Personalized and Context-Based Sensing for Dehydration Monitoring

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ABSTRACT
In this paper, we present a vision for a medical cyber physical system that interacts with the human body for continuous, personalized health monitoring. Internal and external parameters, including health history and environmental factors would be considered in the personalized measurement control process. Here, we discuss dehydration monitoring as one example and include possible scenarios in which such monitoring improves health outcomes. A plasmonic grating biosensor is presented with preliminary results on measuring sodium ions in noninvasive body fluids. A discussion is included of the research challenges and open questions that need further investigation in order to realize such a personalized health monitoring system.

Categories and Subject Descriptors
C.3 [**Special-Purpose and Application-Based Systems**]: Process control systems, Real-time and embedded systems.
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Measurement

Keywords
Medical cyber physical system, health monitoring, eldercare

1. INTRODUCTION
The human body is a complex system affected by the physical setting, the context of that setting, the individual's activity, as well as the individual's age, gender, medications, and health status. As a result, many factors must be considered in designing a sensing system that captures meaningful individualized assessments of potential health problems such as dehydration. There are numerous challenges in the development of such a personalized health monitoring system, which span components in the physical domain (sensing elements and optics) to the cyber domain (networking and distributed data analysis) for personalized calibration and measurement, as well as control methods that integrate and drive these components based on health status and environmental conditions. Overcoming these challenges will lead to extraordinary discoveries in the integration of self-monitoring, smart control systems to detect important medically relevant biomarkers.

Our vision is to develop a compact, smart sensing system that interacts with a human body in a noninvasive but personalized way. In this paper, we present preliminary work on a cyber physical biosensor that measures sodium as a biomarker for dehydration. There are varied scenarios in which monitoring dehydration is clinically relevant. For example, marathon runners in the heat are highly likely to get dehydrated, but so might a frail senior sitting in a temperature-controlled home as a result of diuretic medications. While the marathon runner will probably take action to address the dehydration, the frail senior might not, because she might not be aware of her own dehydration. Thus, seniors are particularly vulnerable and can benefit from a dehydration monitoring system. Understanding the health status and context in which the system is used will provide a more intelligent monitoring system.

Dehydration testing is possible today, but performed infrequently, in part due to the invasive measurement techniques currently available for accurate measurements, which include blood solute concentrations [21] or blood osmolality [2, 3]. As an initial proof-of-concept, we present the measurement of sodium ions from noninvasive biological fluids (sweat and saliva). These offer distinct advantages over blood in terms of noninvasive collection and analysis without further processing. A key challenge is that sodium concentration in sweat [20] is about half the sodium

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concentration in blood. Here, we show that new biosensors based on plasmonic grating nanosensors are capable of detecting these low sodium concentrations. We further demonstrate imaging with a smartphone to detect sodium levels.

In this paper, we first provide background information on the clinical significance of dehydration monitoring, showing possible scenarios. We also lay out our long-term vision for creating a medical cyber physical system (CPS) that couples the human body with a sensing system, networked components, and adaptive reasoning. Environmental sensors and an electronic health record provide keys to the medical history, health status, and the context of the measurement. We present preliminary results on the biosensor and include a discussion of the open research questions and challenges in creating the envisioned system.

2. CLINICAL SIGNIFICANCE OF DEHYDRATION MONITORING

Dehydration is a key measure of overall health of the elderly, firefighters, combat soldiers, athletes, and others in high temperature working conditions. Electrolyte imbalance resulting from dehydration can lead to serious short-term and long-term issues [18, 26, 12], especially for the elderly [13, 31], and is less likely to be addressed than other, more apparent health conditions. Symptoms of dehydration may be particularly hard to recognize for older adults, due to medication use or confusion with other health problems. For example, dehydrated individuals may experience sleepiness, headaches, nausea, confusion, low blood pressure, and/or dizziness [30]. Dehydration is a complex condition that is affected by the age, gender, activity, medications, and health status of the individual, as well as environmental conditions such as temperature and humidity.

Dehydration is sometimes monitored by observing urine volume and color. Accurate dehydration levels can be measured by blood solute concentrations through the blood freezing point depression [21]. Another method uses blood sodium, glucose, and urea concentrations to calculate the blood osmolality (osmo/L); osmo/L = 2[sodium ions] + [glucose] + [urea]. However, osmo/L alone may not be an accurate estimate of dehydration [3, 2]. Galvanic skin response (skin conductance) has been used to estimate hydration level; however, this monitors the sympathetic nervous system, which can skew the moisture measurement [19].

