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(54) Title: BIOELECTRONICS SYSTEM FOR AN IMPLANT DEVICE

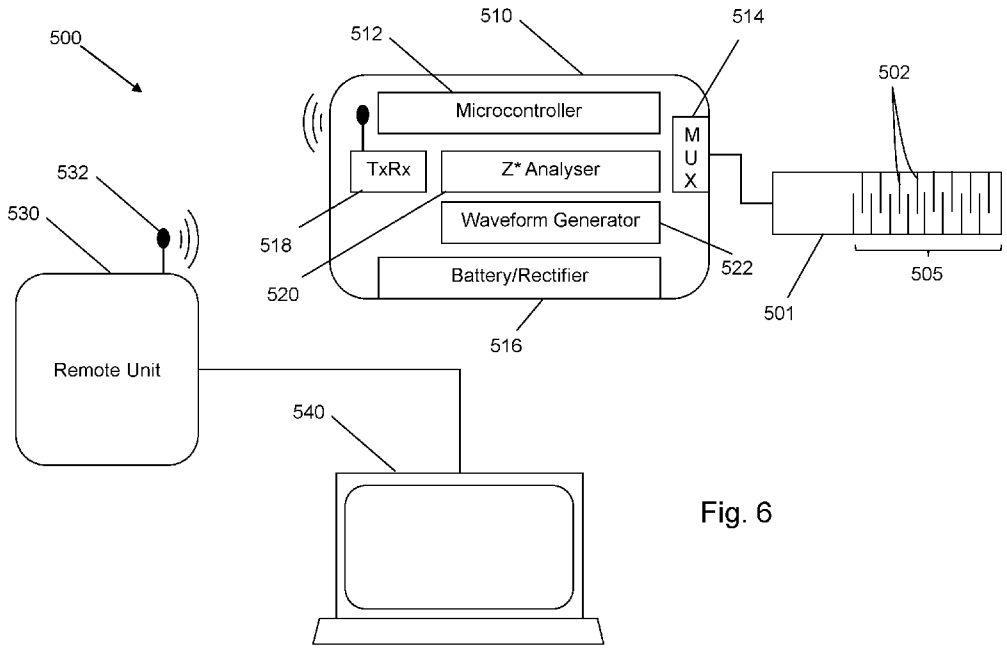


Fig. 6

(57) Abstract: A bioelectronics system is provided. The bioelectronics system comprises an implant device having multiple pairs of electrodes integrated therein and an implantable control electronics module. The implantable control electronics module comprises: a multiplexer configured to enable a separate signal to be independently applied across each pair of electrodes, a microcontroller, and a wireless communication module. The implantable control electronics module further comprises either: (i) an impedance analyser configured to measure a respective complex impedance across each pair of electrodes, wherein the microcontroller is configured to encode the measured complex impedances as complex impedance information, and the wireless communication module is configured to transmit the complex impedance information to a remote unit for analysis; or (ii) a waveform generator configured to apply respectively determined waveform profiles across each pair of electrodes, wherein the microcontroller is configured to determine the respective

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waveform profiles to be applied across each pair of electrodes based on instructions received, from a remote unit and by the wireless communication module, to deliver an electrical signal across the multiple pairs of electrodes.

BIOELECTRONICS SYSTEM FOR AN IMPLANT DEVICE

Field of the Invention

The present invention relates to a bioelectronics system used with an implant device and particularly, although not exclusively, to such systems as applicable to impedance-based analysis and/or electro-therapy using an implantable control electronics module connected to the implant device. Where the implant device is a vascular implant or another transluminal device, e.g. a graft or stent, the bioelectronics system may be used in the detection and prevention of restenosis or thrombosis, for example.

Background

Chronic kidney disease affects over 843.6 million people worldwide, and is anticipated to be the fifth largest cause of mortality by the year 2040. In the United Kingdom alone, over 60,000 patients suffer from chronic kidney disease and the associated cost of treatment is very high. For example, in the financial year 2009-2010, the National Health Service in England spent almost £1.5 billion on treatment for patients with chronic kidney disease.

A common part of treatment for patients with chronic kidney disease is haemodialysis, a schematic of which is shown in Figure 1. Figure 1 shows a patient 100 undergoing a haemodialysis treatment via a vascular access region 102. Haemodialysis treatments are typically repeated frequently (often multiple times a week) meaning that treatment lines 104a, 104b are inserted into and removed from the vascular access region 102 on a regular basis. This can cause the vascular access region 102 to deteriorate to the point that it is no longer possible to find viable blood vessels that the treatment lines 104a, 104b can be inserted into.

