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From EDA to IoT eHealth: Promise, Challenges, and Solutions

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***Abstract*—The interaction between technology and healthcare has a long history. However, recent years have witnessed the rapid growth and adoption of the Internet of Things (IoT) paradigm, the advent of miniature wearable biosensors, and research advances in Big Data techniques for effective manipulation of large, multiscale, multimodal, distributed and heterogeneous data sets. These advances have generated new opportunities for personalized precision eHealth and mHealth services. IoT heralds a paradigm shift in the healthcare horizon by providing many advantages, including availability and accessibility, ability to personalize and tailor content, and cost-effective delivery. Although IoT eHealth has vastly expanded the possibilities to fulfill a number of existing healthcare needs, many challenges must still be addressed in order to develop consistent, suitable, safe, flexible and power-efficient systems that are suitable fit for medical needs. To enable this transformation, it is necessary for a large number of significant technological advancements in the hardware and software communities to come together. This keynote paper addresses all these important aspects of novel IoT technologies for smart healthcare-wearable sensors, body area sensors, advanced pervasive healthcare systems, and Big Data analytics. It identifies new perspectives and highlights compelling research issues and challenges such as scalability, interoperability, device-network-human interfaces, and security, with various case studies. In addition, with the help of examples, we show how knowledge from CAD areas such as large scale analysis and optimization techniques can be applied to the important problems of eHealth.**

I. Introduction

Healthcare research brings together a wide range of disciplines and fields, in such a way that scientist in medicine, microbiology, biomedical engineering, computer science, and big data analytics frequently find themselves working and collaborating on related projects. Physicians and microbiologists work together on laboratory studies and molecular-level diagnostics, in order to maintain or improve patient health [1]. Biomedical engineers use microfluidics and biosensors to engineer new medical tools, and to create novel diagnostic and therapeutic approaches. Computer scientists work to analyze the behaviors of diseases, and algorithmically predict infections based on symptoms through the use of computer systems and artificial intelligence. Data scientists, meanwhile, conduct pharmaceutical research on cures for diseases such as cancer and Ebola, by collaborating with hospitals and clinics to gather data on healthcare, geolocations, and other related fields. Considering all these areas of expertise together, it becomes clear that many gaps remain between them; these gaps present major technological challenges in the way of the development of a unified and highly adaptive framework for healthcare. In our view, the most direct way to develop this framework is to construct an Internet of Things (IoT)-based cyberphysical solution, in order to facilitate breakthroughs in all areas mentioned above.

Advances in the IoT help create significant advances in healthcare. For instance, technologies such as microfluidic biochips and wearable biosensors can improve clinical diagnostics in a variety of applications, from the laboratory to the hospital. In the foreseeable future, IoT-enabled devices will allow health providers to routinely assess patients who suffer from breast, lung, and colorectal cancers, and perform point-of-care molecular testing as an aspect of standard care. This will help provide physicians with the information they need to create truly data-driven treatment plans, significantly improving the chance of a successful recovery. When these repeatest tests are time-stamped, location-tagged, and also tagged with data on the testing environment and other situational information, as well as personal information such as age, weight, height and gender, a data fabric will begin to take shape, spotlighting not only the patients condition, but also overall patterns in the population as a whole (for example, helping predict an outbreak of an epidemic). In short, IoT-enabled healthcare (eHealth) can move disease research forward, enable more accurate diagnoses at the point of care, and speed up the development of beneficial pharmaceuticals. It should be noted that IoT eHealth is not just the simple stack of different worlds. Instead, these pieces are networked together in order to assess, predict, and adapt in close to real-time. The vision for such a system is as follows:

- eHealth will dynamic process queries about patients at the genomic (e.g., DNA methylation profile), cellular (e.g., blood cells), and organ levels (e.g., kidney activity), across a wide array of wearable and microfluidic biosensors. This system will enable an even greater number of IoT-enabled collaborative experiments to take place in real time, as more labs and researchers collaborate to share data, provide mutual guidance, and leverage this shared database to inform judgments on follow-up practices and procedures in the biochemical realm.

- eHealth will cumulatively develop and improve the accuracy of healthcare decision making, by utilizing the big data infrastructure to construct genomic-based patient models, through the use of efficient deployments of real-time pattern recognition techniques.
- eHealth will roll out a physical-aware (self-adaptive) healthcare solution, which will connect cyberphysical integration with big-data infrastructure, and will reconfigure its nodes (i.e., modify the properties of implantable devices used to administer specialized medical therapies) in response to dynamic restructuring of computational models, which can be tailored by human intervention or self-driven learning. This capability will streamline the coupling of patient-related healthcare data with personalized treatment, and allow thousands of nodes to correlate among themselves.

As the above vision is realized, the benefits of adopting IoT eHealth can be summed up as follows (see Fig. 1) [1], [2], [3], [4], [5], [6], [7], [8], [9], [10]:

- *All-Encompassing*: Irrespective of whether people use IoT eHealth to improve their health, exercise, safety, or beauty, it has holistic value for everyone.
- *Resiliency*: The eHealth framework can also be self-learning and resilient to inaccuracies.
- *Seamless Fusion with Different Technologies*: IoT eHealth seamlessly and simply integrates different technologies.
- *Big Data Processing and Analytics*: IoT eHealth can quickly and effectively process, analyze, and manipulate complex data collected by sensors. Its processing power enables it to extract actionable information from health data.
- *Personalized Forecasting*: IoT, when used with big data analytics, can examine a patient's health holistically to forecast future health concerns before the onset of disease. As a result, patients can adapt and prevent these issues problems proactively.
- *Lifetime Monitoring*: Patients are given comprehensive data about their past, present, and future health.
- *Ease of Use*: IoT eHealth can be used with your favorite wearable device and/or smartphone.
- *Cost reduction*: loT eHealth streamlines medical services to avoid duplicative procedures and charges. It also enables patients to more closely monitor their health to determine if medical attention is needed.
- *Physician Oversight*: loT eHealth provides doctors with their patients health status in real-time, saving them time and effort on examinations. Physicians can oversee more patients at a time, although many offices will need to adapt to take advantage of loT eHealths real-time patient data.
- *Availability and Accessibility*: Doctors and patients have access to eHealth data and services anytime, and anywhere. For example, IoT eHealth provides 24/7 online access to health specialists like doctors, dermatologists, and many other medical professionals.
- *Efficient Healthcare Management*: IoT gives patients the power to view their health status at any time. Physicians can use that information to easily monitor patients health.
- *International Impact*: Medical professionals around the world have connected through the IoT eHealth ecosystem, giving patients greater access to international facilities and physicians.

This paper presents the challenges and emerging solutions for IoT-enabled eHealth, and discusses the underlying reasons behind recent success in deploying IoT solutions for healthcare.

The rest of this paper is organized as follows. In Section II, we discuss the challenges and barriers that IoT eHealth must overcome in order to grow further. In Section III, we review the evolution of IoT eHealth systems and summarize the fundamental directions. Section IV describes a three-layer architecture of an IoT eHealth platform. Next, in Section V, we describe the application of IoT eHealth using a real-life case study that demonstrates the role of IoT in the medical domain. Finally, in Section VI, we conclude this paper with a discussion of future challenges and opportunities.

