Injeq IQ-Needle* - A thin needle with bio-impedance measuring probe: tissue recognition performance assessed in in vivo animal study

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Various medical procedures require precise insertion of a needle, or a comparable surgical device, into a specific tissue type or anatomical structure. Injeq has developed a bio-impedance spectroscopy based localized tissue recognition technology at the tip of a hypodermic needle. This study explores the performance of the developed system in two in vivo animal studies. The results demonstrate the feasibility of the proposed tissue recognition system for clinical work.

Bio-impedance based needle guidance using Injeq IQ-Needle and Injeq measurement equipment can be used as a stand-alone system or complementary to the existing imaging modalities.

*Editor's note: IQ-Needle was called BIP-Needle at the time of the study. The product name has only been changed on the cover page.

Background

Needle guidance is still a practical challenge in many common medical operations such as biopsy procedures, intra-articular injections, localized anaesthesia and local drug delivery despite the multiple technological solutions developed for assisting needle guidance.

Bio-impedance has been researched as means for the tissue type determination and needle guidance. The tissue discrimination is based on the differences in the electrical properties between tissue types [1, 2, 3]. The previous research of bioelectrical needle guidance has been done among others by Kalvøy et al. [4], Hernandez et al. [5], Trebbels et al. [6] and Mishra et al. [7]. Their results for the bio-impedance spectroscopy based tissue discrimination seem to be promising.

The previously presented bipolar measurement needles have been rather thick or had otherwise limited clinical applicability. Large diameter needles are suitable for certain operations, but needles of smaller diameter represent the vast majority in the clinical use. In addition, other authors have not presented tissue identification method that would provide real-time information about the tissue around the tip of the needle electrode. The requirement for real-time tissue discrimination, the support for thin needles and simple usability, in combination with the existing imaging modalities are essential for the clinical work. The system presented in this work fulfils these requirements.

Two phenomena relevant to our application are the measurement sensitivity field, and the electrode polarization impedance (EPI), which is traditionally considered an error source. Four-electrode impedance measurement is commonly used to reduce the effects of EPI [1]. However; the presented system is restricted to the bipolar (two-electrode) measurement (figure 2) due to the dimensions of needle tip. The presented bio-impedance spectra are therefore influenced by the EPI. That said, Kalvøy and Trebbels have demonstrated that tissue classification is possible without removal of EPI from the data [4, 6].

Trebbels et al. have presented the sensitivity field for the bipolar measurement system at the tip of the hollow needle. The measurement geometry in this work is similar but smaller. Trebbels et al. reported that 90 % of the sensitivity distribution lies within 1 mm “high” volume directly in front of the bevelled needle tip [6]. The sensitivity field of the needles used in this study is expected to provide very high spatial resolution, similarly to the needles used by Trebbels.

A thin commercial (22 gauge, 0.72 mm) hypodermic needle with the bio-impedance probe (BIP) replacing the conventional stylet, and the related measurement electronics are presented in this work. The aim was to show that the performance of the system is sufficiently high to provide aid for the clinical work, for example as a complementary needle guidance method to ultrasound imaging. The main hypothesis was that such a system can accurately measure and distinguish between tissues commonly encountered in living organisms.

The results obtained from the 1st animal study were used to create a tissue classification model, which was validated in the 2nd animal study. The cross validation was then performed by testing the tissue model based on 2nd animal study with the measurement data obtained from the 1st animal study. In addition, the measurement results of the two animal studies were pooled together and cross-validation method was used on this measurement data set that contained data from both animal studies. The presented tissue identification performance is obtained despite the real-world measurement artefacts that are present in clinical work utilizing the proposed injection system.

Methods

The developed prototype system consists of a commercial spinal needle with a special BIP-stylet, the related measurement electronics and the tissue identification technology. Here the stylet part alone is referred to as the BIP, and the needle together with the stylet as the BIP Needle (figures 1).

