Modeling Opportunities in mHealth Cyber-Physical Systems

Wendy Nilsen, Emre Ertin, Eric B. Hekler, Santosh Kumar, Insup Lee, Rahul Mangharam, Misha Pavel, James M. Rehg, William Riley, Daniel E. Rivera, and Donna Spruijt-Metz

Abstract Cyber-physical systems, with their focus on creating closed-loop systems, have transformed a wide range of areas (e.g., flight systems, industrial plants, robotics, etc.). However, even after a century of health research we still

W. Nilsen (✉)
National Science Foundation, Arlington, VA, USA
e-mail: wnilsen@nsf.gov

E. Ertin
The Ohio State University, Columbus, OH, USA
e-mail: ertin.1@osu.edu

E.B. Hekler
Arizona State University, Tempe, AZ, USA
e-mail: ehekler@gmail.com

S. Kumar
Department of Computer Science, University of Memphis, Memphis, TN, USA
e-mail: skumar4@memphis.edu

I. Lee • R. Mangharam
University of Pennsylvania, Philadelphia, PA, USA
e-mail: lee@cis.upenn.edu; rahulm@seas.upenn.edu

M. Pavel
Northeastern University, Boston, MA, USA
e-mail: m.pavel@neu.edu

J.M. Rehg
College of Computing, Georgia Institute of Technology, Atlanta, GA, USA
e-mail: rehg@gatech.edu

W. Riley
National Institutes of Health, Bethesda, MD, USA
e-mail: wiriley@mail.nih.gov

D.E. Rivera
Control Systems Engineering Laboratory, School for Engineering of Matter, Transport, and Energy, Arizona State University, Tempe, AZ, USA
e-mail: daniel.rivera@asu.edu

D. Spruijt-Metz
University of Southern California, Los Angeles, CA, USA
e-mail: dmetz@usc.edu

J.M. Rehg et al. (eds.), *Mobile Health*, DOI 10.1007/978-3-319-51394-2_23

lack dynamic computational models of human health and its interactions with the environment, let alone a full closed-loop cyber-physical system. A major hurdle to developing cyber-physical systems in the medical and health fields has been the lack of high-resolution data on changes in both outcomes and predictive variables in the natural environment. There are many public and private initiatives addressing these measurement issues and the health research community is witnessing rapid progress in this area. Consequently, there is an emerging opportunity to develop cyber-physical systems for mobile health (mHealth). This chapter describes research challenges in developing cyber-physical system models to build effective and safe mHealth interventions. Doing so involves significant advances in modeling of health, biology, and behavior and their interactions with the environment and response of humans to the mHealth interventions.

Introduction to mHealth Cyber-Physical Systems

Recent advances in mobile health (mHealth) technology have opened up enormous opportunities for scientific advancement and development of new tools that may improve patients' health and well-being. mHealth technologies offer real-time monitoring of both health outcomes and predictive variables at timescales varying from infrequent to continuous, to detect changes in health status, support the adoption and maintenance of a healthy lifestyle, provide rapid diagnosis of health conditions, and facilitate the implementation of interventions ranging from promoting patient self-care to providing remote healthcare services. However, to realize the potential of mHealth, significant innovations in computing are needed. The availability of new means for continuous behavioral, biological, physiological and social monitoring in combination with ecological momentary assessment (EMA) self-reports and new channels for delivery of interventions/treatment provide the basis for a radical new class of cyber-physical systems to improve health [1, 2].

Cyber-physical systems are defined as "engineered systems that are built from, and depend upon, the seamless integration of computational algorithms and physical components" [3]. Often cyber-physical systems are referred to as closed-loop systems because the measurement, actuation and control is all done automatically by complex and dynamic computational models. An example of a cyber-physical system in health is the artificial pancreas which measures the body's glucose and then administers a balance of insulin and glucagon to keep the body's insulin levels in balance without human input [4].

More recently, people have begun to discuss human-in-the-loop cyber-physical systems because the measurement and activation can be done automatically, but the control of the intervention needs to be done by a human. An example of these systems could be an emergency room sensing system which collects all the patient information and merges it with the electronic health record data. When there is a change in status (e.g., a precipitous drop in blood pressure), the health care team (i.e., human-in-the-loop) is notified to intervene. The intervention (e.g., administration of drug, fluids, etc.) that the team administers is also logged in the system and then the effects are monitored, thus closing the loop. Over time, this system will "learn" which interventions have the desired effects for the events sensed. Thus, while it will start as a human-in-the-loop cyber-physical system, over time it may become a closed loop for some interventions.