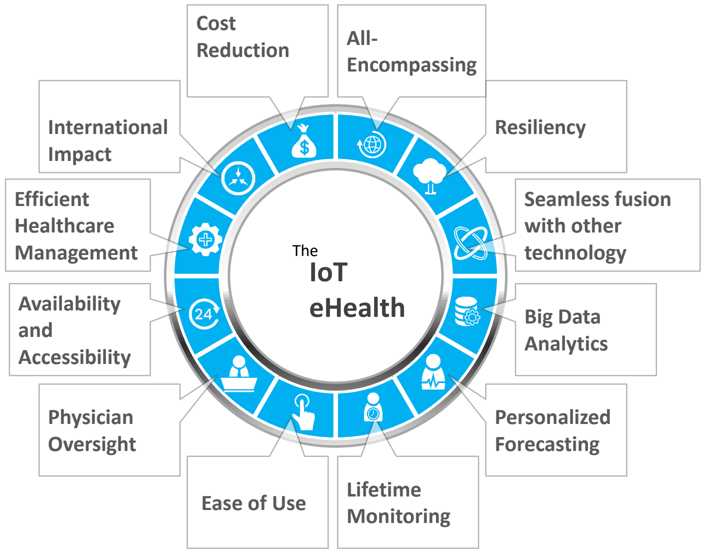
II. IoT eHealth Challenges

IoT eHealth seamlessly connects patients, clinics, and hospitals across a vast variety of locations to coordinate and orchestrate healthcare. There are, however, many research issues that must be carefully addressed before it can become viable for mainstream deployment (see Fig. 1).

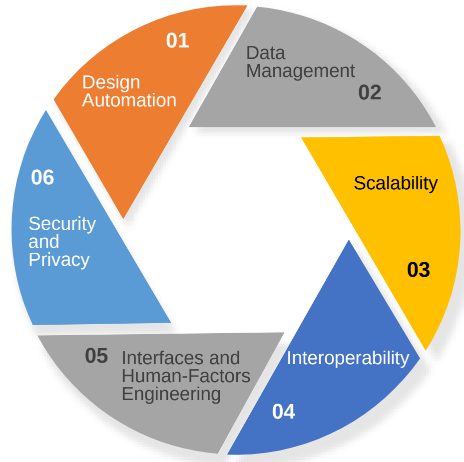
A. Design Automation Challenges

The design challenges for IoT eHealth systems arise from a combination of the following characteristics [11], [1]:

- Cross-domain: IoT eHealth is about the intersection of many fields that spans bioengineering, embedded system, to network design, and to data analytics. Therefore, modeling, design, verification, and monitoring of such a heterogeneous system requires multi-disciplinary knowledge.
- Heterogeneous: IoT eHealth spans the cyber and physical worlds. Therefore, it involves many components such as hardware and software, network, etc. As a result, it is very important to pay detailed attention to interfacing and interoperability of such a holistic system.
- Dynamic environments: IoT eHealth incorporates a significant dynamic environment. Therefore, the system should be able to evolve continually.
- Distributed systems: IoT eHealth is built on top of many layers and physically and/or temporally separated components that are tightly networked.
- Large-scale: IoT eHealth is a swarm of connected devices, network components, computation systems that must deal with data volume, variety, velocity, and veracity.
- Human aspects of the design: Since IoT eHealth is used in close collaboration with humans, it is very important that



(a)



(b)

Fig. 1: (a) IoT eHealth benefits, (b) IoT eHealth challenges.

the design of such a system consider the role of humans as well as human interfacing.

- Learning-based: IoT eHealth should be designed based on suitable data-driven learning techniques to handle the varying dynamics of cyber and physical components.
- Time-aware: Spatial and temporal variations in the dynamics of the cyber and physical components of a IoT eHealth must also be addressed.

B. Data Management

In the healthcare sector, IoT eHealth faces many of the same data management challenges as in other fields [1]. One distinguishing factor, however, is the fact that eHealth data originates from medical sensors worn by human subjects, and the human body is a constantly changing system. Thus, from an IoT eHealth perspective, an ongoing flux of data will continually flow inward from edge sensors via fog computing [1] nodes. On a positive note, sensors and computing are both declining in cost, making big data more cost-effective to be collected in a brief timeframe. IoT eHeath has evolved to deal with the complicated nature of these data, even as their variety, volume and velocity [12], [13], [1], [14] have continued to increase. At the same time, IoT faces a challenge almost unknown 10 years ago: that of data variety. Dozens of healthcare applications targeted at end users use their own data format; for example, ECG data is often encoded in XML, while camera-based IoT devices typically record data in a variety of image formats [15]. Meanwhile, various edge computer manufacturers use their own data formats, which can also vary by customer. Data models on the cloud also vary widely, creating a desperate need for standardization. Difficulties related to data volume and velocity, on the other hand, are more related to ability of the fog node hardware to acquire, analyze, store and transmit data from medical devices (which could be located at hospitals or clinics, or carried with the patient) at high fidelity and resolution. This creates a clear demand for fog administrators capable of supervising the data flux between computing in the cloud and the fog.

[1]Fog or edge computing refers to extending cloud computing to the edge of network.

C. Scalability

In order to engineer a healthcare IoT on a smaller scale, all users will need to have direct access to medical services from portable devices such as smartphones. These services will need their own sensors specialized for data gathering, along with secure central servers for handling user requests. Such an arrangement can also be scaled up to the size of a whole hospital, enabling patients throughout the facility to use their mobile devices to get updates on their care, monitor their status, and utilize other medical services. In fact, the model could be scaled up even further, to the scale of an entire city, provided that sensors and antennae exist to collect the needed data, smart algorithms and APIs exist to process it (and to analyze users requests), and intelligent interfaces exist to pass along real-time information on the status of user requests. In such a smart city, enabled for eHealth, smartphones would handle all the collection, processing and analysis of data through the use of apps, which would also gather and display feedback on patients health status, as well as the results of medical checks. This would save valuable time that would otherwise be spent waiting for appointments and results, and give patients direct access to relevant medical resources, and raise efficiency; all the while strengthening trust between patients and their healthcare providers [16], [1].

D. Interoperability, Standardization and Regulatory Affairs

The prospect of standardization raises a number of concerns for the IoT eHealth [1]. End users, service providers, and manufacturers all desire operability both within individual IoT domains, and among them. This creates complex difficulties, however, because the range of disciplines captured by IoT are regulated by a diverse group of regulatory agencies. This complexity is magnified still further in the field of IoT eHealth, where medical standards necessitate particularly strict regulations. In the USA, for instance, wireless medical devices are standardized and regulated by no less than three agencies [17]: I) the Food and Drug Administration (FDA), ii) the Centers for Medicare and Medicaid Services (CMS), and iii) the Federal Communications Commission (FCC). Companies who aim to develop IoT applications in the medical area must consider the rules and guidelines of all three of these regulatory bodies. In fact, the IoT eHealth path to market will pass through a complicated multi-agency regulatory environment in the US, as well as in other areas of the globe.

