Viewpoint

A Six-Step Framework on Biomedical Signal Analysis for Tackling Noncommunicable Diseases: Current and Future Perspectives

Mohamed Elgendi[1], BSc (Hons), ME, PhD; Newton Howard[2], MSc, MD, HDR, DPhil, PhD; Nigel Lovell[3], BE (Hons), FTSE, PhD; Andrzej Cichocki[4], BE, MSc (Hons), Dr Sc, PhD; Matt Brearley[5], BHMS(Hons), BBus, PhD; Derek Abbott[6], BSc (Hons), PhD; Ian Adatia[7], MBChB, FRCP

[1]Department of Obstetrics & Gynecology, University of British Columbia, Vancouver, BC, Canada

[2]Nuffield Department of Surgical Sciences, University of Oxford, Oxford, United Kingdom

[3]Graduate School of Biomedical Engineering, University of New South Wales, Sydney, Australia

[4]Laboratory for Advanced Brain Signal Processing, RIKEN Brain Science Institute, Wako-shi, Japan

[5]National Critical Care and Trauma Response Centre, Darwin, Australia

[6]School of Electrical & Electronic Engineering, University of Adelaide, Adelaide, Australia

[7]Stollery Children's Hospital, University of Alberta, Edmonton, AB, Canada

Corresponding Author:
Mohamed Elgendi, BSc (Hons), ME, PhD
Department of Obstetrics & Gynecology
University of British Columbia
BC Children's Hospital, C424
4480 Oak Street
Vancouver, BC, V6H 3N1
Canada
Phone: 1 604 600 4139
Fax: 1 604 875 2723
Email: moe.elgendi@gmail.com

Abstract

Low- and middle-income countries (LMICs) continue to face major challenges in providing high-quality and universally accessible health care. Researchers, policy makers, donors, and program implementers consistently strive to develop and provide innovative approaches to eliminate geographical and financial barriers to health care access. Recently, interest has increased in using mobile health (mHealth) as a potential solution to overcome barriers to improving health care in LMICs. Moreover, with use increasing and cost decreasing for mobile phones and Internet, mHealth solutions are becoming considerably more promising and efficient. As part of mHealth solutions, biomedical signals collection and processing may play a major role in improving global health care. Information extracted from biomedical signals might increase diagnostic precision while augmenting the robustness of health care workers' clinical decision making. This paper presents a high-level framework using biomedical signal processing (BSP) for tackling diagnosis of noncommunicable diseases, especially in LMICs. Researchers can consider each of these elements during the research and design of BSP-based devices, enabling them to elevate their work to a level that extends beyond the scope of a particular application and use. This paper includes technical examples to emphasize the applicability of the proposed framework, which is relevant to a wide variety of stakeholders, including researchers, policy makers, clinicians, computer scientists, and engineers.

Introduction

According to 2012 World Health Organization (WHO) estimates, noncommunicable diseases (NCDs) contributed to 38 million deaths globally, accounting for 68% of 56 million total deaths. Meanwhile, nearly 80% of NCD deaths (28 million) occurred in low- and middle-income countries (LMICs) [1]. The leading causes of NCD deaths in 2012 were cardiovascular diseases (17.5 million deaths, or 46% of all NCD deaths),

cancers (8.2 million, or 22% of all NCD deaths), and respiratory diseases, including asthma and chronic obstructive pulmonary disease (4.0 million) [1]. NCDs also include mental and neurological disorders, such as Alzheimer's disease and dementia. By 2050, the WHO expects that 115 million people will have Alzheimer's disease [1].

Biomedical signals always accompany the physiological processes of the human body altered by NCDs, and these signals can reflect the nature and degree of the change. Subjects with NCDs present physiological parameters that differ from those of healthy subjects. If we can analyze these signals and detect their morphologies, we may be able to predict, prevent, and treat NCDs at earlier stages. With recent advances in sensors, machine learning, and mobile technologies, biomedical signals offer practical solutions to tackle NCDs, especially in LMICs.

Biomedical signal analysis represents a significant visualization and interpretation method for detecting, storing, transmitting, analyzing, and displaying valuable information, thus allowing scientists and physicians to obtain quantitative measurements to support scientific hypotheses and medical diagnoses. Various approaches have been and are being applied across multiple scientific disciplines as well as in the health care industry. Interest is increasing in using mobile health (mHealth) to overcome barriers of access to appropriate health care globally (especially in LMICs) and to increase diagnostic accuracy [2,3].

Ultimately, researchers seek to extract meaningful data that can be used to create biomedical signal processing (BSP)-based point-of-care (POC) technologies and to assist in the prediction and diagnosis of diseases. In turn, this knowledge would support health care practitioners and researchers in developing and instituting therapies earlier in the course of disease when they may be most effective. However, scalability and affordability are important factors when it comes to scientific research and medical diagnoses. Without addressing these two considerations, valuable learning and applications may become impossible and impractical.

In the proposed BSP-based framework, we discuss six essential steps that guide scientists from scientific hypotheses and analysis to practical application: simplicity, mining, connecting, reliability, affordability, and scalability (SMCRAS). When considering each of these elements during the research and design of BSP-based devices, researchers are able to extend their work beyond the scope of local application and use.

To our knowledge, this is the first paper of its kind to elucidate a framework for BSP-based POC devices. In 2014, researchers recently began to propose and discuss the idea that biomedical engineering can improve global health [2]. In 2015, researchers also suggested a framework for POC devices, without BSP, based only on affordability [3], which is one element of our framework.

Specific technical examples will be discussed using four recent BSP-based case studies in order to illustrate real-world applications for the proposed framework, including how it will aid in the development of global health care BSP-based technologies.

Overview

The nature of a biomedical signal is like any other: it is information bearing. Signals play a major role in our daily communication whether they be verbal, social, mental, or physical. Measuring a biomedical signal from a certain body part reveals the state of that specific part as well as the whole body. Like any communication system, there is a sender, receiver, and medium through which the signal is sent. With current technological advances (science, computers, etc), we can use algorithms to detect abnormalities and understand the information from the sender (ie, body part or organ). It is becoming increasingly common to use mobile phones to log biomedical signals, thus assisting physicians and health care practitioners in their decisions related to disease prediction, diagnosis, and treatment.

Nonetheless, there remain many challenges in collecting data from mobile devices, such as inconsistent measurement, unreliable signal quality and training, limited computational resources, finite power, time constraints for clinical staff, varying user interface designs, and uncontrolled environments. The guiding principles proposed in this paper address these challenges and create a framework for developing BSP algorithms that can be used for disease classification and prediction. We propose six main objectives: (1) aim for simplicity, (2) mine through noise based on information detection theory, (3) reveal hidden connections, (4) assess robustness, (5) plan for scalability, and (6) strive for affordability.

Simplicity

Einstein famously said, "Any intelligent fool can make things bigger and more complex. It takes a touch of genius and a lot of courage to move in the opposite direction." Simplicity is particularly effective when it comes to mobile computation. Simple methods that achieve high detection accuracy require less storage and power while remaining more suitable for wireless and online processing [4]. For example, Figure 1 shows two algorithms that both detect QRS complexes in electrocardiogram (ECG) signals [5,6]. One algorithm is simpler than the other, and it requires fewer execution steps, thus lowering the complexity.

BSP-based POC devices collect biomedical signals wirelessly (or wired) and send them to a central monitoring station using Global System for Mobile communications (GSM) or Internet for further analysis [7,8]. In such cases, some analyses are executed locally on the POC device before transmission; however, this process is not always recommended as the transmission can consume more power than the ECG analysis itself [9].

Undoubtedly, it is essential that any algorithm used for real-time analysis retain simplicity so long as this simplicity does not decrease accuracy significantly. The simpler the algorithm, the faster it will be in processing large-scaled biomedical signals; it also will consume less power in battery-operated POC devices [4]. For example, Figure 1 shows that the simple method is more sensitive and specific while outperforming the complex

approach. The data reliability are discussed in detail in the "Reliability" section.

Note that there can be a trade-off between algorithm simplicity and accuracy. At times, a more complex algorithm can achieve higher accuracy than a simple algorithm. However, the aim is to develop a simpler algorithm that can achieve the same or even higher accuracy than the complex algorithm. There is currently an unmet need to develop relatively simple but reliable and accurate algorithms for tackling large data [10]. In terms of time, application, and long-term use, it will be beneficial to investigate NCDs, global health care issues, and BSP-based POC devices using simple but efficient algorithms.

