Universal mobile electrochemical detector designed for use in resource-limited applications

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Edited by Alexis T. Bell, University of California, Berkeley, CA, and approved June 30, 2014 (received for review March 30, 2014)

This paper describes an inexpensive, handheld device that couples the most common forms of electrochemical analysis directly to “the cloud” using any mobile phone, for use in resource-limited settings. The device is designed to operate with a wide range of electrode formats, performs on-board mixing of samples by vibration, and transmits data over voice using audio—an approach that guarantees broad compatibility with any available mobile phone (from low-end phones to smartphones) or cellular network (second, third, and fourth generation). The electrochemical methods that we demonstrate enable quantitative, broadly applicable, and inexpensive sensing with flexibility based on a wide variety of important electroanalytical techniques (chronocoulometry, cyclic voltammetry, square wave voltammetry, and potentiometry), each with different uses. Four applications demonstrate the analytical performance of the device: these involve the detection of (i) glucose in the blood for personal health, (ii) trace heavy metals (lead, cadmium, and zinc) in water for in-field environmental monitoring, (iii) sodium in urine for clinical analysis, and (iv) a malarial antigen (Plasmodium falciparum histidine-rich protein 2) for clinical research. The combination of these electrochemical capabilities in an affordable, handheld format that is compatible with any mobile phone or network worldwide guarantees that sophisticated diagnostic testing can be performed by users with a broad spectrum of needs, resources, and levels of technical expertise.

Electrochemistry provides a broad array of quantitative methods for detecting important analytes (e.g., proteins, nucleic acids, metabolites, metals) for personal and public health, clinical analysis, food and water quality, and environmental monitoring (1, 2). Although useful in a variety of settings, these methods—with the important exception of blood glucose meters (3, 4)—are generally limited to well-resourced laboratories run by skilled personnel. If simplified and made inexpensive, however, these versatile methods could become broadly applicable tools in the hands of healthcare workers, clinicians, farmers, and military personnel who need accurate and quantitative results in the field, especially in resource-limited settings. Furthermore, if results of testing were directly linked to “the cloud” using available mobile technology, expertise (and archiving of information) could be geographically decoupled from the site of testing. To enable electrochemical measurements to be performed and communicated in any setting, a useful technology must be (i) able to perform complete electrochemical analyses while remaining low in cost, simple to operate, and as independent of infrastructure as possible; and (ii) compatible with any generation of mobile telecommunications technology, including the low-end phones and 2G networks that continue to dominate communications in much of the developing world.

The parallel development of two successful technologies—mobile health (mHealth) and point-of-care (POC) diagnostics—provides a pair of convergent paths toward a potential solution, although, practically, technical and conceptual connections between them are weak (5, 6). mHealth is the general term given to health-related information technologies that depend on mobile wireless communication for connectivity. Although these networks and devices can capture information relevant to health (and other problems involving chemical and biological sensing) and transmit it globally over the web, they typically do not have the capability to collect data directly, and rely instead on (error-prone) data entry by the user, either alphanumerically or through images. Conversely, although POC diagnostics (e.g., lateral flow immunoassays, urinalysis dipsticks, and handheld glucometers) provide examples of simple, inexpensive devices that enable minimally trained users to perform chemical testing, these devices are typically limited in function and cannot connect easily to networks for mHealth.

Many devices are now being explored that attempt to connect mHealth with POC testing. Because these systems have been developed in, and often implicitly targeted toward, the developed world, they typically require (i) smartphones, (ii) custom application software (apps), (iii) third or fourth generation (3G/4G) data networks, (iv) proprietary connectors for sophisticated sensors that interface with diagnostic tests, and in some cases (v) a substantial level of technical sophistication (7–13). As such, these first-generation hybrid mHealth/POC devices are often too expensive, too restricted to a single type of phone, too limited in function, and too reliant on advanced mobile telecommunication technology to be practically applicable in resource-limited settings.

Significance

The ability to perform electrochemical testing in the field, and in resource-limited environments, and to transmit data automatically to “the cloud” can enable a broad spectrum of analyses useful for personal and public health, clinical analysis, food safety, and environmental monitoring. Although the developed world has many options for analysis and web connection, the developing world does not have broad access to either the expensive equipment necessary to perform these tests or the advanced technologies required for network connectivity. To overcome these limitations, we have developed a simple, affordable, handheld device that can perform all the most common electrochemical analyses, and transmit the results of testing to the cloud from any phone, over any network, anywhere in the world.

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The authors declare no conflict of interest.

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This article contains supporting information online at www.pnas.org/lookup/suppl/doi:10.1073/pnas.1405679111/-/DCSupplemental.

This article is a PNAS Direct Submission.

Edited by Alexis T. Bell, University of California, Berkeley, CA, and approved June 30, 2014 (received for review March 30, 2014)
where 3G/4G networks and smartphones are still not widely used. Although mobile connectivity has spread rapidly across the world, low-end mobile phones and second generation (2G) networks dominate the telecommunications infrastructure (especially in rural areas) in the developing world (14, 15) and will continue to do so for the foreseeable future (Fig. S1). This lack of advanced mobile technologies in much of the developing world, coupled with myriad operating systems, generations of software, and types of connecting ports among all mobile phones, presents a major challenge to any device that requires a specific phone or application to communicate the results of testing.

To provide a system that combines broad flexibility in electrochemical capability with connectivity to the web through widely available technology, we have developed a low-cost (~US$25), handheld device that (i) performs all of the most common electrochemical methods; (ii) interfaces with a variety of commercially available electrodes; (iii) provides on-board vibration to mix samples when necessary; and (iv) is simple to operate. For communication of data, we exploited the ubiquity of the hands-free audio port, a nearly universal interface to mobile phones, and designed a protocol to transmit digital data over a live voice connection. This approach guarantees that (i) any phone can function as a modem to link the results of testing to a remote facility through any available mobile network (2G, 3G, or 4G), and that (ii) the device does not require any specific software application, operating system, or phone model.

We refer to our device as a universal mobile electrochemical detector (uMED) because of (i) its universal compatibility with mobile technology; (ii) the broad range of electrochemical techniques that it can perform, including various forms of amperometry, coulometry, voltammetry (e.g., cyclic, differential pulse, square wave), and potentiometry; and (iii) its broad compatibility with different commercially available and paper-based electrodes. Fig. 1A and B shows the uMED connected to a low-end mobile phone and sketches the flow of information through an in-field measurement to a remote facility.

We demonstrate the electrochemical capabilities of the uMED by first comparing the performance of each implemented mode of sensing to a commercial electrochemical analyzer. We then test the uMED in four representative applications: (i) as a personal diagnostic device for the detection of glucose in blood; (ii) for in-field testing of water quality by detection of heavy metals; (iii) as a low-cost, clinical analyzer for detection of electrolytes; and (iv) to perform an ELISA for the detection of a malarial antigen. We also demonstrate the transmission of POC data over voice through a low-end mobile phone to a remote computer.

