Are Sensors and Data Processing Paving the Way to Completely Non-invasive and Not-painful Medical Tests for Widespread Screening and Diagnosis Purposes?

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Abstract: Effective medical tests are essential in supporting correct clinical decisions by medical doctors. But, have medical tests to be necessarily invasive and painful to be effective? During last decades, new developments of sensors and improvements of data analysis algorithms seem to paying the way to a (more or less near) future with completely non-invasive and not painful medical tests. This work aims to furnish a survey on what is going on within this frame, with an eye to new possibilities.

1 INTRODUCTION

Validated medical tests are essential for medical doctors’ decision-making processes effectiveness. Medical tests can be highly, moderately, minimally, or completely non-invasive. The invasiveness is due to instruments and energy that physically enter or interact with the patient’s body, and can be not painful, relatively painful (e.g. blood sample taking), painful (e.g. biopsy), and potentially dangerous (e.g. x-ray radiation exposure).

Of course, ideally we look forward only to medical tests which are effective, non-invasive and not painful. In addition, the market demands also affordability, safety, in-vivo monitoring, etc. Answers can come from the rapid evolution of electronics and data processing.

The electronics mainly rely on sensors (such as inertial measurement units, optical sensors, electronic nose, etc.), while data processing mainly rely on pattern recognition (such as Principal Components Analysis, Cluster Analysis, Support Vector Machine, Artificial Neural Networks, etc.).

In this work, we aim at investigating the sensors in supporting completely non-invasive and not-painful medical diagnosis and screening, underlining their advantages and their limits. Sensors can be of two main categories: body contact and body contactless ones.

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2 CONTACT SENSORS

Body contact sensors can be touch, clip, bandage, adhesive patch, tattoo, wearable or a mix of them, for a short-term or a long-term usage, and needle-free to avoid pain and discomfort.

2.1 Touch, Clip, Bandage, Patch, Tattoo

Let us start considering body contact sensors for diabetes, which represents a global challenge disease for more than 400 million people worldwide, and requires as-frequently-as possible checks of blood sugar levels. Current clinical/personal practice to measure glycaemia is mainly by the discomfort finger pricking. Conveniently, new non-invasive techniques are ongoing based on touch, patch and clip adopting solutions. An example comes from the DMT (by DiaMonTech, Germany), which detects glucose molecules by using a mid-infrared scanning of the interstitial skin fluids. The shoebox-sized version has the same accuracy as tests strips in preclinical tests, a pocket-sized version will be available at the end of 2020, and a watch-like device will be presumably available in 2024. GlucoWise™ (by MediWise, UK), an under-developing non-invasive glucose monitor solution, is based on low-power high-frequency radio waves transmission through a thin body part (between

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the thumb and forefinger, or earlobe). FreeStyle Libre (by Abbott Diabetes Care, UK) is a sensor patch useful to measures glucose levels in the interstitial fluid between the cells under the subject's skin. GlucoTrack (by Integrity Applications, Israel) is a blood sugar level sensor used with an ear clip, based on a combination of ultrasonic, electromagnetic and thermal waves.

Body contact-skin sensors can measure different bio-parameters, such as pressure, heart-pulse, respiration-quality, sweat and local body part temperature too. As an example, a touch-type system named SensoSCAN® (by Sensogram, USA) has a built-in alerting system triggering blood pressure, heart rate, and oxygen saturation. A Kapton-based flexible sensor can be stuck over the face skin for monitoring inhalations/exhalations moistures, aimed at evidencing breath anomalies (Caccami et al., 2018).

We can continuously measure pH-values from the sweat by a tattoo potentiometric sensor (Dang et al., 2018), or sodium concentration by a sensor belt (Schazmann et al., 2010). Chloride amount measured by an adhesive patch sensor can lead to an early cystic fibrosis diagnosis (Gonzalo-Ruiz et al., 2009).

New adhesive patches provide a continuous and point-to-point body temperature mapping by means of a radio-frequency identification (RFID) module, thanks to a loop antenna and a transponder that change their electromagnetic performance according to the local skin temperature (Miozzi et al., 2017).

From an unusual point of view, we can consider the smartphone as a sensor, for touch and "wearable" passive health sensing (Cornet and Holden, 2018). The digital phenotyping with the smartphone can be used, for instance, to define mental health behavioural patterns, which can be analysed with the purpose to enhancing behaviour and mental health (Onnela and Rauch, 2016).

2.2 Wearables

Wearable electronic sensors (wearables, hereafter) can include sensor(s) embedded in wristbands, headband/headwear, necklaces, gloves, rings and bracelets, chest belts, stretchable clothing, elastic bands, kneepads and socks, all complying with the natural gestures and motions of the wearer.