Figure 1. Comparison between simple and complex QRS detectors for ECG signal analysis (SE=sensitivity; +P=positive predicitivity; simple QRS detector refers to Elgendi's algorithm [5]; complex QRS detector refers to Pan-Tompkins algorithm [6]). Here, N/A stands for Not Applicable.

| Step	Simple QRS Detector [5]	Complex QRS Detector [6]
Resampling	N/A	Resample ECG to 200 Hz
Mean Subtraction	N/A	$ECG = ECG - mean(ECG)$
Frequency Band	$x = bandpass(ECG, 8\text{--}20\ Hz)$	$x = bandpass(ECG, 5\text{--}15\ Hz)$
Differentiation	N/A	$q[n] = \frac{1}{8}(-x[n-2] - 2x[n-1]$ $+2x[n+1] + x[n+2])$
Squaring	$y[n] = (x[n])^2$	$y[n] = (q[n])^2$
Integration	$MA_{QRS}[n] = \frac{1}{W_1}(y[n-(W_1-1)/2] + \ldots$ $+y[n+(W_1-1)/2]),$ where $W_1 = 97$ ms	$MA[n] = \frac{1}{W}(y[n-(W-1)] + y[n] + \ldots$ $+y[n-(W-2)] + \cdots + y[n]),$ where $W = 150$ ms
Thresholds	$MA_{beat}[n] = \frac{1}{W_2}(y[n-(W_2-1)/2] + \ldots$ $+y[n+(W_2-1)/2]),$ where $W_2 = 611$ ms $THR_1 = MA_{beat} + \alpha$ $THR_2 = W_1$	$SPKI = 0.125\ PEAKI + 0.875\ SPKI$ $NPKI = 0.125\ PEAKI + 0.875\ NPKI$ $THR\ I1 = NPKI + 0.25\ (SPKI - NPKI)$ $THR\ I2 = 0.5\ THRESHOLD\ I1$ $SPKI = 0.25\ PEAKI + 0.75\ SPKI$ $SPKF = 0.125\ PEAKF + 0.875\ SPKF$ $NPKF = 0.125\ PEAKF + 0.875\ NPKF$ $THR\ F1 = NPKF + 0.25\ (SPKF - NPKF)$ $THR\ F2 = 0.5\ THR\ F1$ $SPKF = 0.25\ PEAKF + 0.75\ SPKF$
Adjusting thresholds	N/A	$THR\ I1 \leftarrow 0.5\ THR\ I1$ $THR\ F1 \leftarrow 0.5\ THR\ F1$ $RR_{AVG1} = 0.125\ (RR_{n-7} + RR_{n-6} + \cdots + RR_n)$ $RR_{AVG2} = 0.125\ (RR'_{n-7} + RR'_{n-6} + \cdots + RR'_n)$ $RR_{LowLimit} = 0.92\ (RR_{AVG1})$ $RR_{HighLimit} = 1.16\ (RR_{AVG2})$ $RR_{MissedLimit} = 1.66\ (RR_{AVG2})$ $RR_{AVG2} \leftarrow RR_{AVG1}$
	SE = 99.78, +P = 99.87	SE = 90.95, +P = 99.95

Mining

The extraction of the most informative patterns in a given dataset is commonly referred to using different terms depending on the study field (eg, data mining is used as information/knowledge extraction, information/knowledge discovery, information/knowledge harvesting, or data analysis/processing) [11]. "Data mining" is typically the term of preference used by biomedical engineers and computer scientists. In this paper, we refer to the "mining" step as a combination of filtering and feature extraction phases.

When mining noisy biomedical signals, it can be tempting to give up before obtaining an informative waveform. Many studies in the literature used filters to clean the signal on the waveform's account; in other words, we need to filter the signal with techniques that help us preserve the main waveforms of the processed signal, which hold valuable data and information.

When it comes to mining data collected from BSP-based POC devices, the data are very noisy (as mentioned in the Overview section). The accurate detection of the main waveforms within the biomedical signal will increase the accuracy of disease diagnosis and prediction. Figure 2 demonstrates that a mining algorithm was able to successfully demarcate the first (S1) and second (S2) heart sounds, outperforming other mining algorithms (compare [b-e] in Figure 2). For example, if we apply fixed thresholds to the output of the mining algorithms shown in Figure 2, the S1 events would not be detected as they have lower amplitudes compared to S2 events, and therefore, the overall detection rate will decrease [11].

It is critical to provide health care workers with feedback on the quality of the data collected in order to allow a real-time recollection of biomedical signals if needed. Therefore, signal quality assessment algorithms are necessary to distinguish between signals that are clinically acceptable and those that are uninformative. The user can be informed in real time accordingly.

Figure 2. Example of mining heart sounds: (a) Original heart sound signal from a subject with mean pulmonary arterial pressure of 20 mmHg, (b) Mining using second-order Shannon energy of D5 wavelet, (c) Mining using 2nd-order Shannon energy of D6 wavelet, (d) Mining using 3rd-order Shannon energy, (e) Mining using wavelet approximation A6, (f) Mining using two moving averages, black and purple dotted lines, to generate blocks of interest. Here, S1 refers to the first heart sound while S2 refers to the second heart sound.

XSL•FO

RenderX
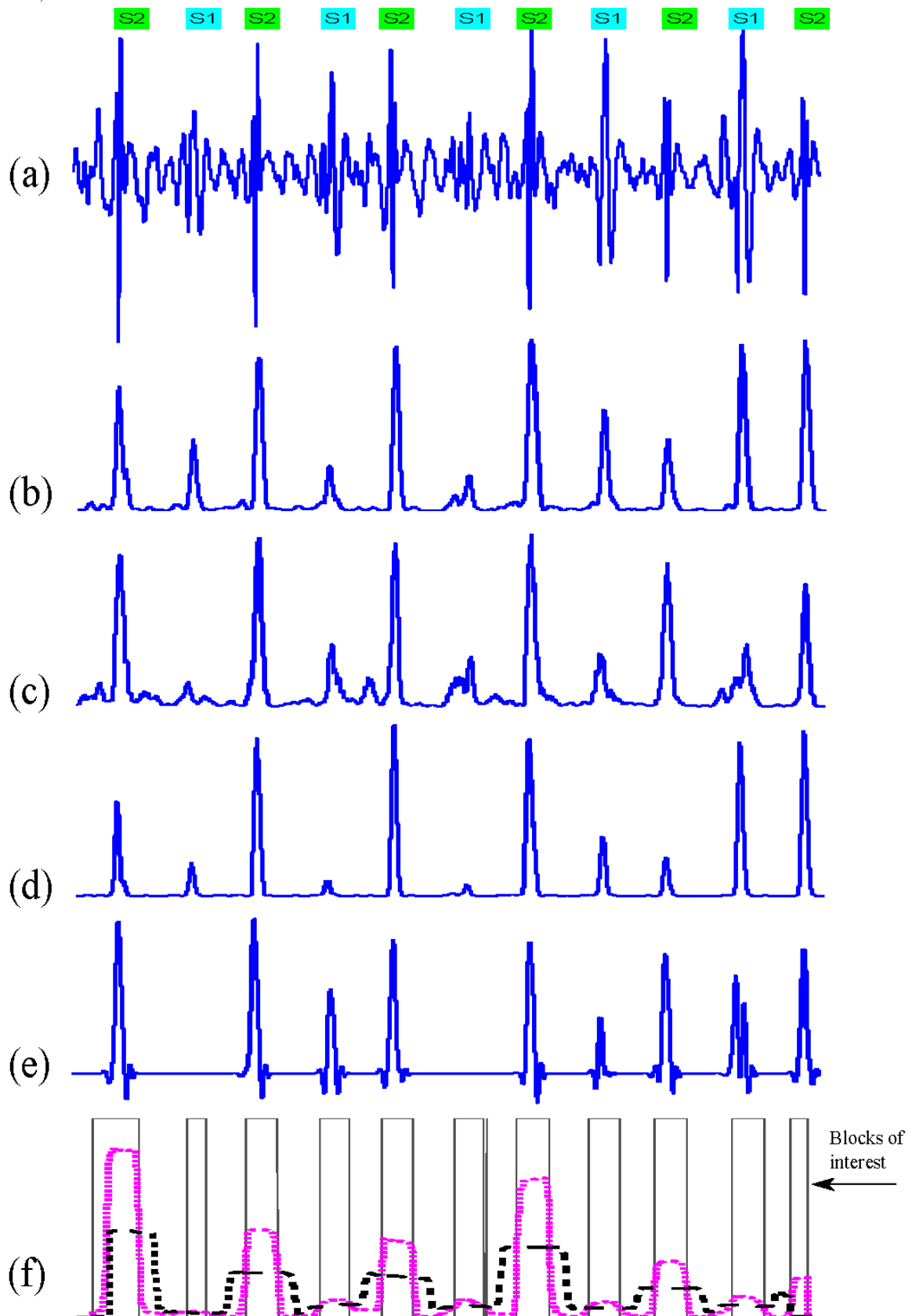
Connecting

To reveal relationships that would otherwise remain hidden, it is imperative to extract multiple features from biomedical signals and find correlations/causalities between these features for abnormality (disease of interest). For example, Figure 3 shows the extraction of relative power features (f1, f2, f3) in three nonoverlapping frequency bands (4-10 Hz, 10-20 Hz, and 20-30 Hz) in healthy and subjects with Alzheimer's disease (AD) [12,13]. It is clear that the relative power of the first frequency band, 4-10 Hz, is associated with AD compared to the 10-20 Hz and 20-30 Hz bands [12,13]. The AD subject had a higher relative power in the 4-10 Hz, while the healthy subject had a lower relative power over the same frequency band. Figure 3

uses topoplots of electroencephalography (EEG) signals. These topoplots are generated using the PyMVPA free software [14].

