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A Wearable System for Heart Failure Monitoring

Dissertação no âmbito do Mestrado Integrado em Engenharia Biomédica, Especialização em Instrumentação Biomédica orientada pelo Professor Doutor José Machado da Silva (FEUP) e pelo Professor Doutor Custódio Francisco Melo Loureiro e apresentada ao Departamento de Física da Faculdade de Ciências e Tecnologia.

Outubro de 2020

Faculdade de Ciências e Tecnologia
da Universidade de Coimbra

A Wearable System for Heart Failure Monitoring

Rafael Carvalho Machado

Dissertação submetida para cumprimento dos requisitos do Mestrado Integrado em Engenharia Biomédica, especialização em Instrumentação Biomédica, Departamento de Física da Faculdade de Ciências e Tecnologia da Universidade de Coimbra, realizada sob orientação de Professor Doutor José Machado da Silva (FEUP) e de Professor Doutor Custódio Francisco Melo Loureiro.

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Agradecimentos

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Resumo

A insuficiência cardíaca é o problema de saúde mais letal e dispendioso nos países desenvolvidos. Neste projecto é proposto um sistema vestível para monitorização de biossinais relacionados com a insuficiência cardíaca, baseado em componentes baratos e acessíveis e em software de código aberto. Recorrendo a um microcontrolador AVR com comunicação Bluetooth e circuitos integrados de processamento de sinais analógicos conseguiu-se adquirir, gravar e transmitir sinais de electrocardiograma e fotopletismograma. Através do desenvolvimento de uma aplicação Android, estes sinais podem ser processados e apresentados em tempo real sendo possível executar pós processamento que seja demasiado pesado para o microcontrolador, e a calcular parâmetros secundários como a tensão arterial e o ritmo cardíaco. Para isso foi implementado um algoritmo de detecção de picos nas formas de onda dos sinais adquiridos assim como funcionalidade de encriptação de forma a garantir a confidencialidade dos dados em transmissão. O principal objectivo deste trabalho é tentar evidenciar o potencial para a utilização de sistemas embebidos em redes sem fios de sensores de forma a expandir a recolha de dados médicos, melhorar abordagens terapêuticas baseadas no autocuidado e dar aos profissionais de saúde uma perspetiva mais abrangente acerca do estado dos seus pacientes.

Palavras chave: Insuficiência cardíaca, sistemas vestíveis, ECG, PPG, pressão sanguínea.

Abstract

Heart failure is the most lethal and costly health problem in the developed world. In this project a wearable device for monitoring heart failure related biosignals based on cheap readily available components and open source software is proposed. Employing a common, Bluetooth enabled, AVR microcontroller and simple analog signal processing integrated circuits, live, high sample rate photoplethysmogram and electrocardiogram data recording and streaming was achieved. Through the development of an Android application, the data can be processed and presented in real-time and computationally expensive postprocessing can be done to infer relevant secondary parameters, blood pressure and heart rate. To enable this, a waveform peak detection algorithm was implemented as well as storage and encryption functionality to ensure data confidentiality. The main purpose of this work is to attempt to highlightt the potential for the employment of embedded devices in wireless sensor networks to expand medical data collection, improve self-care therapeutical approaches and give practitioners more insight into the condition of their patients.

Keywords: *Heart failure, wearable devices, ECG, PPG, blood pressure.*

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FIGURE INDEX

ABBREVIATIONS

AC	Alternate Current
ADC	Analog Digital Converter
Ag/AgCl	Silver/Silver chloride (electrodes)
AI	Artificial Intelligence
ANN	Artificial Neural Networks
API	Advanced Programming Interface
ASIC	Application-Specific Integrated Circuit
ATP	Adenosine Triphosphate
BLE	Bluetooth Low Energy
BP	Blood Pressure
BV	Blood Volume
CA	Certificate Authority
CISC	Complex Instruction Set Computer
CMRR	Common Mode Rejection Ratio
CNT	Carbon Nanotubes
CVD	Cardiovascular Disease
DBP	Diastolic Blood Pressure
DC	Direct current
TDM	Time-Domain Morphology
DWT	Discrete Wavelet Transform
ECG	Electrocardiogram
EDA	Electrodermal Activity
EEG	Electroencephalogram
EEPROM	Electrically-Erasable Programmable Read-Only Memory
EMG	Electromyogram
ESC	European Society of Cardiology
FDA	Federal Drug Administration
FOSS	Free and Open Source Software
FOTA	Firmware Over The Air
FPGA	Field-Programmable Gate Array
GNU	GNU is Not Unix
GDPR	General Data Protection Regulation
GPIO	General-Purpose Input/Output
GPL	GNU Public Licence
Hb	Hemoglobin
HF	Heart Failure
I/O	Input / Output
I^2C	Inter-Integrated Circuit
IA	Instrumentation Amplifier
IC	Integrated Circuit
IR	Infra Red
IV	Intravenous
LED	Light Emitting Diode

LPWA	Low Power Wide Area
MCU	Micro Controller Unit
O2	Oxygen
PAT	Pulse Arrival Time
PCB	Printed Circuit Board
PD	Photodiode
PEP	Pre-Ejection Period
PGP	Pretty Good Protection
PIR	Pulse Intensity Ratio
PPG	Photoplethysmogram
PR	Pulse Rate
PTT	Pulse Transit Time
R&D	Research and Development
RAM	Random Access Memory
RC	Resistor and Capacitor
RISC	Reduced Instruction Set Computer
RLD	Right Leg Drive
RSA	Rivest-Shamir-Adleman cryptography system
RTOS	Real-Time Operating System
SaO2	Arterial Oxygen Saturation
SBP	Systolic Blood Pressure
SHA	Secure Hash Algorithm
SoC	System on a Chip
SPI	Serial Peripheral Interface
SpO2	Pulse Oxygen Saturation
SSL	Secure Socket Layer
StO2	Tissue Oxygen Saturation
SVM	Support Vector Machine
SvO2	Venous Oxygen Saturation
TDP	Thermal Design Power
UART	Universal Asynchronous Receiver-Transmitter
UI	User Interface
UI/UX	User Interface / User Experience

MOTIVATION

Heart diseases ranks among the leading causes of death and hospitalization in the developed world. The American Heart Association in its 2017 report estimates that, in 2013, cardiovascular diseases (CVD) accounted for 17.3 million or 31.5% of all deaths worldwide. It also estimates that, in 2017, 92.1 million US adults suffer from at least one type of CVD and, by 2030, 43.9% of all US adults are expected to suffer from some form of CVD [1]. The European Heart Network 2017's statistics are similar in magnitude, reporting that CVD accounts for 45% of all deaths in Europe and that, in 2015, more that 85 million people were living with CVD [2].

Crimmins *et al* estimate that life expectancy of a 50-year-old person diagnosed with heart disease to be 7.9 years for women and 6.7 years for men, in the US [3]. In the same 2017 report, the American Heart Association estimates that CVD and stroke accounted for 14% of total health expenditures in 2012 to 2013, the most of any major diagnostic group and that the annual direct costs amounted to $189.7 billion and indirect costs of $126.4 billion related to lost future productivity attributed to premature CVD and stroke mortality. Direct costs are projected to increase to $918 billion by 2030 when taking into account nursing home care costs.

Along with symptomatology, analysis of self and family medical history, the existence of risk factors such as smoking or diabetes and the identification of relevant biomarkers, the analysis of biosignals such as blood pressure (BP) and the electrocardiogram signal (ECG) showed to be the most relevant for reliable CVD diagnosis and patient monitoring. Affordable and convenient access to these metrics is crucial for early detection in all three stages of CVD prevention, those being:

- the primary, which is about trying to avoid injury altogether, exposing risk factors and increasing resistance;
- the secondary that addresses reducing the impact and progression of the disease or injury in an effort to maintain function and prevent long-term problems;
- and the tertiary that deals with managing often-complex issues in an attempt to preserve life quality and expectancy.

Also of increasing relevance is the availability of an extensive history and continuous monitoring of these signals, both for historical analysis and real-time remote monitoring, acute episode detection or even prediction. These real-time capabilities can be extremely important to ensure that timely/emergency care can be deployed considering not only the speed of an emergency call but also, in the case of the patient being alone, if such a call even occurs at all.

The advent of the use of Artificial Intelligence (AI) models for medical research in both industrial and academic settings, allows processing more efficiently the high volume of data obtained with the dissemination of wearable devices and communication networks. Consequently, the obtained AI models facilitate the development of means that allow implementing faster and efficient diagnostics models extensively applicable to a wide population. Notice that the size of the dataset is usually considered to be the main bottleneck hindering these potentially paradigm-shifting approaches.

In this time of COVID-19 pandemic one cannnot help but also consider the relevance of such telemedicine practices in the transformations that are occurring in our health systems. Remote and reliable biosignal acquisition ought to play a significant role in the novel protocols for appointments that healthcare professionals are being advised to put in place.

The past decade saw the maturity of the so called “Internet of things”, made possible by the increasing miniaturization, power and price performances and the availability of communication networks to interconnect electronic systems containing microcontrollers, sensors and data storage devices. There are already a number of proof-of-concept and FDA (Federal Drug Administration) approved devices that provide significant capabilities in almost all areas of healthcare from diagnostics to therapeutics [4]. Yet the cost of these devices often reflects both the high demand for such solutions and the high-stakes nature of bleeding-edge R&D and heavily regulated compliance requirements of the medical industry. These high costs represent not only a problem for the extensive deployment of such solutions but also to massively increase the cost-benefit profile of the devices from the healthcare system’s perspective, relegating them to niche or luxury applications and suppressing all advantages in datamining and public health that come from mass adoption.

Free and Open Source Software (FOSS) projects, and more recently hardware as well, represent the quintessential solution to these problems with their permissive licenses and transparent designs reaching a level of maturity that may allow for them to be considered. On top of such open technology, devices could be designed that would allow for drastic cost reduction on healthcare systems, decentralization of production, increasing availability and increased leverage on future research and development. On the other hand, such projects usually require a substantial amount of work to be done in advance and some level of functionality before they can be certified and approved to introduction in the market. This implies a significant investment with no immediate or obvious return.

Another relevant breakthrough is the development of flexible circuitry that allows for seamless, non-invasive integration of such devices in a wearable form factor that minimizes both technical issues, such as high noise and reliability, and the discomfort on the patient from carrying the device, which is still considered one of the major bottlenecks for the wide acceptance of such solutions [5].

Objectives

With the above in mind, the objectives of this Master's project are 1) to assess the state of the art of wearable heart disease related monitoring systems and potential low-cost and open source counterparts, 2) the study and familiarization with such system's components and architecture from an engineering perspective, 3) the development of a proof-of-concept industrial level prototype aiming for low-cost but also quality and feature viability, 4) the comparative study between different possible configurations regarding signal quality and usability and 5) develop along a full-stack approach on circuit design, firmware, device interfacing, signal processing and UI/UX levels.

BIOSIGNALS IN HEART FAILURE

Heart Failure definition, diagnosis and treatment

The European Society of Cardiology (ESC) defines heart failure (HF) as [6]:

> *"a clinical syndrome characterized by typical symptoms (e.g. breathlessness, ankle swelling and fatigue) that may be accompanied by signs (e.g. elevated jugular venous pressure, pulmonary crackles and peripheral edema) caused by a structural and/or functional cardiac abnormality, resulting in a reduced cardiac output and/or elevated intracardiac pressures at rest or during stress."*

Despite this definition being restricted to a stage where the symptoms manifest, ESC guidelines also stress the importance of treatment at the precursor level, to which the detection of asymptomatic structural or functional abnormalities is crucial.

Several direct numerical parameters related to the cardiovascular system are influenced by this condition and can thus be evaluated to help identifying the presence of the syndrome such as the direct causal relation between a decreased cardiac output (CO) and the increased blood pressure (BP) and blood volume (BV) the body promotes in order to compensate for lower oxygen delivery. Other quantities such as ejection fraction (EF), which is based on the left ventricular ejection fraction and is indicative of valve or myocardium damage, are also important and need to be measured by indirect means such as calculations or imaging methods.

In order to assess a non-acute HF diagnosis the physician usually follows an examination algorithm such as the one presented bellow (figure 1) where it is shown that the main factors in consideration are the clinical history of the patient, with respect to risk factors and history of artery disease or hypertension, the presence of typical physical symptoms such as jugular vein dilation and the presence of abnormalities in the ECG. Any of such signs warrants further confirmation of the diagnosis that is usually done by echocardiography or presence of natriuretic peptides in blood analysis which are the most widely used biomarkers for the syndrome.

