

Next-Generation Continuous Metabolite Sensing toward Emerging Sensor Needs

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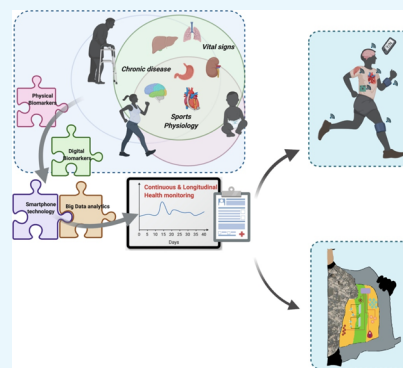


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ABSTRACT: This article discusses the emergent biosensor technology focused on continuous biosensing of metabolites by non-invasive sampling of body fluids emphasized on physiological monitoring in mobility-constrained populations, resource-challenged settings, and harsh environments. The boom of innovative ideas and endless opportunities in healthcare technologies has transformed traditional medicine into a sustainable link between medical practitioners and patients to provide solutions for faster disease diagnosis. The future of healthcare is focused on empowering users to manage their own health. The confluence of big data and predictive analysis and the internet of things (IoT) technology have shown the potential of converting the abundant health profile data amassed from medical diagnosis of patients into useable information, whilst allowing caregivers to provide suitable treatment plans. The implementation of the IoT technology has opened up advanced approaches in real-time, continuous, remote monitoring of patients. Wearable, point-of-care biosensors are the future roadmap to providing direct, real-time information of health status to the user and medical professionals in this digitized era.



1. INTRODUCTION

Continuous biosensing has transformed patient care and is the answer to numerous unmet clinical needs. Continuous monitoring systems serve as primary medical intervention platforms by collecting patient's clinical statistics that can further assist in disease diagnosis, disease progression, and tracking patient therapy.¹ Continuous biochemical sensors (biosensor) enable real-time receptor–biomarker interaction and report quantifiable signals that are proportional to the biomarker concentration. The term “biosensor” refers to an analytical device with a biological recognition element that can selectively bind to the target biomarker, finding its utility in significantly important arenas of disease diagnosis, drug discovery, and biomedicine. Over a period of time, with the advances in technology, biosensors have become skin-integrable and implantable to give a detailed account of the body's vital state and the underlying disease state. For continuous monitoring, the biosensors are required to demonstrate sensitive, specific, reliable, and multiplexed biomarker detection accompanied by skin biocompatibility.² However, current clinical techniques suffer from reproducibility under varying conditions and the inability to report symptoms in real-time. Continuous remote patient monitoring technologies have proven to be effective in monitoring chronic and acute illnesses in older adults. These techniques can assist caregivers to track progressions in the disease, assure continued recovery in remote settings, and prompt immediate

intervention, thereby reducing a monetary burden of \$200 billion on the U.S. health care system.³ Sustainable healthcare emphasizes on the need of real-time monitoring platforms with accessibility in rural and resource-challenged settings. Remote diagnostics rely mainly on the type of sampling wherein non-invasive or minimally invasive approaches are preferred. The sustainable development goals set for 2030 aim at reducing the global death rate amongst neonatal and maternal populations by a significant number, which requires rapid scaling of the intervention technology.⁴ Biosensor technologies can facilitate health monitoring in maternal and neonatal populations to track their physiological parameters, behavioral changes, risk factors, sleep–wake cycles, metabolites, and potential infections.⁵ The use of modern medical equipment for complete biochemical profiling of patient samples in a low socioeconomic and resource-challenged environment such as military and pandemic situations requires trained personnel, bulky equipment, complex operation, and electrical power.⁶ The independency of wearable biosensors from the laboratory infrastructure makes them greatly promising in resource-

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challenged settings. The smart technology of wearable biosensors has enabled bulky laboratory equipment to be miniaturized to a small form factor platform equipped with low-power electronics and a flexible skin-conformable interface.⁷ Wearable physiological monitoring is an important aspect for soldier performance assessment to monitor their work limits, alertness, fitness, fatigue, injury, and neurological status.⁸ This review is focused to introduce and provide a fundamental understanding of continuous metabolite monitoring systems that can identify clinical trends that can have a significant impact on delivering medical care.

2. NON-INVASIVE WEARABLE SENSORS FOR CONTINUOUS HEALTH MONITORING

2.1. Digital Versus Traditional Biomarkers. Biomarkers are defined as quantifiable medical signs that can unequivocally evaluate normalcy of biological processes, underlying pathophysiology, and the body's response to therapeutic intervention. The increasing number of medical data-generating devices, such as health and fitness monitoring wearables, has given way to a new class of biomarkers—"digital biomarkers". These can be defined as "objective, quantifiable physiological and behavioral data that are collected and measured by means of digital devices such as portables, wearables, implantables, or digestibles".⁹ Digital biomarker discovery and development is still in its infancy, and the lack of standardized semantics amongst device manufactures and data collectors is contributing to the delay in its rise. However, with the advent of big data analytics, internet of medical things, and easier access to high-speed secure internet, a boom in the realm of digital biomarkers can be safely forecasted.

