAQ) board. The electromagnet on the coil board is manufactured out of 50 mil (5 × 10^{-5} inch) traces on a four layer FR4 PCB. Magnetic flux-guides made out of cold rolled steel were machined into trapezoids and glued to the PCB. The DAQ board contains two direct digital synthesis integrated circuits (Analog Devices, AD9833) to generate the coil and sensor excitation signals. The front-end contains an instrumentation amplifier (Analog Devices, AD8221) to amplify the differential signal from the bridge. A microprocessor digitizes the signals and performs the necessary signal processing (Microchip, dsPIC30F6012a). All electronic components for the project were purchased from Digikey and assembled in house. The rechargeable battery used was a 3 cell 11.1 V 2000 mAh lithium polymer. The nanoLAB case was designed in AutoCAD and was manufactured by D&K Precision Sheetmetal Inc. (Mountain View, CA).

Results

GMR nanosensors

In order to make a protein and virus detection platform that is compact, robust, and sensitive, we have chosen to employ GMR nanosensors, which are well suited for integration into lab-on-a-chip systems.[15,16] The nanosensors exhibit magnetoresistance, a quantum mechanical property in which a change in the external magnetic field induces a measurable change in the electrical resistance of the sensor. Spin-valve type GMR sensors have demonstrated detection characteristics as low as attomolar concentrations when performing traditional sandwich assays and utilizing a magnetic nanotag as a protein label.[17] In more recent work, we have redesigned the traditional sandwich assay into an autoassembly immunoassay that eliminates the need for washing steps.[18] In its inception, we demonstrated the utility of the autoassembly assay for investigating antibody cross-reactivity in a rapid, high throughput, and scalable manner. In the present work, we leverage a similar autoassembly immunoassay in order to realize the truly POC application of our device. The simple, rapid, and wash-free nature of this assay for protein and virus detection can be performed without any training, bulky external laboratory equipment, or the need for complex microfluidic integration. If desired, however, the system is fully compatible with microfluidic integration (Fig. S1†). By implementing self-powered microfluidics, easy-to-use delivery of assay reagents can be achieved.[19]

Autoassembly wash-free immunoassay

The autoassembly immunoassay entails minimal human intervention comprising three simple steps (Fig. 1a): (1) The operator places the sample (buccal swab, serum, urine, cell lysates, *etc.*) into the reaction well. The reaction well is equipped with an array of GMR nanosensors pre-functionalized with a panel of antibodies targeting predetermined proteins or viruses of interest.

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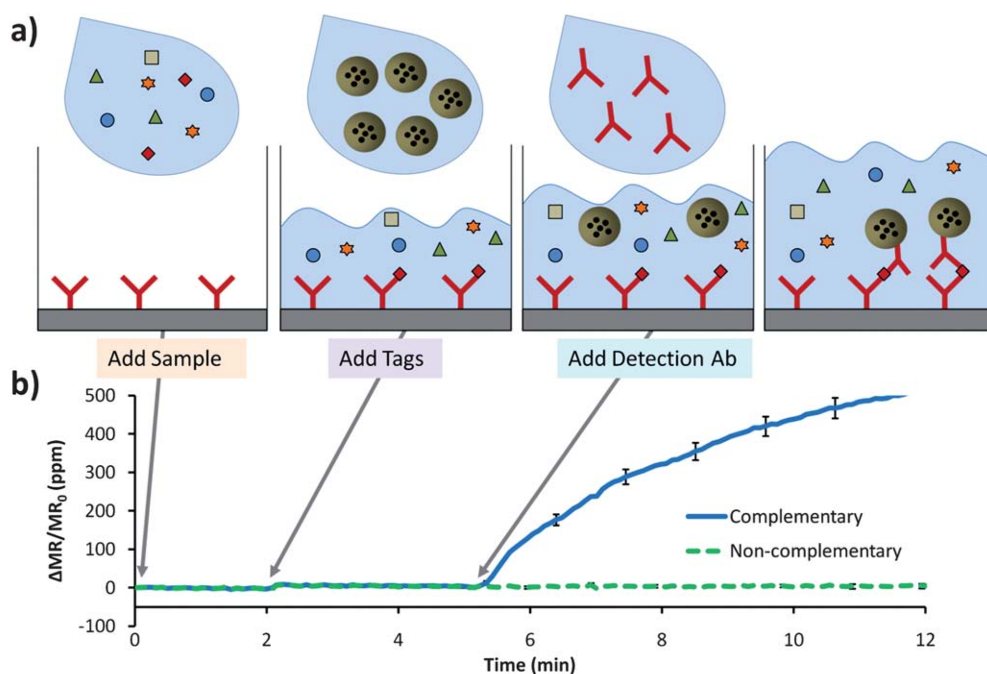

