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Smart central venous port for early detection of bacterial biofilm related infections

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Abstract Central venous catheters (CVC) are commonly used in clinical practice to improve a patient's quality of life. Unfortunately, there is an intrinsic risk of acquiring an infection related to microbial biofilm formation inside the catheter lumen. It has been estimated that 80 % of all human bacterial infections are biofilm-associated. Additionally, 50 % of all nosocomial infections are associated with indwelling devices. Bloodstream infections account for 30–40 % of all cases of severe sepsis and septic shock, and are major causes of morbidity and mortality. Diagnosis of bloodstream infections must be performed promptly so that adequate antimicrobial therapy can be started and patient outcome improved. An ideal diagnostic technology would identify the infecting organism(s) in a timely manner, so that appropriate pathogen-driven therapy could begin promptly. Unfortunately, despite the essential information it provides, blood culture, the gold standard, largely fails in this purpose because time is lost waiting for bacterial or fungal growth. This work presents a new design of a venous access port that allows the monitoring of the inner reservoir surface by means of an impedimetric biosensor. An ad-hoc electronic system was designed to manage the sensor and to allow communication with the external receiver. Historic data recorded and stored in the device was used as the reference value for the detection of bacterial biofilm. The RF communication system sends an alarm signal to the external receiver when a microbial colonization of the port occurs. The successful *in vitro* analysis of the biosensor, the electronics and the antenna of the new indwelling device prototype are shown. The experimental conditions were selected in each case as the closest to the clinical working conditions for the smart central venous catheter (SCVC) testing. The results of this work allow a new generation of this kind of device that could potentially provide more efficient treatments for catheter-related infections.

Keywords Intravascular port · Intelligent implant · Catheter sepsis · *In vivo* diagnostics · Bacterial biofilms

1 Introduction

Microbial biofilms are responsible of a wide range of infectious diseases associated with indwelling medical devices. Intravenous catheters, prosthetic heart valves, prosthetic joints, pacemakers, etc. are widely used in the healthcare attention saving millions of lives, but assuming an intrinsic risk of infection (Hall-Stoodley et al. 2004). Medical implants are the propitious environment for the development of bacterial biofilms, which will lead to an infection. The importance of biofilm-associated infection was estimated to represent over 80 % of human microbial infections (Davies 2003). Approximately, 50 % of nosocomial infections per year in the US are associated with indwelling devices (Harris and Richards 2006).

These bacterial communities are composed of microbes that irreversibely attach to a biological or to an inert surface, and generate an extracellular matrix based on polysaccharide that also meediates in the adhesion process (Donlan 2002).

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The unique physiology, the complexity and heterogeneity of this micro-bio-system provide microorganism antimicrobial resistance at levels extremely higher than planktonic or free-floating microorganisms (Costerton et al. 1999; Davies 2003; Stewart and William Costerton 2001).

Gram positive cocci (*Staphylococcus aureus*, *Staphylococcus epidermidis*, *Enterococcus faecalis*), *Streptococcus vidrians*, *Klebsiella pneumonia*, *Pseudomona aeruginosa*, are some of the most common bacteria isolate from infected implanted devices. These microorganisms arise from the environment, the skin of the patient, the healthcare personnel or other environmental sources (Donlan 2001a; Fux et al. 2005). Within the listed pathogens, *Staphylococcus epidermidis* is presented as the predominant microorganism related to device-associated infections (Wang et al. 2011). Many of the current persistent and chronic bacterial infections have their origin in the antimicrobial resistant characteristic of biofilms (Costerton et al. 1999).

Routine monitoring of patients is usually inefficient for detecting biofilm-related infectious pathologies (Fux et al. 2005). The detection and diagnosis before the treatment of the infectious processes caused by microbial biofilms are not really solved. The period between the infection and the detection, the process to analyze which bacteria is growing, often results too time-consuming.

In this context the infectious process not detected on time may end up in several medical complications for which, in many cases, the only way to ensure a good outcome is removing the infected device (Donlan 2001a; Stewart 2003). These events have a high cost on top of the high importance of the patient health risk under such medical complications. Every achievement made on improving the treatment would be a success (Rupp and Archer 1994; Vuong and Otto 2002; Harris and Richards 2006). For this reason it is necessary to develop new methods to improve biofilm early detection.

Nowadays there is a wide variety of novel techniques that allow in-depth *in vitro* study of the most important aspects of the formation of bacterial biofilms, from gene expression to microscopic characterization. However, there still remains a great demand in the field of *in vivo* detection specially for indwelling devices. To achieve this purpose it would necessary to develop new intravascular catheters that provides a continuous monitoring of the content of the reservoir of the CVC and to send an alarm signal in case of bacterial colonization. The new device should have an electronic module to provide the measurement and to process the communications protocol to the external reader.

2 Smart central venous catheter (SCVC) prototype

The new SCVC (see Fig. 1a) is composed of three complementary modules that provide with full functionality to this device: Biosensor, electronics and antenna. The integration of these modules allows the device to detect the infection at the early stages and to transmit an alarm signal outside the body. An interdigitated microelectrode biosensor (IDM) is used to drive sequentially impedance measurements. This module provides the electrical characteristics monitoring of the reservoir content of the portal. The presence of the initial stage biofilm development is detected onto the biosensors surface. Specific electronics control the biosensor operation and sets a wireless link through the antenna and the body to an external reader.

