Design and evaluation of a new impedance sensor for micro-surgery

Application to retinal vein cannulation

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Abstract *Purpose* Nowadays, millions of people suffer from retinal vein occlusion, a blind-making eye disease. No curative treatment exists for this vascular disorder. A promising treatment consists in injecting a thrombolytic drug directly inside the affected retinal vessel. Successfully puncturing miniature vessels with diameters between $[50 - 400]\mu m$ remains a real challenge, amongst others due to human hand tremor, poor visualization and depth perception. As a consequence, there is a significant risk for double-puncturing the targeted vessel. Sub-surfacic injection of thrombolytic agent could potentially lead to severe retinal damage.

Methods A new bio-impedance sensor has been developed to visually display the instant of vessel puncture. The physical working principle of the sensor has been analysed and a representative electrical model has been derived. Based on this model, the main design parameters were derived to maximise sensor sensitivity. A detailed characterization and experimental validation of this concept were conducted.

Results Stable, repeatable and robust impedance measurements were obtained. In an experimental campaign 35 puncture attempts on *ex-vivo* pig eyes vessels were conducted. A confusion matrix shows a detection accuracy of 80 % if there is a puncture, a double puncture or no puncture. The 20 % of inaccuracy most probably come from the limitations of the employed eye model and the conditions of the experiment.

Conclusions The developed bio-impedance sensor has shown great promise to help avoiding double-punctures when cannulating retinal veins. Compared to other puncture detection methods, the proposed sensor is simple and therefore potentially more affordable. Future research will include validation in an *in-vivo* situation involving vitreo-retinal surgeons.

Keywords Vitreo-retinal surgery · Sensorized instruments · Bio-impedance sensor · Robot-assisted surgery

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1 Introduction

1.1 Medical context

Retinal vein occlusion (RVO) is a widespread disease affecting 16.4 million of people and being the second most common retinal vascular disorder (Klein et al, 2008; Rogers et al, 2010). It consists of a blockage of the retinal vessels and could lead to blindness if not treated (Rehak and Rehak, 2008). Current treatment methods only address the symptoms of the disease and not the cause. A possible treatment to this pathology consists of locally injecting a thrombolytic agent directly into the affected vessels during several minutes (Weiss, 2000). Such procedure is known as retinal vein cannulation (RVC). Due to the small size of the targeted vessels - between 50 and 400 μm (Skovborg et al, 1969) this procedure remains very challenging and is not included in clinical practice today. The force required to puncture a vessel - 7.5 mN on average (Ergeneman et al, 2011) cannot be perceived and is an order of magnitude lower than the friction force at the level of the trocar. Human inherent tremor - RMS amplitude of 180 μm (Riviere and Jensen, 2000) further prevents reliable cannulation of the targeted vessel. The only information available during such a procedure is the visual feedback coming from the microscope. To give an easier access to the retina, a vitrectomy, which consists in replacing the vitreous humour in the eye by a saline solution, is often performed before a vitreoretinal intervention.

Despite its highly experimental character, some positive results of RVC have been reported (Weiss, 2000; Weiss and Bynoe, 2001; van Overdam et al, 2015). E.g. Weiss *et al.* report an improvement of visual acuity in 54 % of the cases. On the contrary, the group of Feltgen *et al.*, following a similar approach to Weiss, reported a high complication rate. They experienced a large number of double-punctures followed by injections in the retinal tissue (Feltgen et al, 2007). In general it is understood that the lack of precision forms one important reason preventing clinical uptake of RVC. Recent developments in instrumentation and robotics, with a first in-human robot-assisted cannulation performed in 2017 (KUL, 2017), might form a turning point. Robotic systems offering tremor filtering and stabilisation have appeared under the form of comanipulation devices (Uneri et al, 2010; Caers et al, 2011; Gijbels et al, 2016), tele-operation systems (Nakano et al, 2009; Meenink, 2011; Ida et al, 2012; Nasser et al, 2013; Rahimy et al, 2013), hand-held devices (MacLachlan et al, 2012) or micro-robots (Kummer et al, 2010; He et al, 2015). But without additional sensing, robots do not improve depth perception. It remains therefore difficult to determine whether the targeted vessel has been punctured or not. Cannulation needles with force-sensitive capabilities have been developed in the past (Gijbels et al, 2014a; Gonenc et al, 2014; Gijbels et al, 2015) but these systems are costly and somewhat cumbersome. The detection of retinal vessels via OCT-probes (Borghesan et al, 2016) is being pursued, but is still in its infancy. At the moment it is still unclear whether the back wall of the targeted vessel can be reliably observed with OCT. This paper explores an alternative method that relies on the detection of a change in impedance when entering a vessel. In order to detect such change a purposely designed bio-impedance sensing cannulation microneedle has been developed.