Mobile cyber-physical systems might be developed to measure and model relevant behaviors and the varied influences on health behavior, e.g., emotional, cognitive, physical, social, biological and environmental. These could be used to develop formal methods for identifying, quantifying, modeling, retaining, repurposing or rejecting variables in a model of any individual's health behaviors. Such health-related cyber-physical systems have the potential for low-cost data capture, model-based approaches for analytics and closing-the-loop interventions/treatments that are personalized, contextualized, delivered just-in-time (i.e. when and where needed), and ecologically valid. Implementing policy through data driven and quantitative models will provide increased transparency, efficiency and safety in person-centric and population-wide health and healthcare.

As an example, consider just-in-time interventions as a showcase of the computing research challenges. Just-in-time interventions (JIT) are a long-standing component of cyber-physical systems and are the next evolution of behavioral interventions in personalized and precision medicine [5–7]. Current perspectives of personalized medicine focus on tailoring the intervention based on the patient's genetics, socio-demographics, stage of change, or other baseline variables. JIT extends its intervention tailoring beyond baseline status and by sensing status changes, the cyber-physical system is actuated and adjusts or adapts the intervention over the course of the intervention [6].

The concept of adapting treatment to the patient's current state and situation is not new. Clinicians have been adapting interventions for decades in an analog manner based on clinical judgments of a patient status at each visit. What has not happened in the conventional health model is to close the loop and measure the immediate and sustained effect of the intervention the provider prescribed. A patient could get better, die, be admitted to the emergency room or see another doctor for a completely different medical or non-conventional treatment without the original provider knowing of any changes. Thus, the ability to adapt interventions using cyber-physical systems to automatically sense on a nearly continuous basis by employing a range of adjustment variables including current physical state, environment, social context, and responses to prior intervention attempts [6] closes the loop in the system.

This chapter explores the research challenges in building mHealth cyber-physical systems. Although intuitively appealing as an improvement over current intervention approaches, there are numerous challenges to implementing mHealth cyber-physical systems. We identify three challenges to establish a scientific agenda for research on health-related cyber-physical systems to develop methods and systems for acquiring low-cost, high density data needed for modeling, integration of critical variables into model development and developing accurate models for cyber-physical system development.

Acquiring Low-Cost, High Density Data for Model Development

The current approaches for data capture 'in the wild' (i.e. ambulatory) are ad hoc and fragmented, often obtrusive and not easy to use, with little standardization on the interfaces and annotation, which lend themselves poorly for model-based analytics [8].

For each health-related need, determining which data should be sampled, at what rate and which are good enough data to assess context (emotional, cognitive, physiological, biological, social, and environmental) and state inference is an essential first step. This first step requires temporally dense and accurate data with minimal patient burden. Indeed if a participant has to keep manually inputting data [9], then the participant is likely to become disengaged and non-adherent. Passive sensor data offer promise to deliver some of this data, but more research and development is needed to provide comprehensive and field-tested sensing of the relevant adjustment variables, and integrating and making sense of these data.

This first 'step', which probably comprises of many 'steps', will need scientists from across disciplines to identify what needs to be, as well as what can, be measured [10]. Determining what to monitor (from among a vast array of possible behaviors and influences) and how frequently to monitor (i.e., what are valid segments or sampling time-frames) will provide a basis to our understanding of the specificity and elasticity of different influence factors in individual health-related behavior, health promotion, and treatment. Identifying how uncertainty in data (due to measurement, estimation and training error) affects individual model accuracy, and how that in turn, affects closed-loop feedback in terms of signaling, intervention and behavioral change, will be key.

To support this infrastructure, we need to establish data and metadata capture standards, standardize interfaces and annotations; and provide controllable privacy for repositories. Given the prevalence of data from low cost sensors that are intermittent and of poor quality [8], developing delay tolerant network architectures to deliver data with minimal information loss is vital to the scalability and credibility of the data capture system. Further, as new sensor technologies and sources of data become available, sensor fusion algorithms that are cognizant to the timescales, contexts and criticality of the use of this data (i.e., accuracy required for electrophysiological pacing vs. dietary intake over more relaxed timescales) are necessary.