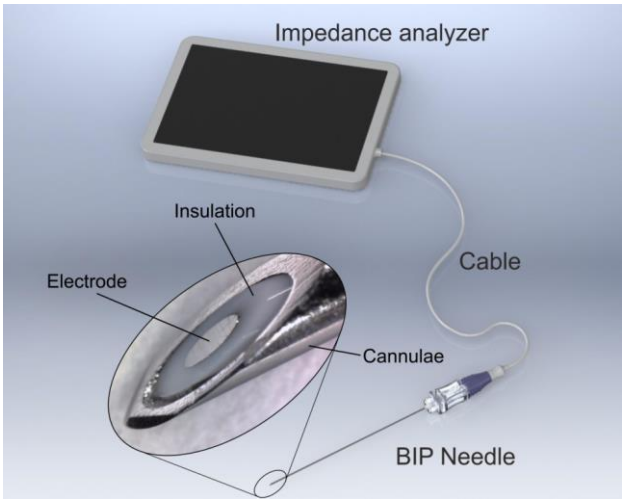

Figure 1 - Illustration of the BIP Needle concept by Injeq Ltd

The BIP Needle is connected to the Impedance Analyzer via a custom made connector and cable. The needle is a commercial spinal needle and the stylet is custom made from insulated stainless steel electrode wire. Standalone impedance analyzer was replaced by dedicated measurement unit, connected to laptop PC for the animal studies.

BIP Needle

The BIP needle consists of a needle and the BIP probe. The hypodermic needle is a compatible commercial spinal needle. The BIP is inserted inside the needle in a way that the electrode contact is located in the needle tip and the needle shaft acts as the other electrode. The electrical contact, between the needle tube and corresponding wiring in the cable, is achieved inside the custom made handle of the probe. The BIP is composed

of biocompatible insulating material and a wire made of stainless steel inside the insulator. The wire on the cut surface of the probe forms the electrode contact.

Impedance is measured in a bipolar configuration between the tip of the BIP and the needle (figure 2). In clinical use, the BIP is kept inside the needle while the needle is positioned to the target location using the real-time tissue identification as guidance. After confirming the right location of the needle tip, the BIP is removed and liquids can be aspirated, the drugs administered or a catheter set in a normal fashion.

The BIP Needles are produced in a pre-production line. The similarity of the products is controlled during the manufacturing process. However, there exists intern-eedle variation in the electrode properties despite the implemented processes to minimize and control the variation.

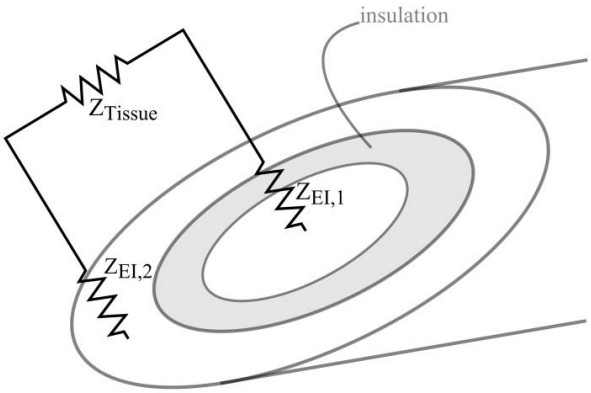

Figure 2 - Bipolar impedance measurement using BIP Needle

In the simplified electrical model of the impedance measurement, Z_{EI} refers to the electrode polarization impedance that is present on both electrode surfaces and Z_{Tissue} to the contribution of the tissue to the overall measured impedance. In addition, the capacitance between the needle tube and electrode wire contributes slightly to the measured impedance.

Measurement electronics

Electrical impedance is a measure of opposition to a sinusoidal excitation current, and can be calculated by Ohm's law: Z = V/I, where Z is the impedance, V is the electrical voltage and I is the electrical current in their complex form. The measurements in this study are performed spectroscopically, which is beneficial for the tissue identification - different tissues exhibit unique frequency dependence of their impedance.

A prototype multifrequency impedance measurement device was used in this study. The device has a sampling rate of 1000 measurements per second, which enables required real-time tissue identification. The end user shall observe only the real-time tissue identification information, which combines the impedance measurement and analysis tasks. During the animal studies an impedance measurement device was connected to a laptop PC. BIP Needles were connected to the impedance analyzer via coaxial cable. The parasitic capacitance caused by the cable is mathematically removed.

