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(54) Determination of biological conditions using impedance measurements

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- **OLLMAR S ET AL: "ELECTRICAL IMPEDANCE FOR ESTIMATION OF IRRITATION IN ORAL MUCOSA AND SKIN" MEDICAL PROGRESS THROUGH TECHNOLOGY, SPRINGER VERLAG. BERLIN, DE, vol. 21, no. 1, 1 February 1995 (1995-02-01), pages 29-37, XP000502787 ISSN: 0047-6552**

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Description

Field of the invention

[0001] This invention is in the field of diagnostics of biological conditions. In one aspect, the invention involves *in vivo* evaluation of the level of a substance in the blood of a subject, particularly blood glucose levels. In another aspect, the invention involves diagnosing a diseased condition of the skin of a subject, particularly the presence of a skin cancer, e.g. basal cell carcinoma or malignant melanoma, a squamous cell carcinoma or precursors thereof. In both instances, the determination is based on skin impedance measurements.

Background of the invention

[0002] Non-invasive methods of making biological determinations are generally desirable over invasive techniques that involve the taking of samples. Non-invasive techniques can be more convenient, e.g., less painful, involve less risk of infection, etc. Non-invasive techniques for evaluating blood glucose levels have been described in the patent literature:

Application No.	Publication No.	Publication Date	Name
	US 5,036,861	August 6, 1991	Sembrowich *et al*.
	US 5,115,133	May 19, 1992	Knudson
	US 5,146,091	September 8, 1992	Knudson
	US 5,197, 951	January 19, 1993	Knudson
	US 5,222,496	June 29, 1993	Clarke *et al*.
PCT/US 94/08816	WO 95/04496	February 16, 1995	Solid State Farms, Inc.
	US 5,433,197	July 18, 1995	Stark
PCT/US 97/13267	WO 98/04190	February 5, 1998	Dermal Therapy (Barbados) Inc.
PCT/US 98/02037	WO 99/39627	August 12, 1999	Dermal Therapy (Barbados) Inc.
PCT/IB 00/01464	WO 01/26538	October 13, 2000	Sηsstrunk, *et al*.

Summary of the invention

[0003] A summary of the invention in its various aspects is provided in the attached claims, bearing in mind that those skilled in the art will understand that a variety of possible combinations and subcombinations of the various elements described in the claims and throughout this specification exist, and all of these combinations and subcombinations should be considered to be within the inventors' contemplation though not explicitly enumerated here. This is also true of the variety of aspects of the processes and the combinations and subcombinations of elements thereof.

Description of drawings

[0004] The invention is described in greater detail below, with reference to the attached figures, in which:

Figure 1(a) shows a spiked electrode of the present invention;
Figure 1 (b) shows details of the spiked array given as electron micrograph;
Figure 2 shows representative Bode plots of impedance (left hand axis, kOhms) and phase (right hand axis; degrees) as a function of frequency number (31 logarithmically distributed frequencies from 1kHz to 1 MHz) for subject B. The results shown in Figure 2(a) were obtained using a conventional probe and those shown in Figure 2(b) were obtained using a spiked electrode. In Figure 2(a), the lower set of curves shows the magnitude of the impedance (at various depths) and the corresponding phase is shown by the upper set of curves. In Figure 2(b), the phase plots display a local maximum around frequency number 21;
Figure 3 shows the blood glucose level as determined directly over the course of the tests for each subject. Subject A (♦), subject B (●);
Figure 4(a) shows a scatter plot of PCA (principle component analysis) for each subject (t1 vs. t2) obtained with the spiked electrode. Figure 4(b) is a corresponding plot for each subject obtained with the conventional probe. In both plots, subject A is to the right and subject B is to the left of the figure;
Figure 5(a) shows a scatter plot of measured blood glucose and index with outliers of subject A obtained with the spiked electrode. Figure 5(b) shows the same plot without outliers, readings number 7, 8, and 13;
Figure 6(a) shows a scatter plot of subject B's blood glucose vs. magnitude of impedance at 1 MHz and depth setting

number 5 measured with the spiked electrode with (left) outlier reading number 10. Figure 6(b) is the same plot without the outlier;

Figure 7 shows a scatter plot of subject B's magnitude at 1 kHz and depth setting number 5 vs. blood glucose;

Figure 8 shows representative Bode plots of impedance (left hand axis; kOhm) and phase angle (right hand axis; degrees) as a function of frequency (kHz), plotted logarithmically, obtained at five depth settings using a spiked electrode. In Figure 8(a), the results were obtained for a normal skin site of a subject. In Figure 8(b), the results were obtained from the same subject but a basal cell carcinoma located near the normal site of Figure 8(a). In Figure 8(c), the results were obtained from a normal skin site of another subject. In Figure 8(d), the results were obtained from this other subject but a malignant melanoma located near the normal site of Figure 8(c). Each ensemble of curves represents five measured depths.

Figure 9 shows a correlation between blood glucose and values obtained from impedance measurements taken using a multi-step inundation method and conventional electrode.

Description of preferred embodiments

[0005] An apparatus for use according to the present invention can generally be regarded as a combination of the device described in international patent application No. PCT/SE 91/00703, published under WO 92/06634 on April 30, 1992 and the "spiked" electrode described in international patent application No. PCT/IB 01/00059, published under WO 01/52731 on July 26, 2001 or in an article entitled "Micromachined Electrodes for Biopotential Measurements" published in the Journal of Microelectromechanical Systems 10(1), pp 10-16, on March 2001 by Griss et al. The electrode used in the tests described below, however, is a variation of that described by Griss *et al.*, and is shown if Figures 1(a) and 1(b). The probe includes of a number of electrodes, at least three according to No. PCT/SE 91/00703, and in the present invention each electrode of the probe has a spiked surface, which permits measurements to be made at a variety of skin depths. The probe is illustrated in Figure 1(b), the probe being viewed looking down onto its spikes (a bottom plan view). The probe includes three rectangular areas or bars each bar containing an array of 35 (7 x5) spikes. Each bar is 1 mm wide and 5 mm long. The distance between the closest bars is 0.2 mm, and the wider between the second and third bars is 1.8 mm. The active part of the probe is thus about 5 x 5 mm. Each spike has a length of approximately 150 micrometer, as measured from its base, and a thickness of approximately 25 micrometer. The spikes are sharpened cylinders, i.e. are needle-like, and spaced approximately 200 micrometers from each other, center to center. The spikes were of silicon and covered with gold approximately 2 micrometer thick. Any material comprising a conductive surface with similar dimensions would work, but should be selected to be biocompatible.

[0006] The apparatus, without the spiked probe known as the SciBase II depth selective spectrometer, may be obtained from SciBase AB of Huddinge, Sweden. The pin assignment for the probe connector was as follows:

1. <START> button
2. sense (first electrode illustrated Figure 1(b); use coaxial (conventional probe) screen 3.
3. gnd (for sense)
4. near exciter (second (middle) electrode illustrated in Figure 1(b) ; use coaxial (conventional probe) screen 5.
5. gnd (for near injection).
6. gnd.
7. far exciter (third (right-most) electrode illustrated in Figure 1(b) ; use coaxial (conventional probe) screen 8.
8. gnd (for far injection).
9. chassis.
10. reserved.
11. reserved.
12. gnd.
13. gnd.
14.
15. charger.

Blood glucose levels

[0007] Tests were conducted using the foregoing apparatus to determine the feasibility of using such apparatus in determining blood glucose levels of human beings. Trials were conducted on two individuals, subjects A and B. Subject A suffers from atopic dermatitis, making the subject a relatively poor candidate for a non-invasive determination involving a skin measurement.

[0008] Tests were thus carried out (i) to assess the correlation between skin impedance measured using the spiked electrodes and the blood glucose, and (ii) to compare the glucose correlation of impedance measured with a conventional

probe and the spiked electrodes.

[0009] Two sites, one on each arm, were marked. One site was used for the spiked probe and the other for the conventional probe. Blood glucose levels were measured directly using the Glucometer Elite (available from Elite Glucometer, Miles Canada, Diagnostics Division, Division of Bayer). The sites were soaked for 60 seconds prior to each impedance measurement using 0.9% saline solution and stopwatch. Impedance was measured using the SciBase II depth selective spectrometer at 31 logarithmically distributed frequencies from 1 kHz to 1 MHz at five depth settings, as described in PCT/SE /00703.

[0010] The correlation between impedance and blood glucose was evaluated in three steps with increasing complexity of the regression models. The first step is linear regression between raw impedance and blood glucose for each frequency, depth setting and impedance presentation (magnitude, phase, real part, and imaginary part). The second step is linear regression between indices and blood glucose. The indices are described in detail below. The last step is partial least squares regression (PLS) models of full impedance spectra and glucose levels.

[0011] As indicated in Figure 2, the magnitude of the impedance measured with the regular probe (Figure 2(a)) was found to be much higher along with the phase, and the characteristic frequency was lower. Hence, impedance measured with the conventional probe was significantly different from the spiked electrodes.

[0012] The tests were carried out over about 5 hours. The electrodes with spikes used to measure impedance of subject B broke down after approximately 10-11 readings. The glucose levels for subject A and B, as measured directly, are shown in Figure 3. The glucose levels of subject A were generally higher than for subject B, and the impedance of the two volunteers was also found to be different, as indicated in Figure 4. This indicates that it might not be possible to use one calibration model for these subjects.

