

© 2020 IEEE. Personal use of this material is permitted. Permission from IEEE must be obtained for all other uses, in any current or future media, including reprinting/republishing this material for advertising or promotional purposes, creating new collective works, for resale or redistribution to servers or lists, or reuse of any copyrighted component of this work in other works. Access to this work was provided by the University of Maryland, Baltimore County (UMBC) ScholarWorks@UMBC digital repository on the Maryland Shared Open Access (MD-SOAR) platform.

Please provide feedback

Please support the ScholarWorks@UMBC repository by emailing scholarworks-group@umbc.edu and telling us what having access to this work means to you and why it's important to you. Thank you.

Department: Head
Editor: Name, xxxx@email

Leveraging Mobile Sensing to Understand and Develop Intervention Strategies to Improve Medication Adherence

Anna N. Baglione

Department of Engineering Systems and Environment, University of Virginia

Jiaqi Gong

Department of Information Systems, University of Maryland, Baltimore County

Mehdi Boukhechba

Department of Engineering Systems and Environment, University of Virginia

Kristen J. Wells

Department of Psychology, San Diego State University

Laura E. Barnes

Department of Engineering Systems and Environment, School of Data Science, University of Virginia

Abstract—Interventions to improve medication adherence have had limited success and can require significant human resources to implement. Research focused on improving medication adherence has undergone a paradigm shift, of late, with a shift towards developing personalized, theory-driven interventions. The current research integrates foundational and translational science to implement a mechanisms-focused, context-aware approach. Increasing adoption of mobile and wearable sensing systems presents new opportunities for understanding how medication-taking behaviors unfold in natural settings, especially in populations who have difficulty adhering to medications. When combined with survey and ecological momentary assessment data, these mobile and wearable sensing systems can directly capture the context of medication adherence *in situ*, including personal, behavioral, and environmental factors. The purpose of this paper is to present a new transdisciplinary research framework in medication adherence, highlight critical advances in this rapidly-evolving research field, and outline potential future directions for both research and clinical applications.

INTRODUCTION

Medication adherence is defined by the World Health Organization (WHO) as "the extent to which a person's behavior (taking a medicine), corresponds with agreed upon recommendations from a health care provider" [19]. Adherence to long term therapy for chronic illness in developed countries is about 50% [19]. Interventions aimed at increasing medication adherence have the potential to provide a significant benefit through both primary prevention of disease risk factors and secondary prevention of adverse health outcomes. In fact, increasing the effectiveness of medication adherence interventions may have a far greater impact on health outcomes than any improvement in specific medical treatments [12]. The impact of poor adherence to medications is expected to continue to increase as the burden of chronic disease increases globally. Endocrine therapy, including aromatase inhibitors and Tamoxifen, is prescribed for at least 5 years after individuals have been treated for hormone receptor-positive breast cancer to prevent recurrence of their cancer. Adherence to these medications (defined as 80% or more doses taken as prescribed) is associated with significant increases in recurrence-free survival [18]. Despite the life-saving benefits of these medications, rates of persistence and adherence are low [18], with post-treatment adherence ranging from 41% to 72% and discontinuation ranging from 31% to 73% [11].

Increasing adoption of smartphones has led to an upsurge in applications targeted at improving medication adherence. However, these technologies have focused mainly on cognitive factors contributing to nonadherence, such as managing multiple medications [5]. Existing mobile applications fail to account for an individual's specific risks and fail to personalize the interventions delivered according to those risks. Furthermore, very few interventions have been assessed for efficacy in supporting adherence [16]. In this paper, we propose a new integrated system for long-term monitoring of medication adherence consisting of sensor-rich smartphones, wireless medication event monitoring systems (MEMS), wireless beacons, and wearable sensors that collect *in situ* data on adherence. This data will be

used to understand and model medication-taking behaviors, develop context-sensitive models to predict nonadherence, and develop and deliver personalized interventions to improve medication adherence. The novelty of this project lies in its capturing of the multidimensional complexities of medication adherence using ubiquitous mobile sensing technologies and in using these sensed data to understand medication-taking behaviors, predict individual risk factors, and design and deliver interventions to improve adherence at the optimal time and in the optimal context.

BACKGROUND

Defining and Measuring Medication Adherence Medication adherence is defined as whether patients take their medication as prescribed [8] and is critically important for effective medical treatment. Methods for assessing medication adherence are categorized as either *direct* (e.g. directly measurement of medicine or biomarkers in blood) or *indirect* [13] (e.g. patient self-report, pill counts, and pharmacy refills [8]). Indirect methods, in particular, have several notable limitations. Self-reports are often biased by inaccurate patient recall or social desirability. Pill counts, meanwhile, do not accurately capture exact timing of medication-taking and can be easily manipulated by patients (e.g., pill dumping). When used alone, these methods fail to provide a deeper contextual understanding of reasons for medication adherence or nonadherence.

Interventions to Increase Medication Adherence

A 2014 systematic review identified 17 randomized controlled trials that evaluated the efficacy of medication adherence interventions [12]. Only five of these studies found medication adherence interventions were associated with both increased adherence and better clinical outcomes, even though most interventions studied were complex and required significant time of health-care staff. This systematic review concluded interventions may not have been effective because there is a lack of understanding of barriers to adherence and *the context in which adherence and nonadherence occurs*. Another review of 229 smartphone reminder applications (apps) determined that a "one size fits all" timer-based reminder was largely ineffective because it did

not consider a user's routine [17]. Taken together, these reviews indicate that previous interventions to increase medication adherence have broadly targeted factors associated with lack of adherence across groups of individuals. However, these intervention approaches may not be relevant to a specific individual at the time and in the context that it is delivered and are not sustainable because of the high burden on health care providers and the healthcare system.