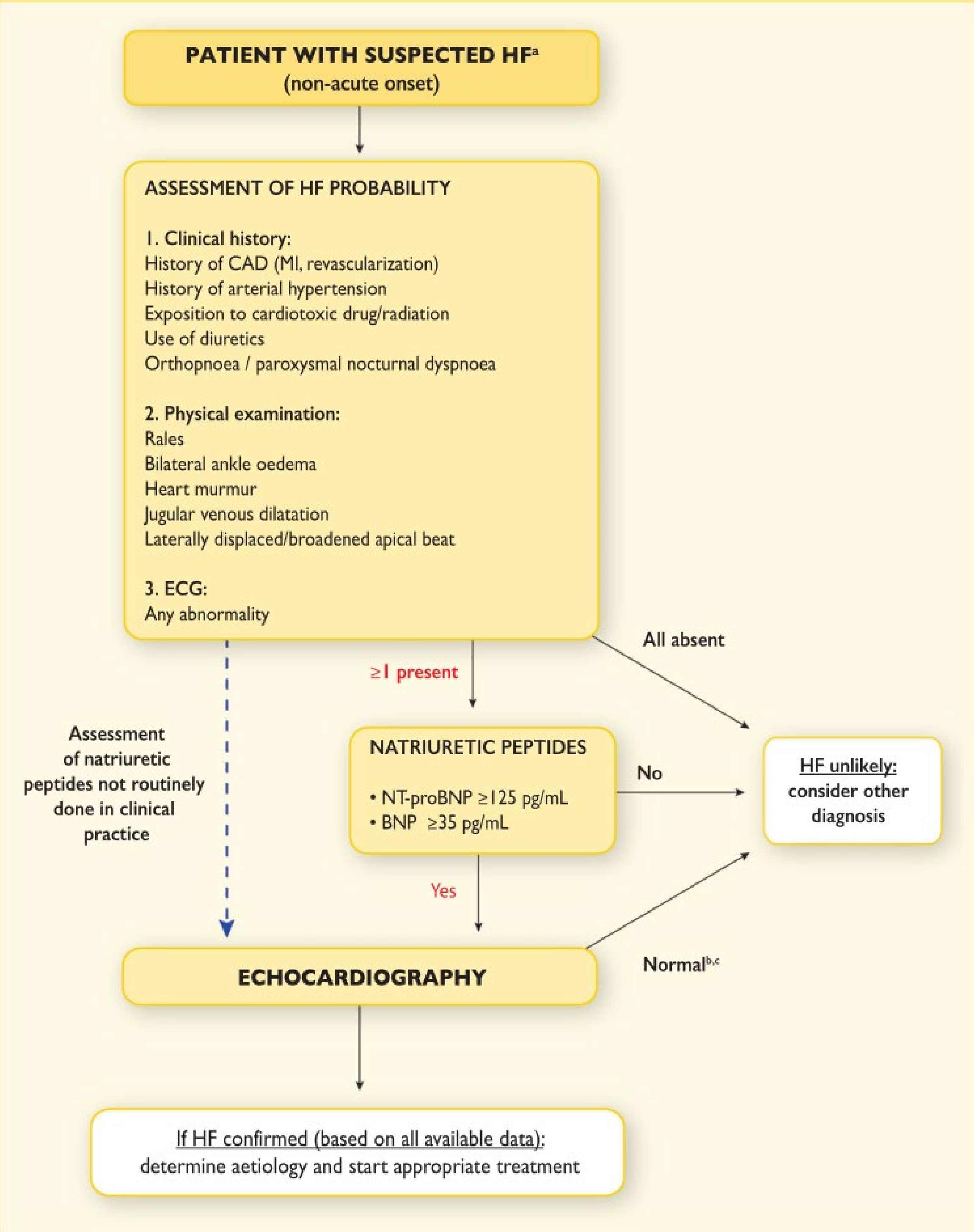


Figure 1 – HF diagnosis algorithm. Any of the indicated symptoms warrants further investigation, usually through blood tests and echocardiogram. [6]

In acute cases, where serious symptoms are present, O2 therapy, intravenous (IV) drug administration and, in extreme cases, resuscitation maneuvers are employed with the purpose of stabilizing the patient. While these can be representative of a first episode that signals the existence of the syndrome, they are usually related to a degradation of an already diagnosed condition often related to problems in the self-care aspects of the therapy.

The demonstration of the etiology of the syndrome, i.e. the underlying cause of the abnormalities, is of utmost importance as well. These are usually issues with either the myocardium and its vasculature, the valves or the heart rhythm, among others, and understanding them is determinant to the establishment of a prognosis and possible courses of treatment.

While the treatment mostly relies on pharmacology, corrective or replacement surgery and medical device implants, it is also very dependent on some level of self-care, be it the correct and timely administration of drugs and the continued monitoring of the cardiovascular system's parameters that remain relevant for the assessment of both the therapeutic effectiveness and the progression of the underlying pathologies. Dealing with these self-care issues is difficult in contexts of complex treatments and procedures, aggravated by the fact that, mostly, patients are of advanced age or show diminished capacity and, usually, the situation implies frequent and expensive visits to healthcare facilities, prolonged stay in continuous care units or some kind of permanent monitoring approach.

Relevant signals and their importance

Many studies have shown the importance of biosignals monitoring in prevention, early detection, diagnosis and treatment of heart failure and its related pathologies [7] [8] [9] [10]. For the convenience of the measurement methods, blood pressure, heart rate, oxygen saturation and the ECG are of the utmost relevance due to their direct quantitative representation of the cardiovascular system.

Blood Pressure

Blood pressure (BP), and more specifically arterial pressure, is an important cardiogenic event that allows for both immediate and long-term considerations regarding the state of the cardiovascular system. Pressure oscillates through the normal functioning of the cardiac cycle between low diastolic and high systolic values. ESC guidelines consider optimal values to be 80 and 120 mmHg respectively [11]. Hypertension is a major health issue in developed countries' populations. It is frequently treated, often times as a chronic condition, with drugs such as diuretics or beta-blockers when lifestyle changes such as salt consumption reduction, obesity control or the avoidance of tobacco and alcohol prove ineffective or insufficient. BP has also been shown to vary along the day, responding to different factors including psychological factors such as stress or anxiety. As noted before, hypertension is in itself a risk factor to HF, leading to increased stress to the heart and in some cases hypertrophic cardiomiopathy. On the other hand, hypotension is also a symptom of HF and in acute episodes can lead to loss of consciousnesses so BP is always an important parameter in HF monitoring and a real-time analysis can even preemptively alert for an imminent event, possibly preventing a fall, a car accident, etc. An extensive history of the signal can shed light on the effectiveness of treatments that rely on the control of this parameter.

Heart Rate

Heart rate is among the most prevalent biosignals. It is regulated through the sympathetic-parasympathetic nervous system and, even in normal functioning, values can vary widely in response to various endocrinal, neurological and external stimuli and can be regulated through the use of drugs such as epinephrine or norepinephrine. Constant HR monitoring can reveal arrhythmia and alert for cardiac arrest.

Pulse Oximetry

Oxygen saturation measures the fraction of oxygenated hemoglobin in a particular bloodstream, being SaO2 the arterial oxygen saturation, SvO2 the venous blood saturation, StO2 the tissue oxygen saturation and SpO2 the peripheral oxygen saturation. Normal SaO2 values are about 95% and hypoxemia, i.e. low oxygen saturation in the blood, can lead to very dangerous hypoxia which is a dangerous condition of deficient oxygen supply to tissues and indicates different pathologies such as anemia or ischemic disease. The constant monitoring of the signal is also useful for the calculation of secondary parameters such as BP or to indicate failure of the respiratory system.

SpO2 is but one of the many cardiovascular related quantities that can be extracted from the photoplethysmogram (PPG). This is an inexpensive and non-invasive measurement of volumetric variations in a tissue that are caused mainly due to blood circulation and are proportional to light reflectance variations on said tissue. While calculation of SpO2 requires the comparison of two light sources of different wavelenghts, effectively two PPGs, important biosignals suchs as HR can be inferred from just one. Novel interpretations of the signal, including from it's second derivative also appear in the literature. The possibility of acquisition from a distance through conventional video cameras [12] or radiofrequency reflection have also been documented hinting for potential innovative future applications as research on this topic develops.

Electrocardiogram

Another very important and prevalent signal is the electrocardiogram (ECG). This signal provides a whole representation of the electric activity of the heart from which one can extract many features of both deterministic and empirical value. This activity arises from ionic transmembrane movements in and out of myocardial cells. Sodium-potassium ATPase pump proteins present in the cells' membrane produce a potential difference, at rest, of about – 90 mV. These proteins maintain concentration differences such that $Na+$ has higher concentration outside and $K+$ is more concentrated inside the cell while also providing thermodynamic energy to a different mechanism that maintains a higher concentration of $Ca2+$ in the extracellular compartment. The selective opening and closing of these channels in a cyclical manner is what constitutes the electric action potential that propagates through the tissue and, at the organ level, from one part of the heart to the other, causing the myocardial muscles to contract and generating the cardiac cycle and thus the electric signal measured by the ECG.

Particular spots in the heart, mainly the sinus node, generate this potential automatically, functioning as a natural pacemaker that dictates heart rate. This signal is measured through an array of usually three, four or ten electrodes placed on the skin surface at specific points in the chest or limbs.

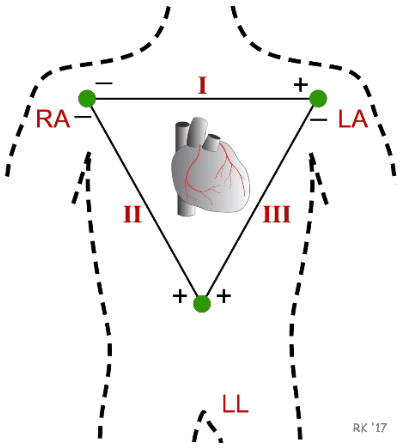


Figure 2 – An illustration of the Einthoven's triangle, showing the correct placement of the limb leads I, II and III. The Einthoven's law expresses the relationship between them: II=I + III (mV) [13].

The potential difference between any two electrodes is called a lead which can also be formed from virtual electrodes corresponding to the average of the three limb electrodes (figure 2).

The ECG graph represents the difference between potentials at two separate leads, one being closer to the source of the activation than the other (called endocardium and epicardium respectively). The action potential is registered by each electrode at distinct times, generating a waveform whose structures represent the propagation of the action potential and thus functional and morphological properties of the heart.

The analysis of the alteration of the typical morphology of the waveform is the basis of the clinical use of the ECG and provides relevant insight to almost all heart related pathologies. The signal is characterized by the characteristic points P, Q, R, S, T, depicted bellow, and a conditional U wave that is not usually present in a healthy patient. The most important features are the R-R interval, from which heart rate is obtained, the QRS complex length, P-R interval, and the ST segment depression elevation (figure 3).

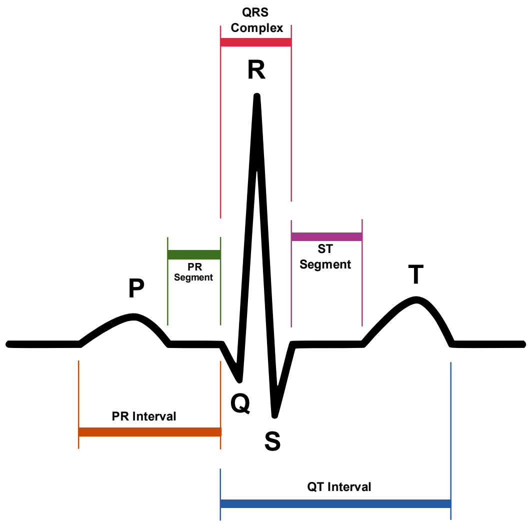


Figure 3 – The main features of the ECG and the important segments that are measured for use in diagnosis [14].

The QRS complex represents the delay in activation between the endocardium and epicardium, i.e. when the former has activated but not the latter. Since action potentials in myocardium cells form a plateau remaining at about 0-10 mV, an interval when there is 0 mV of difference measured is registered, corresponding to the ST segment. Since the first cells to polarize in the endocardium are also the last to depolarize, the T peak forms last. In a similar fashion, a difference in depolarization timing in the atria forms the P wave that precedes the next QRS complex. This PR interval represents the time delay between atrial and ventricular depolarization [15].

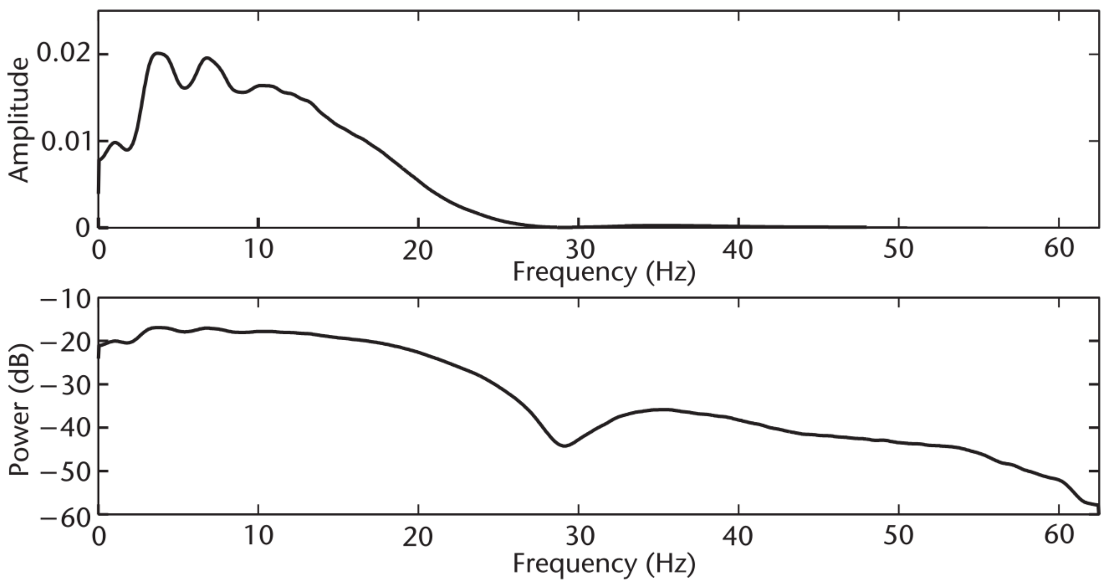


Figure 4 – Frequency spectrum of the ECG signal. A 30 Hz low-pass filter is the most important signal conditioning component [16].

