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A Systematic Approach to Terahertz-based Glucose Monitoring

SASAN ADIBI, LEMAI NGUYEN, ANDREAS HAMPER, FREIMUT BODENDORF & NILMINI WICKRAMASINGHE

Abstract This paper focuses on the design and development of a non-invasive smart and pervasive mobile solution to measure blood glucose without the need for drawing blood or pricking fingers. Specifically, it examines the possibility of sensors using Terahertz (THz) technology to measure blood glucose. This paper reports on a research in progress looking at identifying and then designing superior strategies for measuring blood glucose. It presents the central role that measuring blood glucose plays in diabetes care management. It then highlights the current methods and problems and concerns with finger pricking. From there, the paper proffers a non-invasive solution using THz technology to measure blood glucose and outlines the approach to design and develop such a solution using a decision science methodology.

Keywords: • health informatics • mHealth • diabetes • blood glucose monitoring • non-invasive • terahertz •
Introduction

Diabetes is a chronic disease that occurs when there is too much glucose in the blood because the body is not producing insulin or not using insulin properly (Diabetes Australia, 2007). As noted by the WHO (World Health Organization, 2016), diabetes is at epidemic proportions globally and needs to be addressed. Diabetes management involves a combination of both medical and non-medical approaches with the overall goal for the patient to enjoy a life which is as normal as possible (Australian Institute of Health and Welfare, 2007, 2008). As there is no cure for diabetes, diabetes must be regularly managed and monitored. Critical to this management regimen is the systematic monitoring of blood glucose levels. However, achieving this goal can be challenging because it requires effective lifestyle management as well as careful, meticulous attention and monitoring by the patient and health professionals (Britt et al., 2007). There is a need for identifying a simple and convenient non-invasive approach to monitoring blood glucose (So et al., 2012). This forms the focus of this research.

Background

2.1 Invasive, Semi-Invasive, and Non-Invasive Solutions

A key factor in the management of diabetes has been found to be the patient’s self blood glucose monitoring (SBGM) (Guerci et al., 2003; Haller et al., 2004; Karter et al., 2001). As a result of recent research (Farmer et al., 2009; Malanda et al., 2012), General Practice Management of type 2 diabetes (RACGP and Diabetes Australia, 2014-2015) recommends SMBG for patients with type 2 diabetes who are on insulin. Currently, the dominant method to test blood glucose level is invasive. It requires a blood glucose meter, a lancet device with lancets, and test strips. Further, the patient must prick their finger with the lancet sometimes more than four times a day. Finger pricking in SBGM has been found to have several clinical and psychological disadvantages. These are described below.

Clinically, there is a risk of skin infection and tissue damage. Repeated finger pricking associated with the depth and possible vibrations of the needle tip while penetrating the skin were found to cause soreness (Burge, 2001) and damage the skin and in severe cases could lead to ulcer on their patient fingers (Dahiya et al., 2012; Giannini & Mayr, 2004). Therefore, this SBGM practice can result in damage to the patient body site.

Further, SBGM using a finger prick glucometer is not practical for continuous monitoring of blood glucose (So et al., 2012). As blood glucose levels of a patient change overtime, possible occurrences of hyperglycaemia or hypoglycaemia between measurements may not be recorded. Thus, the measurements may not truly reflect the patient blood glucose pattern (Kannampilly, 2013).
Psychologically, inconvenience and anxiety of constant performing finger pricking and extracting a drop of blood in patients’ daily lives, and associated physical and emotional pain have always been troublesome in SBGM (Burge, 2001; Karges et al., 2008; Pacaud et al., 1999; Wainstein et al., 2013). In a cross-sectional questionnaire survey with 315 patients with diabetes in the UK, about one third of general diabetes patients were found to have anxiety to finger pricking for SBGM (Shlomowitz & Feher, 2014). Positive correlations were found between anxiety due to finger pricking and avoidance of testing as well as between anxiety due to finger pricking and general anxiety. In previous studies (Burge, 2001; Cradock & Hawthorn, 2002; Koschinsky, 2007), pain and discomfort were consistently found to cause a natural resistance to SBGM, and subsequently result in a lack of adherence to this procedure. Anxiety due to the finger prick method and avoidance of testing were found across different ethnic groups and female patients were found to have greater anxiety to finger pricking SBGM (Shlomowitz & Feher, 2014).