Factors Associated with Medication Adherence and Nonadherence

Substantial research documents reasons why individuals do not adhere to prescribed medications, including endocrine therapy, a life saving medication taken by some cancer survivors to slow or stop cancer growth. We examine factors associated with medication adherence and nonadherence through the lens of Social Cognitive Theory (SCT) [1], a commonly used health behavior theory which can facilitate better understanding of the context of medication taking by evaluating how environmental factors, personal factors, and a person's behavior interact. The SCT guides the selection of constructs in our new medication adherence framework and will also guide intervention development.

Personal Factors: *Physiological, cognitive, and affective* states affect long-term adherence to medications. Physiological factors significantly associated with endocrine therapy nonadherence include side and adverse effects and functional impairment [11], [18]. The two strongest cognitive predictors of adherence, generally, and endocrine therapy, specifically, are self-efficacy and positive beliefs regarding the importance and necessity of medications [18]. In addition, individuals who are poorly informed about side effects are less likely to adhere to any medication, including endocrine therapy, and that updating patients' knowledge regularly can improve adherence. [3]. Affective states associated with lack of adherence to medications are distress, depression, and fear of cancer recurrence [11], [18].

Environmental Factors: A person's *social* environment, *physical* environment, and the *health system* environment influence whether or not an individual takes medication. Having less than desired social support for tak-

ing the medication is linked to endocrine therapy nonadherence [11], [18]. Medication adherence is associated with positive interactions with health care providers who provide medication reminders [18]. Family members also facilitate medication adherence through reminders [18]. Medication adherence can also be facilitated by aspects of the physical environment; people frequently place medications in places where they frequently go so that they remember to take them [18]. Health system environments can also affect medication adherence, such as via costs of medication [11], [18].

Behavioral Factors: Medication-taking occurs in the context of other behaviors which can serve as a cue to action to initiate the behavior of interest (e.g., brushing teeth, eating breakfast) [15]. Having a routine or schedule for medication-taking may facilitate adherence [18]. To date, the field has been limited in monitoring multiple factors simultaneously due to limitations in technologies to collect the data and model these factors dynamically. However, the emergence of mobile technologies enabling remote health monitoring and studying human behavioral dynamics [20], [7]. An understanding of the interaction of environmental, personal, and behavioral factors associated with medication-taking in each individual will enable the development of personalized approaches to prevent medication nonadherence [10].

Mobile Sensing and Modeling

Mobile Sensing Smartphones and wearable technologies have arrays of embedded sensors that measure mobility, location, acoustics, and ambient light. These sensors can be harnessed to passively capture information related to users' personal and environmental factors and behaviors, so long as individuals carry or wear the devices. These technologies are modernizing patient care with capabilities such as sending and receiving clinically-relevant messages and supporting illness management and treatment applications. Most approaches require individuals to actively engage with the device by responding to prompts or launching an app. However, smart devices and remote sensing technologies can also facilitate behavioral tracking techniques that require little to no active response from the user, thus *decreas-*

ing patient burden. Mobile behavioral sensing has been used to draw inferences about how and where individuals spend their day and to track behaviors associated with stress and changes in mental health over time. Ben-Zeev et al. used a mobile sensing application to gather GPS, activity, and sleep data in tandem with daily stress ratings gathered via EMA. They identified relationships between sensed data such as sleep and activity and changes in stress and mood [2]. Boukhechba et al. showed that sensed features such as location entropy can be used in tandem with social anxiety baseline measures to predict symptom severity [4]. Further, Gong et al. found that increased accelerometer movement is tied to social anxiety symptoms for activities in certain contexts (e.g. when making a phone call) [7]. The methodologies and metrics from such studies are promising, demonstrating that complex human behavior and psychological states can be inferred from multimodal data. However, no current sensing systems have been implemented to provide continuous monitoring within and outside the home to monitor and support long-term medication adherence.

PROPOSED FRAMEWORK: MULTISCALE MODELING AND INTERVENTION (MMI) SYSTEM

Social Cognitive Theory (SCT) [1] indicates medication-taking behaviors are performed in the context of an individual's environments (e.g., work, social) and other behaviors (e.g., eating) and are influenced by personal factors (e.g., cognition, emotion, experiences of side effects). A deeper understanding of the context of medication-taking will provide us with information about how, when, with whom, and where medication is taken. Consequently, we propose a new sensing systems framework, the **Multiscale Modeling and Intervention (MMI)** system, for modeling the simultaneous interacting behavioral, environmental, and personal factors that influence medication adherence or nonadherence. We are applying this framework to breast cancer survivors who have completed most treatment and are prescribed long term endocrine therapy. This framework is grounded in SCT and accomplishes four main goals: it 1) senses medication-taking behaviors in context (i.e. sense personal, envi-