[0013] The four indices (MIX, PIX, RIX, and IMIX) were originally made to normalise impedance spectra of the spectrometer. It was found that the four indices described a substantial part of the variations in the impedance spectra and were useful in skin irritation assessments, but not necessarily in glucose quantifications. Therefore, new indices, ix, were made using the frequencies, f, depth settings, d, for all impedance presentations, X, according to (1).

$$ix(i,j,k,l,m,n) = \frac{X_i(f_j, d_k)}{X_l(f_m, d_n)} \qquad (1)$$

$i, k \in 1...4$
$X_1 = |Z|$, $X_2 = \theta$, $X_3 = Re(Z)$, $X_4 = Im(Z)$
$f_j, f_m \in$ 1kHz...1Mhz
$d_k, d_n \in 1...5$

[0014] Three impedance readings were abnormal and excluded from the data analysis. Correlation coefficient (R2) of linear regression between an impedance index of the results obtained with the spiked electrode and subject A's blood glucose was 70% (n=11). This is shown in Figure 5. The new index used in this analysis is based on only two frequencies, each frequency measured at different depth settings, and is defined as:

$$ix = \frac{Re(Z_{20\,kHz,\,depth\,\#5})}{|Z_{500\,kHz,\,depth\,\#3}|}$$

[0015] In the case of the conventional probe, no significant correlation was found between impedance measured and blood glucose for subject A.

[0016] In the case of subject B and the results obtained with the spiked electrode, there was one reading with abnormal impedance. The measurement was made just before the spiked probe broke down and it is believed that the impedance of the actual reading was abnormal because the spiked probe was beginning to malfunction when the last measurement was made. Linear regression between the magnitude of the raw impedance at high frequencies and deep depths and blood glucose showed good correlation, $R^2 = 80\%$ (n=9). See Figure 6.

[0017] No significant impedance/glucose correlation was found using the conventional concentric probe if all the measurements were included. However, three readings, number 5, 10, and 11, do not show the same impedance/glucose pattern as the others (Figure 7). If these 3 readings are excluded, the correlation coefficient becomes approximately 95%. If these excluded readings are not considered outliers (there is nothing abnormal about their impedance or glucose levels), the correlation between impedance measured with the regular probe and blood glucose would not be significant. However, suitable inundation and data exclusion criteria that might exclude these flawed measurements

thus permitting accurate glucose predictions using the conventional probe at least under certain conditions.

[0018] The results described herein, summarized in Table 1, establish the improved correlation between measured skin impedance and blood glucose levels obtainable using the spiked electrode described above. It is the experience of the inventors, that a higher correlation can be achieved using the conventional probe with optimization of inundation time of the sample site.

Table 1: Summary of the correlation coefficient (R2) between blood glucose and skin impedance measured with the regular probe and the spikes.

Subject	Conventional Probe	Spiked Electrode
A	Not significant	~70%
B	Not significant	~80%

[0019] It is evident that there was a strong correlation between skin impedance and blood glucose in this experiment. The correlation of the two subjects was found more reliable for the spiked electrodes than the conventional probe.

[0020] The spiked electrodes can improve the glucose correlation by mitigating factors interfering with the impedance tests and reducing the stringency of skin inundation in preparing the site for impedance measurement. Thus the spiked electrodes are likely to permit glucose determination more reliably in a wider variety of situations than such determination with a conventional probe.

[0021] The following inundation procedures can be used to improve results obtained with the conventional probe. Gauze inundation pads are kept in a closed beaker of 0.9% saline or packaged in a saturated state. The skin is inundated by holding the gauze pad in place at the test site for 40 seconds then wiping away any excess solution before the impedance test., with inundation again 10 additional seconds, wiping away any excess solution before the second impedance test and impedance test again. This procedure is repeated until a total of 70 seconds of inundation has been reached.

[0022] Data are included if at 1 Mhz at depth 1 the kOhms value is within the range 1.25 -1.45. Other frequencies can be used. If more than one impedance test was within this range, the kOhm value closest to 1.3 is selected. If the kOhm value is in range and IMIX at depth one value is between 10.2 and 11.5 then this IMIX value is accepted. Results obtained over several days are shown in Figure 9.

[0023] The conditions under which reliable results are obtained using the probe having spiked electrodes are thus more relaxed than with the conventional probe. There is thus less likely to be a need for subjects to use a mild soap, for example, when using the spiked electrode. It may be possible to obtain reliable results with tanned or diseased skin (e.g., atopic dermatis) with the spiked probe where such was not possible with the conventional probe. It is also likely that use of the same site from measurement to measurement is less important when using the spiked probe than when using the conventional probe.

Cancer diagnosis

[0024] Impedance measurements were similarly taken from subjects suffering from basal cell carcinoma or malignant melanoma: at a first site of normal (unaffected skin); and at a second site, of diseased skin. Results obtained are shown in Figure 8. A further description of the approach, in which measurements were obtained using a conventional probe, is given in Emtestam I, Nicander I, Stenström M, Ollmar S. "Electrical impedance of nodular basal cell carcinoma: a pilot study", Dermatology 1998; 197: 313-316, and Kapoor S. "Bioelectric impedance techniques for clinical detection of skin cancer", (MSc-thesis) University of Missouri-Rolla 2001, and Åberg P, Nicander I, Holmgren U, Geladi P, Ollmar S. Assessment of skin lesions and skin cancer using simple electrical impedance indices. Skin Res Technol 2003; 9: 257-261, and Beetner DG, Kapoor S, Manjunath S, Zhou X, Stoecker WV. Differentiation among basal cell carcinoma, benign lesions, and normal skin using electric impedance. IEEE Trans Biomed Eng 2003; 50: 1020-1025.

[0025] It is desirable to detect and remove skin cancers as early as possible. As such, precursors of skin cancer, such as, for example, actinic keratose (a precursor of squamous cell carcinoma) and dysplastic nevi (a precursor of malignant melanoma), as well as other lesions that may be mixed up with various cancers unless surgery and histological evaluation of the catch is made, can be detected using impedance measurements of the present invention in the manner described herein.

Claims

1. An apparatus for the diagnosing of a diseased condition of the skin of a subject, comprising:

   an electrically conducting probe including plurality of electrodes, each electrode comprising at least one spike, which spikes are laterally spaced apart from each other and having a length being sufficient to penetrate the stratum corneum, wherein
   said apparatus is adapted to, when placed against a skin surface of the subject such that said spikes penetrate the stratum corneum, pass an electrical current through the electrodes to obtain values of skin impedance and to use reference data to determine whether the obtained impedance values indicate the diseased condition, and wherein
   said probe comprises three said spike furnished electrodes, the spikes of a first electrode and a second electrode being laterally spaced apart a first distance from each other and the spikes of the first and a third electrode being laterally spaced apart a second distance from each other, said apparatus being adapted to separately pass an electrical current between the first and the second electrode and the first and the third electrode to obtain first and second values of skin impedance.

2. The apparatus according to claim 1, wherein said first distance and said second distance are different from each other.

3. The apparatus according to claim 1 or 2, wherein said first distance is between about 0.1 mm and about 40 mm; or between about 0.1 mm and 30 mm; or between 0.1 mm and 25 mm; or between about 0.1 mm and 20 mm; or between about 0.1 mm and 15 mm, or between about 0.2 mm and 10 mm; or between about 0.2 mm and 8 mm; or between about 0.2 mm and 5 mm; or between about 0.2 mm and 3 mm; or between about 0.2 mm and 2 mm; or between 0.2 mm and 1.5 mm; or between about 0.2 mm and 1 mm; or between about 0.2 mm and 0.5 mm.

4. The apparatus according to claim 3, wherein said second distance is between about 1 mm and about 50 mm; or between about 1 mm and 40 mm; or between about 1 mm and 30 mm; or between about 1 mm and 25 mm; or between about 1 mm and 20 mm; or between about 1 mm and 15 mm; or between about 1 mm and 10 mm; or between about 1 mm and 9 mm; or between about 1 mm and 8 mm; or between about 1 mm and 7 mm; or between about 2 mm and 8 mm; or between about 3 mm and 7 mm; or between about 4 mm and 7 mm; or between 4 mm and 6 mm; or about 5 mm.

5. The apparatus according to any one of the preceding claims, wherein the diseased condition is cancer, preferably skin cancer.

6. The apparatus according to claim 5, wherein skin cancer is a malignant melanoma or precursors of such lesion.

7. The apparatus of any one of the preceding claims, wherein said electrical current has a frequency between 1 kHz and 1 MHz.

8. The apparatus according to any one of preceding claims, wherein the apparatus is adapted to pass the electrical current at a plurality of logarithmically distributed frequencies within the range from 1 kHz to 1 MHz.

9. The apparatus according to any one of preceding claims, wherein each of said spikes has a length being sufficient to penetrate below the skin surface to the Stratum Germinativum or through the Stratum Corneum into the living Epidermis but not into the Dermis.

10. The apparatus according to any one of preceding claims, wherein said apparatus is adapted to use both non-invasive surface electrodes (conventional probes) in conjunction with said spiked electrodes to obtain more aspects of skin properties in order to improve power of discrimination.

11. The apparatus according to any one of preceding claims, wherein each spike has a length of at least about 10 μm

12. The apparatus according to any one of preceding claims, wherein each electrode comprises at least two said spikes; or at least three said spikes; or at least four said spikes; or at least five said spikes; or at least six said spikes; or at least seven said spikes; or at least eight said spikes; or at least nine said spikes; or at least ten said spikes; or at least twelve said spikes; or at least fifteen said spikes; or at least eighteen said spikes; or at least twenty said spikes; or at least twenty-five said spikes; or at least thirty said spikes; or at least thirty-five said spikes; or at least fifty said

spikes.