Materials and Methods

Design of the uMED. Fig. 1C and D shows a block diagram and circuit schematic that describes the electronic design of the device. Briefly, the device includes (i) a custom-made, three-electrode potentiostat, formed from two operational amplifiers, to perform electrochemical measurements; (ii) three digital switches to reconfigure the potentiostat between two- and three-electrode operation and between amperometric or potentiometric measurement; (iii) a small vibration motor to mix fluid samples; (iv) a dual-channel, 16-bit, digital-to-analog converter (DAC) to set the potentials of the reference electrode (RE) and working electrode (WE); (v) a single-channel, 16-bit analog-to-digital converter (ADC) to sample data at high resolution; (vi) a pair of sockets to interface with various electrodes; (vii) a liquid crystal display (LCD) and three buttons to interface with the user; (viii) an audio port to communicate data; (ix) a microcontroller to operate the device; (x) a serial port to program the microcontroller; (xi) a 3.7-V lithium polymer battery to supply power to the device; and (xii) a pair of 3.3-V voltage regulators to supply voltage independently to the digital (microprocessor) and analog (potentiostat, ADC, and DAC) portions of the circuit. We chose the Atmega328 (Atmel) 8-bit microcontroller for its compatibility with the popular Arduino development environment and its many, programmable channels for input and output. The bill of materials (BOM) for uMED was ~US$25, and the range of electrochemical measurements that we could perform were primarily limited by (i) the practical range of applied voltages (±2 V), (ii) the sample-rate of the ADC (800 Hz), (iii) the resolution of the DAC (0.05 mV), and (iv) the electronic noise floor (0.5 nA√Hz). Within these limitations, the uMED can perform the most common electrochemical measurements. We include further technical details, including a circuit diagram (Fig. S2) and a BOM (Table S1) in SI Text.

Modes of Electrochemical Detection. The uMED can perform (but is not limited to) the following five important types of electroanalytical techniques: (i) cyclic voltammetry (CV), (ii) chronoamperometry, (iii) differential pulse voltammetry (DPV), (iv) square wave voltammetry (SWV), and (v) potentiometry. Depending on the selected mode, the microcontroller sets the potentiostat to measure current in a two-electrode (chronoamperometry) or three-electrode (CV, SWV, DPV) configuration, or voltage (potentiometry) in a two-electrode configuration. Fig. S3 shows general schemes of the pulse sequences that we used for the different current-based measurements. To compare the performance of the uMED to that of a commercial, bench-top electrochemical analyzer—a potentiostat (Autolab PGSTAT12, Metrohm) for current-based measurements and a pH meter (443i; Corning) for potentiometric measurements—we used both devices to perform a series of five test measurements for five common electrochemical pulse sequences: (i) CV on a solution of ferricyanide/ferrocyanide redox couple (linear sweep from a potential $E_1 = -0.5$ V to $E_2 = 0.5$ V with a step size $E_{step} = 2.5$ mV and a scan rate of 50 mV/s); (ii) chronoamperometry on a solution of ferrocyanide ions ($E = 0.5$ V for 30 s); (iii) SWV ($E_l = -0.2$ V, $E_2 = 0.6$ V, frequency $f = 10$ Hz, peak-to-peak potential $\Delta E = 50$ mV, and $E_{ref} = 4$ mV) and (iv) DPV ($E_l = -0.2$ V, $E_2 = 0.6$ V, $f = 10$ Hz, $t = 10$ ms, $\Delta E = 140$ mV, $E_{ref} = 7$ mV) on solutions of 1-naphthol, which we adapted from previous literature (16, 17); and (v) potentiometry on solutions of sodium and potassium ions. We include more details in SI Text.

Electrochemical Applications. We used the device in four real applications that involve the detection of (i) glucose in blood by chronoamperometry, (ii) heavy metals in water by square wave anodic stripping voltammetry (SWASV), (iii) sodium in urine by potentiometry, and (iv) the malarial antigen Plasmodium falciparum histidine-rich protein 2 (PFHRP2) through a sandwich, electrochemical ELISA using chronoamperometry for the detection step. The pulse sequence for each application is stored in the device;
when the user selects the appropriate mode using a button, the uMED acquires and computes data automatically without further input from the user. For these measurements, we used commercial glucose test strips, screen-printed electrodes (SPEs), and ion-selective electrodes (ISEs) to evaluate the performance of our device, ensure proper calibration, and determine the limits of detection in all modes of measurement. These electrodes are readily available and guarantee that the device is immediately applicable to real-world testing.

**Detection of Glucose in Blood.** For the detection of blood glucose by chronoamperometry, we used glucose test strips (TrueTrak; CVS) and whole blood samples (Meter Trax Control; BioRad). For each measurement, we selected glcometry from the uMED menu, inserted the test strip, and applied a droplet of blood (~5 μL, a volume easily obtained from a finger prick) to the test strip. Application of the sample triggered the chronoamperometry sequence (Fig. S3B), which began with an incubation period of 5 s at t = 0 followed by a measurement period of 10 s at t = 0.5 V. The uMED sampled the output signal at 8 Hz and digitally averaged the transient signal over the last t = 5 s of the measurement.

**Detection of Heavy Metals in Water.** For the detection of heavy metals [Zn(II), Cd(II) and Pb(II)] by SWASV, we used SPEs (DRP110-CNT; DropSens) that had three electrodes: (i) a WE consisting of carbon ink modified by carbon nanotubes, (ii) a reference electrode consisting of Ag/AgCl ink, and (iii) the RE consisting of Ag/AgCl ink. This procedure requires a four-step pulse sequence (Fig. S3C) that we adapted from Nie et al. (19) and is as follows. (i) Cleaning, where a positive potential (E(clean) = 5 V, 120 s) applied to the WE oxidizes any impurities from the electrode surface to prepare it for the measurement. (ii) Deposition, where a negative potential (E(1) = −1.4 V, 120 s) applied to the WE causes metal ions in solution to reduce onto the electrode surface. (iii) Equilibration, which is the potential maintained at E(1) with no agitation for a short time (30 s) to ensure equilibration of the solution. (iv) Measurement, where SWASV (SVV sequence from E(1) to E(2) = −0.1 V, at ΔE = 50 mV, E(max) = 5 mV, f = 20 Hz) caused the metal ions on the electrode surface to resolve into the solution. The reduction occurs when E matches the oxidation potential of the metal, so that the measured current exhibits a different peak for each metal species.

Typically, a magnetic stirrer is used to provide agitation during deposition and cleaning. To eliminate this added cost and complexity, we instead incorporated a small vibration motor (similar to the ones used in mobile phones) into the uMED to mix the droplet directly on the SPE when necessary. The uMED applies 3.3 V to the motor to vibrate the sample at 530 Hz. This approach enabled us to perform a full measurement by (i) mixing an 80-μL droplet of aqueous sample containing the metal ions with a 20-μL droplet of the reagent solution, on top of the SPE, and then (ii) activating the uMED to execute the fully automatic SWASV sequence in which the uMED mixed the sample, applied the pulse sequence, extracted the peak heights of all elements, and displayed the extracted data to the user. To calculate the concentration of analytes, the uMED performed a baseline correction, calculated the difference between the maximum and minimum current measured, and subtracted the value of the blank (measured on the same SPE).

**Detection of Sodium in Urine.** To detect sodium in urine by potentiometry, we used an ISE (27504-30; Cole-Palmer). We prepared a series of urine samples with different levels of sodium from standard urine samples (Liquichek Urine Chemistry Control; BioRad) and used an ion-specific strength adjustment buffer (4 M NH₄Cl with 4 M NH₄OH) to adjust the pH to ~9.5. To perform the measurement, we dipped the ISE into each sample, and recorded the potential difference between the RE and the WE. This voltage typically stabilized over a period of 0.5–10 min, with longer times required for lower concentrations.

**Detection of Malaria.** To perform a malaria immunoassay, we used chronoamperometry to measure the concentration of PHRP2 through a sandwich ELISA (20) that we augmented for electrochemical detection. The detecting antibody was conjugated to horse radish peroxidase (HRP), which oxidized 3,3',5,5'-tetramethylbenzidine (TMB), a widely used chromogenic substrate. We performed this reaction in a 96-well plate and then pipetted a drop of solution onto a commercial SPE (DRP110-CNT, DropSens). The uMED detected the oxidized product by performing chronoamperometry for 20 s at ΔE = 0.2 V, sampling the output signal at 20 Hz, and digitally averaging the transient signal over the last t = 8 s of the measurement. We include more details for all measurements in *SI Text.*

**Local Acquisition of Data.** The uMED contains enough memory (32 kilobytes) to store approximately 10 different pulse sequences, the code that operates the device, a set of the database, and all the configurations for on-board analysis. The device can, therefore, automatically perform the basic analysis and baseline corrections that are necessary to extract the concentration of an analyte from the raw data, display the measured concentration on the screen, and, if necessary, (using the method described in Telecommunication) upload the information to a remote facility, without user intervention. To analyze the raw data directly, we interfaced a personal computer to the serial port of the uMED through a serial-to-USB converter (USB-09873; SparkFun Electronics) and used a custom application in MATLAB (MathWorks) to acquire and display the received data.