In this section the design of each one of the modules that compose the device is presented highlighting the most relevant characteristics.

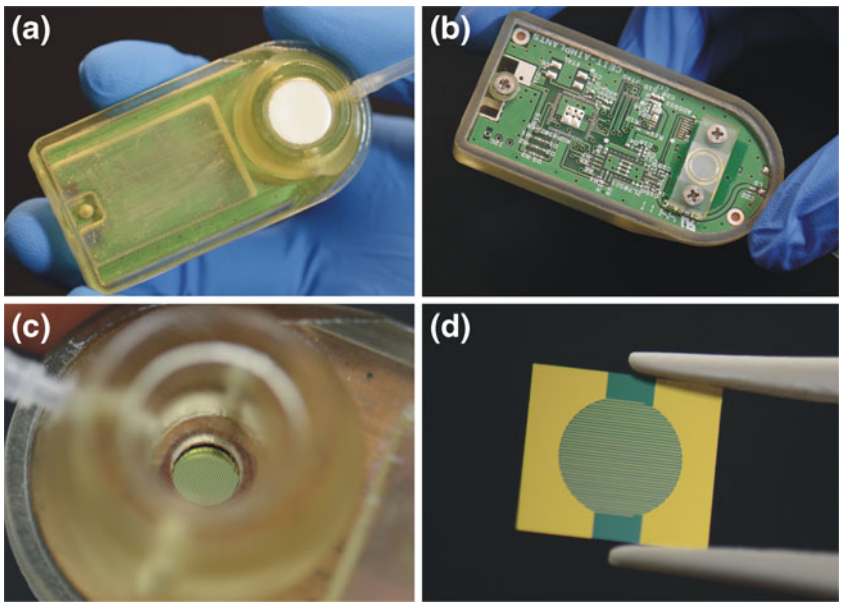

Fig. 1 Photographs of the smart central venous catheter prototype. **a** top side of the prototype; **b** Detail of the electronics inside the implantable device; **c** Detail of the sensor inside the reservoir of the catheter; **d** Photograph of an interdigitated microelectrode biosensor

2.1 Sensing module design

The IDM was proved to be a suitable solution for microbial biofilm detection and monitoring (Varshney and Li 2008; Yang et al. 2004). Previous works (Paredes et al 2012) presented a surface free biosensor used for impedance monitoring according to the long-term application of this. The design and fabrication of this kind of biosensors are traditionally developed by means of silicon technologies that are detailed in the next sections.

The impedance-based IDM will measure the variations of electrical characteristics of the biological sample. The biosensor is placed at the bottom of the reservoir (see Fig. 1c), ensuring a total contact between the content of the chamber (the human fluids) and the sensing surface during the operation. Its design was made according to the device geometry in the chamber as a circular area that covers the whole bottom surface with interdigitated microelectrodes. The biosensor is electrically connected with the electronics that will conduct and analyze impedance measurements. The contact pads of the biosensor shown in (Fig. 1d) ensure the total electric connection of the prototype for experimental assays.

2.2 Electronic module design

The SCVC electronic module is designed in compliance with the Medical Implant Communication Systems, MICS, which is the standard specification for the Ultra Low Power Active Medical Implants and Peripherals, EN301839 (ETSI EN 301 839, v1.3.1 2009-01) and with the global Industrial Scientific and Medical (ISM) band (Loy et al. 2005).

On one hand, a long term device application requires to be powered through the life time making the battery size critical for a full operation of the system during the treatment. In this sense, the overall size of the device is proportional to the battery size (and viceversa), and so the working life. On the other hand, size is critical for patients comfort and functionality, the smallest size the better for the patient's. Therefore the electronic design must suit these two apparently opposite requirements and find a compromised solution. In this first presented prototype a battery is presented as the main supply. However it is clear that alternative or combination of other means of energy supply will make a better medical product.

From the electronics design point of view one of the most important concerns is the energy consumption and so provides the new device the largest operation life. For this reason the module designed, shown in Fig. 2, is based in the MSP430F248 ultra low power microcontroller (Texas Instruments 2013). On the one hand, the biosensor is measured by the AD5933 impedance converter (Analog Devices 2013). On the other hand, the communications system is managed by the ZL70321 transceiver (Zarlink Semiconductors 2013), which uses the ISM band to start the communication link in the MICS band, in order to save energy. These components have software selectable operation modes that enable them to put in low-power modes to save energy.