Traditional biomarkers (physical biomarkers which are traditionally not collected using digital devices) are often collected through expensive invasive sampling methods. Most of these are qualitative (yes/no results) or semi-quantitative and not fully quantitative. The sample preparation for the collection of these biomarkers is often complex, and their quantification often requires some form of labelling or tagging limiting their breadth for at-home point-of-care devices and self-monitoring medical wearables. The collection of these biomarkers is often in the form of static single time point readouts. Consequently, they fail to map the true dynamic and complex nature of the disease ("snapshot" problem) and present an incomplete view of the physiology instead. In contrast, collection of digital biomarkers is non-invasive and cheaper (often done using smartphones) and does not demand intervention by a trained professional. Furthermore, the readouts are quantitative continuous value numbers which make continuous monitoring of medical signs and longitudinal health mapping feasible.

Digital biomarkers are often consumer-centric and do not represent statistics applied across a population. Instead, they offer personalized metrics and individual baselines for physiological and behavioral process tracking, and thus, unlike their traditional biomarker counterparts, digital biomarkers do not have well established baselines or "gold-standard" cut-off points. This can potentially lead to false negatives especially in the case of heterogeneous and demographically diverse populations. Further, the biology behind several novel digital biomarkers is not fully understood. Thus, instead of solely relying on digital biomarkers for health status evaluation, a combinatorial detection strategy with the standard physical biomarkers seems logical. This way, the robustness and

reliability of traditional biomarkers can be leveraged, while at the same time eliminating the "snapshot problem". Due to the growth in the number of novel label-free non-invasive sensing platforms, the cost-effective traditional biomarker collection biosensor market is expected to reach \$34.3 billion by 2025 globally.¹⁰ Upon integration, emerging digital markers can supplement and enhance conclusions from traditional biomarkers and unravel new possibilities for unprecedented holistic understanding of human health and disease, for capturing phenotypic variances in population cohorts, and for longitudinal physiological mapping toward real-time, personalized, preventive, predictive, and participatory health-care.¹¹ Metabolites are intermediates or products of metabolic reactions in the body, the levels of which have been closely studied in clinical diagnostics to determine the health status of an individual. Any homeostatic imbalance of these metabolic biomarkers, either due to abrupt or acute fluctuations or due to serious underlying chronic disease conditions, can help identify irregularities in the functioning of biochemical pathways and metabolic patterns. The major metabolites that have been probed in academic and industrial research for fitness, lifestyle, and disease monitoring include glucose, lactate, alcohol, ions, and electrolytes (sodium, potassium, chloride, and hydrogen/pH). After the success of continuous glucose monitors, continuous tracking of these metabolites is garnering attention. By simultaneous monitoring of multiple such metabolic analytes, comprehensive and longitudinal metabolic profiling can provide actionable information for stringent personal control and timely medical intervention. The success metrics for multiplexed and continuous metabolite biosensing wearables, especially for personalized home-based use, include high sensitivity, a wide linear range, a high signal-to-noise ratio, fast response and sampling time, ease of use, non-invasiveness, minimal sample preparation, and low-cost fabrication. In the subsequent sections, several non-implantable wearable metabolic biomarker monitors (both digital and digital-physical hybrids) in the recent commercial and research space have been discussed with focus on vulnerable population cohorts which require involuntary and continuous health status tracking, namely the mobility-constrained, geriatric, pediatric, and pregnant population (Figure 1).

2.2. Emerging Biosensors for Mobility-Constrained and Geriatric Population. In the next 20 years, the elderly population will increase by 20%, creating a need for high-quality care and high accuracy medical data monitoring.¹² The most commonly reported ailments include cardiac disorders, arthritis, diabetes, chronic obstructive pulmonary disease, chronic kidney disease, depression, Alzheimer's disease, and dementia.¹³ As per the Center for Disease Control and Prevention (CDC), if the current rate persists, 43,000 deaths could result by 2030 in the US alone. To solve in the recent years, a number of wearables specifically targeted to cater to the needs of elderly population have been developed. For elderly patients, continuous health trackers which are easy to use and require minimum intervention are desirable. The most common wearable monitors for this age group are in the form of a smart watch, a smartphone, and smart clothing. Among the three, smart clothing is considered the most superior because of the greater breadth of diverse sensors that can be incorporated in them. A number of smart medical clothing can be found in the recent space for a gamut of conditions ranging from cardiac monitors, chronic obstructive pulmonary disease management, hydration monitoring, stroke rehabilitation,

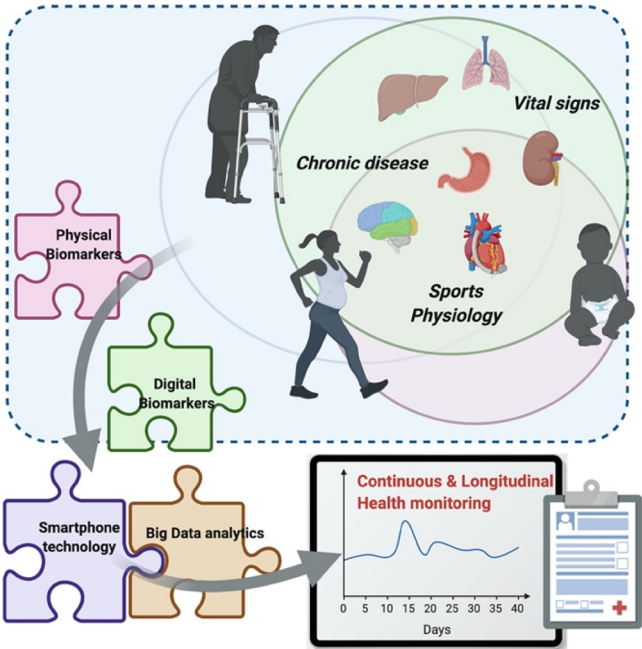


Figure 1. Overview of emergent biosensors that have been explored for continuous monitoring of diseases and vital signs in the mobility-constrained population, created by authors using Biorender.com.