**Telecommunication.** The cellular voice channel is particularly susceptible to signal interruption by burst noise and distortion by voice codes that render analog modulation inappropriate for transmission of numeric data, such as concentrations of analytes or patient identification numbers. It is, therefore, simpler to transmit these data by digital modulation that can be supplemented with error detection or correction. We implemented a basic frequency-shift keying (FSK) protocol to transmit digital data over the audio channel of a mobile phone during a live connection. Because mobile phones are designed to transmit audio frequencies in the range of 500–3,300 Hz (21), we divided the available bandwidth in the voice channel into a band for the data (f = 500–1,500 Hz), a second band for the data (f = 1,500 Hz to 100 Hz), and a third band for header information (0–9 Hz). We also incorporated a 10-bit binary cyclic redundancy check (CRC), which is an error-detecting code that allows the validation of uncorrupted data by the receiving computer and is particularly effective at detecting the kinds of burst errors associated with the mobile voice channel (21, 22).

A pair of standard, 2.5-mm TRRS (tip, ring, ring, sleeve) stereo connectors and a corresponding four-conductor audio cable provided an interface between the uMED and the audio ports of a mobile phone. As a proof-of-concept, we chose a low-end phone from the Nokia 1100 series (model 1112) as it is still among one of the most widely used in developing countries (23). We used the stereo and microphone channels of the mobile phone to transmit and receive FSK signals and to/from the device. We developed a custom application in MATLAB to establish a live voice link, through the Vodafone Internet Protocol (VIP) Internet. The user transmitted data to a mobile phone and a remote personal computer. This application received and decoded the FSK-based data, and sent a short messaging service (SMS) message to back the mobile phone with contents relevant to the data it had received. Fig. 54 shows the flow of data in this network.

**Results**

**Device Performance.** Fig. 2 shows a comparison between analyses performed by the uMED and a commercial electrochemical analyzer—on the same solutions and batch of electrodes or ISE—for each of the five types of electrochemical methods that we implemented. For CV (Fig. 2A), ferricyanide/ferrocyanide provided a model electroactive system; it is the most common redox couple used for probing the performance of modified electrodes. For chronoamperometry (Fig. 2B), ferrocyanide provided a model electroactive compound for chronoamperometric detection; it is one of the most common electrochemical mediators that can be detected by amperometric methods. For SWV and DPV (Fig. 2C), 1-naphthol provided a common substrate used in electrochemical ELISA. For potentiometry (Fig. 2D), sodium and potassium ions provided common, clinically relevant electrolytes that we measured over a physiological range of concentrations. Differences between the commercial device and the uMED were primarily caused by variations between test strips and electrochemical fluctuations during measurements, and not by differences in the performance of the electronics.

**Detection of Glucose by Chronoamperometry.** Self-testing of blood glucose using a glucometer and disposable test strips is the most commonly performed POC measurement globally. To test the uMED as a personal glucometer we used both a commercial glucometer (TrueTrak; CVS) and the uMED to measure the concentration of blood glucose in a series of blood samples (Fig. S3A). The uMED displayed a linear relationship relative to the values measured by the glucometer on the same samples within the physiological range of 50–500 mg/dL. The average relative

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SD (5%) was better than most commercial glucometers (5–20%), and well within the performance criteria set out by the US Food and Drug Administration (3).

Detection of Heavy Metals in Water by SWASV. Lead and cadmium are among the most common toxic heavy metals found in water supplies, and zinc is an essential micronutrient. Trace amounts of these heavy metals can be simultaneously detected by ASV when a differential scanning technique, such as SWV or DPV, is used for the stripping step (24). These techniques can achieve lower limits of detection than linear sweep voltammetry and chronoamperometry because they use differential sampling to reduce the influence of background and non-Faradic currents. Here, we use SWV because it can provide better discrimination between metals with similar redox potentials than DPV. Fig. 3B shows a calibration plot for detection of lead by SWASV, performed with commercial SPEs. Based on these data, we determined a linear dynamic range of 4–40 μg/L and a detection limit of 4.0 ng/L, which is less than the minimum of 10 μg/L imposed by the World Health Organization (25). We also verified the ability of the device to detect Cd, Zn, and Pb simultaneously with SWASV (Fig. 3B, Inset).

Detection of Sodium in Urine by Potentiometry. Sodium content in urine is often used to evaluate the amount of fluid within the body (26). This test may be used when conditions such as hypotension (low sodium levels in the body) are suspected (27). We calibrated the potentiometric response of the uMED using standard solutions of sodium and then applied that calibration to a series of urine control samples (Fig. 3C). The systematic error of the measured concentrations (~5%) falls within the certified range of the assayed urine samples (±14%).

Electrochemical ELISA for Detection of Malaria. ELISA is a sensitive technique often used for the detection of specific proteins. Although typically quantified by measuring optical absorbance, this biological recognition process can also be measured electrochemically (11, 28). To demonstrate the capability to perform electrochemical ELISA in a research or clinical setting, we measured the concentration of the malarial antigen PfHRP2 in a sandwich electrochemical ELISA. The quantification of PfHRP2 is important because the antigen correlates with the parasite load in the body (29). Chronoamperometric measurements (Fig. 3D) performed by the uMED show a linear response for concentrations of PfHRP2 in the clinically relevant range of 0–150 ng/mL (30). In this proof-of-principle experiment, the limit of detection was 20 ng/mL.

Transmission of Results with a Low-End Mobile Phone. We demonstrated the complete capabilities of our system by measuring the concentration of glucose in a sample of blood from a single user and reporting the result to a remote computer through a low-end mobile phone. Fig. 4 shows a typical reporting sequence. We also analyzed the effect of noise and latency of the voice channel on the delivery of FSK-based packets (Fig. S5). Briefly, we found that with our algorithm the optimal tone length was 34 ms (29 symbols per second), which allowed an average successful delivery of 1.4 data packets per second at an effective throughput of 31 bits per second. This data rate is sufficient for the transmission of the results of POC testing (it requires an average of only 2.2 s to send a value and receive an acknowledgment of receipt).

Discussion

Electrochemical detection is a very attractive method to perform simple, in-field testing for several reasons. (i) In contrast to optical sensing, electrochemical signals are not affected by the color of the sample, the lighting conditions, or the presence of particulate matter. (ii) The measured current or voltage can be transformed into a numeric output by simple electronics and the results of testing can be made user blind to eliminate user bias, or provide security if privacy is a concern. (iii) Electrochemical sensors can be used to detect a range of important analytes using different pulse sequences. The popularity and applicability of handheld glucometers demonstrates the advantages of electrochemical detection in a POC setting. It is, however, impractical to adapt these devices to perform complex analyses (e.g., ASV) because they are engineered to perform a single task.

Recently, Rowe et al. (31) demonstrated that a low-cost (~US$80) potentiostat can be assembled from off-the-shelf components and programmed to perform a variety of electrochemical pulse sequences. This device, however, was designed for bench-top applications: It cannot connect to a mobile phone, and requires
a personal computer and a USB connection for operation, full-size expensive electrodes to perform measurements, a magnetic stirrer for the mixing of samples, and glassware to handle a large sample volume. In another paper, Lillehoj et al. (11) demonstrated a simple potentiostat coupled to a smartphone, although it could only perform chronoamperometry and required a sophisticated microfluidic device to handle the sample.