For this reason, arteriovenous fistulas (AVFs) and arteriovenous grafts (AVGs) are often created or inserted into the vascular region 102 of the patient to provide a long-lasting vascular access point for the treatment lines 104a, 104b. AVFs are formed by connecting an artery 106 of the patient 100 to a nearby vein 108. The AVF has a large surface area to allow for repeated cannulation with the treatment lines 104a, 104b. However, AVFs suffer from high clotting and infection rates, and when using an AVG the patient is able to undergo haemodialysis treatment immediately after the AVG is installed, while they must wait several weeks for an AVF to mature so as to be useable in haemodialysis treatment.

For this reason, it may be considered preferable to use AVGs. AVGs may be inserted by connecting the artery 106 of the patient 100 to a nearby vein 108 using a graft 110.

However, AVGs (as illustrated in Figure 2) typically require regular maintenance over the implant's lifetime because they are highly susceptible to both vascular restenosis (vessel narrowing), and thrombosis (blood clotting). As can be seen from Figure 2, the implantation of the arteriovenous graft 110 requires the application of one or more sutures 112. The suturing of the graft 110 to the blood vessels 106, 108 of the patient 100 leads to a wound response in the form of neointimal hyperplasia through the migration and proliferation of smooth muscle cells 114 from the tunica media 116 (vessel wall) of the

blood vessel 104, 106 to an interior luminal surface of the graft 110 due to the removal of endothelial cells in the tunica intima. The proliferation of these smooth muscle cells 114 causes the lumen (channel) of the graft 100 to remodel and narrow – i.e., vascular restenosis. Over time, this restenosis can initiate the formation of a clot 118 that further reduces and, eventually, entirely cuts off the flow through the graft 110. This restenosis and thrombosis of AVGs 110 is the leading limitation in their wider implantation as up to 50% of all AVGs require intervention within one year of implantation to reverse the effects of vascular restenosis. Intervention is both costly and risky as all surgery carries inherent risks. Moreover, the constant monitoring of AVGs to check for the effects of vascular restenosis is usually only carried out in a hospital environment at irregular intervals. This is therefore a suboptimal solution for the monitoring of AVG performance.

Meanwhile, human disease caused by blocked blood vessels are responsible for significant human suffering and contribute to a global economic health burden. Vascular pathologies initiated by blood clotting or other tissue-wound responses are a leading cause in heart attacks, strokes, and peripheral vascular diseases. As with arteriovenous grafts, the monitoring and treatment of occluded blood vessels is costly, inefficient, and risky.

There is therefore a need to provide an improved system and methodology for monitoring and treating the occlusion of implants, particularly vascular implants.

The present invention has been devised in light of the above considerations.

Summary of the Invention

In a general sense, the present invention provides a bioelectronics system that, by virtue of the independent activation of electrodes within an implanted device, is configured to determine a distribution (and type) of tissue in the vicinity of an implant and/or deliver electrical waveforms to break down, reduce or remove said tissue.

This achieves the benefit of both efficiently (and potentially continuously) monitoring the effects of restenosis on these implants, and providing an efficient, non-surgical means of reducing – or even eliminating – the restenosis. As such, the bioelectronics system disclosed herein has the potential to significantly improve patient outcomes and quality of life in a variety of settings, including haemodialysis.

In a first aspect, there is provided a bioelectronics system comprising: an implant device, e.g., a vascular implant, having a tissue interface portion that has multiple pairs of electrodes disposed therein; and an implantable control electronics module communicably connectable to the vascular implant device. The implant device may take any conventional form. For example, it may be configured as a vascular or endovascular device such as a graft or stent, or a heart valve. The tissue interface portion may be a part of the implant device that is intended to be located at a transition between biological tissue and the implant device when in use. For example, the tissue interface portion may be formed at one or both axial ends of a tubular graft or stent. The implant device may have a plurality of tissue interface portions. The

implantable control electronics module may comprise: a multiplexer configured to independently address each pair of electrodes, e.g., to enable a separate signal to be independently applied across each pair of electrodes; an impedance analyser connectable with the multiple pairs of electrodes via the multiplexer and configured to measure a respective complex impedance between each pair of electrodes; a microcontroller configured to encode the measured complex impedances as complex impedance information; and a wireless communication module configured to transmit the complex impedance information to a remote unit for analysis.