activity monitoring, and so forth. Table 1 includes a number of popular wearable sensors available in the commercial space for chronic disease management, vital sign monitoring, fitness tracking, precise positioning, and gait analysis, to name a few, specifically targeted toward the senior population. Smart biosensors, which quantify levels of disease-specific biomarkers in easily accessible body fluid matrices (sweat, tears, saliva, and interstitial fluid), are gaining a lot of traction because of their non-invasive or minimally invasive sampling regime. These body fluid-based wearables are mainly available in the form of colorimetric or electrochemical biosensors. Colorimetric sweat

wearables employ colorimetric or fluorescent assays for biomarker quantification and are most commonly found in the form of “epifluidic” (portmanteau of epidermic and microfluidic) sweat biosensors. Comparatively, electrochemical biosensors output electrical readouts (current, voltage, impedance, and conductance) in response to analyte concentrations expressed in the sweat matrix. Electrochemical sweat biosensors have been reported to be superior in terms of high sensitivity and specificity, response times, and power requirements for real-time sweat analysis.¹⁴ For the elderly population, sweat biosensors are superior to their urine-, saliva-, or tear-based counterparts, mainly because they can be collected without any active sampling. This lends them continuous real-time health status monitoring potential. Most sweat-based biosensors require physical or chemical stimulation of the sweat glands to achieve sufficient volumes for reliable sensing. This is especially in the case of otherwise popular microfluidic sweat sensors which require sweat collection and post-processing to get readouts. This not only defeats the purpose of real-time tracking but also involves additional issues of sweat contamination and evaporation. While exercise-based sweat stimulation is risky and inconvenient for the senior and mobility-constrained population, pilocarpine iontophoresis-based sweat collection has been found to cause deleterious effects on the stratum corneum. For real-time metabolite tracking, on-body or skin-interfaced sweat wearables are effective. Most of these sweat wearables rely on the natural pressure of sweat glands and microfluidic technology wherein the eluted eccrine sweat is navigated through microchannels by capillary action and stored in reservoirs to achieve sufficient volumes for reliable sensing. However, because of the time lag between sweat storage and eventual metabolite quantification, true real-time metabolite sensing is not achieved. To address this issue and to allow for “chronosampling” of sweat metabolites, active and passive valving and sweat mixing strategies have been developed. However, these methods add to the system complexity and demand form factors that are not suitable for wearable

Table 1. Wearable Medical Devices for Geriatric, Maternal, and Pediatric Population

wearable description or type	disease or condition	target population
MC10	temperature, heart rate, and other vital signs	geriatric
KardiaMobile	EKG	
Omron Generation Zero and Withings blood pressure monitor, Microsoft eyeglass	blood pressure	
BodyGuardian Heart	cardiac health	
CarePredict, jawbone	ADL or activities of daily living	
FreeStyle Libre system	diabetes, continuous glucose monitoring	
wearable artificial kidney	kidney disease	
transcranial direct-current stimulation wearable	depression	
GPS tracker shoe insert	cognitive conditions—dementia, Alzheimer’s disease	
Lively Wearable, WalkJoy, TASK Fall Detector, GTX Corp, and Buddi	gait monitor and fall prevention	
Dot Watch—Braille & Tactile Smartwatch	vision	pregnant and maternal
Reemo Health Smartwatch, Freedom Guardian, MobileHelp Smart, Fitbit, Apple watch, and Garmin	fitness monitoring for seniors	
Bloomlife	pregnancy contractions	
Reliefband	morning sickness	pediatric
TempTraq	temperature	
Sproutling	temperature, heart rate, and sleep–wake cycle	
Pixie Scientific	urinary tract infection	
Owlet	vitals, sleep, and movement	

applications.¹⁴ To fully leverage sweat's dynamic biomarker quantification potential in a simple and user-friendly manner, our group has harnessed its passive addressability by demonstrating reliable sensing at healthy natural sweat rates. Easily wickable, hydrophilic, and biocompatible substrate materials that can be directly interfaced with the skin have been utilized for probing ultra-low sweat volumes. To achieve high sensitivity, high resolution, and a high signal-to-noise ratio, non-faradaic or label-free electrochemical detection schemes have been employed which do not require the addition of redox reporter tags. This is desirable for home-based longitudinal health monitoring as it eliminates the intervention of skilled personnel or trained medical caregivers because no additional sample preparation is required. Further, electrochemical biosensing provides a continuous-valued direct electrical readout which allows for high sampling rates for tracking subtle changes for real-time sensing and miniaturization and mass-production opportunities. Our group has contributed in this realm by proposing wearable schemes focusing on lifestyle monitors quantifying metabolites such as alcohol,^{15,16} glucose,^{17,18} lactate,^{18–20} and chloride^{21,22} to name a few.