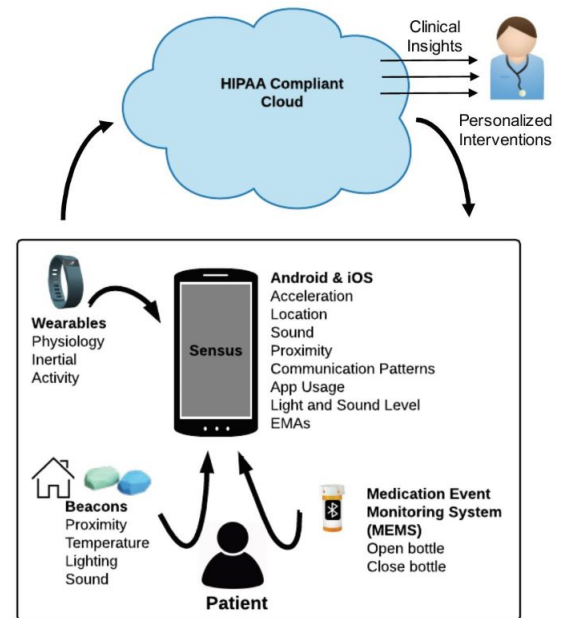


Figure 1: MMI sensing framework and data flow overview

ronmental, and behavioral parameters,) 2) models the complex constructs of medication-taking behavior in context, 3) identifies person-specific constructs and constraints, and 4) establishes a methodological foundation for creating personalized interventions to improve medication-taking behavior. Figure 1 provides an overview of the MMI system, and Table 1 demonstrates how sensed data map to the three key SCT constructs. We now highlight the MMI system components and design considerations in light of the aforementioned goals.

System Components

The MMI sensing system unites multimodal sensor data from smartphones, wearable sensors, wireless beacons, and smartphones. In particular, the Sensus adaptable sensing system [20] is central to the MMI system enabling the collection of behavioral data via ecological momentary assessments (EMAs) and smartphone and wearable sensor data. Medication-taking is measured using MEMS devices which do not provide users with feedback regarding previous opening of the bottle. Bluetooth beacons are integrated into the system to transmit environment-specific contextual information to the user's smartphone. Specifically, these beacons are used to sense

Table 1: SCT Constructs, Measurement Methodology and Exemplar Features

SCT Construct	Data	Technology	Features
Personal (Physiological, Affective, Cognitive)	Hot flashes, pain, fatigue, stress, cognition	Galvanic skin response (GSR), electrocardiogram (ECG), photoplethysmography (PPG), GPS	pattern changes in heart rate variability, body temperature, breathing rate, etc., keystroke patterns, reduced activity level,
Behavioral	Sleeping, eating, medication-taking	ECG, gyroscope, accelerometer, GPS	Heart rate variability, movement variation, semantic location diversity
Environmental (Healthcare System, Social Environment, Physical Environment)	Type and quality of social interactions, patient-provider communication, physical location	Microphone, GPS, accelerometer	Text and call frequency, audio signals, social media activity, location diversity

proximity, temperature, and ambient lighting levels in a participant’s significant physical environment locations (e.g. home). These contextual data are then used to learn an individual’s event patterns. For example, placing a beacon in an individual’s kitchen (e.g., physical environment) will allow the system to learn when they are likely having a meal (e.g. engaging in a common behavior). Passive sensor data from smart devices are coupled with EMAs to collect self-reported ground truth for dynamically changing measures of SCT constructs (e.g., side effects, behaviors related to medication adherence). Participant burden in responding to EMAs is minimized by keeping assessments brief and leveraging smart-sensing plans to trigger prompts. For example, environmental context (e.g., GPS, beacons) can be leveraged to infer that a participant is eating and prompt the user to confirm.

Design Considerations

User-centered Design Including users throughout the process of the MMI system design, as well as keeping users engaged with interventions that arise from the design process, is of critical importance. We will conduct participatory design interviews with breast cancer survivors to assess both the usability and acceptability of MMI system components (e.g. wearable sensors, MEMS caps, and EMAs). We will also examine critical markers of engagement

captured by the system, such as dwell time on tasks (e.g removing a MEMS cap or responding to a survey) and task sequences (e.g. responding to a survey, then removing a MEMS cap). These markers are particularly useful for inferring common behavioral constructs and for optimizing intervention timing to maximize engagement. For example, consider a routine such as brushing one’s teeth at night. Inferring the time at which this behavior typically occurs (e.g. 8pm) and the behavioral context that is likely to follow (e.g. sleeping) could help the MMI system know when to deliver a reminder to take a medication prescribed to be taken at bedtime. Another example of an engagement strategy the MMI system could employ is a web-based dashboard which displays adherence rates for the past week as well as motivational messages encouraging patients to stick to a medication routine.

Privacy and Security The MMI system will collect personal and sensitive data, and thus, specific strategies need to be taken to ensure the preservation of user privacy and data security. We will leverage MEMS and wearable devices that offer a secure on-board storage infrastructure and transmission protocols. Participant data will be transferred via APIs that adhere to industry standards (e.g. use TLS encryption and trusted tokens) and will be stored in a HIPAA compliant

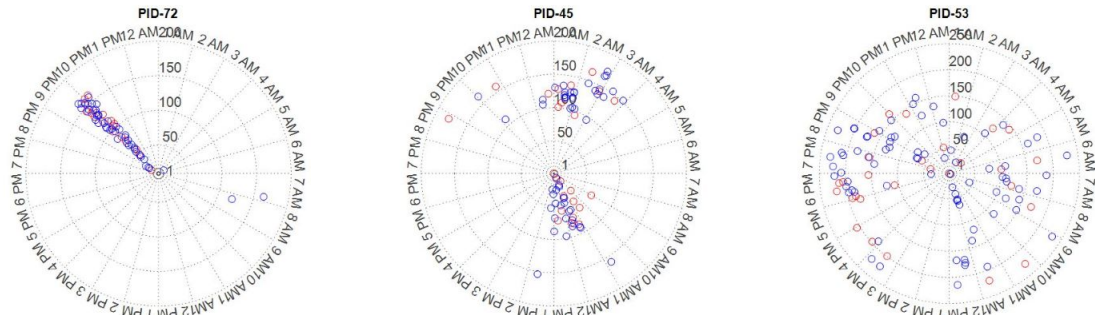


Figure 2: A polar coordinates plot demonstrating patterns of medication-taking behavior in breast cancer survivors leveraging MEMS over a eight-month period; consistent evening pattern (patient ID: 72), changing patterns (patient ID: 45) and random pattern (patient ID: 53). Blue dots are the MEMS data in the weekday and red dots present the data in the weekend.

cloud. We will leverage privacy-preserving data processing methods for potentially identifiable data, such as GPS location, which could be abstracted into clusters to avoid a situation where a user's precise location could be pinpointed.