Such a bioelectronics system may be particularly beneficial because it facilitates straightforward and, optionally, regular monitoring of the build-up of tissue in the vicinity of the implant device when it is implanted in a patient.

The electrodes of the bioelectronics system may define a plurality of electrical contacts for the purpose of achieving electrical impedance spectroscopy, EIS, and/or may define any number of electrodes of an interdigitated electrode array.

The amount of tissue build-up and the type of tissue build-up may be inferred by analysing the measured complex impedances. For example, the magnitude and/or phase (relative to the phase of the electrical signal applied across the corresponding pair of electrodes) of the measured complex impedances may be indicative of a type and/or quantity of tissue building up around the implant device. In some examples, a variation in the magnitude and/or phase of the measured complex impedances across different frequencies may also be indicative of a type and/or quantity of tissue building up around the implant device.

In some embodiments, the impedance analyser may be configured to measure one or more of the respective complex impedances over a range of frequencies.

As mentioned above, a variation in the magnitude and/or phase of the measured complex impedances across different frequencies may be indicative of a type and/or quantity of tissue building up around the implant device. The term “different frequencies” in this context may be understood to mean that electrical signals are applied across the pairs of electrodes with those signals being alternating current signals with different frequencies. The frequencies of the applied alternating current signals may be varied across different pairs of electrodes or over time for a given pair of electrodes.

The complex impedance can be considered to have a resistive component that is, broadly, independent of the frequency of the applied alternating current signal (at least directly – there may be an indirect dependence arising from a functional relationship between the materials’ resistive properties and the frequency of the applied alternating current signal). This resistive component of the complex impedance may principally depend on the resistive properties of the materials through which the electrical signal is propagated (e.g., the ohmic resistance of the tissue building up in the vicinity of the implant device)

The complex impedance can also be considered to have a reactive component that is dependent on the frequency of the applied alternating current signal. This reactive component may have a capacitive reactance inversely proportional to the frequency of the alternating current signal, and inversely

proportional to a capacitance of the material through which the electrical signal is propagating. The reactive component may also have an inductive reactance that is proportional to both the frequency of the alternating current signal, and to an inductance of the material through which the electrical signal is propagating.

In formulaic terms, the complex impedance may therefore be expressed as:

$$Z^* = R + j\left(2\pi fL - \frac{1}{2\pi fC}\right)$$

where Z^* is the complex impedance of a material, R is its resistance, j is the imaginary number ($j = \sqrt{-1}$), f is the frequency of the applied alternating current signal, L is the inductance of the material, and C is the capacitance of said material.

In the context of the present disclosure, the magnitude of the impedance may be measured by the bioelectronics system. Meanwhile, an application-dependent calibration resistor may be used to measure the gain factor associated with the impedance. In such contexts, the impedance and phase angle may be determined as:

$$Z = \frac{1}{Gain\ Factor \times |Z^*|}$$

And the phase of the impedance may be determined as:

$$\phi = \tan^{-1}\left[\frac{2\pi fL - 1/2\pi fC}{R}\right]$$

In some embodiments, the complex impedance information may include a map of the measure complex impedances based on the positions of each pair of electrodes in the implant device. For example, the multiple pairs of electrodes may be arranged around the circumference of a tubular implant device, where each pair of electrodes that is addressable by the multiplexer corresponds to a specific location on the circumference. A map of the locations, e.g., within the frame of reference of the implant device, may be used by the microcontroller when encoding the measured complex impedances as the complex impedance information. For example, the impedance data may be interpolated to create an impedance tomographic map, or other similar representation.

The multiple pairs of electrodes may be provided as an array of independent electrodes elements that are pairwise combinable by the multiplexer under the instruction of the microcontroller. In such an arrangement, the pairs of electrodes may not be predetermined, e.g. before the implant device is deployed. Instead, the microcontroller may be configured to select electrodes to form each pair when the device is in use. Any given electrode may belong to a plurality of pairs. In an example where the array of electrodes is arranged around the circumference of a tubular implant device, electrode pairs may be selected to measure complex impedance both around the circumference of the implant device and across the space enclosed by the device. This gathered impedance data may be interpolated to create an impedance tomographic map, or other suitable representation of the distribution of impedances.

The tissue interface portion may comprise a biocompatible structure having the electrodes formed or otherwise disposed therein or thereon. The electrodes may be integrated with the tissue interface portion, i.e., formed within the structure thereof.