2.3. Emerging Biosensors for Prenatal, Pediatric, and Maternal Population. According to the most recent data from the United Nations Population Fund (UNPF), approximately 808 women die every day from preventable causes related to pregnancy and childbirth, which accounts for about one woman every 2 min. Nearly 10–25% of pregnancies end in miscarriage (about 1.1. million in 6.5 million pregnancies in 2008 in the US),²³ and in a majority of those affected, symptoms persist for 1–3 years, impacting quality of life and subsequent pregnancies.²⁴

“Sudden unexpected infant death (SUID) is a term used to describe the sudden and unexpected death of a baby less than 1 year old in which the cause was not obvious before investigation”. According to CDC, nearly 3500 sudden unexpected infant deaths (less than 1 year old) occur annually in the US alone.²⁵ Zhu et al., in their review article, tabulate the common biomarkers and physiological vital signs monitored during neonatal intensive care and the relative sensing principles and transducers.²⁶ Hassan et al. in their review article—“wearable technology for baby monitoring: a review”—discuss several commercially available baby monitors involving both traditional and digital biomarkers in detail.²⁷ For infant health monitoring, non-invasive biosensors that can be seamlessly integrated in the commodities of everyday use without discomfort or frequent intervention are in demand. Garcia-Carmona et al. have developed a fully integrated pacifier for enzyme-based amperometric monitoring of glucose levels in a baby's saliva.²⁸ Table 1 includes a number of popular non-invasive wearable sensors available in the commercial space for infant and maternal health monitoring. For reliable monitoring of premature infants in the newborn intensive care unit (NICU), multi-biomarker monitoring is imperative for a comprehensive, safe, reliable, and accurate understanding of the health status. For instance, a baby glove swaddle has been developed which wraps and secures the baby comfortably with two plates on the front and back of the torso, which contain sensors inside that monitor temperature, hydration, and pulse rate.²⁹ Linti et al. developed a baby vest based on an oximetry module and a triaxial accelerometer for mapping multiple biomedical parameters for respiration, heart rate, temperature, and humidity for continuous monitoring of infants in the

NICU and/or home environments.³⁰ Multi-parameter biomarker monitoring systems have been reported to suffer from issues of large energy consumption. For easy and effective home-based childcare, low cost and low maintenance devices with a long battery life is desired, which make electrochemical biosensors an attractive option. This is because they are compatible with microfabrication, which makes them mass-producible, and a direct electrical output is afforded, which allows for high sensitivity and lower detection limits. To cater to the real-time critical monitoring needs and skin-mountable “kangaroo care” applications, non-invasive electrochemical sweat sensors are paradigm shifters. One of the challenges that the sweat biosensing poses is that factors like sweat rate, body temperature, pH, and other non-specific metabolites and electrolytes in the milieu influence the measurement of the target analyte.³¹ Thus, for accurate understanding of the physiological status, combinatorial evaluation of all these factors is apparent. Our group has proposed a biomarker benchmarking scheme to underline the importance of combinatorial electrochemical biosensing to minimize the diagnostic error rates for sweat-based wearable diagnostics.²¹ For the reasons mentioned in the previous section (for elderly people), physical and chemical sweat gland stimulation is unsuitable for babies. Thus, passive sweat-based electrochemical biosensors developed by our group can be extended for neonatal and infant care.^{15,16,18,21}

3. SOLDIER WELLNESS MONITORING THROUGH WEARABLE SENSORS FOR CONTINUOUS HEALTH MONITORING

3.1. Need for Biosensors in Hostile and Harsh Environmental Settings. Military personnel often operate in hostile settings and extreme environmental conditions, requiring them to move on harsh terrains while carrying excess loads. As a result, the stress on the body causes dehydration, altitude sickness, fatigue, and loss of electrolytes, adding to the wounds caused in case of warfare trauma. Active physiological status monitoring of military personnel will equip squad leaders with real-time information to detect and triage casualties and prepare for emergency deployment of healthy personnel. Comprehensive performance-tracking biomarkers on the individual level give key real-time information that assists team leaders in making tactical decisions (Figure 2). Lovalekar et al. found that research on soldier resiliency and assessment of physiological status was a top priority, while sleep and nutrition were emerging priorities.³² Therefore, technological innovation is needed to continuously and accurately sense the levels of several key metabolites directly from body fluids under harsh environmental conditions. Tracking levels of exhaustion, hydration, core body temperature, glucose, sweat lactate, and pH are most useful to assess the state of military personnel. These biomarkers predict peak on-field performance and physical fitness. Soldiers routinely perform strenuous physical activity for training or job duties in hot or warm conditions for extended periods, which can lead to exertional heat illness (EHI). Though non-fatal, EHI leads to loss of duty time, degrades on-field performance, and increases future risk of heat illness. Hence, it is critical to have hydration trackers in real time in the form of wearable patches that translate the status to a base station on the body. Emerging physical health trackers for the battlefield must be body-worn or integrated into uniforms and provide real-time monitoring of multiplex biomarkers, on-body processing,

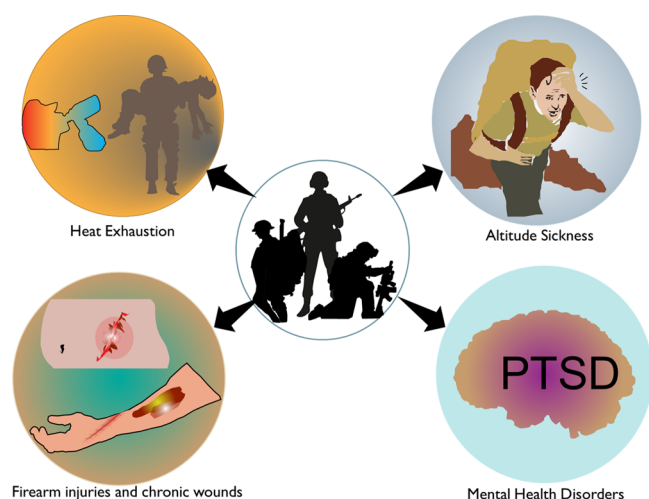


Figure 2. Biosensing needs for continuous monitoring of soldier wellness in harsh and hostile environments, created by authors using Biorender.com.

wireless data transmission, and a miniature form factor. There is also an emerging need for detection of neuroendocrine hormonal markers such as cortisol, catecholamines, and immune system and inflammatory markers such as cytokines, chemokines, and growth factors to treat PTSD in the military.