Tissue identification algorithm

Tissue classification is a pattern recognition problem. Continuous multifrequency measurement with high sampling rate requires algorithm, which is capable of analysing the measurement data in real time during clinical use. The tissue identification algorithm is designed to operate in a standalone medical device. However, in this study the measurement data was classified afterwards, in addition to the real time classification during animal studies, using the same algorithm running on PC.

Animal studies

Two animal studies were performed using the described measurement setup. Both studies were done on live anaesthetized piglets weighting approximately 25 kg. The measurement setup and the technique were identical in the two studies. The measured tissues and measurement locations are listed in the table 1.

Table 1 - Tissue measurement locations on the two animal studies

Tissue	Measurement location
Fat	Subcutaneous fat, back neck
Muscle	Outer ham muscles, both legs
Tendon	Achille's tendon, both legs
Blood	Venous blood aspirated to the test tube, replaced often to limit cooling and coagulation
Synovial fluid	Synovial fluid aspirated from various joints to the test tube
Liver	Intact liver, measured via dissected abdomen
Spleen	Intact spleen, measured via dissected abdomen

The total number of injections, needles used, and the duration of the measurements in a study are listed in the table 2. The veterinarian and anaesthesiologists, performing the measurement punctures, were advised to avoid measuring the tissue that had become damaged from previous injections (figure 3). They were also instructed to advance the needle into the tissue slowly, while the measurement was in progress. Movement induced artefacts are therefore present in the measurement data. Blood and synovial fluid samples were measured in test tubes. The temperature of these liquid samples was stabilized using a heath bath, and blood samples were replaced approximately every two minutes in order to minimize the coagulation. Each

measurement was done manually and the animal was dissected to visually identify the target tissue by physician or vet performing the procedure. The core temperature of the animals was monitored during the studies and was found to be stable. Both animals were euthanized by the vet at the end of the studies. The study was authorized by the Animal Study Board of the Regional State Administrative Agency of Southern Finland

(ESAVI/7283/04.10.03/2012).

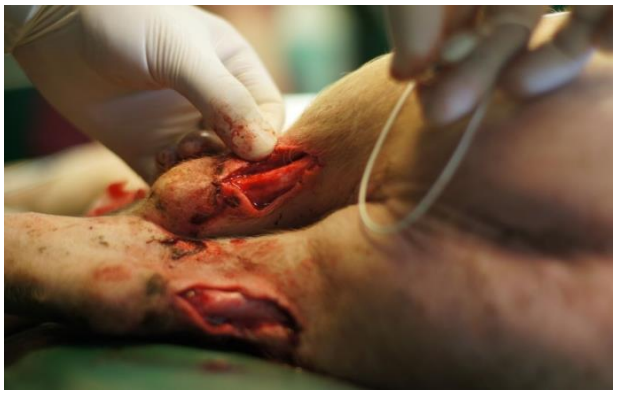

Figure 3 - The measurement of the Achille's tendon in progress.

Bleeding of the damaged tendon and surrounding tissues is clearly visible.

Data processing and generation and testing of classification models

Training- and testing data sets were created from the measurement data of both animal studies. Obvious measurement errors, significant needle movement induced measurement artefacts and measurement data likely originating from incorrect tissue type, were manually removed to obtain the training data sets that were used for creation of the classification parameters.

Data sets were also combined to form data sets, which represent the best obtainable understanding of the impedance of various tissues using the presented measurement technology. These data sets were named Training set C and Testing set C.

The tissue classification results are presented in two ways. We present true cross-validation classification results between the two studies, using the respective training and testing sets, and to complement the analysis, evaluate the classifier performance by stratified 10-fold cross-validation [9] on the pooled data set. The pooled training dataset of the two animal experiments (Training set C) was randomly divided into 10 disjoint sets with stratification. At a time, 9 of these were used for training the classifier and the remaining one was used for testing the classifier, together with randomized 10 % of the data unique to the pooled testing dataset (Testing set C). This process was repeated 10 times to cycle through all the testing data once. Using the described procedure we obtain an estimation of the classification performance with data sets that are better representations of population.

Results

Bio-impedance spectra of the measured tissue types

The mean magnitude and phase angle spectra are plotted for both animal studies in figure 4.