13. The apparatus according to any one of preceding claims, wherein each of said spikes has a length up to about 250 μm, or up to 240 μm, or up to 230 μm, or up to 220 μm, or up to 210 μm, or up to 200 μm, or up to 190 μm, or up to 180 μm, or up to 170 μm, or up to 160 μm, or up to 150 μm, or up to 140 μm, or up to 130 μm, or up to 120 μm, or up to 110 μm, or up to 100 μm.

14. The apparatus according to any one of preceding claims, wherein each spike is at least 20; or at least 30; or at least 40; or at least 50; or at least 60; or at least 70; or at least 80, or at least 90 μm in length.

15. The apparatus according to any one of preceding claims, wherein an outer diameter of each of said spikes is between about 20 μm and about 50 μm.

16. A method for diagnosing of a diseased condition of the skin of a subject, comprising the steps of:

placing an electrically conducting probe against a skin surface of the subject, said probe comprising three spike furnished electrodes, which spikes are laterally spaced apart from each other and having a length being sufficient to penetrate the stratum corneum, the spikes of a first electrode and a second electrode being laterally spaced apart a first distance from each other and the spikes of the first and a third electrode being laterally spaced apart a second distance from each other;
passing an electrical current through the electrodes to obtain values of skin impedance, wherein the electrical current is separately passed between the first and the second electrode and the first and the third electrode to obtain first and second values of skin impedance; and
using, by means of an apparatus, reference data to determine whether the obtained impedance values indicate the diseased condition.

17. The method of claim 16, wherein the diseased condition is a malignant melanoma or precursors of such lesion.

Patentansprüche

1. Vorrichtung zum Diagnostizieren eines Erkrankungszustandes der Haut eines Subjekts, wobei die Vorrichtung Folgendes umfasst:

eine elektrisch leitende Sonde, die mehrere Elektroden einschließt, wobei jede Elektrode wenigstens einen Dorn umfasst, wobei diese Dorne mit seitlichem Abstand entfernt voneinander angeordnet sind und eine Länge haben, die ausreichend ist, um das Stratum corneum zu durchdringen, wobei
die Vorrichtung dafür eingerichtet ist, wenn sie an einer Hautoberfläche des Subjekts angeordnet wird derart, dass die Dorne das Stratum corneum durchdringen, einen elektrischen Strom durch die Elektroden hindurchzuleiten, um Werte der Hautimpedanz zu erlangen, und Referenzdaten zu verwenden, um festzustellen, ob die erlangten Impedanzwerte auf den Erkrankungszustand hinweisen, und wobei
die Sonde drei mit Dornen ausgestattete Elektroden umfasst, wobei die Dorne der ersten Elektrode und einer zweiten Elektrode mit einem ersten seitlichen Abstand entfernt voneinander angeordnet sind und die Dorne der ersten Elektrode und einer dritten Elektrode mit einem zweiten seitlichen Abstand entfernt voneinander angeordnet sind, wobei die Vorrichtung dafür eingerichtet ist, gesondert einen elektrischen Strom zwischen der ersten und der zweiten Elektrode und der ersten und der dritten Elektrode hindurchzuleiten, um erste und zweite Werte der Hautimpedanz zu erlangen.

2. Vorrichtung nach Anspruch 1, wobei sich der erste Abstand und der zweite Abstand voneinander unterscheiden.

3. Vorrichtung nach Anspruch 1 oder 2, wobei der erste Abstand zwischen etwa 0,1 mm und etwa 40 mm oder zwischen etwa 0,1 mm und 30 mm oder zwischen etwa 0,1 mm und 25 mm oder zwischen etwa 0,1 mm und 20 mm oder zwischen etwa 0,1 mm und 15 mm oder zwischen etwa 0,2 mm und 10 mm oder zwischen etwa 0,2 mm und 8 mm oder zwischen etwa 0,2 mm und 5 mm oder zwischen etwa 0,2 mm und 3 mm oder zwischen 0,2 mm und 2 mm oder zwischen 0,2 mm und 1,5 mm oder zwischen etwa 0,2 mm und 1 mm oder zwischen etwa 0,2 mm und 0,5 mm beträgt.

4. Vorrichtung nach Anspruch 3, wobei der zweite Abstand zwischen etwa 1 mm und etwa 50 mm oder zwischen etwa

1 mm und 40 mm oder zwischen etwa 1 mm und 30 mm oder zwischen etwa 1 mm und 25 mm oder zwischen etwa 1 mm und 20 mm oder zwischen etwa 1 mm und 15 mm oder zwischen etwa 1 mm und 10 mm oder zwischen etwa 1 mm und 9 mm oder zwischen etwa 1 mm und 8 mm oder zwischen etwa 1 mm und 7 mm oder zwischen etwa 2 mm und 8 mm oder zwischen etwa 3 mm und 7 mm oder zwischen etwa 4 mm und 6 mm oder etwa 5 mm beträgt.

5. Vorrichtung nach einem der vorhergehenden Ansprüche, wobei der Erkrankungszustand Krebs, vorzugsweise Hautkrebs, ist.

6. Vorrichtung nach Anspruch 5, wobei der Hautkrebs ein malignes Melanom oder Vorläufer einer solchen Läsion ist.

7. Vorrichtung nach einem der vorhergehenden Ansprüche, wobei der elektrische Strom eine Frequenz zwischen 1 kHz und 1 MHz hat.

8. Vorrichtung nach einem der vorhergehenden Ansprüche, wobei die Vorrichtung dafür eingerichtet ist, den elektrischen Strom mit mehreren logarithmisch verteilten Frequenzen innerhalb des Bereichs von 1 kHz bis 1 MHz hindurchzuleiten.

9. Vorrichtung nach einem der vorhergehenden Ansprüche, wobei jeder der Dorne eine Länge hat, die ausreichend ist, um unter die Hautoberfläche bis zum Stratum germinativum oder durch das Stratum corneum in die lebende Epidermis, aber nicht in die Dermis, einzudringen.

10. Vorrichtung nach einem der vorhergehenden Ansprüche, wobei die Vorrichtung dafür eingerichtet ist, sowohl nicht invasive Oberflächenelektroden (herkömmliche Sonden) in Verbindung mit den mit Dornen versehenen Elektroden zu verwenden, um mehr Aspekte von Hauteigenschaften zu erlangen, um das Unterscheidungsvermögen zu verbessern.

11. Vorrichtung nach einem der vorhergehenden Ansprüche, wobei jeder Dorn eine Länge von wenigstens etwa 10 μm hat.

12. Vorrichtung nach einem der vorhergehenden Ansprüche, wobei jede Elektrode wenigstens zwei Dorne oder wenigstens drei Dorne oder wenigstens vier Dorne oder wenigstens fünf Dorne oder wenigstens sechs Dorne oder wenigstens sieben Dorne oder wenigstens acht Dorne oder wenigstens neun Dorne oder wenigstens zehn Dorne oder wenigstens zwölf Dorne oder wenigstens fünfzehn Dorne oder wenigstens achtzehn Dorne oder wenigstens zwanzig Dorne oder wenigstens fünfundzwanzig Dorne oder wenigstens dreißig Dorne oder wenigstens fünfunddreißig Dorne oder wenigstens fünfzig Dorne umfasst.

13. Vorrichtung nach einem der vorhergehenden Ansprüche, wobei jeder der Dorne eine Länge von bis zu etwa 250 μm oder bis zu 240 μm oder bis zu 230 μm oder bis zu 220 μm oder bis zu 210 μm oder bis zu 200 μm oder bis zu 190 μm oder bis zu 180 μm oder bis zu 170 μm oder bis zu 160 μm oder bis zu 150 μm oder bis zu 140 μm oder bis zu 130 μm oder bis zu 120 μm oder bis zu 110 μm oder bis zu 100 μm hat.

14. Vorrichtung nach einem der vorhergehenden Ansprüche, wobei jeder Dorn wenigstens 20 μm oder wenigstens 30 μm oder wenigstens 40 μm oder wenigstens 50 μm oder wenigstens 60 μm oder wenigstens 70 μm oder wenigstens 80 μm oder wenigstens 90 μm lang ist.

15. Vorrichtung nach einem der vorhergehenden Ansprüche, wobei ein Außendurchmesser jedes der Dorne zwischen etwa 20 μm und etwa 50 μm beträgt.

16. Verfahren zum Diagnostizieren eines Erkrankungszustandes der Haut eines Subjekts, wobei das Verfahren die folgenden Schritte umfasst:

das Anordnen einer elektrisch leitenden Sonde an einer Hautoberfläche des Subjekts, wobei die Sonde drei mit Dornen ausgestattete Elektroden umfasst, wobei diese Dorne mit seitlichem Abstand entfernt voneinander angeordnet sind und eine Länge haben, die ausreichend ist, um das Stratum corneum zu durchdringen, wobei die Dorne der ersten Elektrode und einer zweiten Elektrode mit einem ersten seitlichen Abstand entfernt voneinander angeordnet sind und die Dorne der ersten Elektrode und einer dritten Elektrode mit einem zweiten seitlichen Abstand entfernt voneinander angeordnet sind,
das Hindurchleiten eines elektrischen Stroms durch die Elektroden, um Werte der Hautimpedanz zu erlangen,

wobei der elektrische Strom gesondert zwischen der ersten und der zweiten Elektrode und der ersten und der dritten Elektrode hindurchgeleitet wird, um erste und zweite Werte der Hautimpedanz zu erlangen und das Verwenden von Referenzdaten, mit Hilfe einer Vorrichtung, um festzustellen, ob die erlangten Impedanzwerte auf den Erkrankungszustand hinweisen.

17. Verfahren nach Anspruch 16, wobei der Erkrankungszustand ein malignes Melanom oder Vorläufer einer solchen Läsion ist.