1.2 Related work

Over the last decades, various research groups have developed instruments measuring bio-impedance in order to detect the instant when different tissue layers are entered. One common application is for instance prostate cancer detection. Lee *et al.* demonstrated to be able to differentiate between cancerous and benign cells on *ex-vivo* prostates (Lee et al, 1999). Lee's instrument consisted of two 1 mm-diameter stainless steel needles, insulated and located at a distance of 1 mm from each other. Especially at a measurement rate of 2 MHz the distinction was clear. The tool by Lee *et al.* was further developed to detect human tumors (Ko and Smith, 2003). Hernandez *et al.* used an impedance-sensing needle to confirm successful percutaneous access to the renal collecting system. This setup was demonstrated on *ex-vivo* porcine kidneys showing a clear and sharp impedance change when penetrating the collecting system (Hernandez et al, 2001). The impedance was measured between a 18 Gauge needle sheath and an insulated inner stylet (Stoianovici et al, 2002). Lum *et al.* propose to assess the penetration depth of skin tissue via impedance measurement. Lum uses a needle composed of an outer conductive coated tip insulated from an inner metallic wire (Lum et al, 2002). Via such needle, the specific punctured layer is estimated given that each layer possesses its specific impedance signature. A similar approach was employed to detect the puncture of a vessel in *in-vivo* rabbits (Saito et al, 2006). Saito *et al.* used an insulated metallic wire inside a standard hypodermic needle as system to measure bio-impedance. A clear impedance drop was observed after each successful puncture. More recently, a similar venipuncture detection system for robot-assisted intravenous catheterization was reported by Cheng *et al.* to detect the entry into the vascular system (Cheng et al, 2016).

Nowadays, companies such as Injeq are developing commercial biopsy tools capable of identifying tissues in real-time (Inj, 2017). Injeq's IQ-NeedleTM is for instance based on a hypodermic needle with a stylet. The tip and the stylet serve as electrodes between which at different frequencies the tip impedance is measured. Animal studies with this needle are detailed by Kari *et al.* (Kari et al, 2015). Tissue types can be identified in real-time as the needle progresses, based on variations in impedance (amplitude and shape) and impedance signatures. Another use of impedance sensing tools consists in the detection of the presence of spinal fluid. This information may help conducting proper lumbar puncture. Halonen *et al.* described a clinical study on this matter (Halonen et al, 2016). In another track NG Needle is developing a needle with multiple channels in order to measure the bio-impedance in parallel (NGN, 2016). This approach allows tissue cartography all along the needle tip.

1.3 Contributions of this work

So far, bio-impedance measurement have been applied in hypodermic needles, mostly on minimally invasive procedures. A similar bio-impedance measurement concept could in theory be applied to detect the puncture of retinal vessels. Given the strict requirements in terms of size, force and sensitivity, the design and implementation of such sensor is not straightforward. To the best of our knowledge, this is the first time that a functional bio-impedance sensitive cannulation needle

is developed in the field of eye surgery. This type of sensor could become a suitable alternative to current other technologies developed within this field where the scale plays an important role. Moreover, impedance sensors remain usually a cheap solution.

The paper is built up as follows. Section 2 explains the general working principle of the proposed method and introduces a theoretical model of the instrument. Section 3 contains a description of the prototype that was built; it also includes a first characterisation of the prototype. Section 4 demonstrates the feasibility of the proposed concept. The experiments show a noticeable impedance change upon puncture. The experiments conducted on *ex-vivo* pig eye vessels are reported in this section. Finally, section 5 concludes this work and describes some future perspectives of this work.

2 Principle and modeling

2.1 Introduction to vessel cannulation and impedance sensing

Fig. 1 gives an overview of the principle of retinal vein cannulation and of the possible role of impedance sensing during its execution. The procedure starts by introducing a trocar in the sclera at a distance of 4mm from the corneal limbus (Fig. 1(a)). During a vitrectomy the vitreous humour is replaced by a 0.9% saline solution which will fill the entire eye globe. Next the cannulation needle is introduced through the trocar and passed through the medium of saline solution towards the retina in the vicinity of the blocked vessel. When cannulating, upon first contact with the vessel, the needle lumen will be occluded briefly as shown in Fig. 1(b). After having pierced the first vessel wall, the needle comes into contact with the blood in the vessel. At this instant, the needle is to be halted and the dissolving agent can be injected. The envisioned thrombolytic agents (e.g. tPA and ocriplasmin) are conductive fluids. Electrolytes inside these fluids allow passage of an electrical current. A conductive path exists from the supply line of the dissolving agent through the internal instrument lumen up to the needle tip. The path then crosses the medium that surrounds the needle tip and returns via a conductive part that is provided at the instrument's outer surface. When an electrical potential is applied between the interior and exterior of the needle, an electrical current will flow through the needle tip along this electrical path. The magnitude and phase of the impedance mainly depends on the nature of the variable medium that surrounds the needle tip. It is understood that especially during the puncture, the impedance will undergo large variations. By measuring in real-time the governing impedance, the surrounding medium is estimated and the cannulation state and progress of the puncture event might be inferred. This principle is explained in greater detail in the following subsections.