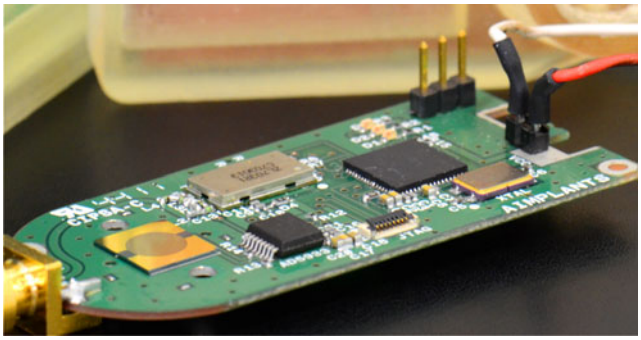

Fig. 2 Photograph of the hardware designed PCB used for electronic testing, which shows the shape of the bottom part of the implantable prototype and over which is placed an IDM biosensor in its inverted final location for the electronic connection

In order to manage the operation modes it has been designed specific software which controls the electronics by the microcontroller. Software reduces the energy consumption by choosing the lowest consumption mode in each case.

2.3 Antenna module design

Along with an efficient electronics, an optimal antenna design is required to achieve long range communication with low power consumption. In the current application, it has to be dual band to operate within a patient in the MICS frequency band (402–405 MHz) as well as in the global ISM band (2.4–2.5GHz). The antenna also requires broadband behavior to avoid detuning when facing a changing live environment. Although the top part of the reservoir is the closest surface to the skin, this area is disregarded as the antenna locus, since it is to be unobstructed for liquid exchange capability purposes between the implant inner reservoir and external catheters or syringes. As a result, the antenna is determined to be three-dimensional, conformal to the side walls of the reservoir and low-profile, i.e. with ideally no extra volume added on the SCVC. The antenna should be compact, insulated from the body and as efficient as possible.

The shape of the supporting reservoir is given to be a truncated cone with a base radius r_b=16 mm, upper radius r_{ur}=10 mm and height hc=16 mm (Fig. 3a). The constraints mentioned above are taken into account when selecting a monopole-like structure as a radiating element. A round ground plane covers the base of the cone. A short circuit between the end of the monopole and the ground plane is implemented as miniaturization technique. By using a closed loop on the top of the implant, which can be seen as an additional inductance, the input impedance matches quite

accurately the desired 50Ω. This loop is narrow enough to leave clear the top of the implant. The whole radiating structure is herein after referred to as CVC antenna (CVCA) (Fig. 3) (Schmidt et al. 2014). The CVCA was coated with a 0.5 mm biocompatible synthetic film and sealed with silicone adhesive to prevent physiological interaction with the media. The chosen antenna topology is designed within a single skin tissue phantom as a surrounding environment, which is considered accurate enough for the body simulation (Fig. 5b).

3 Material and methods

3.1 Bacterial growth impedance monitoring

3.1.1 Design and fabrication of biosensors

Biosensors was fabricated and characterized under clean room environment. A 100 nm thin film layer of gold forms the interdigitated microelectrodes deposited by RF sputtering onto 3" oxidized silicon wafers. Each sensor has a 6 mm diameter circle active sensitive surface composed of 210 pairs of 30 μm wide, 3,980 μm of long fingers with a separation of 30 μm between them.

Before carrying out the measurements all chips were cleaned with Hellmanex dissolution in ultrasonic bath for 10 min. They were rinsed with deionized water again in ultrasonic bath for other 10 min, and finally another 10 min in ethanol absolute (99,5 % ICT.S.L. ref: 161086.1211). Once the biosensors were set up in the chips holder the complete array was sterilized at 121ºC for 1 h in the autoclave.

3.1.2 Impedance spectroscopy (IS) measurements

IS monitoring was performed with a Solartron 1260 Impedance/Gain-phase Analyzer (Solartron Analytical) connected to an own-developed multiplexer system that sequentially connects each biosensor to the impedance analyzer. Through specific LabVIEW®-based software the impedance changes were tracked in real time during the microbial culture development. IDM biosensors were measured every 10 min during the assays with the same electrical conditions. The measurement settings were: 100 mV of sinusoidal excitation signals without polarization, applying variable frequency between 10 Hz and 10 kHz. All the data were measured inside the incubator system at 37 °C and 10 % of CO_2.

3.1.3 Microbiological biofilm samples

A biofilm generator strain of *Staphylococcus epidermidis* was used on this work: the ATCC 35984 obtained from the Colección Española de Cultivos Tipo (CECT). Isolation of pure cultures was carried out following the protocol reported before (Paredes et al. 2012) where an impedimetric monitoring of bacterial growth were carried out inside a modified CDC biofilm reactor system.

Diluted sample from a 0.5 McFarland vial was incubated in Tryptic Soy Broth, TSB (BBL™, ref: 211768), enriched with 5 % glucose (Dextrose from Difco™, ref: 215530) for 1 h to leave the microbes reach the exponential growth point. Two milliliters of infected broth with different bacterial concentration in each assay were injected at the initial moment in each one or the *Lab-Tester* devices.

3.2 Electronics lifetime test

The objective of the lifetime test is to evaluate the operation lifetime of the device. The lifetime is evaluated by analyzing the normal use of the device, which can be summarized in three operations: sniff operation, alive request operation and measure request operation. In addition, there is one operation related to an emergency communication created by a medical event. The consumption of the operations is obtained by using the methodology exposed in (Benini et al. 1998), related to the evaluation of the power consumption by analyzing a power state machine.

