Chemical sensors integrated with mobile phones for remote medical diagnostics: state-of-the-art and beyond

Amann Anton[1,2]
[1]Breath Research Institute of the University of Innsbruck, Rathausplatz 4, A-6850 Dornbirn, Austria
[2]Univ.-Clinic for Anesthesia, Innsbruck Medical University, Anichstr, 35, A-6020 Innsbruck, Austria
anton.amann@i-med.ac.at

Milt Statheropoulos[3]
[3]School of Chemical Engineering, National Technical University of Athens (NTUA), Field Analytical Chemistry and Technology Unit, 9 Iroon Polytechniou Str., 157 73 Athens, Greece
stathero@chemeng.ntua.gr

Abstract— Human breath and sweat are sources of biogenic volatile organic compounds (VOCs) which can be sampled non-invasively providing medical information. Smartphones can be equipped with a variety of classical sensors (e.g. camera, audio, temperature/humidity, geomagnetic, proximity, barometer, accelerometer, GPS, gyroscope, etc.) but also with chemical sensors for gases and VOCs monitoring and then be used as personalized health monitoring devices. The goal of this paper is to highlight the latest research efforts towards the direction of transforming smartphones to revolutionary diagnostic medical tools, being able to detect and process chemical profiles related to vital signs but also with the potential to therapeutic monitoring.

***Keywords*— smartphones; skin; exhaled breath; volatile organic conpounds (VOCs); human odor; sensors; gases; chemicals.**

I. INTRODUCTION

Over the last 30 years, significant research activity has been placed on Volatile Organic Compounds (VOCs). VOCs are a large group of anthropogenic (xenobiotic) or biogenic organic compounds with relatively high vapor pressures. The term *"volatile"* implies that these compounds evaporate or turn into the gas phase at room temperature, while the term *"organic"* declares the existence of carbon in their molecule (few exceptions exist). VOCs are emitted by all living organisms and can also be found in numerous domestic or industrial products.

In humans, the use of breath and its smell for medical diagnosis was first used by Hippocrates (460–370 BC, Kos, Greece). In 1971, Linus Pauling showed the presence of many low molecular-weight compounds (<300 amu) in exhaled breath by gas chromatographic techniques. The latter investigation has boosted the biochemical interest in human-origin VOCs. Overall, there are several routes of VOCs within the human body. Firstly, VOCs are continuously produced as products of normal metabolic processes. These endogenously produced biogenic VOCs are the products of the degradation of possibly larger molecules, as well as food, beverages and drugs and directly linked with internal biochemical processes of the human metabolism, thus carrying important medical information (i.e. acetone, isoprene, etc.). Another source of volatile compounds is by exposure to environmental contaminants, which enter the human body either by inhalation or through skin. Classic examples are acetonitrile (found in smokers), methyl-tertiary butyl ether (MTBE), a gasoline additive, and the resulting exhaled metabolite, tertiary butyl alcohol (TBA), which can be used for exposure reconstruction. An additional source of volatiles are bacteria in the gut, or in the airways. Prominent examples for compounds released by bacteria are hydrogen (H_2) and methane (CH_4), with many other compounds being explored. Since VOCs are transported in the blood, they can be exchanged across the alveolar-blood capillary membrane and vice-versa.

II. ANALYTICAL METHODS

For analysis of volatiles in breath, skin emanations, urine, blood, feces and headspace of bacteria, a variety of combined analytical instrumentation is used. The gold standard for the detection and identification of VOCs is considered to be gas chromatography-mass spectrometry (GC-MS). It has high analytical identification power (using mass spectra *and* retention time), but is too bulky and inflexible for on-line and/or on-site applications. Two other interesting technologies widely applied for on-line measurements are proton transfer reaction-mass spectrometry (PTR-MS) and selected ion flow tube-mass spectrometry (SIFT-MS). The increasing need and demand for near real-time measurements led to the use of different kinds of ion mobility spectrometry (IMS) systems; MCC-IMS (multi-capillary column-IMS), aspiration-IMS and D-IMS (differential-IMS, also known as FAIMS; field asymmetric-IMS). Another quite promising technique, especially for small molecules (i.e. ethane, propane, methane, hydrogen, carbonyl sulfide or pentane) is laser spectroscopy. In addition, electronic noses and sensors fulfill the criteria for on-line and on-site applications with great potential for the future. Since electronic noses are mostly not specific for some particular compound, often arrays of sensors are used and evaluated by pattern recognition methods. Recent advancements in sensor technology are summarized in Table 1. Nevertheless, there is not yet a fully developed application