Tissue classification results

Tissue classification results are presented using confusion matrices. In a confusion matrix, the classification

Table 2 - Information about the measurements done in animal studies

The last column lists the amount of measurement data. 1000 measurement vectors (15 magnitudes and 15 phase angles) are present in one second of active measurement data due to the high sampling rate.

Tissue type	The number of measurements	The number of BIP Needles	The amount of tissue class data in study specific Training set
Study A			
Fat	61	17	97692
Muscle	75	16	183455
Tendon	51	16	114818
Blood	20	20	4919
Synovial fluid	20	20	5334
Liver	5	1	13674
Spleen	2	1	2859
Study B			
Fat	42	8	134441
Muscle	35	8	174783
Tendon	40	8	180207
Blood	12	12	57391
Synovial fluid	12	12	59270
Liver	17	2	89838
Spleen	18	2	105910

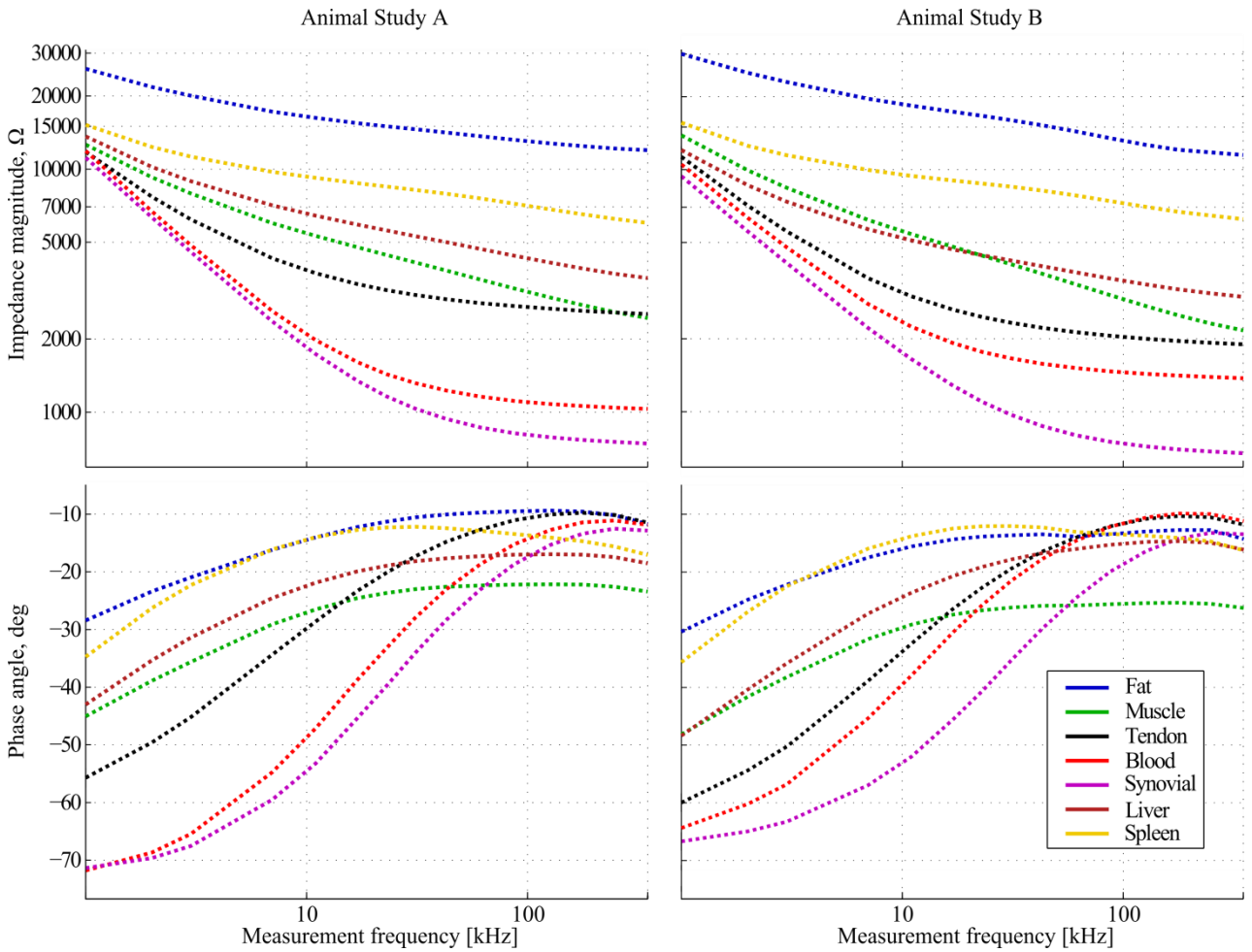

Figure 4 - Mean impedance and phase angle spectra obtained in the two animal studies