There are several important features to investigate first when analyzing the statistical and deterministic properties of biomedical signals: kurtosis, skewness, energy, entropy, line length/curve length, minima/maxima, activity (1st Hjorth parameter), mobility (2nd Hjorth parameter), complexity (3rd Hjorth parameter), root mean square amplitude, zero crossings, and relative power.

The features extracted from biomedical signals and correlated with an NCD are used as biomarkers. Once the biomarkers are tested rigorously, we can either train practitioners to identify them, or we can develop machine-learning algorithms to identify and report them automatically to the user.

Figure 3. Connecting hidden relationship between frequency bands and early diagnosis of patients with Alzheimer's: (a) Topoplot of EEG signals in a healthy subject, (b) Topoplot of EEG signals in a patient with Alzheimer's (color scale from blue to red represents the relative EEG power value from 0-1 respectively).
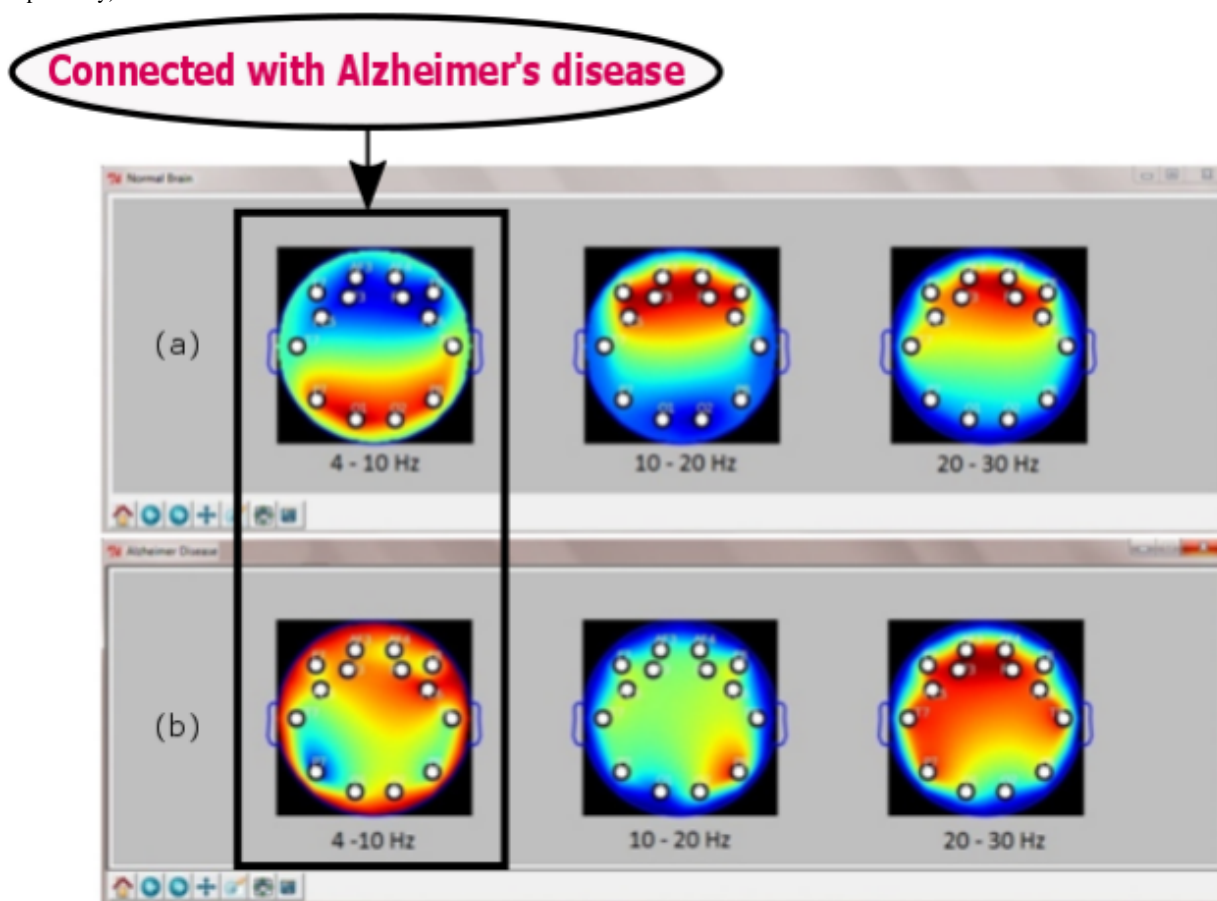
Reliability

As said, "Simplicity is a prerequisite for reliability." Thus, the simplicity step cannot be achieved unless reliability is also achieved. Simplicity goes hand-in-hand with reliability and must be established in conjunction with simplicity.

After applying the *simplicity, mining,* and *connecting* steps, the accuracy of the developed solution needs to be verified. This assessment is needed to check if the algorithm/device meets current international standards. Moreover, it is important that the BSP-based POC solution performs as well as the current diagnostic tools, if not even better.

The reliability of a BSP-based algorithm is mainly assessed using four distinct results: true positives, true negatives, false positives, and false negatives. Based on these four results, several statistical measures can be used to assess reliability of simple algorithms, such as sensitivity, specificity, and positive predictivity.

Quality control needs to be implemented in order to detect and prevent errors before deployment of the BSP-based POC device. It is worthy to note that BSP-based sensors typically undergo quality control and risk management reviews during the manufacturing process. Beyond this, device quality needs to

also be assessed by the initial health care professional using the device to ensure it is appropriate for the intended purpose, before mass usage. Moreover, the systematic management of the device quality and reliability needs to be maintained through institution policies and procedures, user training, evaluation of these procedures and policies, and an overall evaluation of these components on a regular basis to ensure and maintain reliability and quality.

Affordability

The difference in health care quality between high-income and low-income countries primarily results from the lack of trained health care professionals, poor infrastructure, limited physical accessibility to health care, and the relative cost of health care delivery. As mobile broadband network penetration has reached 89% in LMICs, the use of mobile devices has increased to collect biomedical signals to address some of the NCD challenges. This increase allows for the easy conversion of mobile phones into BSP-based POC devices. Sensors, which are low-cost items, can be hooked into these mobile devices to collect the needed biomedical signals.

Affordability also applies to high-income developed countries because they are increasingly facing shortages of funds and health care professionals.

Once an affordable BSP-based POC device has been implemented, it is important to continue exploring alternative affordable methods to ensure utilization of the most cost-efficient option. For example, instead of using ECG to detect heart rate variability, we could use photoplethysmogram (PPG) signals. We also can create an inexpensive solution, such as a digital stethoscope.

The use of BSP-based POC devices, including wearable sensors, as diagnostic tool is a feasible and affordable way to reach larger populations for improved health care outcomes. In developed countries, BSP-based POC devices are already being used by affluent populations (eg, heart rate monitoring using wearable watches and mobile phones). Most of the current apps focus on heart rate monitoring and number of steps walked in a day; we can predict that the same technology can be modified and used to tackle more serious problems, such as diagnosis of NCDs. In rural/remote areas and developing countries, there is a paradigm shift towards using devices related to affordable global health care for both preventative, diagnostic, and treatment purposes using smart and mobile technology. The proposed framework therefore blends well with this paradigm shift and seeks to help address current needs in rural/remote areas and in developing and developed countries with vulnerable populations [3].

Scalability

It is intuitive to think that simplicity ensures scalability for both algorithm development and BSP-based POC device use (ie, simpler algorithms require less processing time and simpler devices are more likely to be used by nonspecialized individuals; therefore, scalability is a certainty). This assumption is partially correct and accounts for only part of the meaning of scalability here. For example, simple algorithms/devices can be patient-specific or environment-specific (ie, the simplicity of

the algorithm can be applied to a specific patient subset in a specific environment). Scalability shifts disease diagnosis to the community level by developing simpler algorithms/devices that can be used outside a formal clinic setting and on different patient subsets.

Scalability ties the previous four elements of the framework together for the purpose of mass implementation of technology into the real world. Moreover, scalability must include a user-friendly approach with clear directive instructions. In developing algorithms/solutions, it is essential that they have the capacity to be used with different applications and devices. For instance, we need to provide algorithms that can work with different sampling frequencies and not require an adjustment for a particular sampling frequency or parameter and condition. When reaching this final step of the framework, we begin to reap the benefits of knowledge sharing, having reached the point where we can impact global health outcomes meaningfully.

Successful scalability occurs when users with limited experience/knowledge are able to use the provided BSP-based mHealth technologies successfully in real time with minimal complications and in multiple environments (eg, in a clinical setting, offsite in remote areas, in a patient's home community, on-the-go in areas of need).