As separate electrical signals can be independently applied across each pair of electrodes in the implant device, it may be possible for the microcontroller – as part of the analysis associated with encoding the measured complex impedances as the complex impedance information – to obtain information about the positional distribution across the dimensions of the implant device for both the quantity and type of tissue build-up. In other words, by providing pairs of electrodes that are independently addressable it is possible to encode a map that can display the quantity of tissue build-up and/or the type of tissue in that tissue build-up in the vicinity of the implant device across its dimensions.

In some embodiments, the remote unit may be configured to transmit the complex impedance information, and/or analysed complex impedance information to a third-party device.

In some examples, the analysed complex impedance information may be used to calculate other pertinent clinical values such as rate of flow within the implant,

In other words, the wireless communication unit of the control electronics module may be configured only for short-term low-power communication (e.g., via short-distance radio-frequency transmissions, Bluetooth® communication, or similar). When in use, therefore, the patient may keep the remote unit on or close to their person (e.g., as a wearable band) so that it may receive the complex impedance information (e.g., a tissue map) from the wireless communication module of the implantable control electronics module. The remote unit may then be configured for long-range communication (e.g., secure mobile data communication such as 4G or 5G) with a third-party, for example the patient's doctor or another suitable healthcare professional that can evaluate the need for medical intervention with respect to the implant device (e.g., in the case of vascular restenosis of a vascular implant, such as an arteriovenous graft).

In a further aspect, there is provided a bioelectronics system comprising a similar implant device to that discussed above, but used with an implantable control electronics module that is configured to enable the electrodes to be used in therapy, i.e., to remove or reduce unwanted tissue build up. In this aspect, the implantable control electronics module may comprise: a multiplexer configured to independently address each pair of electrodes; a wireless communication module configured to receive instructions, e.g., from a remote unit, to deliver an electrical signal across the multiple pairs of electrodes; a microcontroller configured to determine a respective waveform profile to be applied across each pair of electrodes based on the received instructions; and a waveform generator connectable with the multiple pairs of electrodes via the multiplexer and configured to apply the respectively determined waveform profiles across each pair of electrodes.

In some examples, a DC source may be used to deliver a DC impulse as opposed to an alternating current waveform.

The delivery of a waveform profile across one or more of the pairs of electrodes may induce electroporation in the cells of tissue in the vicinity of the implant device (i.e., in tissue building up around the implant device). Electroporation is typically a reversible and transient increase in cell permeability induced by the application of an electric field (e.g., in the form of an electrical signal). The applied electric field creates hydrophilic pores in the cell membranes. When applied at strengths of around 100 V cm^{-1} over time periods of up to 1 ms, the induced electroporation can yield nanopores that are of a sufficient size, and remain open for a sufficient amount of time, to enable the delivery of dyes and/or genetic reagents to a cell membrane.

When the strength of the applied electric field is increased to 1-10 kV cm^{-1} and/or is applied for longer time periods (e.g., longer than 1 ms), then cell death can be induced by acute necrosis. Under the application of so much energy, the intracellular cytoplasmic milieu is extruded outside the cell envelope meaning that the homeostasis of the cell can no longer be maintained. This damage is irreparable and causes the cell to die.

In some embodiments, wherein the one or more waveform profiles are configured to induce apoptosis in cells in the vicinity of the implant device, when in use.

The waveform profile may have any suitable waveform shape such as a sawtooth profile, a square wave profile, or a sinusoidal profile.

The peak-to-peak voltage of the waveform profile may, for example, by 0.2 V or more, 0.5 V or more, 1 V or more, 1.5 V or more, 2 V or more, 2.5 or more, 3 V or more, or 5 V or more.

The frequency of the waveform profile may be 10 kHz or more, 25 kHz or more, 50 kHz or more, or 100 kHz or more.

The pulse duration of the waveform profile may be 1 minute or more, 2 minutes or more, 5 minutes or more, or 10 minutes or more.

In a particular example, the waveform profile may be a sinusoidal waveform having a peak-to-peak voltage of approximately 2 V, a frequency of 40 kHz, and a pulse duration of 2 minutes.

The bioelectronics system may be configured to deliver the waveform repeatedly over the course of a treatment. The treatment may last for between 1 minute and 60 minutes and involve the repeated application of generated waveform profiles. In a particular example, the bioelectronics system may be configured to deliver a treatment by repeatedly delivering a waveform profile having a sinusoidal waveform having a peak-to-peak voltage of approximately 2 V, a frequency of 40 kHz, and a pulse duration of 2 minutes, with a rest-time (i.e., time between successive waveform profiles) of approximately 3 minutes.