Energy-Efficient Sensing One of the critical challenges of mobile sensing research is creating energy efficient systems that minimize power consumption while capturing enough information to measure / predict user context. Adaptive sensing methods can be used to control low-level sensing cycles to collect data only when needed hence minimizing the a device's computational usage (e.g. collect motion data only when the device is moving). Furthermore, machine learning methods can be leveraged to learn when to turn on a specific sensor based on an individual's patterns of daily living.

Social Cognitive Theory: A Strong Theoretical Foundation

SCT has been used extensively in understanding, predicting, and facilitating adherence to a wide range of behaviors, including medication adherence. The benefit of applying SCT to complex behaviors like medication adherence is that it includes the concept of *reciprocal determinism* and thus considers interactions among environmental, personal, and behavioral factors associated with the medication-taking behavior. We hypothesize not only that the interaction between these factors

contributes to medication use, but that a change in one factor may affect other factors to increase or decrease the likelihood of medication adherence. Other health behavior theories, which are less complex, use similar constructs but do not include reciprocal determinism.

Payne et al.'s systematic review showed frequent adaptation of SCT constructs to mHealth interventions, providing evidence of feasibility for our approach [14]. Notably, however, none of the previous works mentioned in this review present a framework that has been developed and validated for the purpose of medication adherence. The MMI system represents the first framework developed by a transdisciplinary team of researchers oriented toward improving medication adherence *in situ*.

Preliminary work from our team has already yielded rich insights into medication-taking behavior patterns and represents a key first step toward building the MMI framework on SCT constructs. Boukhechba et al. analyzed data assessing medication adherence of 33 breast cancer survivors taking endocrine therapy medication using MEMS over an eight-month period [3]. These results indicate that breast cancer survivors have diverse patterns of medication-taking behavior over the course of the monitoring period.

Figure 2, provides a visualization of three of these breast cancer survivors' patterns of endocrine therapy medication taking over the study period according to the time of day that each

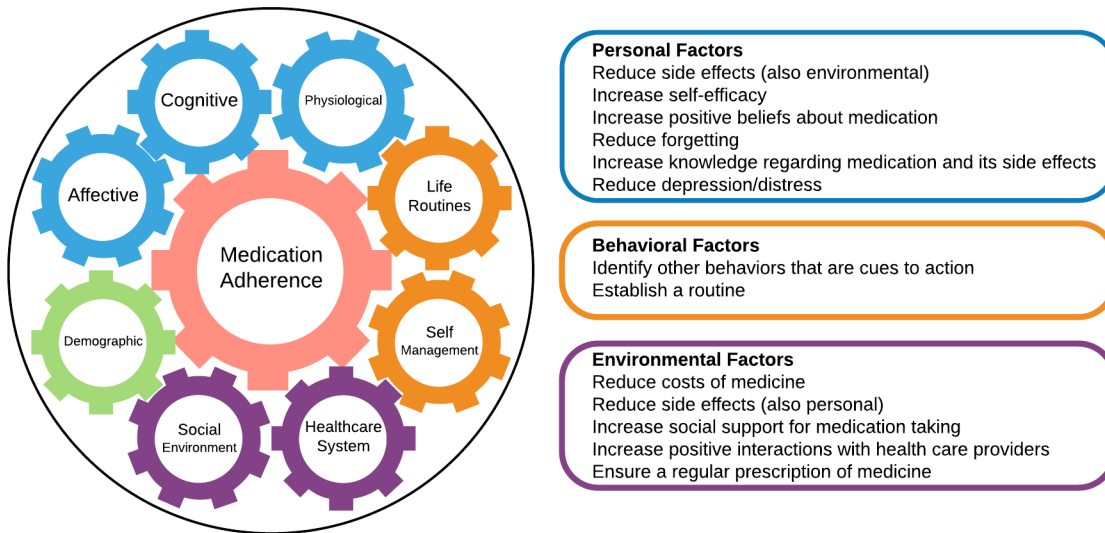


Figure 3: Conceptual representation of SCT framework. Medication adherence is a part of human behavior system, and itself is a system. Interventions will be designed to influence the personal, behavioral, and environmental factors and then facilitate better medication adherence.

person took her medicine. Participant 72 nearly always took the once daily pill in the evening, participant 45 took the pill in the morning initially and then switched to the evening, and participant 53 took the daily medication at various times of the day with no noticeable pattern. It is important to note that, the MEMS devices used in this study provide no feedback to the user; however, we saw numerous instances of medication non-adherence suggesting that there was not a substantial Hawthorne effect.

MMI FRAMEWORK GOALS

Sensing and Modeling Medication-Taking Behaviors in Context

Medication-taking behavior is part of a person-specific human behavior system and is a system itself. Understanding the complex system of adherence-related context requires comprehension of both stable and dynamic variables. *Static* variables refer to characteristics of one's life which infrequently or never change, such as personality, intelligence, and some demographics. *Dynamic* variables, on the other hand, refer to frequently-changing characteristics such as medication side effects, disease symptoms, health

system interactions, social interactions, and behavioral contexts. In order to capture both static and dynamic variables, the data collected from the MMI system is translated into contextual features within the SCT framework (Figure 3). Machine learning methodologies (e.g., network analysis, hierarchical sampling for active learning) can then be used to discover the complex structure of medication-taking behavior.

