MEASUREMENT ISSUES ON CYSTIC FIBROSIS DIAGNOSTIC

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Abstract: - Physiological measurements are necessary for determining parameters of interest. If they deal with indirect measurements, they are not invasive and much more attractive than others. Sweat is a physiological material that can be characterized because its content is useful. It encompasses direct and indirect parameters for measuring health status. One of the parameters is sodium chloride that is an indicator of cystic fibrosis. The main scope of the paper is to illustrate results and findings of designing an acquisition board for conditioning and processing physiological signal containing information about sodium chloride.

Keywords: Physiological measurements,   biomedical sensors, cystic fibrosis, skin characterization

1. RATIONALE

Skin generally plays a role of a special buffer between the air (or outside world) and the human body. Skin also produces sweat thanks to the transepidermal water loss (TWL or TEWL) [1] that is the rate at which water, eventually containing salt, migrates from the viable dermal tissues through the layers of the stratum corneum to the external environment. In the absence of profuse sweating, the TWL is predominantly controlled by the diffusion of water vapour in the stratum corneum [2] caused by the difference in vapour concentration between the inside and the outside surfaces. The main carrier of salt movements in the sweat is the perspiration produced by the sweat glands. Sweat flows to the skin surface by means of narrow ducts. In this way, salt reaches body outside by the skin pores and is reabsorbed in the body in order to regulate the right salt concentration in the organism. When gene is defective, the protein does not work properly. The epithelium, which lines the ducts of sweat glands, fails to take up chloride from the lumen of the glands. Consequently, salt movement is stopped causing an accumulation of sodium chloride on the skin surface. Sweat is a solution of water with sodium and chloride ions. During the way inside the ducts of the sweat glands, the ions goes towards the epithelium leaving the water. Consequently in normal subjects, the sweat which reaches the skin surface is slightly salty. In individuals with Cystic Fibrosis [3], the epithelial tissue is not able to reabsorb the chloride, with consequent insufficient absorption of sodium from the ducts. Excess of sodium and chloride in perspiration is the reason because this pathology

is known to be cause of sweat tasting salty. This is responsible of an unbalanced minerals concentration in the body. Yet it is not the most important issue concerning Cystic Fibrosis. The main consequence is an abnormal production of thick sticky mucus on the outside of the cells. In fact salt loss, and consequently its low concentration in the mucus, alters its consistency making it more sticky. So in the organs affected by Cystic Fibrosis, the mucus produced by cells reaches the ducts of the organ. In particular, lung cells are mostly affected from this pathology. The mucus clogs the airways (bronchial tubes and bronchioles) so respiration is made more difficult [4] [5]. In a healthy individual, ducts are usually covered by a thin layer of mucus. It has the important role to capture extraneous inhaled particles, carrying they to the upper respiratory system (throat)for removal. In presence of Cystic Fibrosis, mucus is more solid and resistant to be removed. When mucus obstructs the airways [6], the risk of infection increases, because bacteria remain in the air passages. Infection can become chronic so destroying progressively bronchioles and airways. Mucus production affects even pancreas cells so obstructing the ducts carrying the digestive enzymes towards the intestines. As a result, food is not properly digested and nutrients are not extracted. For this reason, children with Cystic Fibrosis suffer typically from slow growth. With the same mechanism, further serious disorders can regard intestines and liver. The most common symptoms are [7]: cough, wheeze, respiratory disease (bronchitis or pneumonia), salty sweat, weight loss. Nevertheless, the main cause of death is due to lungs infections. Actually, Cystic Fibrosis diagnoses regard principally children. The main technique [8] of diagnosis today used in practice is based on the malfunction of the salt movement in and out the epithelium. The salt accumulation on the skin surface is the peculiarity of Cystic Fibrosis. In fact the amount of salt in perspiration is between 2 and 5 times the normal one. As a consequence, in order to diagnose the pathology, physicians use the sweat test. It is a relatively non-invasive and low cost test measuring the amount of sodium chloride in the sweat. Sweat is collected from leg or arm and is analyzed in laboratory. Differently, for newborns, a blood test is performed to measure the amount of *trypsinogen protein*. High levels of such protein are index of a possible Cystic Fibrosis. More complex genetic tests allow specialist to indentify the defective gene in a sample of patient's blood. In the past, this disease was responsible of children death in infancy due to the loss of an

excessive amount of chloride and sodium ions in sweat. Nowadays, no cure for Cystic Fibrosis exists yet. The study of pathology mechanism has taken several years. Current treatments allow patient to live longer than some years ago, the actual life expectancy is approximately 30 years. Symptoms may be mild or severe according to the pathology stage. Since, the respiratory system is mostly injured, the mechanism of such treatments is based on the removal of the mucus from the lungs to facilitate breathing.