Spectral analysis of the ECG waveform shows most frequency components of the signal to be in the 0.5 – 30 Hz range (figure 4) and the American Heart Association recommends that a digitally processed ECG should deviate less than 25 μV or 5% from the correspondent analog signal to ensure the required fidelity for visual interpretation [17].

Together these signals provide significant insight into the state and function of the cardiovascular system, proving useful in all stages of diagnosis and treatment in both hospital and self-care settings. The literature also stresses the relevance of continued monitoring of these signals to ensure successful treatment and prevent hospitalization [18]. Since both HR and BP can be derived from the ECG and PPG signals, the acquisition of these two will be the main focus of this project.

Data Acquisition Methods

ECG

ECG monitoring devices come in varied form factors and specifications related to the different applications to which they were designed for, such as resting vs. stress ECG measurements, wired and wireless Holter monitors, as well as cardiac event recorders used in both clinical and home settings.

Clinical devices provide many, usually 12-lead, ECG signals for clinical interpretation that are recorded either during a short period examination or in a context of prolonged hospitalization (figure 5).

Figure 5 – An Avante True ECG Advance 12-Channel ECG portable system. It has an included monitor and also prints on conventional ECG paper [19].

Holter monitors (figure 6) are given to patients to use on ambulatory to record an ECG for a continued period of about one or two days, in order to detect pathologies such as arrhythmia.

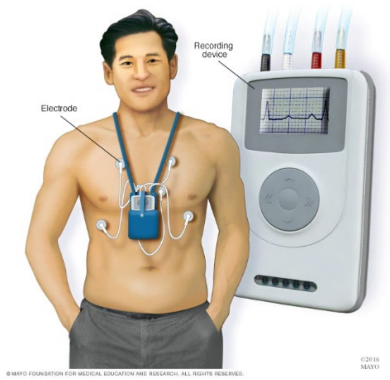


Figure 6 – An illustration of a typical Holter monitor. It records continuously for a couple of days but has no transmission capabilities [20].

Cardiac event recorders are used in much longer time frames and can record and transmit ECG activity continuously or only when symptoms occur, either by detecting them, or by user input (figure 7).

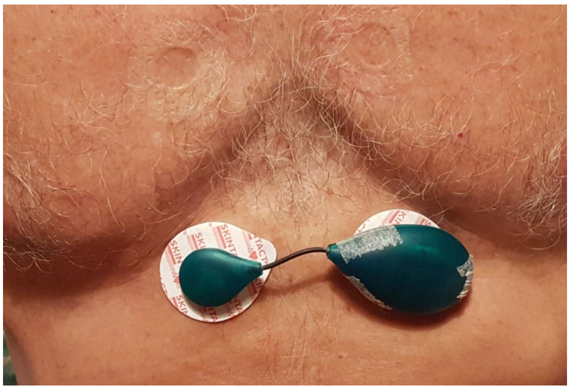


Figure 7 – A Savvy ECG sensor. It transmits to a smartphone application and includes all the required components in plastic enclosures on the electrodes [21].

Although price information is not readily available for these devices, their cost almost always includes large R&D overheads, technical support contracts that ensure higher reliability and fault tolerance that may not be required in certain applications, and may or may not provide convenient and open interfaces to easily integrate them with different components.

The ECG instrument comprises generically a few basic processing features, from the acquisition of the signal itself to its delivery into a processing unit.

A number of electrodes are connected to the skin surface, usually through adhesive or a suction mechanism, either directly (dry electrode) or mediated by a conductive gel aimed at minimizing and homogenizing electric impedance in the skin-electrode interface, providing clearer measurements. The most common silver/silver chloride (Ag-AgCl) disposable electrodes are ubiquitous in clinical settings but have disadvantages in continuous monitoring, being single use, with their impedance rapidly increasing as they dry and patients in many cases developing skin reactions after using them for more than a couple of days. To avoid these issues novel and perhaps more expensive alternatives (figure 8) such as textile or carbon nanotube (CNT) based electrodes can and should be considered for a long-term continued monitoring.

Figure 8 – a) The conventional Ag-AgCl electrodes used in this project [22]; b) The Nuubo wearable ECG sensor [23], based on textile electrodes to increase durability and comfort; c) CNT based electrodes promise small footprint and very high durability [24].

The skin-electrode interface can be modelled as a double time constant system [25] and the different alternatives don't seem to alter the parameters of this model in a way that requires changes in the front-end analog signal capture device's specifications.

As the electrodes themselves are supposed to be easily and frequently replaced and the usage of different types of electrodes warrants no changes in the rest of the system, the choice of a particular model will be left outside the scope of this project and the generic disposable Ag-AgCl electrodes readily available will be used for all measurements.

The electric cables conducting the raw signals should be shielded and provide a common interface for connecting the electrodes via snap connector to the rest of the system, such as 3.5 mm jack, USB or in our case UC-E6.

A front-end analog signal conditioning circuit containing the equivalents of an instrumentation amplifier (IA), provides signal amplification and common mode rejection. These are crucial due to the differential nature of the measurement and to filter common mode noise such as the 50 Hz powerline interference. It should also contain low-pass and high-pass filters cutting components unrelated to the ECG itself such as low-frequency oscillations and artifact distortions (< 0.05 Hz) and high-frequency muscle tremor (> 150 Hz) [26]. Many integrated circuits (IC) designed specifically for ECG signal conditioning that integrate all or most of these components are commercially available from different vendors such as Analog Devices or Texas Instruments and in varied specifications suited for different applications such as resolution, cost, temperature range, form factor, power consumption, etc;

In the case of historical fully analog instruments, a galvanometer is used to record the signal in grid paper with standard resolution of 25 mm/s and 10 mm/mV, in the x and y axes, respectively. The recommendations regarding digital instruments used in clinical setting are specified to provide signal fidelity equivalent to these analog devices. In the case of digital instruments, the sensor must contain an analog to digital converter (ADC) of sufficient resolution and sampling rate to ensure said fidelity and avoid aliasing. A second stage amplifier is usually also implemented in the analog signal conditioning front-end to provide additional gain for the signal to achieve the dynamic input range of the ADC.

PPG

A PPG sensor comprises of a light emitting diode (LED) source and a photodiode (PD) along with front-end signal conditioning electronics. In conventional sensors these are set up in contact with the skin surface on opposing sides of the measurement site, usually an extremity such as a fingertip or earlobe, called in transmission mode, or both on the same side, called reflectance mode. The transmission mode is mostly used in SpO_2 sensors as a clip in the fingertip, but reflectance mode (figure 9) is otherwise preferred in wearable unobtrusive system for its ease of placement.

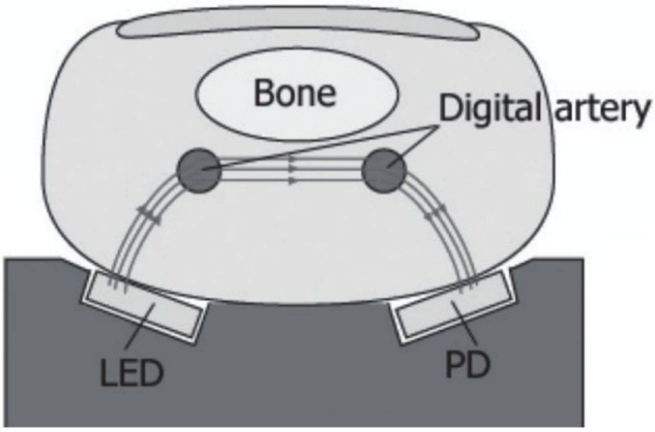


Figure 9 – Illustration of the basic functioning of a PPG sensor in a reflectance mode configuration. Light is emitted by a LED and the scattered components are measured by a photodiode. The main source of time variation of this signal is the arterial blood flow [27].

The light interacts with the tissue and is acquired by the sensor and contains both alternating current (AC) and direct current (DC) components.

The DC component represents the portion of the optical signal transmitted or reflected by the tissue and changes slowly depending on respiration and physiological conditions such as vasoregulation by the autonomous nervous system. The AC component is a pulse waveform that represents the volume fluctuations related to the cardiac cycle and its fundamental frequency depends on HR.

Figure 10 – A consumer grade Easy@Home Fingertip Pulse Oximeter. This wireless device, in a transmission configuration, costs 20$ and provides real-time SpO_2 and HR measurements [28].

Different light sources are used for different applications. In a traditional SpO_2 sensor two sources are used, red (R, 660 nm) and infrared (IR, 940 nm) for comparison (figure 10). In regular PPG green (600 nm) is usually selected, corresponding to a peak in the absorption spectrum of hemoglobin (Hb). Shorter wavelengths are strongly absorbed by melanin and are not as useful. Also, the increased power per Watt of green LEDs make those the preferred choice [29].

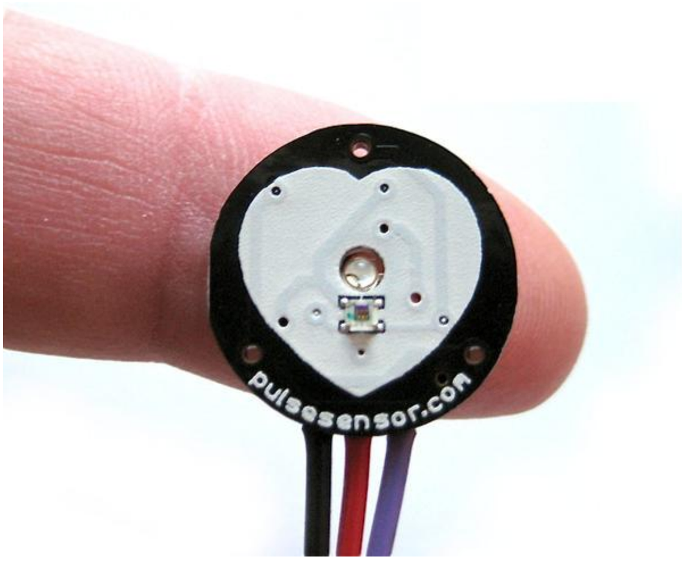


Figure 11 – The PulseSensor PPG device used in this project. It is an open hardware project with a very simple design and a small footprint. It measures the PPG signal in a reflectance using a green LED and a photodiode [30].

The PPG signal is strongly influenced by undesirable external factors such as contact force, motion artifacts or ambient light intensity making the DC component less reliable for inferring physiological information in context of prolonged measurement [31]. Front-end signal conditioning circuitry should consist of an amplifier, a high-pass filter cutting at 0.1 Hz to eliminate the DC component, a low-pass filter at around 30 Hz to eliminate unnecessary high-frequency components and noise and an ADC to convert the signal to be post-processed and recorded.

Due to its simplicity, PPG sensors are cheap and readily available and one could even almost trivially design one oneself. Open source designs such as Pulse Sensor (figure 11) are available and integrated solutions for both PPG and SpO_2 are also relatively inexpensive and come in varied form factors from ICs integrated in smartwatches and other devices to Arduino shields, a popular example being the MAX30101 IC from Maxim Integrated [32].

SYSTEM COMPONENTS

Overview

A portable biosignal acquisition system is, in a general sense implemented by integrating a few different components:

- A biosensor like the ones described above, containing the instrument itself and the required analog front-end signal conditioning components;
- A microcontroller, that interfaces with the different sensors to capture data and the transmission modules with which data is sent to other devices and / or the cloud. The microcontroller controls the overall operation, defining, namely, the acquisition sampling rate and transmission periodicity;
- The wireless communication module and/or the recording component with which communication is established with external devices to send the captured data and eventually receive configuration commands;
- The interface that receives the acquired data so it can be postprocessed through computationally heavier algorithms and presented in a human readable format.

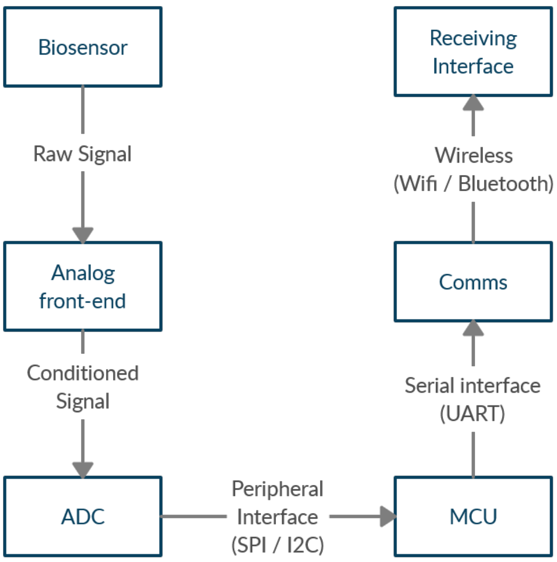


Figure 12 – A block diagram of the components and the information transmission pipeline in a biosignal acquisition system.

Microcontrollers

The microcontroller module is a system on a chip (SoC) responsible for connecting the sensors to the rest of the system components it can access through a variety of interfaces. It integrates the ADCs responsible for the signal acquisition, the clock, volatile memory (RAM), peripheral communication interfaces such as I^2C, UART and SPI and the microprocessor. The microprocessor itself runs the computational processes that make up the acquisition as its firmware that is written (flashed) in a semi-permanent memory chip, usually EEPROM.

In general, for a wearable device application, the requirements for selecting a microcontroller are:

- Low power consumption;
- Low thermal design power (TDP);
- Small form factor;
- Availability of digital interfaces for peripherals and communication;
- Optionally but desirably, ADCs of sufficient resolution;
- Sufficient performance for the application;
- Availability of the software libraries and frameworks required for development.