Here, we aim to solve a greater challenge: whether a low-cost device can provide a nearly universal solution by overcoming the challenges of performing field-based electroanalytical analyses in any resource-limited setting. To qualify as a universal solution, we have designed the uMED to be (i) capable of performing a variety of complete and accurate analyses; (ii) simple enough to be used by minimally trained users (Table S2); (iii) require a minimum of resources; (iv) be able to acquire, process, display, and transmit data automatically; (v) be reprogrammable in the field using available technology; and most importantly, (vi) be compatible with any phone and network.

We have demonstrated the broad electroanalytical capabilities of our device within a variety of important applications and contexts. The uMED detected blood glucose by chronoamperometry with a linearity and precision equivalent to that of a commercial handheld glucometer, an indication that the uMED can replace a glucometer. In water samples, the uMED used SWV to provide acceptable accuracy over the clinically relevant range, indicating that this device could benefit researchers studying this disease, as well as aid in the development of other high sensitivity diagnostics.

Because the performance of the uMED and the variety of important pulse sequences that it can perform are comparable to the commercial comparison, the uMED can, in principle, be used in place of an expensive (US$1,000–50,000) bench-top potentiostat in other applications that use these common electrochemical methods. For example, the uMED could use amperometry to detect metabolites (33), proteins, or other biomolecules, or voltammetry to perform immunoassays in which an antibody is labeled with an enzyme (e.g., electrochemical ELISA), metal nanoparticle, or quantum dot (2, 24). The vast and fast-growing field of ISEs also provides many opportunities to couple new electrodes with the uMED to measure diverse analytes by potentiometry (34), such as blood urea nitrogen and creatinine (35), which are biomarkers for kidney function. Our approach the electrochemical ELISA can also be generalized to many other assays without significant modification of the protocol because we selected the commonly used substrate TMB for HRP-based systems.

The high fixed cost of commercial instrumentation (e.g., electrochemical analyzer, magnetic stirrer) remains one of the largest barriers to entry to performing electrochemical analysis in resource-limited settings. By providing an integrated system, the uMED eliminates the need for these cumbersome instruments in many important applications, makes it more affordable to replace—rather than repair—broken equipment (SI Text), and enables a shift in focus from fixed cost to variable cost per test. The use of commercially available SPEs and test strips ensures reproducibility, guarantees that the device is useful immediately, and reduces the cost per test by decreasing the required sample volume to a single droplet (thereby also significantly reducing the amount of reagent consumed and the need for glassware, compared with reactions performed in bulk). Other costs can be reduced by using disposable plastic pipettes to collect samples and microdroppers to dispense precise amounts of reagent. These procedures can be further simplified and cost per test reduced by using electrochemical microfluidic paper analytical devices that we and others have developed (19, 36–38) to yield comparable performance to SPEs while enabling the sampling of precise volumes by wicking and the prestorage of all reagents directly on the test strip.

The handheld, stand-alone format of the uMED, and use of low-power, commercial electronic components offer several important benefits. (i) The uMED can be used to collect data by someone who does not own a mobile phone. (ii) The device can last for months to years on a single battery charge (SI Text). (iii) The electronic components we used are specified to operate stably over a broad range of temperatures (−40 to 85 °C); this stability makes the uMED well suited for use in a variety of climates around the world. Ultimately, however, the temperature range will be governed by the stability of the biochemical reagents and chemical processes (SI Text).

Our adaptable design ensures that the performance and features of the uMED can also be upgraded relatively easily. The compatibility of the uMED with the popular Arduino (www.arduino.cc) development environment makes it extremely simple to reprogram the device to alter or add pulse sequences. The dynamic range of the measurements can be adjusted according to need by changing the experimental parameters (e.g., vibration time, deposition time, scan rate, step size, feedback resistance). The voltage range, sensitivity, accuracy, and speed (e.g., for dielectric spectroscopy) of the electronics can all be improved with simple modifications to the system and without significantly affecting the design or cost of the device. The range of analyses that can also, in principle, be expanded to include those that require optical techniques (e.g., electrochemiluminescence, fluorometry, or spectrophotometry) with the addition of an optical detector and/or source. Finally, the throughput of data over voice can be improved as necessary with additional error correction or a dedicated tone generator (39).
Our use of audio-based FSK to transmit data provides a number of advantages over a smartphone-centric approach. It ensures that the uMED (i) is compatible with any phone (from low-end phones to smartphones); (ii) is compatible with all generations of cellular networks (2G—4G); (iii) does not require any phone-based applications to operate; and (iv) guarantees, in combination with our choice of error-detecting code, that uncorrupted data can be uploaded to the cloud. This approach enables the kind of broad compatibility with mobile technology that presents challenges for all current hybrid mHealth/POC devices because each is typically developed to operate with a specific smartphone that requires custom applications. Nearly 2.8 billion people, however, continue to use low-end phones, most of worldwide users of mobile phones, and, although the use of smartphones is rising rapidly, it is projected that by 2017 nearly 2.6 billion mobile subscribers will remain without a smartphone (40). A majority of these low-end phones are, and will be, used in low to middle-income countries, such as those found in Sub-Saharan Africa as well as Brazil, Russia, India, China, and Indonesia. These regions alone will account for nearly 2 billion of the users of low-end phones by 2017 (Fig. S1). Furthermore, although some nonsmartphones (feature phones) may have limited Internet access via 3G, it is impractical to develop compatibility with all of the hundreds of variations of software applications, operating systems, types of data ports, and cellular networks. It is clear that compatibility with low-end phones and 2G networks, especially in resource-limited settings, will be a requirement for years to come.

Conclusion

The uMED is an inexpensive, versatile tool that links all of the most common electrochemical methods with the telecommunication technology most widely available across the globe. The unique combination of capabilities of the uMED enables sensitive and quantitative analysis in resource-limited settings by (i) eliminating the need for expensive laboratory equipment (such as a commercial potentiostat, pH meter, glassware, or a magnetic stirrer); (ii) reducing the need for expensive or limited resources (such as reagents or blood samples) by reducing the sample volume to a single droplet (∼10–100 μL, depending on the application) on a test strip or SPE; (iii) enabling remote expertise, monitoring, or archiving to be provided using any available mobile technology; and (iv) minimizing the training required to perform sophisticated electrochemical analyses by using appropriate design to make the system as simple as possible. All that is required is to insert the strip, select the test, apply the sample, and place a phone call.

ACKNOWLEDGMENTS. This work was funded in part by Bill and Melinda Gates Foundation Award 51308 (as salary support to A.N., J.W.H., and A.A.K.), the Defense Threat Reduction Agency and the Lawrence Livermore National Laboratory Award B603629 (as salary support to D.C.C.). A.A.K. was also supported by the National Science Foundation Graduate Research Fellowship Program, E.J.M. was supported by a fellowship from the Natural Sciences and Engineering Research Council of Canada, and M.T.F.-A. was supported by University of Oviedo and Ministerio de Economía y Competitividad Spanish Award MICINN-CQ2011-25814.
Supporting Information

Nemiroski et al. 10.1073/pnas.1405679111

SI Text

Current and Future Use of Mobile Phones in the Developing World

We compiled data on current and projected mobile phone use for Brazil (1, 2), Russia (3–5), India (6, 7), China (8), Indonesia (9), and Sub-Saharan Africa (10) and present the data in Fig. S1.

Experimental Design

Device Design and Fabrication. We used the microcontroller to sample and compute data acquired from the potentiostat, to encode and decode frequency-modulated data, and to display a graphical user interface on the liquid crystal display (LCD). We configured six digital input/output channels to operate the external digital-to-analog converter (DAC), analog-to-digital converter (ADC), and LCD over a serial peripheral interface (SPI) protocol, and one digital output channel to transmit data over audio by frequency-shift keying. We configured four analog input channels to sample the voltages associated with the potentiostat, one analog input channel to receive data over audio, and three digital input channels to detect the states of the buttons.