E. Interfaces and Human-Factors Engineering

The interface between front-end technologies such as sensors, computers, tablets and other mobile devices provides one of the most immediate challenges for IoT eHealth development. End users (many of whom have little or no knowledge of wireless networking, sensor syncing and similar operations) will be required to self-train in order to use the the devices correctly. In addition, many of the devices will be deployed in remote locations; elderly populations in particular will be some of the most notable IoT users, highlighting a clear need for eHealth systems that can be deployed simply and autonomously. Expert involvement will need to be minimized through the use of patient-friendly interfaces. One possible approach is to utilize participatory design [18], and involve stakeholders and/or end users in the feedback process, in order to make the devices more comfortable and enjoyable to use.

F. Security and Privacy

IoT eHealth devices, like all networked devices, will present some level of potential risk to the security and privacy of end users, through the use of unauthorized authentications. This is an especially significant concern in the area of healthcare, where personal safety could be put at risk. In fact, the entire lifecycle of IoT eHealth is built around privacy and security, from specification generation and all the way to implementation and deployment [19], [20], [21], [22], [23], [24], [25], [26], [27]. Even so, a holistic multi-layered set of strategies will be necessary in order to overcome the complex security challenges of engineering an IoT healthcare ecosystem. This approach can be described as follows [1]:

- Device layer: Connected devices such as sensors, medical devices, gateways, fog nodes, and mobile devices, when are involved in capturing, aggregating, processing and transferring medical data to the cloud. Widespread forms of attacks in the device layer include *tag cloning*, *spoofing*, *RF jamming*, *cloud polling* and *direct connection*. In a cloud polling attack, network traffic is redirected in order to inject commands directly to a device [20], [28], through the use of Man-in-the-Middle (MITM) attacks as well as changes to domain name system (DNS) configuration. The most effective defense against this attack is an ongoing policy of evaluation and verification of certifications, at the device level, in order to ensure that every certificate actually belongs to the eHealth cloud. A direct connection attack, meanwhile, involves the use of a *Service Discovery Protocol* like Universal Plug and Play (SSDP/UPNP), or the on-board properties of BLE, to locate and target IoT devices. This type of attack is best prevented by a policy of ignoring and blocking unauthenticated requests at the device level, through the use of robust cryptographic algorithms, along with a key management system. Other device-layer security measures include identity, authentication, and authorization management, secure booting (i.e., prevent unauthorized applications to be executed), application sandboxing, whitelisting, fine-grained access control capability of resources, protection of data during capture, storage, and transit, traffic filtering feature, fault tolerance, password enforcement policies, secure pairing protocols, and secure transmission mechanisms [28], [29]. It is also important to take into account the extremely limited memory, processing capabilities, power resource, network range, embedded operating systems, and thin embedded network protocol stacks of many devices while implementing security algorithms in an IoT Health system [24].
- Network layer: In this layer, a multitude of diverse network protocols, including Wi-Fi, BLE and ZigBee can be leveraged to establish appropriate connections among sensors. Eavesdropping, Sybil attacks, Sinkhole attacks, Sleep Deprivation attacks, and Man-in-the-Middle attacks are all typical at this level. Thus, the use of trusted routing mechanisms is crucial, as is the use of message integrity verification techniques (using hashing mechanisms like MD5 and SHA) and point-to-point encryption techniques based on cryptographic algorithms. These algorithms fall broadly into two groups: symmetric algorithms such as AES, DES, Blowfish, and Skipjack, as well as asymmetric public-key algorithms such as the Rabins Scheme, NtruEncrypt, and Elliptic Curve Cryptography. As a rule, symmetric algorithms are less computationally intensive, making them for low-power 8-bit/16-bit IoT devices. At the same time, problematic key exchange mechanisms and confidentiality issues often create difficulties [30].
- Cloud layer: A large body of literature exists on the security issues involved in the deployment of cloud applications. Any provider of eHealth products and services will need to establish an efficient, effective set of tactics for proactively combating the negative impacts of attacks. Widespread vulnerabilities in the cloud include Denial-of-service (DoS) attacks, SQL injections, malicious code

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injections, Spear-Phishing attacks, sniffing attacks, path traversals, unrestricted file uploading (remote code execution), cross-site scripting (XSS), Trojan horses, viruses, and brute-force attacks using weak password recovery methods [28].

- Human layer: The fundamental principle of IoT eHealth security is that individuals should receive training on how and when to avoid disclosing private healthcare information. If a knowledgeable group of attackers gains physical access to an end user's IoT eHealth device, those attackers could directly pull data from the device's internal memory and firmware, and modify its settings to obtain partial or complete control over it. In addition, it will be crucial to train users to avoid common security pitfalls such as sharing physical or electronic keys, choosing weak passwords, or purchasing used medical equipment.

III. Fundamental Directions

A. From EDA to IoT eHealth

Recently, it has been observed that much of silicon R&D can be applied to other domains [31]. Over the past decades, semiconductor companies have invested trillion dollars in the development of sophisticated EDA tools [32]. The problems that stand most to benefit from the application of EDA approaches are no longer to be found only on a silicon chip, but in the large-scale issues faced by human society on the whole. Indeed, although electronics will remain the primary focus of EDA in the near future, this is nonetheless one of the first engineering disciplines that has emphasized an interdisciplinary approach. The work of chemists, device physicists, electrical engineers, computer scientists, applied mathematicians, operations researchers, and optimization experts has influenced abstractions, computational models, algorithms, methodologies, and tools. Nowadays, EDA tools can synthesize, optimize, simulate and verify data across all levels of a given abstraction, automatically transforming a complex system-on-chip design from a high-level functional description to a detailed geometric one. A key research question that emerges is: how can we utilize the research approaches and concepts of EDA for design automation (DA) in new domains that are now emerging, in order to solve concrete and critical problems of the modern world?

Pioneering work has recently applied knowledge from VLSI to the important area of Proton radiation cancer therapy [32]. It has been shown how EDA can move beyond its E-roots and how the field can evolve and grow. Another interesting example in such area is applying EDA to sport analytics. For instance, in recent years, many teams in American National Football League have significantly shown interest in utilizing data analytics for sports applications [33]. Not surprisingly, traditional EDA algorithms have considerable overlap with the algorithm techniques used in sports applications. For example, Monte Carlo simulation can be utilized in and playoff prediction tools. Alternatively, model-order reduction can be used to model the actual values of players [33]. In this regard, it has been shown in [33] how the knowledge from EDA can be exploited in sport analytics. Yet another application area of EDA lies in the design of microfluidic biochips [34].

B. From Benchtop to Lab-on-Chips

Point-of-care (POC) tests have the potential to improve the management and treatment of infectious diseases, especially in resource-limited settings. An example of an emerging technology that has achieved remarkable success in miniaturizing POC testing is lab-on-chip (LoC) technology [35]. The basic idea of an LoC (also known as a microfluidic biochip) is to integrate all necessary elementary functions for biochemical analysis using microfluidics technology; such functions include assay operations, detection, and sample preparation [34]. A large number of design-automation techniques have been proposed to optimize the design and operation of biochips and therefore to facilitate the adoption of this microfluidics technology in POC settings [36]. Methodologies of design automation for LoCs are highlighted in Section III-C.

