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Microcontroller Based Device for Capacitive Biosensor Readout

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Abstract

Nowadays, problems in healthcare sector seem to be more crucial than ever. In a bid to reduce the number of deaths due to several diseases by taking precautions, science has turned to the development of biosensors able to offer early diagnosis. Therefore, in the present study, an attempt is made to design and construct a device based on a microcontroller, able to detect the capacitance change of a capacitive biosensor during the biorecognition. An accurate electronic circuit allows the construction of smart and rapid biosensing devices that can detect various substances in human serum and provide an easy and early diagnosis. The developed device measured capacitance change caused by liquid samples with a limit of detection of 35,4nL/mm2.

Keywords: Electronic Readout Circuit; Biosensor; Biomolecule Recognition; Capacitive Sensor; Microcontroller.

Introduction

It is widely accepted that nowadays, healthcare sector is in a state of global turmoil. Science and technology are called to sustain medicine by consisting a weapon to fight all life-threatening ailments and diseases. Lately, there has been a growing demand for the development of portable, fast and low-cost devices that are used to prevent diseases. In these circumstances, biosensors play an important role, as they enable early diagnosis with no need for a hospital visit associated with costly and time-consuming laboratory tests.

A biosensor consists of two components connected via electrical wires: the biological part and the electronic part for reading and transmitting the information. The former part is able to interact with biological particles and the latter part detects this interaction via changes of the electric properties. In a biosensor, the bioreceptor (antibody, enzyme, nucleic acid, aptamer) is designed to interact with the desired biomolecule (target) with high selectivity [1,2]. Consequently, the detection of biomolecules or even the creation of a multiple detection system by a set of capacitors with different bioreceptors is feasible only by measuring the capacitance alteration of a capacitive biosensor. The second part is the readout circuit of the sensor. Mainly at capacitance readout circuits, the sensor provides a differential capacitance output and the circuit detects the capacitance change while single-ended readout circuits have also been developed. At each device, the readout circuit design should be developed considering the circuit performance which is affected by the sensor and packaging specifications [3,4,5,6].

In this work, the electronic part of an interdigitated capacitive sensor was constructed and tested. The capacitance measurement technique was chosen as these sensors can provide the results with high accuracy and sensitivity. Interdigitated electrodes (IDEs) are very sensitive and this makes them one of the most favored transducers in the field of biosensors since they have been used as capacitance or impedance biosensors for various applications. Interdigitated electrodes serve as the transducer, when used on biosensors [7,8,9,10]. A receptor is immobilized on the electrode surface and when it interacts with an analyte, a change in the material's dielectric properties or in the thickness of the dielectric layer occur [11,12]. The basic equation according to which the IDE capacitance changes is given by Equation (A).

$$C = \varepsilon_0 \in_r \frac{A}{d} \qquad \text{(A)}$$

Where **n** is the number of the electrodes, $\boldsymbol{\varepsilon_0}$ is the vacuum permittivity, $\boldsymbol{\varepsilon_r}$ is the relative permittivity of the medium, A is the electrodes' surface area and d is the distance between the electrodes [13].

The device constructed, consists of the interdigitated capacitor connected to a microcontroller-based readout circuit that provides the capacitance measurements [14]. A bioreceptors' solution is placed on the surface of the capacitor and its capacitance is measured. With this known, human serum can be placed above the surface and the capacitance is measured again. Any alteration in capacitance observed is due to the interaction of the target-biomolecule with the pre-existing bioreceptors and thus, its existence is indicated.

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Materials and methods

For the device constructure and testing, the following components have been used: Funduino Uno R3 (Arduino Uno R3 type board) with ATmega328P microcontroller; Resistors of 4.7 kΩ, 1kΩ, 100kΩ, 8.2kΩ and 2kΩ (connected in series to create 10.2kΩ); Breadboard and Circuit Board PCB; Jumper Wires; Interdigitated capacitor. The above components were provided by the Laboratory of Electronic Sensors of the School of Electrical and Computer Engineering, National Technical University of Athens (NTUA). Gold interdigitated electrodes were purchased from DropSens (Asturias, Spain), cat. N.: IDEAU200. Each IDE has a finger width and spacing of 200 µm, 22.8mm length, 7.6mm width and 1mm height.