In Fig. 4 the main states and the different events of the software designed are shown. The states are defined in Table 1

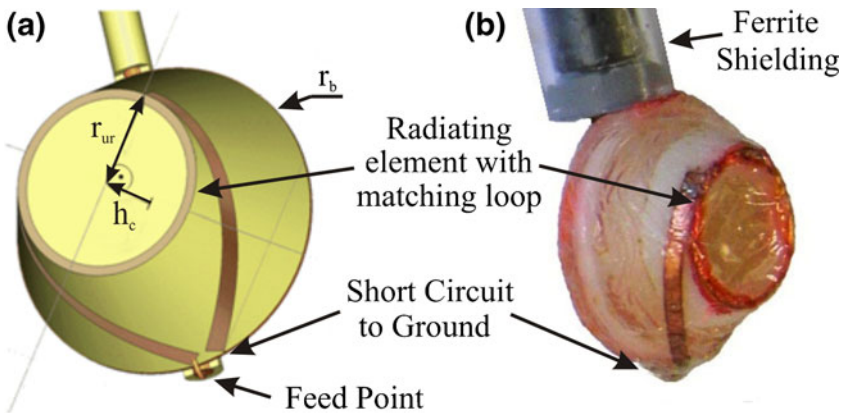

Fig. 3 **a** CVCA layout computer design with feeding cable at the bottom part **b** Real prototype of the CVCA

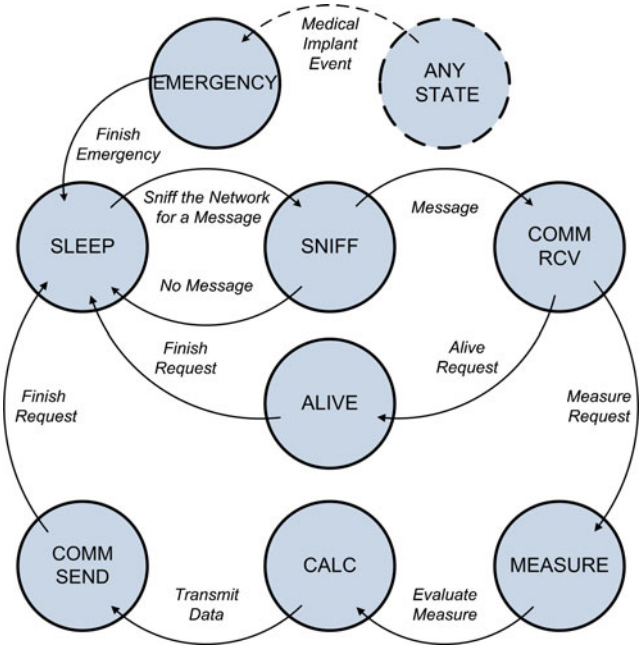

Fig. 4 Power state machine for the SCVC. Different stages of the electronics are shown in the graph and the normal flow between them while operating normally

each state is composed of different sub-states, and address some functions. The SNIFF state addresses the pool of the 2.4GHz frequency band looking for a connection request from the external device, in case a request it is detected the platform moves to the COMM RCV state is performed. This state addresses the reception and decodes of the message, and decides the next state to be performed. Two different requests or operations are defined, the alive request which consist in answering that it is working fine (ALIVE state), and the measure request consist in measuring the sensor (MEASURE state), making some math calculations (CALC state) and sending the information out to the external device (COMM SEND state).

Table 1 Power states machine definition

State name	Definition
Sleep	All the devices are in power-down mode or the best low power mode.
Sniff	It includes all the processes/actions to poll for its code in the network in the 2.4 GHz ISM band.
Comm RCV	It includes all processes/actions to communicate with the external device in the 402–405 MHz band under the Listen Before Talk (LBT) and Adaptative Frequency Agility (AFA) conditions explained in more detail in [ref].
Comm send	It includes all processes/actions to start and to communicate with the external device in the 402–405 MHz band under the Listen Before Talk (LBT) and Adaptative Frequency Agility (AFA) conditions explained in more detail in (Zarlink Semiconductors,).
Alive	It includes all processes/actions to answer to the external device that the device it is alive.
Measure	It includes all processes/actions to measure a complex EBI in the sensor through the Analog-to-Digital converter.
Calc	It includes all processes/actions to perform all operations required to transform data into information.
Emergency	It includes all processes/actions to communicate with the external device by using an emergency communication caused by a Medical Implant Event, explained in more detail in (Zarlink Semiconductors,).

The power consumption and time evaluation of the states is performed by measuring the voltage drop across a 19.6Ω resistor placed in series with the *Hewlett Packard E3631A* power supply unit with the *Agilent 54622A oscilloscope*. The Base Station Mezzanine (BSM100 rev E) included in the ZL70101 Application Development Kit (ADK) (Zarlink Semiconductors 2013) is used for the control and setting-up of the communication link. In addition to the evaluation, the node is configured with the worst case in terms of output power transmission.