The aforementioned disadvantages served to motivate the need for new approaches to SBGM. They can be categorised into two groups. The first group is to support for measuring blood glucose levels in a less painful manner. Wainstein et al. (2013) used a CoolSense device to reduce local pain sensation due to finger pricking. They conducted an experiment with 177 adult patients with type 2 diabetes and concluded that the CoolSense device significantly reduced subjective pain felt by the patients while maintaining the same level of clinical accuracy. Other studies suggest that instead of pricking fingers, patients can prick other areas such as the forearm, knee, earlobe, thigh and abdomen skin (Castilla-Peón et al., 2015; Heinemann, 2008; Nakayama et al., 2008). While pricking alternative body sites were commonly found to reduce pricking fingers to some extent, it did not eliminate the pain completely. Disadvantages of pricking other body sites include lack of accuracy, inconvenience and difficulty of pricking in public, and technology switching costs to purchase new equipment for pricking and measurement (Castilla-Peón et al., 2015; Cradock & Hawthorn, 2002; Heinemann, 2008).

The second group of approaches to SBGM is to developing semi-invasive and non-invasive technologies for blood measuring without needle pricks (Makaram et al., 2014; So et al., 2012). Du et al. (2016) propose a biosensor that can detect low-level glucose in saliva. They conducted a study of ten healthy human subjects and conducted that the proposed biosensor can be seen as a potential alternative to SBGM using finger pricking. The protocol of use is still rather complex, consisting of nine steps requiring the patient to chew a sponge in his/her mouth to collect saliva, and later squeeze the collected saliva into the device with a sensor, thus is not easy to use. More studies are required to investigate the accuracy of sensors in detecting low salivary glucose levels, efficiency and practicality of the proposed approach. Zhang et al. (2011) review current developments of non-invasive continuous SBGM methods using ocular glucose. These authors review studies in ocular glucose monitoring: (1) using contact lens-based sensors and (2) using nanostructured lens-based sensors. They concluded that lens sensors have the potential to monitor a wide range of glucose levels quickly and accurately, however there is a safety concern because boronic acid and concanavalin A may be released from
the lens into the patient body. Nanostructured lens-based sensors have several advantages (for example better accuracy and sensitivity, less interference with patient vision), further studies are required to improve resolution and sensitivity of the lens, and to determine physiologically relevance and baseline tear glucose concentration (Zhang et al., 2011). Another review of current nanomaterial-based solutions using saliva, sweat, breath and tears as a medium for SBGM suggests that they are far from optimal; further nanotechnology sensing devices need to be manufactured at a low cost to compete with established blood glucose meters (Makaram et al., 2014).

One of the most recent advances in the area of semi-invasive glucose monitoring is Abbott’s Freestyle Libre System (HT Correspondent, 2015) which is based on a body attached sensor and a smartphone loaded with the application (Figure 1, adapted from HT Correspondence, 2015). This disposable body attached device (sensor) is equipped with a thin and flexible fibre needle, which is the only invasive part, however the fibre is inserted only once and under the skin of the back of the arm. The sensor can be used continually for 14 days without the need to be replaced. The sensor captures glucose concentration information and once the smartphone that runs the required app scans the sensor, the current and up to 8 hours of glucose levels are read and uploaded to the smartphone (Timothy et al., 2015)

According to Timothy et al. (2015), the accuracy of the FreeStyle Libre system as dependent function of a number of patient-related factors (e.g., diabetes type, gender, insertion site/administration, body mass index, hemoglobin A1c “HbA1c”, age, and rate of change) has been found to be above 85.2% up to 14 days of testing.
Overall, studies in issues associated with SBGM using finger pricking devices and learnings from in current developments of new SBGM methods suggest the following key factors: technology (technical soundness, sensitivity of device, and sufficient quantity and reproduction of medium), clinical accuracy (accuracy of measures, continuity of monitoring), clinical and safety interference with vision patient vision (infection, damage to patient body sites, release of chemicals to patient body, interference with patient vision), ease of use (level of invasiveness, practicality of sample collection and protocols of use), psychological effects (pain and discomfort, anxiety, fear, inconvenience and difficulty of performing tests in public), and costs (manufacturing costs and patient technology switching costs). We develop Table 1 to present the key aspects of problems and concerns identified in the extant literature relating to SBGM.

