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## ROLE OF BIOSENSORS IN DIGITAL MEDICINE

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### ABSTRACT

The demand for digital medicine has grown predominantly along with an increase in people's mindfulness of their health. The betterment of the well-being of individuals is greatly supported by digital medicine, which can be accomplished in a number of ways, including by monitoring patient adherence to medication, daily energy utilization etc. Digital medicine and the field of biomedical engineering, which uses sensors, signal transmissions, antennas, mobile applications, etc., could potentially be associated with one another. The present paper reveals various types of sensors employed, and their advancements which aids in digital health as well as digital medicine. Various mechanisms and types of sensors; advantages and limitations of digital medicine were epitomized. The purpose and significance of digital medicine in medication adherence is explained in the current review.

**Keywords: Biosensors; Medication adherence; Digital medicine; Ingestible sensors**

### INTRODUCTION:

The revolution of digital medicine is arising with an intention of metamorphosing biomedical research and practice of medicine which can be suitable to deliver valid health data to patients directly with

increased treatment by personalized medicine as well as health perfecting interventions. The use of digital medicine has its significant impact on knowing about the feelings and symptoms in children as

well as patients with mania or psychosis where they cannot have the competence of describing their exact feelings and state [1].

According to the expertise of Research & Development department of Interuniversity Microelectronics Centre (IMEC), a digital electronics company, an ingestible sensor in real time, when it enters formerly into the digestive system, it must be suitable for perceiving or detecting the mechanical movements of gastrointestinal tract (GIT); chemical processes like breakdown of food which involves enzymes and also hormones; also, the electrical impulses which will govern the contraction of muscles inside the GIT. The data detected accordingly from the sensor will be transmitted to a wearable device. This sensor or the device may include various elements like:

- i. An infinitesimal electro-chemical sensor – helps in giving high particularity in different types of challenging ambiances inside the body.
- ii. An Ultra-low power miniature interfaces and signal processing electronics – which must be co-designed with sensors
- iii. A Volume-constrained wireless power and data communication technology – Which is required to prepare a truly ingestible sensor
- iv. A Bio-compatible packaging which will be safe and thinner.

Such ingestible sensors are now used for both diagnostic and preventative uses [2].

As per World Health Organization, Medication adherence is the degree to which the person's conduct corresponds with the agreed recommendations from a health care provider. Even though compliance and adherence are synonymous, compliance is the obedience of the patient to the advice of the physician and adherence is upgrading the patient's health by considering physician's opinion as well as quality of life of the patient. Non-adherence to the remedy not only effects the patient, but also the physician, provider and also the investigators who works on establishing the value of medication. Measuring medication adherence may be established by direct strategies like observed therapy; estimating pharmaceutical levels in blood or urine; and other indirect methods like pill counts; questionnaires; electronic medication monitors etc, every form having its own advantages as well as disadvantages.

Medication adherence can be upgraded by:

- i. Streamlining and simplifying the regimen,
- ii. Using medication adherence bettering aids like medication charts,
- iii. Proper follow up and assessing adherence during follow ups [3].

Adherence is oppositely proportional to the frequency or the number of times medication has to be taken by that particular

person in a day. Studies reported that adherence depleted with increase in number of daily dosages; 79% for single dose to 51% for four doses. On an average, cost of hospitalization of nonadherent patients is \$3575 additional than that of adherent patients. In 2010, United Healthcare claimed that \$20 will be reduced for those who refills medication for asthma and depression on time. Likewise, in University of Pennsylvania, a study was conducted to know the chances of enriching medication adherence by employing scheme of winning cash prizes.

Major reasons leading to poor adherence include:

- i. Mental problems, particularly depression
- ii. Cognitive impairment
- iii. Inappropriate follow up
- iv. Side effects of medication being employed

- v. Lack of belief in treatment
- vi. Poor relation between patient and health care provider
- vii. Complexity of the treatment
- viii. Lack of health insurance
- ix. Monetary factors etc. [4].

Studies revealed that non-adherence results in accelerated progression of illness, emergence of drug resistance, increased mortalities and multiple irrevocable health complications. It was reported that in United States (US) alone, annually 1,00,000 deaths and billions of dollars were spent on healthcare because of poor adherence to medication.

The summary of major applications, advantages and drawbacks of various frequently employed technologies in medication adherence and patient monitoring was given in **Table 1**.

Table 1: Summary of main applications, strengths and limitations of different technologies used in medication adherence [5]

		Main application differences	Strengths	Limitations
Sensor systems	Smart Pill Container	Detects cap opening and bottle pick up	Possibility to allow mobility Non-invasive	System's life is constrained by battery Detect medication taking activity with low accuracy
	Wearable Sensors	Detects motions related to cap twisting, hand-to-mouth, pouring pill into the hand and pill swallowing	Possibility to detect medication intake activity with high accuracy Relatively easy to use Allow mobility	User's comfort and social acceptance due to their possible invasiveness Require frequent battery charging or replacement
	Ingestible Sensors	Detect pill ingestion	Possibility to detect concurrent pills ingestion Allow mobility	User's comfort System's lifetime is constrained by battery Security issues due to their limited resources
Proximity-based systems		Detects medication presence or absence within the proximity of reader's antenna	Non-invasive	Need to be coupled with other monitoring or sensing techniques for verification
Vision-based systems		Detects medication presence or absence within the scope of the camera	Non-invasive	Need to be coupled with tech or sensing techniques for verification
Fusion-based systems		Try to verify the operation of monitoring the medication taking activity	Higher accuracy as compared individual/ standalone techniques.	Resource consuming Do not usually support mobility [5]

Various challenges for these different types of devices for adherence monitoring are system preciseness, energy consumption for battery-rested systems, satisfactoriness and user's comfort, authentication tampering etc.