3.3 Reflection and transmission test

The objective of the reflection and transmission test is to define the read range of the communication link between the SCVC and an external base station in an indoor scenario for the future application. The base station makes use of the same Z70102 transceiver chip by Zarlink, corresponding to the ADK, with a helix antenna. The range measurement will be contrasted with the estimated one in the literature.

The CVCA is placed into a phantom that models a human torso. The phantom is composed of a polystyrene tank of 35 cm×25 cm cross section that is filled with 14.5 l of tissue simulating liquid (Karacolak et al. 2008). The antenna is placed at 9 mm from the front phantom wall and with an offset of 60 mm with respect to the vertical center axis. The reflection coefficient S_{11} is measured with Agilent 8714ET Vector Analyzer.

Then, the implanted electronics is fed by a 3 V battery. The implant transceiver is programmed to transmit an emergency signal every few seconds. Both wake up and communication signals are transmitted in the MICS band at 403 MHz to test the longest read range. By connecting an Agilent E4402B Spectrum Analyzer to the output of the circuit without antenna, the transmitted power is found to be −15.7 dBm, which is closely related to the maximum approved power according to the MICS standard (−16 dBm, 25 μw) [ETSI EN 301 839, v1.3.1, 2009-01].

Finally, the implanted electronics and the CVCA into the human phantom are assembled to form an SCVC prototype facing the base station (Fig. 5a). The whole setup, including a control unit, is shown in Fig. 4b. The base station and the SCVC are placed at 74 cm and 94 cm from the floor, respectively, in a laboratory environment. The phantom is progressively separated from the base station once the session was established.

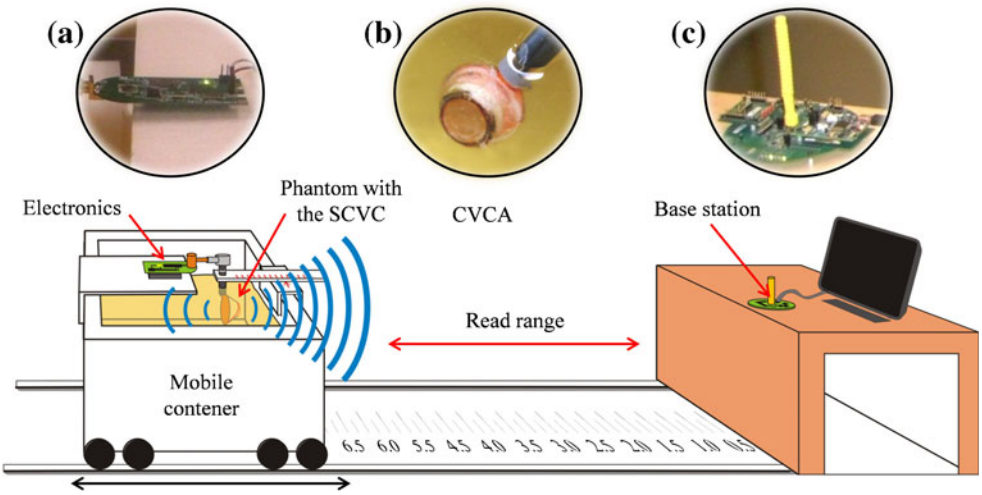

Fig. 5 **a** Electronics connected to the **b** CVCA placed into the phantom (in the laboratory environment), **c** with base station and control unit at maximum operating distance

4 Results and discussion

4.1 Bacterial growth impedance monitoring

Impedance monitoring of bacterial biofilm development principles was previously described (Paredes et al. 2012), where an equivalent electrical circuit is proposed for electric analysis. Figure 6 represents the relative variation of the impedance magnitude in panel (a) and the equivalent serial capacitance (C_{Serial}) in panel (b) at different frequencies, from 10 Hz to 10 kHz for the total duration of the trial. In Fig. 6b a comparison of the impedance monitoring between two different initial concentrations is shown as the relative variations of the C_{Serial}.

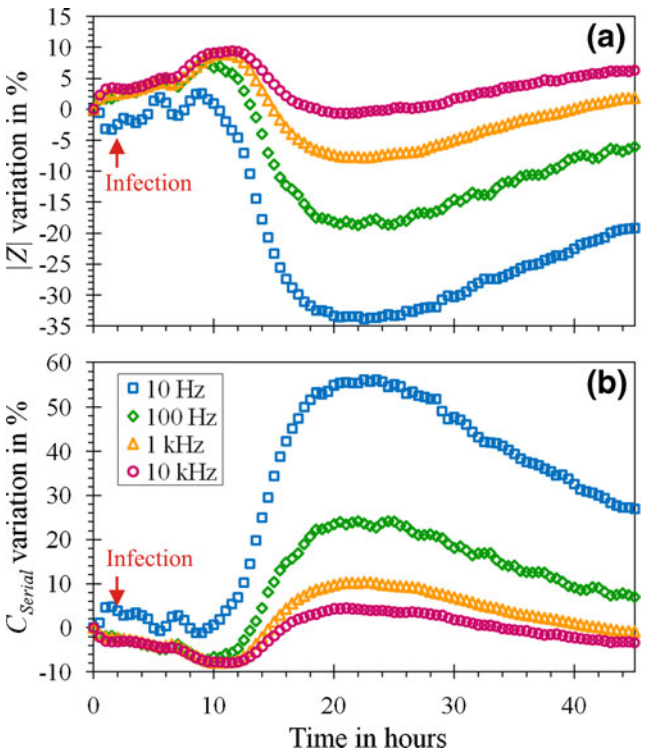

Fig. 6 **a** Relative changes at different frequencies of the serial magnitude of impedance measurements and **b** relative changes of the equivalent serial capacitance during Staphylococcus epidermidis ATCC 35984 biofilm development inside the lab prototype with an initial bacterial concentration of ~1.2×10^5 CFU/mL