Table 1 shows the normal range of sodium for different body fluids. The noninvasive fluids such as saliva and sweat have lower concentrations, which provide challenges in achieving accurate measurements. Interstitial fluid (ISF – tissue fluid) has normal sodium levels comparable to blood. It may be possible to noninvasively pull out small amounts of ISF with micro-suction devices.

Table 1. Normal Adult Physiological Range of Sodium (mM)

Blood	*Urine*	*Saliva*	*ISF*	*Sweat*
136–145 [10]	90–180 (mM/day) [32, 11]	10–100 [6]	136–145 [10]	20–70 [15, 11]

To illustrate how dehydration monitoring can improve health outcomes, we offer two scenarios. Imagine Cora, a fiercely independent 82 year old woman living alone in her home of 50 years. She gets frequent urinary tract infections and has had several hospitalizations in the intensive care unit for dehydration associated with urinary tract infections. At her daughter's insistence, Cora agrees to remote monitoring for dehydration. One day Cora's daughter receives an alert that her mom seems to be dehydrated. She calls her mom, who does admit to feeling "a little under the weather" and they arrange a doctor's appointment. The doctor confirms the presence of a urinary tract infection, but Cora agrees to drink plenty of water and take the prescribed antibiotics. In a few days, Cora is feeling better. A follow-up visit to the doctor confirms that the urinary tract infection is resolved, this time without hospitalization.

The second scenario illustrates how dehydration monitoring can help in a younger subject. Andrea is a 32 year old woman experiencing her first pregnancy, but her pregnancy is complicated by heart failure due to her history of congenital heart disease. Andrea and her doctors knew the pregnancy was a risk and are managing it with diuretics to control accumulation of body fluid and swelling. Because dehydration is dangerous in pregnancy, Andrea and her doctors opt for daily monitoring of her hydration status. After an increase in diuretics for increased swelling during the 32nd week of her pregnancy, Andrea and her doctors receive an alert that she has become dehydrated. They schedule an immediate appointment. While sitting in the doctor's exam room, Andrea begins to experience contractions. Her doctor immediately begins intravenous fluids and the contractions stop. They adjust her medications, control her heart failure symptoms, and avoid premature birth of the baby.

Cora and Andrea have very different health histories and different needs, which may result in dissimilar measurement schedules with distinct types of alert conditions. An athlete or soldier in uncontrolled temperature and humidity will have much different needs. A dehydration monitoring system that is truly personalized will need to accommodate these differences.

3. SYSTEM OVERVIEW: THE VISION

Our vision is to develop a compact, smart sensing module that interacts with a human body noninvasively and provides personalized diagnostic health measurements and analysis. To address the lower biomarker concentration levels found in noninvasive body fluids such as sweat and saliva, we have been investigating plasmonic-enhanced sensing elements. Here, we demonstrate an example of noninvasive dehydration sensing with a plasmonic biosensor and a smartphone. The long-term goal is to develop a clinical-quality, compact sensor system that could be incorporated into a self-powered, wearable system, or built into a furniture item that naturally couples with the body (such as an armchair), or designed as a smartphone add-on.

Figure 1 illustrates the control process that drives the personalized measurement of the biomarkers such as sodium, based on internal factors, stored parameters in the electronic health record (EHR), and environmental factors. This measurement control process is personalized to the individual in the sense that it uses the individual's historical readings of sodium and other biomarkers, the age, gender, medications, and health of the individual, the current activity level of the individual as determined from the smartphone or wearable accelerometer, and ambient environmental conditions such as temperature and humidity. The uncertainty of the biomarker readings, as well as the factors just mentioned, will determine personalized measurements that are scheduled specifically for the individual's health and conditions.

Depending on the readings and conditions, the control output may be (1) data request to schedule another biomarker reading, (2) data request to get the activity or location from the accelerometer or

GPS, (3) data request to get environmental conditions, (4) user notification with a suggested action (e.g., get a drink of water), (5) send a health change alert to a clinician monitoring the user, or (6) send an urgent alert if the condition persists. The health alerts are done in the context of our previous Eldertech work [27] in which in-home sensor data are monitored to find patterns; health change alerts are generated automatically to clinicians when the sensor data patterns change [28, 29, 24, 25]. The health alert system has been tested in multiple senior housing sites starting in 2010 [1].