Revendications

1. Appareil pour le diagnostic d'un état pathologique de la peau d'un sujet, comprenant :

une sonde conductrice électrique incluant une pluralité d'électrodes, chaque électrode comprenant au moins une aiguille, lesquelles aiguilles étant latéralement espacées les unes des autres et ayant une longueur suffisante pour pénétrer dans le stratum corneum,
ledit appareil étant, une fois placé contre une surface de peau du sujet de manière à ce que lesdites aiguilles pénètrent dans le stratum corneum, apte à faire passer un courant électrique dans les électrodes pour obtenir des valeurs d'impédance de la peau et à utiliser des données de référence pour déterminer si les valeurs d"impédance obtenues indiquent l'état pathologique, et
ladite sonde comprenant trois dites électrodes équipées d'aiguilles, les aiguilles d'une première électrode et d'une deuxième électrode étant latéralement espacées d'une première distance les unes des autres et les aiguilles des première et troisième électrodes étant latéralement espacées d'une deuxième distance les unes des autres, ledit appareil étant apte à faire passer séparément un courant électrique entre les première et deuxième électrodes et les première et troisième électrodes pour obtenir des première et seconde valeurs d'impédance de la peau.

2. Appareil selon la revendication 1, dans lequel ladite première distance et ladite deuxième distance sont différentes l'une de l'autre.

3. Appareil selon la revendication 1 ou 2, dans lequel ladite première distance est comprise entre environ 0,1 mm et environ 40 mm ; ou entre environ 0,1 mm et 30 mm; ou entre 0,1 mm et 25 mm ; ou entre environ 0,1 mm et 20 mm ; ou entre environ 0,1 mm et 15 mm ; ou entre environ 0,2 mm et 10 mm ; ou entre environ 0,2 mm et 8 mm ; ou entre 0,2 mm et 5 mm ; ou entre environ 0,2 mm et 3 mm ; ou entre environ 0,2 mm et 2 mm ; ou entre 0,2 mm et 1,5 mm ; ou entre environ 0,2 mm et 1 mm ; ou entre environ 0,2 et 0,5 mm.

4. Appareil selon la revendication 3, dans lequel ladite première deuxième distance est comprise entre environ 1 mm et environ 50 mm ; ou entre 1 mm et 40 mm; ou entre environ 1 mm et 30 mm ; ou entre environ 1 mm et 25 mm ; ou entre environ 1 mm et 20 mm ; ou entre environ 1 mm et 15 mm ; ou entre environ 1 mm et 10 mm ; ou entre environ 1 mm et 9 mm ; ou entre environ 1 mm et 8 mm ; ou entre environ 1 mm et 7 mm ; ou entre environ 2 mm et 8 mm ; ou entre environ 3 mm et 7 mm ; ou entre environ 4 mm et 7 mm ; ou entre 4 mm et 6 mm ; ou étant d'environ 5 mm.

5. Appareil selon l'une quelconque des revendications précédentes, dans lequel l'état pathologique est le cancer, de préférence le cancer de la peau.

6. Appareil selon la revendication 5, dans lequel le cancer de la peau est un mélanome malin ou des précurseurs de cette lésion.

7. Appareil selon l'une quelconque des revendications précédentes, dans lequel ledit courant électrique a une fréquence comprise entre 1 kHz et 1 MHz.

8. Appareil selon l'une quelconque des revendications précédentes, dans lequel l'appareil est apte à faire passer le courant électrique à une pluralité de fréquences réparties de manière logarithmique dans la plage de 1 kHz à 1 MHz.

9. Appareil selon l'une quelconque des revendications précédentes, dans lequel chacune desdites aiguilles a une longueur suffisante pour pénétrer sous la surface de la peau jusqu'au stratum germinativum ou dans le stratum corneum dans l'épiderme vivant mais pas dans le derme.

10. Appareil selon l'une quelconque des revendications précédentes, dans lequel ledit appareil est apte à utiliser à la fois des électrodes de surface non invasives (sondes conventionnelles) en conjonction avec lesdites électrodes à aiguilles pour obtenir plus d'aspects de propriétés de la peau afin d'améliorer la capacité de discrimination.

11. Appareil selon l'une quelconque des revendications précédentes, dans lequel chaque aiguille a une longueur d'au moins environ 10 μm.

12. Appareil selon l'une quelconque des revendications précédentes, dans lequel chaque électrode comprend au moins deux dites aiguilles ; ou au moins trois dites aiguilles ; ou au moins cinq dites aiguilles ; ou au moins six dites aiguilles ; ou au moins sept dites aiguilles ; ou au moins huit dites aiguilles ; ou au moins neuf dites aiguilles ; ou au moins dix dites aiguilles ; ou au moins douze dites aiguilles ; ou au moins quinze dites aiguilles ; ou au moins dix-huit dites aiguilles ; ou au moins vingt dites aiguilles ; ou au moins vingt-cinq dites aiguilles ; ou au moins trente dites aiguilles ; ou au moins trente-cinq dites aiguilles ; ou au moins cinquante dites aiguilles.

13. Appareil selon l'une quelconque des revendications précédentes, dans lequel chacune desdites aiguilles a une longueur allant jusqu'à 250 μm ou jusqu'à 240 μm ou jusqu'à 230 μm ou jusqu'à 220 μm ou jusqu'à 210 μm ou jusqu'à 200 μm ou jusqu'à 190 μm ou jusqu'à 180 μm ou jusqu'à 170 μm ou jusqu'à 160 μm ou jusqu'à 150 μm ou jusqu'à 140 μm ou jusqu'à 130 μm ou jusqu'à 120 μm ou jusqu'à 110 μm ou jusqu'à 100 μm.

14. Appareil selon l'une quelconque des revendications précédentes, dans lequel chaque aiguille a une longueur d'au moins 20 ou d'au moins 30 ou d'au moins 40 ou d'au moins 50 ou d'au moins 40 ou d'au moins 60 ou d'au moins 80 ou d'au moins 90 μm.

15. Appareil selon l'une quelconque des revendications précédentes, dans lequel un diamètre extérieur de chacune desdites aiguilles est compris entre environ 20 μm et environ 50 μm.

16. Procédé de diagnostic d'un état pathologique de la peau d'un sujet, comprenant les étapes consistant à :

placer une sonde conductrice électrique contre une surface de peau du sujet, ladite sonde comprenant trois électrodes équipées d'aiguilles, lesquelles aiguilles étant latéralement espacées les unes des autres et ayant une longueur suffisante pour pénétrer dans le stratum corneum, les aiguilles d'une première électrode et d'une deuxième électrode étant latéralement espacées d'une première distance les unes des autres et les aiguilles d'une première électrode et d'une troisième électrode étant latéralement espacées d'une deuxième distance les unes des autres,
faire passer un courant électrique dans les électrodes pour obtenir des valeurs d'impédance de la peau, le courant électrique passant séparément entre les première et deuxième électrodes et les première et troisième électrodes pour obtenir des première et deuxième valeurs d'impédance de la peau ; et
utiliser, au moyen d'un appareil, les données de référence pour déterminer si les valeurs d'"impédance obtenues indiquent l'état pathologique.

17. Procédé selon la revendication 16, dans lequel l'état pathologique est un mélanome malin ou des précurseurs de cette lésion.

Figure 1(a)

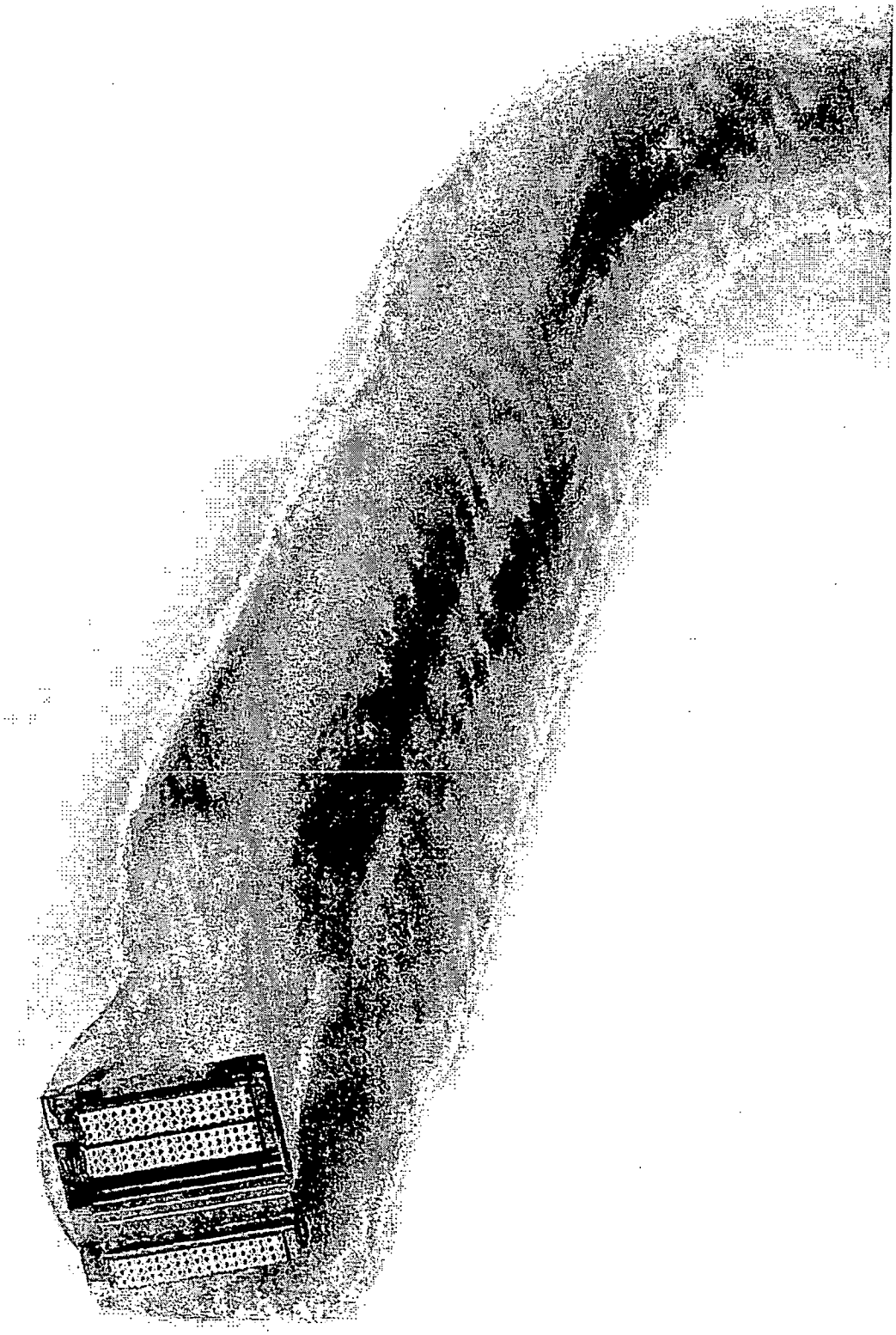


Figure 1(b)