Different vendors, employing different architectures, offer many solutions that fill these requirements. The chosen architecture, provided the unit fullfills the requirements, is what most heavily influences both the design and the development process of the system.

AVR is an 8-bit RISC (reduced instruction set) architecture developed by Atmel, now acquired by Microchip. It spawns a family of SoCs designed for embedded electronic applications with heavy focus on extensive I/O and low power consumption and popularized by the Arduino project. The most relevant families, that include the required UART, SPI and I^2C interfaces, hardware timers and ADC pins are the ATtiny and the ATmega. The ATtiny does not include hardware interrupts which can be a problem. These come in a variety of specifications and, usually, one can be selected to specifically fill them. They are all considered low power devices but there are some specifically designed for ultra low power consumption such as the ATtiny 1634 that consumes only 0.2 mA/MHz.

Cortex-M0 SoCs are based on the 32-bit ARMv6-M RISC architecture (figure 13), comprising of ARM's small silicon dies and lowest price chips and are designed for more heavy computational requirements in embedded contexts of minimal resource availability and very low power consumption while still providing the necessary interfaces.

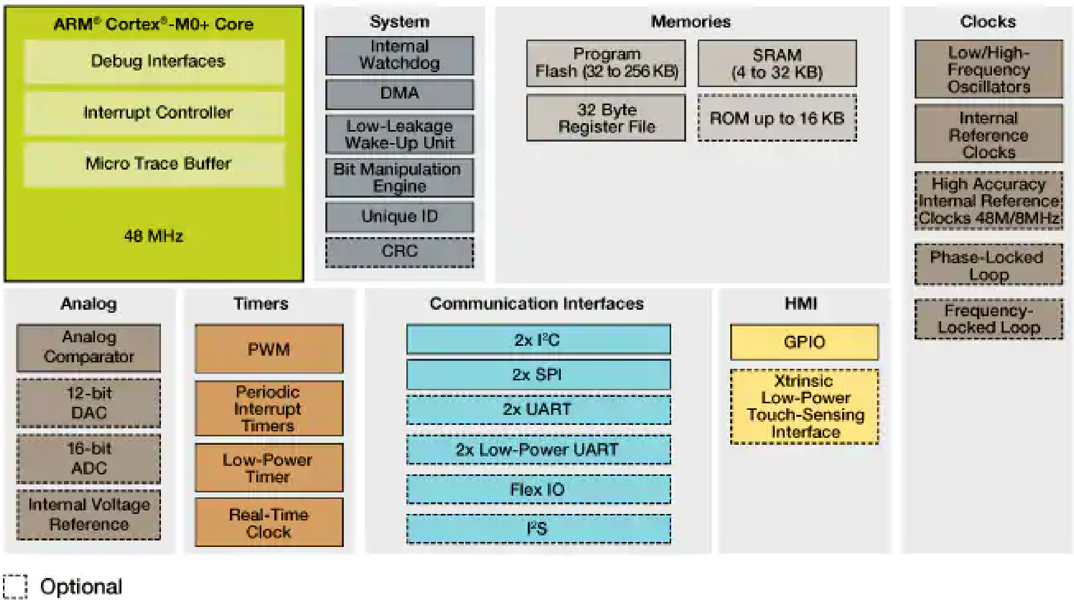


Figure 13 – Block diagram for the Kinetis KL1x series of MCUs. While not being as I/O centric as the AVR architecture, Cortex-M0 MCUs provide the necessary components on a much more flexible programming environment while maintaining very low power consumption [33].

The Cortex-A family are powerful 32 and 64-bit processors based on the ARMv7-A RISC architecture available in a multitude of devices from small smartwatches and fitness trackers to multi core smartphones and computers capable of running sophisticated operating systems and complex software and hardware stacks. While these are harder to fit in very low power applications, they may be able to integrate the postprocessing component, making for an overall cheaper and more flexible system.

There are other, less common, architectures such as PIC SoCs that are geared more towards the industrial machinery segment and can achieve much lower power consumptions while still retaining good I/O specifications, such as the PIC18F that consumes an impressive 0.032 mA / MHz but the cost of these chips is larger and software support and availability is much reduced, especially in the open source realm.

Communication

In order to achieve good autonomy, the microcontroller has to be able to send the acquired data to a more powerful system for it to be recorded, processed, visualized and eventually sent over the internet. From the physical hardware interfaces available, I^2C, UART and SPI, different components can be connected to provide such communication that meet the requirements of bandwidth, power consumption and overall convenience.

Bluetooth

Bluetooth modules are available in small form factor and are capable of interfacing with the controller through UART or SPI, provide wireless communication at a medium range of less than 10 meters and a bandwidth of about 1 Mb/s or more, depending on the version of the protocol. Bluetooth is ubiquitous on most modern computer devices making it an obvious choice for connectivity. Devices are available at different operating voltages and a typical serial module draws about 30 mA, 150 mW @ 5V during operation. The equipment is required to be paired with the device it communicates with, which may pose additional setup steps or if otherwise using default settings, some security problems.

Also worth considering are Bluetooth Low Energy (BLE) modules that are not that much expensive (about 1€ extra) and provide a sleep mode with consumption of about 1.5 mA and 8.5 mA in active mode without any notable disadvantages.

LoRaWAN

LoRaWAN is a Low Power, Wide Area (LPWA) network protocol designed for the Internet of Things. Somewhat like Wi-Fi, it connects devices directly to the internet through gateways but also allows for device to device connection and bridging through implementing different device classes on the network structure.

This protocol allows for current draws of about 1-2 μA in sleep mode and much faster data rates in operation (for about 117 mA), almost eliminating the communication module's contribution to the overall power consumption of the system [34]. Along with its low power features the protocol implements useful features for managing embedded devices such as Firmware Over The Air (FOTA).

Despite the promising specifications this technology requires some level of infrastructure development to be successfully deployed and doesn't seem yet available and mature enough for such a low scale application to be seriously considered.

Local storage

Another alternative is to write to local storage via wired communication to a medium like an SD card or USB flash drive and then either manually extract the data or automatically upload it to the postprocessing device when it becomes available through one of the previous considered channels.

This allows for much better autonomy both in terms of power consumption, since the wireless device is not required to be always connected, and convenience as the sensors don't have to be always in range of the recorder. MicroSD card readers are small, relatively inexpensive and can be connected to the controller through the UART or SPI interfaces and provide good data-rate and power consumption, depending mostly on the card itself and not on the reader. They are very simple devices only requiring appropriate pin breakout and, in the case of 5V controllers, a voltage regulator and logic-level shifter to make them work with SD which uses 3.3V logic.

Interfaces

In order to preserve autonomy on the controller, acquired data should be transferred to a more powerful and capable device for postprocessing, storage and eventually delivery over the internet to other centralized systems such as the doctor's computer or medical databases. This device should be able to communicate with the sensor system through one or more of the previously considered channels and, in an ideal case, in an asynchronous manner in order to not require it to be physically available all the time during the recording process. Different computational devices can fill this role, from mobile devices such as smartphones to full desktop computers.

Android

The Android platform, developed by Google, is based on the GNU/Linux operating system (OS) and is present in most smartphones today. It includes many useful libraries and APIs designed specifically for mobile devices that allow for easier development of application-based solutions. Depending on the API version selected one can be sure the application can be deployed in most Android already existing devices but also low cost dedicated solutions can be employed, allowing for more control of the device specifications and configuration by the developer. These run ARM Cortex A multicore processors and a full range of communication stacks, from mobile 3G, 4G and 4.5G networks to Wi-Fi, Bluetooth and NFC, allowing for a wide range of solutions.

Rasberry Pi

The Raspberry Pi and similar ARM based single board computers provide full GNU/Linux OS network and Bluetooth stacks and conventional computer I/O in a small form factor and relatively low power requirements, making them a compelling alternative for dedicated devices. Although more flexible, they don't benefit from the same highly developed APIs as the Android platform, being somewhat dependent on general Linux support from the manufacturers of the devices they're interfacing. They also require external hardware for portability, I/O and storage, when those are required.

Computer

Interfacing with a full-scale computer is the more powerful, less portable solution. Through a x86 PC and the OS of choice one can most easily visualize the data, develop and test postprocessing algorithms using advanced tools like MATLAB and make use of APIs and toolchains available in different programming languages and frameworks. Although the most useful for the developer, it should not be considered for production use with the patient due to the severe limiting factors of poor convenience and mobility as well as high power consumption.

Form factor

Form factor, i.e. the size and shape of the components, is evidently an important aspect of any wearable device. A system designed to be attached to the body for prolonged periods of time has to be as small and light as possible. The wiring between the sensors and the microcontroller unit can only be avoided with a level of miniaturization that still cannot be achieved in the scope of a low budget approach like the one in this project but is undoubtedly what the future holds for these devices. High-end ECG devices already integrate all the required circuitry on the electrodes themselves and PPG sensors can be easily integrated in comfortable wearables such as smartwatches. Flexible circuitry and sensors are starting to become a reality that will allow for more comfortable and resistant electrodes and probes as well as electrochemical sensors that are much less viable in rigid PCB implementations.

In the scope of this project effective usability is compromised for proof of concept, simplicity and cost minimization yet still a small form factor is somewhat achievable. The largest component in the system is the 4 x 3 x 0.5 cm battery and the PCB components can be stacked onto each other so it is expected that the complete microcontroller unit can fit in a 3D printed plastic case of about 4 x 3 x 2 cm which can be strapped to a wristband, on the waist or any other place for the convenience of the user. The wiring remains the biggest challenge, being easier to integrate the necessary circuitry in the sensors themselves than to implement unobtrusive and effective wiring along the body as the ECG requires. A vest containing the sensors can also be considered that includes flexible wiring inside the fabric but such an approach presents its own challenges such as the need to have more than one unit so they can be washed and the unnecessary discomfort it may produce for the benefit of supporting the wiring, somewhat minimizing motion artifacts and accidental disconnections.

Prototyping platform

After considering all the components required for the system two biosignal focused prototyping platforms were available and were considered for the development of the project.

Hexiwear

This system (figure 14) comes in a smartwatch form factor, is based on an ARM Cortex-A microprocessor and includes a built in SpO_2 sensor (MAX30101), all the wired interfaces (UART, SPI, I^2C), a micro SD card slot, 16-bit ADCs, a BLE communication module controlled by an auxiliary Cortex-M microcontroller, a 190mAh battery with its respective charging circuitry and a 1.1" OLED display.

Figure 14 – The Hexiwear system in its docking station with two custom made clickboards plugged in. It has wireless connectivity with the smartphone and a small OLED display. Requires the docking station for expandability [35].

Some of the components are available through a docking station that increases the size of the system considerably and provides the proprietary mikroBUS interface slots for the necessary ECG expansion module. The MCU can be programmed with all the standard ARM toolchains in bare metal or integrated in any of the available ARM compatible real time operating systems (RTOS) such as mbedOS or freeRTOS.

Maxim MAXREFDES100#

Maxim's development board (figure 15) designed for their hSensor platform for integrating sensors for medical and high-end fitness applications. The system is based on an ARM M4F MCU, the MAX32620 and provides USB and Bluetooth communication interfaces, as well I^{2}C and SPI for the peripherals. An SpO$_2$ MAX30101 optical sensor is included, soldered directly onto the PCB.

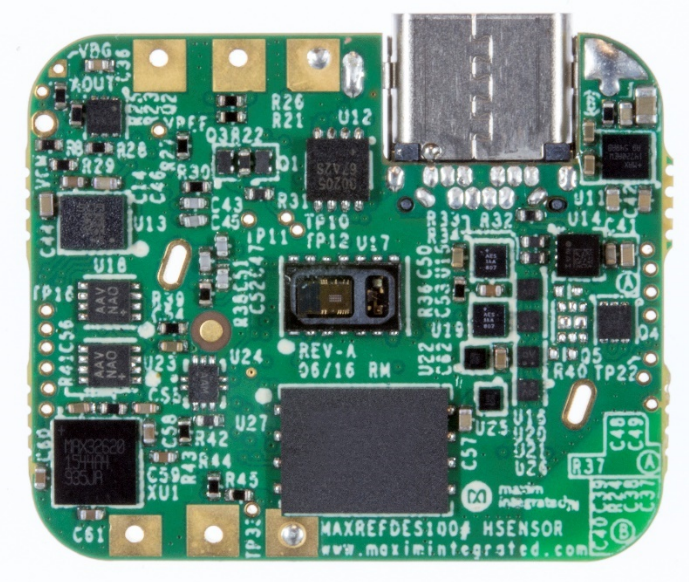


Figure 15 – The MAXREFDES100# Health Sensor Platform. It includes a SpO$_2$ sensor soldered into the board and the ECG cables need to be soldered in. The only I/O port is a USB plug but it includes a Bluetooth module for communications [36].

Also included is a pair of ECG cables that need to be soldered onto de board and an analog front-end for ECG (MAX30003) with an included HR detection algorithm (R-R). A few additional health related sensors are included like a skin temperature sensor and an accelerometer but no additional expansion pins are provided for easy expandability. The MCU programming is based on ARM toolchains and the mbedOS RTOS like in the Hexiwear device. A battery is not included but can be acquired separately and the system can also be powered directly through USB.

HealthyPi

The HealthyPi board (figure 16), from Protocentral, is based on an ESP32 SoC, a 32-bit dual core architecture, that can be programmed with the Arduino SDK through its ESP3 Core. It includes UART, BLE and Wi-Fi communication interfaces as well as SPI and I^{2}C for peripherals but there are no readily available expansion pins. Also included are front-ends for ECG (ASD1292R from TI) and SpO$_2$ (AFE4400 also from TI) as well as a digital body temperature sensor (MAX30205).