In this section, we present the technologies for non-invasive sensing of the glucose, lactate, pH, and hydration status and the challenges and potential for innovation. Recent studies by Jankowska et al. reported simultaneous glucose and pH monitoring to assess progression of wound healing.³³ Acute wounds occurring on the battlefield take a long time to heal. Continuous monitoring of pH is an indicator of wound healing, and the value of wound pH allows timely intervention should it worsen. Similarly, glucose concentration is higher for acute wounds, which is common in military combat. Current research is trending toward the development of wound dressings embedded with pH, humidity sensors, and drug compounds within the scaffolding for controllable drug release and electronic readouts for remote monitoring. This method could be employed to develop on-body and wear-and-forget sensing systems to measure the pH and glucose concentrations from wound liquid and to release necessary drugs depending on the environmental conditions. For example, in warm weather when there is less chance for wounds to heal quickly, sensors could measure wound pH, humidity, and glucose concentration and relay it locally to the drug release dressing where an active control system will set the drug release rate for timely localized delivery. Physical demands that come with military work can cause extreme dehydration by sweating, causing rapid electrolyte imbalance and resulting in heat illness and heat stroke. Hydration assessment is key to prevent heat stress and numerous illnesses associated with dehydration. Urine markers for dehydration such as color, volume, specific gravity, and osmolality cannot be used in the field because of the inherent difficulty in sampling. Sweat is the most relevant body fluid that could be utilized for on-field sensing. Reliable measurement of hydration levels in such environments involves real-time accurate monitoring of water loss. Sweat secretion on the skin and the subsequent loss to the environment is dictated by surrounding temperature, radiation, moisture, altitude, and clothing. Yao et al. at NCSU developed a wireless wearable hydration sensor to track skin hydration through a flexible

silver nanowire–PDMS electrode in real time.³⁴ This technology was adopted into a multifunctional sensing chest-worn adhesive patch for continuous skin hydration monitoring along with ECG and skin strain under rest and in motion. Data obtained from the sensors were transmitted via Bluetooth, ideal for on-ground operations in military settings. Alternately, Carr et al. developed resonant stickers to monitor undercoat perspiration to analyze the sweat rate and sweat conductivity.³⁵ They demonstrated the ability to read the output from the sticker through thick PPE. Wireless smart bandages, such as the one developed by Kassal et al. could be integrated within the fabric of military uniforms for optical sensing of pH to monitor the wound status.³⁶ Chest pockets, shoulder pockets, underarm vests, and collar cuffs are common sites to embed the sensors where sweat accumulation is perceived. The challenges associated with the above sensors include the need for on-body power supply and wireless circuitry for transmission of data, equipment for data readout from close proximity, and robustness under vigorous movement such as in battle scenarios. Smart clothing and body armors form a natural segue to addressing the above constraints. Intelligent textiles or smart clothing must have sensors that are lightweight, noise-free, artifact-proof, replaceable with low cost to manufacture, and overall comfortable to attach (Figure 3). Although stickers and patches on the skin are available, they are prone to errors in measurement and may deteriorate due to the rigorous nature of the battlefield. E-textiles covering the torso can aid in medical monitoring better than discrete patches or stickers. Mostafalu et al. have developed a thread-based toolkit including sensors, electronics, and microfluidics for medical diagnostics.³⁷ Research on weaving fiber-optic

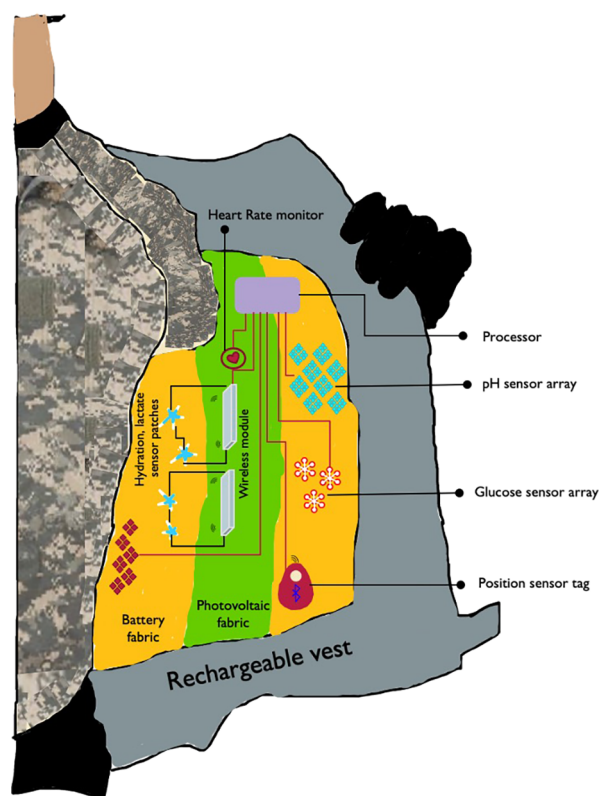


Figure 3. Smart vest integrated with biosensors for continuous monitoring of metabolite levels and pH, created by authors using Biorender.com.