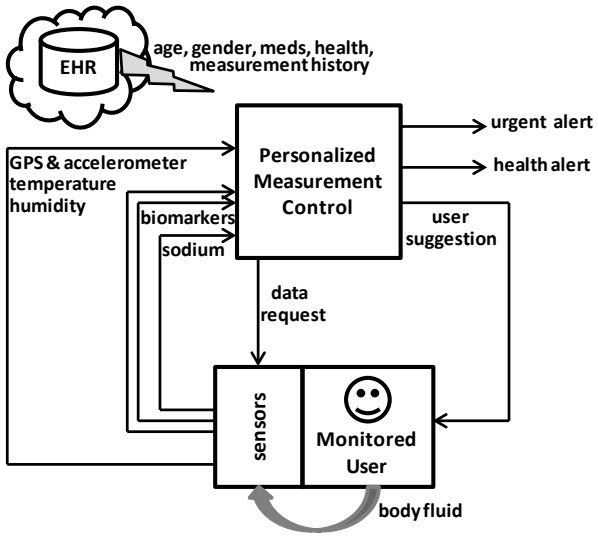

Figure 1. Personalized measurement control of sodium and other biomarkers, taking into account measurement uncertainties, the health and history of the individual, the current activity, and environmental conditions. The system would produce different levels of outputs including non-urgent user suggestions and health change alerts as well as urgent alerts that need immediate attention.

The smartphone is a convenient platform for testing the concept due to the processing and communication capabilities, allowing image capture and analysis, input of other pertinent data and recorded health histories, processing for personalized measurement control, and communication of the measurement result including reporting of urgent alerts. While smartphone-based sensor systems are becoming more common in the literature, most use only the basic smartphone imaging and analysis abilities [5, 17], few are able to display biomarker concentrations, and most require significant sample preparation prior to sensing [7, 8, 33]. There are currently no commercially available fluorescence-based smartphone sensor systems.

Figure 2 shows a design example of a black box enclosure that incorporates plasmonic grating nanosensors to measure biomarkers and a smartphone for imaging, analysis, and communication. In this configuration, the fluids would be introduced manually. Utilizing filters and magnifying/objective lenses, the smartphone light (or external light source) is directed at the immobilized biomolecules on the plasmonic grating nanosensor surface. Cut-off filters remove excitation light and direct emitted fluorescence onto the smartphone camera.

Fluorescent signal intensity is proportional to the biomarker (e.g., sodium ion) concentration. To ensure good calibrated readings, a blank control (no sensing element) and two positive controls (known spiked samples, upper and lower concentrations) are also

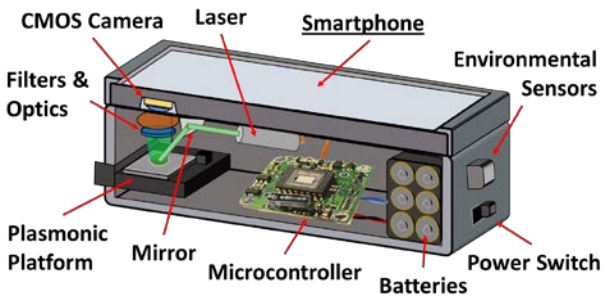

Figure 2. Schematic of a black box enclosure for health monitoring with plasmonic grating substrate enclosed in the control unit and integrated with a smartphone camera. The enclosure ensures consistent lighting and optics for accurate measurements.

imaged. The experimental sample measurements are compared to control channels for instant calibration. Sensor optics are controlled by a microcontroller to "turn-on" the sensor when needed and modulate detector exposure time and gain in order to maximize the measurement dynamic range. Frequent opportunistic sensing will rapidly generate a large volume of detailed fluorescence imaging data that needs to be assimilated, analyzed and converted into useful physiological information in real time, for processing as outlined in Figure 1.

4. PLASMONIC DEHYDRATION BIOSENSOR

A system that interfaces with unprocessed noninvasive body fluids and sensitively detects biomarkers of interest requires advanced sensing technologies. Here, we demonstrate highly sensitive sodium ion sensors for dehydration monitoring by leveraging plasmonic nanostructures. We have developed a soft nanoimprint lithography process to inexpensively replicate the periodic structure of commercially available HD DVDs using a rapidly curing polymer "ink" (polymethylsilsesquioxane, PMSSQ) and polydimethylsiloxane (PDMS) "stamps" [4]. Coating these gratings with thin silver films produces nanostructures that couple visible light wavelengths at specific incidence angles through surface plasmon resonance [16, 23, 22], which appears as sharp dips in reflectivity measurements [4, 14, 9]. Figure 3 shows an atomic force microscopy (AFM) image of the stamped HD DVD silver grating surface. Grating light coupling results in a propagating evanescent electromagnetic field at the grating surface, which can be used to excite and enhance fluorescence of nearby fluorophores.