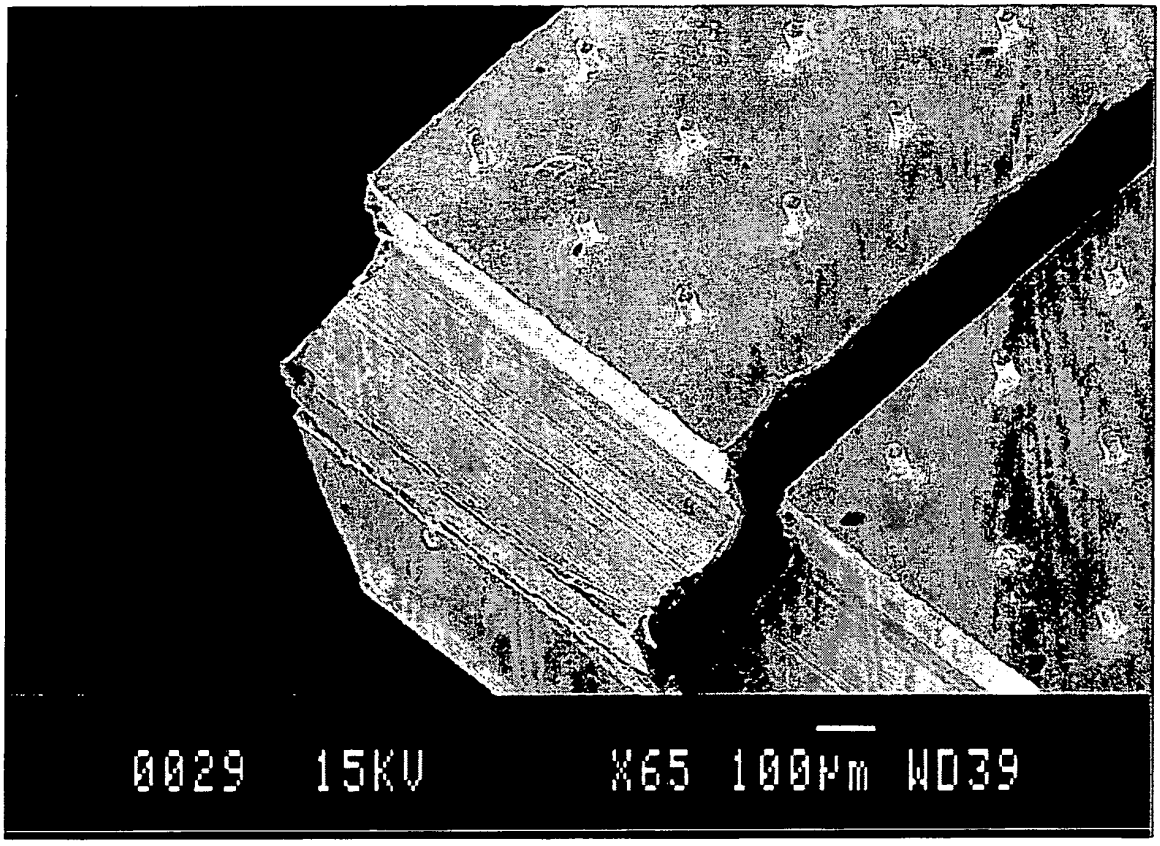


Figure 2

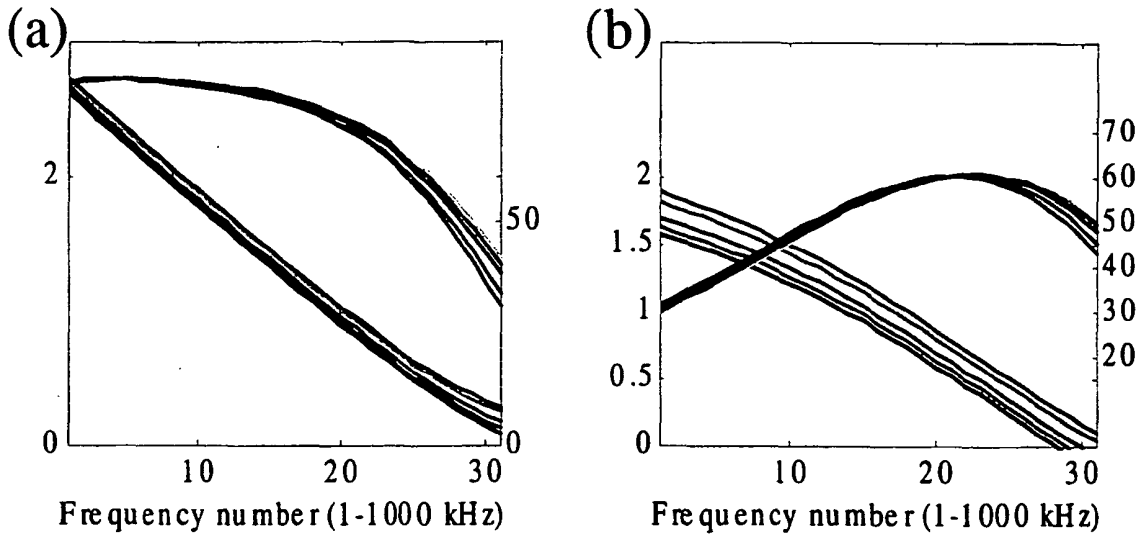

(a)
2
0
50
0
10
20
30
Frequency number (1-1000 kHz)
(b)
2
1.5
1
0.5
0
70
60
50
40
30
20
10
20
30
Frequency number (1-1000 kHz)

Figure 3

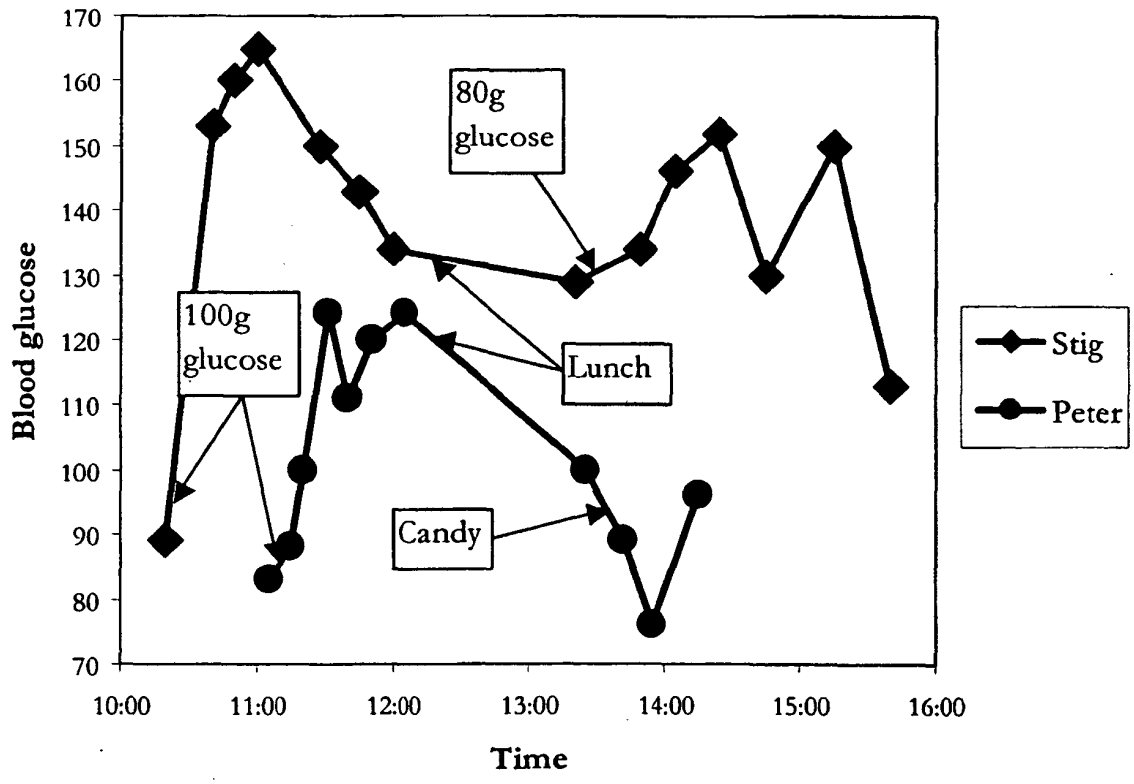

170
160
150
140
130
120
110
100
90
80
70
Blood glucose
10:00
11:00
12:00
13:00
14:00
15:00
16:00
Time
80g glucose
100g glucose
Lunch
Candy
Stig
Peter