It may be preferable for the waveform profile to be configured such that the electrical signal applied across the pair of electrodes induces apoptosis in the cells of tissue in the vicinity of the implant device.

In contrast with induced necrosis which promotes inflammation, apoptosis is a more controlled (low inflammation) form of cell death that provides a more targeted approach and reduces the risk of

collaterally damaging surrounding tissue that need not be destroyed. Apoptosis may also induce the so-called “bystander effect” whereby controlled cell death is further induced at a distance local from the origin of transactivation. Apoptosis may be initiated by applying high field strength pulses over very short periods of time.

For example, the electrical signal may be applied with electric field strengths in the range of 10-100 kV cm^{-1} and/or over a time period ranging from 1 ns to 1 µs.

In some embodiments, the waveform generator may include an amplifier to amplify the signal to a predetermined voltage.

An amplifier may be needed to increase the field strength to a sufficient level to be able to induce apoptosis. It may be preferable to only amplify the field strength at a position proximal to the electrodes integrated within the implant device so that high currents are not propagating through the entire bioelectronics system, thereby risking unnecessary heating effects which could induce discomfort in a patient within which the implant device and the control electronics module are implanted.

In some embodiments, the remote unit may be configured to receive the instructions from a third-party device.

In other words, the wireless communication unit of the control electronics module may be configured only for short-term low-power communication (e.g., via short-distance radio-frequency transmissions, Bluetooth® communication, or similar). When in use, therefore, the patient may keep the remote unit on or close to their person so that it may transmit the instructions to the microcontroller. Meanwhile, the remote unit may be configured for long-range communication with a third-party, for example the patient’s doctor or another suitable healthcare professional that can evaluate the need for medical intervention with respect to the implant device (e.g., in the case of vascular restenosis of a vascular implant, such as an arteriovenous graft). This long-distance remote individual may then be able to provide the necessary instructions for the bioelectronics system to be able to deliver a waveform profile that achieves the desired effect (e.g., apoptosis in the cells of tissue building up around the implant, when in use).

The bioelectronics system may contain the functionalities of both aspects described above. For example, the control electronics module may further comprise an impedance analyser connectable with the multiple pairs of electrodes via the multiplexer and configured to measure a respective complex impedance between each pair of electrodes, wherein the microcontroller is further configured to encode the measured complex impedances as complex impedance information, and wherein the wireless communication module is configured to transmit the complex impedance information to a remote unit for analysis.

In some embodiments, the functionalities may be provided by separate control modules (which may be implantable independently, e.g., in different locations). For example, the implantable control electronics module may be a first implantable control electronics module, and the system may further comprise a second implantable control electronics module. The second implantable control electronics module may comprise: a multiplexer configured to enable a separate signal to be independently applied across each

pair of electrodes; an impedance analyser configured to measure a respective complex impedance between each pair of electrodes; a microcontroller configured to encode the measured complex impedances as complex impedance information; and a wireless communication module configured to transmit the complex impedance information to the remote unit for analysis.

A bioelectronics system having both functionalities (in, effectively, a closed-loop system) may be particularly beneficial. With a first functionality, the bioelectronics system facilitates straightforward and, optionally, regular monitoring of the build-up of tissue in the vicinity of the implant device when it is implanted in a patient. As discussed above, the amount of tissue build-up and the type of tissue involved in the tissue build-up may be inferred by analysed the measured complex impedances. For example, the magnitude and/or phase (relative to the phase of the electrical signal applied across the corresponding pair of electrodes) of the measured complex impedances may be indicative of a type and/or quantity of tissue building up around the implant device. In some examples, a variation in the magnitude and/or phase of the measured complex impedances across different frequencies may also be indicative of a type and/or quantity of tissue building up around the implant device.

Meanwhile, the second functionality, the delivery of waveform profiles across the pairs of electrodes, may achieve the benefit of killing and removing the cells of the tissue building up in the vicinity of the implant device – for example, by inducing apoptosis.

In this way, the bioelectronics system may be able to both detect and remedy tissue build-up in the vicinity of implant devices so that their functional lifetime is increased without requiring surgical interventions. This will thereby improve patient outcomes because they are not exposed to the risk of surgery but can continue to benefit from the effects of their implant.