Device Fabrication. We mounted these electronics on a custom-made printed circuit board (Advanced Circuits) and housed all components in a plastic case that we fabricated with 3D printing (Fortus 250mc; Stratasys). The assembled device measured 56 × 106 × 18 mm and weighed 63 g. The bill of materials (BOM) was ~US$25 (not counting the case and assuming a purchase volume of at least 1,000 components each). We show the full circuit diagram in Fig. S2 and the BOM in Table S1.

Design of the Potentiostat. Together with a feedback resistor $R_b$, the op-amp controlling the working electrode (WE) formed a transimpedance amplifier that converted the current $I$ into an output voltage $V_o = V_{in} - IR_b$ while maintaining the WE at $V_{in}$ set by the DAC. The feedback resistance $R_f$ set the sensitivity of the system. We chose $R_b = 8$ kΩ for all measurements, and suitable DC offsets for all electrodes to place the desired measurements in the range of the potentiostat.

To set $V_{in}$ and $V_{we}$, we chose a two-channel, 16-bit DAC (DAC8552; Texas Instruments) programmed by the popular three-wire SPI protocol. The smallest potential step required in our applications was ~5 mV, and because the nonlinearity of most DACs is within a few least-significant bits, the 16-bit resolution provided us with sufficient voltage resolution (3.3 V/2^{16} ≈ 50 μV) to ensure that any nonidealities in the voltage generation were at most a few percent of the smallest voltage steps. We updated the output of the DAC at a rate of ~2 kHz, although in principle the system could support rates up to ~20 kHz if necessary. To sample the output signal with high resolution, we also incorporated a 16-bit ADC. With its required 1.25-V reference, this ADC provided us with a raw resolution of 1.25 V/2^{16} ≈ 20 μV.

The practical minimum voltage that we could resolve, while maintaining the WE at $V_{in}$, was $V_{in}/16$ (applied between the RE and WE), which for $V_{in} = 10$ V resulted in a raw current resolution of 5 nA. We further reduced the electronic noise by configuring the universal mobile electrochemical detector (uMED) to collect 10 consecutive measurements, at 800 Hz, and to average them together to constitute a single data point of the acquired transient signal. In all cases, we found that the electrochemical noise was substantially (10–100×) greater than the electronic noise. Therefore, for all pulse sequences, we also configured the uMED to apply a 10-point moving average filter on all traces automatically to reduce the influence of electrochemical noise. These two digital filters combined to reduce the measured voltage noise down to 4 μV rms and to reduce the effective current resolution down to 0.5 nA (for $R_b = 8$ kΩ).

After the uMED performed these various forms of signal averaging automatically, it then extracted a concentration by comparing to a saved calibration or sent the acquired values to a personal computer for further analysis.

 Acquisition of Data. To evaluate the performance of the uMED we needed to extract the raw data from the device. We interfaced with and collected raw data from the uMED by connecting a personal computer to the serial port of the uMED through a serial-to-universal serial bus (USB) converter (FT232RL; FTDI). We developed a custom application in MATLAB (MathWorks) to acquire, convert, and display raw data received over a USB from the uMED. Once we calibrated the uMED for chronoamperometry, square wave anodic stripping voltammetry (SWASV), and potentiometry, we programmed the microcontroller to perform these measurements (e.g., signal averaging, baseline correction, peak extraction) automatically, without an external computer.

Modes of Electrochemical Detection. Fig. S3 shows a scheme of the time and voltage sequences implemented for the different types of measurements and, where necessary, the expected transient behavior of the measured current.

For cyclic voltammetry (CV), the uMED sweeps the potential $E$ applied between the reference electrode (RE) and WE linearly from $E_1$ to $E_2$ (and back again), and measures the current $I$ consumed by the electrochemical cell. Steps in voltage $V$ to ensure that any nonidealities in the voltage generation were at most a few percent of the smallest voltage steps. We updated the output of the DAC at a rate of ~2 kHz, although in principle the system could support rates up to ~20 kHz if necessary. To sample the output signal with high resolution, we also incorporated a 16-bit ADC. With its required 1.25-V reference, this ADC provided us with a raw resolution of 1.25 V/2^{16} ≈ 20 μV.

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After the uMED performed these various forms of signal averaging automatically, it then extracted a concentration by comparing to a saved calibration or sent the acquired values to a personal computer for further analysis.

For chronoamperometry, the uMED applies a potential step $E$ between the counter electrode (CE) and WE for a fixed duration and measures the transient current $I$. Typically, the current $I$ will be dominated by (i) an initially large, non-Faradaic, capacitive decay that is related to total area (including surface roughness) of the electrodes and not to the concentration $C$ of the analyte; then, by (ii) a slow Faradaic, Cottrellian decay that is proportional to the concentration ($I ∝ C^{1/2}$); and finally, (iii) a Faradaic steady-state current proportional to the concentration ($I ∝ C$) and primarily due to radial diffusion around an electrode of finite size and convective disturbance of the diffusion layer (14).

To suppress background currents and noise, the uMED (i) begins sampling the current several seconds after the application of the voltage step (when the Faradaic current is dominant) and (ii) averages $I$ over a fixed length of time $Δt$ to decrease the influence of random electrochemical and thermal fluctuations by a factor of $\sqrt{Δt}$.

For differential pulse voltammetry (DPV) and square wave voltammetry (SWV), the uMED measures the current generated in the electrochemical cell during a series of regular voltage pulses (applied between the RE and WE) that are superimposed on a linear sweep from $E_1$ to $E_2$, have a peak-to-peak height $ΔE$, and a frequency $f = (t_1 + t_2)^{-1}$, where $t_1$ is the pulse duration and $t_2$ is the time between pulses. In these differential techniques, the device records the currents $I_1$ and $I_2$ immediately before...
a change in the applied voltage (i.e., at end of the pulse); the peak value of the consecutive differences $\Delta I = I_2 - I_1$ is proportional to the concentration of the analyte ($\Delta I \propto C$).

For potentiometry, the uMED measures the constant voltage $E$ generated by the electrochemical species. To prevent destabilization of $E$, the uMED incorporates operational amplifiers with a high input impedance ($\approx 10^{12} \Omega$) that limit the current flowing during measurement to $<0.1 \mu A$.

Fig. S3B shows an example of chronoamperometry in context of glucometry. Fig. S3C shows an example of these DPV and SWV used in context of ASV. In DPV, the differential current is formed by consecutive values $\Delta I(n) = I_2(n) - I_1(n)$, where $I_1(n)$ is the current immediately before forward pulse $n$, and $I_2(n)$ is the current at the end of forward pulse $n$. For this type of measurement, $t_2 > t_1$ to allow the solution to attain a diffusive equilibrium before each forward voltage pulse. In SWV, the differential current is formed by consecutive values $\Delta I(n) = I_2(n) - I_1(n + 1)$, where $I_1(n + 1)$ is the current at the end of reverse pulse $n + 1$ (immediately before the next forward pulse). For this type of measurement $t_2 = t_1$ to suppress the contribution of background Faradaic processes to the signal, and to enable a faster voltage sweep than DPV.

Procedure for Performing a Point-of-Care Test. Table S2 lists the general procedure for some of the tests that can be performed with minimal training (after initial calibration) and for uploading data over voice.