The capacitance was measured using the capacitor charging-discharging method which offers high accuracy even for small values [15]. To measure the capacitance and its alteration and therefore to detect the biological substances levels, an electrical resistor-capacitor (RC) circuit and a microcontroller [16,17] were used as described below.

In a RC circuit where a source voltage Vs is applied, the capacitor voltage Vc increases exponentially towards Vs according to the following equation:

$$V_c(t) = V_s\left(1 - e^{\left(-\frac{t}{RC}\right)}\right) \qquad (I)$$

Considering V_c (t=0) = 0.

A reference voltage is used in a comparator to find the time t, when the capacitor reaches this voltage. The reference voltage is generated by a voltage divider circuit. In such a circuit with two identical resistors (R1 = R2) a constant voltage Vr=Vs/2 is produced.

According to equation (I), the moment t when the capacitor voltage reaches the reference voltage Vr (assuming Vc = Vr = Vs/2), the capacitance will be given by the formula:

$$(I) \Rightarrow \frac{Vs}{2} = Vs\left(1 - e^{\left(\frac{t}{RC}\right)}\right) \Rightarrow \frac{1}{2} = 1 - \frac{1}{e^{\left(\frac{t}{RC}\right)}} \Rightarrow C = \frac{t}{R\ln\left(\frac{1}{2}\right)} \qquad (II)$$

Therefore, by programming properly the microcontroller to measure the time t, the capacitance value C is easily known by the equation (II).

The schematic diagram of the circuit (Figure A(i)) and a simulation image in Tinkercad (Figure A(ii)) are shown below.

The capacitor under test is connected to the terminal probes “+” and “-”.

As explained previously, in an RC circuit where voltage Vs is applied, the voltage across capacitor Vc is given by the equation (I). In this device, using the built-in analog comparator of Funduino ATmega328P microcontroller, the time when the capacitor voltage becomes greater than half of the applied voltage (Vc > Vs/2) will be detected.

A voltage divider is created consisting of two identical resistors of 4.7 kΩ. More specifically, the two resistors are connected in series, the one terminal to the ground of Funduino and the other to voltage Vs, i.e. the 5V voltage of Funduino that is used as the supply voltage. Their common terminal, the voltage of which will be equal to Vs/2, i.e. 2.5V, is connected to the digital pin 6, which is the non-inverting input (+) of the analog comparator (AIN0 pin of Atmega328). The positive (non-grounded) end of the capacitor is connected to the inverting input (-) of the analog comparator via Funduino analog pin A5 (Atmega328 AIN1 pin) [18]. This pin also reads the voltage of the capacitor during discharging.