Fig. 1 Wash-free protein detection assay. (a) A schematic representation of the protein detection assay. Step 1, addition of heterogeneous sample containing the target of interest. Step 2, introduction of the magnetic nanotags functionalized with streptavidin. Step 3, addition of biotin-labeled detection antibody. The detection antibody autoassembles to link the magnetic nanotags within close proximity to the captured antigen, enabling detection by the underlying GMR sensor. Each step is performed sequentially, so no washing steps are required. (b) Real-time monitoring of sensors during the wash-free assay. Addition of the sample and magnetic tags contribute negligible signal, however, once the detection antibody is introduced, the magnetic tags are finally detectable over the sensors with the appropriate capture antibody. The negative control sensors, coated with antibodies to another protein, remain flat, indicating negligible non-specific binding. The *y*-axis units are the change in magnetoresistance normalized to the initial magnetoresistance presented in parts per million (ppm).

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The appropriate analytes in the sample selectively bind to the immobilized antibodies. No signal is detected by the sensors at this point because the sample lacks a detectable magnetic content. (2) Magnetic nanotags containing streptavidin functional groups are subsequently added to the reaction well using a disposable, pre-aliquoted vial. The tags simply remain in solution un-reacted until the final step as there is nothing currently present in the reaction well to cause the magnetic tags to congregate over the sensor surface in high enough concentration to be detected. Of note, a slight rise in the sensor signal is observable due to the presence of a few magnetic nanotags simply floating over the sensor surface (Fig. 1b). (3) Pre-aliquoted, biotinylated detection antibodies are finally added to the reaction well. These detection antibodies diffuse toward the sensor surface and act to autoassemble, linking the magnetic nanotags directly over the sensor surface. Each of the eight sensors in the array is monitored in real-time, providing multiplex protein or virus detection capabilities (Fig. S2†). By providing the reagents in pre-aliquoted vials (similar to a disposable eye drop vial) and the reaction chamber in a well format, the assay can be easy to setup and use by the general public.

GMR spin-valve sensors with an ultrathin passivation are well suited for the novel wash-free assay because they are proximity based sensors—only magnetic nanotags within ∼150 nm of the surface are detected.[20] The magnetic nanotags are stable in solution, therefore, they do not settle or precipitate, contributing negligible signal in the absence of the detection antibody. This occurrence is apparent in Fig. 1b where no rise in signal is observed between two and five minutes while the magnetic nanotags are in solution above the GMR sensor. The colloidal stability of our magnetic nanotags offers a significant advantage over the majority of protein detection platforms which require washing steps to remove excess antibodies and tags prior to detection. These washing steps are difficult to perform in a POC setting and often require the supervision of trained lab technicians. Because the nanoLAB obviates the need for washing steps, it offers a fast, simple testing process that allows the device to be used by untrained laymen in non-laboratory settings.