2.2 Measurement principle

Fig. 2 provides a detailed view upon the different constituents of the electrical path. A first part of the electrical path consists of the thrombolytic agent that fills the cannulation needle and is to be injected through the needle's lumen at the needle tip Fig. 2(a). Both blood and saline solution are conductive each with different conductivity. They form the last part of the electrical path. When piercing the vessel, the vessel wall will obstruct the needle tip lumen, resulting in an impedance increase. Note that a similar obstruction would happen if the needle tip were to contact the back wall of the targeted vessel, i.e. prior to a double puncture.

The impedance sensing concept that is developed here consists of positioning an inner electrode in contact with the thrombolytic agent and an outer electrode on the outside of the instrument tip. Through the presence of electrolytes' in the saline solution or the blood at the instrument tip a closed electrical path is established between the inner and outer electrode. To prevent a short-circuit, both electrodes are to be isolated electrically from each other. Isolation should take place along the entire instrument length. The outer electrode should reach sufficiently deep so that the part of the conductive path that travels through the external medium is

Fig. 1 Cannulation procedure of a retinal vein; the different elements influencing the environmental conditions.

sufficiently short. This allows a very local impedance measurement which is needed as one wants to be able to react sufficiently fast upon puncture detection.

2.3 Electrical model, study of the impedance sensor

In order to assess the efficiency and limitations of the proposed sensing principle, an electrical model is presented in SubSec.2.3.1 and SubSec.2.3.2. A sensitivity analysis is conducted next in SubSec.2.3.3. From this analysis some requirements for reliable impedance-based puncture detection are then extracted.

2.3.1 Modeling assumptions

The electrical model that is sketched in SubSec. 2.3.2 by Fig. 3 departs from following assumptions on the properties of the instrument and the environment:

1. the inner electrode is insulated from the outer electrode. From electrical view-point, the insulation corresponds to a capacitor C_{insul} between both electrodes;
2. the electrodes are considered to be perfect conductors. Therefore no parasitic resistive, capacitive or inductive effects need to be incorporated;
3. the direct electrical path between the inner and outer electrodes is ensured by the electrolytes present in the thrombolytic agent, saline solution and blood in the case of a vessel puncture. This path made out of electrolytes can be modeled by a:
 - resistance R_{tip} of which the magnitude depends on the dimensions of the electrodes and the conductivity of the fluids. The conductivity depends on the ion concentration which is an intrinsic property of the fluids. At this point it is assumed that the ion concentrations remain constant both in

Fig. 2 Detailed view upon conductive paths and impedance measurement principle

the thrombolytic agent and the saline solution over the duration of the measurement period and across different experiments. In the case of the saline solution, the ions are Na^+ and Cl^- . R_{tip} takes into account the resistance from the thrombolytic agent, saline solution or blood. Hence it is this variable that is considered of interest to detect the vessel puncture.

- double layer capacitance C_{dl} . At low frequency levels, the ions accumulate preferentially at the surface of the electrodes. This accumulation creates a parasitic capacitive effect on each electrode. As the excitation frequency rises the ion concentration at the electrode's surfaces diminishes. This leads to a reduced parasitic capacitive effect. Note that in Fig. 3(a), C_{dl} represents the electrical simplification of the double layer capacitances in series from the inner and outer electrodes.

Fig. 3 Electrical model of the bio-impedance sensor

2.3.2 Electrical Model

Based on above assumptions, an electrical model of the impedance sensing needle can be pictured as in Fig. 3. As simplification of this scheme, Fig. 3(b) provides an equivalent electrical model in terms of impedances Z_{tip} and Z_{insul} as defined in (1) and (2):

$$Z_{tip} = R_{tip} + \frac{1}{j\omega C_{dl}} \quad (1)$$

$$Z_{insul} = \frac{1}{j\omega C_{insul}}. \quad (2)$$

The impedances Z_{tip} and Z_{insul} vary as function of the frequency ω . The overall impedance of this model becomes

$$Z_{tot} = \left(\frac{1}{R_{tip} + \frac{1}{j\omega C_{dl}}} + j\omega C_{insul} \right)^{-1}, \quad (3)$$

which can be written out as

$$Z_{tot} = \frac{1 + j\omega R_{tip} C_{dl}}{j\omega(C_{dl} + C_{insul}) + (j\omega)^2 R_{tip} C_{dl} C_{insul}} \quad (4)$$

and then be reorganised as

$$Z_{tot} = K \cdot \frac{1 + j\frac{\omega}{\omega_0}}{j\omega \cdot (1 + j\frac{\omega}{\omega_1})}. \quad (5)$$