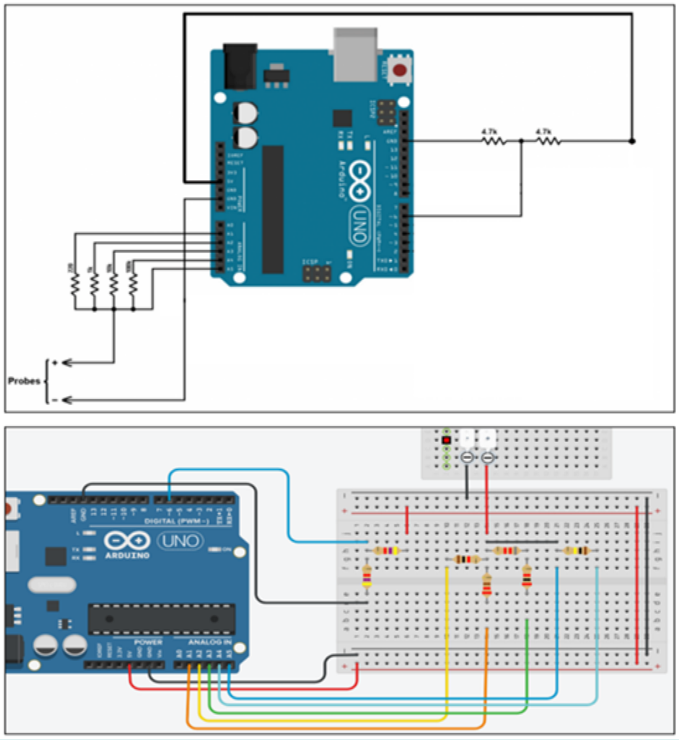

Figure-A: (i) Schematic diagram, (ii) Simulation in Tinkercad.

A timer module called Timer1, is programmed to measure the time from the moment when Vc=0 to the moment when Vc=Vs/2, based on the output of the comparator. The resistors of 1kΩ, 10.2kΩ and 100kΩ are used to charge the capacitor according to the order of magnitude of its capacitance and to display the indication with the appropriate unit. The resistor of 220Ω is used to discharge it. Thus, the Funduino outputs a maximum current Ic = 5V/1kΩ = 5mA while charging and sinks a maximum current Id = 5V/220Ω = 22.7mA while discharging. The one terminal of the capacitor is grounded. Funduino analog pin A1 is used for discharging and is connected to the non-grounded terminal of the capacitor via the 220Ω resistor. For its charging, the analog pins A2, A3, A4 are used, which are connected to the non-grounded end of the capacitor through the resistors 1kΩ, 10.2kΩ and 100kΩ, respectively.

The Funduino starts discharging the capacitor by writing logic LOW to discharge_pin, until the capacitor is fully discharged through the 220 Ohms resistor. During this time period, the ADC module is monitoring the capacitor voltage via pin A5. ATMega328 provides an on-chip successive approximation ADC which is of 10-bit resolution. A successive-approximation ADC is a type of analog-to-digital converter that converts a continuous analog waveform into a discrete digital representation using a binary search through all possible quantization levels before finally converging upon a digital output for each conversion. The ADC is connected to an 8-channel analog multiplexer which allows eight single-ended voltage inputs constructed from the pins of Port A. The single-ended voltage inputs refer to 0V (GND) [19,20].

After the capacitor is fully discharged, the ADC module is switched off, the analog comparator interrupt is activated, and the capacitor is charged by applying a voltage through one of the 1k, 10.2k, 100k resistors. Timer1 [21] starts counting time until the analog comparator interrupt occurs. This interruption informs the microcontroller that the capacitor voltage is approximately equal to the reference voltage of 2.5V. The Timer1 unit is set to increase by 1 every 62.5 microseconds (prescaler = 1).

Thus, the capacitance value is calculated by equation (II), since the values of the supply voltage (5V), the series resistance (1k, 10.2k or 100k) and the time t are known. Figure B presents the block level schematic diagram of the circuit in use.