Miniaturization

In order to facilitate effective deployment in the field by non-technical users, it is important that the wash-free assay be integrated into an ultraportable and battery-powered test module.[21] This advancement removes the need for a constant supply of electricity or a designated laboratory. Since, the form factor of GMR sensors is very small, only dictated by lithography used in their fabrication, by miniaturizing the electronic components of the current setup and utilizing nanosensors, we are able to replace a laboratory full of equipment with a handheld and battery powered device (Fig. 2). No lasers or expensive charge coupled device (CCD) cameras are required for the platform, which uniquely positions GMR based biosensors for

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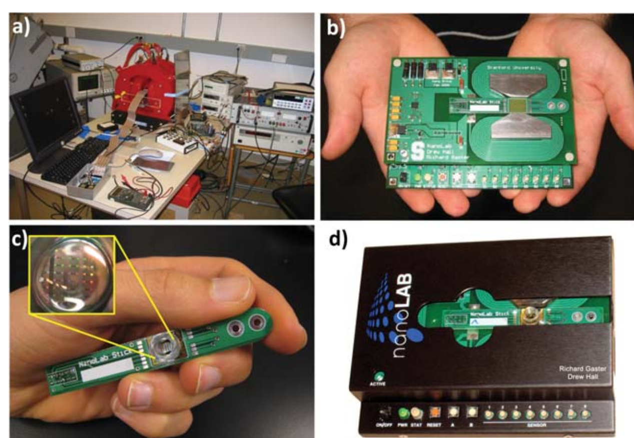

Fig. 2 Miniaturization of the original biostation into a handheld, battery powered device. Demonstration of miniaturization from (a) the initial laboratory test station which occupied an entire room into (b) handheld point-of-care diagnostic device. All components of the laboratory setup have been miniaturized and incorporated into an ultraportable platform. (c) Photograph of the disposable stick and reaction well in which the assay is run. Insert: Inside the reaction well is an array of GMR sensors capable of simultaneously monitoring multiple different proteins in a 20–50 μL sample. (d) Image of the "nanoLAB" device with case and test stick.

ultraportable, POC applications (refer to Fig. S3–S5† for more details on miniaturization of the electronics).

One of the largest and most difficult components to miniaturize in the research grade biostation[22] was the Helmholtz electromagnet (the large red object in Fig. S3†). This bulky component alone weighs over 100 kg and when coupled with the associated power amplifier, consumes over a hundred watts of power from a wall outlet. Reducing the form factor and power consumption to create a handheld, ultraportable device posed several engineering challenges. To accomplish this miniturization, a planar electromagnet was designed using the traces on a 4 layer PCB (Fig. 3a). This miniature electromagnet generates a magnetic field perpendicular to the board (out of the plane). To re-orient this field to be in-plane with the GMR nanosensors, soft magnetic flux guides manufactured out of cold rolled steel were added. The trapezoidal geometry of these flux guides concentrate the magnetic flux over a small region, acting as a form of passive amplification. This electromagnet is driven by a custom designed class-A power amplifier. Fig. 3b depicts the relationship between the current through the electromagnet and the measured field across the sensor array. Power consumption was minimized by power cycling the power amplifier and electromagnet when it is not being used.

While progress has been made towards implementing a true POC testing device using magnetic sensing,[23,24,25] these implementations have relied on an external power source and an external PDA (either a pocket PC or a laptop) for signal processing, data logging, and display. In this work, we have designed a fully integrated, cost effective unit with a built-in microprocessor to perform all of these tasks. GMR spin-valves typically exhibit high flicker noise (also called 1/*f* noise because it is inversely proportional to frequency). To increase the signal to noise ratio (SNR) and improve the detection capability of the device, the signal from the magnetic nanotags is modulated to a higher frequency, away from the low frequency noise.[26] To recover this signal, the microprocessor digitizes the response from the GMR nanosensors and performs the filtering and demodulation. Fig. 3c,d illustrates this process with the incoming modulated signal and the clean output signal after a 113th order digital filter has been applied. Due to the limited computational power of the microprocessor, a minimalistic version of the computationally intensive signal processing algorithms used in our desktop station was implemented.[27] With the integration of a power source, signal processing, and display functionality into the nanoLAB, no additional components are required to run and measure an assay, allowing it to truly be a POC testing device.