2. PROCESSING PHYSIOLOGICAL SIGNALS

The use of hardware for conditioning physiological signals instead of pure software processing is an special approach thanks to low noisy devices and systems. There are conditioners for different physiological signals. Voltage conditioners, both single-ended amplifiers and differential amplifiers, may also be included in the group of signal conditioners. Operational amplifiers single-ended voltage amplifiers are commonly used in measurement circuits and systems. An amplifier feature [9] required in a measurement system is a possibility of controlling the voltage gain. The interferences, due to different reasons (skin contact resistance, hardware, etc...), are amplified by the operational amplifier with the great open-loop gain G. G varies from 10^5 to 10^6 V/V for operational amplifiers. The amplification change in the amplifier is possible by the exchange resistor, which is not directly connected to the operational amplifier input. So the interferences immunity of this circuit is considerably greater than that of the circuit used in this paper. Amplifier with high voltage sensitivity, characterized with low input offset V_{0s}, small temperature drift of this voltage dV_{0s}/dT, and low noise voltage V_{noise}, in particular the noise of type 1/f, are of major importance. Operational amplifiers, with commuting auto-zero (CAZ) and chopper amplifiers, have the lowest offset voltage.

Differential amplifiers are very frequently used to amplify the measuring signal. The task of the differential amplifier is to amplify the potential difference of voltage on two amplifier inputs (V_1-V_2), the differential voltage $V_d=(V_1-V_2)$. The differential amplifier amplifies the input signal from the measurement Wheatstone bridge.

The kind of signal to be processed requires the use of voltage conditioners . An analog circuit matching the signal with the operational range of an ADC is called a conditioner, or a signal standardizing circuit. Conditioners are manufactured in two groups. Typical ranges of output signals in conditioners are from 0V to +5V, from -5V to + 5V, from 0 to 20 mA, and from 4 to 20 mA. Conditioners which are analog converters of common use, usually have their ranges of input voltage >(optionally) and output current ranges defined. The conditioner is equipped with circuits useful to the manufacturer and to the user of the measurement system. These are:

- Break signalling on the output circuit;
- Possibility of connecting an external transistor in order to decrease the power and temperature of the conditioner integrated circuit;
- Source of reference voltage.

A particular device is needed to handle physiological signals in an appropriate way. That is a microprocessor as used in this paper. The structure of microprocessor-based systems is similar to that of the microcomputer except that it contains fewer modules. For example, a clinical ECG monitoring system contains microprocessor, ROM for a program, RAM for data and an I/O port for ECG signals. It does not have mass storage, keyboard, or monitor for display, but may have some keys to choose functions or small printer to print out the ECG signals. Compared to a microcomputer, a microprocessor-based system contains less memory and fewer devices. The advantages are its small size and flexibility. Some microprocessors even have ADC/DAC circuits, communication circuits and other devices on the chip so that one single chip satisfies all the needs of the application.

3. HARDWARE DESIGN AND RESULTS

The concentration of the desired parameters is the basis for designing the measurement system. Na^+ and Cl^- concentration in perspiration varies from person to person, nevertheless reference values have been characterized by statistical studies. In the medical practice, high incidence of false-positive results has been observed by considering the only measurement of sodium concentration. For this reason, typically the sweat chloride concentration is considered as reference parameter to diagnose Cystic Fibrosis as indicated in Tab.1.

Parameter (age)	Cystic Fibrosis		
	Unlikely	*Possible*	*Likely*
Na^+ [mmol/l] (>6 months)	≤ 40	41-69	≥ 70
Cl^- [mmol/l] (>6 months)	≤ 39	40-59	≥ 60
Na^+ [mmol/l] (<6months)	≤ 29	30-89	≥ 90
Cl^- [mmol/l] (<6months)	≤ 29	30-59	≥ 60

Tab. 1 Matching concentrations.