Four Noncommunicable Disease Case Studies Related to Biomedical Signal Processing

Case I: Detection of Pulmonary Arterial Hypertension Using Heart Sounds

Pulmonary Arterial Hypertension (PAH) is progressive and fatal [15]. Complicating other conditions, it is estimated to affect 100 million people worldwide [16,17]. PAH is difficult to diagnose because symptoms appear late in the disease, and signs in clinical examination are easily missed. Despite the remarkable advances in cardiac catheterization, which is the gold standard for measuring pulmonary artery pressure [18], there is a pressing need for alternative techniques to diagnose pulmonary hypertension noninvasively. Traditional stethoscope-based auscultation remains a valuable noninvasive tool for diagnosing PAH; however, physicians require years of training to become adept at diagnosing PAH. Auscultation lacks hemodynamic accuracy and is insufficient for monitoring the effects of therapy or indicating an abnormality. Although the clinical significance of heart sounds has been investigated thoroughly, there remains a lack of research focusing on the automatic detection of PAH in heart sounds. Prior to developing any automated algorithm, it is important to investigate the optimal features for detecting PAH. However, there have been few attempts to extract features from the heart sound in PAH subjects [19-22]. One complete normal heart sound cycle primarily consists of the first heart sound (S1) followed by the second heart sound (S2). The interval between the S1 and S2 is the systole, and the interval between the S2 and S1 is the diastole. The components of the S1 are M1 and T1 due to the closure of the mitral and tricuspid valves [23,24]. The second sound (S2) has two components (A2 and P2) due to the closure of the aortic and pulmonary valves

[23,24]. It is well known that the A2-P2 interval increases during inspiration in PAH; meanwhile, during expiration, this interval decreases [24,25]. However, measuring the A2-P2 interval is not easy because of their relatively short duration and their significant overlap with each other in the time domain [22]. The relative intensities of A2 and P2 in PAH have been well studied [19,26]; specifically, Sutton et al [19] found that the A2 was less than the P2 in all PAH subjects. However, this feature has not been validated statistically for developing algorithms to detect PAH.

Simplicity

Catheterization is the gold standard for diagnosing PAH; however, it is a very complex, risky, and costly operation, requiring a highly expert clinician. The diagnosis process can be simplified by using the digital stethoscope (noninvasive method) instead of catheterization (invasive method).

In the past, clinicians have also used standard stethoscopes to diagnose PAH; however, this method faces limitations in detecting PAH. With current advances in science and technology, we now have digital stethoscopes that can be used to detect PAH by using machine-learning algorithms that support clinicians in their decision making.

Mining

It is necessary to filter heart sounds while preserving the waveforms of the S1 and S2 heart sounds [11]. In the literature, wavelet-based Shannon energy was the most-used method for emphasizing the S1 and S2 [11]. This method emphasizes medium-intensity signals and attenuates the effect of low-energy signals much more than that of high-intensity signals. Liang et al [27] first recommended the use of Shannon energy after comparing its performance to the Shannon entropy, absolute value, and energy on heart sounds.

Kumar et al [28] tried to improve Method I by introducing multiple wavelet coefficients and a duration-based threshold. Wang et al [29] found that Method I was sensitive to noise and heart murmurs, which easily leads to false segmentation. Therefore, they investigated different wavelet features and introduced a higher-order Shannon energy, specifically third order, to emphasize the S1 and S2 and to suppress the noise and murmurs.

Another mining method that can be used is based on the sequential wavelet analysis introduced by Zhong and Scalzo [30]. They developed algorithms based on the Daubechies db5 wavelet, not the db6 used in Methods I, II, and III.

Connecting

Features extracted from heart sounds, such as relative power and sinusoids, have been investigated recently, and the literature has reported on the correlations between them and the detection of PAH [31,32].

Reliability

The algorithm in [31] used the relative power and achieved an SE of 79% and SP of 77% over 27 subjects (12 males) with a median age of 7 years (range 3 months-19 years) undergoing simultaneous cardiac catheterization. Thirteen subjects had a mean pulmonary artery pressure (mPAp) <25 mmHg (range 8-24 mmHg). Fourteen subjects had mPAp ≥25 mmHg (range 25-97 mmHg). The results were acceptable.

The algorithm in [32] used the entropy of the first sinusoid formant and achieved sensitivity of 93% and specificity of 92% over the same data used in [31]. The results of [32] were more reliable than the results in [31].

Note, the data in [31,32] were collected in clinical settings and analyzed offline on a laptop computer, not a mobile phone. Having said that, these two studies can be considered as proof-of-concept studies for a BSP-based POC implementation.

Affordability

Digital stethoscopes can be quite expensive, costing at least US $450 per unit in developed countries, and the cost is even higher in LMICs. Making it even more costly is the additional expense of a computer to analyze the heart sounds recorded by the digital stethoscope.

Locally made digital stethoscopes are an inexpensive alternative that are manufactured with available parts. Designing an inexpensive digital stethoscope consists of three components. The first component is the chest piece, which is placed on the skin to capture the heart sounds. The second component is the electret microphone, which records the heart sounds captured by the chest piece. The third component is the transmitter that sends the recorded heart sounds to a device where heart sounds can be visualized and played back for diagnosis. The following are three examples of inexpensive digital stethoscopes:

1. Hands-free kit, eggcup, and rubber O-ring. In 2010, Kuan [33] developed an inexpensive digital stethoscope that can be made for a maximum of US $40 in low volumes. The first component is a combination of a rubber gasket (US $1), a soup ladle (US $1), a plastic folder (US $1), and a hand towel (US $1). The second and third components (the electret microphone and the transmitter) are a hands-free headset (ranging from US $20-$35 per device), which captures the heart sounds and then transmits them via the headset cable to the mobile phone.

2. Mobile stethoscope. Fletcher and Chamberlain [34] developed a simple mobile stethoscope in 2015 that can be made for a maximum of US $50 in low volumes. The first component of this system is the chest piece of the traditional nondigital stethoscope (US $22). The second and third components (the electret microphone and the transmitter) are a hands-free headset (US$27) that captures and transmits heart sounds to a mobile phone.

3. Microphone with wireless kit. In 2012, Sangasoongsong et al [35] developed a wireless sensor platform that can be made for US $13 in large volumes. The first and second components of this digital stethoscope are the phonocardiography sensor and its wire (US $4). About 70% of the unit cost comes from the third component, which consists of a microprocessor (US $5) and a Zigbee transceiver chip (US $4).

Creating alternatives to the expensive digital stethoscope to capture heart sounds is a plausible and sustainable solution. Moreover, the development of these inexpensive digital

XSL•FO

RenderX

stethoscopes utilizes already-existing parts for the devices, making them easily accessible and relatively more affordable.

Scalability

The digital stethoscope is widely used by clinicians all over the globe. One of the main advantages of the digital stethoscope is that it can be used inside and outside any clinical setting.

In developing a robust algorithm to detect PAH that accompanies the digital stethoscope, there needs to be a graphical user interface that allows clinicians with varying backgrounds and knowledge levels to easily interact with it.

Case II: Detection of Heat Stress in a Changing Climate

According to the Intergovernmental Panel on Climatic Change, accelerated global warming will result from increasing anthropogenic greenhouse gas emissions. Global warming will manifest itself in higher mean ambient temperatures and an increased frequency and intensity of heatwaves [36]. Both factors increase the likelihood of heat stress, defined as the net heat load to which an individual is exposed. Warmer environments limit the gradient for body heat dissipation. Meanwhile, due to the physical nature of their tasks and resultant body heat production, workers in labor-intensive industries are a cohort susceptible to heat stress [37] due to the impact of global warming [38]. Sustained heat stress can result in heat illness, with potential for permanent harm and even death [39]. In this regard, worker heat illness is approximately 4-7 times more likely during heatwave periods [40], and worker injury claims are positively related to ambient temperature [41].

Given the heat-stress risk profile of labor-intensive workers, screening for heat tolerance [42] and physiological monitoring during work shifts could be part of the mitigation strategy [37]. The literature identifies two primary physiological heat stress indices during physical activity: body core temperature (BCT) and heart rate (HR). The standard site for BCT assessment is the rectum [43]; however, due to the invasive nature of this measurement, alternative sites have been assessed as BCT surrogates. Despite their ease of measurement, forehead, temporal, oral, aural, and axilla temperature do not provide accurate indices of BCT during physical activity [44]. Therefore, BCT assessment remains problematic in most occupational settings.

