# In the spotlight: Bioinstrumentation

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## Introduction

Significant advances in the field of biomedical instrumentation have continued to contribute towards improvements in the quality of clinical diagnosis and treatment, which could have important implications for health and welfare. Up to the present, progress in several topics has been reviewed within the "In the Spotlight" column, including new and noteworthy measurement methods [1], ballistocardiography revisited [2], wearable monitoring [3], and home healthcare technologies [4]. The present review deals with three notable topics from recent publications in the field of bioinstrumentation. These are: (1) new conducting polymer electrodes for *in vivo* bio-electrical measurements, (2) mHealth technology using mobile communication devices such as mobile phones and personal digital assistants (PDAs), and (3) non-invasive *in vivo* measurement of blood constituents. These topics are of recent or renewed interest and, where appropriate, progress since the previous reviews [1], [2] will be highlighted.

## Conducting polymer electrodes for *in vivo* bio-electrical measurements

The design of electrodes coated with an appropriate conductive polymer to achieve long-term stability of *in vivo* bio-electrical measurements has been the focus of effort for a considerable time. Ongoing studies have been bringing some success, for example that Green *et al.* have recently demonstrated good stability of their electrodes, which are coated by poly-ethylene dioxythiophene doped with paratoluene sulfonate [5]. In the studies by these authors the electrodes were immersed in high serum content cell culture medium and were subjected to continuous electrical stimulation. They performed well, showing stable electrode characteristics during 1.3 billion pulses of stimulation.

In addition to the use of polymer-coated metal electrodes, there have been continuing interesting efforts to fabricate entire electrodes from conducting polymers. This type of conducting polymer electrode can be fabricated, for example, by chemical deposition methods and/or printing procedures usually used in the laboratory-based experimental production of biosensors [6], [7]. Conducting polymer electrodes fabricated in this way have become more sophisticated, enabling them to be used successfully for *in vivo* measurements [8]. Strongpoints of this electrode design as compared with a conventional electrode are (i) high flexibility, (ii) thin, (iii) lightweight, as well as (iv) long-term stability due to its material property [7-9].

Khodagholy *et al.* have described a very small, thin, and highly conformable electrode-array, fabricated using a photolithographic process. The electrode-array was found to have appropriate properties to yield *in vivo* recording of the electrocorticogram with a high SN ratio in rats [10]. The use of a conducting polymer (CP)-modified electrode in small animals has also been reported by Forcelli *et al.* [11] By comparison with the conventionally used platinum electrode, their CP-modified electrode showed a significant decrease in anomalous reaction of astrocytes, detecting intracranial electroencephalographic signals measured with a high SN ratio.

In addition to their use for biopotential recording there are noteworthy applications of conducting polymers in other areas, including in biosensors. Rahman *et al.* have demonstrated a superoxide anion radical micro-biosensor with enhanced stability and sensitivity, fabricated by the sequential immobilization of lipid and cytochrome c that were covalently bonded onto a conducting polymer layer. This micro-biosensor was implanted into a rat brain to determine successfully the extracellular level of the superoxide anion radical induced by acute and repeated injections of cocaine [12].

Taking the advantageous mechanical and electrical properties of greater flexibility, thinner, more lightweight devices, and long-term stability into consideration, the conducting polymer electrode appears promising for wide-ranging bioelectrical measurements. However, further research in terms of safety and efficacy for much longer-term use will be necessary for human applications.

## Recent advances in mHealth and mobile bioinstrumentation

mHealth (also written as m-health or mobile health) is a part of eHealth (electronic health) and is the provision of health services and information by using mobile communication devices such as mobile phones and PDAs. Applications include collection of clinical health data, delivery of healthcare information to practitioners, researchers and patients, as well as handy bioinstrumentation for real-time monitoring of patient vital signs, and direct provision of care *via* mobile telemedicine [13]. The mHealth field could also make key contributions to point-of-care testing (POCT), which is now of widespread interest as a component of emerging clinical medicine [14]. Rapid advances in the field of mHealth strongly depend on significant recent progress in information and communication technology (ICT), which of course includes mobile communication technologies.

Historically, the basic concept of mHealth was first described relatively recently, one of the first approaches for medical diagnosis being reported by Martinez *et al.* in 2008 [15]. They proposed a system consisting of paper-based microfluidic devices for multiple assays and camera phones for digitizing the colorimetric information to transfer the results. Granot *et al.*

reported a quite different application in which the cellular phone is used with associated instrumentation for medical imaging based on electrical impedance tomography [16].

Details of current progress in mHealth have been reviewed by Kyriacou *et al*. [17] and Boulos *et al*. [18]. Among recent research publications on mHealth [19]-[28], one can see that the configuration for PDA-based instrumentation systems is categorized into two types, as shown in Fig. 1: Type-A (Fig. 1(a)) is to combine a PDA with external healthcare equipment [19]-[21], and type-B (Fig. 1(b)) is to use only a PDA which can measure medical images and physiological signals utilizing the built-in CCD camera and/or the camera flash as a light source [22]-[29]. Some noteworthy studies are introduced as follows.