Microorganisms were inoculated at the first hours of the experiment, injecting the infected media through the silicon cop of the lab prototype. Approximate 10 h after the infection the serial capacitance starts changing reaching a maximum relative variation another 10 h later. The time that is needed until significant variations on the impedance curves were recorded, is related to the lag phase of growth. Microbes need to get used to the new culturing conditions to start multiplying exponentially. Once the microbes start to grow up, both the $|Z|$ and C_{Serial} show the significant relative changes. After that maximum the curves slowly start to decrease regarding the death phase of the biofilm shape growth. The other electrical parameters as the magnitude, the phase or the equivalent serial resistance are not shown due to the smaller changes that present.

Bacterial culture development produces a decrease on the values of the electrical impedance characteristic due to microbe's growth in the media. Under those conditions, the low range of the frequency has been previously reported as the suitable configuration for bacterial detection in real samples (Yang et al. 2004). The changes of conductivity related with the ionic concentration result of the metabolic activity reach the maximum variation for higher frequencies (Varshney and Li 2008).

The capacitance is the most sensitivity electrical parameter for tracking the biofilm development. This parameter is closely related with the biosensor geometry based on interdigitated microelectrodes and has been proved as effective tool for microbial detection and growth monitoring (Laczka et al. 2008). The maximum response is related to the lowest frequency of 10 Hz achieving a 55 % of maximum variation. So it is clear that, the higher frequency of measurement the lower relative recorded sensitivity.

The detection time is critical for the prophylactic capability of the SCVP. The detection method proposed in this work is based on the analysis of the impedance trends during its performance. The profile of the impedimetric measurements will provide a certain shape that could be uniquely associated with the biofilm development and discard other effects. Indeed just one bacterial cell is necessary to develop a biofilm composed by millions of cells. So, with at least with one microorganism a bacterial biofilm could be developed and therefore detected inside the reservoir. Although the experiments were performed with a fairly high initial concentration of microorganisms (~1.2×10^5 CFU/mL) theoretically, the detection limit as best as one microbe alone. Rather the performance of the SCVP should be analyzed in terms of detection time since the infection of the device.

Bacterial growth kinetics follows a logarithmic profile, which provoke a rapid increase of organisms in a short time. This fact is only limited or affected by the amount of nutrients effectively present in the media inside the catheter and other dynamic effects. The sensor is capable of measuring the increase on the number of cells by comparing the relative changes of the impedance characteristics. When a patient developed biofilm colonization the immunological system will provoke a response that will increase the sensors response to impedance changes. Other biological effects as protein coating, clots, molecular aggregates and other effects usually happen right after the first biological exposition of the surfaces of the catheter. These transient effects usually get stabilize after a shorter in time in comparison with biofilm development.

Electronic performance was design trigger the measurements after any use of the device with an external signal following a specific sequence pattern. In this way non-steady stages can be identified and ignored or corrected during the measurements. Other minor or long term drifts such as thermal momentum or other biological processes can be compensated electronically. But even with these electronic corrections there is still a risk of false positives form the device. At this point medical care should resolve these dilemmas by traditional identification methods.

Clinical findings are unreliable for establishing the diagnosis of intravascular device–related infection because of their poor sensitivity and specificity. The most sensitive clinical finding, fever, has poor specificity (Maki and Mermel 1998). Laboratory criteria for diagnosing intravascular catheter-related infections are precise, but differences in definitions and methodologies among various studies have made data difficult to compare (Pearson 1996). When a catheter segment is submitted for culture, it is adequate to culture only the catheter tip and not the subcutaneous portion of the catheter. Semiquantitative (roll plate) or quantitative catheter culture techniques (luminal flushing or sonication methods) are the most reliable diagnostic methodologies and have much greater specificity than qualitative broth cultures. Intraluminal spread of microbes from the catheter hub into the bloodstream is increasingly important for long-term catheters (i.e., those that have been indwelling 14 days). In some studies, the rollplate method was less sensitive than other methods that also sampled the internal surface of such catheters, but other studies have not found this to be the case (Bouza et al. 2005). For subcutaneous ports, culture of the material inside the port reservoir is more sensitive than catheter tip culture for the diagnosis of CRBSI (Whitman and Boatman 1995).