MOBIHEALTH 2014, November 03-05, Athens, Greece
Copyright © 2014 ICST
DOI 10.4108/icst.mobihealth.2014.257397

Table I: Promising sensors for medical applications

Sensor Manufacturer	LOD	Application	Literature
NO (IT-Gambert, Wismar, Germany)	ppb-range	Aerocrine hand-held devices for asthma monitoring	[1]
Acetone (ETH Zurich)	~15 ppb	Diabetes	[2]
Nanosensors (Technion Institute of Technology, Israel)	~600 ppb	Lung cancer	[3]
Semiconducting metal oxides (Univ. of Tuebingen, Germany)	ppb-range	More generic	[4]
FAIMS (Owlstone-Nanotech, Cambridge, UK)	ppt	More generic	[5]
DNA-carbon nanotubes (Monell Chemical Senses Center, Philadelphia, USA)	50 ppb	Breath analysis	[6]

with high credibility based on endogenous VOCs. Towards this direction, more research is needed. Breath and sweat volatiles are continuously emanating from the body (non-stop emissions) with non-invasive sampling being easily applicable and cost-effective. Since the concentration of the majority of breath volatiles is in the low ppb_v-ppt_v (parts per billion per volume of air, parts per trillion) range, an enrichment step may be desirable; this is achieved by adsorbent-based materials (thermo-desorption tubes, needle traps or solid phase microextraction (SPME)). The most abundant VOCs in breath are acetone (approximately 400 ppbv) followed by isoprene and methanol (approximately 150 ppbv). Methane is of special interest, and may appear in certain persons' breath at ppm concentrations, even after fasting. Other VOCs are usually excreted in lower concentrations. Similarly, sweat analysis is mainly performed through the use of cotton pads followed by solvent extraction, adsorption to porous polymers and collection to adsorbent traps. Acetone and the inorganic ammonia (NH_3) are exemplary compounds emitted both from human skin and breath. The detection and identification of breath and sweat volatiles is applicable for the early diagnosis and monitoring of various diseases and metabolic disorders such as cancer, diabetes, asthma, liver or kidney failure, for forensic applications, for hygiene purposes and for biological and environmental reasons. In Table 2, an indicative list of breath volatiles associated with diagnostic applications is presented [7].

III. SMARTPHONES APPLICATIONS

Nowadays, smartphones are ubiquitous and an integral part of humans' modern life. Equipping smartphones with sensors is presently explored by various companies, to serve as a platform for merging chemical analysis for detection of indoor air contamination and potentially also for medical diagnosis. Biosensing on cell phones is a new reality [8] leading to multi-functional devices. Towards this, a number of personalized health applications were initiated. Indicatively, portable laser absorption spectroscopy (LAS) was used to measure breath

Table II: Indicative applications of breath analysis

Volatile	Association
Hydrogen (H_2), Methane (CH_4)	Carbohydrate malabsorption
Hydrogen sulfide (H_2S), Methanethiol	Oral malodor
Carbon monoxide (CO)	Smoking cessation
Nitrogen monoxide (NO)	Asthma
Ethanol	Law-enforcement (alcohol consumption)
Acetone	Fat burning (lipolysis), diabetes
Aldehyde	Cancer and oxidative stress
Isoprene	Mevalonate pathway
Pentane	Lipid peroxidation product
Sevoflurane	Post-anesthesia units
3-Heptanone	Metabolization of valproic acid, which is administered against seizures
Acetonitrile, Furan, Furan, 2,5-dimethyl, Benzene	Smoking indicators
$^{13}CO_2$	Endogenous and exogenous (resulting from administration of ^{13}C-labeled compounds such as ^{13}C-urea, ^{13}C-dextromethorphan, ^{13}C-fluorouracil or ^{13}C-pantoprazol)

oxygen on an Android platform [9]. Moreover, an inter-phone repeatability algorithm was developed for both Android and iOS operating systems for quantifying commercial colorimetric urine tests for pH, protein, and glucose measurements [10]. Also, a wearable VOC-sensor that can communicate with a common smartphone for assessing personal exposure to VOCs was also shown [11]. Furthermore, a variety of wearable sensors and systems were developed for monitoring human health and wellness [12]. In the same context, sensor manufacturing companies (e.g. Sensirion AG, Switzerland) are also driving the market, by offering multi-gas sensor capabilities for smartphone companies [13]. Owlstone (UK) is working on a desktop "disease breathalyser" targeting for a mobile breath analyzer for early diagnosis of cancer [14]. On the other hand, BACtrack for iPhones and Breathometer for iPhones and Android, are two novel examples of smartphones applications in measuring blood alcohol levels aiming to prevent drunk driving. A mobile-phone-based breath carbon monoxide (CO) meter for detecting breath CO of smokers was also proposed [15]. SpiroSmart and SpiroCall is another smartphone medical application measuring the lung function (mobile spirometer) [16].