Identifying Person-Specific Constructs and Constraints

Recent works in multiscale pattern recognition has demonstrated that information fusion methods provide richer information than isolated data-driven models [7], [4]. The MMI framework uses pairwise sensor fusion methods at several junctures. For example, fusing information from communication events (identified from call and text logs) and fine-grained motion sensor data yields a reliable behavioral marker of social anxiety levels [7]. High-fidelity time-series data can generate features from sliding windows or change-detected windows, and extracted features can be clustered to identify the semantics of activities. For instance, the relationship between accelerometer

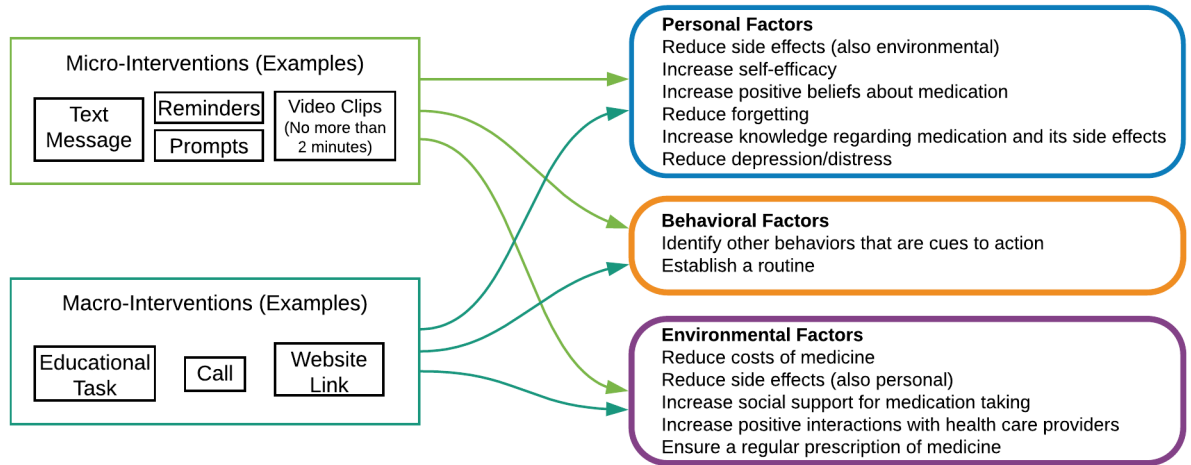


Figure 4: Mapping personalized intervention options to contextual factors

data and heart rate data can be examined to understand how stress manifests in daily life. Although the information from an accelerometer sensor is not accurate enough to identify the complex entities of the human activities in daily life (e.g., sleeping, typing), additional integrative models which include heart rate, skin temperature, skin conductance, and other information (e.g., GPS changes, call and text, and EMAs) can be used in combination to more closely approximate activity.

Development of Personalized Interventions

Development of personalized interventions within the MMI system is achieved via *intervention modules*, which address patient-specific needs or barriers to medication-taking at time and place that is most convenient for the patient. Modules incorporate constructs from SCT and include delivery of brief content (e.g., text, audio, video) on the mobile phone via an app, or on the smartwatch, as well as phone calls and text messages providing personalized content. Interventions are designed to only involve the patient's health care team in addressing barriers that require their assistance, reducing the burden on both patients and health care providers. We note that frequent low-level interventions, such as reminders, may annoy the users or the users may habituate to them and ignore them. Therefore, determining drawbacks and constraints of contextual factors such as notification fatigue will

be a critical step in designing future intervention modules.

Intervention modules are guided by Intervention Mapping [6], an intervention development model used in public health and behavioral sciences. Intervention Mapping includes six steps: logic model of the problem, a logic model of change, program design, program production, program implementation plan, and evaluation. The knowledge learned from the computational models employed in the MMI framework, such as the contextual factors of medication-taking behavior and the constraints of these factors, are uniquely tied to the intervention approaches in the following ways: 1) determining behavioral and environmental outcomes the intervention is targeting (e.g., remembering to take the medication on weekends); 2) stating performance objectives for each outcome; (e.g., realizing that your routine is different on weekends, linking medication to a behavior performed every weekend); and 3) determining essential and changeable determinants using SCT (e.g., determining behaviors that are performed every weekend, placing medication in a visible place after it is taken on Friday) of behavioral and environmental outcomes as indicated in the data collected from the MMI system.

Figure 4 demonstrates how computational models are tied to Intervention Mapping within the MMI system. The computational models help identify the SCT construct(s) of the person-

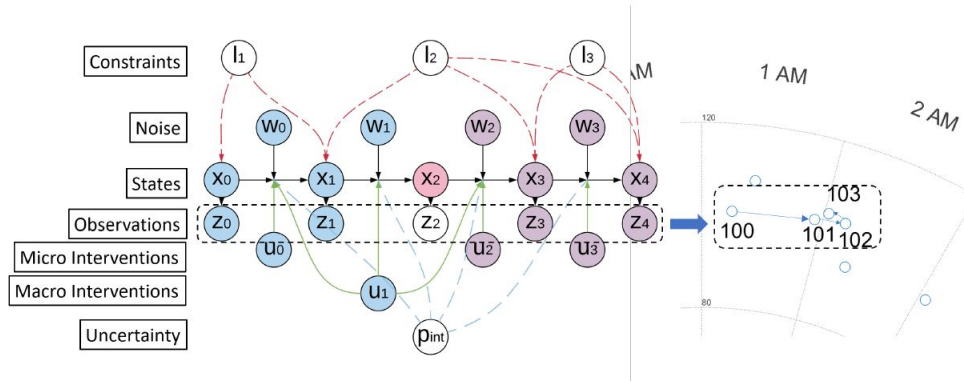


Figure 5: Hierarchical control theory to deliver interventions. The trajectory of medication-taking behavior is captured by MEMS (day 100 to day 103, Patient ID: 45).

specific medication-taking behavior, while Intervention Mapping helps identify the relationship between the targeted constructs and the goals of the intervention modules, such as reducing side effects, reducing forgetting, establishing a routine, increasing social support, and increasing positive interactions with healthcare providers.