In some embodiments, one or more of: (i) the multiplexers of the first and second implantable control electronics modules; (ii) the microcontrollers of the first and second implantable control electronics modules; and (iii) the wireless communication modules of the first and second control electronics modules are common shared components between the first and second control electronics modules.

In other words, the first and second implantable control electronics modules may share a common multiplexer, a common microcontroller, a common wireless communication module, a common multiplexer and a common microcontroller, a common multiplexer and a common wireless communication module, a common microcontroller and a common wireless communication module, or a common multiplexer and a common microcontroller and a common wireless communication module.

By sharing components in common across the first and second control electronics modules, it is possible to reduce the size and complexity of the overall bioelectronics system. With a reduced footprint (i.e., size) it is easier to find the necessary space to be able to implant the first and second control electronics modules in a patient with both connected to the electrodes of the implant device.

In some embodiments, the impedance analyser may be configured to measure one or more of the respective complex impedances over a range of frequencies.

As discussed above, a variation in the magnitude and/or phase of the measured complex impedances across different frequencies may be indicative of a type and/or quantity of tissue building up around the implant device. The term “different frequencies” in this context may be understood to mean that electrical signals are applied across the pairs of electrodes with those signals being alternating current signals with different frequencies. The frequencies of the applied alternating current signals may be varied across different pairs of electrodes or over time for a given pair of electrodes. The variation in frequencies may facilitate a comparison between the resistive and reactive components of the complex impedances to provide more nuanced and/or detailed analysis.

In some embodiments, the complex impedance information may include a map of the measured complex impedances based on the positions of each pair of electrodes in the implant device.

As discussed above, the multiplexer(s) of the control electronics module(s) may allow separate electrical signals to be independently applied across each pair of electrodes integrated into the implant device, it may therefore be possible for the microcontroller – as part of the analysis associated with encoding the measured complex impedances as the complex impedance information – to obtain information about the positional distribution across the dimensions of the implant device for both the quantity and type of tissue build-up. In other words, by providing pairs of electrodes that are independently activable it is possible to encode a map that can display the quantity of tissue build-up and/or the type of tissue in that tissue build-up in the vicinity of the implant device across its dimensions.

In some embodiments, the remote unit may be configured to transmit the complex impedance information, and/or analysed complex impedance information to a third-party device.

In other words, as discussed above, the wireless communication unit of the control electronics module may be configured only for short-term low-power communication (e.g., via short-distance radio-frequency transmissions, Bluetooth ^{RTM} communication, or similar). When in use, therefore, the patient may keep the remote unit on or close to their person so that it may receive the complex impedance information (e.g., a tissue map) from the wireless communication module of the implantable control electronics module. The remote unit may then be configured for long-range communication with a third-party, for example the patient’s doctor or another suitable healthcare professional that can evaluate the need for medical intervention with respect to the implant device (e.g., in the case of vascular restenosis of a vascular implant, such as an arteriovenous graft). Alternatively a decision could be made by a microcontroller in the implant device itself such that therapy may be applied automatically by the bioelectronics system.

In some examples, the (or each if there is more than one) implantable control electronics module may be powered by a respective (or common) battery.

In some embodiments, of either aspect, the implantable control electronics module(s) may further comprise a rectifier configured to receive a wireless transmission and convert the wireless transmission to a direct current signal to power said implantable control electronics module.

A rectifier may be a preferable source of power, in the form of a wireless power circuit, (as opposed to a battery) because it ensures that the control electronics module(s) and the components thereof are only

powered up (and therefore only generating electricity and heat) when it is necessary or desired by the patient/user of the bioelectronics system. Additionally, by providing the power source as a rectifier configured to convert received alternating current radio-frequency transmissions into a direct current power source, it is possible to extend the lifetime of the bioelectronics system indefinitely because a rectifier will always be activated by the receipt of an alternating current radio-frequency transmission, while a battery will eventually run out of charge and no longer be able to power the bioelectronics system.

In some examples, power may be delivered to the bioelectronics system via any other suitable wireless means, such as ultrasound.

In some embodiments, of either aspect, the implantable control electronics module(s) may be contained within a hermetically sealed housing.

In some examples, the implantable control electronics module(s) may be miniaturised to a series of application-specific integrated circuits (ASICs), thereby creating a programmable system on a chip (PSoC) contained within the hermetically sealed housing, and directly or indirectly connected to the implant electrodes.

By providing the control electronics module(s) within a hermetically sealed housing, it is possible to ensure that the module(s) is safe for percutaneous (i.e., through the skin) implantation to a target vessel in the body of a patient, in particular that the risk of ohmic heating of any circuitry does not damage any tissue surrounding the module(s).