Figure 4

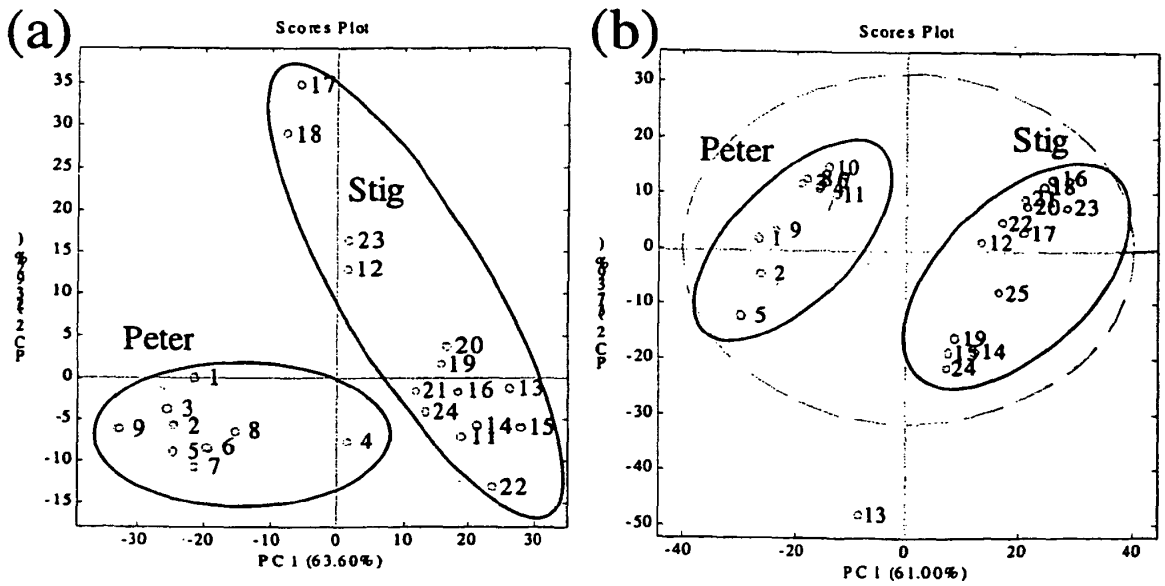

(a)
Scores Plot
Stig
Peter
PC 1 (63.60%)
(b)
Scores Plot
Peter
Stig
PC 1 (61.00%)

Figure 5

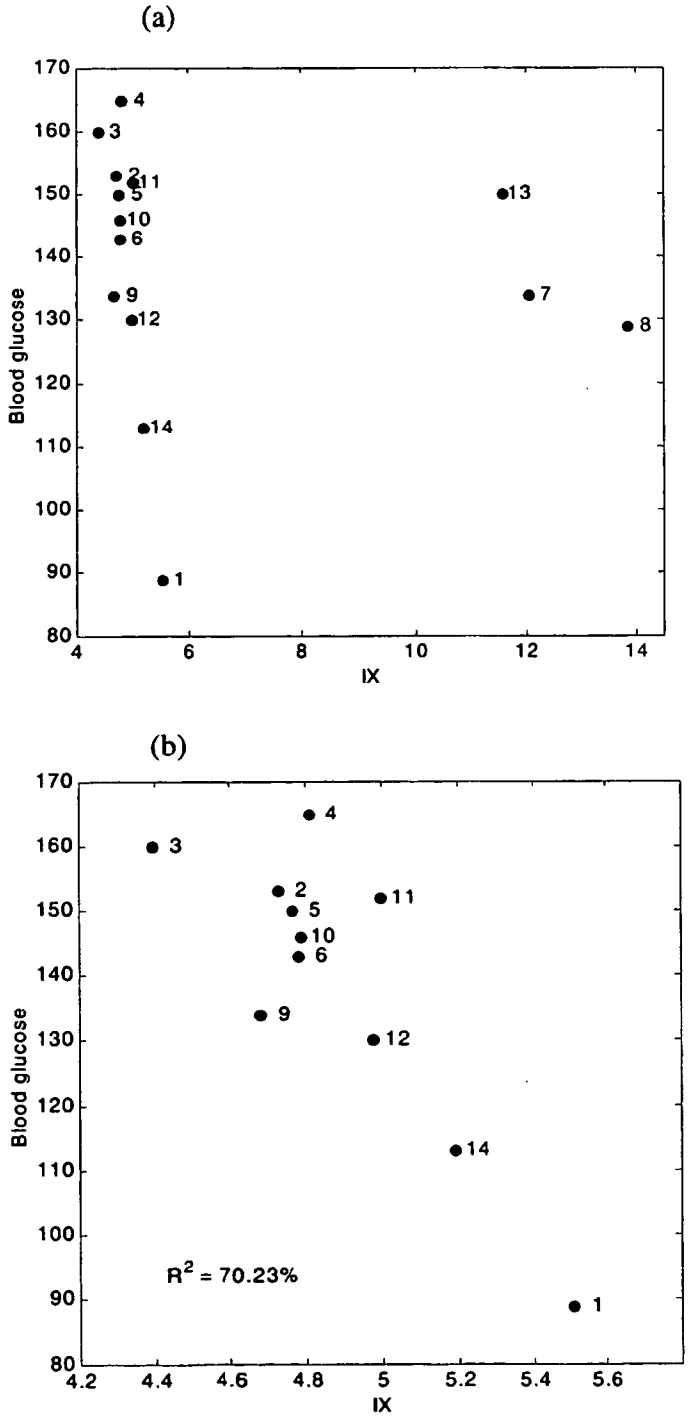
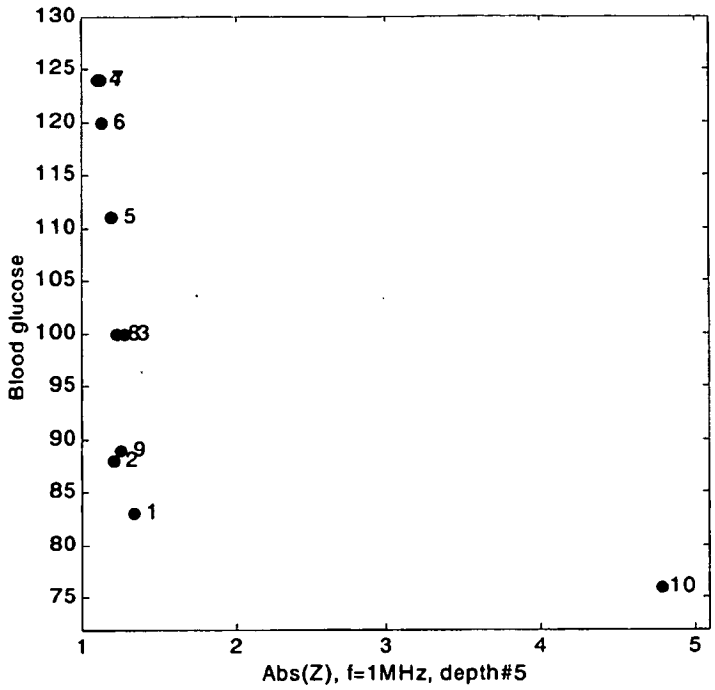


Figure 6

(a)


Blood glucose
Abs(Z), f=1MHz, depth#5
130
125
120
115
110
105
100
95
90
85
80
75
1
2
3
4
5
4
6
5
3
9
2
1
10

(b)

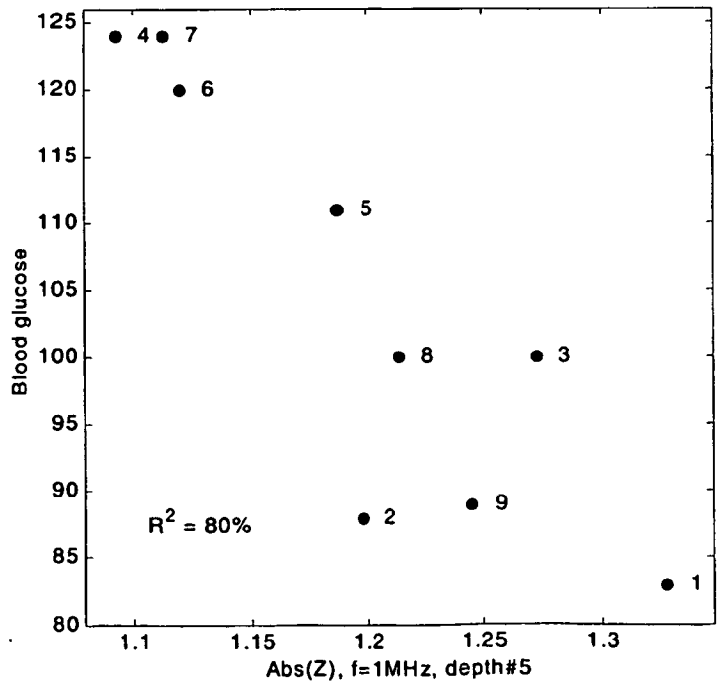

Blood glucose
Abs(Z), f=1MHz, depth#5
125
120
115
110
105
100
95
90
85
80
1.1
1.15
1.2
1.25
1.3
4
7
6
5
8
3
9
2
1
R2 = 80%

