An Architecture to Support Real-World Studies that Investigate the Autonomic Nervous System

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Abstract. Diabetes is a chronic disease with complications related to the autonomic nervous system (ANS) that can affect quality of life and lead to mortality. Clinicians and researchers currently rely on subjective and/or invasive means that don't necessarily translate to real-world setting when assessing severity of certain diabetes complications. We elicited use-cases of studies aimed at understanding ANS in the context of diabetes to gather system requirements for designing an architecture to support sensor-based studies. Real-world studies would need to be capable of gathering contextual data as well as proxies for ANS symptoms from digital markers from an evolving sensor landscape, while also supporting the data needs of researchers before, during, and after data acquisition. The proposed architecture makes use of open source and commercially available mobile health technologies, and informatics platforms to meet the design criteria. Building and testing a prototype of the proposed architecture is planned to confirm the system performs as expected.

Keywords: Real-world studies · Diabetes complications · Autonomic nervous system · Software architecture · Sensors · Digital biomarkers

1 Introduction

Diabetes is a chronic disease that effects 30.3 million in the US; about 5% have type 1 diabetes (T1D) [1]. When diabetes is treated with insulin, patients are at risk for developing hypoglycemic associated autonomic failure (HAAF) and impaired awareness of hypoglycemia (IAH) [2], which can lead to life-threatening acute episodes of hypoglycemia. Hyperglycemia can lead to diabetic neuropathy (DN) and associated pain (DN-P). DN-P is often treated with opioids, which is concerning due to current epidemic [3]. Clinicians and researchers in both these areas of complications rely on validated surveys or invasive methods that pose risks to patients to properly diagnose [4–6]. Improved understanding of the autonomic nervous system (ANS) as well as its

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measurement in real-world scenarios using sensors could provide insightful data and information for biomedical researchers and lead to new therapies, treatments, and minimally-invasive methods for diagnosing diabetes related complications.

While many Internet-of-Things (IoT) and mobile health (mHealth) systems have been proposed to support patients with self-management of diseases that allow their health care providers to have real-time access to data [7], these systems do not provide all the necessary components to support investigators who desire to conduct research in real-world settings, nor do they provide sufficient security to guarantee privacy and accuracy. The objective of this study was to gather requirements for conducting real-world studies of the ANS and propose an informatics architecture to support the studies.

2 Methods

We elicited use-cases of studies focused on ANS and diabetes from researchers with whom we have ongoing collaborations [8]. Using the general model for software architecture design, which encompasses the process of translating system requirements into real world solutions in terms of software code, frameworks, and components; we gathered the requirements necessary to conduct studies related to IAH/HAAF and DN/DN-P. We selected existing technologies and informatics methods that could support the studies. We pinpointed where current technologies would need to interface and additional component development needed, resulting in a prototype architecture.

3 Results

3.1 Use Case Descriptions

Crossover Clinical Trial of a Pharmacological Intervention for IAH. Patients with T1D and history of IAH would be randomized to receive a pharmaceutical intervention or placebo for several weeks, then crossover after a washout period. The following ANS symptoms and other clinically relevant information would be measured: shaking, trembling, skin surface temperature, palpitation, perspiration, blood flow, blood glucose, physical activity, and injected insulin. Other symptoms, such as anxiety, nervousness, irritability, dry mouth, and hunger, would be self-reported by the participants. Time-series analysis would be conducted to assess the efficacy of the intervention in improving IAH and to validate a non-invasive methodology to diagnose IAH [9].

Case-Control Observational Study of DN and DN-P. Patients with T2D diagnosed with DN/DN-P would be matched with controls. The following ANS symptoms would be gathered: skin surface temperature, palpitation, perspiration, blood flow, muscle contractions, physical activity, and urine output. Participants would self-report on tingling, numbness, burning, pain, digestive and sexual irregularities, dizziness, and healing of cuts. Data analyses would develop a model that uses ANS symptoms collected by sensors to classify DN/DN-P.

3.2 Requirements for Conducting Real-World ANS Studies

Surrogates for measuring ANS symptoms and an understanding of their uncertainty would be necessary. Data sources for ANS symptoms and clinically relevant information, which are primarily generated by non-invasive sensors or self-report, have been identified, Table 1 [8]. The assimilation of sensor data streams along with their contextual information would be required for analyses and event detection.

Preferably sensor data streams would be acquired centrally in real-time fashion. This would allow for participants to be solicited for contextual information by sending a message that can be triggered by an event-detection algorithm, a method know as ecological momentary assessment (EMA). The frequency at which participants are sent messages would need monitoring, and the event-detection algorithms would need mid-study calibration to ensure sufficient capture of contextual information while also preventing alert-fatigue in patients. Flexibility for sending EMA messages would also be important. Sending messages at regular intervals (e.g. daily, weekly) would need to be supported, as well as triggering messages peripherally (i.e. participant's devices) and centrally. Both studies would also need to conduct data analyses on assimilated data that would generate hypotheses for future bench or bedside studies.