Some well-known sensory wristbands, such as Fitbit Flex, Mi Band, Garmin Vivoactive, for instance, and are useful for activity recognition, step detection, and distance estimation.

The sensory headwear (Piscitelli et al., 2019) can monitor neck motion handicaps and help in evaluating neck functionality rehabilitation.

Equipped with sensors, the sensory glove can measure fingers' movements (Saggio and Bizzarri, 2014). The sensors can be of different types, including optical fibers (Wise et al., 1990), Hall-effect based sensors (Portillo-Rodriguez et al., 2007), inertial measurement units (IMUs) (G. Saggio et al., 1995) (Hsiao et al., 2015), piezoelectric (Cha et al., 2017), stretch (Sbernini et al., 2016), and resistive flex sensors (Saggio et al., 2016). The sensory glove has been adopted for the analysis of hand tremor in Parkinson's disease patients (Cavallo et al., 2013), for determining the fingers' range-of-motion and the fingers' deformity of arthritic patients (Condell et al., 2011), for measuring handgrip capabilities (Grandez et al., 2010), and for assessing rehabilitation in surgery patients (O'Flynn et al., 2013). Moreover, the sensory glove has been useful in evaluating hand movement capabilities (Hsiao et al., 2015) (Saggio et al., 2015), finger muscle therapy effectiveness (Hidayat et al., 2015), functional recovery improvements after stroke (Merians et al., 2006), and hand rehabilitation after traumas (Hsiao et al., 2015).

SensoRing® (by Sensogram, USA) is a ring with built-in biosensors and wireless connectivity, to measure (among others) blood pressure, heart rate, respiration rate, perfusion index, and oxygen saturation.

The stretchable sensory clothing can non-invasively measure the 3D trunk movements for biomedical applications (Saggio and Sbernini, 2011) with an accuracy of the order of one degree (Mokhlespour et al., 2017).

The sensory elastic band system equipped with IMUs can be located in whichever human body segments. This is to evaluate postural deficit in vestibular failure (Alessandrini et al., 2017), enhance body standing balance recovery (Costantini et al., 2018), determine children's motor impairments (Ricci et al., 2019a), assess dyskinesia (Ricci et al., 2018) and transcranial direct current stimulation effectiveness (Ricci et al., 2019b) in Parkinson's disease patients, and gait harmony during walking (Gnucci et al., 2018).

The sensory kneepad (Saggio et al., 2014) furnishes useful data of knee motion capabilities to trace on-going patients' motor rehabilitation.

The Sensory Socks (by SensoRia, USA) can provide ongoing monitoring of plantar pressure in diabetic foot complications, so to early evidence diabetic foot ulcers, aiming at reducing part of the over 15 million of amputations in the world.

Gyrocardiography (GCG) is a new term coined for recordings of electrocardiography (ECG) based on heart motion assessment through a gyroscope. This allows obtaining reliable information on systolic and diastolic time intervals (Jafari et al., 2017).

3 CONTACTLESS SENSORS

As body contactless sensors, we refer to proximity sensors and interacting with body's fluids sensors.

3.1 Image Processing

Image acquisition and processing has been allowing the development of non-contact and non-invasive devices, for the evaluation of different health statuses and the assessment of different clinical conditions.

We can start mentioning a work devoted to 2D image acquisition for monitoring and evaluating sleeping behavioural patterns (Papakostas et al., 2015).

Imagine techniques, such as hyperspectral, plantar and photographic ones, and data analysis, allow detection of early developing feet and legs' ulcers (Toledo et al., 2014).

The image gathered by a webcam in front of a subject during typing can be useful to extract physiological signs of face-skin colour changes to determine the heart rate (Ariyanti et al., 2016).

Heart and respiratory rates can be measured by time-lapse imaging acquired from a camera, and data processing of the images can result with rates with an accuracy higher than 90% (Takano and Ohta, 2007).

Imaging methods were usefully exploited to evidence the melanin pigment concentration distribution map of a specific area of the subjects' skin (Stamatas et al., 2004). Malignant melanoma can be detected by smartphone-captured images: Lubax (lubax.com) send pictures to a data lake for visual inspection of dermatologists; an automatic solution is based on algorithms for evaluation of colour variation and border irregularity (Thanh-Toan et al., 2014).

Chronic fatigue syndrome can be revealed, 98% in accuracy, by means of hybrid facial features gathered from face pictures acquired by a camera (Chen et al., 2015).

A non-invasive detection modality for breast tumour relies on thermography, able to reveal heat patterns and blood flow in tissues (Ng, 2009).

Camera-smartphone based picture acquisitions can estimate wounds' conditions considering sizes and tissue classifications. Apps related to the wound size are Wound Tracker, Wound Analysis, and WoundMAP. Apps related to the assessment of wound conditions are WoundMAP, MOWA, Wound Analyzer, and AWAMS.