Figure 7

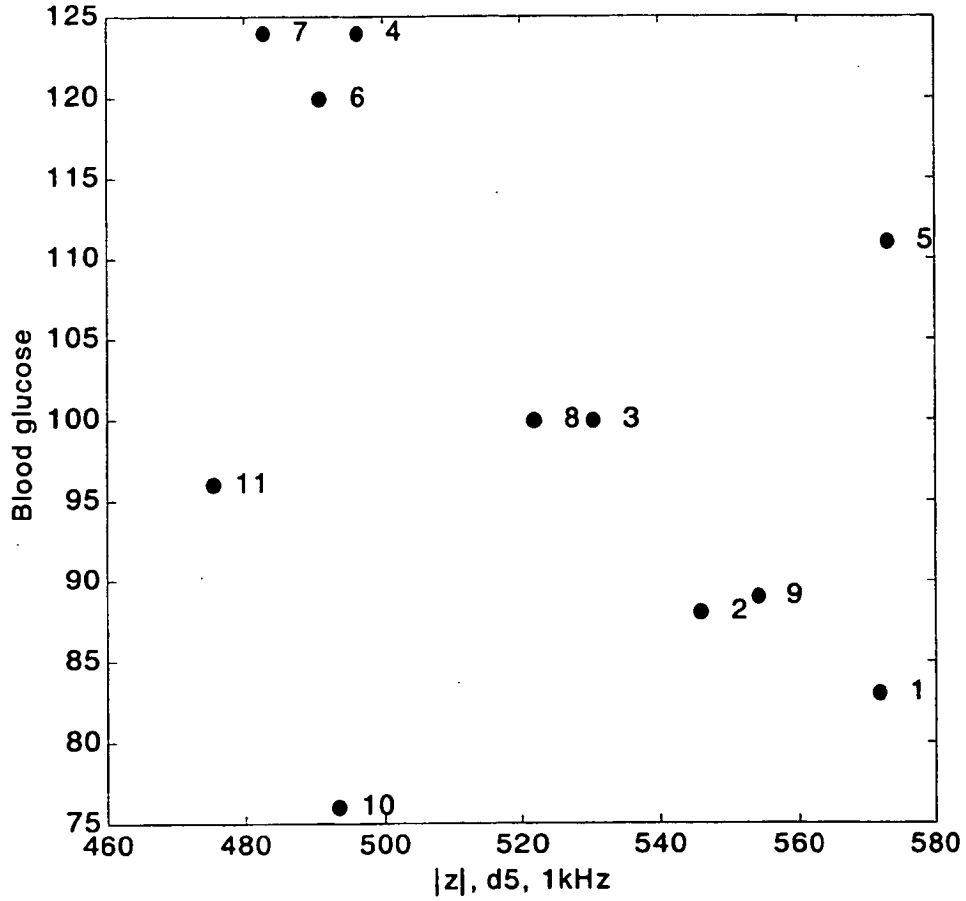

Blood glucose
|z|, d5, 1kHz
125
120
115
110
105
100
95
90
85
80
75
460
480
500
520
540
560
580
7
4
6
5
8
3
11
2
9
1
10

Figure 8(a)

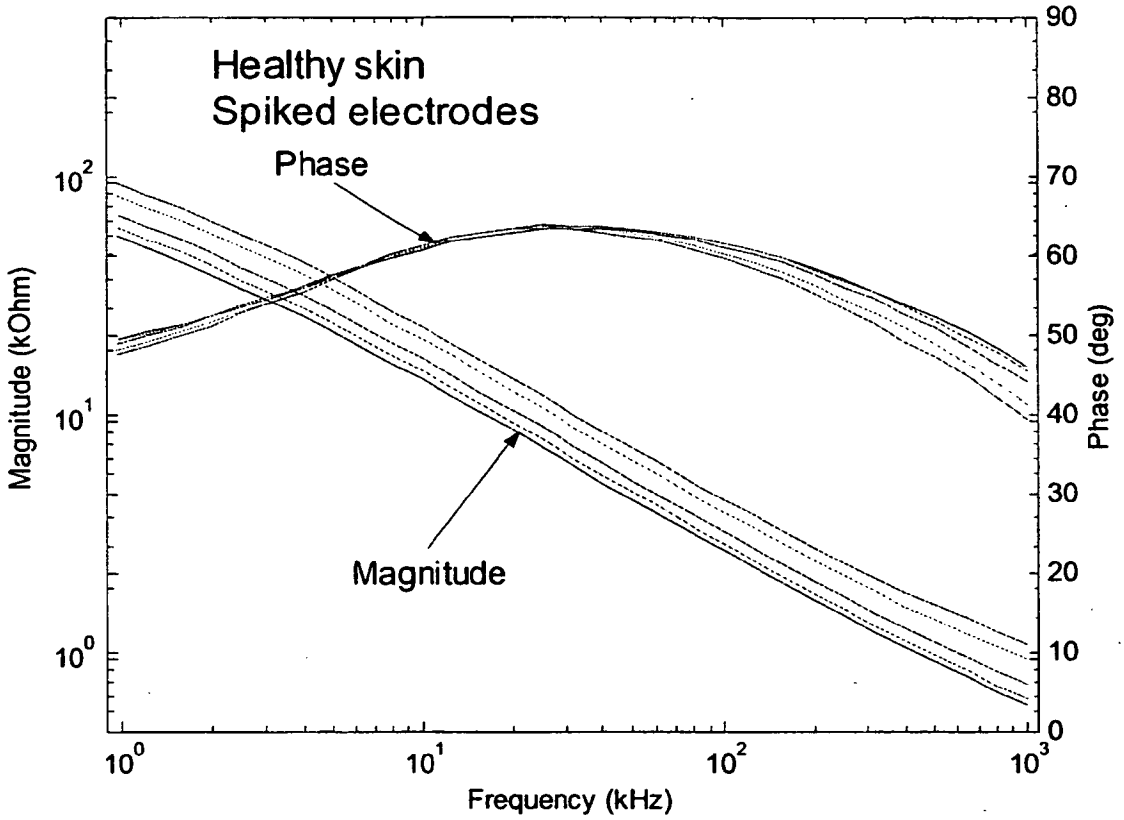

Healthy skin
Spiked electrodes
Phase
Magnitude
Magnitude (kOhm)
Phase (deg)
Frequency (kHz)
10^0
10^1
10^2
10^3
0
10
20
30
40
50
60
70
80
90

Figure 8(b)

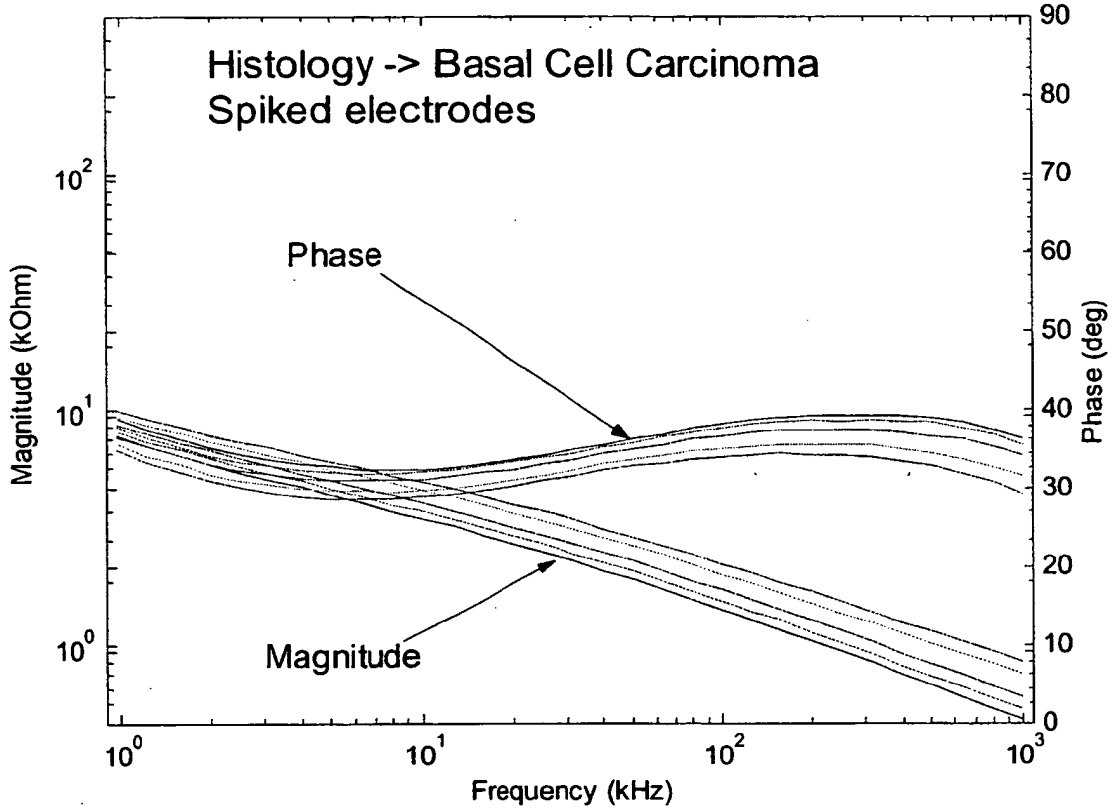

Histology -> Basal Cell Carcinoma
Spiked electrodes
Phase
Magnitude
Magnitude (kOhm)
Phase (deg)
Frequency (kHz)
10^0
10^1
10^2
10^3
0
10
20
30
40
50
60
70
80
90

Figure 8(c)