Estimation of Behavioral States for Delivery of Personalized Interventions

We will formulate the MMI framework as a computational model for optimal estimation of the behavioral constructs and control strategies of the interventions. We propose to use factor graphs as a common framework to represent both estimation and control problems. Our work will complement the gap between low-level computational models and high-level behavioral science knowledge. Figure 5 shows an example of our factor graph that includes both the past estimation and future control part. The behavioral states ($x(t)$) will be represented as a vector of contextual factors we learned from the multimodal and multiscale data. The transmission matrix between states ($x(t)$) and ($x(t + 1)$) will be initially estimated in the network analysis approach. The influence mechanisms between interventions and the behavioral states will be initiated through human-in-the-loop design of the intervention modules such as the Intervention Mapping process. The noise ($w(t)$) and the constraints ($l_{1...k}$) will be initially determined by the probability functions among contextual factors. With this initial information process, the format of the factor graph will be initialized.

The first step of this model-predictive control is to estimate the behavioral states since the behavioral states will evolve along with time and control strategies. Otherwise, constraints of the behavioral states might also slightly change along with the evolution of the behavior states and contextual factors. Therefore, to better develop control strategies under these constraints (e.g., reminders might not work as well during the weekend as social influence-based interventions), estimating the behavioral states to obtain an optimal estimate of all constraints, uncertainty parameters, and past process noise. Leveraging previous work in optimal control theory, we will estimate the cost function J_{est} as the negative log of the posterior $p(x_{0:c}, w_{0:c}, l_{1...k}, p_{int} | \{z_{ij}, u_{0:c-1}\})$ which provides the maximum a-posterior (MAP) estimate. The fundamental challenge here is to examine whether or not the construct and constraints of medication-taking behavior fit a Gaussian prior assumption. Our work will explore and advance this knowledge in medication-taking behavior.

OPEN CHALLENGES

The MMI system establishes a foundation on which to build personalized interventions for medication adherence, but it is not the only answer to such a complex problem. Even after decades of behavioral health research, modeling human behavior still presents significant knowledge discovery challenges. Researchers in human behavior monitoring have noted that lab-based models cannot solve the challenges in real-world deployment due to the complexity and uncertain-

ties in long-term human behavior [2].

Several promising solutions have been proposed to improve performance of the models, such as active learning and information fusion. Active learning methods adopt queries or questionnaires to ask users' help to annotate labels of the uncertain data. Researchers in information fusion, meanwhile, develop advanced machine learning methods to cope with incomplete multichannel data. While these advances are promising, there remain systematic challenges to long-term deployment of such systems and models, which we now briefly review.

Grounding mHealth Interventions in Health Behavior Theories

Though mHealth interventions for human health and behavior have proliferated in recent years, too few interventions are explicitly grounded in health behavior theories such as SCT. A strong understanding of such theories is critical for both practitioners and researchers alike. Such an understanding allows practitioners to assess the fundamental factors contributing to behaviors such as medication nonadherence. Selecting an appropriate theory in which to ground an mHealth intervention is no small matter and requires strong interdisciplinary collaborations between researchers from the behavioral sciences, information science, and computer systems engineering, among other fields.

In addition to forging stronger connections between mobile interventions and existing behavioral theories, new theories that encapsulate the flexible, personalized nature of mHealth interventions are needed. In particular, theories which leverage control systems engineering and other dynamic feedback models would be powerful, modern additions to the behavior theory literature.

Accounting for User Context

The dynamics of deciding exactly when, where, how, and how much to intervene when promoting and increasing medication-taking behavior are complex. A fundamental understanding of the *context* of health behavior states is critical for generating clinical insights from sensed data. Moreover, knowledge of context is especially powerful for reducing patient burden and optimizing intervention effectiveness. For example,

consider a patient who must take a medication that causes an upset stomach when taken without food. An application which detects motions such as sitting down (indicating a possible break for a meal) and opening a pill bottle, based on accelerometer sensor readings, could 1) determine when a user typically eats meals, 2) encourage the user to take the medication at detected mealtimes, and 3) draw inference about whether the patient is taking their medication at the recommended times (e.g. mealtimes). The clinical insights gathered through this detection process could help a clinician determine whether adverse reactions such as an upset stomach and subsequent medication nonadherence are being caused by taking the medication at non-optimal times (e.g. outside mealtimes).

This example illustrates why the content and timing of mHealth interventions must be carefully designed with user context in mind. Researchers must consider factors such as the temporal characteristics of the target behavior (e.g., in the case of medication adherence, timing of medication taking or missed doses) and the quality and granularity of sensed data available. Many mHealth researchers have shifted towards developing automated *just-in-time adaptive interventions* (JITAI). JITAI enable collecting intensive longitudinal data via sensors and EMA, presenting new opportunities to use tools from control engineering in service of mHealth interventions. Researchers must continue to investigate how these "human-in-the-loop" models can incentivize users to leverage interventions for the betterment of their health.