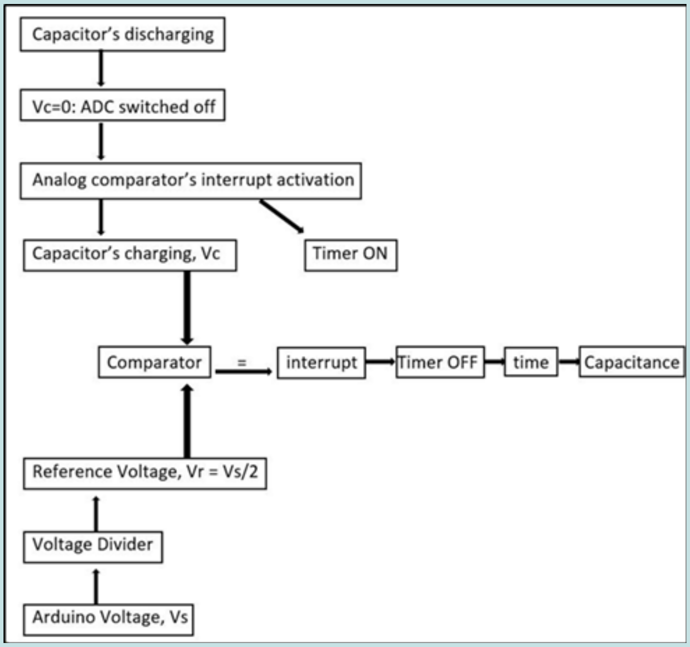

Figure-B: The block level schematic diagram.

After the construction of the electronic part, its correct operation was verified by using fixed ceramic capacitors and dropping water or other aqueous solution on the interdigitated capacitor surface. In this way, the device's ability to both measure the capacitance and distinguish substances by its change was tested.

The initial form of the circuit is shown in Figure C.

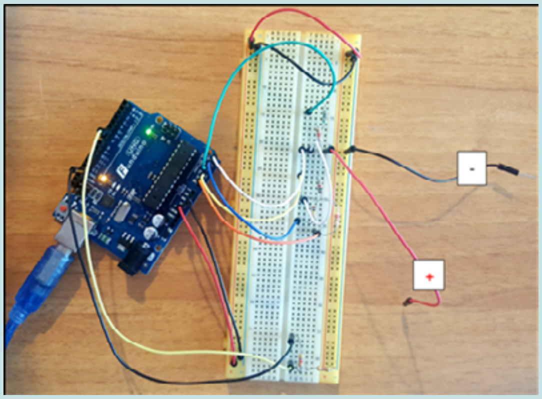

Figure-C: The prototype circuit.

Afterwards, the miniaturization of the device was examined. The breadboard was replaced by a small printed circuit board (PCB) constructed to fit on the Funduino. The layout of the board was designed using the KiCad software. The copper layer was printed on a slide, which was placed onto the board with light-sensitive coating and then they were exposed to ultraviolet light. Afterwards, the PCB was rinsed with water and placed in NaOH solution to remove the UV exposed areas. After the appearance of the conductive tracks, the etching followed and the board was placed in FeCl3 solution, on a stirrer to remove the unwanted copper from the PCB. Finally, the appropriate holes were drilled and the resistors of the breadboard were soldered to the board. The black components are the socket pins to which the capacitor to be measured is connected. The small PCB was finally placed on the Funduino with the pins connected properly so that the device has smaller dimensions, 8cm x 6cm x 1.6cm (length x width x height) and weighs about 70g.

The steps of modifying the layout are shown in Figure D and the final form of the device is shown in Figure E.

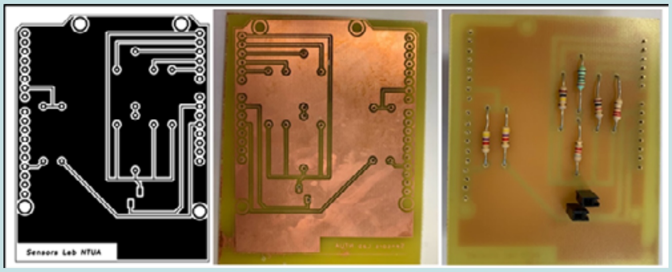

Figure-D: Steps of layout modification.