Table 1. Measurement data sources of ANS symptoms and clinically relevant information.

ANS symptom	Measurement data source	ANS symptom	Measurement data source
Anxiety	Self-report	Muscle Contractions	EEG
Blood Flow	Thermal Actuator	Nervousness	Self-report
Blood Glucose	CGMS	Numbness	Self-report
Burning	Self-report	Palpitation	ECG
Digestive Patterns	Self-report	Perspiration	Galvanic Skin Response
Dizziness	Self-report	Physical Activity	Activity Tracker
Dry Mouth	Self-report	Shaking	Accelerometer
Healing of cuts	Self-report	Sexual Patterns	Self-report
Hunger	Self-report	Skin Temperature	Thermometer
Insulin	Insulin pump/pen	Trembling	Self-report
Irritability	Self-report	Urine Output	Strain Gage

After reviewing IAH/HAAF and DN/DN-P studies, we identified the following requirements that would inform the architecture for conducting real-world studies: (1) ability to discover, evaluate, and develop new digital biomarkers, (2) capture contextual information related to sensor measurements, (3) support multiple means for gathering real-time status of participants, e.g. EMA at regular intervals and at the time of specific events, as well as digital journals, (4) mid-study calibration of EMA triggering algorithms, (5) integration and assimilation of big data that can support analyses required to identify correlations and associations of ANS symptoms and contextual information with the status of diabetes complications, and (6) provisioning of integrated data in different data models to varied analysis including temporal reasoning, machine learning, and traditional statistics.

3.3 An Existing Informatics Platform that Supports Real-World Studies

The Exposure Health Informatics Ecosystem (EHIE), is a scalable informatics structure that has been developed by informatics researchers at the University of Utah [10–12]. EHIE has been designed to address challenges faced when conducting sensor-based exposomic research. The infrastructure is a standards-based and open-source informatics platform that employs an event-driven architecture and graph and document store technologies. This allows the system to provide semantically consistent, metadata-driven, and event-based management of exposomic study related data. EHIE currently consists of the following components, Fig. 1:

Data Acquisition Pipeline. Consists of hardware, software, and networking protocols to support sensor deployment and sensor data collection. EpiFi was developed to observe devices and notify the study team of their status and to prevent data loss [13].

Participant Facing Tools. Allows participants to collect and annotate data and provides feedback to them. REDCap [14], an open-source study data management tool, has been extended to support the sending and receiving of text message based EMAs.

Researcher Facing Platforms. Provides tools and processes for researchers conducting exposomic research or for clinical care. Tools provide assistance with study design, collecting data, study monitoring, and data analysis.

Computational Modeling Platform. Resources are provided to quantify the uncertainty that might be present in the data, which can be used to augment data analysis and interpretation of results.

Big Data Federation And Integration. Integrates measured and computationally generated data with biomedical data along with characterizing uncertainties associated with the data. EHIE leverages and extends the OpenFurther (OF) platform, which was developed for data integration and federation [15–17]. OF provides syntactic and semantic interoperability for dynamically federating data and information. OF contains a Sensor Common Metadata Specification (SCMS), which includes all types of sensors including nanosensors, satellites, wearables, and monitoring stations. The Event Document Store (EDS) is a primitive storage format that allows linkage across different root objects and transformation of events into higher analytical models to support diverse translational archetypes. Data is stored in the EDS on a study by study basis.

Many of the functionalities and services provided by EHIE that support exposomic research are also necessary for conducting real-world studies of ANS and diabetes complications, particularly the flexibility in data acquisition and integration. Where EHIE does not meet the needs for real-world ANS studies lies in the assimilation of data on the fly to facilitate real-time event detection of sensor data streams to trigger interventions or further automated data collections. Supporting these ANS studies would require augmenting EHIE with decision support for researchers to design and monitor studies in real-time, as well as the computational modeling platforms with data assimilation capabilities to create event-detection algorithms.

3.4 Diabetes Technology Informatics Capabilities

Digital diabetes medical devices have capabilities that vary across vendors. For example, many CGMS have Bluetooth connectivity between the transmitter and the device manufacturer's proprietary FDA approved smartphone application (app) (e.g. Dexcom) for real-time viewing by the patient. In some cases, CGMS data sent to an app can be shared with health data frameworks, e.g. GoogleFit for Android or HealthKit for iOS. The CGMS data can then be shared within an ecosystem of mHealth apps. Also, CGMS data can be transmitted directly to an insulin pump, and the assimilated data from the CGMS and insulin pump can be uploaded to manufacturer specific web portals (e.g. CareLink) and data can be retrieved in raw flat files or static reports.