Figure 16 – The HealthyPi hat comes in a Raspberry Pi "Hat" form factor but can also be used standalone with a battery connected (top right). It includes I/O for a pulse oxymeter (RS232 9 pin) and ECG (3.5 mm) sensors as well as BLE and Wi-Fi communication [37].

A battery can be plugged directly onto the board to operate it in wearable mode from which smartphone apps for Android and iOS as well as a convenient Webservice interface are provided to interact with the device. The complete kit is designed to be plugged inside an enclosure to a Raspberry Pi (HAT mode) and includes a large touchscreen interface.

MySignals HW

MySignals (figure 17) is an Arduino compatible board based on the ATmega328 that provides 18 analog inputs, 12 of them in the form of 3.5 mm jack plugs, BLE and Wi-Fi communication, TFT screen, UART, I^2C and SPI interfaces and an onboard encryption module. In the eHealth kit an SpO_2 sensor is included as well as body temperature, BP, glucometer and position sensors but no ECG sensor or interface.

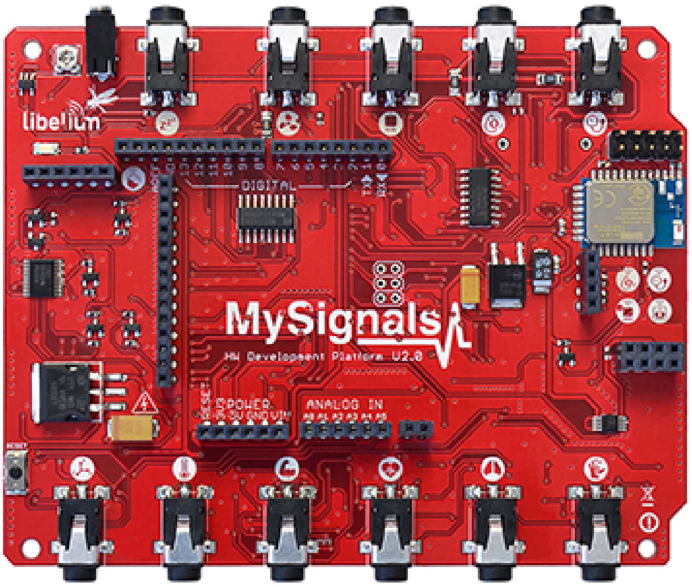


Figure 17 – The MySignals HW board is an Arduino Uno compatible that includes a lot of I/O and connectivity. Can also be plugged to an Arduino like a regular shield to connect to a computer for programming [38].

The system is designed to work with their proprietary Libelium Cloud for data storage and smartphone clients are also provided to visualize the data. The system can also be programmed as an Arduino with the Arduino SDK and IDE and should also be possible to program bare-metal using the regular avr-gcc toolchain although that would have to be done from scratch as no firnware source code is provided. There is also a SW version based on the ATmega2560 that comes in a plastic enclosure with an integrated TFT and a graphical interface geared towards mobile app development.

BITalino

BITalino (figure 18), developed by PLUX, comes in a simple and fully modular PCB form factor designed specifically for biosignal acquisition. It is based on the popular ATmega328P MCU, the same as Arduino Uno, and includes a 10-bit ADC, an ECG front-end (AD8232) along with other modules for electromyogram (EMG), electroencephalogram (EEG) and electrodermal activity (EDA) sensors as well as a many breakout pin slots for expandability. Also included is a Bluetooth module (BLE optional), all the wired interfaces (UART, SPI, I^{2}C) and a 700 mAh battery along with the respective charging and power circuitry.

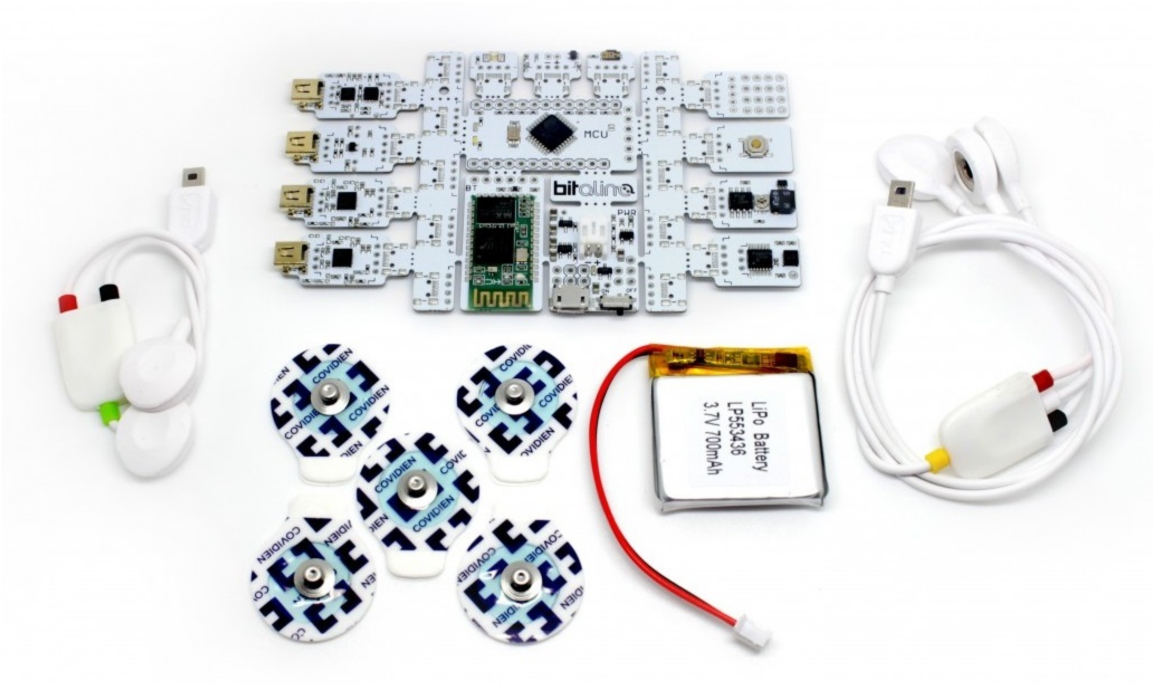


Figure 18 – The BITalino (r)evolution kit. Its perforated PCB is designed so every module can be snapped off to use with different devices or configurations. It includes analog signal conditioning modules (on the left) for ECG, EEG, EMG and EDA [39].

The MCU is programmable bare metal with any AVR toolchain or with the Arduino bootloader and an opensource firmware is included. Many APIs are also provided for interacting with the default firmware from Android (Java), Linux (C++, Python), MATLAB and most other computer platforms for development and testing of the postprocessing algorithms. The PCB comes perforated so each module can be snapped off and used in other systems or soldered back in different configurations allowing for flexibility regarding form factor. This system is based fully on open source software and hardware which allows it to be easily extensible. Relatively low ADC and sample rate are the main inconvenients of this system.

Final considerations

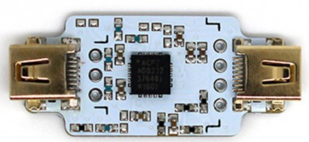
All things considered the BITalino platform was chosen for the simplicity of its design, that would be much easier to translate into an industrial prototype later in development, the inclusion of the sensor front-ends that allow for easier expandability and the lower overall cost of the components and power requirements of the MCU. A very simple, open hardware, PPG sensor (PulseSensor.com) was acquired to make up for the lack of a SpO_2 that was present in the other platforms. Although this sensor will not be capable, by itself, of measuring the SpO_2 signal, it should be enough to determine the secondary measurements and can easily be replaced by a proper SpO_2 sensor such as the MAX30101 in future revisions. A simple SPI microSD card reader was also acquired to provide mass storage capability to the device.

SIGNAL PROCESSING

Preprocessing

Signal preprocessing in the context of the device developed in this project consists in the manipulation of the acquired analog signals in order for them to be accurately and precisely read by the ADC on the MCU, if possible with no loss of relevant information and filtering out known sources of interference, noise and other undesirable components that accompany the raw signals.

In the case of the ECG signal, conditioning requires high amplification of the small acquired potentials and high input impedance to facilitate reading from the ADCs as well as powerline, low and high-pass filtering and high common mode rejection. This is achieved, in this case, with the AD8232 integrated circuit (figure 19). This unit provides an instrumentation amplifier (IA), a 2-pole high-pass filter and a 3-pole adjustable low-pass filter as well as some other convenient features like an additional operational amplifier to allow for extra gain or low-pass filtering, a right leg drive amplifier (RLD) to improve common mode rejection, a reference buffer, a fast restore circuit to improve response time and leads off detection to allow for automatic configuration of either two or three electrode setups.



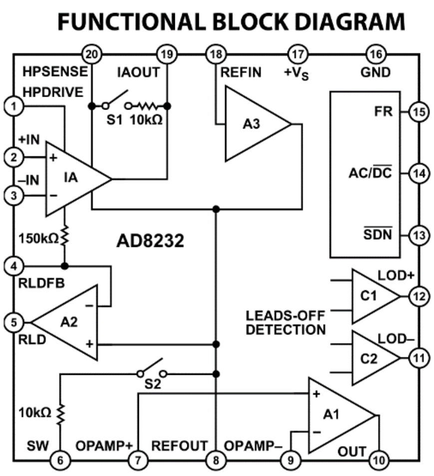


Figure 19 – a) The BITalino module containing the AD8232 ECG analog front-end [40] and b) its functional block diagram. It contains an IA and 3 additional Op Amps, 2 for filtering and one to be configured freely by the end user [41].

The performance of the component is highly configurable through the careful choice of the external passive components on the circuitry in which the IC is integrated. In the case of the provided PCB in the BITalino board the specifications are:

Gain: 1100, Range: +/- 1.5 mV, Bandwidth: 0.5 – 40 Hz, Input Impedance: 100 GOhm and CMRR: 110 dB [41].

As for the PPG sensor (figure 20), as it was designed specifically for the ATmega 328P and similar MCU's ADCs, it already includes all the necessary components to provide a conditioned signal: an MCP6001 operational amplifier and a passive RC low-pass filter cutting off at about 339 Hz. Further conditioning such as the filtering off of powerline noise and low-frequency components was deemed unnecessary since this is a relatively simple signal from which the only features to be extracted are the occurrence of wave peaks and such filtering would not solve the problem of motion artifacts that is the only one detected on the signal, but can be considered if further precision is deemed necessary.

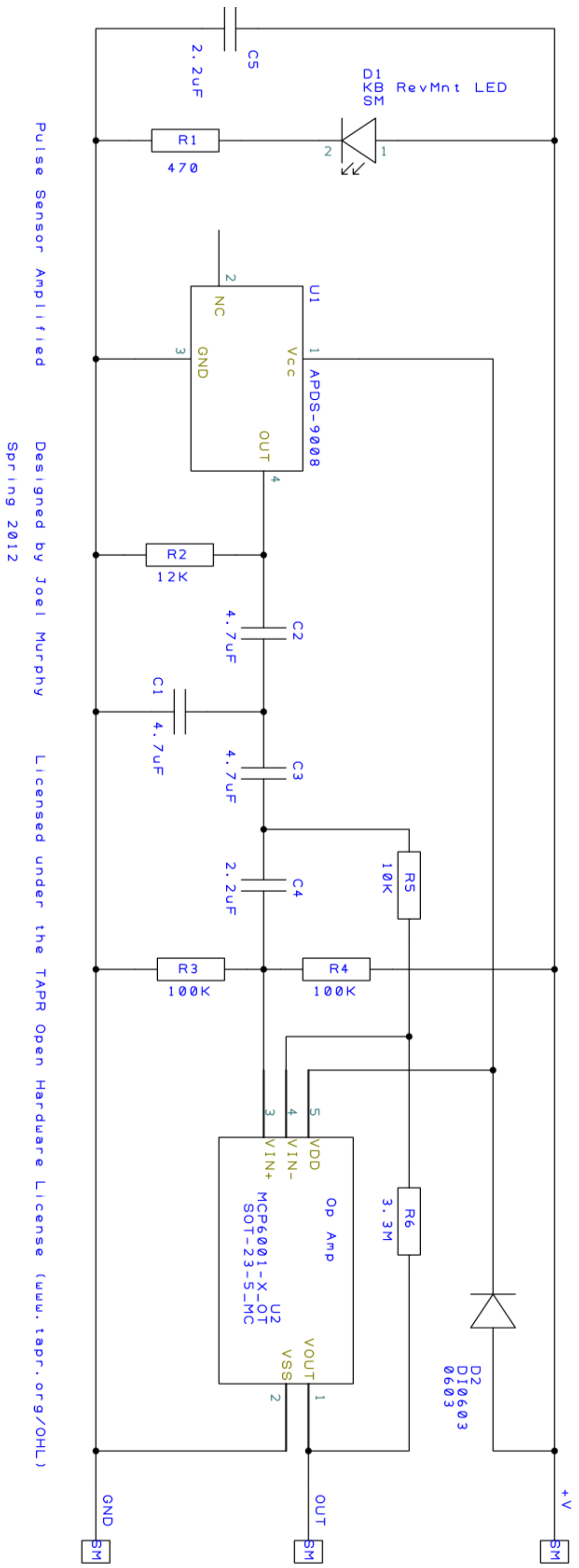


Figure 20 – Schematics for the PulseSensor device. This open hardware design includes just a few simple components: a green LED, the APDS-9008 photodiode, an operational amplifier and a passive low-pass filter [42].