Developing Patient-Centered Interventions that Cross Disciplinary Boundaries

Human health behavior is a complex system. The efficacy and long-term success of mHealth interventions depends heavily on collaboration with healthcare professionals such as psychiatrists, doctors, and nurses, who are well-versed in the clinical needs and concerns of patients. In the context of medication adherence, interventions must be developed alongside care providers in order to identify risk factors for non-adherence (e.g. adverse reactions) and ways to minimize these risks *in situ*. To develop mHealth interventions in a vacuum, divorced from clinical care settings, is

to risk the creation of sub-optimal interventions that fail to put the patient first. We encourage researchers to forge interdisciplinary partnerships in the creation of these interventions.

Transforming the multimodal health data captured by mobile technologies into clinical insights requires knowledge from multiple domains, including data science, psychology, and medicine. Moreover, new paradigms in machine learning are needed to analyze subjective (e.g. EMA survey responses) and objective (e.g. motion signals) measures of social and behavioral health in the same pipeline. One possible approach to this challenge is to reframe mobile behavioral interventions as closed-loop dynamical systems amenable to control systems engineering solutions. Regardless of the approach taken, we encourage researchers to consult experts outside their field throughout the intervention development process.

Experimental Design and Evaluation

While mHealth interventions have great potential to transform healthcare, there are still many open challenges to evaluating their efficacy in practice. We are moving from a “one-size-fits all” model to a model in which interventions are tailored and personalized to an individual's unique context. The experimental design and metrics for the evaluation are of utmost importance; however, gold standard methodologies such as randomized control trials (RCTs) are impractical. New experimental designs such as micro-randomized trials [9], which enable both the determination of when an intervention should be delivered and whether it was effective, are needed to truly evaluate the efficacy of just-in-time-adaptive interventions.

FUTURE WORK

Deployment of the System with Integrated Personalized Interventions

The natural progression of the development of the MMI system will be deployment with real breast cancer survivors prescribed endocrine therapy. This deployment will enable our team to refine the MMI system based on user feedback. Participants will be instructed to use the MMI system for several months so that the MMI system can learn about the participants' natural

medication taking behaviors. Based on data collected during this period, our team will then develop and clinically validate specific intervention approaches targeting reasons for non-adherence.

The MMI system offers both flexibility and personalization in delivery of interventions. For example, modules may include delivery of brief content (e.g., text, audio, video) through the mobile phone via an application or through the smartwatch, phone calls, and text messages providing personalized content, or contact with healthcare providers or other significant people in the patient's life. Modules will be delivered at the precise time that the intervention is needed. For example, patients who are at risk for not taking their medication at the time of a side effect, such as severe joint pain, will be provided with one or more intervention modules that addresses that issue when the experience of pain is detected by the MMI system (e.g., educational content for addressing joint pain).

We will examine the relationship between the intervention and the changing medication-taking behaviors (as measured by MEMS devices) under different environmental, personal, and behavioral contexts. Once the MMI system is evaluated with respect to feasibility, usability, and efficacy, it should be evaluated in a larger trial.

CONCLUSION

This work presents the MMI system, a trans-disciplinary, integrated approach to understanding and developing intervention strategies targeted at medication adherence in context, and discusses its application to adherence to endocrine therapy prescribed to breast cancer survivors. The proposed framework consists of sensor-rich smartphones, wireless medication event monitoring systems (MEMS), wireless beacons, and wearable sensors that collect *in situ* data on medication adherence. The MMI system is a comprehensive framework for studying the relationships between medication-taking behaviors (as measured by MEMS devices) and various environmental, personal, and behavioral contextual factors. This framework can also guide the development of context-sensitive models to predict nonadherence, and the design of personalized interventions that improve medication adherence, with a focus on endocrine therapy. Moreover, the MMI system

establishes a new paradigm in designing personalized mobile health interventions targeting behaviors beyond medication adherence. For example, the same information fusion methods used to identify links between sensor data and behavior (e.g. accelerometer data showing the motion of unscrewing a pill bottle cap) can be extended to detect other adherence behaviors, such as pricking one's finger for testing insulin levels (i.e. for diabetics). The MMI system is a promising step forward for personalized health behavior interventions.

ACKNOWLEDGMENT

Research reported in this publication was supported by the National Cancer Institute of the National Institutes of Health under award numbers R01CA239246 and R21CA161077. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