If the system comprises first and second implantable control electronics modules, they may be contained within a common hermetically sealed housing. This may be particularly beneficial as it may reduce the overall size of the bioelectronics system making it easier to implant into the body of a patient, thanks to the system's reduced footprint.

In some embodiments, of either aspect, the hermetically sealed housing comprises a body made from a radio frequency insulating material, wherein the body may comprise a radio frequency window through which signals to or from the wireless communication module are transmissible, e.g., to permit communication with the remote unit.

In other words, the majority of the hermetically sealed housing may be formed from a de facto radio frequency shield – that is, a radio opaque shield. For example, the hermetically sealed housing may be formed (at least in part) from any suitable material such silicone, ceramic, titanium (singly or in any combination), or similar.

In a preferred example, the hermetically sealed housing is formed from titanium. Titanium may be a particularly suitable choice because it is a particularly effective radio-frequency shield and exhibits an exceptional resistance to corrosion in the body of a patient making it very durable and long-lasting – all of which are desirable qualities for an implantable housing.

Meanwhile, the radio frequency window may be formed from any suitable durable material that is transparent to radio frequency signals. For example, the radio frequency window may be formed from any

suitable thermoplastic or biocompatible ceramic. One such example of a suitable thermoplastic is polylactic acid (PLA).

In some embodiments, of either aspect, the multiple pairs of electrodes may consist of an array of interdigitated electrodes.

An interdigitated configuration may be particularly beneficial because, in such a configuration, it is possible to minimise the distance between the electrodes in each pair of electrodes. In this way, a higher electric field may be achieved with a modest voltage, thus allowing lower voltages to be used. This aids the) collection of complex impedance data and/or delivery of a generated waveform profile. This, accordingly, makes the operations of the bioelectronics systems described herein more efficient.

In some examples, of any of the aspects or embodiments described herein, the electrodes may be formed from gold. Gold may be a particularly suitable choice because it is a good conductor of electricity, and does not suffer from oxidation or corrosion – even in the wet and oxygen-rich environments in which implant devices are typically implanted into a patient.

In some examples, of any of the aspects or embodiments described herein, the bioelectronics system may be configured to operate continuously. For example, the bioelectronics system may be configured to continuously monitor measured complex impedance data when the implant device is implanted so that the build-up of tissue in the vicinity of the implant device can be continuously monitored.

In some examples, of any of the aspects or embodiments described herein, the bioelectronics system may be configured to operate automatically or semi-automatically.

For example, the monitoring functionality of the bioelectronics system (i.e., the measurement and analysis of complex impedance data/information) may be carried out continuously, substantially continuously, or at regular intervals. For example, the complex impedances may be measured on a monthly, fortnightly, weekly, daily, or hourly basis, or at another suitable interval.

Meanwhile, the delivery of the generated waveform profile(s) may be carried out automatically or semi-automatically based on the remote unit (or a third-party device) determining that the measured complex impedances are indicative of sufficient tissue build-up in the vicinity of the implant device to warrant intervention. In other words, the delivery of the generated waveform profile(s) may be automatically triggered if one or more of the measured complex impedances passes a predetermined threshold that is indicative of significant tissue build-up in the vicinity of the implant device. By “significant” it should be understood that the tissue build-up is sufficient to substantially increase the risk of restenosis and/or thrombosis in the implant device.

In some examples, the delivery of the generated waveform profile(s) may be carried out on a regular or semi-regular basis to pre-emptively reduce the risks of restenosis and/or thrombosis in the implant device. For example, the generated waveform profile(s) may be delivered on a monthly, fortnightly, weekly, daily, or hourly basis, or at any other suitable time interval.

In some examples, of any of the aspects or embodiments described herein, the bioelectronics system may be configured to operate “on demand”. For example, a medical professional at a third-party device in communication with the remote unit and/or a patient in possession of the remote unit and in whom the bioelectronics system is implanted may decide to carry out complex impedance measurements and/or deliver generated waveform profiles based on what they decide to be necessary or desirable.

In some embodiments, of either aspect, the implant device may be an arteriovenous graft.

The bioelectronics systems described herein may be particularly applicable to monitoring and reducing vascular restenosis and thrombosis in arteriovenous grafts, cardiovascular and non-cardiovascular stents and heart valves.