Heart rate measurement, on the other hand, is less complex and provides insight into heat stress due to significantly higher HR during both seated rest [45,46] and standardized physical activity in hotter climates [47]. Higher HRs are attributed to the aforementioned narrow body heat dissipation gradient in hotter climates, with the resultant increase in BCT and skin temperature triggering augmented blood flow to the cutaneous circuit in order to permit greater heat dissipation [48]. In turn, stroke volume—the amount of blood pumped by the heart per beat—decreases and requires a compensatory HR increase in an attempt to maintain cardiac output [49]. Higher HRs in the heat also may reflect the perfusion of warmer blood on the sinoatrial node [50]. Part of the HR increase from rest values is achieved through a significant reduction in parasympathetic tone, reflected in heart rate variability (HRV) analysis as reduced

root mean square of the differences of successive differences. Hence, HRV indices have been proposed as objective indicators of heat stress [46]. Application of BCT-based and HRV-based heat stress indices can be problematic owing to the invasiveness of BCT assessment. Meanwhile, calculating HRV typically requires long, recorded electrocardiogram signals. Therefore, there remains a need for a simple, noninvasive, in-the-field method to assess heat stress. Such a method would allow monitoring of workers during their shifts to prevent heat stress symptoms and ultimately, heat-related illnesses and deaths.

Simplicity

Diagnostic tests to predict individuals susceptible to heat stress include assessment of maximal aerobic power and/or heat tolerance in controlled settings [42,51]. These tests require specialized equipment and a controlled climate while inducing high levels of physiological strain. Physiological monitoring of BCT and HRV also can require specialized equipment; they may suffer from invasiveness of measurement and complex analysis, respectively.

Alternatively, PPG signal collection is a simple-to-measure and noninvasive test that can be conducted on a fingertip during scheduled breaks at work. Recent improvements in wearable sensor technology allow for the continuous measurement of PPG for the purpose of measuring HR. Information derived from the PPG signal can be analyzed to provide additional insight into physiological strain, heat stress, and autonomic arousal. While HRV standards of heat stress have yet to be developed, heat stress analysis techniques have been determined [52].

Mining

The bandpass filter is used as an essential mining step that preserves the saliency of the systolic and diastolic waves as well as the dicrotic notch. Researchers have recommended a zero-phase second-order Butterworth filter, with bandpass 0.5-8 Hz, to remove the baseline wander and high frequencies [53].

Recent investigations to detect systolic peaks in PPG signals measured after exercise reflected challenges due to motion artifacts, sweat, and nonstationary effects [53]. Studies have examined several filters and algorithms to analyze the PPG wave contour; however, they continue to lack accuracy and reproducibility [54]. As a result of these challenges, researchers have started to apply the second derivative to emphasize and easily quantify the delicate changes in the PPG contour [55]. For these reasons, a second derivative is used to improve the mining and increase accuracy.

Connecting

There has been a recent attempt to connect PPG features to the effect of heat stress while investigating global warming [52]. We have examined existing PPG features used in the literature to diagnose different diseases, such as the b/a index, the amplitude of the a wave, and the amplitude of the b wave in the acceleration photoplethysmogram (APG). Furthermore, we tested new features to determine the optimal PPG feature for heat stress detection, such as the energy of the aa area, the energy of the ab area, the energy of the ba area, and the slope

of the *ab* segment. In total, we tested 14 time-domain features—seven features extracted from the PPG signals and seven features extracted from the APG signals [52].

Reliability

The algorithm in [52] used the combination of entropy and HRV index and achieved a sensitivity of 95% and positive predictivity of 90.48% on 40 healthy, heat-acclimatized emergency responders (30 males and 10 females) with a median age of 34 years. The participants were normotensive (mean systolic blood pressure of 129.3 mmHg, range 110-165 mmHg) and had no known cardiovascular, neurological, or respiratory disease. The range of systolic blood pressure exceeds the usual normotensive range. The results were considered reliable and more robust against the existing method.

Note, the data in [52] were collected in the in Australia as part of the National Critical Care and Trauma Response Centre project to assess the physiological and perceptual responses of emergency responders to simulated chemical, biological, and radiological incidents in tropical environmental conditions to compare the efficacy of various cooling methods.

The PPG signals were collected in a very noisy setting and were analyzed offline on a laptop computer, not a mobile phone. Given the challenging environment, the work is considered promising for BSP-based POC implementation.

Affordability

Current PPG devices in developing countries are quite costly at around US $300 per unit [56]. An affordable alternative solution is converting a mobile phone into a BSP-based POC device. The comparative cost for a mobile phone in some developing countries is approximately US $15, and the addition of the PPG costs approximately only US $3 more. Clearly, the option of using the mobile phone is very promising in terms of affordability when compared to stand-alone PPG devices.

Scalability

In the developed world, the use of the PPG signal for anesthesia monitoring during surgery has been the standard of care for more than 20 years. The WHO is now leading the Global Pulse Oximetry Project, which aims to make the PPG component available in every operating room in the world [57].

A minimum amount of knowledge is needed to use the device as the PPG probe is very intuitive. The user simply places the clip on the patient's finger to collect the PPG signal. The software will show the PPG signal in real time along with the automatic diagnosis.

Case III: Predict Adverse Outcomes Related to Hypertension and Preeclampsia

Preeclampsia (PE) is a disorder of pregnancy characterized by high blood pressure and proteinuria. It affects approximately 3-8% of all pregnancies worldwide and accounts for 18.5% of maternal deaths each year [58]. Although PE threatens the lives of pregnant women around the world, the burden is disproportionately felt in LMICs, where it is believed that 99% of the estimated 70,000-80,000 annual maternal and 500,000 annual perinatal PE-related deaths occur [59].

Simplicity

To diagnosis preeclampsia, both hypertension and proteinuria must be present [60]. Therefore, there is a need for two items. First, a blood pressure cuff is needed to check if blood pressure is ≥140 mm Hg (systolic), or ≥90 mm Hg (diastolic) after 20 weeks of gestation in a woman with previously normal blood pressure. The second component is a urine test to check if proteinuria is ≥0.3 g of protein in a 24-hour urine collection [60]. These two tests are usually unavailable in developing countries; therefore, there is a need to improve (or replace) current PE diagnosis with a simple method, such as PPG signals.

Oxygen saturation (SpO2) is related to hypertension [61], and therefore, the use of pulse oximeter can be a simpler way to improve the diagnosis/detection of PE and its related complications.

Mining

This mining step is similar to the mining step discussed in Case II.

Connecting

Oxygen saturation (SpO2) is related to hypertension [61]; therefore, we use it to calculate the risk prediction index. The light transmitted from the light-emitting diode (LED) in the PPG probe can be detected on the same side (reflectance mode) or on the other side (transmittance mode) of the tissue by a photodetector. The output from the photodetector is converted into a voltage and then further processed producing PPG [62]. The signal can be divided into a pulsatile (alternating current [ac]) and a relatively constant (direct current [dc]) PPG component. The SpO2 then is calculated using the ratios of the ac and dc components of the red and infrared PPG signals along with a calibration curve [63]. The SpO2 values then are calculated every 10 seconds ac, and the dc PPG amplitudes are determined using the empirically calibrated equation [63,64].

Reliability

Recently, the use of SpO2 has been tested as part of the miniPIERS prediction model [65] in a proof-of-concept study including a cohort of 726 women (118 of whom had adverse pregnancy outcomes) in South Africa and Pakistan. These women were admitted into hospitals with suspected or confirmed PE (ie, with any hypertensive disorder of pregnancy). Interestingly, the preliminary results showed that adding oxygen saturation derived from the PPG signals improved prediction accuracy from 81% to 84% [61].

The PPG signals were collected using a mobile phone with a real-time analysis capability and can be viewed as a real-world practical implementation for BSP-based POC devices.

Affordability

The affordability step is similar to the affordability step discussed in Case II.

Scalability

The scalability step is similar to the scalability step discussed in Case II.

Case IV: Early Detection of Alzheimer's Disease

Alzheimer's disease (AD) is the most common form of dementia, eventually leading to death. AD is one of the most costly diseases worldwide; the health care cost associated with the disease is estimated to have been US $604 billion in 2010 [66,67]. As the world population ages, we truly face a looming global epidemic with AD. Epidemiological studies indicate that the number of AD cases will nearly double every 20 years, to 65.7 million in 2030 and 115.4 million in 2050, affecting 1 in 85 people globally [68]. With this in mind, it becomes clear that AD is a global problem with a dramatic impact on the health of the population. New approaches need to be considered in terms of prevention, diagnosis, and treatment.

Simplicity

Researchers have put forward EEG as a potential low-cost diagnostic tool in the early stages of AD. Compared to other systems like functional magnetic resonance imaging or positron emission tomography, EEG systems are simple, easy to use, and cost efficient.

Until now, most technological solutions addressing AD have focused on the satisfaction of a specific need, such as position tracking, memory and skill enhancement, and daily needs reminders [69,70]. Neural feedback may improve the user's (or patient's) ability to control brain activity, help with the diagnosis of medical conditions, and assist in the rehabilitation of neurological or psychiatric disorders. Several psychological and medical studies have confirmed that neurofeedback activity is enjoyable, stimulating, and potentially healing. Neurofeedback is generated from the EEG signals of AD patients and healthy subjects. The auditory and visual representations of AD EEG differ substantially from healthy EEGs, potentially yielding novel diagnostic tools. Moreover, such alternative representations of AD EEG are natural and intuitive, making them easily accessible to laypeople (AD patients and family members) while providing insight into the abnormal brainwaves associated with AD.