In 1950's, the first generation of ingestible electronics was developed. First commercially available ingestible temperature sensors underwent clinical testing in late 1980's and early 1990's. The first extensively used ingestible electronic device i.e., PillCam was introduced in 2000, which is a capsule endoscopy system that got approved by US Food and Drug Administration (FDA) in a year [6].

Sensors that could detect pressure readings or pH, also for watching medication were developed. Ingestible sensors have become an excellent tool in human health monitoring. A pilot study in humans was conducted with electronic capsules which have ingestible sensors for detecting various gases in the gut. These capsules contain sensors to detect CO<sub>2</sub>, H<sub>2</sub> and O<sub>2</sub> gases in both aerobic and anaerobic conditions; and a sensor for temperature; a microcontroller; transmission system of 433 MHz and silver oxide batteries [7]. Biosensors for detecting changes in pH or gas or humidity were developed. Humidity sensor was developed by considering the effect of environmental conditions on dielectric properties of proteins. The

changes in dielectric properties can be altered by using plasticizers [8].

A retail digital medicine (FDA approved in 2002) i.e., Abilify MyCite is used as an antipsychotic. It contains an edible sensor which gets actuated when it gets in contact with the gastric fluids after ingestion. A wearable sensor will be placed on the trunk of the patient which is capable of receiving signals from the ingestible edible sensor. All this data will be fostered to an application on phone as well as saved in a cloud-based server, which in turn helps physicians or caregivers to access and monitor the adherence.

Along with the stated illustration, there were also many digital medicine systems which underwent clinical trials to study the enhancement of medication adherence in schizophrenic patients. Apart from the advantage of this, there were certain limitations like chances of erythema or dermatitis because of the wearable sensor; certain manipulations like – placing the tablet in a fluid other than ingesting which will be a false count indicating that the medication was consumed even if it was actually not [9].

Market size of ingestible sensors was roughly estimated to be 491 million dollars in the year 2016, which was anticipated to be increased at a CAGR (compound annual growth rate) of 19% by 2024 [10].

Various U.S. FDA approved wearable sensors and that are connected to smart phones were developed such as

- i. The Apple Series 4 Smartwatch – Uninterrupted heart rate and rhythm detection
- ii. AliveCor – Six-lead electrocardiogram
- iii. Dexcom G6 and Abbott Libre sensors – Continuous glucose tracking with factory calibration and without fingerstick calibration
- iv. Omron HeartGuide smartwatch
- v. Few smartwatches that can measure blood pressure and few with oximetry that can help in detecting sleep apnea.

The main reason beyond approvals of all these is the ‘**Digital Health Action Plan**’ made by FDA with an objective of “ensuring all Americans have timely access to high-quality, safe and effective digital health products.”

Cameras lodged in the smart phones were now competent of capturing skin lesions with better resolution and smartphone ultrasound (i.e., connecting smartphone to an ultrasound probe) had the capability of overseeing beyond the skin imaging nearly numerous parts of the body

except brain and showed the resembling quality as that of high-end imaging equipment that are used in hospitals. The achievement in development of smartphone lab assays is being developed extensively with or without wearable sensors and now are capable of determining electrolytes via sweat; quantification of nucleic acids; transcutaneous haemoglobin concentrations, nitrite content via breath (in cases of asthma) etc. [11].

A Smart Pad system containing 3 different components which are – a wireless device; actuator system and a mobile application was developed. The wireless device was designed such that it includes sensors that detect carbon dioxide as well as environmental conditions like temperature, pressure, humidity and this entire measurement module was set up in the rear of the seat pad. The system shown in fig 1 was designed to record and study energy expenditure as well as resting energy expenditure. Carbon dioxide magnitudes were studied during resting, exercise and also in subjects with varying Body Mass Index (BMI) and Resting Energy Expenditure (REE) [12].

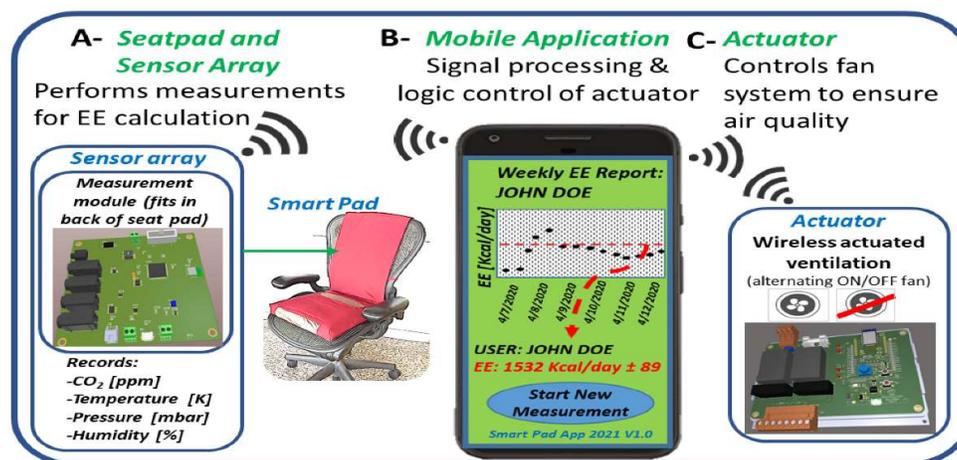


Figure 1: Smart Pad System [12]

A – Wireless device, B – Mobile application, and C – Actuator

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