In POC settings, it is not practical to perform sample preparation prior to running the experiment. The platform must have reproducible detection despite differences in the sample fluid (buccal swab, serum, urine, cell lysates, *etc.*), pH, and temperature. Fortunately, GMR spin-valve sensors have been reported to be insensitive to different sample matrices making the platform highly generalizable to a diversity of biologically relevant samples, removing the need for any complex sample preparation.[17] This subtle requirement is often overlooked or ignored when discussing POC diagnostics, but is critical to the utility of such a diagnostic device in real-world settings.

Detection of HIV p24 protein

The user interface of the test module has been designed to provide both a rapid readout and an easy-to-comprehend, user-friendly display. The microprocessor monitors the real-time binding events and predicts the saturation signal based on the initial binding trajectory. Monitoring the binding trajectory in real-time significantly reduces the assay time and produces a more reliable final readout than taking a single point measurement at an arbitrary time prior to signal saturation. Fig. 4a shows the binding curves of various concentrations of human immunodeficiency virus (HIV) p24 protein ranging from 100 ng mL^{-1} down to 32 pg mL^{-1}. We used these binding trajectories to train the microprocessor for future experiments. The assay runs for 15 min to allow sufficient time for differentiable signals to emerge while still providing rapid results for POC utility. Each disposable nanoLAB stick is equipped with 8 sensors allowing for up to 8-plex protein detection simultaneously in a single assay and permitting entire panels of markers to be monitored in real-time. The signals detected by each sensor are displayed to the user in a very simple manner, *via* colored light emitting diodes (LEDs). The microprocessor is pre-programmed with tables that contain calibration curves for each target protein as well as the corresponding concentration thresholds (undetectable, low, medium, and high) which are predetermined by physicians according to clinically relevant therapy regimens (Fig. 4b). As the assay runs, the colored LEDs dynamically change and are presented to the user. At the end of the 15 min incubation time, the computed saturation signal is compared to threshold values and the microprocessor selects the appropriate final color for each LED. For example, when a 10 ng mL^{-1} of p24 capsid protein was tested on the nanoLAB, a signal of 39 ppm was measured and the LED for

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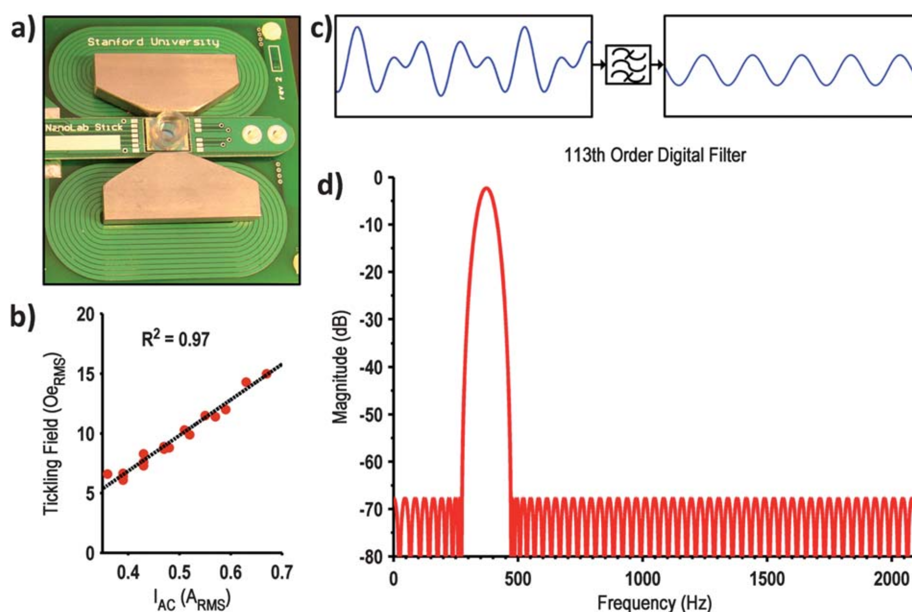