REFERENCES

1. A. BANDURA, *Social foundations of thought and action: A social cognitive theory*, Prentice-Hall series in social learning theory., Prentice-Hall, Inc, Englewood Cliffs, NJ, US, 1986.
2. D. BEN-ZEEV, E. A. SCHERER, R. WANG, H. XIE, AND A. T. CAMPBELL, *Next-generation psychiatric assessment: Using smartphone sensors to monitor behavior and mental health*, *Psychiatric Rehabilitation Journal*, 38 (2015), pp. 218–226.
3. M. BOUKHECHBA, S. BAE, A. L. NOBLES, J. GONG, K. WELLS, AND L. E. BARNES, *A social cognitive theory-based framework for monitoring medication adherence applied to endocrine therapy in breast cancer survivors*, in *Biomedical & Health Informatics (BHI)*, 2018 IEEE EMBS International Conference on, IEEE, 2018, pp. 275–278.
4. M. BOUKHECHBA, P. CHOW, K. FUA, B. A. TEACHMAN, AND L. E. BARNES, *Predicting Social Anxiety From Global Positioning System Traces of College Students: Feasibility Study*, *JMIR Mental Health*, 5 (2018), p. e10101.
5. V. S. CONN, T. M. RUPPAR, M. ENRIQUEZ, AND P. COOPER, *Medication adherence interventions that target subjects with adherence problems: Systematic review and meta-analysis*, *Research in Social and Administrative Pharmacy*, 12 (2016), pp. 218–246.
6. L. K. B. ELDREDGE, C. M. MARKHAM, R. A. RUITER, G. KOK, AND G. S. PARCEL, *Planning health promotion programs: an intervention mapping approach*, John Wiley & Sons, 2016.
7. J. GONG, Y. HUANG, P. I. CHOW, K. FUA, M. S. GERBER, B. A. TEACHMAN, AND L. E. BARNES, *Understanding behavioral dynamics of social anxiety among college students through smartphone sensors*, *Information Fusion*, 49 (2019), pp. 57–68.
8. P. M. HO, C. L. BRYSON, AND J. S. RUMSFELD, *Medication adherence*, *Circulation*, 119 (2009), pp. 3028–3035.
9. P. KLASNJA, E. B. HEKLER, S. SHIFFMAN, A. BORUVKA, D. ALMIRALL, A. TEWARI, AND S. A. MURPHY, *Micro-randomized trials: An experimental design for developing just-in-time adaptive interventions*, *Health psychology : official journal of the Division of Health Psychology*, American Psychological Association, 34S (2015), pp. 1220–1228.
10. L. R. MARTIN, S. L. WILLIAMS, K. B. HASKARD, AND M. R. DIMATTEO, *The challenge of patient adherence*, *Therapeutics and Clinical Risk Management*, 1 (2005), pp. 189–199.
11. C. C. MURPHY, L. K. BARTHOLOMEW, M. Y. CARPENTIER, S. M. BLUETHMANN, AND S. W. VERNON, *Adherence to adjuvant hormonal therapy among breast cancer survivors in clinical practice: a systematic review*, *Breast Cancer Res Treat*, 134 (2012), pp. 459–78.
12. R. NIEUWLAAT, N. WILCZYNSKI, T. NAVARRO, N. HOBSON, R. JEFFERY, A. KEEPANASSERIL, T. AGORITSAS, N. MISTRY, A. IORIO, S. JACK, B. SIVARAMALINGAM, E. ISERMAN, R. MUSTAFA, D. JEDRASZEWSKI, C. COTOI, AND R. HAYNES, *Interventions for helping patients to follow prescriptions for medications*, *Cochrane Database of Systematic Reviews*, (2014), pp. 1–732.
13. L. OSTERBERG AND T. BLASCHKE, *Adherence to medication*, *New England Journal of Medicine*, 353 (2005), pp. 487–497.
14. H. E. PAYNE, C. LISTER, J. H. WEST, AND J. M. BERNHARDT, *Behavioral Functionality of Mobile Apps in Health Interventions: A Systematic Review of the Literature*, *JMIR mHealth and uHealth*, 3 (2015), p. e20.
15. W. T. RILEY, A. CESAR, MARTIN, AND D. E. RIVERA, *The importance of behavior theory in control system modeling of physical activity sensor data*, in *Annual International Conference of the IEEE Engineering in Medicine and Biology Society*, 2014, pp. 6880–6883.
16. K. SANTO, S. S. RICHTER, J. CHALMERS, A. THIAGALINGAM, K. C. CHOW, AND J. REDFERN, *Mobile phone apps to improve medication adherence: A sys-*

tematic stepwise process to identify high-quality apps, JMIR Mhealth Uhealth, 4 (2016), p. e132.

17. K. STAWARZ, A. L. COX, AND A. BLANDFORD, *Don't forget your pill!: designing effective medication reminder apps that support users' daily routines*, in Proceedings of the SIGCHI Conference on Human Factors in Computing Systems, ACM, 2014, pp. 2269–2278.
18. K. J. WELLS, T. M. PAN, C. VÁZQUEZ-OTERO, D. UNG, A. E. USTJANAUSKAS, D. MUÑOZ, C. LARONGA, R. G. ROETZHEIM, M. GOLDENSTEIN, C. CARRIZOSA, S. NUHAILY, K. JOHNSON, M. NORTON, E. SIMS, AND G. P. QUINN, *Barriers and facilitators to endocrine therapy adherence among underserved hormone-receptor-positive breast cancer survivors: a qualitative study*, Supportive Care in Cancer, 24 (2016), pp. 4123–4130.
19. WORLD HEALTH ORGANIZATION, *Adherence to long-term therapies: Evidence for action*, (2003).
20. H. XIONG, Y. HUANG, L. E. BARNES, AND M. S. GERBER, *Sensus: A cross-platform, general-purpose system for mobile crowdsensing in human-subject studies*, in Proceedings of the 2016 ACM International Joint Conference on Pervasive and Ubiquitous Computing, ACM, Aug 2016, pp. 415–426.

Anna Baglione is a PhD student in Systems Engineering and the Sensing Systems for Health Lab at the University of Virginia. She researches user engagement in mHealth interventions.

Jiaqi Gong is an Assistant Professor in the Department of Information Systems at UMBC. He is director of the Sensor-Accelerated Intelligent Learning Laboratory (SAIL lab).

Mehdi Boukhechba is an Assistant professor in the Engineering Systems and Environment Department at the University of Virginia.

Kristen J. Wells is an Associate Professor of Psychology, Director of the Cancer Disparities and Cancer Communication Lab, and Co-Director of the HealthLINK Center at San Diego State University.

Laura Barnes is an Associate professor in the Engineering Systems and Environment Department and the School of Data Science and also directs the the Sensing Systems for Health Lab at the University of Virginia.