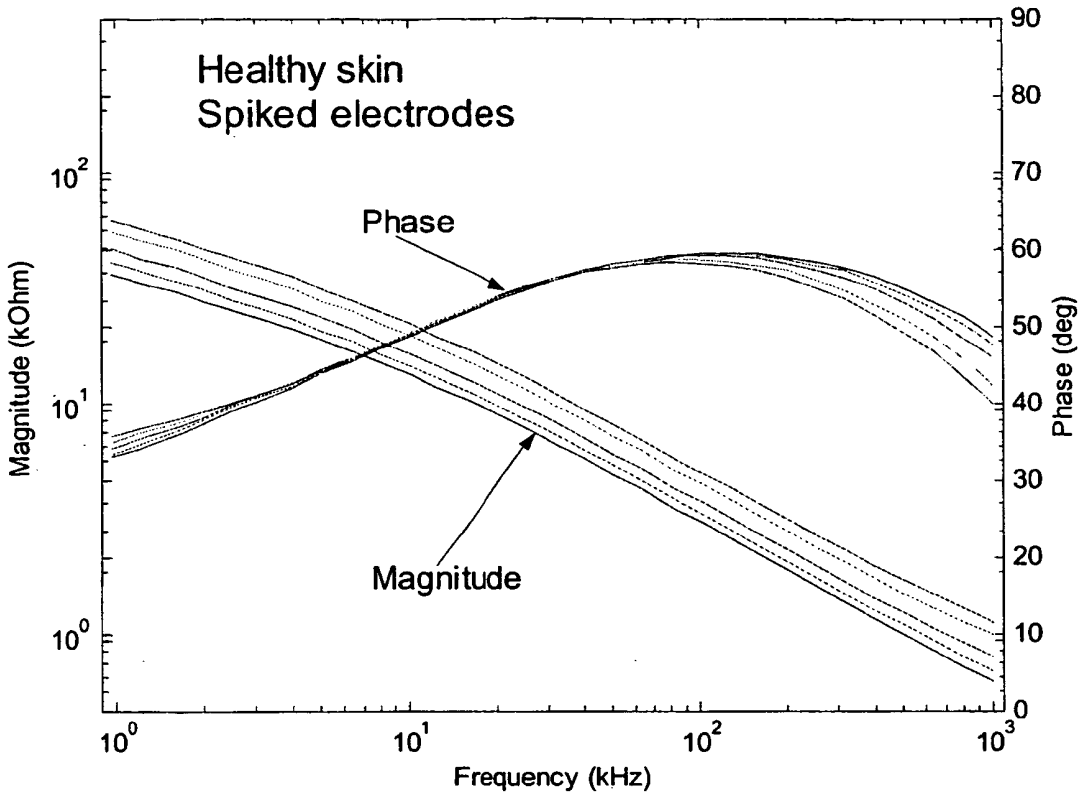

Healthy skin
Spiked electrodes
Phase
Magnitude
Magnitude (kOhm)
Phase (deg)
Frequency (kHz)
10^0
10^1
10^2
10^3
0
10
20
30
40
50
60
70
80
90

Figure 8(d)

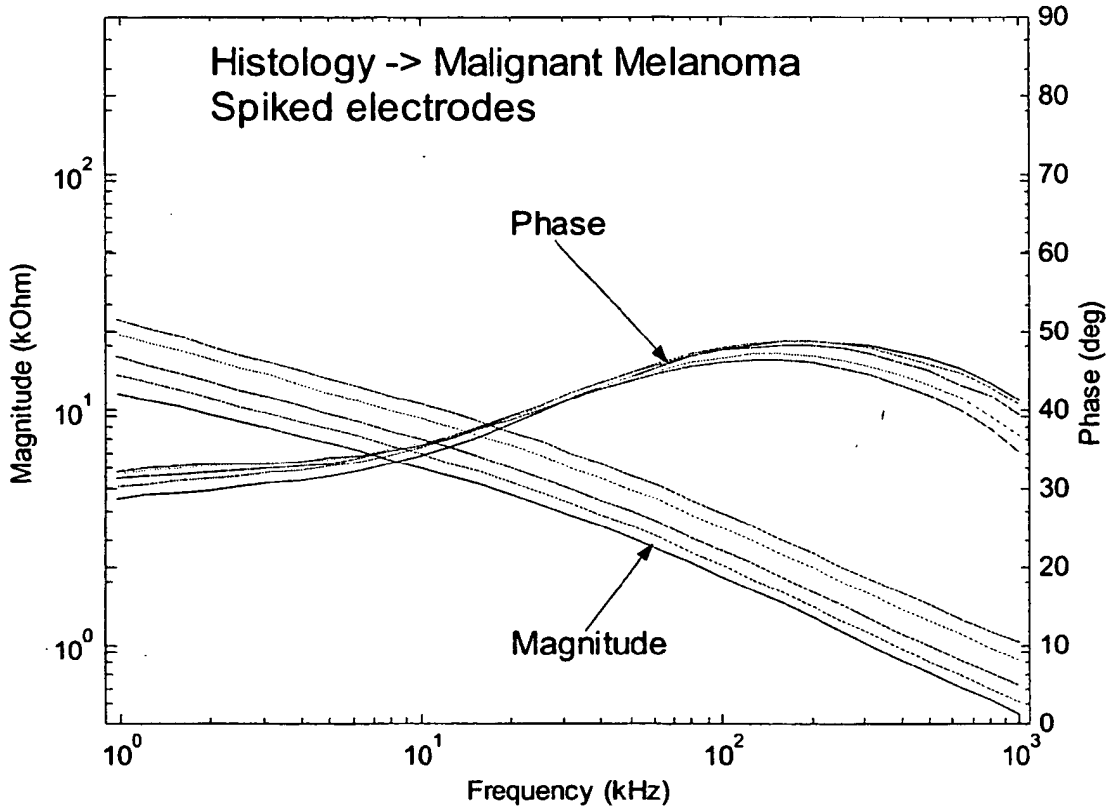
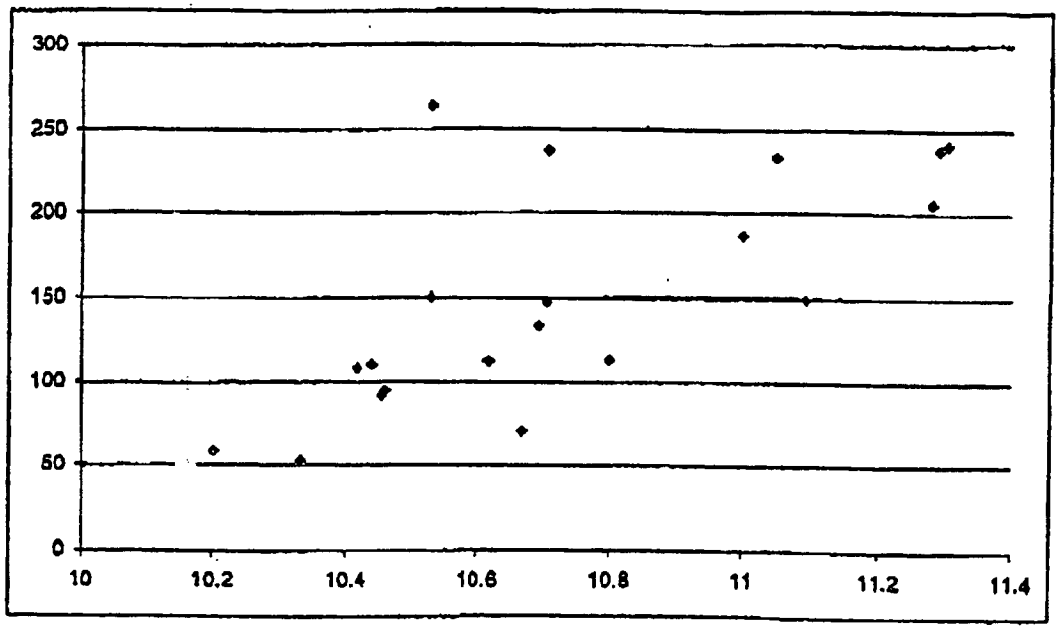

Histology -> Malignant Melanoma
Spiked electrodes
Phase
Magnitude
Magnitude (kOhm)
Phase (deg)
Frequency (kHz)
10^0
10^1
10^2
10^3
0
10
20
30
40
50
60
70
80
90

Figure 9



REFERENCES CITED IN THE DESCRIPTION

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专利名称(译)	使用阻抗测量确定生物条件		
公开(公告)号	EP1437091B1	公开(公告)日	2011-04-20
申请号	EP2003023156	申请日	2003-10-10
[标]申请(专利权)人(译)	OLLMAR STIG ABERG PETER NICANDER INGRID		
申请(专利权)人(译)	OLLMAR，STIG ABERG，PETER NICANDER，INGRID		
当前申请(专利权)人(译)	SCIBASE AB		
[标]发明人	OLLMAR STIG ABERG PETER NICANDER INGRID		
发明人	OLLMAR, STIG ÅBERG, PETER NICANDER, INGRID		
IPC分类号	A61B5/053 A61B5/00 A61B5/103		
CPC分类号	A61B5/0531 A61B5/061 A61B5/14532 A61B5/411 A61B5/444 A61B5/6839		
优先权	60/417561 2002-10-11 US		
其他公开文献	EP1437091A1		
外部链接	Espacenet		

摘要(译)

用于诊断生物学病症和用于无创测定受试者血液中物质（葡萄糖）浓度的装置和方法，该方法包括以下步骤：（a）将导电探针放置在皮肤表面上该探针包括多个电极，每个电极包括尖钉，所述尖钉彼此横向间隔开并且具有足够的长度以穿透角质层;（b）使电流通过电极以获得皮肤的阻抗值;（c）将阻抗转换成所述浓度。