We conceptualise the problem in diabetes care management with the above factors. Therefore, we propose an approach to solution development consisting of patients analytics to focus on the targeted patient cohort, design science engaging patients in testing when it's safe, not early design, to finally propose a new solution to address their concerns and ensuring appropriate monitoring of the care management plan.
Table 1: Problems and concerns in current SBGM methods

<table>
<thead>
<tr>
<th>Key aspects</th>
<th>Factors</th>
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</thead>
<tbody>
<tr>
<td>Technical feasibility</td>
<td>Sufficient quantity and reproduction of medium (Makaram et al., 2014).</td>
</tr>
<tr>
<td></td>
<td>Sensitivity of device (Zhang et al., 2011)</td>
</tr>
<tr>
<td></td>
<td>Technical soundness (Makaram et al., 2014; So et al., 2012)</td>
</tr>
<tr>
<td>Clinical accuracy</td>
<td>Accuracy of result (Castilla-Peón et al., 2015; Nakayama et al., 2008;</td>
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<tr>
<td></td>
<td>Timothy et al., 2015)</td>
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<td></td>
<td>Continuity of monitoring (Kannampilly, 2013; So et al., 2012)</td>
</tr>
<tr>
<td>Side effects and</td>
<td>Infection (Dahiya et al., 2012; Giannini &amp; Mayr, 2004)</td>
</tr>
<tr>
<td>safety</td>
<td>Physical damage to the body site (Burge, 2001; Dahiya et al., 2012;</td>
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<td></td>
<td>Giannini &amp; Mayr, 2004)</td>
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<td></td>
<td>Release of chemical to body (Zhang et al., 2011)</td>
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<td></td>
<td>Interference with vision (Zhang et al., 2011)</td>
</tr>
<tr>
<td>Easy of use</td>
<td>Level of invasiveness (Castilla-Peón et al., 2015; Heinemann, 2008;</td>
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<tr>
<td></td>
<td>So et al., 2012; Wainstein et al., 2013)</td>
</tr>
<tr>
<td></td>
<td>Practicality of device, sample collection and protocols of use (Du et</td>
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<td></td>
<td>al., 2016; Heinemann, 2008)</td>
</tr>
<tr>
<td>Psychological</td>
<td>Pain and discomfort (Burge, 2001; Heinemann, 2008; Karges et al., 2008;</td>
</tr>
<tr>
<td>effects</td>
<td>Koschinsky, 2007; Pacaud et al., 1999; Wainstein et al., 2013)</td>
</tr>
<tr>
<td></td>
<td>Anxiety and distress (Cradock &amp; Hawthorn, 2002; Shlomowitz &amp; Feher, 201</td>
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<td>4)</td>
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<tr>
<td></td>
<td>Fear of needles and blood (Burge, 2001; Shlomowitz &amp; Feher, 2014)</td>
</tr>
<tr>
<td></td>
<td>Inconvenience and difficulty of performing tests in public (Castilla-Pe</td>
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<tr>
<td></td>
<td>ón et al., 2015; Heinemann, 2008)</td>
</tr>
<tr>
<td>Costs</td>
<td>Manufacturing costs (Makaram et al., 2014)</td>
</tr>
<tr>
<td></td>
<td>Patient technology switching costs (Heinemann, 2008)</td>
</tr>
</tbody>
</table>

2.2 Non-Invasive Terahertz Technology Solution

The ultimate approach in managing diabetes is based on non-invasive solutions, one approach is using Terahertz technology which is the focus of this section. Terahertz refers to the electromagnetic waves with the frequency range between millimetre-wave and infrared, approximately from 100 GHz up to 10 THz (see Figure 2 adapted from Adibi, 2013). The THz spectrum, also known as the “terahertz gap” is the last portion of the electromagnetic spectrum which has not been fully explored and exploited (Tonouchi, 2007). Terahertz technology is a fast-growing field with applications in biology and medicine, medical imaging, material spectroscopy and sensing, security, monitoring and spectroscopy in pharmaceutical industry, and high-data-rate communications.
In biomedicine, Terahertz technology has so far been used in a variety of medical applications, including: skin/breast cancer detection, wound inspection, and dental imaging (Panwar et al., 2013; Yang et al., 2016).

![Figure 2: Frequency Spectrum of EMR Imaging Technologies, adapted from Adibi (2013)](image)

The THz studies have uniquely revealed that medical image diagnoses are possible over a wide range of tissues, however much further detailed analyses are required to identify the degree of precision achieved in monitoring blood glucose concentration using THz technology.

### 3 Proposed solution

The technology methods behind the operation of this solution’s proof of concept are based on the following approaches (Jackson et al., 2011):

- Terahertz time-domain spectroscopy (THz-TDS)
- Terahertz frequency-domain spectroscopy (THz-FDS)
- Terahertz imaging using non-destructive evaluation (NDE)

These methods are considered to pinpoint the best option for blood-glucose level monitoring from the transmitter/receiver perspectives. The THz transmitter, the operational power, energy consumption level, and safety factors are of significant importance since the solution is ultimately deployed in a smartphone application.