There are two main types of biochips according to the mechanism of biochemical liquid manipulation: continuous-flow microfluidic biochips (CMFBs) [37] and digital-microfluidic biochips (DMFBs) [35]. Continuous-flow microfluidic technology is based on the the continuous flow of liquid through microfabricated channels and the flow is governed by pressure sources at the inlets. On the other hand, DMFBs allow the manipulation of discrete volumes (droplets) of liquids on a 2-D array of electrodes. Biochemical droplets can be transported over the array by applying a software-driven sequence of voltage actuations through the electrodes; such a transportation mechanism is known as electrowetting-on-dielectric (EWOD) [35].

An example of microfluidic biochips, specifically DMFBs, for POC diagnostics is the application of a colorimetric assay for the in vitro measurement of glucose in human physiological fluids [38]. The on-chip process includes: (1) loading of pre-diluted samples and reagents; (2) dispensing analyte and reagents; (3) droplet transportation; (4) mixing of analyte solutions; (5) detection of reaction result using an absorbance-measurement sensor. The reaction forms a violet-colored compound that emits light with intensity proportional to the rate of reaction. With an adequate EDA technique, these steps can be optimized and automated to allow POC glucose test.

C. EDA Support: From SoC to LoC

Emerging technologies used in healthcare, such as LoCs, are maturing rapidly thanks to advances in fabrication techniques. These end-devices are key to the deployment of IoT-based eHealth solutions. Because of the trend of increasing biochip complexity and the integration of an increasing number of on-chip devices (e.g., heaters), manual design of biochips is no longer practical. In this context, design-automation tools can play a key role to ensure that manufactured biochips are versatile and can be reliably used in healthcare settings.

Motivated by advances in CAD support for the semiconductor industry, efforts have been made for automated design of LoCs such that users, e.g., clinicians and chemists, can adapt easily to this technology. Design automation (synthesis) solutions for LoCs includes the following categories:

- Architectural-level synthesis, in which the major goal is to schedule corresponding biochemical operations and to bind each operation to a limited set of resources (e.g., magnet, heater, and mixer) to satisfy objectives such as minimization of execution time [39], [40], [41], [42].
- Physical-level synthesis, which addresses the placement of resources and the routing of droplets to satisfy objectives such as area minimization or throughput maximization. Note that droplet routes during biochemical execution are viewed as virtual routes, which makes droplet routing different from the classical VLSI routing problem [43], [44], [45], [46], [47].
- Chip-level synthesis, which is focused on optimization of LoC control and electrical/pneumatic signal planning. In DMFBs, chip-level synthesis handles electrode addressing and wire routing to satisfy objectives such as cost-effectiveness and reduction of manufacturing complexity [48], [49].
- Fault tolerance-aware synthesis, which ensures that the execution of a biochemical assay is not affected by defects[2] or operational faults [50], [51], [52]. In this context and similar to fault tolerance in VLSI systems, fault models are utilized to capture the effect of such defects, whereas real-time recovery from associated errors can be performed with the aid of on-chip detectors through cyberphysical adaptation [53], [54], [55], [56].
- Synthesis for microbiology applications, which enables realistic modeling of biomolecular protocols and provides optimization methodologies for the realization of such protocols [57], [58], [59], [60].

Such a design-automation methodology can also be applied to other technologies such as biosensors to foster their adoption in eHealth.

D. Combined Model: Model-Based vs Data-Driven Design

Model-based design, which is widely used in industry, starts with an abstract mathematical model in order to analyze the behavior of the design. After bugs are removed, the focus moves to implementation details and sub-components. However, this methodology might not be very effective in the IoT era [11], due to the fact that eHealth systems usually are operated in highly variable and uncertain environments. Due to this uncertainty, the system should be able to learn from data in order to adequately evolve, and adapt itself and react to the events.

IV. Architecture of an IoT eHealth Ecosystem

In this section, we explain the general architectural elements required for IoT eHealth systems [61], [62], [63], [64], [65], [66], [67], [68]. As shown in Fig. 2, this system consists of three main layers [1]: *IoT eHealth Device Layer*, *IoT eHealth Fog Layer* and *IoT eHealth Cloud Layer*.

A. IoT eHealth Device Layer

With a rich set of IoT medical devices, patients can monitor their health data in real time on any computer or mobile device and their information is securely synchronized with a cloud-based eHealth platform [69]. All that is needed is a connection with appropriate communication protocol to a gateway or fog node [1]. In this context, there is a vast variety of Personal Area Networks (PAN) and WSN protocols. Fig. 3 and Fig. 4 show the IoT eHealth protocol stack. Note that the selection of the best connectivity and the communication protocol depends on the application and the specific use-case. For example, a Wi-Fi connection is ideal when transferring many documents. However, BLE works well for short-range, low-power communications. The state-of-the-art IoT eHealth devices is typically classified into two categories:

- Physical sensor: in general, any wired/wireless medical device can be used in an eHealth ecosystem to track the physical wellness of patients, and digitally monitor their health [23]. This includes ECG/EKG monitors [70], [71], [72], [73], [74], [75], [76], [77], [78], [79], [80], [81], heart rate monitors [82], [83], glucose monitors [84], [85], [86], blood pressure monitors [87], [88], [89], body temperature monitors [90], pulse oximeter [91], hemoglobin monitor [92], activity monitor [93], smart shoes [94], smart garments or e-textiles [95], [96], [97], sleep monitor [98], knee sensor [99], skin conductance sensor [100], PPG [101], elderly monitor [102], [103], [104], [105], [106], medication management [107], [108], food contamination detection device [109], early warning system [110], [111].
- Virtual Sensors: Virtual sensors use software and mobile applications to gain patients health and contextual data from the environment [112], [113], [114], [115]. A virtual sensor includes many categories such as remote monitoring, remote consultation, diagnostic, patient health record, nutrition, and medical reference applications.

B. Communications and Connectivity Layer

There is a need to enable multi-protocol data communication between devices at the edge as well as between endpoint devices/gateways, the network, and the data center.

1) Proximity networks and local area networks (PAN/LAN): connect to sensors, actuators, devices, control systems, and assets, which are collectively called edge nodes. PANs are usually wireless and more constrained by antenna distance (and sometimes battery life) than LANs.

2) Wide area networks (WAN): provide connectivity for data and control flow between the endpoint devices and the remote data center services. They may be corporate networks, overlays of private networks over the public Internet, 4G/5G mobile networks, or even satellite networks.

[2]A possible cause of defects is dielectric breakdown which is caused by high-voltage actuation.

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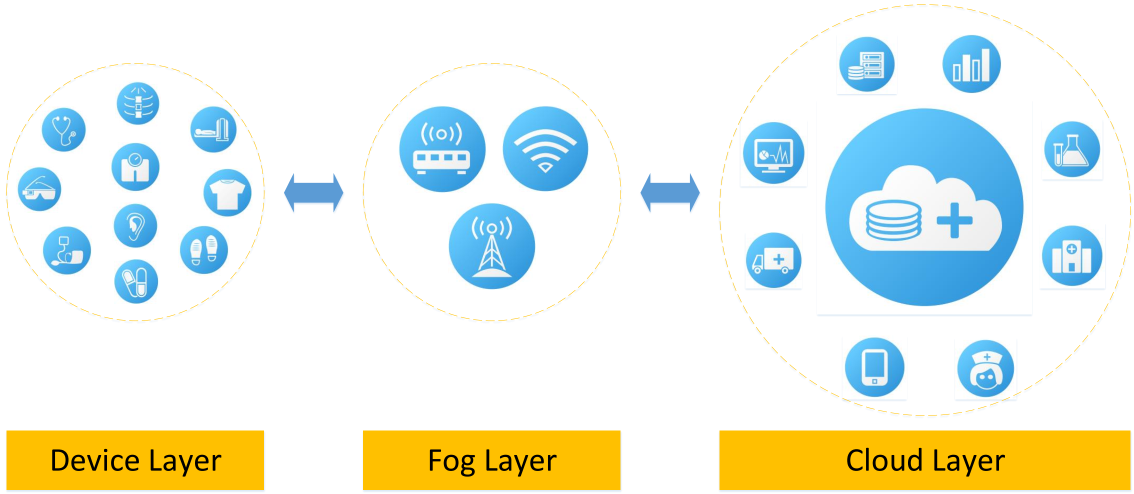

Fig. 2: IoT eHealth ecosystem.