The first description of a type-A system has very recently been reported by Huang *et al.* [19], who have developed a smartphone-based portable pulse-wave ultrasound Doppler blood flowmeter. Doppler shift signals obtained from a compact external circuit unit are led directly to the phone which processes and displays Doppler spectrograms corresponding to arterial blood flow. These authors successfully made *in vivo* measurements of blood flow in a rat, showing the potential for using a smartphone in portable medical ultrasound applications. Based on this concept, mobile phone-based diagnostic systems incorporating an external device have been reported to monitor such physiological variables as the ECG [20], respiration rate, cardiac R-R intervals and blood oxygen saturation [21]. The full potential of this approach to bioinstrumentation development will be reached when the necessary external medical equipment becomes more compact and capable of measuring the required variety of vital signs and sensor-derived data. Widespread medical applications are then anticipated.

In a different form of imaging Breslauer *et al.* [22] reported a mobile phone-mounted microscope for diagnostic imaging and telemedicine. They demonstrated the potential for clinical use by capturing and displaying images of falciparum-infected and sickle red blood cells and microorganism morphology using tuberculosis-infected sputum samples. Such uses point the way to mobile phone-based global healthcare for disease diagnosis and screening. Smith *et al.* [23] also presented a smartphone-based spectrometer with a transmission grating to obtain the transmission spectrum of a human finger-tip.

Although an extra unit attached to the phone is needed in the systems mentioned above, there have been several trials of system without any extra units using only a smartphone, defined above as type-B [24]-[29]. Among them, a system reported by Jonathan and Leahy for reflectance-type photoplethysmographic imaging from a finger-tip is particularly notable [24], [26]. With this approach the phone-embedded camera is used as a photo-sensor and the camera flash LED is used as the light source. Based on this technique, the monitoring and performance assessment of heart rate (HR) and/or HR variability determined by a mobile phone or smartphone have also been reported [25], [28]. Most recently, it is in particular noteworthy that a smartphone-based monitoring of HR together with normalized pulse volume, which is an index of finger vascular tone [29], has been newly developed [30] and now available for practical use [31].

In a feasibility study of a similar system described above a challenging attempt has been made to achieve non-contact multiparameter physiological measurement using a webcam to obtain HR, HR variability and respiration rate processed by color images of the human face [27]. Although the range of physiological quantities that can be obtained by type-B systems are significantly limited at present as compared to type-A, type-B is naturally the most desirable for medical applications, particularly as a convenient tool in point-of-care testing.

There can be little doubt that mobile bioinstrumentation using a smartphone or one of a variety of PDAs, which are commonly carried around nowadays in normal daily life, will become the ideal platform for data processing, storage and communication. In the not-too-distant future, one can foresee an innovative change from the conventional system configuration for ambulatory/wearable physiological measurement such as the Holter ECG recorder, ambulatory blood pressure monitor (ABPM), and so on. In this respect, the approach of using mobile-based bioinstrumentation has a significant potential for providing a much more convenient, compact and easier-to-use tool not only for medical diagnosis but also for general healthcare in normal daily living.

**Further challenges in non-invasive optical measurement of blood constituents**

In the previous issues, an overview of the current status in non-invasive optical measurement of blood constituents was surveyed [1], [2]. This challenging topic remains even now a major interest worldwide, and thus in this Spotlight column the most recent developments since 2009 will be described.

The background research upon which *in vivo* spectroscopic analysis is based necessarily requires a full understanding of the *in vitro* absorption spectra (ABS) of relevant test fluids. This work also includes determination of the sensitivity ratio (STR), representing the absorbance change with respect to the change in concentration of the solution in specified wavelength bands. Accurate *in vitro* measurements of ABS and STRs of solutions of such substances as glucose (GLU), human serum albumin (HSA) and ethyl alcohol (EAL) have been reported [32]-[34]. Unlike ABS of oxy- and deoxy-hemoglobin, the ABS changes in association with the concentration change in each substance are well known to be considerably small, and these reports clearly demonstrated ABS of each single and mixed solutions of GLU and HAS [32], [33] and that of EAL and mixed solutions of EAL, GLU and acetaldehyde in the range of 750 – 2500 nm [34], together with very small but significantly discernible values of STRs at some specific wavelength regions. These findings provide useful and valuable information for quantifying concentrations of these blood constituents determined *in vitro* as well as possibly *in vivo* by optical techniques.

Despite the importance of *in vivo* blood constituent measurement there have been few definitive reports that represent significant and scientifically sound methodological advances in non-invasive techniques. Nevertheless, some reports concerning blood glucose [35]-[37] and alcohol measurements [38] are briefly introduced here.

There have been attempts to use electrical impedance spectroscopy for non-invasive blood glucose (BGL) monitoring, although trials revealed significant problems [39]. An interesting new multisensor method for non-invasive BGL measurement based on the combination of dielectric spectroscopy and optical reflectance spectroscopy has been reported [35], [36]. In this approach, measurements are made of impedance spectrogram together with reflected light intensity from the tissue, skin temperature, humidity surrounding the tissue and measuring site movement. In trials Clark error-grid analyses showed relatively good results. However, there are still some issues to be clarified before this multisensor approach is successful.