Device	Parameters	Formulation	Component
Preamplification circuit two-stage	R1=500 Ω R2=10 Ω R3=1 MΩ R41=100 Ω R51=1.25 KΩ RV1=10 KΩ	$Av1 = -\dfrac{R2 + RV2}{R1}$ $Av2 = -\left(1 + \dfrac{R5}{R4}\right)V_{ref}$ $V_{ref} = R3 * R4 * i_{test}$	4 Resistors 1 Variable resistor 2 opamp UA741
Tow-Thomas biquadratic cell	R4=R5=R6=10KΩ R7=R8=R9=10KΩ C1=10 μF C2=100 μF $f_1 = 32$ Hz	$H_{LPF}(s) = \dfrac{V_{02}}{V_1} =$ $= \dfrac{\frac{1}{C1C2R2R4}s}{s^2 + \frac{1}{C1R1}s + \frac{1}{C1C2R2R3}}$ $H_{LPF}(0) = \dfrac{R2}{R5}$ $\omega_0 = \sqrt{\dfrac{1}{R2R4C1C2}}$ $Q = \sqrt{\dfrac{R3^2C2}{R4R2C1}}$	6 Resistors 2 Capacitors 3 Opamp AU741
Monitoring circuit architecture	Quartz oscillator= 8 MHz C4=C5= 18 pF C3=100 nF R10= 47 KΩ RV1= 1 KΩ		PIC16f877A Display LCD LM016L 3 Capacitors 1 Resistor 1 Variable resistor

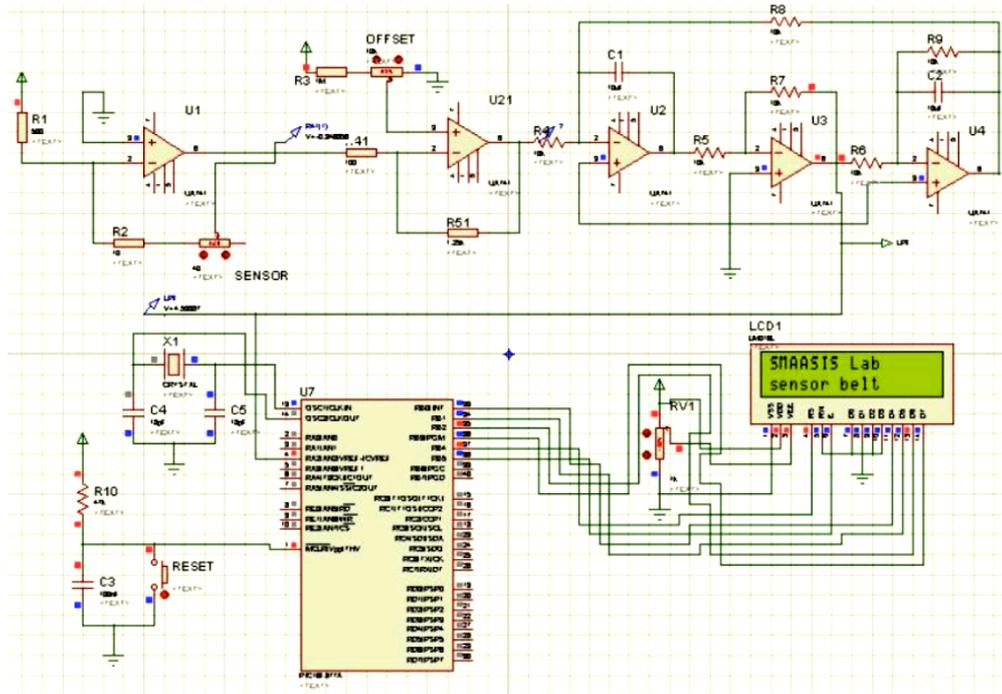**Fig.1:** Main components of post sensor circuits
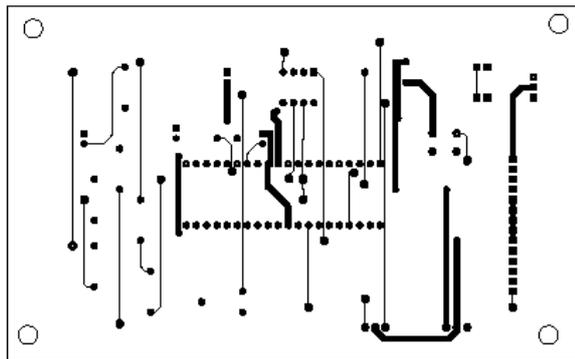
Fig. 2: Full circuit design.
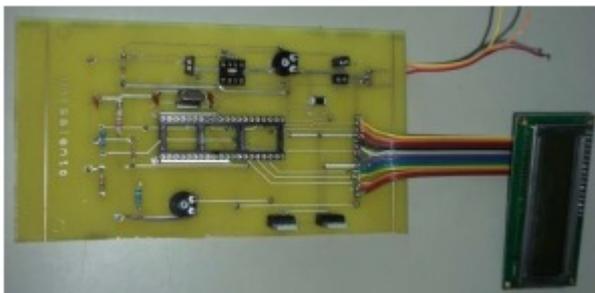

Fig.3: PCB design of circuit

Fig.4: Mounted components

The main components of the designed hardware are illustrated in Fig. 1. The full design, reflecting the main idea of the hardware is shown in Fig.2. Once the PCB has been simulated, according to Fig. 3, it has been constructed taking into account reference parameter to diagnose Cystic Fibrosis as indicated in Tab.1. The constructed hardware is illustrated in Fig.4 with the displaying depicting the reading process of sodium chloride concentration.