Elaboration of data gathered from digital photos were used to quantifying conjunctival pallor useful as screening test for anaemia (Collings et al., 2016)

The image processing can be related not only to visible light-waves, but to microwaves too. So, a non-invasive microwave head imaging system was adopted to detect and localize intracranial haemorrhage (Mobashsher et al., 2016). Microwave Doppler radar images were useful for rapid detection of fall events, so to alarm for interventions (Mercuri et al., 2013).

3.2 e-nose and e-tongue

As bio-inspired sensors, the electronic nose (e-nose) and the electronic tongue (e-tongue) sense the aroma and the taste of different compounds. When those compounds are related to human, e-nose and e-tongue sensing combined with pattern recognition have been used to assess pathologies.

Human skin emanations (odour, sweat) and excreted materials (breath, saliva, urine, seminal fluids, faeces), are the result of complex volatile organic compounds (VOCs), which offer unique insights into ongoing biochemical processes. VOCs can be successfully analysed through spectroscopy, chromatography and spectrometry, such as the gas chromatography-mass spectrometry (gold reference), the proton transfer reaction-mass spectrometry, the selected ion flow tube-mass spectrometry, the ion mobility spectrometry, and the laser spectrometry. Inconveniently, those techniques are quite expensive, time-consuming, cumbersome, and requires specialized personnel, so that cannot represent widespread procedures. Conversely, the e-nose joints the non-invasive approach to an easy handling, low-cost, rapid and mass procedure, well suited for its high sensitivity, specificity, repeatability and reproducibility (Wojnowski et al., 2019). The term e-nose, coined in 1994 (Gardner and Bartlett, 1994), refers to an array or a matrix of sensors, individually sensitive to different VOCs thus providing multiple detection, for a sort of "smell-signature". The e-nose can be made using different approaches, surface acoustic wave (SAW) (Wang et al., 2008), chemi-resistor (Peng et al., 2009), organically functionalized gold nanoparticles (GNPs) (Peng et al., 2010), and quartz microbalances (D'Amico et al., 2010), among others. Then, pattern recognition algorithms relate the "smell-signature" to a particular pathology.

Some commercially available e-noses are (Fig. 1) the Cyranose® 320 (by Sensigent LLC, USA), the Aeonose™ (by The eNose Company, The Netherlands), the PEN (Portable Electronic Nose, by Airsense Analytics, Germany), the Lonestar VOC Analyzer (by Owlstone, UK), the zNose® (by Electronic Sensor Technology, USA).

(a) (b) (c)

Figure 1: (a) Cyranose® 320 by Sensigent LLC; (b) Aeonose™ by The eNose Company; (c) zNose by Electronic Sensor Technilogy Inc. Pictures are reprinted with kind permissions.

The first work reporting breath analysis dates 1972 by the double Nobel Prize winner Linus Pauling. Since then, the e-nose applied to the exhaled breath has been discriminating a number of pathologies. We can start mentioning the lung cancer, which causes more than 1 million deaths per year worldwide (Saalberg and Wolff, 2016), invasively revealed by bronchoscopy or by spectrometry, with the aforementioned drawbacks. The usage of the e-nose allows discriminating 90% of patients from controls (Dragonieri et al., 2009), a classification accuracy as high as 80% (McWilliams et al., 2015), a 91% of specificity, and a sensitivity up to 92.8% (D'Amico et al., 2010). Other e-nose applications about tumour revelations were breast cancer (Peng et al., 2010), skin cancer (Kwak et al., 2013), thyroid cancer (Guo et al., 2015), ovarian cancer (Amal et al., 2015), head-and-neck cancer (Hakim et al., 2011), and bronchogenic carcinoma (Machado et al., 2005).

Colorectal cancer is a leading cause of cancer death worldwide. Current gold standard test method is the colonoscopy, but it is time consuming, expensive and does not allow mass screening. Another method is the faecal immunochemical blood testing, but presents a high variation in sensitivity. The e-nose was successfully adopted to reveal VOC content of urine obtaining 78% of sensitivity (Westenbrink et al., 2015), and promising results are reported in a work reviewing analysis of VOC in the faecal headspace (Di Lena et al., 2016). In addition, e-nose has been successfully adopted for revealing fungal infections (Acharige et al., 2018), tuberculosis (Saktiawati et al., 2019), sclerosis multiplex (Ionescu et al., 2011), allergic rhinitis (Saidi et al., 2015), and wound odour quantification (Akhmetova et al., 2016).