results (rows) are compared against the golden standard identification method (columns). The values are percentages of samples of a known tissue type that were given a row specific classification.

At first, the tissue identification performance was studied by classifying the data obtained in Animal study B using the tissue model generated from the data gathered from Animal Study A (table 4). These classifications are therefore exactly the same, as observed during the Animal Study B.

In order to conduct a valid cross-validation between the two animal studies, the measured bio-impedance data from the Animal Study B was used to create another tissue model. This tissue model was then tested using the data from the Animal Study A (table 5).

Cross-validation of the pooled data (using Training and Testing set C) was conducted to obtain an estimate of the future tissue identification performance. The results of this test are shown in table 6.

Discussion

BIP Needles produced by Injeq Ltd were used in two independent animal studies and the tissue recognition performance was assessed using cross-validation methods.

Bio-impedance spectra of the measured tissue types

The impedance spectra presented in this work are not directly comparable with the other published bio-impedance spectra from in-vivo tissue measurements. Measurement electronics was optimized towards greater repeatability, instead of high absolute accuracy, and geometry of the electrodes varied from other published research. However, some general conclusions can be drawn about the impedance magnitude spectra of different tissues.

Impedance spectra are affected by the EPI, which is evident by the significant increase in the measured impedance at low frequencies. The increase in the impedance is not due to the frequency dependence of the electrical properties of the tissues because the properties are frequency independent over the used frequency band [2,3]. On the high end of the frequency spectrum, the measured impedance values correlate well with the reported conductivity values of the tissues [1, 2, 3].

Tissue classification results

During the Animal Study B (table 4), we observed adequate classification sensitivity for muscle and ten-

don and very high sensitivity for fat and synovial fluid. Also, the tissue model of the fat class appears too wide as a significant amount of other tissues are incorrectly classified as fat. Classification of blood samples into the correct class did not work. Measurement of liquid tissue types is sensitive to the changes in the BIP Needle EPI but also to the condition of the samples. Small blood samples (~10 ml) cool and coagulate rapidly, which may explain why the blood measurements produced significantly different values in two studies.

When classifying the data from the Animal study A, by using the model from animal study B, the sensitivity of

Table 4 - The observed classification results in the Animal study B

A hyphen instead of a percentage value indicates that there were no classifications to that category.

		Visual inspection of tissue type in Animal Study B				
		Fat	Muscle	Tendon	Blood	Synovial fluid
Classification result (%)	Fat	**94,6**	8,3	11,9	9,0	0,0
	Muscle	0,1	**87,0**	7,8	0,0	0,0
	Tendon	5,3	4,7	**79,8**	36,1	0,0
	Blood	0,0	0,0	0,0	**0,2**	0,0
	Synovial fluid	0,0	0,0	0,4	54,8	**100,0**
	Overall duration [sec]	130 s	170 s	173 s	57,4 s	59,3 s

Table 5 - Testing set A is classified using the classification parameters extracted from the Training set B

		Visual inspection of tissue type in Animal Study A						
		Fat	Muscle	Tendon	Blood	Synovial fluid	Liver	Spleen
Classification results (%)	Fat	**64,8**	1,8	0,6	0,0	6,8	1,2	10,2
	Muscle	12,3	**93,0**	3,0	0,0	0,1	15,1	6,4
	Tendon	21,2	3,4	**83,2**	71,4	16,3	18,4	0,5
	Blood	0,0	0,0	11,6	**28,6**	76,8	0,0	0,0
	Synovial fluid	0,0	0,0	0,0	0,0	**0,0**	0,0	0,0
	Liver	1,4	1,7	1,4	0,0	0,0	**64,2**	0,1
	Spleen	0,3	0,0	0,2	0,0	0,0	1,1	**82,8**
	Overall duration [sec]	142 s	194 s	166 s	5,2 s	5,7 s	13,8 s	3,1 s