Researchers recently developed a simple neurofeedback methodology that uses real-time collection of EEG signals with a wireless EEG headset, specifically the Emotiv EPOC wireless headset, with a sampling frequency of 128 Hz. The headset has 14 data-collecting electrodes and two reference electrodes. The electrodes are placed at 10-20 locations, AF3/4, F3/4, FC5/6, F7/8, T7/8, P7/8, and O1/2. The BCI2000 software package [71] was used to interface with the Emotiv EPOC wireless headset. The headset transmits encrypted data wirelessly to a laptop computer.

Mining

Low-cost EEG headsets, such as Emotiv (14 electrodes) and OpenBCI (16 electrodes) were originally designed for entertainment purposes (eg, video games) [72]; however, these devices seem to be prone to various artifacts, such as eye blinking, ECG, electromyogram (EMG), body movements, and power sources. These artifacts easily obscure the EEG signal and make analysis difficult. Currently, a study has been proposed to combine the gyroscope with EEG signals to optimally remove artifacts from EEG signals collected using wireless EEG headsets [73].

EEG signals are corrupted by noise and artifacts: 50/60 Hz powerline interference, motion, eye-blinking artifacts, EMG signals from muscles, and artifacts due to changes in the electrode-skin interface [74]. The gamma range (30-100 Hz) has a particularly low signal-to-noise ratio, and researchers exclude it from further analysis. Therefore, the frequency range of investigation is 4-30 Hz [75].

Connecting

The literature has reported a strong relationship between the slowing of EEG and AD. The results presented in [12] demonstrate that relative power, specifically within the 4-10 Hz band, holds discriminative features to detect AD.

Researchers consistently found and confirmed that AD is associated with the slowing of EEG (frequency reduction in the power spectrum density) [12]. There is also a reduced overall synchrony [76] between EEG leads when compared to healthy subjects.

Connecting the relative power features with the classification of AD using sonification is proposed in [13]. The system computes the relative power features (f1, f2, f3) in three nonoverlapping frequency bands (4-10 Hz, 10-20 Hz, and 20-30 Hz).

The EEG sonification system then generates melody notes from the computed values depending on whether the values are above or below a predetermined threshold. To prove the concept, we used notes from only one octave (MIDI Octave -1) with the pentatonic scale (five notes per octave), and the study was limited to only one instrument (acoustic bass). Obviously, it is possible to incorporate additional musical instruments and multiple octaves. However, the extracted sound easily becomes cacophonic and difficult to parse. In the future, there is a need to explore alternative schemes to generate music from EEG relative power and other EEG patterns in the time-frequency domain.

Reliability

As a proof-of-concept study [77], two databases were used. One contained mild cognitive impairment (MCI) and healthy subjects (patient age 71.9, SD 10.2; healthy subject age 71.7, SD 8.3), and the other contained mild AD and healthy subjects (patient age 77.6, SD 10.0; healthy subject age 69.4, SD 11.5). The use of a single feature achieved a detection rate of 78.33% for the MCI dataset and 97.56% for mild AD. When multiple features were used, the detection rate improved. More specifically, 11 features achieved 95% in the MCI dataset, and four features achieved 100% in the mild AD dataset. The results were very promising and were considered reliable.

The EEG signals were collected in a clinical setting; however, the data analysis was applied in real-time using a portable laptop, not a mobile phone. This work is considered promising for BSP-based POC devices.

Affordability

EEG systems are relatively inexpensive; with suitable signal processing, they may become useful for research and clinical purposes. In developing countries, several EEG headsets are affordable while the computer/phone accompanying the headset is relatively costly.

Scalability

EEG systems are easy to use and commonly utilized by neurologists all over the world. Minimal knowledge is needed to use the EEG device.

Conclusion

Biomedical signals analysis and processing could play a major role in early detection of disease. With the current barriers to accessing health care in LMICs (eg, lack of resources, lack of funding, and environmental factors), advances in technology offer promise based on the proposed BSP-based SMCRAS framework. Moreover, there is a need to find inexpensive alternative tools that are diagnostic and noninvasive, relying on signal processing to reduce the occurrence of death, disease, and disability, particularly in developing countries.

This paper proposes a new framework as a roadmap to biomedical signal analysis and implementation. The six key objectives of the proposed SMCRAS framework are simplicity, mining, connecting, reliability, affordability, and scalability. We have presented and discussed four case studies relevant to biomedical signal analysis and the application of the SMCRAS framework. The proposed framework represents a promising method when considering these six crucial objectives. It may increase our capability to develop BSP-based POC technologies that significantly impact mortality and morbidity rates, especially for those living in LMICs.

Conflicts of Interest

None declared.

References

1. World Health Organization. Global status report on noncommunicable diseases 2014. 2014. URL: http://apps.who.int/iris/bitstream/10665/148114/1/9789241564854_eng.pdf [accessed 2016-10-11] [WebCite Cache ID 6lBPfdfFf]

2. LeDuc P, Agaba M, Cheng CM, Gracio J, Guzman A, Middelberg A. Beyond disease, how biomedical engineering can improve global health. Sci Transl Med 2014 Dec 10;6(266):266fs48. [doi: 10.1126/scitranslmed.3009067] [Medline: 25504880]

3. Dhawan AP, Heetderks WJ, Pavel M, Acharya S, Akay M, Mairal A, et al. Current and Future Challenges in Point-of-Care Technologies: A Paradigm-Shift in Affordable Global Healthcare With Personalized and Preventive Medicine. IEEE J Transl Eng Health Med 2015;3:2800110 [FREE Full text] [doi: 10.1109/JTEHM.2015.2400919] [Medline: 27170902]

4. Elgendi M, Eskofier B, Dokos S, Abbott D. Revisiting QRS detection methodologies for portable, wearable, battery-operated, and wireless ECG systems. PLoS One 2014;9(1):e84018 [FREE Full text] [doi: 10.1371/journal.pone.0084018] [Medline: 24409290]

5. Elgendi M. Fast QRS detection with an optimized knowledge-based method: evaluation on 11 standard ECG databases. PLoS One 2013;8(9):e73557 [FREE Full text] [doi: 10.1371/journal.pone.0073557] [Medline: 24066054]

6. Pan J, Tompkins WJ. A real-time QRS detection algorithm. IEEE Trans Biomed Eng 1985 Mar;32(3):230-236. [doi: 10.1109/TBME.1985.325532] [Medline: 3997178]

7. Jasemian Y, Arendt-Nielsen L. Evaluation of a realtime, remote monitoring telemedicine system using the Bluetooth protocol and a mobile phone network. J Telemed Telecare 2005;11(5):256-260. [doi: 10.1258/1357633054471911] [Medline: 16035969]

8. Jurik A, Weaver A. Remote Medical Monitoring. Computer 2008 Apr;41(4):96-99. [doi: 10.1109/MC.2008.133]

9. Baig MM, Gholamhosseini H, Connolly MJ. A comprehensive survey of wearable and wireless ECG monitoring systems for older adults. Med Biol Eng Comput 2013 May;51(5):485-495. [doi: 10.1007/s11517-012-1021-6] [Medline: 23334714]

10. Blahut RE. Fast algorithms for signal processing. Cambridge: Cambridge University Press; 2010.

11. Elgendi M, Kumar S, Guo L, Rutledge J, Coe JY, Zemp R, et al. Detection of Heart Sounds in Children with and without Pulmonary Arterial Hypertension--Daubechies Wavelets Approach. PLoS One 2015;10(12):e0143146 [FREE Full text] [doi: 10.1371/journal.pone.0143146] [Medline: 26629704]

12. Elgendi M, Vialatte F, Cichocki A, Latchoumane C, Jeong J, Dauwels J. Optimization of EEG frequency bands for improved diagnosis of Alzheimer disease. Conf Proc IEEE Eng Med Biol Soc 2011;2011:6087-6091. [doi: 10.1109/IEMBS.2011.6091504] [Medline: 22255728]

XSL•FO

RenderX

13. Elgendi M, Dauwels J, Rebsamen B, Shukla R, Putra Y, Gamez J, et al. From auditory and visual to immersive neurofeedback: application to diagnosis of Alzheimer's disease. In: Neural Computation, Neural Devices, and Neural Prosthesis. New York, NY: Springer; 2014:63-97.