IV. SKIN AND BREATH MEASUREMENTS

Being the largest human organ, human skin emits hundred of VOCs. These are either released from blood vessels through skin or result from the interaction of skin bacteria with eccrine, sebaceous and apocrine gland secretions. Sweat odor is more intense at hands, in legs, underarms and in the face. Therefore, skin sampling mainly focused onto these areas, especially for hygiene purposes or in the whole body emissions, considered as human body odor. Studies of volunteers enclosed in chambers were carried out with the scope of detecting and analysing VOCs of skin emanations and/or breath, as shown in figure 1.

The underarm area is especially targeted in skin applications because of the high density of all three glands (eccrine, sebaceous and apocrine) and due to the presence of a huge number of bacteria as an airless and moistness area. This triggered scientists to use a hand-held e-nose for measuring the VOCs generated from the armpit area of a volunteer during twelve hours [17]. Principal component analysis (PCA) was further needed to classify and analyze the produced VOCs fingerprint. Such low-cost and light-weight devices can be quite useful for studying skin hygiene and identify possible disease biomarkers; nevertheless, selectivity and sensitivity of e-noses is a big issue [17].

Fig. 1. Skin emanations from human body.

Another similar application which included the use of sensor arrays was focused on the differentiation of skin cancer melanoma and naevi [18]. Lately, melanoma attracted the interest of scientists due to the high increase of occurrence, especially in the USA. It is considered to be the deadliest form of skin cancer and can rapidly spread over the parts of the body. Sun exposure in the young age is considered the main cause. In a similar study, a number of VOCs were found to differ between cancer and normal cells; isoamyl alcohol was higher in melanoma cells than in normal melanocytes but isovaleric acid was lower in melanoma cells. Moreover, melanoma cells produced dimethyldisulfide and dimethyltrisulfide that were not detected in normal melanocytes. Also, dimethylsulfone was found in greater amounts in metastatic melanoma cells vs. normal cells [19].

The natural variation in nonaxillary skin odorants was studied using SPME and solvent extraction. More than 100 VOCs were identified and detected [20]. Some of them were associated with aging. Currently, a simple, non-invasive headspace sampling method was presented for sampling volatile compounds emanating from human skin, using a thin film, as the extraction phase format [21]. The method was tested and validated for dietary biomarkers investigation. Other interesting applications revealed the correlation of 2-nonenal, as an age-specific component [22] and the relation of skin VOCs, as mosquito attractants [23].

Body odor studies can also be performed by use of humans which are placed in confined spaces, monitoring their emissions in time by direct mass-spectrometric techniques or ion mobility sensors [24,25]. Ethical approval is mandatory in such investigations. Towards this, ten volunteers were enclosed for 6h in an environmental chamber supplied with air and humidity, while their breath and sweat metabolites were monitored. This so-called Trapped Human Experiment (THE) revealed the ability of carbon dioxide, ammonia, acetone and isoprene to travel through the building debris [26]. In the same study, the use of MCC-IMS, revealed the presence of 12 human metabolites [27]. Near-real time measurements of human-skin VOCs were also achieved through the use of MCC-IMS. Overall, 33 VOCs omnipresent in forearm skin emanations were identified and quantified [24]. The most abundant VOCs were 3-methyl-2-butenal, 6-methylhept-5-en-2-one, sec-butyl acetate, benzaldehyde, octanal, 2-ethylhexanol, nonanal and decanal in the low ppb_v range [24]. 6-Methylhept-5-en-2-one is a particularly interesting volatile compound which is produced by oxidative degradation of squalene. Near-real time whole-skin emanations sampling was further performed using selective reagent ionization Time of Flight MS in NO^+ mode (SRI-TOF-MS-NO^+) [25]. Ten healthy volunteers were closed in a body plethysmography chamber for an hour mimicking the entrapment environment. The experimental procedure is reviewed in Figure 2 [25].