Network Connection, Packet Structure, and Error Correction. Fig. S4 shows the flow of data from a point-of-care measurement to a remote facility. We used a simple packet structure with two sections: (i) a header to identify the type of measurement being transmitted (glucose, lead, sodium, or malaria) and (ii) a body to store the numeric data, modified by the cyclic redundancy check (CRC). The header contained a single 50-ms tone that identified whether the data being transmitted corresponded to glucose ($f = 1,600$ Hz), lead ($f = 1,700$ Hz), sodium ($f = 1,800$ Hz), or malaria ($f = 1,900$ Hz). The body contained an integer-valued, base-10 representation of the concentration of a single measured analyte, encoded with the CRC. We encoded each integer in the sequence by a 50-ms tone at a frequency corresponding to the integer value. Because the ATMega328 can only output digital signals, we represented data as a sequence of square wave tones and passed the output through a passive, low-pass filter to attenuate all but the lowest-order, sinusoidal harmonic. In our implementation, we used a 10-bit CRC (0b1000000001) that enables detection of errors for sent values up to $2^{10} = 1,024$. For larger values, it would be necessary to use a longer CRC for to reliably detect errors.

Power Consumption. The total number of measurements $N$, the uMED can perform on a single battery charge can be calculated by

$$N = \frac{Q_{\text{BATT}}}{(I) \times T}$$  \[S1\]

where $Q_{\text{BATT}}$ is the battery lifetime, $(I)$ is the average current consumption, and $T$ is the total time spent in operation. The rechargeable, 3.7-V lithium polymer battery (PL-651628-2C; AA Portable Power Corp) that we used had a lifetime $Q_{\text{BATT}} = 210$ mAh. The uMED consumed $I_{\text{avg}} = 10$ mA during standby (no measurement) and while sending data ($T_{\text{data}} = 2.2$ s). The current consumed during measurements ranged from $I_{\text{ASV}} = 11$ mA for glucometry ($T_{\text{gluc}} \approx 20$ s) to $I_{\text{ASV}} = 24$ mA for ASV ($T_{\text{ASV}} = 280$ s), for which the power consumption was dominated by the vibration motor used for mixing. For an initially fully charged battery, these values indicate that the uMED can perform a maximum of $N_{\text{gluc}} \approx 3,440$ glucose measurements, $N_{\text{ASV}} \approx 110$ ASV measurements, or send $N_{\text{data}} \approx 34,500$ POC measurements over audio before depletion. Depending on which measurements are performed and the frequency of use, the uMED can, therefore, last from one month to several months before needing to be recharged.

SI Materials and Methods

Chemical Reagents. All chemicals were used without further purification. For the performance of the different electrochemical pulse sequences we used potassium ferrocyanide, potassium ferricyanide, 1-naphthol, sodium chloride, and potassium chloride purchased from Sigma-Aldrich. For detection of heavy metals we used sodium chloride (NaCl, 99.999%), sodium acetate Trace SELECTA (99.999%), water trace SELECT Ultra (AGS Reagent), bismuth standard for atomic absorption spectroscopy (999 ± 4 mg/L), cadmium standard for inductively coupled plasma emission spectrometry (ICP-ES, 1,000 ± 2 mg/L), zinc standard for ICP (1,000 ± 2 mg/L), and lead standard solution for ICP (10.127 ppm) purchased from Sigma-Aldrich. For detection of recombinant Plasmodium falciparum histidine-rich protein 2 (PfHRP2) (PIP001; AbD Serotec) we used 96-well plates (Costar 3590; Corning), anti-P. falciparum antibody (ab9206) and anti-P. falciparum horse radish peroxidase (HRP) conjugate-detection antibody (ab30384; Abcam), BSA and Tween-20 (Sigma-Aldrich), and Ultra 3,3’,5,5’-tetramethylbenzidine (TMB)-ELISA (ThermoScientific). For the determination of glucose in assayed blood samples and the determination of sodium in assayed urine samples, we used the Liquicheck Urine Chemistry Control Level 1 and 2 (LOT 64360) and Trilevel minipole control Meter Trax Control (LOT 92510; BioRad). Fingerstick samples for glucose testing were obtained from consenting volunteers at Harvard University under a protocol approved by the Committee on the Use of Human Subjects at Harvard University (Protocol #16779).

Materials and Instrumentation. For the evaluation of chronoamperometry, CV, SWV, and DPV, we used unmodified screen-printed carbon electrodes (SPEs) (DRP110; DropSens). For potentiometry we used ion-selective electrodes (ISEs) for sodium (K27504-30; Cole-Palmer) and potassium (WU-27504-26; Cole-Palmer). For detection of glucose, we used commercial test strips (TRUEtrack; Nipro Diagnostics). For SWASV and chronoamperometric detection of PfHRP2, we used carbon nanotube-modified SPEs (DRP110-CNT; DropSens) for enhanced sensitivity.

Measurement Procedure. For measurement of glucose, we used a new test strip for each measurement. For detection of heavy metals, we measured the entire dilution series (six samples, including the blank) on a single SPE in order of increasing concentration. We performed seven replicates of this series of measurements, each with a new SPE. We conditioned each new SPE by first performing a full sequence on a sample with no metal ions to ensure the electrode was free of any contaminants that could be removed by sampling conditions. After the cleaning step of each measurement, we rinsed the electrode with ultrapure deionized water and dried with $N_2$. For detection of malaria, we measured the entire dilution series (five samples, including the blank) on a single SPE in order of increasing concentration. We performed seven replicates of this series of measurements, each with a new SPE. Before taking measurements with a new electrode, we performed chronoamperometry at $E = 0.2$ V for 40 s on a solution of PBS to ensure the electrode was free of any contaminants that could be removed by sampling conditions. Each SPE was rinsed with PBS and dried with $N_2$ between each measurement.
Glucometry. The glucose test strips that we use have a pair of electrodes (WE and CE) defined by carbon ink, and all of the necessary reagents (e.g., enzymes and electrochemical mediator) prestored on the test strip. A typical handheld glucometer uses a two-electrode (CE and WE) potentiostat to apply a simple voltage sequence that consists of an incubation period at zero applied voltage, followed by a measurement period at a fixed applied voltage (typically \( E = 0.5 \) V). The glucose oxidase (an enzyme) present in the test strip converts glucose (the analyte) and potassium ferricyanide (an electrochemical mediator) to gluconic acid and potassium ferrocyanide, the oxidation of which can be measured by chronoamperometry, which is one of most common techniques for monitoring an enzymatic reaction that produces a redox-active species, such that the measured current correlates to the concentration of the redox species. We adapted this type of sequence and programmed the uMED to first apply \( E = 0.5 \) V to test for the presence of the sample in the reaction zone (Fig. S3B). With the test strip inserted, but no sample present, there were no mobile ions to carry a charge (current) between the electrodes. When we placed a sample on the test strip, the presence of ions in the solution gave sufficient conductance to the test zone that it could be measured as current. In principle, this technique can also be adapted to analytes other than glucose that are amenable to chronoamperometric detection at 0.5 V. We and others have demonstrated that glucometers using this type of pulse sequence can also quantify lactate, cholesterol, and ethanol (15); cocaine, adenosine, and uranium (16); or a specific DNA aptamer (17).

Detection of Heavy Metals by SWASV. To test the device for detection of metals [Zn(II), Cd(II), and Pb(II)] in water samples we first prepared a solution containing all of the necessary reagents: 2 mg/L bismuth ions as a codeposition agent in a solution of 0.5 M acetic acid, 0.5 M sodium acetate, and 0.25 M sodium chloride. Next we prepared a series of sample solutions of Zn, Cd, and Pb ions (blank and 2–40 μg/L each) in water. To measure the concentration of these ions, we mixed 20 μL reagent solution with 80 μL sample solution on the top of the SPE and activated the uMED to perform the SWASV sequence automatically.