The parameters K , ω_0 and ω_1 are defined as:

$$K = \frac{1}{(C_{insul} + C_{dl})}, \quad (6)$$

$$\omega_0 = \frac{1}{R_{tip} C_{dl}}, \quad (7)$$

$$\omega_1 = \frac{C_{insul} + C_{dl}}{R_{tip} C_{dl} C_{insul}}. \quad (8)$$

Equation (5) shows a frequency response function with gain K , a zero at $-j\omega_0$ and two poles. A first pole is located at the origin and a second in $-j\omega_1$. The magnitude $|Z_{tot}|$ and phase Φ_{tot} of the overall impedance of the sensory system are:

$$|Z_{tot}| = \frac{\sqrt{1 + (\frac{\omega}{\omega_0})^2}}{(C_{insul} + C_{dl}) \cdot \omega \cdot \sqrt{1 + (\frac{\omega}{\omega_1})^2}} = \frac{f}{g} \quad [\Omega], \quad (9)$$

with f and g respectively the numerator and denominator of this expression, and

$$\Phi_{tot} = -\pi/2 - \arctan(\frac{\omega_0}{\omega}) + \arctan(\frac{\omega_1}{\omega}) \quad [rad]. \quad (10)$$

The impedance sensor needs to be excited at an optimal frequency in order to minimize the parasitic capacitive effect and maximize the sensitivity of the needle

tip impedance relatively to R_{tip} . The sensitivity follows by differentiating (9) and (10) towards R_{tip} , giving:

$$\frac{\partial |Z_{tot}|}{\partial R_{tip}} = \frac{2R_{tip}\omega^4 C_{dl}^3 (C_{dl} + 2.C_{insul})}{2fg^3} \quad [-], \quad (11)$$

$$\frac{\partial \Phi_{tot}}{\partial R_{tip}} = \left(\frac{\frac{\omega_0}{\omega}}{R_{tip} \cdot (1 + (\frac{\omega_0}{\omega})^2)} \right) - \left(\frac{\frac{\omega_1}{\omega}}{R_{tip} \cdot (1 + (\frac{\omega_1}{\omega})^2)} \right) \quad [\frac{rad}{\Omega}]. \quad (12)$$

2.3.3 Optimisation of the electrical model for an accurate puncture detection

From (11) and (12) the sensitivity of the system as function of impedance magnitude and phase is depicted in Fig. 4 and 5 for some combinations of C_{dl} and C_{insul} . One can notice that as the excitation frequency rises, the sensitivity tends towards 0. This is in line with (1) and (2) where impedance Z_{tip} and Z_{insul} tend respectively to R_{tip} and 0 at high frequencies. The electrical model simplifies to a resistance R_{tip} in parallel with a short-circuit, leading to a total impedance equal to zero and hence a sensitivity tending towards zero.

One can observe that for a ratio $\frac{C_{dl}}{C_{insul}}$ going to 0 the maxima from Fig. 4 and extrema from Fig. 5 move to higher frequencies. Their value tends to 0. The ratio $\frac{C_{dl}}{C_{insul}}$ strongly impacts the maximal sensitivity of the prototype. Therefore, the prototype should preferably show $C_{insul} \ll C_{dl}$ so that variations of R_{tip} due to a puncture event can be clearly observed. The theoretical maximum sensitivity of 1 implies that the variation of R_{tip} is fully reflected in $|Z_{tot}|$. Also variations in phase can be expected and may thus help improving estimation of the puncture. For this reason also the phase sensitivity is shown in Fig. 12.

Fig. 4 Electrical model sensitivity $\frac{\partial |Z_{tot}|}{\partial R_{tip}}$ for different ratios of $\frac{C_{dl}}{C_{insul}}$. The maximum of the curve tends to zero as $\frac{C_{dl}}{C_{insul}}$ tends to zero. The theoretical maximum sensitivity is 1 which basically means that the whole variation of R_{tip} is reflected in $|Z_{tot}|$.

Fig. 5 Electrical model sensitivity $\frac{\partial \Phi_{tot}}{\partial R_{tip}}$ for different ratios $\frac{C_{dl}}{C_{insul}}$. The extrema of the curve tend to zero as the ratio $\frac{C_{dl}}{C_{insul}}$ goes to zero.