14. Hanke M, Halchenko YO, Sederberg PB, Olivetti E, Fründ I, Rieger JW, et al. PyMVPA: A Unifying Approach to the Analysis of Neuroscientific Data. Front Neuroinform 2009;3:3 [FREE Full text] [doi: 10.3389/neuro.11.003.2009] [Medline: 19212459]

15. Humbert M, Sitbon O, Chaouat A, Bertocchi M, Habib G, Gressin V, et al. Survival in patients with idiopathic, familial, and anorexigen-associated pulmonary arterial hypertension in the modern management era. Circulation 2010 Jul 13;122(2):156-163 [FREE Full text] [doi: 10.1161/CIRCULATIONAHA.109.911818] [Medline: 20585011]

16. Butrous G, Ghofrani HA, Grimminger F. Pulmonary vascular disease in the developing world. Circulation 2008 Oct 21;118(17):1758-1766 [FREE Full text] [doi: 10.1161/CIRCULATIONAHA.107.727289] [Medline: 18936338]

17. Adatia I, Kothari SS, Feinstein JA. Pulmonary hypertension associated with congenital heart disease: pulmonary vascular disease: the global perspective. Chest 2010 Jun;137(6 Suppl):52S-61S. [doi: 10.1378/chest.09-2861] [Medline: 20522580]

18. Mahjoub H, Levy F, Cassol M, Meimoun P, Peltier M, Rusinaru D, et al. Effects of age on pulmonary artery systolic pressure at rest and during exercise in normal adults. Eur J Echocardiogr 2009 Jul;10(5):635-640 [FREE Full text] [doi: 10.1093/ejechocard/jep024] [Medline: 19342386]

19. Sutton G, Harris A, Leatham A. Second heart sound in pulmonary hypertension. Br Heart J 1968 Nov;30(6):743-756 [FREE Full text] [Medline: 5718984]

20. Chen D, Pibarot P, Honos G, Durand LG. Estimation of pulmonary artery pressure by spectral analysis of the second heart sound. Am J Cardiol 1996 Oct 1;78(7):785-789. [Medline: 8857483]

21. Xu J, Durand LG, Pibarot P. A new, simple, and accurate method for non-invasive estimation of pulmonary arterial pressure. Heart 2002 Jul;88(1):76-80 [FREE Full text] [Medline: 12067952]

22. Nigam V, Priemer R. A dynamic method to estimate the time split between the A2 and P2 components of the S2 heart sound. Physiol Meas 2006 Jul;27(7):553-567. [doi: 10.1088/0967-3334/27/7/001] [Medline: 16705255]

23. Harris AE, Sutton GH, Towers M. Physiological and clinical aspects of cardiac auscultation. London, UK: Medi-Cine Ltd for ICI Pharmaceuticals Division; 1976.

24. Shaver JA, Salerni R, Reddy PS. Normal and abnormal heart sounds in cardiac diagnosis. Part I: Systolic sounds. Curr Probl Cardiol 1985 Mar;10(3):1-68. [Medline: 3996020]

25. Xu J, Durand LG, Pibarot P. Nonlinear transient chirp signal modeling of the aortic and pulmonary components of the second heart sound. IEEE Trans Biomed Eng 2000 Oct;47(10):1328-1335. [doi: 10.1109/10.871405] [Medline: 11059167]

26. Leatham A, Vogelpoel L. The early systolic sound in dilatation of the pulmonary artery. Br Heart J 1954 Jan;16(1):21-33 [FREE Full text] [Medline: 13126355]

27. Liang H, Lukkarinen S, Hartimo I. Heart sound segmentation algorithm based on heart sound envelogram. In: Proc IEEE Comp Cardiol. 1997 Presented at: IEEE Computers in Cardiology; Sep. 7-10, 1997; Lund, Sweden p. 105-108.

28. Kumar D, Carvalho P, Antunes M, Henriques J, Eugenio L, Schmidt R, et al. Detection of S1 and S2 heart sounds by high frequency signatures. Conf Proc IEEE Eng Med Biol Soc 2006;1:1410-1416. [doi: 10.1109/IEMBS.2006.260735] [Medline: 17946890]

29. Wang X, Li Y, Sun C, Liping L. Detection of the first and second heart sound using heart sound energy. 2009 Presented at: International Conference on Biomedical Engineering and Informatics; Oct. 17–19, 2009; Tianjin, China p. 1-4.

30. Zhong J, Scalzo F. Automatic heart sound signal analysis with reused multi-scale wavelet transform. International Journal of Engineering and Science 2013;2(50):50-57 [FREE Full text]

31. Elgendi M, Bobhate P, Jain S, Guo L, Rutledge J, Coe Y, et al. Spectral analysis of the heart sounds in children with and without pulmonary artery hypertension. Int J Cardiol 2014 Apr 15;173(1):92-99. [doi: 10.1016/j.ijcard.2014.02.025] [Medline: 24630336]

32. Elgendi M, Bobhate P, Jain S, Guo L, Kumar S, Rutledge J, et al. The unique heart sound signature of children with pulmonary artery hypertension. Pulm Circ 2015 Dec;5(4):631-639 [FREE Full text] [doi: 10.1086/683694] [Medline: 26697170]

33. Kuan KL. Massachusetts Institute of Technology. 2010. A framework for automated heart and lung sound analysis using a mobile telemedicine platform URL: http://dspace.mit.edu/handle/1721.1/62658 [accessed 2016-10-06] [WebCite Cache ID 6l49TmfCp]

34. Fletcher R, Chamberlain D. MIT News. 2015. D-lab and tata center team wins $100k vodafone award for mobile stethoscope URL: http://news.mit.edu/2015/d-lab-tata-center-team-wins-vodafone-award-mobile-stethoscope-0624 [accessed 2016-10-06] [WebCite Cache ID 6l49d0ycb]

35. Sa-Ngasoongsong A, Kunthong J, Sarangan V, Cai X, Bukkapatnam STS. A low-cost, portable, high-throughput wireless sensor system for phonocardiography applications. Sensors (Basel) 2012;12(8):10851-10870 [FREE Full text] [doi: 10.3390/s120810851] [Medline: 23112633]

36. Orlowsky B, Seneviratne S. Global changes in extreme events: regional and seasonal dimension. Climatic Change 2011 Jul 22;110(3-4):669-696. [doi: 10.1007/s10584-011-0122-9]

37. Brearley M. Cooling Methods to Prevent Heat-Related Illness in the Workplace. Workplace Health Saf 2016 Feb;64(2):80. [doi: 10.1177/2165079915613353] [Medline: 26585173]

38. Lundgren K, Kuklane K, Gao C, Holmér I. Effects of heat stress on working populations when facing climate change. Ind Health 2013;51(1):3-15 [FREE Full text] [Medline: 23411752]

39. Carter R, Cheuvront SN, Williams JO, Kolka MA, Stephenson LA, Sawka MN, et al. Epidemiology of hospitalizations and deaths from heat illness in soldiers. Med Sci Sports Exerc 2005 Aug;37(8):1338-1344. [Medline: 16118581]

40. Xiang J, Hansen A, Pisaniello D, Bi P. Extreme heat and occupational heat illnesses in South Australia, 2001-2010. Occup Environ Med 2015 Aug;72(8):580-586. [doi: 10.1136/oemed-2014-102706] [Medline: 26081622]

41. Xiang J, Bi P, Pisaniello D, Hansen A. The impact of heatwaves on workers' health and safety in Adelaide, South Australia. Environ Res 2014 Aug;133:90-95. [doi: 10.1016/j.envres.2014.04.042] [Medline: 24906072]

42. Moran DS, Erlich T, Epstein Y. The heat tolerance test: an efficient screening tool for evaluating susceptibility to heat. J Sport Rehabil 2007 Aug;16(3):215-221. [Medline: 17923727]

43. Binkley HM, Beckett J, Casa DJ, Kleiner DM, Plummer PE. National Athletic Trainers' Association Position Statement: Exertional Heat Illnesses. J Athl Train 2002 Sep;37(3):329-343 [FREE Full text] [Medline: 12937591]

44. Casa DJ, Becker SM, Ganio MS, Brown CM, Yeargin SW, Roti MW, et al. Validity of devices that assess body temperature during outdoor exercise in the heat. J Athl Train 2007;42(3):333-342 [FREE Full text] [Medline: 18059987]

45. Bruce-Low SS, Cotterrell D, Jones GE. Heart rate variability during high ambient heat exposure. Aviat Space Environ Med 2006 Sep;77(9):915-920. [Medline: 16964740]

46. Yamamoto S, Iwamoto M, Inoue M, Harada N. Evaluation of the effect of heat exposure on the autonomic nervous system by heart rate variability and urinary catecholamines. J Occup Health 2007 May;49(3):199-204 [FREE Full text] [Medline: 17575400]

47. Galloway SD, Maughan RJ. Effects of ambient temperature on the capacity to perform prolonged cycle exercise in man. Med Sci Sports Exerc 1997 Sep;29(9):1240-1249. [Medline: 9309637]

48. Crandall CG, Johnson JM, Convertino VA, Raven PB, Engelke KA. Altered thermoregulatory responses after 15 days of head-down tilt. J Appl Physiol (1985) 1994 Oct;77(4):1863-1867. [Medline: 7836211]