Fig. 3 (a) Photograph of planar electromagnet and flux guides (b) Measured magnetic field *versus* current applied to the electromagnet (c) Time domain signal from the GMR nanosensors before and after applying the digital filter. (d) Transfer function of the 113th order digital finite impulse response (FIR) filter.

sensor 3 (on the device named S4) turned orange, indicating a moderate level of protein content (Fig. 4b,c). All the other sensors, functionalized with non-complementary antibodies, registered no signal. Similar experiments have been demonstrated with detection of hepatitis C virus capsid protein,[28] presented in Fig. S6. The combination of a simple assay and user-friendly readout system will facilitate the POC utility of this platform in remote field settings.

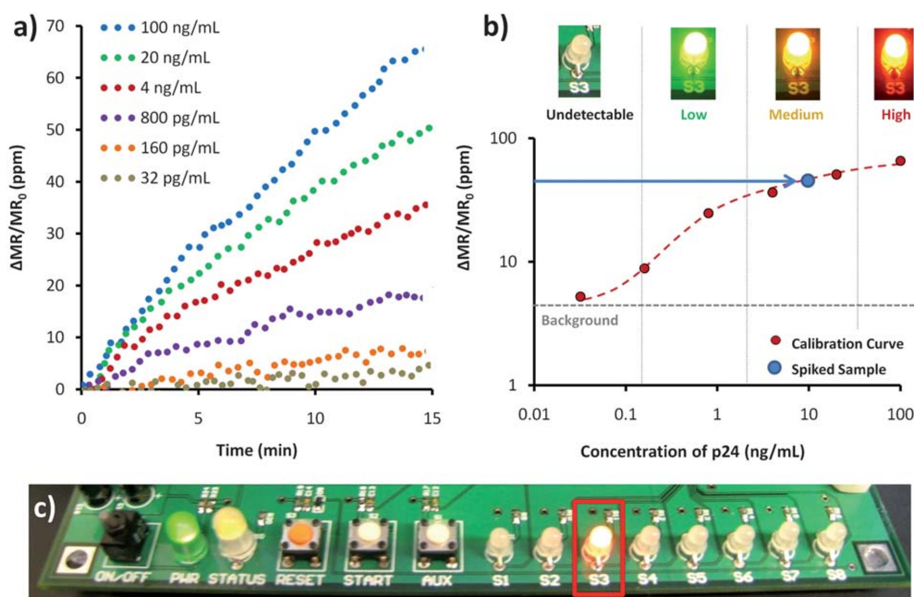

Fig. 4 Detection characteristics and readout of the nanoLAB. (a) Real-time binding curves of diluted HIV p24 protein at concentrations ranging from 100 ng mL^{-1} to 32 pg mL^{-1}. The sensors, functionalized with bovine serum albumin (BSA) as a negative control, gave minimal signal indicating negligible non-specific binding of the wash-free assay. (b) Calibration curves for each marker of interest were generated after 15 min of incubation time. The final curve can be subsequently divided into 4 pre-determined concentration ranges and will be presented *via* color coded LEDs to the end user. If the signal is undetectable, the indicator light will not be lit. If the signal is low, medium, or high, then the light indicator will display green, orange, or red light respectively. (c) To demonstrate the specificity and readout of the device, we functionalized each of the eight sensors with a different capture antibody. For example, sensor S3 was functionalized with anti-p24 antibody. When 10 ng mL^{-1} of p24 antigen was spiked into the reaction well, only sensor S3 lit up in the medium concentration regime.