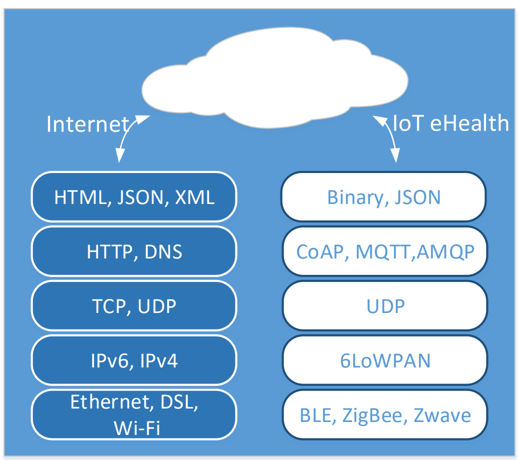

Fig. 3: IoT eHealth protocol stack.

C. Edge Computing

Todays eHealth cloud architectures are not designed to adequately handle volume, variety, and velocity of data generated by eHealth devices [117]. To tackle this issue, there is a need to revisit the network architecture, pushing certain data, processing, and services away from the massive centralized infrastructure of the cloud to the edge of the network where the data originates. An Edge node (sometimes nicknamed Fog node) is defined as a device with integrated computing, storage, and networking. The edge node is inserted between the cloud and all IoT eHealth devices adds two important features to the system:

- Real-time analytics and decision making: Some important applications of IoT eHealth such as Myocardial Infarction (MI) detection cannot tolerate latency. In these time-sensitive application, it is a necessity to process and act on health data in seconds. In such applications, it is not practical to transfer patients' sensitive medical data, vital signs, and bio-signals across a wide geographical area in the presence of various environmental conditions, and store and process them in different data centers or the cloud. Instead, moving intelligence to the edge is a promising approach to eliminate latency and evolve IoT eHealth solutions. In this approach, an edge node with localized processing capability enables us to respond more quickly than the cloud by making time-sensitive decisions more closer to the source of data. Thereby, this solution results in a more efficient solution that can better handle low-latency demands of eHealth applications.
- Traffic reduction on overburdened networks: Considering the limited network bandwidth, it is not practical and in certain use cases even not necessary to transfer enormous volume of raw big data from millions of eHealth devices to the cloud. Edge computing reduces the data transport costs, which can be significant for data-intensive applications, such as genomic-association analysis, generating several GBs of raw time-series data within a day. In this regards, edge nodes can process, filter and compact the medical data before delivering it to the cloud to dramatically minimizes bandwidth requirements.

Other important tasks of a fog node are explained below:

- Two-way connectivity: Fog nodes establish a secure reliable bi-directional data flowing between eHealth devices and the cloud platform. An edge node gathers feeds in real time from health devices using an appropriate protocol, and after processing, sends the corresponding summary periodically to the cloud to facilitate the long-term data sets aggregation, exploration, analysis and globally intelligent decision making. On the other hand, it might also need to receive commands, configuration data, etc., from the cloud. Note that the edge node is also dealing with the compliance challenges associated with connectivity such as protocol translation, security, switching, routing, and networking analytics. For example, nodes might not be assigned with a public IP address. Therefore,

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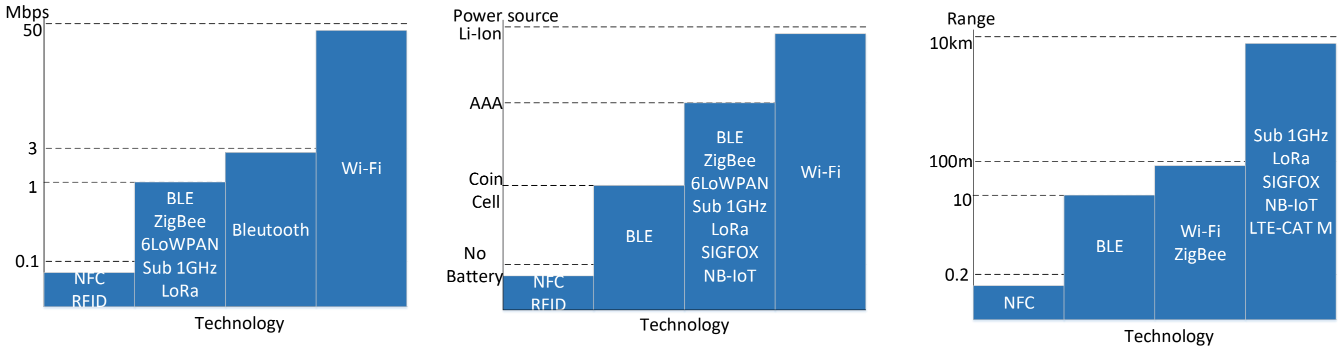

Fig. 4: Maximum throughput, range, and power source for various PAN and WSN [116].

to enable reachability from the cloud, an edge node can rely on different mechanisms such as WebSocket, MQTT (Message Queue Telemetry Transport), and IP tunneling.