Detection of early biofilm development inside a port will depend on several factors such as concentration, location of the biofilm and sample procedure. Besides increasing the number of samples will also increase the infection risk, as it was reviewed that manipulation of the devices is often the cause of infection. A device infected episode requires suspension of the ongoing treatment and sampling for bacterial identification. Decision made post-diagnostic chooses between antibiotic block or device removal, which are the main procedures followed by clinicians according to the guidelines (Donlan 2001b).

The SCVP should detect the biofilm development before the host start presenting infection symptoms. However at this point is still not possible to differentiate which specific pathogen is causing the colonization, so medical participation is required for evaluating the best treatment regarding infection pathogenesis.

4.2 Electronics lifetime test

The states power consumption is obtained by analyzing the power profile obtained with the oscilloscope, Fig. 7 shows a

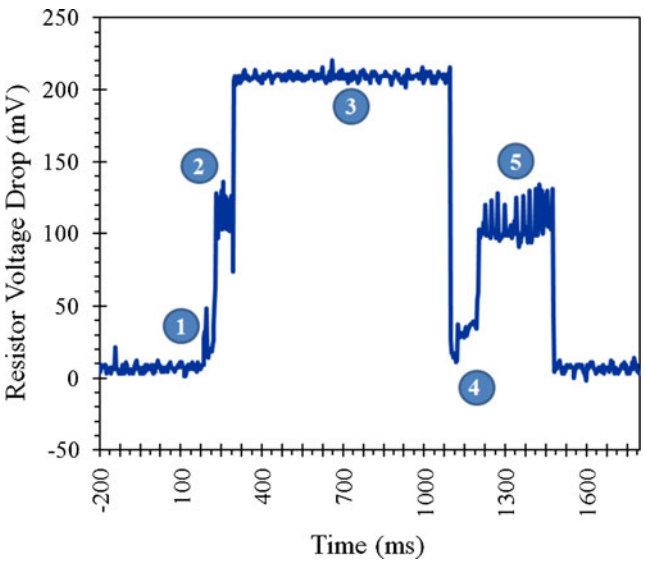

Fig. 7 Power profiles for different concatenated states: 1 corresponds to Sniff state; 2 corresponds to a Comm Rcv state and the acknowledge; 3 corresponds to Measure state; 4 corresponds to Calc state and 5 corresponds to Emergency Communication

Table 2 Experimental results

	Voltage drop mV	Current mA	Time ms	Consumption ms mA
Sleep	0.031	0.002	–	–
Sniff	28.381	1.448	6	8.688
Comm RCV	89.547	4.569	104	475.147
Comm send	92.799	4.735	365	1728.275
Alive	–	–	–	–
Measure	209.092	10.668	752	8022.336
Calc[a]	15.683	0.799	28	22.372
Emergency	92.799	4.735	365	1728.275

[a] The calculation is composed of 2 square roots and 2 multiplications of 16-bit float point values

capture of some states. The average results of ten measures' average are presented in Table 2.

The lifetime result depends on the period used for the measurements and for the alive requests. For this application the measurements are performed every hour and the device is called for an alive request operation every minute. Taking into account that a general coin-cell battery has 50 mAh and the use of a normal cycle, the lifetime estimation result is around 330 days.

4.3 Reflection and transmission test

4.3.1 CVCA reflection coefficient

The CVCA reflection coefficient S_{11} is found to be below −10 dB from 345 to 555 MHz and from 960 to 3,000 MHz that is the limit of the analyzer (Fig. 8). Therefore it covers the expected MICS and ISM bands with broadband behavior.

4.3.2 Transmission tests

The transmission measurements according to Fig. 5 showed that the communication link is lost (transition from "in session" to "session lost") at an average distance of 6.36 m and the communication is reestablished (transition from "session lost" to "in session") at 5.76 m when bringing the phantom closer to the base station again.

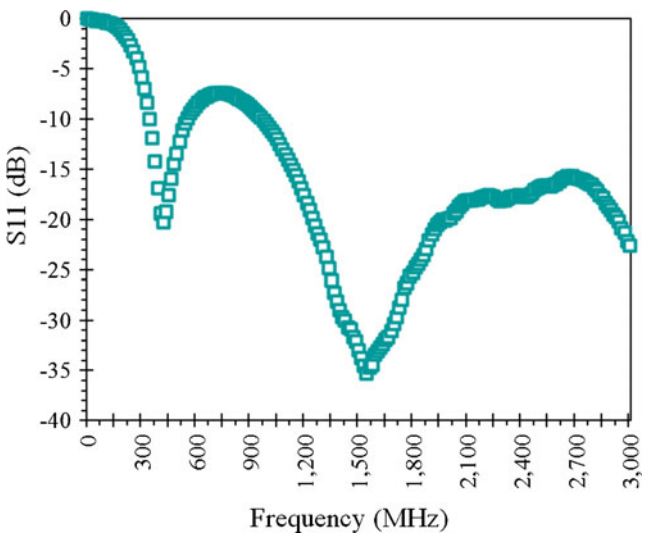

Fig. 8 Reflection coefficient (dB) vs. frequency (MHz) of the CVCA into the human phantom

In order to verify the obtained data, an indoor propagation model according to (Rappaport 1996) and (Seidel and Rappaport 1992) is applied for the laboratory measurements. This empirical model is based on measurements and statistical analysis (Eq. 1).

$$PL(d)[dB] = PL(d_0)[dB] + 10n_{SF}\log\left(\frac{d}{d_0}\right) + FAF[dB] \quad (1)$$

Where:

n_{SF} []	is single floor path loss exponent
PL(d)[dB]	average path loss
FAF [dB]	floor attenuation factor and
d_0 [m]	is the close-in reference distance, taken as free space distance from which indoor attenuation is applied.