From the mentioned approaches, the THz-TDS approach has shown promising behavior since it was used to measure the full dielectric-based function representing as the absorption coefficient and the refraction index of glucose and galactose between 0.2 THz to 3.0 THz (Zhang, 2008). A few distinct absorption features are identified as the signatures of intra- and intermolecular modes of the hydrogen bonded crystalline structure.
The design of the related app that runs on the smartphone platform requires a number of features, including: a fast Digital Signal Processing (DSP) system based on the microcontroller system used in the Arduino platform. The hardware side of the system consists of an open-source 32-bit Atmel ARM processor, which is capable of running fast concurrent processes. The software system features a fast and optimised image processing algorithm aided with Kalman filtering for higher accuracy. The high accuracy results are needed due to highly variable testing environment (handheld application). The system also features remote monitoring and cloud-computing capability. The proof-of-concept involves the identification of the optimal THz sensor, power, frequency spectrum, and reflection analysis for the most optimal application of the Terahertz technology in monitoring under-skin blood glucose levels.

The framework is the continuation of the work of reference (Shen et al., 2002), which is based on the Fourier Transform Infrared (FTIR) Spectroscopy. This reference shows the successful deployment of infrared in detecting glucose level of the blood. The lessons learned from this work can directly be used in this project.

Once the specific THz approach is selected, the methodological approach is to model the existing solutions and study the physical behaviour of Terahertz technology when radiated onto the human skin and study the depth of penetration and the variations in the reflections. This requires sophisticated THz lab equipment to run experiments on a test dummy, which mimics the human skin and underlying soft tissues. The results between the traditional needle-based sensing are then compared and the precision figures for the Terahertz-based method are evaluated. Then the approach need to be fine-tuned and also other health issues (e.g., technology implications, training, health-hazards, etc.) are then considered.

4 Proposed solution

A Design Science Research Methodology (DSRM) will be used to operationalize this research. This approach is particularly appropriate where improving an existing solution is desired and/or there is a need for a new solution to address specific unsolved or unique aspects (Hevner & Chatterjee, 2010; Hevner et al., 2004). DSRM as a process model to carry out research is widely used in the information systems research to create new solutions or to improve existing ones. DSRM process model consists of six process elements (Peffers et al., 2007), starting from identifying the problem and the motivation to conduct research, and concluding with communicating the results and outcomes of the research. Table 2 maps the proposed project to DSRM process elements (Peffers et al., 2007).
Table 2: Mapping the proposed research to DSRM

<table>
<thead>
<tr>
<th>DSRM process elements</th>
<th>DSRM description</th>
<th>Application on this study</th>
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</thead>
<tbody>
<tr>
<td>Problem identification and motivation</td>
<td>Defining the specific research problem and justifying the value of a solution based on knowledge of the state of the problem.</td>
<td>With the increased diabetes population, and the disadvantages of conventional blood glucose tests, the lack of a reliable and easy to use non-invasive technology to monitor blood glucose motivates this research.</td>
</tr>
<tr>
<td>Definition of objectives of the solution</td>
<td>The objectives can be qualitative or quantitative i.e. create or improve an artefact respectively based on knowledge of the state of the problem and current solutions, if any, and their efficacy.</td>
<td>The objective is to create and refine an artefact; i.e. the sensors.</td>
</tr>
<tr>
<td>Design and development</td>
<td>Creating the artefact, including the desired functionality and its architecture based of knowledge of theory that can be used to bear in a solution. This is usually an iterative process.</td>
<td>Through several iterations the exact range for the frequency for the needed Terahertz wave beam will be identified. Once the narrow range for the frequency for the Terahertz wave is identified, the CAD/CAM programming will occur.</td>
</tr>
<tr>
<td>Demonstration</td>
<td>Demonstrate the use of the artefact to solve the problem.</td>
<td>Simulation-based: This will be done in a lab using their simulation set up and mannequins. Clinical: Demonstration of the use of a new device to a sample of targeted patient population.</td>
</tr>
<tr>
<td>Evaluation</td>
<td>Iterate back to better design the artefact if needed.</td>
<td>Simulation-based: As needed, iterations will take place, to fine tune the needed range for the Terahertz wave projections. Clinical: Iterative evaluations to ensure that the prototype is truly tailored to meet clinical requirements for the targeted population.</td>
</tr>
<tr>
<td>Communication</td>
<td>Publish and let the value of the solution talk about itself.</td>
<td>This will include conference publications, journal publications and other presentation activities.</td>
</tr>
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</table>
Based on our systematic review of the literature to date, we have identified problems and concerns with the current methods for blood glucose monitoring as well as the need for a simple, accurate non-invasive solution to it. To address this void we have proffered a technology solution using sensor technology combined with a smart phone. The next steps now include the design and development of the solutions coupled with establishment of proof of concept, usability and fidelity. This involves four key steps as follows:

Phase 1: This phase will involve the conducting of multi-dimensional analysis of provided data sets from a diabetic population (in China). The results will provide a clear picture of the current state, reveal critical trends and important patterns regarding this population and assist to identify the patient sample. It is anticipated that target patient cohorts and their demographics as well as geographic and clinical characteristics will be identified for the project to identify who would benefit most from the non-invasive smart solutions. This phase aims to address the first DSRM process elements including problem identification and motivation, and definition of objectives of the solution (see Table 2).

Phase 2: Phase 2 will include designing and developing the appropriate sensor technology. The patented solution we have developed uses THz to identify blood sugar readings but this requires critical analysis to isolate the specific THz band. Inputs for this are derived from aspects of the data analytics performed in phase 1 above. Once this is done the required specifications for designing the sensors must be generated. Thus the results at the end of this phase include the design specification for the sensors to be used in the specific context so they are truly tailored to that context. This phase aims to address the subsequent DSRM process elements including design and development, simulation-based demonstration, and associated simulation-based evaluation.

Phase 3: Phase 3 will focus on the design and development of the software solution necessary to develop the prototype to be used to measure blood glucose readings. Contemporaneously, the health literacy issues will be examined and an appropriate education and coaching program will be developed for the targeted population. This phase aims to continue the DSRM process element design and development.

Phase 4: Phase 4 involves establishment of proof of concept, usability, fidelity and functionality. This will be conducted by running a field study on the selected patient population of 50 patients based on results from phase 1. It is anticipated that the field study will involve and iterative process to ensure that the prototype is truly tailored to the selected population’s needs and requirements. In addition, HbA1C the standard diabetes marker will be tested at 3 month intervals over a 6 month time frame to assess success of the solution and changes to health literacy at these points will also be assessed. This phase aims to address the DSRM process elements including clinical demonstration, and clinical evaluation using the key aspects (technical feasibility, clinical accuracy, clinical
side effects and safety, ease of use, psychological effects, and costs) and relevant factors presented in Table 1. As a result, the list of factors will be refined to inform future implementations and evaluations.

The DSRM process element communication will take place through the whole project when findings from each phase become available.

6 Discussion and Conclusion

Concurrent and independent from the exponential rise of diabetes has been the rise of mobile and sensor technology. The maturing and sophistication of these technologies has enabled them to be sued in many aspects of healthcare and wellness management. The preceding has served to outline another potential area for the adoption of mobile and sensors; namely, to assist with a non-invasive approach for the monitoring and management of diabetes. Specifically, we have identified an opportunity to use Terahertz frequencies to detect blood glucose levels in individuals. Further, we envisage designing and developing this solution by combining sensors with a mobile phone so that detection of blood glucose can not only be non-invasive but truly pervasive.

The implications for theory and practice are wide and far reaching. From a theoretical perspective we combine two technology genres mobile and sensors to address a healthcare issue – detection of blood glucose levels using a design science research methodology. This can lead to a better understanding and application of sensor technology in mobile technology. Scientifically backed roadmaps for including innovative sensors (i.e. terahertz sensors) in mobile technology can support further DSRM based research in the field. From the perspective of practice, diabetes as noted by World Health Organization (2016) is global and at epidemic proportions with an estimated of 422 million adults living with diabetes in 2014, and 1.5 million deaths caused by diabetes in 2012. Complications from diabetes can lead to other serious conditions such as heart attack, stroke, blindness, kidney failure and lower limb amputation. Further, the number of pre-diabetic individuals is also considerable. Monitoring and management is the only recognised strategy to maintaining appropriate blood glucose levels and thereby managing diabetes and/or preventing a pre-diabetic becoming a diabetic. Given, the problems and criticisms of finger pricking and other invasive approaches to SBGM, the most prevalent approach to testing blood glucose using a non-invasive Terahertz technology solution which we propose is very attractive to individuals. By learning from glucose monitoring, there is an opportunity to transfer the use of Terahertz technology to test other blood values in a non-invasive way. When such a solution is truly pervasive, it becomes even more attractive. Thus, we believe that the proffered solution will enable diabetic and pre-diabetic individuals to enjoy a better quality approach to monitoring and managing their blood glucose levels.

Our future work will focus on establishing usability, fidelity and acceptability of the proffered non-invasive pervasive solution.
References