New Experimental Designs to Guide Data Collection for Model Development

To accurately model a closed-loop cyber-physical system, appropriate data must be on hand. But these appropriate data need to not only include high quality data, but data at the correct timescale and at the appropriate granularity. These data could reveal at what frequency the phenomena should be or could be (in the case of patient-generated data) collected. How the data collection impacts the phenomena under study and how the humans in the loop can be incentivized to use the system so that functions optimally.

An example of this arises in the physical activity literature where efforts have been made to identify which prompts are most helpful and how often they might be delivered before they have an adverse effect (e.g., [11]). Generating new experimental designs geared to populate these models would provide the data and validation for new cyber-physical systems. The focus could be on idiographic (i.e., single-subject) experiments, such as system identification experiments [12], appropriate for idiographic or group-level estimates of phenomena such as time-varying moderation of an intervention, such as micro-randomized trials [11] that are informative, recognize participant limitations and phenomena, etc. While research efforts have already begun in this domain, additional research is required to identify the duration of these experiments, and how many participants may be required to understand between participant variability [13].

Identification and Integration of Critical Variables into Closed-Loop Models

Along with a need for high quality data, is the need for the identification and understanding of the full range of critical variables in these cyber-physical systems. With the development of multi-scale models, we need to develop closed-loop approaches that consider the individual context, dynamics, physiological condition and environment effects to ensure interventions are safe and effective. Further, new models should move beyond specific areas of health and integrate models of biopsychosocial processes.

Physiological, biological, behavioral and social factors are intertwined, and measures can shed valuable light on emerging health risks and potentially serve to build complete cyber-physical systems. In order to inform prediction of risk, modeling the dynamic interplay of these systems is critical. Multiple modes of delivering individual-specific feedback need to be explored with an appreciation of the tradeoff between invasiveness and effectiveness.

While exploring automated (closed loop) or semi-automated (human-in-the-loop) feedback approaches, it is important to consider the extensive literature in health behavior change. Furthermore, new ‘variables’ will emerge because we are capturing behavior and its influences with unprecedented density and in new ways [10, 14].

Interdisciplinary collaborations between computer scientists, engineers, and biobehavioral researchers will be required to tease out these new variables, and access their usefulness in the dynamic modeling of ongoing health-related behavior. Therefore, the integration of computational models with semantically informal observations on individual behavior that have direct linkages to control frameworks are essential to the success of closing-the-loop on individual-specific interventions.

Developing Appropriate Model-based Approaches for mHealth

Identifying 'good' models and modeling techniques (across the spectrum of regression-based statistical, purely data-driven black-box models, reduced-order grey-box models and complex high-order glass-box) is an essential building block for cyber-physical systems to incorporate the dynamics, context and environmental conditions in determining the appropriate level of intervention. A statistically rigorous framework is required for model training/tuning with minimal data to minimize false positive/negative alarms. This will not only reduce the overhead of monitoring a large population of individuals in the wild, but also provide a minimum level of credibility in the decision support service. It will also let us model uncertainty (beyond standard additive and multiplicative bounded-input, bounded-output disturbances) and acknowledges the inherent complexity and time variant structure of biobehavioral processes.

Despite the successes of the data-driven approaches, the complexity of human behaviors currently limits their generalizability and predictive power. In contrast, principle-based or mechanistic models frequently studied in laboratory environments characterizing the underlying neurophysiological, biomechanical and psychological processes may not have the capability to account for the uncertainties and diversity of contexts in the wild. When mechanistic models alone are not feasible or do not provide a complete account of the phenomenon, it is useful to combine data-driven approaches with the mechanistic models as regularizers forming so called data assimilation approaches that have been successful in a number of application areas [15].

To support this cyber-physical systems approach for person-centered and population-wide health, we will need to develop open model repositories for competitive analysis of feature identification, classification and matching with an appropriate feedback approach. While all models may be considered to be flawed because they do not perfectly reflect the real world, some models are useful. Detailed models allow us to use high-fidelity simulations that take real system dynamics into account in designing interventions for any person. After developing these individual based models, we can perturb the model parameters and inputs to generate a large number of virtual models for parametric model-based interventions.