49. Rowell LB, Marx HJ, Bruce RA, Conn RD, Kusumi F. Reductions in cardiac output, central blood volume, and stroke volume with thermal stress in normal men during exercise. J Clin Invest 1966 Nov;45(11):1801-1816 [FREE Full text] [doi: 10.1172/JCI105484] [Medline: 5926447]

50. Rubin SA. Core temperature regulation of heart rate during exercise in humans. J Appl Physiol (1985) 1987 May;62(5):1997-2002. [Medline: 3597272]

51. Lisman P, Kazman JB, O'Connor FG, Heled Y, Deuster PA. Heat tolerance testing: association between heat intolerance and anthropometric and fitness measurements. Mil Med 2014 Nov;179(11):1339-1346. [doi: 10.7205/MILMED-D-14-00169] [Medline: 25373064]

52. Elgendi M, Norton I, Brearley M, Fletcher R, Abbott D, Lovell NH, et al. Towards Investigating Global Warming Impact on Human Health Using Derivatives of Photoplethysmogram Signals. Int J Environ Res Public Health 2015 Oct;12(10):12776-12791 [FREE Full text] [doi: 10.3390/ijerph121012776] [Medline: 26473907]

53. Elgendi M, Norton I, Brearley M, Abbott D, Schuurmans D. Systolic peak detection in acceleration photoplethysmograms measured from emergency responders in tropical conditions. PLoS One 2013;8(10):e76585 [FREE Full text] [doi: 10.1371/journal.pone.0076585] [Medline: 24167546]

54. Tamura T, Maeda Y, Sekine M, Yoshida M. Wearable Photoplethysmographic Sensors—Past and Present. Electronics 2014 Apr 23;3(2):282-302. [doi: 10.3390/electronics3020282]

55. Seki H. Classification of wave contour by first and second derivative of plethysmogram (in Japanese). Pulse Wave 1977;7(42):42-50.

56. Edwards J. Taking the pulse of pulse oximetry in Africa. CMAJ 2012 Mar 20;184(5):E244-E245 [FREE Full text] [doi: 10.1503/cmaj.109-4121] [Medline: 22353586]

57. Kwok AC, Funk LM, Baltaga R, Lipsitz SR, Merry AF, Dziekan G, et al. Implementation of the World Health Organization surgical safety checklist, including introduction of pulse oximetry, in a resource-limited setting. Ann Surg 2013 Apr;257(4):633-639. [doi: 10.1097/SLA.0b013e3182777fa4] [Medline: 23207242]

58. Lozano R, Naghavi M, Foreman K, Lim S, Shibuya K, Aboyans V, de Vaccaro Karen Courville, Des Jarlais Don C, et al. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet 2012 Dec 15;380(9859):2095-2128. [doi: 10.1016/S0140-6736(12)61728-0] [Medline: 23245604]

59. Hutcheon JA, Lisonkova S, Joseph KS. Epidemiology of pre-eclampsia and the other hypertensive disorders of pregnancy. Best Pract Res Clin Obstet Gynaecol 2011 Aug;25(4):391-403. [doi: 10.1016/j.bpobgyn.2011.01.006] [Medline: 21333604]

60. Wagner LK. Diagnosis and management of preeclampsia. Am Fam Physician 2004 Dec 15;70(12):2317-2324 [FREE Full text] [Medline: 15617295]

61. Payne BA, Hutcheon JA, Dunsmuir D, Cloete G, Dumont G, Hall D, et al. Assessing the incremental value of blood oxygen saturation (SpO(2)) in the miniPIERS (Pre-eclampsia Integrated Estimate of RiSk) Risk Prediction Model. J Obstet Gynaecol Can 2015 Jan;37(1):16-24. [Medline: 25764032]

62. Kyriacou PA, Moye AR, Choi DM, Langford RM, Jones DP. Investigation of the human oesophagus as a new monitoring site for blood oxygen saturation. Physiol Meas 2001 Feb;22(1):223-232. [Medline: 11236883]

63. Webster JG. Electrical measurement, signal processing and displays. Boca Raton, FL: CRC Press; 2004.

64. Shafique M, Kyriacou PA. Photoplethysmographic signals and blood oxygen saturation values during artificial hypothermia in healthy volunteers. Physiol Meas 2012 Dec;33(12):2065-2078. [doi: 10.1088/0967-3334/33/12/2065] [Medline: 23171523]

65. Payne BA, Hutcheon JA, Ansermino JM, Hall DR, Bhutta ZA, Bhutta SZ, miniPIERS Study Working Group. A risk prediction model for the assessment and triage of women with hypertensive disorders of pregnancy in low-resourced settings: the miniPIERS (Pre-eclampsia Integrated Estimate of RiSk) multi-country prospective cohort study. PLoS Med 2014 Jan;11(1):e1001589 [FREE Full text] [doi: 10.1371/journal.pmed.1001589] [Medline: 24465185]

66. Meek PD, McKeithan K, Schumock GT. Economic considerations in Alzheimer's disease. Pharmacotherapy 1998;18(2 Pt 2):68-73; discussion 79. [Medline: 9543467]

67. Brookmeyer R, Johnson E, Ziegler-Graham K, Arrighi HM. Forecasting the global burden of Alzheimer's disease. Alzheimers Dement 2007 Jul;3(3):186-191. [doi: 10.1016/j.jalz.2007.04.381] [Medline: 19595937]

68. Förstl H, Kurz A. Clinical features of Alzheimer's disease. Eur Arch Psychiatry Clin Neurosci 1999;249(6):288-290. [Medline: 10653284]

69. Shute V, Ventura M, Ke F. The power of play: The effects of Portal 2 and Lumosity on cognitive and noncognitive skills. Computers & Education 2015 Jan;80:58-67. [doi: 10.1016/j.compedu.2014.08.013]

70. AlRomi A, AlOfisan G, AlRomi N, AlMagooshi S, Al-wabil A. Requirements engineering of ambient assisted living technologies for people with Alzheimer's. In: HCI International 2015-Posters Extended Abstracts. Switzerland: Springer; 2015:381-387.

71. Schalk G, McFarland DJ, Hinterberger T, Birbaumer N, Wolpaw JR. BCI2000: a general-purpose brain-computer interface (BCI) system. IEEE Trans Biomed Eng 2004 Jun;51(6):1034-1043. [doi: 10.1109/TBME.2004.827072] [Medline: 15188875]

72. McMahan T, Parberry I, Parsons TD. Modality specific assessment of video game player's experience using the Emotiv. Entertainment Computing 2015 Mar;7:1-6. [doi: 10.1016/j.entcom.2015.03.001]

73. O'Regan S, Faul S, Marnane W. Automatic detection of EEG artefacts arising from head movements using EEG and gyroscope signals. Med Eng Phys 2013 Jul;35(7):867-874; discussion 867. [doi: 10.1016/j.medengphy.2012.08.017] [Medline: 23018030]

74. Cichocki A, Shishkin SL, Musha T, Leonowicz Z, Asada T, Kurachi T. EEG filtering based on blind source separation (BSS) for early detection of Alzheimer's disease. Clin Neurophysiol 2005 Mar;116(3):729-737. [doi: 10.1016/j.clinph.2004.09.017] [Medline: 15721088]

75. Latchoumane CF, Vialatte FB, Solé-Casals J, Maurice M, Wimalaratna SR, Hudson N, et al. Multiway array decomposition analysis of EEGs in Alzheimer's disease. J Neurosci Methods 2012 May 30;207(1):41-50. [doi: 10.1016/j.jneumeth.2012.03.005] [Medline: 22480988]

76. Gallego-Jutglà E, Elgendi M, Vialatte F, Solé-Casals J, Cichocki A, Latchoumane C, et al. Diagnosis of Alzheimer's disease from EEG by means of synchrony measures in optimized frequency bands. Conf Proc IEEE Eng Med Biol Soc 2012;2012:4266-4270. [doi: 10.1109/EMBC.2012.6346909] [Medline: 23366870]

77. Gallego-Jutglà E, Solé-Casals J, Vialatte FB, Elgendi M, Cichocki A, Dauwels J. A hybrid feature selection approach for the early diagnosis of Alzheimer's disease. J Neural Eng 2015 Feb;12(1):016018. [doi: 10.1088/1741-2560/12/1/016018] [Medline: 25605667]

Abbreviations

APG: acceleration photoplethysmogram

AD: Alzheimer's disease

BCT: body core temperature

BSP: biomedical signal processing

ECG: electrocardiogram

EEG: electroencephalogram

EMG: electromyogram

HR: heart rate

HRV: heart rate variability

LMICs: low- and middle-income countries

MCI: mild cognitive impairment

NCD: noncommunicable diseases

PAH: pulmonary arterial hypertension

POC: point-of-care

PPG: photoplethysmogram

PE: preeclampsia

SMCRAS: Simplicity, Mining, Connecting, Reliability, Affordability, and Scalability

SpO2: Oxygen saturation
WHO: World Health Organization

XSL•FO

RenderX