Postprocessing

Postprocessing in the context of the device proposed in this project consists of all the signal manipulation that occurs after its acquisition by the MCU. This consists of signal interpretation such as feature extraction and calculation of the relevant secondary quantities, BP in this case, as well as further modification of the data for the purpose of storing and transmitting it to other systems, be it formatting, encryption and compression. All postprocessing in this case will be done on the Android device to which the data is transferred from the MCU but, in an ideal scenario, to optimize power consumption and assuming proper algorithm optimization, feature extraction processing could be done on application specific integrated circuits (ASIC). Despite this, an intermediate approach would be to program the postprocessing algorithms in field-programmable gate array (FPGA) chips. The use of these devices is only justifiable when reconfiguration to implement different processing algorithms in dedicated hardware is required.

Heart Rate and Pulse Rate

Hear Rate and Pulse Rate can be measured directly from the ECG and PPG waveforms respectively by identifying any specific feature in them and determining the time between two consecutive occurrences of said feature, considering the sampling rate of the controller, 1000 Hz. In the case of the ECG the R peak will be used and in the case of the PPG the peak of the waveform, since these points will also be used for the estimation of pulse transit time (PTT), a quantity that will be measured for the estimation of BP. These difference values, in seconds, are inverted and multiplied by 60 to be presented in the conventional notation of beats per minute (bpm).

Blood Pressure

There are many references in the literature regarding cuffless and non-invasive methods of determining BP, most of them refer to its inverse relation with PTT and related features [27] [43] [44] [45] [46]. Pulse transit time refers to the delay between the heart beat itself, detected through its electrical activity through the ECG as the R peak, and the arrival of the respective pressure wave to some arbitrary peripheral point in the vascular system. Peak pressure is greater further away from the heart due to the contributing component of the reflected backwave so the measurement is best made at an extremity such as the fingertip or earlobe.

Along with PTT others features are considered in the literature, such as PTT^2, diastolic time which is the descending period of the PPG curve and pulse arrival time (PAT) which can be measured at varied points on the curve, called PATf, when measured on the foot of the wave, PATd, on the peak of the derivative and PATp, on the peak of the wave itself. A PAT measure is made from the R peak to the specific point and doesn't subtract the pre-ejection period (PEP).

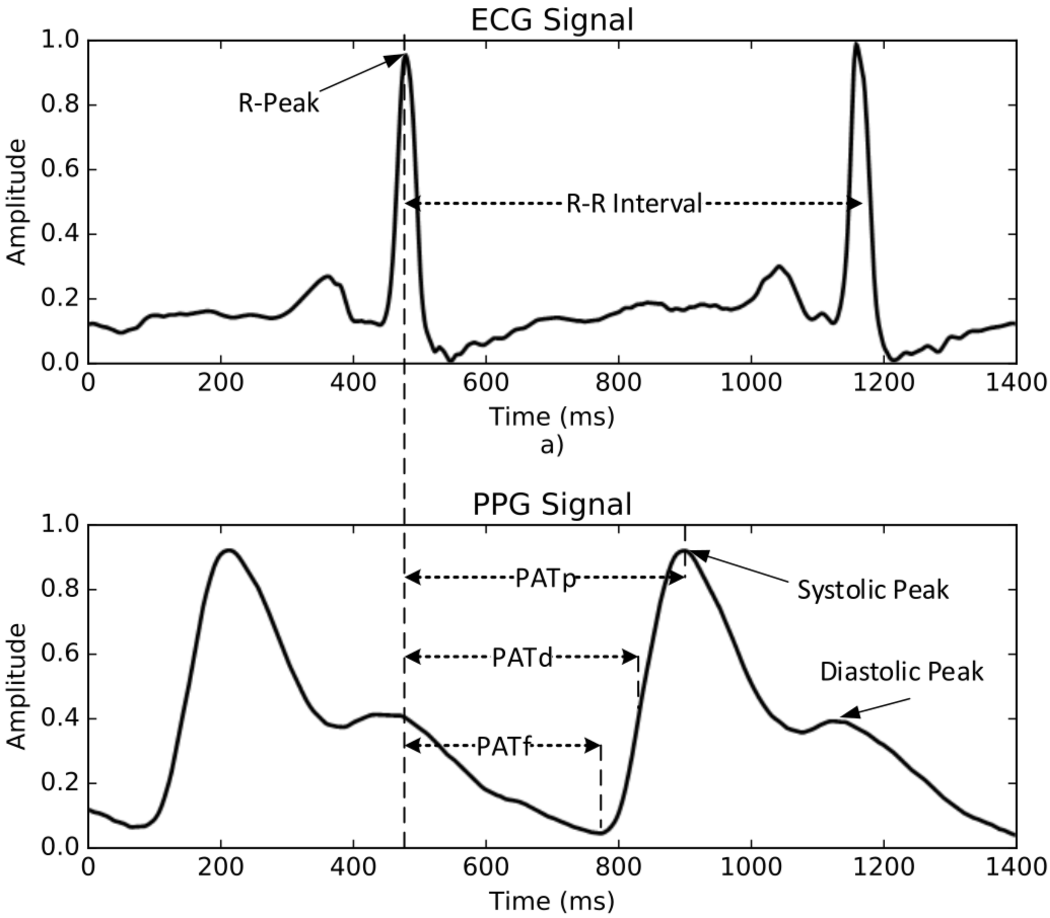


Figure 21 – Illustration of different pulse times that can be used to determine BP. All of these blood pressure wave velocity related measurements correlate significantly with BP in inverse proportionality [47].

All of these correlate significantly with BP. There is no consensus on what PPG feature is best to consider for the calculation but the crucial factor required for estimating BP is that the feature detected in the PPG wave to be compared with the R peak of the ECG is consistent across measurements and with the calibration procedure. Other studies show that correlating PTT with different features such as pulse intensity ratio (PIR) [48] [49], wavelet analysis [50] or machine learning approaches using many PPG features can also improve correlation [51] [52].

In this case, for computational convenience PATp will be used so the same basic peak discovery algorithm (figure 21) can be used in both R peak and PATp detection.

```
1) In the 10 x samplerate ECG buffer:
find max A(i) of last 2 * samplerate → A(i)
```

```
2) if (A < 1000 | A > 10) A → threshold else break
```

```
3) start = 600 x samplerate, end = start - 0.2 * samplerate
```

```
4) for i from start to end
find max A(i)
if (1.25 * threshold > A > 0.75 * threshold V A(i-1) < A(i) > A(i+1))
A(i) → threshold, i → start, [I, start] → I[] (peak found)
```

```
5) repeat 3) and 4) until end <= 0
```

```
repeat 1) to 5) for the PPG series getting two arrays of indexes I[]
and J[] corresponding to the peaks
```

```
6) for k in I if J[k] > I[k] then PTT = (J[k] - I[k]) / samplerate
else PTT = (J[k+1] - I[k]) / samplerate
```

Figure 22 – The algorithm used to find signal peaks. Due to good signal conditioning the waves mostly oscillate around 500 and artifacting usually saturates the ADC at 1023. One should wait for stable waveforms before considering PTT and HR measurements as appropriate. The considered window of 20 ms for looking for a peak is the physiological limit for two consecutive action potentials in the heart [53].

The algorithm checks for all peaks within an adaptive amplitude threshold to ignore the P and T waves and exclusive to a moving window of 20 ms corresponding to the physical minimum physiological latency between two heartbeats. An array is obtained containing the position of these peaks in the buffer. PTT is then obtained from the difference in the position of a given R peak (a peak in the ECG buffer) and the next corresponding

PTT peak. Heart Rate and Pulse rate is calculated as 60 times the difference between any two consecutive peaks divided by the sample rate for each buffer, respectively.

As the system only refreshes once every second, moving average of the last n peak-to-peak differences can also be used to smooth out the measurement.

The calibration parameters are shown to be related to blood density, average arterial cross-section, distance between the heart and the PPG measurement site and the compliance of the arterial walls. All of these are subject specific and can also change in the long time, especially as coronary disease progresses. As such, calibration must be made for every subject and repeated periodically. Studies indicate that a single calibration should maintain measured values within the Advanced of Medical Instrumentation (AAMI) standard's tolerance of 5 mmHg for DBP and 8 mmHg for SBP for at least 2 years, not considering the intrinsic error of the instrument itself. The calibration process can be performed using linear regression methods such as least squares or random forest on a dataset such as the one presented on figure 22.

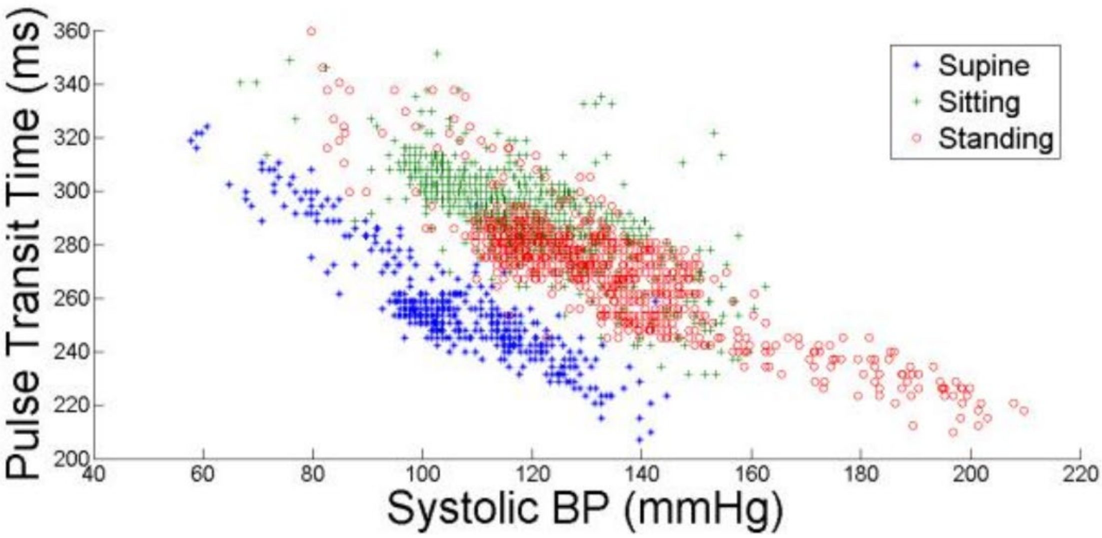


Figure 23 – A typical plot of the relation between PTT and BP used for determining the calibration line. A significant bias is introduced depending on the posture of the subject and should be considered when interpreting the measurement [44].

When access to a continuous BP reference signal is not possible or convenient, then at least two measurements should be made, at rest and after physical stress.

Two calibration lines should be determined, one for SBP and another for DBP. Pairs of values DBP/SBP – PTT are measured using a conventional BP device and PTT readings from our system. From them the appropriate fit should be calculated and inserted in the system through its settings menu. In the case of a simple measurement of just two points, at rest and under stress, BP_1 and BP_2, as is considered that:

$$BP_1 = m \times PTT_1 + b$$

and

$$BP_2 = m \times PTT_2 + b$$

follows that

$$m = \frac{BP_2 - BP_1}{PTT_2 - PTT_1}$$

and

$$b = BP_1 - m \times PTT_1$$

The two pairs of m and b values, one for SBP and another for DBP can then be inserted in the settings activity of the application so these values can be displayed in real-time, as PTT is recalculated based on the ECG and PPG measurements.

ECG feature extraction

The literature is rich in both conventional and novel methods of computationally determining ECG features [16] but the most common is still the visual inspection of the graph by a trained practitioner. The simplest method is analysis of the time domain morphology (TDM) of the wave via the discovery of the local maxima and minima of each pulse [53] as well as the study of the signal's derivatives. This approach presents many problems related to baseline wander of the signal as well as inability to interpret often common not well behaved curves, be it due to motion artifacts or existing pathologies. Since most of the features rely on some level of precision to be meaningful, this approach is mostly considered insufficient.

To solve this problem many more complex approaches are the focus of much research in the literature and present much better results in correctly identifying the features. The most common and most cited studies rely on methods using discrete wavelet transform (DWT) analysis. Studies show that even the computationally simplest Haar wavelet based algorithms present very good results [54] [55].

Also common in the literature is the employment of more general and probabilistic mathematical models for classification such as artificial neural networks (ANN), support vector machines (SVM) or hidden Markov models [56] [57]. These approaches can yield very good results, both based on the quality of the model itself but also, and most importantly, on the quality of the datasets used for training and validation.

As the implementation of these more complex models is beyond the scope of this project, the determination of simple features like the R peak will be done through TDM, isolating single waves and determining their maximum, as described above, for these are the most relevant features for determining the other variables of interest HR and BP.

Nonetheless, a more accurate and complete processing algorithm should be added to the Android App when available. The full ECG graph is recorded and can somewhat easily be analyzed a posteriori in a computer using dedicated software or even more common powerful tools like MATLAB's Signal Processing Toolbox.

Encryption

In an increasingly integrated digital world, personal user data, and specifically medical data should be handled with the utmost care. Any leak, malicious disclosure or theft of user data invariably ends up in profiling databases to be used, sold, resold, merged and eventually used for all sorts of predatorial behavior, from aggressive advertising to credit score and health or life insurance denial.

For this reason governments are finally realizing and taking action to protect citizen's data from aggressive collectors and aggregators through legislation such as the recent European Union's General Data Protection Regulation (GDPR) but go as far as the '90s when the Clinton administration produced legislation deeming email and related non-encrypted internet communications improper for the transmission of medical records as it was already at the time considered unsafe from a privacy perspective.