- Time-series data capture: Edge nodes can either use an interrupt or a polling mechanism for data acquisition. Depending on the application, time precision might also be required to be able to extract the trend over time. In such a case, accuracy is increased if the time stamp is generated in close proximity to the eHealth device generating the data. In this regard, edge nodes time-stamp the incoming data and store it in a historian database.
- Transient data storage: Fog nodes are required to provide a short-time historical storage for eHealth device data. For example, filtering outliers of data (i.e., in the case of deviation from normal) depends on previous samples of the data.
- Device management: This includes device discovery, device registration, and device control.
- Edge processing: A rich set of applications can be executed on the edge node. For example, edge nodes are capable of on-demand data cleaning, data normalization, filtering, data reducing, compressing, integrity check, and formatting, data sharing, data purging, and data buffering. An edge node may also include, as an example, signal processing, concurrent streaming, event handling, embedded web server, embedded WebSocket server, etc.
- Streaming edge analytics: In some eHealth applications such as anomaly detection, it is a major necessity to learn actionable insight and actionable information in real time close to the local context. Keeping this in mind, edge nodes should be able to analyze the stream of device and sensor data with millisecond response time. To do so, edge nodes can incorporate lightweight feature extraction, data mining, time-series pattern recognition, machine learning, rule-based event processing, and automated reasoning.
- Data delivery: Edge nodes can rely on either of the following message-exchange techniques to deliver the IoT data: (i) Message-based (ii) Request-based, and (iii) Publish-Subscribe.
- Security and data protection: To protect patient data, the fog node offers multi-layer security measures for authentication, encryption and access control to fully meet the requirements of FDA standards.
- Flexible integration: Considering the availability of different device vendors and OEMs, edge nodes should implement a wide-range of interface standards to maintain interoperability. To address the integration concern, edge nodes should be compatible with a large variety of communication protocols and peripherals (e.g., UART, SPI and USB), PAN and WSN protocols (e.g., RFID, BLE, Zigbee, Wi-Fi, 3G/4G, and Ethernet), and wired protocols (e.g., Ethernet).
- Protocol translation: Another challenge arises from the fact that there is a large number of communication protocols at different levels of abstraction as follow:
  - Network layer: An IoT eHealth network is scattered among various networking protocols (e.g., BLE, ZigBee, Wi-Fi). To bridge the gap among these protocols, the edge node needs to convert and translate the incoming stream to an appropriate format and propagate it to the destination network.
  - Message layer: A large number of application-level protocols (e.g., MQTT, CoAP and XMPP) or processing messages exists. Thereby, it is very crucial that edge nodes despite the underlying differences of standards, be able to transfer messages among different protocols.
  - Data annotation layer: Different organizations proposed distinct standards for integration, exchange, and retrieval of eHealth information (such as HL7 [118]). Whenever it is required, edge nodes should be capable of understanding, processing, and translating the data.

D. *IoT eHealth Cloud Layer*

Cloud-based big-data analytics can be seamlessly utilized for sophisticated machine learning and data mining, providing a notable advantage for health researchers. For instance, high-dimensional Bayesian inference can be used for analyzing cancer risk or for predicting survivorship [1]. The cloud also allows us to build progressive models with higher dimensions

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(i.e. number of features) over time for each patient. In addition, it enables us to facilitate our understanding of the evolutionary changes of diseases.

The cloud platform can benefit from a multi-layer architecture that consists of the following layers (see Fig. 5) [1]:

- Input integration: Integration includes many built-in features needed to create a connection between IoT things such as eHealth devices, sensors, actuators, fog/edge nodes, BI tools, dashboards, social networks, external databases, applications, and the cloud. This layer delivers ultimate flexibility to select an appropriate communication method based on different protocols (e.g., MQTT, WebSocket, Representational State Transfer APIs, ODBC, JDBC, etc.) that suits the requirements of the given health application.
- Data lake: James Dixon, the CTO of Pentaho and the creator of the term data lake, defines this term as: If you think of a traditional database as a store of bottled water cleaned and packaged and structured for easy consumption, the data lake is a large body of water in a more natural state. The content of the data lake stream in from a source to fill the lake, and various users of the lake can come to examine, dive in, or take samples. The main advantages of a data lake are as follow:
  - It is capable of deriving values from many different data sources.
  - It can store and converge both structured and instructed data from sensor data, to eHealth documents, to social media data.
  - It can efficiently handle a growing amount of data by leveraging a distributed file system such as the Hadoop Distributed File System (HDFS).
  - It can process a large and diverse set of data.
  - It is very flexible in a way that it can be extended by several distributed applications to enable different access and process patterns of the stored data: batch (MapReduce), SQL Query (Hive, Impala, Spark SQL), Script (Pig), Stream (Spark), and many other processing engines.
  - It changes the old Early-binding ETL (Extract: Retrieving raw data, Transform: Structuring the raw data and storing it in a data repository, Load: Loading the structured data for analysis) paradigm of the traditional databases and data warehouses to process the data. Indeed, a data lake follows a Late-binding ELT approach, leading to more flexibility and faster access to all data at any time responding to any and all future needs.
- Data warehouse: It is a highly-structured repository used mainly for reporting and representing an abstracted picture of the eHealth system. The data stored in this repository can be uploaded from the data lake or from the operational systems (such as sales). However, note that before storing any data, we need to process, model, and give the data a specific structure.
- Data flow manager: This is software (such as Apache NiFi) that automates and orchestrates the data flow among the modules of the cloud.
- User, device and data management: The cloud integrates data from multiple sources. It captures data from many fog nodes and stores the data in a safe and secure manner. In this way, the data is always there to be accessed by those engaged in patient care. This platform seamlessly integrates with non-sensor sources such as EHRs, e-prescriptions, web sources, and more. As a result, patients, physicians, or any other member of a patients care team can access vital health data when needed [1]. This significantly increases collaboration across all disciplines, increasing the efficiency of the healthcare plan. Moreover, Cloud-based platforms offer a unified schema to capture and query transactions. In doing so, versatility to create new applications is increased. This module is also used to manage users, groups, devices, and fog nodes, and access permissions and roles.
- Big data analytics: This is a key component for analyzing medical data. The use of analytics allows the platform to use event- and rule-based processing, data mining, machine learning, and automated reasoning-based algorithms on stored historical records. This way, the platform can make meaningful insights about patient health. Having these early health insights could be a game-changer for a patient who can begin to take preventative action against an otherwise fatal ailment. The configurations of the connected eHealth devices can also be adjusted using the extracted insights. For instance, users may alter the frequency and type of information collected, as well as the multimedia (images and videos) resolution. Note that, there are two different engines in the analytical module. The first one handles all requests that are subject to (near) real-time constrains. The second one deals with batch data and extracting historical intelligence.
- Output integration: This is typically based on an Enterprise Service and Integration Bus such as Apache Camel with a rich set of protocols (e.g., REST API, Message Broker, Websocket, etc.) that enables connection with any system, application, or portal. It should also be noted that this module can exploit in-memory databases (such as Redis and HBase) to answer fast incoming queries by merging and caching the results from warehouse, data lake, analytics, etc. However, this database only stores very recent data and results.

V. Case Study: Integrative Multi-Omic Investigation of Breast Cancer

Breast cancer is a disease that involves abnormal changes in the biological mechanisms of the human cells, e.g., DNA methylation and gene mutation–such biological mechanisms are cooperatively responsible for regulating the growth of the human cells. Since an abnormal change in any mechanism is usually triggered by the activity of specific genes (also known as biomarkers), it is necessary to identify these genes to build a