Ultimately, these efforts will let us build models for cyber-physical systems that do not have to predict perfectly, but "good enough" for the end-use application. For example, if the target is control of blood pressure, one might create or deploy a model that predicts blood pressure values within a range that is considered safe rather than pinpointing specific blood pressure value. This model will create a more generalizable and understandable intervention for a cyber-physical system and one in which the model can learn about responses for each individual. Further, explicit use of models in which good enough is explicitly identified will allow practitioners/scientists to make effective use of these models, and be able to develop these automatically (or via a guided manager) without having to be experts in the underlying technology.

Modeling Safety in mHealth Cyber-Physical Systems

An overarching goal of mHealth research is to create the tools that support systems and individuals so that people can live healthy, fulfilled lives. But, ensuring safety of the user and efficacy of the intervention are equally important.

This section highlights the research challenges in dealing with safety in mHealth cyber-physical systems. These issues include: ways in which researchers can capture adverse events and potential points of danger in model development; methods by which sub-models around safety, effectiveness and burden can be merged to create true closed-loop systems and the need to develop models based on both experimental lab data and those collected in the wild.

Capturing Risks to Enhance Safety

At present, mHealth systems, particularly interventions, are not balancing the need to be safe, effective, and fit into a person's life. *A core stumbling block, particularly with clinical populations, is that the models that are developed around each of these metrics of optimization (i.e., safety, effectiveness, and usability) are largely developed within siloed research areas.*

Further, for each of these metrics to be optimized they have idiosyncratic modeling requirements and constraints placed upon them. For example, related to safety, closed-loop models are being developed that can provide a better orchestration of the medical cyber-physical systems within hospitals that contribute to improved patient management.

An example of this would be a cyber-physical system for medication regulation. The system would sense the variables of interest, actuate the system when the medication is to be taken (either by prompting the patient or directly releasing the medication into the system) and then monitoring the patient and system's response to the medication. This will allow for better administration of medications, as well as determine for whom and when is the medication effective. Important to this work is articulating best strategies that can foster model generation, particularly by taking advantage of moments of exploration for improving the model for an individual as opposed to simply exploiting the model for increasing safety.

The core problem is that these points of exploration are, by design, moments when the risk of detrimental outcomes are greatest. Thus, in the medication regulation example above, adverse reactions to the medications are highly informative for model development and tuning, but not for the patients. This issue presents a fundamental research challenge of how to fully populate the model to asses both safety and burden. Thus, this challenge requires a balance of experimental data and real world observation (e.g., from mHealth data or electronic health records) to create models that fully encompass safety and effectiveness.

Merging Sub-models of Safety, Effectiveness and Burden

The problem of model generation where each of the sub-models is developed individually and the issues are not aggregated into a complex model is common in mHealth. For example, work is currently underway to develop closed loop systems for Type I diabetes management that balances glucose levels via the delivery of insulin and glucagon [4]. Interestingly, the current work largely ignores human behavior (e.g., food consumption, activity, sleep patterns), with the implication that the human provides too much noise to provide appropriate signals for creating safe and reliable systems (and thus potentially introducing a large safety risk when an individual engages in actions that are outside of the constraints of the closed loop controller). However, if human behavior is ignored here, the loop can never be truly 'closed', but it will rather be 'leaky', with the model endlessly trying to extract the monkey wrench that poor human health behavior throws into the works.

Other examples of this safety versus effectiveness siloeing is currently underway within the realm of mHealth behavioral interventions that are explicitly trying to model the balance between effectiveness and usability. For example, Hekler and Rivera [6, 12, 16] are currently working to develop a robust cyber-physical systems focused on increasing walking among otherwise healthy individuals. By design, the focus within this cyber-physical systems effort is modeling the dynamics for determining exactly when, where, how, and how much to intervene for promoting and increasing walking. Since walking, particularly among healthy individuals is effectively "safe", safety is largely ignored in the current phase of research.

Finally, when safety is considered, the measurement device, software, and systems must also be considered in the context of other cyber-physical systems. For example, between 1990 and 2000, 600,000 devices for pacemakers and implantable cardioverter defibrillators were recalled by the Food and Drug Administration (FDA) because of issues in the software systems [17]. As Jiang [12] notes, in the device development process, the FDA does not look at code, but, instead, explores the medical outcomes. Given the many software issues that can disrupt these cyber-physical systems, the mHealth research community needs to integrate formal and functional models that will allow us to know exactly how a system is functioning, so that we can identify system issues before they affect safety.