Monte-Moreno [37] has proposed a very interesting method based on machine learning techniques for the simultaneous estimation of BGL levels together with systolic and diastolic blood pressure from the waveform shape of the photoplethysmogram (PPG) measured in a finger. The theory is that there is functional relationship between the shape of the PPG waveform and the blood pressure and BGL levels. Very favorable results were obtained in a study on 410 volunteers, the machine learning techniques tested being: ridge linear regression; a multilayer perception neural network; support vector machines; and random forests. According to their study, the best results were obtained with the random forest technique. This approach appears attractive and will no doubt be examined further.

Very recently, for the purpose of developing an alcohol-based vehicle ignition-interlock device, the non-invasive quantification of blood alcohol concentration (BAC) using near-infrared (NIR) light has been proposed [38]. This method, named “*pulse alcometry*”, is based, firstly, on the evidence that ethyl alcohol has an absorption peak in the NIR region at 1185 nm [34], and, secondly, on the principles used in “*pulse oximetry*” and the recently developed “*pulse glucometry*” for the non-invasive optical measurement of blood oxygen saturation and BGL levels respectively [40]. Using second derivative values of the absorbance changes calculated from transmittance photoplethysmographic pulsations in a finger measured with the close-set of 3 wavelengths (1150, 1185 and 1220 nm), a simple linear regression analysis was made to predict BAC levels, showing good agreements between the predicted and the measured BAC values obtained from blood sampling. Since this method appears to be an initial development, further investigations using a number of subjects will be needed in order to strengthen the method for the ultimate use as an alcohol-based ignition-interlock device.

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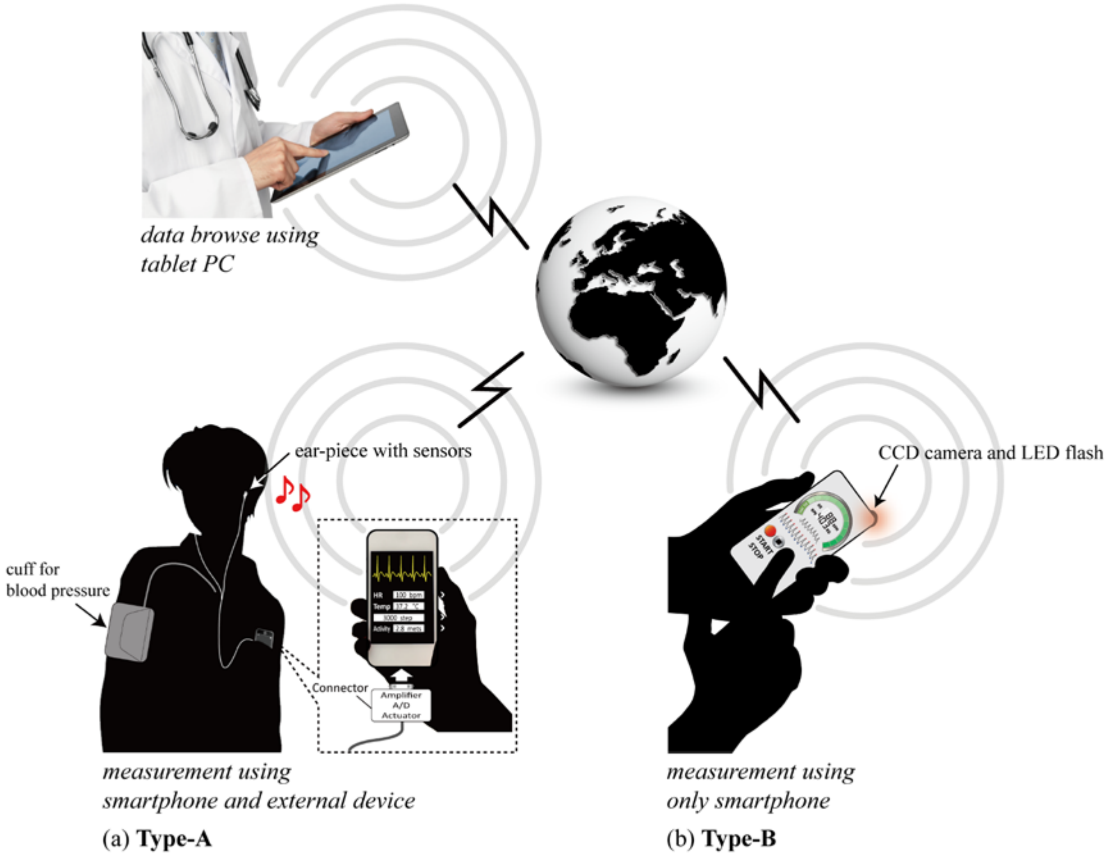


(Fig. 1: K. Yamakoshi)

**Figure Legend**

Fig. 1: Configuration for the PDA-based instrumentation systems: (a) shows type-A, that is to combine a PDA (smartphone in this figure) with an external healthcare equipment such as a sphygmomanometer, ear sensors for pulse rate and temperature measurements, and so on, while (b) indicates type-B, that is to use only a PDA. See text for further explanation.