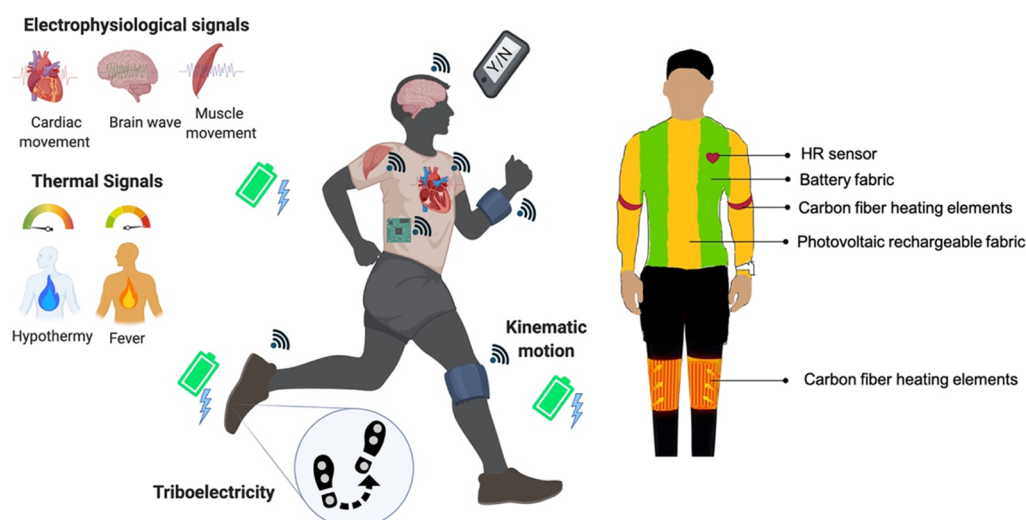


Figure 4. Self-powered biosensors harnessed from body signals for energizing the next generation of wearables for POCD in resource-challenged settings, created by authors with BioRender.com.

wires into the soldier's uniform as a continuous network of multi-use sensors is being carried out at the US Army's Institute for Soldier Nanotechnologies at MIT.³⁸ In spite of advancements, technological issues such as integration of the power supply to power the sensors, on-uniform data processing, and wireless data transmission need optimization to make sensorized body armor suits a reality. Additionally, in scenarios where soldiers are exposed to harmful environments, uniforms which detect chemical, radiation, and biological exposure are useful.³⁹ Here, the embedded sensors must embrace a tight-fit fabric such as vests for body fluid sampling and a stretchable fabric for conforming with mobility. In either case, the sensors must be strategically interspersed within the matrix of the clothing and positioned close to the key areas of the body such as the under arms and lower back where the build-up of body fluid is maximum.

3.2. Non-invasive Biosensing in Rapidly Changing Environments. A pandemic environment, where the causal agents for communicable infections are virulent, affect the human body adversely when there is a metabolic imbalance. We see this evident in the ongoing COVID-19 pandemic, where populations with diabetes, obesity, hypertension, and other pre-existing metabolic abnormalities are at a greater risk to contract infection. In such a situation, it becomes crucial to monitor our metabolic status through diagnostic methods to promote strong defense against infection and associated damage and prepare the body for disease tolerance. Diagnostic tests detect environmental exposure to infection from pandemic viruses and seasonal flu viruses. Evidence suggests that the viral load is present primarily in blood and consequently in other body fluids such as sweat, saliva, and urine. It is therefore critical to continuously monitor the expressed inflammatory response biomarkers such as C-reactive protein, reactive oxygen species, IL-6, chemokines, and so forth in these bodily fluids. Emerging biosensors need to quantitatively demonstrate the levels of these markers for preventing re-infection and maintaining metabolic homeostasis. Parupudi et al. show that biosensors backed by clinical evidence are also imperative to the staging of the clinical course of a pandemic disease.⁴⁰ They allow stratifying patients based on the levels of several key biomarkers as mildly ill, critically ill, or needing ICU admission. Our group has

addressed the technological gap by incorporating electrochemical sensors in textiles and in wearable devices to track the inflammatory response through combinatorial and multiplex biomarker sensing.⁴¹ When integrated with upcoming platforms such as the IoT for real-time continuous monitoring, these biosensors could pave the way to predicting future outbreaks and reduce the overall burden of pandemics.

4. BIOSENSORS FOR RESOURCE-CHALLENGED SETTINGS WHERE ACCESS TO ELECTRICITY COULD ALSO BE A CHALLENGE

The wearable biosensor market is fast developing to meet the demands of a wide consumer base for continuous and longitudinal health monitoring. In the past few decades, we have largely moved away from bulky medical devices which required large rigid battery packs to power the electronic circuitry and are now inching toward miniaturized, skin conformable, flexible, and low-power wearables. Albeit small in size and reusable, these devices still use batteries and suffer from limitations such as frequent charging and replacement. Thus, such batteries are unsuitable for harsh conditions and resource-challenged situations. Further, rechargeable batteries also pose a risk of explosion and other safe concerns after periods of extreme charging and necessitate the development of safer, little-to-no maintenance, and cost-effective power source alternatives.