Using Experimental and Real World Data to Enhance Models of Safety

An example of how multiple sub-models have been merged can be found in one common cyber-physical systems, the pacemaker. To develop an effective cyber-physical systems to address abnormal heart rhythms, a model of what the heart does and how it works had to be developed. Researchers used electro-physiological signals and then mapped the signals to timers. They captured these into nodes and paths to see progression of the system over time and actually captures the physiological phenomena of the heart. These data were merged with information on abnormal heart events (e.g., when the heart was malfunctioning). With these data, researchers and physicians could examine the conduction pathways and model the natural timings of the heart.

These models lead to the development of the closed-loop strategy the pacemaker uses for interrupting conduction and correcting the signals of the heart. This allowed for formal and functional validation of the pacemaker. Thus to enhance effectiveness and safety, we need a model based on the desired level of complexity. This is because there is no single "golden" model, but instead multiple models that build on the complexity inherent in human systems.

Over time, it is likely that more complex models will be chosen, but researchers can take advantage of model simplifications and increasing complexity to help identify the ambiguities for poor responses within the system. This allows for a debugging strategy to increase confidence in the software. For the pacemaker, this model-based framework can be verified through all the possible interactions with the heart [18], including the code for a pacemaker process to ensure reliability, effectiveness and safety.

Thus, creating safe, effective, and usable mHealth interventions will require the development of robust dynamical sub-models for optimizing each outcome (e.g., usability, safety, and effectiveness) that can then be combined. The development of these sub-models, particularly those that can then be combined is no simple task. For example, the dynamical models for physical activity and eating currently being developed by Hekler and Rivera and others [6, 12, 15, 16] could likely provide valuable insights for improved management of diabetes, particularly when complemented with a continuous glucose monitor and an insulin pump that incorporates delivery both of insulin and glucagon. Integrated models will also support model-based clinical trials for implantable cardiac devices that will let researchers have confidence in a cyber-physical system before a trial begins in humans. Much more work is required both for developing sub-models on safety, security, usability, and effectiveness, and on techniques for composing them into models that can be used to analyze and balance the competing interests [19].

Conclusion

This chapter highlights the some of the research challenges in generating effective mHealth cyber-physical systems. Many research challenges are apparent and include the development of valid, temporally dense and precise data collection systems with minimal patient burden. They also require the development of new dynamical models of health that can be deployed in both fully closed-loop cyber-physical systems in which all of the control decisions are made by the system and with human-in-the-loop, semi-closed loop systems where activating and deactivating the system under specific conditions is controlled by a human (user, care team, etc.). Creating either type of cyber-physical systems requires an understanding of effectiveness and safety, based on the quality of the data and compromises inherent in giving the user control. Over time, these cyber-physical systems will evolve to handle the unpredictability that are the results of poor data or user error.

Advances in mHealth cyber-physical systems also usher in the just-in-time (JIT) interventions that can help realize the promise of personalized medicine. These changes will also move us to models of interventions that can be tested in-situ before they are deployed in humans at both great cost and potential risk. The models inherent in these cyber-physical system should also speed up the evaluation process and allow effective systems to be deployed much faster than is currently possible in health. Overall, the future of mHealth cyber-physical systems is clear as a way forward to both improve health, increase safety and speed up the evaluation process.

Acknowledgments This chapter summarizes some of the research agenda that emerged at the National Workshop on Computational Challenges in Future Mobile Health (mHealth) Systems and Applications, sponsored by the National Science Foundation (NSF) under its award number IIS-1446409. Any opinions, findings, and conclusion or recommendations expressed in this chapter are those of the authors and do not necessarily reflect the view of the NSF.