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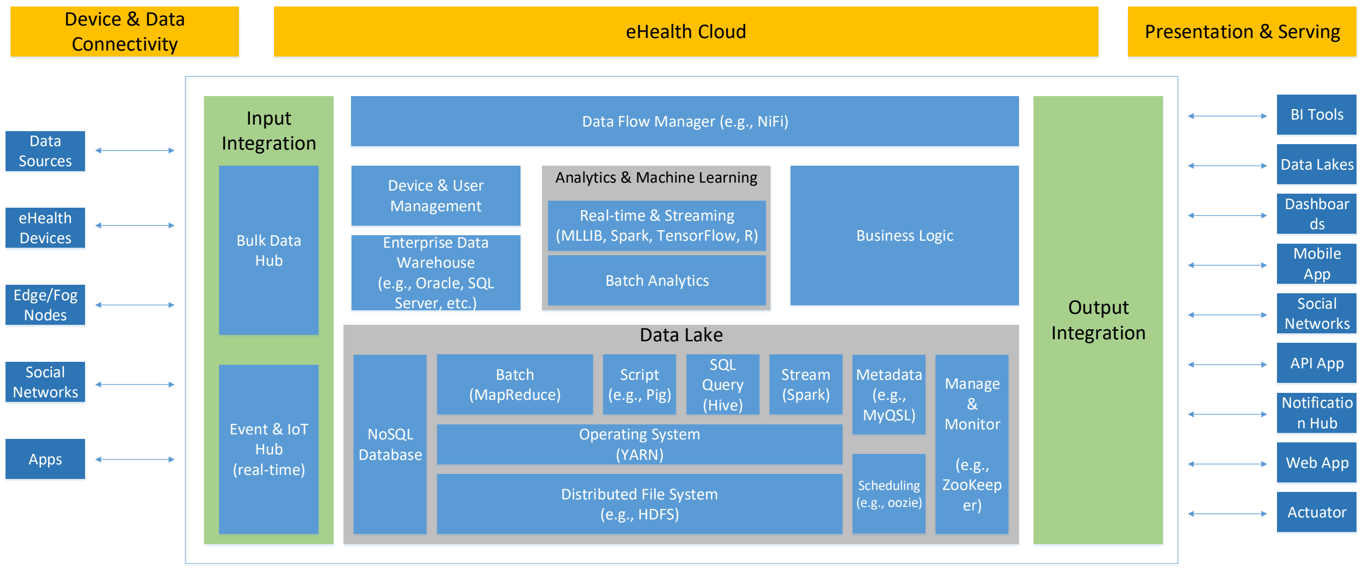

Fig. 5: Multi-layer architecture of the eHealth cloud.

genomic network, which elucidates the dynamics of the breast cancer through a multivariate association model.

Our interactive IoT-based framework facilitates the construction of such a disease model using a progressive approach. Therefore, with the help of several eHealth devices such as microfluidic biochips, our framework can advance our understanding of how the breast cancer is initiated and how cancerous tumors evolve/adapt over time [119]. To motivate our progressive approach, an example of progressive studies has been already introduced for investigating metabolic processes in biological systems [120].

Herein, we present a simplified case study that elucidates the need for an integrative multi-omic analysis for investigating breast cancer [121]. We also explain the role of the proposed eHealth ecosystem in exploring complex models of such a disease. A similar framework, known as BioCyBig, has been introduced earlier for multi-omics investigation [122]; however, BioCyBig depends only on microfluidic nodes for biochemical analysis and it is therefore limited to clinical diagnostics. The proposed eHealth architecture, on the other hand, allows real-time monitoring of cancer disease since it supports a wide range of eHealth devices (e.g., physical sensors). Hence, the proposed ecosystem is generic and can seamlessly be adapted to different classes of healthcare systems [123].

A. *Disease Model of Breast Cancer*

The following steps need to be performed to identify the biomarkers of breast cancer: (1) numerous cancerous cells must be extracted from fresh tumor tissue; (2) these cells need to be biochemically processed while observing different aspects of the biological behaviour (e.g., targeting genomic, epigenomic, proteomic, or metabolic associations) to construct a precise disease model using the generated multi-omic data. Note that it is difficult to obtain a large number of samples from a fresh tissue at the same site or from a single patient in a single treatment session; such a limitation represents one of the bottlenecks for today's analysis techniques. Obviously, an IoT-enabled eHealth service facilitates "spatial" data integration and coordination among multiple sites and also allows "temporal" adaptation in the disease model.

To construct the breast-cancer model, we need to measure and integrate four types of omic data [122]: common genetic variants (genome level), DNA methylation (epigenome level), gene expression (transcriptome level), and protein expression (proteome level). The objective is to construct a representative breast-cancer model based on these omics data, where gene expression is co-regulated by both DNA methylation and genetic variants. This model can be used as a disease signature to identify patients with similar tumor characteristics via clustering techniques. Thus, the model description is given below:

- **[Constraints]** Number of cancerous samples extracted from fresh tumor tissue per site and patient's condition over time.
- **[Variables]** x : Selected gene probes; y : SNPs around each gene probe per window size[3] (genomic data); z : CpGs around each gene probe per window size (epigenomic data); w : protein expression (proteomic data).
- **[Output]** f : Gene expression (transcriptomic data).
- **[Integrative Analysis]** Multi-staged, concatenation-based regression techniques.

Fig. 6 shows the multi-omic analysis flow for breast cancer investigation [121]—we apply this flow to both cancer and normal cells for comparison. First, genotyping of tumor samples is performed to select gene probes and to determine the associated SNPs per each gene probe within a pre-specified window size (e.g., 1 MB window). Next, regression techniques

[3] A window encompassing the gene of interest is measured in terms of megabases (MBs).

are applied to assess the association between each expression probe and the SNPs in single and multivariate models (e.g., SNP-CpG [124]). The SNPs of probes with increasing expression activity, such as CYP1B1 gene, *may* result in high risks of carcinogenic instances. Likewise, genetic rare variants (or SNPs) in COMT gene can reduce the metabolism of carcinogenic product, resulting in a higher level of DNA damage. Even so, these variations may not increase the risk of cancer if the DNA-damage repair can adequately absorb carcinogenic metabolites. In other words, using variations in genetic and transcriptomic association solely as a signature for breast cancer could be misleading.

To refine the model, epigenomic and proteomic data must be integrated in the analysis flow; thus, CpG methylation data is generated and associated with gene expression. Accordingly, higher levels of methylation at the XRCC1 gene and variation in the gene expression of XRCC3 result in reduced transcription levels, and the repair mechanism may no longer be able to adequately keep DNA repair at necessary levels. Even though an inadequate rate of DNA-damage repair likely indicates a carcinogenic tissue, dysregulated protein expression of genes in the cell cycle pathway (e.g., CDK1) may result in a rate of cell replication that is higher than average and therefore reduces the impact of damaged cells. Hence, protein-expression analysis is equally important.

To realize the above model, several biochemical assays can be implemented using microfluidic devices [125]. For example, to perform epigenetic analysis, microfluidics-based methylation assays can be employed to study novel DNA methyltransferase activity or proteins involved in DNA methylation regulation [126]. This study is conducted in two main steps that can be integrated on the same chip: (1) sample preprocessing module for on-chip DNA bisulfite conversion; (2) detection module employing thermal amplification/detection technique after immobilization with either methyl- or non-methyl-specific primer for analysis of the DNA methylation status. By using appropriate EDA tools, our framework can enable high-throughput bisulfite-based methylation analysis of thousands of samples concurrently [127].

Similarly, to investigate the dysregulation of protein expression, the analysis of protein expression is performed using microfluidic devices [128]. The process involves tumor disaggregation into single cells, cell sorting to select only live cells of a chosen type, and then transferring the cells to individual analysis chamber and analyzing them to quantify the levels of selected protein species. Microfluidic fluorescence-based detection can be employed to monitor the expression of proteins *in vivo*. EDA tools can also be developed to automate this process and allow real-time monitoring of the expression level.

To improve the early detection of breast cancer, a real-time pathological study can be launched in parallel to examine chemicals related to the disease. This study is performed using IoT-connected biosensors such as electronic noses [129], which are utilized to monitor the health conditions of cancer patients. Our eHealth framework can play a significant role in recording and analyzing the signals generated by these sensors in real time. The findings of this pathological study can also be correlated with the above association model using proper statistical means; thus increasing the probability of cancer recognition at early stages.