The medical industry, and the development of telemedicine devices in particular, would benefit greatly from a centralized and common standard for aggregating and ensuring confidentiality of medical records. The vast diversity of measurements and formats and sheer quantity of data makes this a non-trivial task. If pseudo-anonymity is achieved, allowing for compliance with GDPR and similar regulations, such a database could also contribute greatly for the advancement of machine learning models, identification of public health trends and many others fields where large datasets are crucial both for research and validation.

While this is still not the case one can still take measures to prevent common security holes from disclosing our medical data. Most leaks occur during transmission over the internet or are extracted from the storage of a compromised machine. The most common, simple and effective way to protect against this is through the use of public-key cryptography systems such as PGP or SSL certificates. These utilize asymmetric functions such as SHA or RSA that encrypt a message with a publicly distributed public key and can only be decrypted with the respective private key, ensuring a message can only be read by its supposed recipient. The main difference between PGP and SSL is that in PGP these public keys are traded peer-to-peer, requiring some level of trust in the transmission protocol, and in the case of SSL certificates, there is a centralized certificate authority (CA) issuing and potentially revoking the credentials. Through such a trust authority is much easier to achieve pseudo-anonymity for the participants but the problem is only transferred to the authority itself which must then be publicly auditable somehow.

This is an ongoing issue much debated in the computational security community and transversal to many fields such as medical, finance, governance, etc. Many Android libraries are available that implement the PGP and SSL and in the case of our own application, a private public key pair can be hardcoded in the firmware of the device or even at the application level (Bluetooth provides its own layer of encryption during that transmission stage) and distributed with the device itself. It is worth considering that placing encryption process at the MCU level is a computationally intensive task that would significantly degrade autonomy. In this case a dedicated co-processor for cryptography should be added to the system as ASICs are much more energy efficient and these are relatively cheap and readily available (the ATECC508A for example).

For this project, a simple encryption scheme was designed, consisting the generation of two PGP keys, one for the acquisition system and another for an authorized party to decrypt the data. This authorized party needs to be defined at the system setup as encryption requires the receiver's public key to encrypt the file with PGP. In a more advanced system keys could be added dynamically, provided the necessary security considerations are taken into account in such a transaction.

System design

The complete system (figures 24, 25) consists of the ECG system containing 3 Ag/AgCl electrodes and the respective sensor module provided by Plux and the PulseSensor PPG sensor can be applied either to the fingertip or the earlobe. The sites for the sensors can be chosen to improve convenience and comfort, but, specially the PPG sensor site, must remain the same after BP calibration.

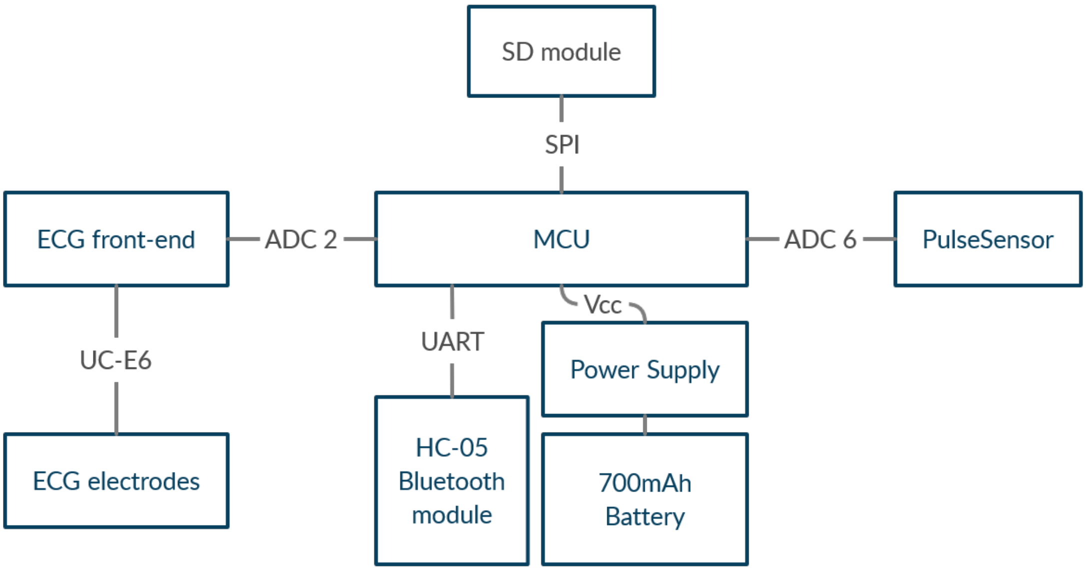


Figure 24 – A block diagram of the wearable part of the developed system. It shows the individual parts and the interface through which they connect to each other.

These sensors attach to the BITalino platform through the available UC-E6 ports but can also be soldered directly to the respective MCU's SPI pins in a future design. The MCU unit itself is a simple PCB containing the ATmega328P SoC, its required 16 MHz oscillator, a status LED and some pull resistors for the interfaces. Attached to it are also the Bluetooth module, a HC-05 board, using the UART interface and the power supply and battery charging unit, containing a status LED, an ON/OFF switch, a microUSB plug exclusively for power delivery, the necessary logic level converters for 5 V and 3.3 V operation of different components and the auxiliary passive components (capacitors and resistors). An SD card module, to record the sensor data in parallel to the Bluetooth transmission, was also added through the SPI interface. It is a simple breakout board containing a single logic level converter and the standard microSD socket where a 1 GB microSD card was used.

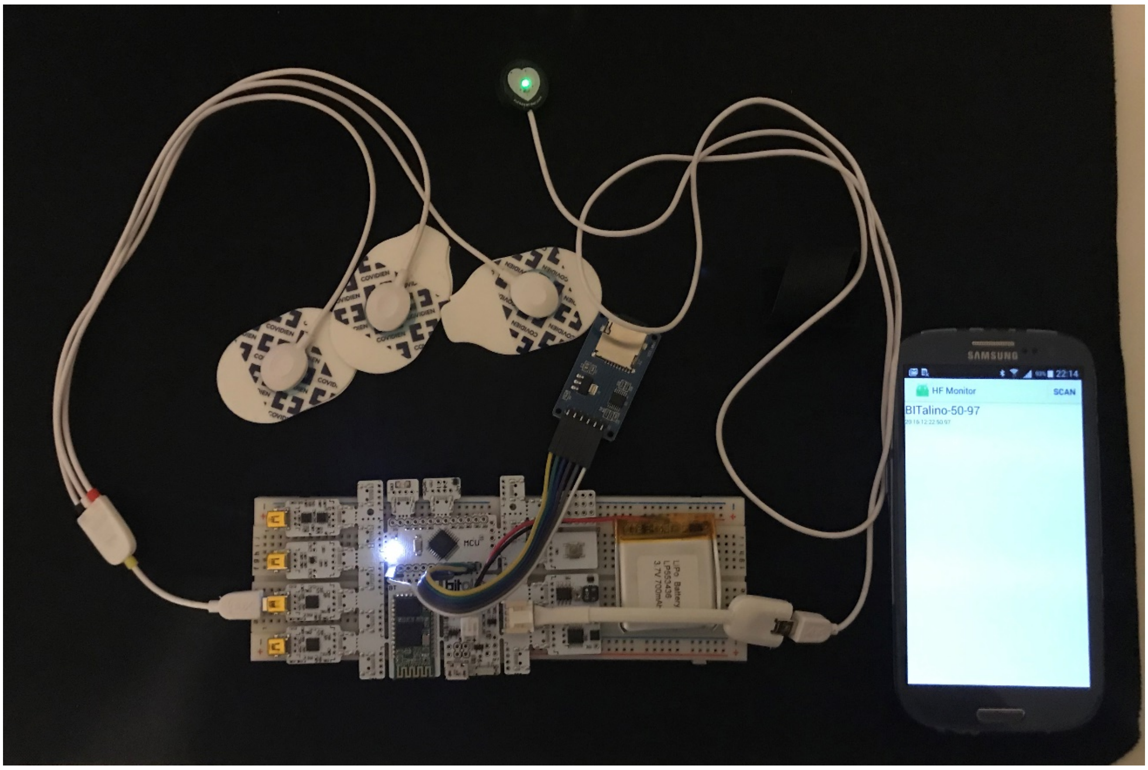


Figure 25 – A picture of the complete system assemble. The ECG electrodes plug into the ECG analog front-end module, the PulseSensor plugs directly into the A6 ADC via an UC-E6 adapter. The battery plugs into the power supply module and the SD module connects to the SPI pins on the MCU module.

The remaining modules on the BITalino development board are not used and are disabled in firmware settings to reduce power consumption. The system communicates with a Samsung Galaxy S3 Neo (GT-I9301I) running Android 4.4.2 KitKat and the developed HF Monitor App. The system can also be connected via Bluetooth to a computer where data can be streamed and analyzed through any of the available programming APIs or through the BITalino MATLAB toolbox.

Firmware

The BITalino firmware [58], distributed as open source and with the GNU General Public License (GPL) v3.0, is mostly sufficient and can be flashed to any ATmega328P system containing a compatible Bluetooth module. The only adaptation that needs to be done to the firmware is enabling the microSD card functionality which was done through the use of Roland Riegel's AVR SD card library [59] that is also GPL licensed. A buffer is implemented in the firmware and right as each BITalino frame (a data structure containing the state of all sensors) is through the Bluetooth interface it is also added to the buffer. When this buffer is full it is written to the SD card and cleared. The firmware was compiled using the avr-gcc toolchain 10.2.0 and flashed to the MCU, as per the instructions on the firmware GitHub page, using the GPIO pins of a Raspberry Pi to connect to the ISP pins of the MCU and using the program avrdude 6.3 to perform the flash process. A critical problem of this implementation is that the hex image produced with the BITalino firmware plus the SD and Fat libraries required to operate the microSD card is larger than the 32Kb program size capacity of the ATmega328P. This limitation could be surpassed either by using an auxiliary MCU to handle just the writing process (such as the OpenLog implementation that contains another ATmega328P), trying to minimize the SD library by removing unnecessary features or simply by deploying an MCU with more memory such as the ATmega2560.

Android application

The Android application was developed using the Android Studio IDE and uses the BITalino API [60] provided by Plux to interact with the BITalino firmware, open-keychain's openpgp-api [61] for encryption and jjoe64's GraphView library [62] to display the signals' waveforms, both under the Apache 2.0 license. The application consists of 3 activities, a scan activity to discover and connect to compatible Bluetooth devices, a settings activity where the BP calibration curves, sample rate and file encryption can be configured and the main activity (figure 26) where signal acquisition can be started and stopped and the relevant signal information is displayed. The BITalino API exposes the BITalinoCommunication object containing a device specific address hardcoded in the firmware (btspp://201612225097) as well as the methods to interact with the device, the most relevant being:

```
init(), connect(String address),start(int[] settings, int sampleRate),
stop(), disconnect(), state()
```

After a successful start method is invoked, messages are received via the Android messaging pipeline, one for each sample, or BITalino frame, that are consumed by a BroadcastReceiver and passed to a message handler. Two fixed size buffers containing 10 seconds of data are implemented as LinkedList objects as well as a simple counter. The handler method gets the raw sensor data from the BITalino frame and places it on the top of the list, removes the last value and increments the counter. When the counter reaches the size of the buffers the handler calls the refreshUi method and resets the counter. The refreshUi method appends the buffers' contents to the GraphView objects responsible for drawing the graphs on the UI and calls the methods that implement the signal processing of the secondary variables, PTT, SBP, DBP, HR and PR to recalculate them based on the new data and refresh them on the UI. Since all the signal processing elements are implemented as their own methods in the main class, these can be easily adapted and even multiple methods can be implemented and selected through the settings activity. The refreshUi method also appends the raw data to a file being written to the SD card of the device that can then be extracted and processed on a computer using software such as a MATLAB script that was developed and can be used to display further relevant information from the file.

Optionally, the stop method calls the openpgp-api method that encrypts the data text file that was written during acquisition using the devices PGP private key and a hardcoded recipient's public key and deletes the plaintext file.