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Discussion

Currently, proteomics in clinical laboratory settings utilize fluorescent detection based on the ELISA, which rely on enzyme labels, has a detection limit of around 10–15 ng mL^{-1},[29] and 2 orders of dynamic range. The wash-free assay presented here has a similar dynamic range but achieves over an order of magnitude higher sensitivity in a fraction of the time. The higher sensitivity is largely due to the use of magnetic rather than fluorescent labeling. With this technology, detection below 100 pg mL^{-1} in a 25 μL sample was demonstrated. While the sensitivity requirements are typically not as stringent in POC settings, the increased sensitivity allows our assay time to be significantly shortened, leading to faster diagnostic times and earlier treatment of disease. Bruls *et al.* recently described a POC device using magnetic nanoparticles for sample manipulation and a reduced assay time.[30] Their magnetic immunoassay is also wash-free; however, it requires two additional electromagnets positioned directly above and below the reaction site to remove the unbound magnetic nanoparticles. While necessary in their optical measurement setup, the un-reacted tags in our assay do not contribute any signal and thus do not need to be magnetically removed. Their approach does have the benefit of even shorter incubation times and is something that we are currently investigating. Their technique utilizes optical detection, however, as discussed in their paper, this actuation mechanism is more difficult to implement with magnetic sensors such as the GMR nanosensors used in this work.

An important requirement for POC applications is that the platform is cost effective. The re-usable platform can be constructed for under $200 (Table S1†). More importantly, the total cost of each disposable stick (including the antibodies, magnetic tags, sensors, assembly, *etc.*) in high volume is less than $3.50 (Table S2†) making this diagnostic tool cost effective enough to be used in both developing and developed nations. Furthermore, we believe the cost could be substantially reduced to less than $1 with slight changes to the sensor array and by preparing the magnetic nanoparticles in-house.

A universal concern in POC diagnostic tests is the reproducibility of the assay in extreme environments. In particular, some locations across the globe can experience high temperature swings and variable humidity. Several solutions, however, have been proposed to help mitigate this concern. It has been demonstrated that on-chip dry reagents can be preserved using trehalose stabilization. Trehalose is a non-reducing sugar, unable to undergo the Maillard reaction and remains in a glassy state under 106 °C, preventing degradation or crystallization.[31] According to the CDC, the shelf life of dried anti-p24 antibodies can range from 6 months to 2 years in current POC devices.[32] We believe, using similar reagent storage techniques, we too can accomplish shelf-life for our reagents of six months or more. In addition, we have begun to investigate the use of more stable affinity reagents such as aptamers, which are even more robust than antibodies over time and across temperatures. By packaging the disposable sticks into sealed and vacuumed containers, storage in humid environments will not be an issue either. Finally, many diagnostic assays require enzymes to catalyze reactions as part of the diagnostic process. The use of enzymes can vary quite a bit in their activity over a range of temperatures. The nanoLAB, however, does not rely on any enzyme labels and therefore, the assay is significantly less sensitive to fluctuations in temperature.

In summary, as demands for medical services increase due to population growth and societal mandates for universal healthcare in the developed and developing worlds, innovations in diagnostic testing will be necessary to provide timely, easily accessible, and inexpensive results. To this end, a cost-effective, portable and easy-to-use device has been developed that will allow individuals to conduct their own molecular diagnostic tests without the need for a centralized laboratory, laboratory technicians, clinic or emergency room visits, or in some instances visits to a physician's office altogether. With this device, in a matter of minutes, patients can receive accurate molecular based diagnosis on their own. In addition, due to the versatility of the sensing platform, the potential applications are vast, especially in the realm of infectious diseases. By interchanging nanoLAB sticks pre-functionalized with different capture antibodies or aptamers, this technology can be deployed for detection of infectious diseases that pose large scale public health risks, such as HIV, HCV, tuberculosis, *Salmonella typhii*, toxigenic *E. coli*, as well as swine (H1N1) flu and avian (H5N1) flu. In addition, screening for enteric infections is of particular interest, as the device will enable public health officials to inspect and immediately detect contamination on-site to help safeguard food and water supplies for populations worldwide. This technology has the potential to change the practice of medicine by providing society with a new medical infrastructure: one that allows individuals to literally take health care into their own hands.

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