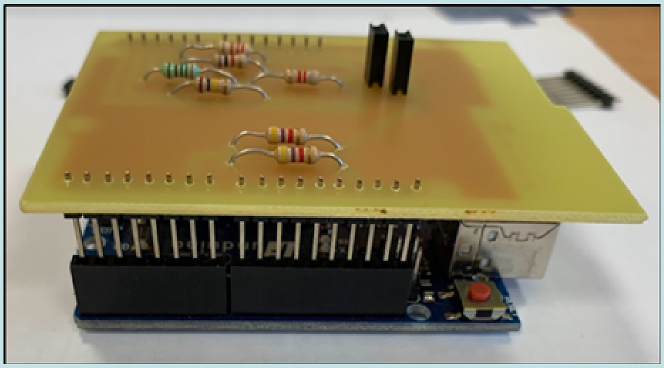

Figure-E: Final form of the device.

Results and Discussion

Measurement of Fixed Ceramic Capacitors:

To test the ability of the electronic part for capacitance measurement, fixed ceramic capacitors were initially measured using both an Extech 380193 multimeter (Extech Instruments, USA) and the device developed. The results are presented in Table 1.

It is easy to conclude that this is a device capable of measuring the capacitance up to the order of pF with satisfactory accuracy. Subsequently, it constitutes a suitable electronic part for the sensor since the goal is to detect changes greater than those of few pF which the device is able to detect.

Table-1: Comparison of device results and multimeter results.

Capacitance results by the multimeter	Capacitance results by Extech 380193
9 pF	9 pF
505 pF	504 pF
10.6 nF	10 nF
98 nF	96 nF

Measurements with Water and Aqueous Solution:

The function of the interdigitated capacitor was then tested when connected to the electronic circuit. The capacitor was connected to the device and drops of 0.5 ml of deionized water were placed on its surface, using a pipette. It became obvious that the capacitance was increasing, as more drops were placed. After a few drops, the capacitance remained almost constant despite the increase in the amount of water. This is explained by the fact that the change in capacitance is due to the change in relative permittivity, which does not depend on the volume of the medium on the capacitor but on the surface that it covers. Thus, when the entire surface is covered with water, adding extra drops increases the volume of water but there is no change in capacitance as the coverage area cannot be further increased.

Approximately 30 measurements were performed for the cases no water, 1, 2, 3 and 4 drops of water on the surface. A large increase was observed as the capacitance changed from 91pF to 4.1 μF at 2 drops and remained almost stable. Based on these, the capacitance change diagram of the normalized values was created (Figure F). Each point represents a measurement. The horizontal axis represents the number of drops on the surface of the capacitor and the vertical axis represents the capacitance. The dash line represents the 3rd order polynomial trendline of the diagram and R^2 is the coefficient of determination.

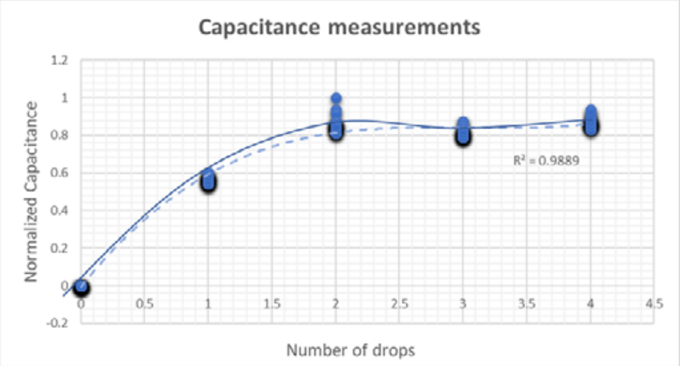

Figure-F: Capacitance change diagram (normalized values) while adding water.

As expected, the diagram presents that for the first two drops the capacitance shows an increase while for more drops it remains almost stable at the value reached after the surface of the capacitor is covered.

Then, for each of the cases, the normalized means, standard deviation, variance and margin of error were calculated and the results are shown at Table 2.

Sensor sensitivity was calculated according to the formula:

$$LoD = \frac{3.3\times\sigma}{S\times A} \qquad \text{(III)}$$

Where σ is the maximum standard deviation, S is the slope of the calibration curve and A is the total electrode surface.

Therefore, sensor for water was calculated equal to 35,4nL/mm^2.