In the following, the parameters R_{tip} , C_{dl} and C_{insul} will be measured on the prototype needle to determine the optimal excitation frequency in SubSec.3.1. SubSec.3.2 shows that in practice the measurement frequency is limited for the impedance measurement device that was used in this study.

3 Development and characterization of a new bio-impedance sensor

The design of the new bio-impedance sensor (SubSec. 3.1) and the entire measurement system (SubSec. 3.2) is presented in this section. The link between the measurement principle (Fig. 2(b)) and the sensor design is described. Next, the different electrical components of the model (5) are identified. An analysis is conducted to verify whether the design meets the requirements described in SubSec. 2.3.3. Next, a characterisation of the repeatability, the stability and of the transient response upon a change in temperature has been conducted. Finally, the feasibility and the reliability of puncture detection with the micro-needle with integrated bio-impedance sensor is assessed.

3.1 Design prototype of an impedance sensing micro-needle

A prototype impedance sensing micro-needle was designed and developed. Fig. 6(a) shows the resulting prototype that was built. The manufactured sensor is shown in Fig. 6(b). The inner and outer electrodes are respectively made of a stainless steel tube (0.75 mm outer diameter) introduced into a bent glass micropipette and a stainless steel outer sleeve (1.2 mm outer diameter) surrounding the glass micropipette. The two electrodes are separated by an insulating layer of glass. The outer electrode is in contact with a biocompatible conductive coating made of platinum and titanium applied over the entire outer surface of the glass micropipette. The thickness of the coating is estimated to be about 200 nm. The coating establishes an electrical path from the base of the micropipette towards its tip so that the impedance variation can be measured very locally at the tip itself. As a useful side-effect the coating also improves the visibility of the glass micro-needle under the microscope. The different elements and materials making up the instrument tip are depicted in Fig. 6(c). The tip has an outer diameter of 30 μm and an inner diameter of 23 μm .

Fig. 6 Sketches and picture of the prototype bio-impedance sensing cannulation needle.

3.2 Description of the impedance measurement device

An impedance measuring sensor AD5933 (Analog Devices, Norwood, Massachusetts) is hooked up to the pair of electrodes completing the impedance measurement system. From this the impedance magnitude and phase are computed. The AD5933 has the following relevant specifications:

- output excitation voltage programmable from 1 kHz to 100 kHz.
- impedance magnitude measurement range from 1 k Ω to 10 M Ω .
- accuracy of 0.5%.
- analog to digital conversion at 1 mega samples per second. With 1024 samples used in a discrete Fourier transform to compute the magnitude and phase for a certain frequency point, a sampling frequency of 976 Hz may be reached when measuring at a single frequency. This sampling rate is fast enough as a registration period of 0.1 s is considered sufficient (Gijbels et al, 2015).

A feedback resistor is used together with the AD5933 in order to set the gain of the current-to-voltage amplifier on the chip. To obtain an accurate measurement, this feedback resistor should have a similar magnitude as the magnitude of the impedance that is being investigated, namely $R_{unknown}$. Therefore, a preliminary experiment is needed to determine an appropriate feedback resistor considering the excitation frequency. When the measured impedance differs significantly from that of the feedback resistor, the accuracy drops and the AD5933 may wrongly estimate the impedance at low frequencies. This phenomenon is depicted in Fig. 7. It is illustrated with a feedback resistor of 560 k Ω which is further used to properly assess the instrument impedance in SubSec 3.4.2. First, a resistance of 679 k Ω is connected to the chip, showing a significant impedance drop below 6 kHz and a slight drop at higher frequencies (left Fig. 7). Second, a resistor equal to the feedback resistor is connected, involving no noticeable error over the frequency range (right Fig. 7). This effect is further taken into account when determining the optimal excitation voltage frequency.

Fig. 7 Deviation of a resistor measurement (left: $R_{unknown} = 679 \text{ k}\Omega$, right: $R_{unknown} = 560 \text{ k}\Omega$) at low and high frequencies with a feedback resistor of 560 k Ω .

3.3 Estimation of the electrical model parameters

In order to properly set the measurement range, the bio-impedance sensor is mounted in parallel with a resistor which is equal to the feedback resistor. The electrical equivalent is summarized on Fig. 8. This setup is solely used to determine the parameters R_{tip} , C_{dl} and C_{insul} from the instrument. Hence the resistance $R_{feedback}$ will not be used for the further steps in order not to impact the maximum sensitivity of the bio-impedance sensor.