Malaria Immunobssay with Chronoamperometric Detection. Preparation of the 96-well plates was performed following the procedure by Noedl et al. (18). We coated high-binding 96-well plates with 100 μL 1.0-μg/mL solution of anti-P. falciparum antibody in PBS (1×). The plates were sealed and incubated overnight at 4 °C after which the supernatant was discarded and the wells incubated with 200 μL per well of 2% (vol/vol) BSA in PBS for 2 h. After washing 3× in 0.05% Tween-20 PBS, the plates were sealed and stored at −20 °C until use. Recombinant P/HRP-2 was diluted in PBS to the desired concentration (0–200 ng/mL) and 100 μL was added to each well followed by 1 h incubation at room temperature. The wells were washed 3× with PBS-Tween solution before the addition of 100-μL anti-P. falciaparum HRP conjugate detection antibody at a concentration of 0.5 μg/mL in a solution of PBS with 2% BSA and 1% Tween-20. After 1 h incubation at room temperature, wells were washed in PBS-Tween solution 3×. The final washing solution was left in the well until just before the addition of 100 μL Ultra TMB-ELISA. The TMB solution was incubated at room temperature for 2 min in the dark before the reaction was stopped with 50 μL 10% (vol/vol) sulfuric acid. A 75-μL drop was immediately placed on the SPE. Chronoamperometry was performed at \( E = 0.2 \) V for 20 s. The potential used for amperometry was selected by first performing a CV scan from \( E_1 = 0 \) V to \( E_2 = 0.7 \) V at a scan rate of 0.05 V/s with a step size of \( E_{\text{step}} = 2.5 \) mV. The position of the oxidation and reduction peaks is highly dependent of the pH of the system. We chose \( E = 0.2 \) V to ensure that reduction could be completed with minimal contribution from oxidation.

We programmed the uMED to automatically check whether the output current followed the expected chronoamperometric sequence (negative current monotonically increasing to zero and reaching a stable plateau after \( ∼20 \) s) by automatically discarding any sequences for which \( I(t) - I(t - 5 \text{ s}) < -43 \) nA (a value that we determined empirically) for any time \( t \). This process is similar to the way a handheld glucometer displays an error message when the chronoamperometric sequence yields data that is not consistent with the expected transient behavior.

Verification of Packet Structure and Data Throughput. It is important that physiological, medical, and environmental data received by a remote computer be correct. Our choice of CRC error detection guarantees that any three-digit value can be determined to be completely error free after transmission. This reliability, however, does not prevent corrupt data from arriving at the destination, effectively slowing down the transmission rate to the time it takes to deliver a correct packet of data. The rate at which packets are corrupted depends on the quality of the data channel and the method of decoding used. Fig. S5 A–C shows a frequency-modulated packet with a randomly chosen value, its frequency spectrum, and its decoded value. We sent the data from the uMED through a Nokia 1112 over the AT&T voice network and received the data through a custom MATLAB application via Skype on a remote personal computer. We sampled the data at 44.1 kHz, and performed a rolling fast Fourier transform (FFT) to analyze the frequency content of the packet and decode the sequence of integers. We characterized the effect of errors during transmission on the average throughput of data by determining the packet success rate (PSR) by

\[
\text{PSR} = \frac{\text{number of uncorrupted packets}}{\text{number of sent packets}} \quad [S2]
\]

and the effective packet rate (EPR) by \( \text{EPR} = \text{PSR} \times \text{PR} \), where \( \text{PR} \) is the raw packet rate (packets per second). The EPR quantifies the average rate at which correct packets are received, and signifies the average throughput of uncorrupted data. Fig. S5 D–F shows how the PSR and EPR depend on the symbol rate—the rate at which individual digits are transmitted. We characterized the PSR and its effect on the EPR by (i) establishing a live connection to a remote computer through a mobile phone; (ii) sending a sequence of packets containing random numeric data, encoded by CRC, from the uMED to the remote computer; and (iii) comparing the received packets with the sent packets to determine the fraction of corrupted packets. We found that the PSR was constant around 98% at low symbol rates, but decreased dramatically for PSR > 25 symbols per second, where the symbols began to be too short to be properly identified by the simple FFT due to the distortion present in the voice channel. We found that the EPR was maximized at 29 symbols per second, indicating an optimal tradeoff between PSR and the PR. Each packet consisted of an average of six digits of CRC-encoded, numeric data (20 bits)—including three digits of underlying numeric data (10 bits)—and a header (2 bits). At the maximal EPR (1.4 packets per second), the effective bit rate of CRC-encoded data and header was 31 bits per second (bps) and the effective bit rate of the underlying data and header was 17 bps. Although we used a binary header, there was enough bandwidth to signify up to 16 different identifiers (4 bits), which would increase the effective bit rates by 3 bps each. We never identified an instance where the CRC failed to properly discriminate between corrupted and uncorrupted packets of data. When receiving data from a user, the remote computer responds with an acknowledgment tone (ACK) as soon as it receives a single
uncorrupted packet. The signal delay between the user and the remote computer can vary depending on signal strength and other factors, but is usually ~0.5 s. We found that at the optimal EPR, the median time a user had to wait for an ACK after beginning to send data was 2.2 s.

**Biochemical Stability Defines the Temperature Range of the System.**

For some tests, the chemistry or biochemistry (e.g., enzymatic kinetics, stability of proteins and reagents, rates of electrochemical reactions) and some physical properties of the system (e.g., viscosity of liquids, and rates of mass transport) may be the source of temperature-dependent properties. In fact, any system relying on molecular recognition or enzymatic processes will have the same issues with (possibly) limited ranges of temperature. This device accomplishes the readout of chemical processes using electronic components that are stable with temperature, and therefore the operating temperature range of the system will be determined largely or entirely by its chemistry and biochemistry.

**Low Cost and Battery Operation Enable Affordable Replacement.**

By making the device small and inexpensive, we address a critical problem in the developing world: repair or replacement when a device is damaged (e.g., by a power surge, or by misuse). It is, in practice, very difficult or impossible to arrange repair in many parts of the developing world because parts and repair technicians are not available; this difficulty compromises the usefulness of larger (and perhaps more automated) devices intended for central laboratory use. Our device is designed to deal with this issue in two ways. First, by making our device as inexpensive as possible, it can simply be replaced when it is broken. For example, a US$50 device (which is more expensive than we would anticipate in large-scale production) used for 1,000 tests before it becoming damaged (a number much lower than we would anticipate for this device) would contribute only US$0.05 per test to the cost of the delivered test. Second, by making the device very efficient in use of power, it is possible to operate it with batteries; battery operation automatically protects it against certain common problems in wall power (especially surges) in the developing world. The device is thus designed more on the power model of the cellphone rather than a developed-world clinical analyzer.

**Images of Commercial Devices**

For Fig. 1A and B, we photographed the following devices: (i) a 2G mobile phone (Nokia 1112), (ii) a 4G mobile phone (Samsung Galaxy S4), (iii) an ISE (InLab Redox, Mettler Toledo), (iv) a SPE (DS110, DropSens), and (v) a glucose test strip (TRUEtrack, Nipro Diagnostics). We also include an image of a 3G mobile phone (Blackberry Bold 9700) that we obtained from http://commons.wikimedia.org/wiki/File:BlackBerry_Bold_9700.jpg. This image is in the public domain under a Creative Commons license.