3.5 Next Generation ANS Research Informatics Platform

We propose an architecture to support real-life ANS studies, Fig. 1. It uses open-source informatics infrastructure (EHIE), messaging standards (Open mHealth, FHIR, SensorML), and commercial products (GoogleFit, HealthKit, Dexcom). Many of the components exist, but researcher and participant tools would need to be developed.

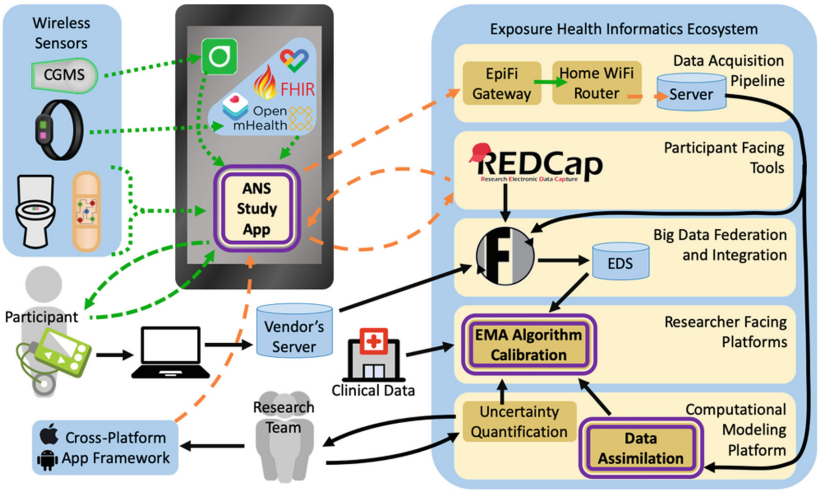

Fig. 1. Green lines represent real-time streaming of data, orange lines represent data transfers that prevent data loss, and black lines represent user- or client-initiated requests for data. Double purple outlined objects do not currently exist and would need to be developed and tested. (Color figure online)

4 Discussion

Depending on the study design, our proposed architecture supports various deployment designs. Wireless sensors and IoT devices transmit data in real-time through participants' smartphones and home networks. Having participants bring their own smart device to the study would exclude few individuals from participating since most Americans own a smartphone [18]. The smartphone provides a participant facing platform for study specific apps. These study apps would have data assimilation and storage capabilities arising from various sensor data streams and self-tracked data. Storing data on the smartphone provides two functionalities important to real-world studies, it helps to prevent data loss if mobile networks, gateway, or WiFi connections are unavailable and in conjunction with storing EMA logic within the study app, it allows peripheral EMAs and participant initiated self-tracking to proceed even when the smartphone is offline.

As the architecture builds on the meta-data centric EHIE, it is capable of accommodating different health data frameworks (e.g. GoogleFit or HealthKit), and messaging standards (e.g. Open mHealth, Fast Healthcare Interoperability Resources (FHIR), SensorML). Participant facing tools, which could be a smartphone app, software deployed on any other form factor, text messaging, email, or a patient portal, would be capable of EMAs by sending structured messages to the participant at regular intervals (e.g. nightly, weekly, etc.) or when triggered by an algorithm that considers the assimilated data stream. These tools would also support participant-initiated self-tracking. Participant's access to a gateway or home WiFi router would allow for secure transmission of data stored on sensors or a mobile device (e.g. smartphone) to a dedicated study server.

The EHIE computational platform currently supports post-study analysis of study data. The computational module, along with researcher facing tools, would need to be expanded to allow for the research team to calibrate EMA algorithms before the study begins by using pilot or simulated data, and potentially during the study on currently acquired study data. The EMA calibration would be capable of supporting all aspects of artificial intelligence: rule-based, Bayesian/statistics, and neural networks. Researchers could benefit from decision support during the study design process, data collection stage, and when conducting data analysis. The data analysis stage could be supported by a process workflow module that would facilitate reproducibility by documenting data assimilation and analyses pipelines [19, 20].

Future work includes building and testing a prototype of the proposed architecture to ensure the design requirements are met and to conduct testing with a performance modeling framework to guarantee the system performs and scales as expected [21]. Comparing the system's capabilities against requirements for real-world studies of other chronic diseases would indicate the generalizability of the system.

5 Conclusion

We identified requirements for conducting next-generation ANS studies and designed an architecture that would support the informatics aspects of such studies. These real-world studies would be capable of gathering contextual data from participants engaged in real-time self-tracking and objectively measured ANS responses from streaming wireless sensors, while also supporting the data needs of researchers before, during, and after data acquisition. The architecture makes use of commercially available and open source mHealth technologies and informatics platforms to support virtual clinical trials. There plans to build the and test a prototype of the proposed architecture.

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