Table 6 - The results of the cross-validation test to estimate the classification performance using all the available tissue measurement data

		Visual inspection of tissue type, combination of the two animal studies						
		Fat	Muscle	Tendon	Blood	Synovial fluid	Liver	Spleen
Classification results (%)	Fat	**72,9**	3,9	3,0	0,0	0,5	0,6	3,2
	Muscle	4,5	**86,1**	4,5	0,0	0,0	1,3	0,1
	Tendon	20,9	3,0	**79,1**	2,7	0,6	7,7	0,5
	Blood	0,0	0,0	9,0	**80,6**	3,5	0,0	0,0
	Synovial fluid	0,0	0,1	1,9	13,9	**95,4**	0,0	0,0
	Liver	1,5	6,8	1,9	0,0	0,0	**89,5**	1,7
	Spleen	0,2	0,1	0,6	2,8	0,0	0,9	**94,5**
	Overall data points	269 s	359 s	335 s	14,8 s	16,3 s	39,1 s	8,9 s

muscle tissue classifications is over 90 %, but the sensitivity of the other tissue types is rather poor. Clearly two animal studies did not produce sufficiently identical impedance spectra, especially from the liquid tissue types, for the classification to be reliable. The variation between the test animals and varying EPI levels of the BIP Needles are the most likely reasons for the differences. The EPI induced variation between the commercial needles is a known factor that increases the variance between the animal studies [8]. As shown in the Table 2, the number of BIP Needles, especially in study B, is not sufficiently high to average out the effects of the EPI variation.

Cross validation between just two independent animal studies cannot be considered a sufficient test to draw reliable conclusions about the performance of the proposed system in larger test subject population. The results presented here demonstrate that the technique works but the sample size for both training and testing sets must be increased for more reliable results.

The 10-fold cross-validation with all of the available data (table 6) produces more promising classification performance than the cross-validations between the two animal studies. It shows that the tissue identification performance can be expected to improve with the increasing sample size. The mean sensitivity of the tissue classes was 86,4 %, mean specificity was 97,6 % and the overall accuracy 85,4 %. The given classification performance figures are a strong indication of the future clinical applicability of the proposed needle guidance system.

Potential error sources

Physiological differences between the test subjects warrant that the bio-impedance measurements are not likely to produce exactly same results. Differences between the BIP Needle electrode impedances (EPI) also contribute to the overall observed variance. As with the test subjects, the BIP Needle variance is not yet adequately represented in the available training data sets. The BIP parts were manufactured in the prototype production line. Interneedle variance is expected to decrease as the production methods are stabilized.

Possible incorrect needle placement during the measurement and extensive bleeding in the area of the measurement injection will have affected both the training and testing data sets. Similarly, varying levels of cooling and coagulation in the blood, and cooling of the synovial fluid samples in the test tubes, may have had different effect on training and testing data sets. Lastly, poor or non-existent contact between the tissue and the BIP Needle, may be present in different testing data sets. Generally, these situations are incorrectly classified as the fat tissue.

Conclusions

We presented a complete measurement system, aimed for clinically feasible real-time tissue discrimination at the tip of the 22 gauge* needle, by means of the bio-impedance measurement. Removable stylet enables injections or biopsies once the needle is positioned. We proposed pattern classification technique for performing the real-time tissue identification from the multifrequency bio-impedance measurement data. The two in-vivo animal studies have demonstrated the feasibility of the proposed technique and the clinical studies on human patients are justifiable. While the tissue classification performance in the two cross-validation tests was somewhat unsatisfactory, we expect the tissue model to improve iteratively, as the sample size increases. This was demonstrated by cross-validation of the pooled data, which produced significantly better tissue classification performance than other classification tests. Further animal studies or clinical testing on human patients are necessary to prove the clinical benefit of the proposed technology.

***Note:** Injeq IQ-Needles are available in sizes 18G, 22G, 24G and 27G. Every IQ-Needle size provides similar tissue identification performance.

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