Fig. 8 Complete electrical equivalent of the instrument connected to the measurement device

The resistor $R_{feedback}$ should be equal to the feedback resistor connected to the AD5933. Additionally, both should be chosen small enough compared to $|Z_{tot}|$ (total impedance computed from electrical circuit on Fig. 8) so that the measurement device measures a total impedance magnitude close to that of the feedback resistor. Considering the scheme from Fig. 8, the following approximative parameter values have been assessed by sweeping the excitation frequency over the frequency range available:

- $R_{tip} = 230 [k\Omega]$
- $C_{dl} = 4 \cdot 10^{-10} [F]$
- $C_{insul} = 6 \cdot 10^{-11} [F]$

One can thus conclude that this setup respects the earlier mentioned requirements that $C_{insul} \ll C_{dl}$. Hence, the bio-impedance sensor is likely going to be well capable to sense variations over R_{tip} . Nevertheless, the appropriate measurement frequency is still to be optimised. The sensitivity analysis of the electrical model has been revisited to this end. Based on the computed parameters, the sensitivity curves are depicted in Fig. 9. The excitation voltage frequency is chosen at 6 kHz for the next experiments taking into account the behaviour depicted in Fig. 7 and explained in the SubSec. 3.2.

Based on (11) and Fig.9, the bio-impedance sensor is expected to sense 62 % of any disturbance over R_{tip} on its impedance magnitude at an excitation frequency of 6 kHz. Latter frequency is the lower bound determined from the experiments on Fig. 7. In the same way, a phase sensitivity of $0.5 \cdot 10^{-6} [\frac{rad}{\Omega}]$ can be computed according to (12).

3.4 Characterisation of the bio-impedance sensor

Following properties of the sensor have been studied:

Fig. 9 Sensitivity curves from (11) with estimated parameters from SubSec. 3.3.

- Repeatability: to align the instrument to a target vessel several back and forth motions might be needed. The measured impedance should ideally remain identical for measurements conducted at the same location. This property is investigated in SubSec. 3.4.1 and is referred to as the sensor’s repeatability.
- Stability of the bio-impedance measurement (SubSec. 3.4.2): the impedance measurement should remain stable for the period the sensor is introduced into the eye. Surgeons indicated that this will not exceed one hour.
- Temperature dependence: at the start of the intervention the bio-impedance sensor is at ambient temperature. While entering the eye globe, the temperature gradually rises to body temperature ($\approx 37^\circ\text{C}$). The transient response is evaluated in SubSec. 3.4.3. The reality is simulated by submerging the sensor in a thermal bath of 37°C . Ideally the impedance transient should differ significantly from an impedance transients upon vessel cannulation.
- SubSec. 3.4.4 reports on the impedance and impedance variations that arise while moving the sensor through the eye globe towards the target vessels. To avoid false-positive puncture detections also here the impedance and variation thereof should differ sufficiently from puncture measurements.

3.4.1 Repeatability of the bio-impedance sensor

The surgeon might move the instrument back and forth towards the retina repeatedly e.g. aiming to align the instrument tip properly along the retinal vessel. The repeatability of the sensor is a measure of the variation over multiple measurements. The sensor displays good repeatability provided that under similar conditions similar measurements are obtained. The repeatability of the sensor is gauged by moving the instrument 10 times to the same location in a saline solution and within a period of 30 seconds. The total traveled distance is about 15 mm. Moreover different concentrations of saline solution are tested to allow verifying the repeatability across the sensor range. The data of this experiment is summarized in Table 1. Note that the standard deviation stays within the range $[0.02, 0.04]$ % of the mean value (Table 2).

Table 1 Repeatability - over 10 insertions (30 seconds each) in saline solution.

Parameters	Concentration (0.9 %)	Concentration (0.8 %)	Concentration (0.7 %)
Temperature	ambient	ambient	ambient
Repeatability (stddev)	$\pm 171.4\Omega$	$\pm 109.4\Omega$	$\pm 121.4\Omega$
Repeatability (stddev as % of mean)	0.032 %	0.021 %	0.023 %

3.4.2 Stability of the bio-impedance sensor

To investigate the sensor's stability the instrument tip is submerged into a saline solution during one hour. The setup remains at rest and at ambient temperature ($\approx 22^\circ$) for this period. The outcome of the experiment is summarised in Table 2. A small variation (standard deviation) in impedance and a small drift of $-0.56\Omega/s$ is visible. The impedance decreases $2k\Omega$ over the duration of one hour. This corresponds to less than 0.4 % of its mean value. The impedance sensor is thus found to behave stably over long periods of time.

Table 2 Characterisation of the sensor's stability over measurement window of one hour.