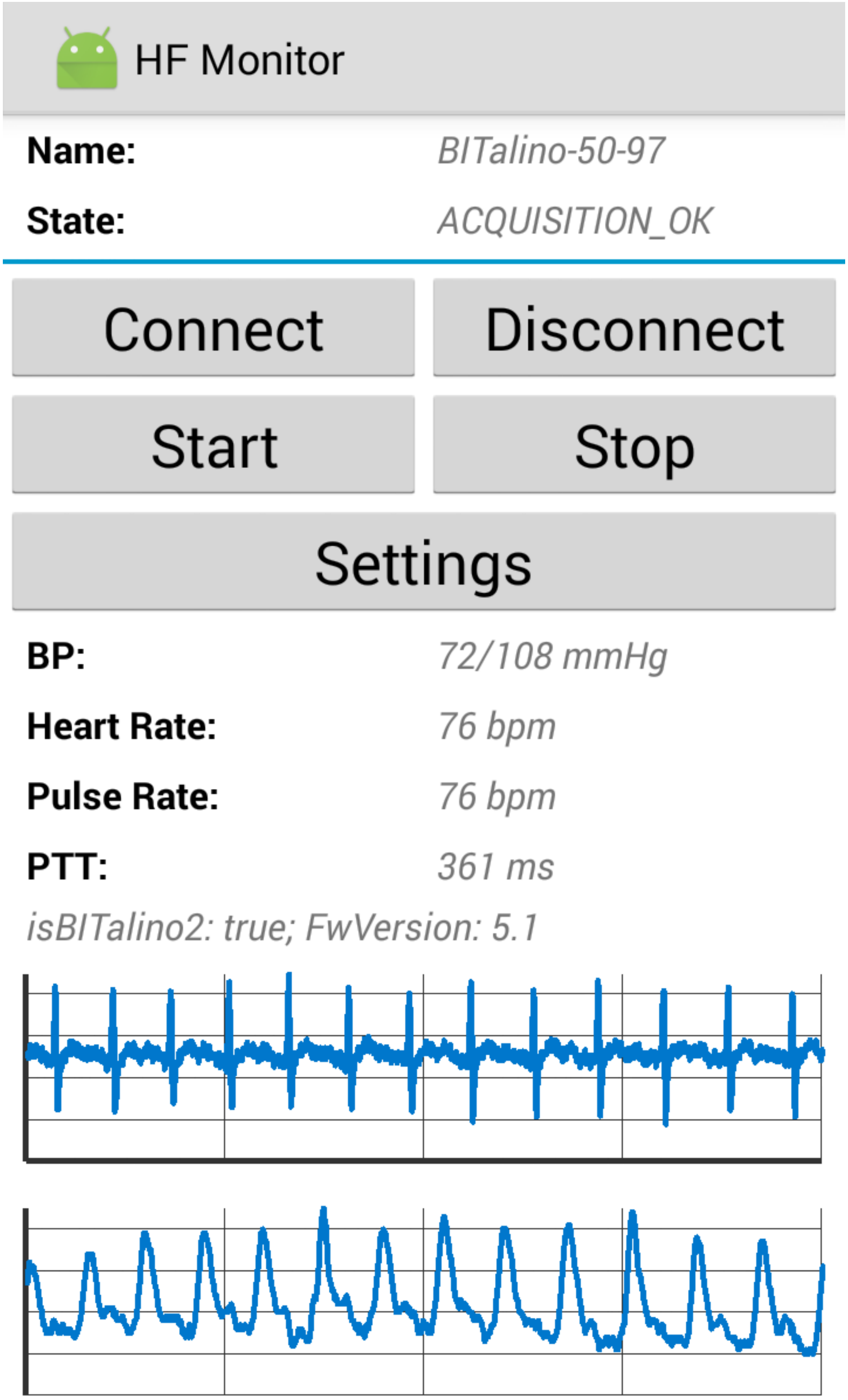


Figure 26 – The HF Monitor application's main activity. The measured signals ECG and PPG are graphed on the bottom and the calculated variables are shown in the middle. The information refreshes every second. A settings button allows access to a settings activity where sample rate and the BP calibration parameters can be selected. PTT is shown to be used in the BP calibration calculations.

RESULTS

Signal quality

Despite many limitations the important BP, HR and waveform information can successfully be acquired with this system. Further comparative analysis is required to access the clinical viability of the algorithms employed as well as the precision, accuracy and error margins of the sensors and the device presents itself as a useful platform to deploy them and conduct such studies. This was not possible during the course of this project since the required data was not collected due to the necessary reference devices not being available. The author assumes full responsibility for this most significant omission and expects to have the opportunity to conclude this work in the future.

Sample rate was even reduced from 1000 Hz down to 100 Hz with no significant decline in fidelity since the morphological and time domain features of the signals and not the amplitude values were the most relevant in this context. For smaller features such as the QRS interval the extra resolution is more appropriate but for the PTT calculation, the 10 ms precision of the 100 Hz sampling rate produces insignificant error compared to the tolerance level of the employed models.

The 10-bit resolution of the ADC was also enough for the algorithms employed but the use of 12-bit or even 24-bit could help in better identifying smaller, amplitude related features such as the ST segment elevation.

The sensors recover quickly to motion related disturbances that mostly completely deplete or saturate the signal making it easy to discard those occurrences in statistical analysis.

Both fresh new and really old electrodes were tested and besides a small decrease in magnitude, the analog front-end controller seems to work well enough considering the algorithm thresholds that were used, even using electrodes that have passed their specified life-time, with corroded contacts, dried contact gel and poor adhesion.

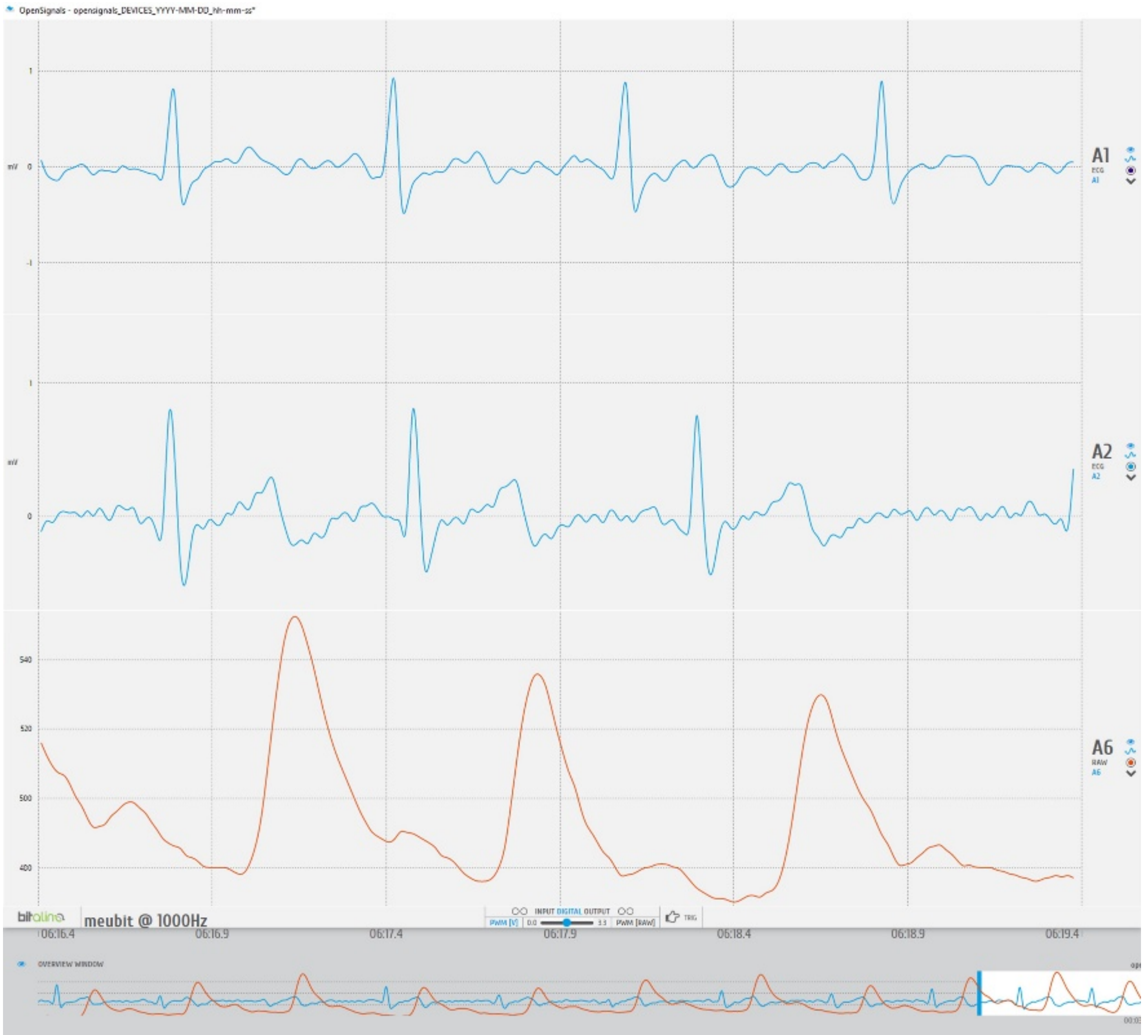


Figure 27 – Two ECG and a PPG signal acquired simultaneously for comparison, drawn on the OpenSignals. On the top is the signal acquired with used electrodes in very poor condition and placed in a hairy male chest. On the middle is the signal acquired from fresh electrodes placed on a clean female chest. No difference is evident on the peaks but there are clearer ST segments and T wave acquired in better conditions. A PPG signal, on the bottom, was also acquired simultaneously on the female subject.

Cost

The complete setup has a cost of about 130€, not considering the smartphone. Plux also provides a more complete unit for 149€ that includes some other sensors and devices minus the SD card interface and the PulseSensor that cost about 7€ and 35€ respectively. This cost can be reduced significantly by acquiring generic components and not the development centric ones provided by Plux. For example, the MCU is sold for 17,50€ but is little more than a ATmega328p and a 16 MHz oscillator which can be bought from chinese vendors for less than 1€ each. The same can be said for the ECG module that contains an AD8232 IC and a few passive components that can be bought and shipped for about 3€.

Plux does not publish their PCB designs and in this case the project will refrain from disclosing them but careful visual inspection of the PCBs is enough to understand their wiring and the components' data sheets usually describe in detail how the passive components should be wired. If cost minimization was to be achieved, in a prototype or academic setting, a bootleg BITalino device with only the necessary components could be assembled for less than 50€, being the cables, electrodes and battery the most expensive components.

Further along development, in an industrial production context, the marginal cost of a device could be reduced much further, but fixed costs regarding production such as labour, supply chain, marketing, support, etc, would add significantly to the overall cost and would have to be considered.

Ergonomics

The device lacks the ergonomic convenience of modern commercial integrated sensors. This is a necessary trade-off between cost and comfort that should naturally be overcome in time. The wiring can be discomforting at times and should be attached to some kind of clothing to prevent being pulled with motion. The earlobe PPG sensor is almost unnoticeable to the wearer after some time but is not aesthetically pleasing at all. These issues are not very significant in contexts such as staying at home or participating in academic studies.

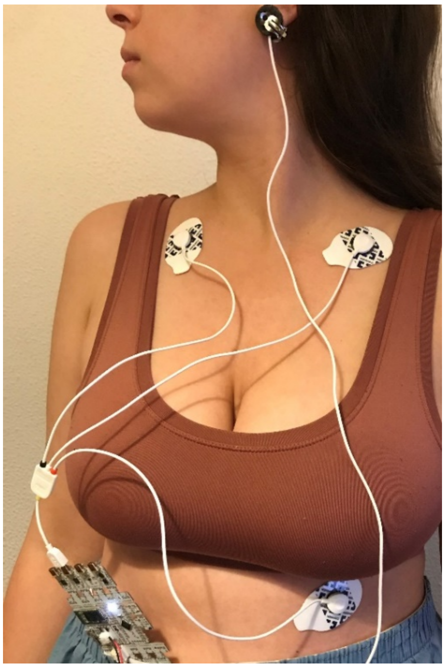


Figure 28 – The system being used in acquisition. The electrodes are placed in a standard RA – LA – LL configuration. The PPG sensor is placed in the earlobe.

Autonomy

The 700 mAh battery can sustain continued streaming of the data for more than 10 hours but cannot be charged without interrupting signal acquisition which is a problem in this case. Plux also sells a 1500 mAh battery that should more than double the autonomy but it would be ideal to have battery capacity of at least 4000 mAh to ensure 48 hours of autonomy.

Concerning the Ag/AgCl electrodes used in this device, these should be replaced timely to avoid any adverse reactions on the skin surface. In this scenario a second battery could be replaced alongside the electrodes giving the device the full 48h of complete autonomy.

CONCLUSION AND FUTURE WORK

The main objectives of this project can be considered successfully achieved. It was demonstrated that a simple device, based entirely on cheap and readily available parts and free, open source software, delivering a versatile, modular and extensible solution for continuous and real-time monitoring of HF related biosignals and capable of processing and delivering those signals conveniently for both medical and research purposes. Sensors can be integrated with common AVR MCUs leveraging the existing large ecosystem of libraries, frameworks and development tools with little compromise to performance, resolution and specification.

Existing open source software is shown to be more easily adapted to add additional, sometimes application specific features compared to proprietary solutions. Such an open platform can be useful when integrating novel, cutting-edge sensors for rapid deployment in research settings in order to test their clinical applicability and the potential contribution of the signals they acquire to the development of powerful medical diagnosis and event detection algorithms.

Finally, it is made clear how cheaply can the large-scale wireless sensor networks that will be required to feed the huge amount of data the next generation of AI based development in the medical field will require. On the other hand, it is evident that a large amount of infrastructural development is still required in the open source space to successfully implement the cutting-edge biosignal processing algorithms present in the literature of the past 10 years. A lot of work is yet to be done!

As for this project, integration of additional sensors like the SpO_2 and the novel skin surface NaCl electrochemical sensor would provide a broader perspective on the HF problem that was the object of study, potentially allowing for the a priori detection of imminent acute episodes which would be a major development. Integration of the application with some high-level infrastructure that could handle responsible distribution of the data would make the device much more useful and convenient. The integration with Android APIs for generating alerts and even automatic emergency calls seems at reach when validation of the proper detection algorithms is completed. Clinical tests for validation of the fidelity of the selected instruments compared to the gold standards used in hospital settings as well as validation of the implemented algorithms is unfortunately yet to be done. More powerful algorithms can and should be implemented leveraging the power of the Android device and provide more useful information.

In conclusion, the multidisciplinary field of embedded medical devices is rich in potential. Opportunities to grow and learn are abundant. A rapid proliferation of these devices should be expected in the coming years that has the potential to participate in a paradigm shift regarding self-care and AI powered medical solutions.

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