One strategy for battery-free efficient systems is through near-field communications systems. However, they are only applicable for short distances. These drawbacks have paved the way for unconventional, sustainable, and facile power sources, such as solar, wind, and tidal power, to power up the devices for continuous longitudinal health monitoring. Several innovative approaches for harnessing energy from the biofluids, human kinematic motion and mechanical forces, vibrational energy, and the hybrid of the multitude to power future wireless wearable electronics can be found in the literature. Harnessing energy from ambient sources such as the sun, heat sources, vibration, and kinematic mechanical motion have been proposed as a viable option for energizing next-generation sensors and wearable medical electronic devices (Figure 4). The key advantage of these power sources is that they are

simple and ubiquitous, such that their energy could be harvested anytime anywhere, and, hence, are suitable for deployment in resource-challenged settings where access to electricity is tricky. In addition, there are challenges with the various signal transduction modes to sense bio-analytes from bodily fluids. Some of the most common include electrochemical, optical, electrical, or mechanical transduction modes. However common issues such as the gap between signal transduction to signal processing and thereafter signal transmission via wireless channels causes latency, data corruption, and lifetime usability issues. For example, noise in the channel can result in false positive signals leading to misdiagnosis of the condition of the person. An additional challenge that must be addressed for a sensor's usability is its form factor, which includes the sensor's size, shape, and the conformability or bendability to match the user's skin. With a small form factor, the sensor design must ensure that the biofluid wicking mechanism allows efficient transport to the sensor surface. In addition to the even distribution of a biofluid on the sensor surface, issues such as calibrating the active biorecognition element quantities and reliable detection of multiple analytes become important for real-world applicability. There is a tremendous need in this regard to develop failsafe mechanisms to address aforesaid issues and reduce the risk in field settings. This section discusses the major self-powering schemes that can be incorporated in health sensors, in resource-limited and remote settings, toward continuous and fully autonomous real-time tracking of digital and physical biomarkers for a wholistic visualization of the underlying physiological and its subtle changes.

4.1. Triboelectric Nanogenerators. Triboelectric nanogenerators (TENGs) are a new class of energy harvesting systems which transduce mechanical energy from ambient sources to electricity by the principles of contact electrification and electrostatic induction.⁴² These are suitable candidates for powering biosensors as they can harness the mechanical energy generated by bodily motions of routine activity.⁴³ These nanogenerators operate based on Maxwell's displacement current^{44,45} and have been reported to detect even faint mechanical motions (such as breathing and heart beat) with high sensitivity to generate a reliable electrical output.^{46–48} In their recent review article, the authors discuss the mechanism and types of TENGs in detail.⁴⁹ Unlike their piezoelectric counterparts [(PENGs) piezoelectric nanogenerators], TENGs can be manufactured using a wide variety of materials and can be worn as flexible on-body sensors or woven into smart textiles. This makes them highly suitable for continuous health status monitoring, especially for real-time sweat-based biosensing. Further, these require a simple and low-cost fabrication process which make them suitable for powering wearable medical devices and portable point-of-care health monitoring systems, especially in resource-challenged settings.⁴⁶ Since its invention by Zhong Lin Wang's team,⁵⁰ TENGs have emerged in the healthcare diagnostics space, especially for affordable, self-powered biosensing applications, either for (i) directly sensing biological signals or (ii) acting as a power source for actuating these biosensor systems.⁴⁶ Kaner et al. demonstrated the first fire-retardant triboelectric nanogenerator in the form of a miniaturized motion sensor device that could be embedded in shoes or clothing of people working in extreme temperatures and harsh environments such as firefighters, mine workers, and so forth.⁵¹ A novel eco-friendly lightweight heat-resistant material made from a carbon

aerogel nanocomposite demonstrated improved mechanical properties and was used as a triboelectric material. The TENG was driven by the kinematic movements of the user, and by sensing the difference between the sedentary position and body movements, the sensor determined if the wearer was in danger, especially in remote and perilous settings. The generated power outcome from the device was reported to be enough to power up the motion sensor. Wang et al. demonstrated the technological proof for integrating the TENG on layered clothes toward building a self-powered glucose biosensor.⁵² The TENG was based on the contact–separation mode between a patterned polydimethylsiloxane (PDMS) film and an aluminum foil stuck to clothing. In this work, the authors claim that the developed TENG outputs a signal by harvesting body motion energy sufficient to power a biosensor.

Gong et al. developed a silk-protein-derived, biocompatible, fully degradable, and highly flexible bio-TENG device for self-powered, wearable, and implantable medical health-sensing electronic devices. The authors utilized hollow silver nanofibers to form a breathable, stretchable, biocompatible, and degradable friction electrode which outputs instantaneous peak power density that can drive wearable electronics.⁵³ Dudem et al. created microarchitected silkworm fibroin films and leveraged their high surface roughness and superior ability to lose electrons to develop TENGs. This work was aimed for obtaining stable electrical outputs in harsh and humid environments wherein the silk films were intended for use in harnessing biomechanical activities under unfavorable conditions for real-time feeding of low-power portable biosensors and bioelectronics.⁵⁴

4.2. Piezoelectric Nanogenerators. PENGs harvest energy from mechanical vibrations, muscle contraction, kinematic motion, and so forth. In materials such as zinc oxide, charge separation can be induced as a result of mechanical bending to generate a sufficient potential difference to act as a voltage source. Wang and Song have demonstrated this in the format of ZnO nanowire arrays which could power on-body sensors when embedded inside clothing.⁵⁵ The rapid limb movements in several settings could allow enough power generation for activating biosensors. The major advantages of piezoelectric nanogenerators include the availability of numerous piezoelectric materials and composites, harvesting energy from low-intensity, low-frequency, and a wide range of mechanical movements, the ability to array the nanogenerators over a large surface area, and the ability to achieve scalable films which could be fabricated through mass manufacturing methods such as roll-to-roll printing.