Parameter	Value
Temperature	ambient
Mean value over 1 hour	$530,69 k\Omega$
Standard deviation	$\pm 1,815 k\Omega$
Stddev, % of mean	0.34 %
Drift	$-0.5581 \Omega/s$

3.4.3 Transient response of the bio-impedance sensor due to temperature variation

When the instrument is inserted through the trocar in the eye globe it is being immersed in an environment of about 37°C . The temperature difference could lead to a variation in measured impedance relative to the impedance measured at ambient temperature (at $\approx 22^\circ$). In order to verify whether such temperature change would not lead to false puncture detections some experiments are conducted here. The instrument tip is submerged in a 37°C saline solution (as measured by a separate thermocouple). The obtained impedance measurements are reported in Table 3.

Table 3 Transient response of the bio-impedance sensor when the instrument tip is plunged in a saline solution at 37°C .

Parameters	Values
Temperature solution	37°C
$\Delta Z = Z_{tot} _{ambient} - Z_{tot} _{37^\circ\text{C}}$	$15k\Omega$
Variation in impedance vs main impedance	$\leq 2.8\%$
Time to stabilise the impedance magnitude	6 s

An impedance difference of $15\text{ k}\Omega$ is measured between the case where the sensor is submerged in a solution at ambient temperature and the case where it is submerged in a solution at 37°C . Such error is negligible since it remains less than 2.8% of the mean value reported in Table 2. If one wants to avoid the temperature effect one could easily wait a short period of time until the temperature is stabilised. Currently only 6s are required to stabilize the sensor. This is fast enough. In comparison with the time needed to prepare the eye and e.g. conduct a vitrectomy this is negligible.

3.4.4 Impedance variation when moving through the eye globe

On the way to puncture the targeted blood vessel the needle and sensor move through the eye globe. A number of impedance measurements have been conducted to capture the level of impedance as well as variations in impedance that are picked up during this approach and/or retraction phase. To avoid false positives, the impedance levels and variations should differ sufficiently from those that are measured when cannulating retinal vessels.

To study the variation of the measured impedance under such gesture, the instrument is plunged into a saline solution. Subsequently the saline solution is stirred, exaggerating the expected relative motion between fluid and instrument. The test ran over a period of 10 minutes. The experiment showed impedance variations at a standard deviation of $\pm 0.660\text{ k}\Omega$. Note that such variation is negligible. Therefore one can conclude that the instrument approach and retraction phase through the eye globe should not cause false-positive puncture detections.

4 Experimental results

In order to assess the proper functioning of the bio-impedance sensor, experiments on *ex-vivo* pig eyes were conducted. In total, 12 punctures including 5 double punctures were performed. After describing the experimental setup in SubSec. 4.1, the experimental results are summarized in SubSec. 4.2. Some limitations of the experiments are discussed at the end of SubSec. 4.2.

4.1 Materials and Methods

The bio-impedance sensor was mounted on a comanipulation robot that was developed for vitreoretinal surgery (Gijbels et al, 2014b). The instrument was filled with a 0.9 % saline solution rather than a proper thrombolytic agent after it was confirmed that this composition does not differ much from that of traditional thrombololytic agents. *Ex-vivo* (enucleated) pig eyes were prepared for cannulation. First the eyes were cut open to a so-called *open-sky* form. An open-sky model simplifies access and visualisation of the targeted the retinal vessels. The vitreous humour was removed and the retina was submerged by a thin layer of 0.9 % saline solution. Hence when cannulating, the bio-impedance sensor tip was immersed in saline solution. In the end the situation is very much like the envisioned scenario.

The experiments took place under visual guidance of a medical-grade stereo-microscope (HS-Hi-R-NEO-900, Haagstreit Surgical GmbH, Wedel, Germany) positioned above the open-sky model. Digital cameras mounted on the stereocamera allowed recording the experiments as seen through the microscope's binoculars. The impedance was measured and recorded over the time span of the experiments.

A researcher with quite some experience in cannulating pig vessels was asked to comanipulate the robot and puncture vessels of the open-sky pig eye. Whenever the researcher gauged that the vessel was correctly cannulated, the researcher was asked to inject saline solution by pushing the syringe. This formed a visual confirmation of correct puncture as properly injected fluid would flush and wash out the remaining blood in the cannulated vessel.

Fig. 10(a) and Fig. 10(b) show how a puncture event can be visually confirmed fairly easy. If after injection the retina starts to swell this is reported as a failed puncture as such swelling is typically caused by a double puncture. Upon a double puncture the instrument pierces completely through the vessel and the injected fluid ends up below the retina. Such situation is visible in Fig. 10(c) and Fig. 10(d). After the injection an oedema - recognisable as a white circle below the surface near the blood vessel - appears.