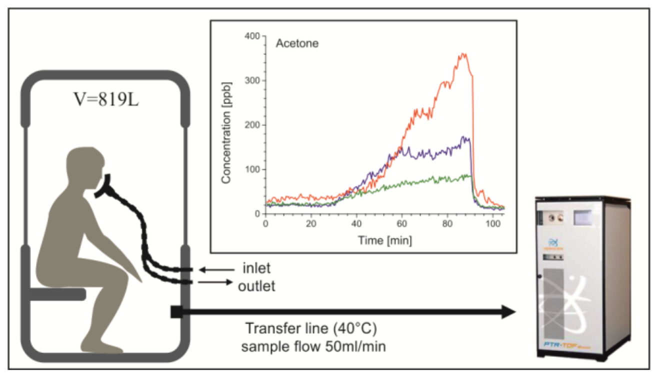

Fig. 2. Body odor emanations [25].

The study revealed that the majority of the released chemical moieties were aldehydes (n-propanal, n-hexanal, n-heptanal, n-octanal, n-nonanal, 2-methyl 2-propenal) and ketones (acetone, 2-butanone, 3-buten-2-one, 6-methyl-5-hepten-2-one). A hydrocarbon (2-methyl 2-pentene), and a terpene (DL-limonene) were also detected [25].

V. CONCLUSIONS

Human's biological fluids are a source of medical information, thus detection and identification of emitted volatiles is targeted. In general, breath collection methodology and analysis needs standardization. Expensive, time and power consuming analysis instruments need to be replaced with portable, easy-to-use screening systems enabling smart sensing. The potentiality of using smartphones for medical diagnostics seems feasible as some applications have already appeared in the market. Future research in integration of chemical sensors in mobile phones needs mainly to include: selection of scenarios for particular applications, sensors size reduction and miniaturization, identification of use model, and remote calibration. Main hurdles in the application include the miniaturization of sensors and the extremely low concentrations of the emitted volatiles. If the latter obstacles get ahead, smartphones can become novel point-of-care medical devices, totally changing the so far roadmap of medical diagnostic tools.

ACKNOWLEDGMENT

A. Amann appreciates funding from the Austrian Federal Ministry for Transport, Innovation, and Technology (BMVIT/BMWA, project 836308, KIRAS) and thanks the government of Vorarlberg (Austria) for its generous support.