References

1. L. G. Jaimes, J. Calderon, J. Lopez and A. Raij, "Trends in Mobile Cyber-Physical Systems for health Just-in time interventions," *SoutheastCon 2015*, Fort Lauderdale, FL, 2015, pp. 1–6.
2. Hekler E, Michie S, Rivera DE, Collins LM, Pavel M, Jimison H, Garnett C, Parral S, Spruijt-Metz D. *Developing and refining models and theories suitable for digital behavior change interventions.* Am J Prev Med.
3. National Science Foundation (2016). Cyber-Physical Systems solicitation. Retrieved from https://www.nsf.gov/funding/pgm_summ.jsp?pims_id=503286 on July 30, 2016.
4. Stephen D. Patek, Sanjian Chen, Patrick Keith-Hynes, Insup Lee. *Distributed Aspects of the Artificial Pancreas*, 51st Annual Allerton Conf. on Communication, Control and Computing, 2013.
5. Nahum-Shani I, Hekler E, Spruijt-Metz D. *Building Health Behavior Models to Guide the Development of Just-in-Time Adaptive Interventions: A Pragmatic Framework*. Health Psychol. 2015; 34.Suppl 1209–19.

6. Hekler EB, Klasnja P, Riley WT, et al. *Agile science: creating useful products for behavior change in the real world.* Translational Behavioral Medicine. 2016:1–12.
7. Patrick K, Hekler EB, Estrin D, et al. *Rapid rate of technological development and its implications for research on digital health behavior interventions.* American Journal of Preventive Medicine. 2016.
8. Kumar, S., et al., Mobile Health Technology Evaluation: The mHealth Evidence Workshop. American Journal of Preventive Medicine, 2013. 45(2): p. 228–236.
9. Hekler EB, Klasnja P, Traver V, Hendriks M. Realizing Effective Behavioral Management of Health: The Metamorphosis of Behavioral Science Methods. *IEEE Pulse* 2013;4(4):29–34
10. Riley WT, Rivera DE, Atienza AA, Nilsen W, Allison SM, Mermelstein R. *Health behavior models in the age of mobile interventions: are our theories up to the task?* Translational Behavioral Medicine. 2011;1(1):53–71.
11. Klasnja P, Hekler EB, Shiffman S, et al. Micro-randomized trials: An experimental design for developing just-in-time adaptive interventions. *Health Psychology.* 2016;34(Suppl):1220–1228.
12. Martin CA, Desphande S, Hekler EB, Rivera DE. A system identification approach for improving behavioral interventions based on social cognitive theory. Paper presented at: American Control Conference (ACC)2015; Chicago, IL USA.
13. Liao P, Klasnja P, Tewari A, Murphy SA. Sample size calculations for micro-randomized trials in Mhealth. Statistics in Medicine. 2015;35(12):1944–1971.
14. Spruijt-Metz D, Hekler E, Saranummi N, Intille S, Korhonen I, Nilsen W, Rivera DE, Spring B, Michie S, Asch DA, Sanna A, Salcedo VT, Kukakfa R, Pavel M. *Building new computational models to support health behavior change and maintenance: new opportunities in behavioral research.* Translational Behavioral Medicine. 2015; 5(3): 335–46.
15. Pavel M, Jimison HB, Korhonen I, Gordon CM, Saranummi N. Behavioral Informatics and Computational Modeling in Support of Proactive Health Management and Care. Biomedical Engineering, IEEE Transactions on 2015; 62(12): 2763–75.
16. Martin CA, Rivera DE, Hekler EB. A decision framework for an adaptive behavioral intervention for physical activity using hybrid model predictive control. Paper presented at: American Control Conference (ACC)2016; Boston, MA USA.
17. Jiang Z., Pajic M., and Manghara R. Cyber–Physical Modeling of Implantable Cardiac Medical Devices. Proceedings of the IEEE | Vol. 100,No. 1, January 2012, pp 122–137.
18. Eunkyoung Jee, Shaohui Wang, Jeong Ki Kim, Jaewoo Lee, Oleg Sokolsky and Insup Lee, *A Safety-Assured Development Approach for Real-Time Pacemaker Software.* IEEE Conference on Embedded and Real-Time Computing Systems and Applications (RTCSA) 2010.
19. Insup Lee, Oleg Sokolsky, Sanjian Chen, John Hatcliff, Eunkyoung Jee, BaekGyu Kim, Andrew King, Margaret Mullen-Fortino, Soojin Park, Alexander Roederer, and Krishna Venkatasubramanian, Challenges and Research Directions in Medical Cyber-Physical Systems, in Special Issue on Cyber-Physical Systems, IEEE Proceedings, 100(1), pp. 75–90, Jan 2012.