4.2 Experimental results

A number of possible explanations for failure to identify a correct vessel puncture - all related to the *ex-vivo* pig eye model that was used - are :

- the low pressure level in the blood vessels of the *ex-vivo* pig eyes slows down the response. The pressure in the vessels drops over time. As the vessel deforms

(a) Retinal blood vessel before puncture: the instrument tip is aligned with the vessel.

(b) Correct cannulation - the blood is flushed from out of the vessel when injecting the saline solution.

(c) Retinal blood vessel before double puncture: the instrument tip is aligned with the vessel.

(d) Situation after injecting saline solution. A double puncture is apparent as a white circle appears under the blood vessel, a clear mark of a subretinal injection.

Fig. 10 Cannulation experiments illustrating a correct puncture (Fig. 10(a) and Fig. 10(b)) and the occurrence of a double puncture (Fig. 10(c) and Fig. 10(d)).

Table 4 Confusion matrix from the experiments on *ex-vivo* pig eyes

	True puncture	True double puncture	True non puncture
Detected puncture	6	0	4
Detected double puncture	0	4	0
Nothing detected	1	2	18

Table 5 Accuracy and precision to detect a puncture, a double puncture or no puncture

Accuracy of the sensor	80 %
Precision (to detect a puncture)	85 %
Precision (to detect a double puncture)	66.7 %
Precision (to detect no puncture)	81.8 %
Recall (to detect a puncture)	60 %
Recall (to detect a double puncture)	100 %
Recall (to detect no puncture)	85.7 %

(a) Detection profile for a puncture: the instrument tip pierces the vessel wall. The time derivative over $|Z_{tot}|$ and Φ_{tot} are multiplied to improve the detection capability.

(b) Detection profile for a double puncture: two peaks appear indicating that the instrument tip completely pierced the retinal vessel. The time derivatives over $|Z_{tot}|$ and Φ_{tot} are multiplied to improve detection capability.

Fig. 11 Cannulation procedure of a retinal vessel and environment conditions

rather than resists the puncture the puncture and consequent impedance variations are slower. The resulting impedance peak is less outspoken than in reality.

- the blood is pushed away when trying to puncture the vessel. Since there is no internal pressure in the vessel to resist the puncture event, the vessel tends to collapse and blood is pushed away before the puncture even starts. It follows that the instrument tip may not make a proper contact with the blood in these cases.

5 Conclusion and future work

This paper describes a new bio-impedance sensor that was developed to identify punctures of retinal vessels. The paper describes most aspects of this development starting from the general theoretical principle up to a first proof of concept demonstrated on *ex-vivo* experiments. A detailed model was constructed to help in the design of the first functional prototype. The developed prototype has been characterized and validated.

After presenting the general working principle, an electrical model was built. The electrical model takes different practical aspects of the development into account. The parameters from this model were assessed by measuring the electrical response over a wide frequency range. The sensitivity was tuned to optimise the impedance change upon a puncture event. The instrument was then characterized in terms of repeatability, stability, robustness against temperature variations and was studied further in operating conditions. The overall performance is in line with the expectations. With this in mind a number of experiments on open-sky *ex-vivo* pig eyes were conducted. Despite the preliminary nature of the development, the tests showed already very promising results. Both punctures and double-punctures were recognised in 80 % of the cases. One can expect to obtain better results on living tissues because the vessels remain all the time under pressure.

Further work will look more deeply into the working of the developed measurement principle. Indeed, as the purpose of this work was to propose a first proof of concept, the current setup contains a sub-optimal low-cost measurement device which requires a feedback resistor to accurately measure the impedance. Some preliminary experiments are therefore necessary to determine the size of the feedback resistor. In addition, the added resistor could introduce incorrect measurements if the impedance is too far away from that of the feedback resistor. Currently measurements take place at 6kHz, however a measurement over the entire frequency spectrum may further improve the puncture detection quality. The current device is able to sweep over different frequencies sequentially which leads to an increase of computing time. A real-time puncture detection algorithm that is currently under development, could help inform the surgeon in real-time of a successful puncture. Note in this paper punctures were identified through visual inspection of the measurements. Note that the instrument without the sensitive part was initially developed to cannulate human eye vessels. This instrument is currently used in the clinic, so its bio-compatibility and sterilisability have already been demonstrated. It is expected that the changes that were applied to integrate the bio-impedance sensor do not impact the instrument's sterilisability or bio-compatibility.

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Conflict of Interest

The authors declare that they have no conflict of interest.

Ethical approval

This article does not contain any studies with human participants or living animals performed by any of the authors. All applicable national, and/or institutional guidelines for the care and use of *ex-vivo* animal material were followed.

Informed consent

This article does not contain patient data.

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