Table-2: Processing data (normalized values).

	No water	1 drop	2 drops	3 drops	4 drops
Arithmetic mean, x	0.000019	0.5654	0.8548	0.8148	0.8687
Geometric mean, l	0.000019	0.5652	0.854	0.8145	0.8684
Harmonic mean, p	0.000019	0.5649	0.8533	0.8141	0.8681
UNCERTAINTY 100%					
Standard Deviation, σ	0.0000032	0.01735	0.03751	0.02347	0.02373
Variance, σ2	0.1024 · 10-10	0.000301	0.001407	0.00055	0.000563
Margin of error, σx	0.000585	0.00317	0.006849	0.00428	0.004332
UNCERTAINTY 95.4%					
Standard Deviation, σ	0.0005624	0.01708	0.03694	0.021359	0.02385
Variance, σ2	0.3163 · 10-6	0.000292	0.001365	0.000456	0.000569
Margin of error, σx	0.0001063	0.003229	0.006981	0.004036	0.004507

Measurements with Aqueous Solution of Polyvinyl Alcohol:

Following, the capacitance was measured with one drop (0.5 ml) of aqueous polyvinyl alcohol solution containing povidone and chloride, placed on capacitor surface. Thirty measurements were performed and the same values (Table 3) were calculated.

Observing the above results, it appears that even though the volume of liquids was the same in both cases (0.5 ml), the capacitance in case of water was about 2.7 μF while in case of the second solution was 26.2 μF. This confirms that the capacitance of an interdigitated sensor changes according to the dielectric properties of the medium and this, enables the sensor to distinguish and identify substances.

Table-3: Data from measurements with aqueous solution.

MEANS	UNCERTAINTY 100%					UNCERTAINTY 95.4%		
Arithmetic	Geometric	Harmonic	Standard Deviation	Variance	Margin of error	Standard Deviation	Variance	Margin of error
26.21 μF	26.14 μF	26.08μF	1.849	3.419	0.338	1.669	2.785	0.315

Discussion

The device's prospect is to become an accurate electronic readout circuit capable of capacitance measurement that can be part of many biosensors. In the present work, it became obvious that the device is actually able to detect the capacitance alteration of the interdigitated capacitor and therefore the presence of a biomolecule in solutions such as human serum. Notwithstanding that the results are preliminary; they are validated at the laboratory. This work is in research level but the concept is proved experimentally, providing a technical readiness level 3 [22].

Although this study seems to fulfill its objectives, it is experimental and should be extended and improved. In fact, it constitutes the starting point for future work by researchers and engineers, in order to develop easy-to-use and fast biosensor readout devices. To this end, following projects would focus on the selectivity of the device and its function at blood samples. Further analysis of this sensory system would also make it capable of precise measurement through experiments using more capacitors, different bioreceptors and solutions of various concentrations. Another important improvement would be the portability and the smart connectivity of the system: miniaturization, battery power supply, wireless connections. Funduino provides the ability for wireless data transfer via Bluetooth or Wi-Fi technology by using an auxiliary device e.g.

HC-05 or ESP8266. These modules are electronically connected to the Funduino board, receive the data and then transmit it wirelessly to any device (Laptop, Smartphone).

Conclusion

It is, undoubtedly, a challenge for engineering science and technology, to contribute to medicine by providing new tools that can tackle serious health problems. Via this work, an attempt was made to design and construct an electronic part of detection biosensors. The capacitive detection technique was chosen for the construction, relating an alteration in the capacitance of the interdigitated capacitor with the indication of the presence of the desired biomolecule. The electronic part of the sensor was designed, implemented, tested and finally measurements in water and aqueous solution were performed and analyzed. The results showed that the device constructed is able to measure with accuracy and stability the capacitance and its alteration. Thereby, it can be claimed that this is an approach to build the readout circuit of smart and compact biosensors capable of rapid detection.

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