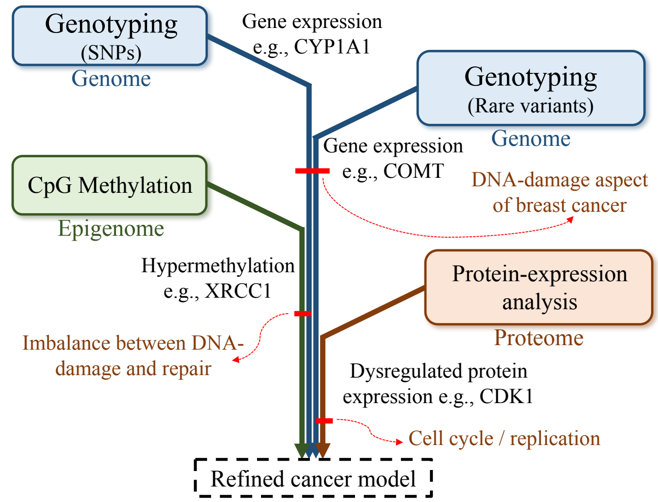

Fig. 6: Flow of integrative genomic-association analysis for breast cancer [121], [122].

While it is evident that a study of all of the variation mentioned above is required to assess cancer development, constructing such a model requires significant quantities of samples, major effort in experimental work and interactive research, and sophisticated computation utility. In addition, using wearable sensors such as electronic noses for early detection of cancer involves real-time monitoring and analytics. These requirements can be realized using the proposed eHealth framework.

B. The Role of EDA Tools

EDA tools are key enablers for benchtop biomolecular analysis, such as epigenetic and proteomic studies, on programmable cyber-physical microfluidic devices. Algorithmic innovations will fill the gap between control/monitoring in the physical space and online biochemistry-on-chip synthesis in the cyber space, and will coordinate the operations for multiple sample pathways. For example, an EDA tool was developed to enable gene-expression analysis using DMFBs [57]. The developed tool includes: (1) a spatial-reconfiguration technique that incorporates resource-sharing specifications into the EDA flow; (2) an interactive firmware that collects and analyzes sensor data based on quantitative polymerase chain reaction; and (3) a real-time resource-allocation scheme that responds promptly to decisions about the protocol flow received from the firmware layer. This framework has been extended in [58] to account for temporal conditions and to allow epigenetic analysis.

Another EDA tool has focused on adapting the above design techniques for scalable biomolecular analysis that is conducted at the cell level, namely single-cell analysis [59].

To enable practical single-cell studies, the synthesis framework is advanced as follows: (1) it supports online decision making in order to classify a pool of heterogeneous cells into "sub-populations", where each sub-population will be subjected to a specific flow of quantitative analysis; (2) it allows cells to be tagged (i.e., DNA-barcoded) automatically based on the cell's sub-population, and this barcode can be used to keep track of the identity of the cell during biomolecular analysis. More discussion on the EDA for biochemistry-on-chip can be found in [130].

By adopting these tools, the proposed eHealth solution can seamlessly coordinate the synthesis of biomolecular analysis across several microfluidic devices, and therefore construct a progressive disease model in a short period of time.

C. The Role of IoT-Based eHealth

The adoption of IoT-based eHealth as a solution for breast-cancer analysis brings the following advantages.

- The dynamic environment of the eHealth system provides unification of research goals, which enables efficient exploitation of multi-site resources (e.g., tissue samples, reagents, workers, and sensors). Such a coordination allows precise modeling of cancer, for example, through directing a research site to focus their study on specific genome loci; enabling them to increase the number of gene probes per locus and thereby the system precision. In analogy with electronic systems, this is similar to increasing the number of representation bits of an analog signal during analog-to-digital conversion.
- The big-data infrastructure can be seamlessly exploited for high-dimensional machine learning and data mining, giving a significant advantage for cancer researchers. For example, wearable sensors and sophisticated Bayesian inference can be employed for assessing cancer risk or for predicting patient survivorship.
  While the above two advantages can also be provided by BioCyBig [122], the proposed eHealth system can outperform BioCyBig in the early-detection aspect. Due to the integration of multi-omics studies with pathological real-time monitoring, our framework can significantly improve the disease model and even provide timely decision support for patients in critical conditions.

Fig. 7 shows the timeline of a typical scenario for the interactions between the eHealth system and breast-cancer researchers, following the logical sequence in Fig. 6. Note that a microfluidics-based facility can communicate with the system, via a handshaking mechanism, to run a bioassay protocol and augment the genomic model of a disease (i.e., "write" mode) based on a "call" from the eHealth framework. Alternatively, a researcher can inquire about the current status of the model (i.e., "read" mode) for diagnosis purposes. The same hand-shaking sequence can also apply to electronic noses to record information related to defined pathologies.

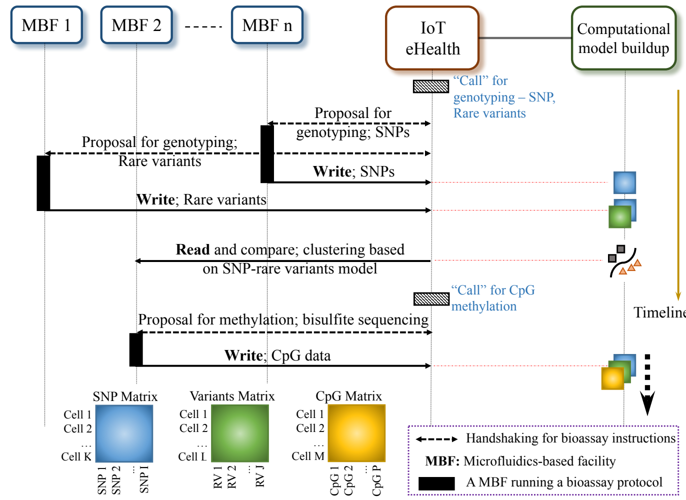

Fig. 7: The interaction between the IoT-based eHealth system and microfluidics-based facilities (device layer) for constructing the breast-cancer model [122].

VI. Conclusions

Technology has been a key part of health care for many years. As the Internet of Things (IoT) paradigm becomes more widespread, a host of novel opportunities have arisen. Technologies such as miniature wearable biosensors, along with advances in Big Data, especially with respect to efficient handling of large, multiscale, multimodal, distributed and heterogeneous data sets, have opened the floodgates for eHealth and mHealth services that are more personalized and precise than ever before. However, IoT hints at an even greater change in health care paradigms; it promises greater accessibility and availability, personalization and tailored content, and improved returns on investments in delivery. Even so, as IoT eHealth broadens the horizons of fulfillment in terms of existing health care needs, quite a few major hurdles remain before consistent, suitable, safe, flexible and power-efficient solutions can be deployed to address many medical demands. The only way to cross these hurdles is to facilitate collaboration between the software and hardware communities, in order to push technology forward. Before a truly IoT-based health care world can emerge, significant advancements are needed in bioelectronics, communication devices, EDA and software, and networks. In addition, breakthroughs are also needed in pattern recognition, sophisticated data-analytics, Big Data and cloud computing, and information technologies.

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