Therefore, the resulting path loss exponent n_{SF} and the floor attenuation factor FAF represent the additional attenuation in a real indoor environment, compared to the ideal free space propagation. The equivalent value to n_{SF} for free space communications (without floor and obstacles) is 2, whereas the value for environments with obstacles between the transmitter and the receiver is much higher.

In this manner, n_{SF} exponent was calculated to verify the indoor performance of the system according to Eq. (1). Equation (2) obtains n_{SF} by rearranging the terms:

$$n_{SF} = \frac{PL(d)[dB] - PL(d_0)[dB]}{10\log\left(\frac{d}{d_0}\right)} \quad (2)$$

The floor attenuation factor FAF [dB] is set to zero, as the measurements are performed over the same floor. By de-embedding the antenna gains and mismatch losses from the ratio between the implanted electronics sensitivity and the measured transmitted power of the base station (P_{TX}= −15.7 dBm), a path loss of PL(d)=47.1 dB is computed. By

using the free space loss equation for the reference distance d_0=1 m, the reference path loss PL(d_0) is 24.5 dB. With these data, Eq. (2) leads to a path loss exponent of n_{SF}=2.81 for the distance of d=6.36 m (on-off) and n_{SF}=2.97 for d=5.76 m (off-on).

According to the indoor propagation model (Rappaport 1996), the path loss exponent n_{SF} should be close to 3.27 for office buildings at 914 MHz with a variance of 11.2 dB. The obtained values (2.81 and 2.97) are therefore consistent. The slight difference to the expected one (3.27) is likely due to the frequency difference effect: lower frequency (403 MHz compared to 914 MHz) means lower path loss and therefore lower n_{SF}.

Another indoor path loss model is proposed by Vaughan and Andersen (Vaughan and Andersen 2003). The empirical model (Eq. 3) is obtained from measurement data taken in the ISM 433 MHz band, therefore closer to the MICS band, in several European building types.

$$PL(dB) = -23 + 90\log_{10}(d) \tag{3}$$

In the expression, d[m] is the distance between transmitter and receiver, for d >3 m.

The equation reflects the best case scenario calculation, i.e., only the best 1 % of all measurement positions are below this low path loss. The scenario in the present experiment can be considered close to the optimal, as it is a line of sight transmission in a not cluttered office. By applying d=6.36 m to Eq. 3, an indoor path loss of PL=49.3 dB is calculated, which is a quiet good estimate to PL=47.1 dB, which is employed in Eq. 2. This reveals again the consistency of theoretical and measured results.

5 Conclusions

A new smart central venous catheter was developed for early detection of bacterial biofilm associated infectious processes. The three complementary modules, biosensor, electronics and antenna were successfully developed and *in vitro* tested.

S. epidermidis, reviewed as one of the most relevant device-associated pathogens, was probed to be detected by impedance spectroscopy technique. Label-free interdigitated microelectrode biosensors are an easy and effective solution to be integrated in any kind of indwelling device. The low range of the frequency was found as the more sensitive setting to track changes related to biofilm development.

From an electronic point of view, the set designed consisting of hardware and software has been tested and evaluated. The obtained results validates as a solution with the key feature of a lifetime of more than 11 months with a coin-cell battery of 50 mAh.

A low profile, broadband UHF antenna has been integrated onto the surface of the SCVC with a truncated cone shape for wireless interaction with an external base station. The 3D antenna exhibits compact and broadband features due to the application of short circuit and inductive loading techniques. A transmission test revealed a maximum operational range of 6.36 m in a line-of-sight indoor environment using the MICS frequency band, which fits the theoretical expected results. This analysis sets the limits and read range potentials for biofilms growth monitoring in SCVC within current regulation framework.

Direct detection technologies for pathogenic microorganisms are emerging to be applied in the diagnosis of catheter-related bloodstream infections. Standard blood cultures as the current gold standard for detection of bacteraemia/sepsis and other culture-based microbiological identification procedures are comparatively slow and have limited sensitivity. Technologies for the correct and timely diagnosis of bloodstream infections are urgently needed. This new medical device should provide a better knowledge of the bacterial biofilm colonization process inside a central venous catheter allowing more effective treatments and therefore improving patient's quality life during that pathology. *In vivo* assays now must be carried out to probe the real working functionality of this intelligent CVC.

Finally, we realize that the development of this prototype into a commercial one will suppose a real challenge, but the real motivation of this research is the fact of its application will enhance the quality life of the patients and we provide the physicians a new tool for saving life.

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