The e-tongue operates in liquid mediums to recognize a particular sample tasting it, similarly as it occurs for the human taste buds. The first work reporting a sensor matrix in liquid media dates 1985 (Otto and Thomas, 1985). Currently, the e-tongue is mainly used in food industry for determining types, quality, and freshness of olive, apples, spices, sauces, honeys, water, wine, vinegar, tea, milk, oil, etc. More rarely, the e-tongue is used for healthcare, for obtaining the "taste fingerprint" of urine, or for assessing prostate cancer "sensing" prostatic or seminal fluids (Bax et al., 2018), or for the evaluation of saliva metabolome for providing a sort of measure of stress and anxiety (Fitzgerald and Fenniri, 2017).

3.3 Voice

It has been largely demonstrated that, if we purge the voice sound from emotions, confidence and feelings, what we get are parameters linked to the health conditions of the speaker. The voice production depends on four main parts: the lungs that provide air with energy content; the vocal chords that produce sound vibrating accordingly to the amount of air; the cavities (mouth, nose, chest, ear) that produce resonations; the articulators (lips, tongue, teeth) that shape the sound. In turn, these parts depend on the brain that coordinates. When one or more of these parts are subjected to alterations or infections, the resulting disease affects the voice production system to a significant and measurable extent.

We can report how voice features were correlated to upper respiratory diseases (Bothe, 2017), lung tuberculosis (Saggio and Bothe, 2016) and chronic obstructive pulmonary disease (Mohamed et al., 2014). Benign thyroid disease (Pernambuco et al., 2015) and level of asthma (Walia and Sharma, 2016) were found to be related to some voice parameters.

For brain related diseases, data analysis of the voice can lead to around 90% in accuracy for Parkinson's disease in early stages (Bocklet et al., 2011) and in overt conditions too (Jeancolas et al., 2017). Vocal parameters can be translated into markers of Alzheimer's disease (Meilan et al., 2018), and bipolar disease (Guidi et al., 2015).

Some voice features were related to diabetes (Chitkara and Sharma, 2016), and some others exceeded 97% of correlation with blood pressure values (Sakai, 2015). From speech analysis, it was observed the presence and severity of amyotrophic lateral sclerosis with an accuracy of 92% in (Suhas et al., 2019). By reflecting the loss of articulatory processing, children with Down syndrome speak with less distinction between vowels with respect to individuals without (Moura et al., 2008). The work (Alves et al, 2019) reviews at which extent the dehydration conditions affect the voice performances.

According to (Manfredi et al., 2017), in a near future, the possibilities of early detection of an amount of pathologies via voice analysis can be obtained directly via smartphones' microphones, leading to new tele-health-check possibilities.

Currently, Sonde Health Inc. (sondehealth.com) is developing a voice-based technology platform to monitoring and diagnosing physical health; BeyondVerbal (beyondverbal.com) is developing voice-enabled artificial intelligence to create vocal biomarkers for healthcare screening; VoiceWise (voicewise.eu) processes voice samples by means of machine learning algorithms for medical diagnosis and health screening purposes.

Apart from the voice, the "sound" of the breath furnishes elements too. SpiroSmart is a smartphone app by which the user has to forceful exhaling the breath in the direction of the phone's microphone. Audio data are analysed to calculate the exhaled flow rate, with a mean error of 5.1% in comparison to measure of lung functionality (Larson et al., 2013).

4 CONCLUSIONS

Data gathered by body contact and body contactless sensors represent a more and more evolving tool for non-invasive and not-painful medical tests. Data analysis by means of machine learning algorithms furnish a new paradigm for personalized medicine.

Since it is not possible to represent all the pathologies and because more and more possibilities enhance rapidly, this work cannot represent the entire picture of the status-of-art of the completely non-invasive medical tests, however a meaningful survey was provided underlying the profitable aspects.

Nevertheless, the advantages have to be balanced by issues due to confounding factors due to different physiological aspects such as gender, age-range, ethnicity, smoke-habits, diet, motor exercises, sleep habits, taking medication, comorbidities, pregnancy, etc. Considering the e-nose applications, for instance, men have higher isoprene levels in breath with respect to women (Lechner et al., 2006). Volatile alkanes contents of the human breath (Phillips et al., 2000) and lung cancer breath-print (Bikov et al., 2014) differ for different age, as well as exhaled air of healthy subjects with asthma depends on age (Dragonieri et al., 2007). A gluten-free diet changes the values of 12 volatile compounds excreted in exhaled breath (Baranska et al., 2013). The exhaled pentane levels differs after sleep in patients with obstructive sleep apnoea (Olopade et al., 1997). The tobacco smoking alters the breath VOC profile (Gordon et al., 2002). Physiological hormonal changes due to the ovarian cycle can alter the exhaled VOCs (Dragonieri et al., 2018).

All considered, to date, data acquisition by sensors and data analysis by machine learning algorithms represent a new frontier for non-invasive not-painful but accurate disease screening and diagnosis, with all the credentials to become routinely applied in medical practice.

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