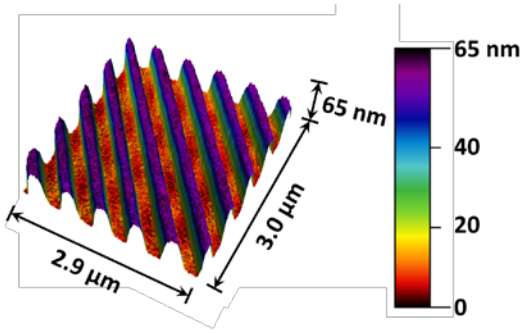

Figure 3. AFM image of PMSSQ HD DVD grating (h = 65 nm, Λ = 400 nm).

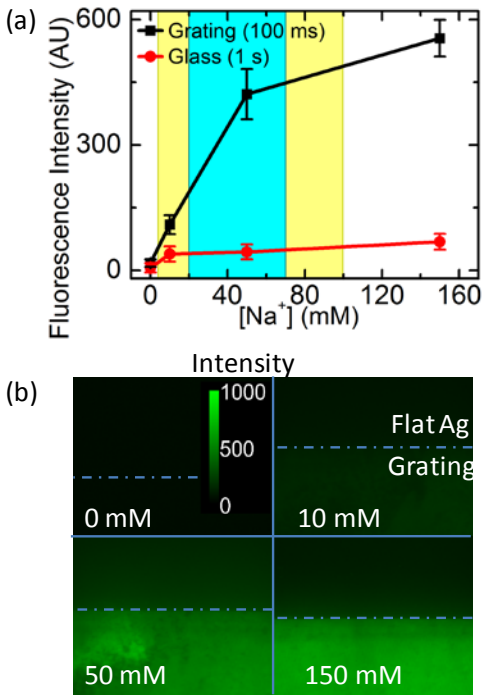

Figure 4. (a) Fluorescence titration of (sodium) NaTRIUM-doped PMSSQ thin film with aqueous NaCl, comparing grating platform to glass. Normal (*blue region*) and abnormal (*yellow region*) [Na^+] ranges from sweat are indicated with the vertical bars. (b) Images of grating-enhanced fluorescence. NOTE: Exposure time for glass is 10× higher than for gratings but still shows significantly lower image intensity.

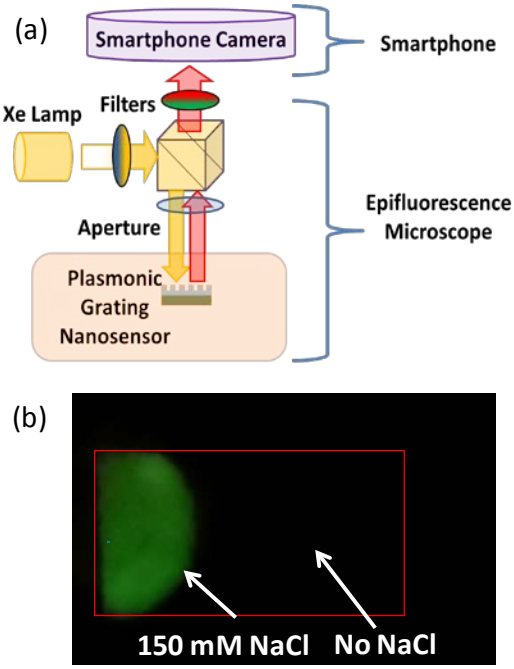

Figure 5. (a) Setup with plasmonic grating nanosensor in line with epifluorescence microscope optics and smartphone camera. (b) Smartphone image of ANG-2 fluorescence with/without exposure to 150 mM NaCl. NOTE: Red box indicates area of stamped plasmonic grating.