REFERENCES

1. T. Hemmingsson, D. Linnarsson and R. Gambert, "Novel hand-held device for exhaled nitric oxide-analysis in research and clinical applications**,** Journal of Clinical Monitoring and Computing 18 (2004) 379–387.
2. M. Righettoni, A. Tricoli, S. Gass, A. Schmidt, A. Amman and S.E. Pratsinis, "Breath acetone monitoring by portable Si:WO3 gas sensors", Analytica Chimica Acta 738 (2012) 69-75.
3. G. Peng, M. Hakim, Y.Y. Broza, S. Billan, R. Abdah-Bortnyak, A. Kuten, U. Tisch and H. Haick, "Detection of lung, breast, colorectal, and prostate cancers from exhaled breath using a single array of nanosensors", British J. Cancer 103 (2010) 542-551.
4. K. Grossmann, U. Weimar and N. Barsan, "Semiconducting metal oxides based gas sensors", In B.G. Svensson, S.J. Pearton and C. Jagadish, editors: Semiconductors and Semimetals, Vol. 88, Burlington: Academic Press, (2013) 261-282.
5. B.M. Kolakowski and Z. Mester, "Review of applications of high-field asymmetric waveform ion mobility spectrometry (FAIMS) and differential mobility spectrometry (DMS)", Analyst 132 (2007) 842-864. A.T. Charlie Johnson, S.M. Khamis, G. Preti, J. Kwak and A. Gelperin, "DNA-Coated Nanosensors for breath analysis, IEEE Sensors Journal, vol. 10, no. 1, January 2010, 159-166.
7. A. Amann and D. Smith, "Biomarkers: Non-invasive Diagnosis in Physiology and Medicine", Elsevier, Amsterdam, 2013.
8. P. Preechaburana, A. Suska and D. Filippini, "Biosensing with cell phones", Trends in Biotechnology 32 (7) 2014, 351-355.
9. S. Gupta, P. Breen, D. Wu and A. Sabharwal, "Breath analysis with laser sensors on an Android platform", Wireless Health '10, October 5-7, 2010, San Diego, USA.
10. A.K. Yetisen, J.L. Martinez-Hurtado, A. Garcia-Melendrez, F.C. Vasconcellos and C.R. Lowe, "A smartphone algorithm with inter-phone repeatability for the analysis of colorimetric tests", Sensors and Actuators B 196 (2014) 156–160.
11. C. Chen, K.D. Campbell, I. Negi, R.A. Iglesias, P. Owens, N. Tao, F. Tsow and E.S. Forzani, "A new sensor for the assessment of personal exposure to volatile organic compounds", Atmospheric Environment 54 (2012) 679-687.
12. S. Patel, H. Park, P. Bonato, L. Chan and M. Rodgers, "A review of wearable sensors and systems with application in rehabilitation", Journal of NeuroEngineering and Rehabilitation 9:21 (2012) 1-17.
13. http://www.electronics-eetimes.com/en/sensirion-preps-multi-gas-sensor-nose-for-smartphones.html?cmp_id=7&news_id=222919117
14. http://www.dailymail.co.uk/health/article-2613856/Theres-app-Mobile-phone-breath-test-check-signs-cancer.html
15. S E. Meredith, A. Robinson, P. Erb, C.A. Spieler, N. Klugman, P. Dutta and J. Dallery, "A mobile-phone-based breath carbon monoxide meter to detect cigarette smoking", Nicotine & Tobacco Research Advance (2014) 1-8.
16. E.C. Larson, M. Goel, M. Redfield, G. Boriello, M. Rosenfeld and S.N. Patel, "Tracking lung function on any phone", DEV '13, Bangalore, India, January 11-12, 2013.
17. P. Lorwongtragool, T. Seesaard and T. Kerdcharoen, "A point-of-care and routine clinical instrument based on artificial nose: study of volatile emission from axillary skin", The 2012 Biomedical Engineering International Conference (BMEiCON-2012), 978-1-4673-4892-8/12, IEEE, 2012.
18. A. D'Amico, R. Bono, G. Pennazza, M. Santonico, G. Mantini, M. Bernabei, M. Zarlenga, C. Roscioni, E. Martinelli, R. Paolesse and C. Di Natale, "Identification of melanoma with a gas sensor array", Skin Research and Technology 14 (2008) 226–236.
19. J. Kwak, M. Gallagher, M.H. Ozdener, C.J. Wysocki, B.R. Goldsmith, A. Isamah, A. Faranda, S.S. Fakharzadeh, M. Herlyne, A.T.C. Johnson and G. Preti, "Volatile biomarkers from human melanoma cells", Journal of Chromatography B 931 (2013) 90–96.
20. M. Gallagher, C.J. Wysocki, J.J. Leyden, A.I. Spielman, X. Sun and G. Preti, "Analyses of volatile organic compounds from human skin", British Journal of Dermatology 159 (2008) 780–791.
21. R. Jiang, E. Cudjoe, B. Bojko, T. Abaffy and J. Pawliszyn, "A non-invasive method for in vivo skin volatile compounds sampling", Analytica Chimica Acta 804 (2013) 111– 119.
22. S. Haze, Y. Gozu, S. Nakamura, Y. Kohno, K. Sawano, H. Ohta and K. Yamazaki, "2-Nonenal newly found in human body odor tends to increase with aging", J. Invest. Dermatol. 116 (2001) 520–524.
23. U.R. Bernier, D.L. Kline, D.R. Barnard, C.E. Schreck and R.A. Yost, "Analysis of human skin emanations by gas chromatography/mass spectrometry. 2. Identification of volatile compounds that are candidate attractants for the yellow fever mosquito (Aedes aegypti)", Anal. Chem. 72 (2000) 747–756.
24. V. Ruzsanyi, P. Mochalski, A. Schmid, H. Wiesenhofer, M. Klieber, H. Hinterhuber and A. Amann, "Ion mobility spectrometry for detection of skin volatiles", Journal of Chromatography B 911 (2012) 84– 92.
25. P. Mochalski, K. Unterkofler, H. Hinterhuber and A. Amann, "Monitoring of selected skin-borne volatile markers of entrapped humans by selective reagent ionization time of flight mass spectrometry in NO^+ mode", Analytical Chemistry 86 (2014) 3915-3923.
26. R. Huo, A. Agapiou, V. Bocos-Bintintan, L. Brown, C. Burns, C. S. Creaser, N. Davenport, B. Gao-Lau, C. Guallar-Hoyas, L. Hildebrand, A. Malkar, H. Martin, V. H. Moll, P. Patel, A. Ratiu, J.C. Reynolds, S. Sielmann, R. Slodzynski, M. Statheropoulos, M. Turner, W. Vautz, V. Wright and C.L.P. Thomas, "The Trapped Human Experiment", Journal of Breath Research 5 (2011) 046006.
27. W. Vautz, R. Slodzynski, C. Hariharan, L. Seifert, J. Nolte, R. Fobbe, S. Sielemann, B.C. Lao, R. Huo, C.L. Thomas, L. Hildebrand, "Detection of metabolites of trapped humans using ion mobility spectrometry coupled with gas chromatography", Analytical chemistry 2013; 85 (4) 2135-42.