Ultrasound powering using piezoelectric materials such as lead zirconate titanate (PZT) has extensively been in use to power implantable devices and sensors deep within the human body. They operate by transducing the ultrasound energy into an alternating current which is rectified by an on-board chip to a direct current (DC) voltage output to power the biosensors. The form factor of such implants can be greatly reduced to fit within catheters, to be attached inside capsules for controlled drug release, and also to activate biosensors. Zhang et al. demonstrated the possibilities of using a thin membrane poly(vinylidene difluoride) (PVDF) to scavenge the biomechanical energy from the kinematic movement of the pulsating porcine aorta, generating an output electric potential of nearly 1.5 V and an electric current of 300 nA.⁵⁶ Zhao and You describes a multilayer PVDF film-based energy harvester producing power

output from human locomotion that could be embedded within the shoes for continuous powering.⁵⁷ The ability to develop film-based PENGs that can be embedded within the socks can enable monitoring of sweat glucose, cortisol, and several other metabolites from under the feet in a continuous manner. Being the dynamic energy harvesting system, a low frequency and low intensity of mechanical force could be converted to electrical output for all ranges of kinematic motion using piezoelectric materials. Piezoelectric nanogenerators have potential applications such as rechargeable power sources for continuous sensing in body area sensor networks for civilian, maternal, and geriatric populations.

4.3. Solar Photovoltaics. In principle, the clean and renewable solar energy has immense potential to act as a local power source for wearables and biosensors. Particularly in applications that involve smart clothing or body armor for the military, it is attractive to have sunlight power the on-body sensor networks for physiological monitoring. Recent advances in soft, bio-integrated device technologies, miniaturization of solar panels and embedment of photovoltaic fabric materials can bypass the need for bulky batteries and enable a new generation of ultrathin, ultraminiaturized thin-film solar batteries directly sewn onto the fabric or placed on the skin as inks. Zhao et al. demonstrated a smartwatch that is completely self-powered for longitudinal monitoring of glucose levels in the sweat.⁵⁸ The smart watch is charged with flexible amorphous silicon (a-Si) photovoltaic cells, and a Zn–MnO₂ battery is used as an intermediate energy storage source. A simple electrochemical sensor for sweat glucose monitoring is integrated with the printed circuit board and electronic ink (E-ink) display to facilitate direct and real-time monitoring. The harvested energy can be stored in the batteries to power the functions of the integrated system that includes real-time digital signal processing and data visualization. Such fully integrated systems provide convenience and safety and are reliable for real-time glucose level monitoring in all populations and environments. People who work in extreme conditions and may be exposed to occupational hazards not commonly seen in other communities viz. army soldiers, navy seals, astronauts, firefighters, and so forth would significantly benefit from remote monitoring systems. The health status of the body in such extreme conditions must be assessed with accuracy and reliability to enable quick and timely decisions. Carrying and situating huge medical equipment for remote assessment of the health status of such individuals is cumbersome and not possible everywhere. It is paramount to have personalized health monitoring that could serve as a predictive measure for disease diagnosis and field-induced fatigue or performance decline. Unconventional energy harvesters address the key gap in the energy management of these devices. Self-powered sensors show promising results not only in the sensing aspect but also in the efficient power management system.

5. CRITICAL ANALYSIS AND FUTURE OUTLOOK

The novel emerging field of wearable biosensing devices has revolutionized the way healthcare is delivered by allowing extended monitoring of biomarkers in an arena of fields from aging and newborn populations to military personnel in order to better evaluate their body status in emergency and hazardous situations. In this mini review, we have surveyed the next-generation biosensors that can continuously monitor metabolites for disease diagnosis and self-health management toward the development of future clinical grade wearables.

Herein, the main focus has been given to biosensors that detect metabolites in a non-invasive manner due to the ease of fluid accessibility, unobtrusive real-time monitoring of biomarkers, and their ability to be embedded into daily used wearables. However, as wearable sensors are in a stage of infancy, the major technical gaps in wearable sensing that need to be addressed are low sample volumes, low biomarker concentrations, mechanical resilience, biocompatibility, sensor stability, and fouling.⁵⁹ Biomarkers are physiological cues that give an overall view of the underlying health status qualitatively or quantitatively, thus redefining diagnosis and supporting medical professionals in their treatment approaches. Non-invasive wearables are integrated into smart clothing, watches, patches, bands, and diapers for chronic disease monitoring, critical health vital management, contractions monitoring, nausea management, and inflammation monitoring through body fluid-based metabolite analysis in morbid and mobility-constrained population encompassing old-aged people, infants, and pregnant mothers. Wearable sensors are increasingly being developed in temporary patch or tattoo forms to detect and track core body temperature, blood pressure, electrical heart and muscle activity, hydration levels, and a host of other biomarkers in hostile military settings for soldier wellness monitoring. In resource-challenged settings where access to electricity is limited, harvesting energy from natural resources, vibration, and human motion is the future energy source for powering future wearable devices. Highly attractive research has gone into the development of efficient battery-free systems such as nanogenerators, biofuel cells, and photovoltaic cells for self-powering health and disease monitoring devices in defense and pandemic environments. The current advances in wearable research will help migrate lab prototypes into futuristic commercial devices for seamless health monitoring in physically demanding tasks and in day-to-day lives.

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