We have tested the plasmonic grating nanosensors with sodium concentrations, using an epifluorescence microscope and CCD camera to image and calibrate the fluorescence emitted from the biosensors. Figure 4 shows results of image-based sensing of aqueous sodium ion concentration ([Na^+]) using the sodium-sensitive fluorescent dye Asante NaTRIUM Green 2 (ANG-2) embedded in a PMSSQ polymer matrix. A 15 nm thin film of 10 µM ANG-2/PMSSQ was then spun on glass and our plasmonic grating nanosensor for comparison. We used an epifluorescence microscope with 40× lens for illumination and focus, an ORCAflash2.8 CCD camera for image capture, and ImageJ for image processing and analysis. As shown in Figure 4a, the plasmonic grating nanosensor displayed a much higher fluorescent signal than the glass platform sensors. We calculated a 1.5 mM limit of detection on 5 minute exposure to [Na^+]. More importantly, the linear range of the plasmonic grating nanosensor falls nicely in the expected physiological range for Na^+ in sweat [20]. This linear range can be expanded by tuning the ANG-2 concentration to allow for a broad range of [Na^+] sensitivity in case of abnormal individual readings.

We have also tested a smartphone platform for imaging. Measurements were taken using a Samsung Galaxy S5 (Figure 5a) to showcase our ability to detect physiologically relevant [Na^+] (Figure 5b). The plasmonic grating nanosensor area (outlined in red) is shown with/without exposure to 150 mM NaCl isolated by a silicone microwell. As can be seen, there is a clear fluorescence difference between the two regions. Meanwhile, no fluorescence was observed from films on glass even after exposure to 150 mM NaCl. This experiment demonstrates that the smartphone is capable of image capture of the plasmonic grating-enhanced fluorescence.

5. RESEARCH QUESTIONS AND CHALLENGES

The aim of this paper is to begin to explore how a cyber physical system can and should interact with a human body to provide a more intimate, personalized medical control system. However, there are many challenges and research questions that need further investigation. We have organized these into three categories.

First, there are open questions and challenges on creating *clinical-quality biosensors* for capturing dehydration and other biomarkers that can be used by non-clinical individuals to track changes in their own health. For the example provided here of measuring sodium concentration in body fluids, it is not clear what type of body fluid provides the best tradeoffs of ease in use, noninvasiveness, and sensitivity of measurement. Also, more experimentation is required to determine the best optical parameters to acquire sensitive measurements with the plasmonic grating nanosensors, for example, the magnification level, and the strength and angle of the excitation beam. There is also the challenge of getting the fluids to the sensor, for example, using microfluidics. We have envisioned a system that operates automatically, capturing fluids as necessary to fulfill the individual's measurement schedule. Whether this is feasible may depend on the type of body fluid needed for accurate measurements.

Second, there are *computational challenges* to be investigated. For the example presented in this paper, robust image processing and

analysis methods will be required that provide consistent measurements in varying environmental conditions. We have presented one example of a closed system (Figure 2) which may offer some control over the lighting and optics. However, for use in unstructured settings, the system will have to provide its own controlled environment and/or include self-monitoring, self-calibrating, and adaptive methods in order to achieve clinical quality measurements. There are trade-offs to investigate between local processing and a distributed intelligent system in which data are sent to a server and processed remotely. Networking issues must also be considered; for example, if the system is used in extreme conditions, networking access might not be consistently available. Finally, there are challenges in how to achieve the personalized measurement control process. There will be temporal and other dependencies among the input parameters and the outputs. Interaction with the human body complexities will make a data-driven approach problematic, due to the challenges in collecting a dataset that comprehensively spans the feature space. As an alternative, other automated approaches should be investigated for exploring the structure in the control space, to achieve the type of personalized measurement control process outlined in Section 3.

Third, there are *system-level challenges* in creating the type of medical cyber physical system proposed here. To make the system useful in varying settings, it should be compact and portable, which will mean constraints in size, power, networking, and computational resources. Further research will be necessary to determine practical limitations. The system should use a modular design so that other medically relevant biomarkers can be detected in the future by refitting with appropriate sensing elements. In addition, there is the issue of how to test the system. As a new project concept, there is considerable work to be done before this can be tested on human subjects. Some type of simulation process may be necessary for initial testing.

6. CONCLUSION

In this paper, we introduced our vision for a medical cyber physical system that provides personalized health monitoring of biomarkers and presented an example of a biosensor that could be used to measure sodium concentration for dehydration monitoring. Many challenges must be overcome before the envisioned personalized monitoring system can be realized. Furthering the research in this area will advance the state of the art in self-monitoring, self-calibrating, and adaptive health monitoring systems that offer the potential to impact many lives, especially vulnerable groups such as seniors. With the envisioned system, a more proactive healthcare model is possible.

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