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Fig. S1. Comparison of relative use of smartphones versus nonsmartphones (low-end phones) in Brazil, Russia, India, China, and Indonesia (BRICI) and Sub-Saharan Africa (SSA) in (A) 2014, (B) 2016–2017 (projected), and (C) combined.
Fig. S2. Full circuit diagram for uMED.
Fig. S3. Examples of the timed sequence of applied potentials and measurement for a representative sample of possible pulse sequences. (A) CV. (B) Chronoamperometry in the context of glucometery. (C) SWV and DPV in the context of ASV. We use the shaded regions to indicate the times when the current is recorded.
Fig. S4. A flowchart describing the sequence of operations involved in establishing error-free communication over a mobile voice network between the uMED and a remote computer. We developed a custom application in MATLAB to (i) sample the audio stream received by Voice over Internet Protocol (VoIP); (ii) analyze and identify the frequency content of each packet; (iii) convert the sequence of tones into a corresponding sequence of integers; (iv) identify the type of measurement; (v) verify the integrity of the received data with a CRC; and if error free, (vi) log and display the data to the remote user; (vii) play an ACK (5 s, 500 Hz) to the VoIP application; and (viii) send the decoded value, or a diagnostic interpretation, to the local user’s mobile phone in the form of a text message over short messaging service (SMS), sent through the web portal of the chosen mobile carrier (here, AT&T). We configured the uMED to send packets continuously until it received an ACK from the remote computer and, upon receipt, to cease the transmission of data packets and display a message informing the user.
Fig. S5. An example of a successfully transmitted packet and an analysis of the average throughput of data versus symbol rate. We encoded the randomly chosen value 274 mg/dL of glucose (encoded as 2-8-1-1-2-4-11 after CRC; the 11 corresponds to glucose) and transmitted it over an active voice connection. (A) The audio signal received by the data acquisition application. (B) An FFT of the entire packet demonstrating the presence of seven distinct frequency signals and the values to which they correspond. (C) The decoded packet containing the sequence (read in reverse) 2-8-1-1-2-4-11, which, after removing the CRC value, decodes to the value 274-11, or 274 mg/dL of glucose. (D) The overall PSR versus the symbol rate. (E) The PR versus the symbol rate. (F) The EPR versus the symbol rate ($EPR = PSR \times PR$). The optimal $EPR = 1.4$ packets per second occurred at 29 symbols per second. The error bars in $D$ signify the SEM $\sqrt{PSR(1 - PSR)/N}$, where PSR is the packet success rate and $N = 300$. The error bars in $E$ are $\sigma_{PR}$, the SD of the measured PR. The error bars in $F$ are propagated from $D$ and $E$ by $\sigma_{EPR} = \sqrt{\left(\frac{\partial EPR}{\partial PSR}\right)^2 \sigma_{PSR}^2 + \left(\frac{\partial EPR}{\partial PR}\right)^2 \sigma_{PR}^2}$. 

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Table S1. BOM for the uMED

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<td>RMCF0805FT8K06CT-ND</td>
<td>1</td>
<td>0.01</td>
<td>0.01</td>
<td>Digikey</td>
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<tr>
<td>Resistor 0805 (16.2 kΩ)</td>
<td>P16.2KCTR-ND</td>
<td>1</td>
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<td>Digikey</td>
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<tr>
<td>Resistor 0805 (845 kΩ)</td>
<td>P845CDKR-ND</td>
<td>1</td>
<td>0.01</td>
<td>0.01</td>
<td>Digikey</td>
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<tr>
<td>Resistor 0805 (29.4 kΩ)</td>
<td>P29.4KCCT-ND</td>
<td>1</td>
<td>0.01</td>
<td>0.01</td>
<td>Digikey</td>
</tr>
<tr>
<td>Resistor 0805 (1.2 kΩ)</td>
<td>P1.2KADKR-ND</td>
<td>1</td>
<td>0.01</td>
<td>0.01</td>
<td>Digikey</td>
</tr>
<tr>
<td>Capacitor 0805 (470 pF)</td>
<td>1276-2516-1-ND</td>
<td>1</td>
<td>0.01</td>
<td>0.01</td>
<td>Digikey</td>
</tr>
<tr>
<td>Capacitor 0805 (10 nF)</td>
<td>490-1664-1-ND</td>
<td>2</td>
<td>0.01</td>
<td>0.02</td>
<td>Digikey</td>
</tr>
<tr>
<td>Capacitor 0805 (0.1 μF)</td>
<td>399-1167-6-ND</td>
<td>10</td>
<td>0.02</td>
<td>0.21</td>
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<tr>
<td>Capacitor 0805 (2 nF)</td>
<td>490-1627-1-ND</td>
<td>1</td>
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<td>0.04</td>
<td>Digikey</td>
</tr>
<tr>
<td>Capacitor 0805 (4 nF)</td>
<td>311-1132-1-ND</td>
<td>1</td>
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<td>0.01</td>
<td>Digikey</td>
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<tr>
<td>Capacitor 0402 (1 μF) ceramic</td>
<td>587-1231-1-ND</td>
<td>1</td>
<td>0.01</td>
<td>0.01</td>
<td>Digikey</td>
</tr>
<tr>
<td>Capacitor 0805 (10 μF) ceramic</td>
<td>587-1300-1-ND</td>
<td>4</td>
<td>0.01</td>
<td>0.06</td>
<td>Digikey</td>
</tr>
<tr>
<td>Capacitor 1206 (10 μF) tantalum</td>
<td>495-2174-1-ND</td>
<td>2</td>
<td>0.04</td>
<td>0.08</td>
<td>Digikey</td>
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<tr>
<td>Analog switch SPST (dual channel)</td>
<td>MAX4643</td>
<td>1</td>
<td>1.01</td>
<td>1.01</td>
<td>Mouser</td>
</tr>
<tr>
<td>Analog switch SPDT (single channel)</td>
<td>MAX4644</td>
<td>1</td>
<td>0.86</td>
<td>0.86</td>
<td>Mouser</td>
</tr>
<tr>
<td>Vibration motor, flat coin</td>
<td>28821-ND</td>
<td>1</td>
<td>3.99</td>
<td>3.99</td>
<td>Digikey</td>
</tr>
<tr>
<td>Printed circuit board</td>
<td>Custom</td>
<td>1</td>
<td>1.03</td>
<td>1.03</td>
<td>4PCB</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td></td>
<td><strong>24.46</strong></td>
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<td></td>
</tr>
</tbody>
</table>

For the price, we quote for >1,000 units. SDST, single pole, double throw; SPST, single pole, single throw.

Table S2. Basic procedure for using the uMED for glucometry, detection of lead in water, detection of sodium in urine, and uploading the test results over a mobile phone

<table>
<thead>
<tr>
<th>Glucometry</th>
<th>Lead detection</th>
<th>Sodium detection</th>
<th>Uploading data over voice</th>
</tr>
</thead>
<tbody>
<tr>
<td>i) Insert glucose test strip</td>
<td>i) Select “Glucose” from the uMED on-screen menu</td>
<td>i) Attach ISE</td>
<td>i) Connect audio cable</td>
</tr>
<tr>
<td>ii) Select “Glucose” from the uMED on-screen menu</td>
<td>ii) Select “Lead” from the uMED on-screen menu</td>
<td>ii) Wait until data collection is finished</td>
<td>ii) Wait until data collection is finished</td>
</tr>
<tr>
<td>iii) Apply the sample to electrode zone</td>
<td>iii) Collect sample in container</td>
<td>iii) Call medical facility or database</td>
<td>iii) Call medical facility or database</td>
</tr>
<tr>
<td>iv) After 15 s, the measured concentration automatically appears on screen</td>
<td>iv) Add buffer</td>
<td>iv) uMED automatically uploads data</td>
<td>iv) uMED automatically uploads data</td>
</tr>
<tr>
<td>v) After 5 min, the measured concentration automatically appears on screen</td>
<td>v) Dip ISE into sample</td>
<td>v) Receive acknowledgment of data transfer on uMED</td>
<td>v) Receive acknowledgment of data transfer on uMED</td>
</tr>
<tr>
<td>vi) Press button to begin test</td>
<td>vi) Measured concentration automatically appears on screen</td>
<td>vi) Receive text message (if applicable)</td>
<td>vi) Receive text message (if applicable)</td>
</tr>
</tbody>
</table>

Nemiroski et al. www.pnas.org/cgi/content/short/1405679111