4. DISCUSSIONS

The paper has illustrated the design of a necessary hardware for treating signals from sensor dedicated to sodium chloride concentration in the effort to contribute to know the presence of Cystic Fibrosis in the body by characterizing the sweat. Moreover the constructed hardware can be used to characterized other fluid on the skin like humidity. The flux of water vapor out of fixed area of the skin, during flow hygrometry, is determined by measuring the increase in water vapor concentration in the flowing gas stream. The increase in humidity [10] is read at a sensor output once steady-state conditions have been reached. The constructed hardware can be reduced in a small board using microelectronics or nanoelectronics [11] [12] [13]. This possibility is very helpful for wearable sensors as embedded architectures.

5. REFERENCES

[1]   R. Marks, R.A. Payne (Eds)," Bioengineering and the skin", MTP Press, 1981, Boston.

[2]   S.N. Andrews, E. Jeong, M.R. Prausnitz, "Transdermal Delivery of Molecules is Limited by Full Epidermis, Not Just Stratum Corneum", Pharm Res Vol. 30, pp.1099–1109, 2013.

[3]   D.A. Margarida, K. Kunzelmann, "Cystic Fibrosis", Methods in Molecular Biology, Springer, Vol. 741, 2011.

[4]   A. Lay-Ekuakille, P. Vergallo, A. Trabacca, M. De Rinaldis, F. Angelillo, F. Conversano, S. Casciaro, "Low-Frequency Detection in ECG Signals and Joint EEG-Ergospirometric Measurements for Precautionary Diagnosis", Measurement, Vol. 46, Issue 1, pp 97-107, 2013.

[5]   D. Labate, F. La Foresta, G. Occhiuto, F.C. Morabito, A. Lay-Ekuakille, P. Vergallo, "Empirical Mode Decomposition vs. Wavelet Decomposition for the extraction of respiratory signal from single-channel ECG: a comparison", IEEE Sensors Journal, vol.13, n.7, pp. 2666-2674,2013.

[6]   A. Lay Ekuakille, G. Vendramin, A. Trotta, "Spirometric Measurement Post-Processing: Expiration Data Recovery", IEEE Sensors Journal, Vol.10, n.1, pp.25-33, 2010.

[7]   D. Labate, F. La Foresta, M. Campolo, A. Lay-Ekuakille, P. Vergallo, C. Morabito, "ECG-Derived Respiratory Signal using Empirical Mode Decomposition", IEEE International Symposium on Medical Measurements and Application, MEMEA 2011, Bari, 30-31 May 2011.

[8]   D. K. De Boeck et al., "New clinical diagnostic procedures for cystic fibrosis in Europe", Journal of Cystic Fibrosis, Elsevier , Vol. 10, Supplement 2, pp. S53-S66, 2011.

[9]   R. Morello, A. Lay-Ekuakille, C. De Capua, G. Griffo, M.C. Lugara', P. Vergallo, "Design of a Wearable Sweat Sensor for Diagnosing Cystic Fibrosis in Children", 2013 IEEE MEMEA, 4-5 May, 2013, Gatineau – Ottawa, Canada.

[10] M. Yasin (Eds), Selected Topics on Optical Fiber Technology: A. F. Omar, M. Z. MatJafri, "Optical Fiber Near Infrared Spectroscopy for Skin Moisture Measurement", Intech, 2012.

[11] A. Massaro, F. Spano, A. Lay-Ekuakille, P. Cazzato, R. Cingolani, A. Athanassiou, "Design and Characterization of Nanocomposite Pressure Sensor Implemented in Tactile Robotic System", IEEE Transactions on Instrumentation & Measurement, Issue 8, vol. 60, pp 2967 – 2975, 2011.

[12] N.I. Giannoccaro, A. Massaro, L. Spedicato, F. Spano, A. Lay-Ekuakille, P. Vergallo, "Mechanical Characterization of Totally Optical Tactile Sensor Oriented on Bio-Applications", IEEE MeMea 2012, May 18-19, 2012, Budapest, Hungary

[13] D. Caratelli, A. Yarovoy, A. Lay-Ekuakille, P. Vergallo, A. Massaro, Z.H. Li, "Design and Full-Wave Analysis of Nonconformal Fermat-like Spiral Multi-Port Microantenna Sensors", IEEE SENSORS 2011, october 28-31, Limerick, Ireland.