In some examples, the implant device may instead be a stent, an artificial valve, a vena cava filter, or an artificial heart pump, or any other implant through which blood is required to flow within the patient. Such devices may all benefit from the monitoring and intervention that is available via the bioelectronics systems described herein to monitor and reduce vascular restenosis and thrombosis.

In some embodiments, of either aspect, the remote unit may be part of a wearable device.

For example, the remote unit may be a smart-watch worn by the user having an application installed thereon that enables the smart-watch to carry out the functionality of the remote unit described herein. Alternatively, the remote unit may be a smartphone with an application installed thereon that enables the smartphone to carry out the functionality of the remote unit described herein. Additionally or alternatively, the remote unit may be any wearable device with the functionality described herein. By providing the remote unit as a wearable device, it is more convenient for the patient to keep the remote unit on their person, thereby ensuring that the remote unit stays within communicable range of the control electronics module(s) of the bioelectronics system when it is implanted in the patient.

The invention includes the combination of the aspects and preferred features described except where such a combination is clearly impermissible or expressly avoided.

Summary of the Figures

Embodiments and experiments illustrating the principles of the invention will now be discussed with reference to the accompanying figures in which:

Figure 1 shows a patient undergoing a haemodialysis treatment via a vascular access region.

Figure 2 is an illustration of the build-up of tissue in the vicinity of an arteriovenous graft post-implantation.

Figure 3 is an illustration of an implanted bioelectronics system including an arteriovenous graft.

Figure 4 is a schematic of a bioelectronics system configured to measure complex impedance values.

Figure 5 is a schematic of a bioelectronics system configured to generate and deliver waveform profiles to the vicinity of an implant device.

Figure 6 is a schematic of a bioelectronics system configured to both measure complex impedance values, and generate and deliver waveform profiles to the vicinity of an implant device.

Figure 7 is a schematic of all the possible pairings of electrodes within an exemplary bioelectronics system superimposed.

Figure 8 shows a series of stimulated tissue maps where excitation has been induced across different pairs of electrodes in the presence of blood only, emboli, and occlusive clots.

Figure 9a shows a photograph of an exemplary array of interdigitated electrodes.

Figure 9b shows a magnified image of the array of interdigitated electrodes of Fig. 9a.

Figure 9c shows a blown-up schematic of an individual electrode within the interdigitated arrays of Figures 9a and 9b.

Figure 10 shows various measured complex impedance data by a bioelectronics system.

Figure 11 shows a comparison of data collected by a bioelectronics system for blood clot and human plaque detection in an arteriovenous graft.

Figure 12 shows results of impedance measurements from preclinical studies using a bioelectronics system that includes an arteriovenous graft.

Figure 13 shows the results of experiments into the effectiveness of inducing apoptosis in cells in the vicinity of an implant device.

Figure 14 shows the results of experiments illustrating differential cell-killing efficacy in different contexts.

Detailed Description of the Invention

Aspects and embodiments of the present invention will now be discussed with reference to the accompanying figures. Further aspects and embodiments will be apparent to those skilled in the art. All documents mentioned in this text are incorporated herein by reference.

As discussed above, Figure 1 shows a patient 100 undergoing haemodialysis treatment via a vascular access region 102, while Figure 2 is an illustration of the build-up of tissue (e.g., smooth muscle cells 114 and blood clots 118) in the lumen of an implanted arteriovenous graft 110.

Figure 3 is an illustration of an implanted bioelectronics system 200. The bioelectronics system comprises an implant device, in the form of an arteriovenous graft 202 that connects an artery 204 of the patient to a vein 206 of the patient in a so-called horseshoe connection. The arteriovenous graft 202 comprises a plurality of electrodes (discussed in more detail below), configured to function as electrical impedance spectroscopy sensors – i.e., to measure complex impedances between pairs of the plurality of electrodes. The measured complex impedances may be useable to infer (i.e., detect) the presence of various vascular pathologies 210. These vascular pathologies 210 may include stenoses caused by the

proliferation of smooth muscle cells 114, or thromboses caused by blood clot 118 formation within the lumen of the arteriovenous graft 110, 202, as illustrated in Figure 2.

The bioelectronics system 200 further comprises a control electronics module 212 that may be connected to the arteriovenous graft 202 by a tether 214.

Figures 4 to 6 are schematics illustrating the various functionalities that are achievable with the bioelectronics system 200 of Figure 2.

For example, Figure 4 is a schematic of a bioelectronics system 300 that is configured to measure complex impedance values. The bioelectronics system 300 comprises an implant device 301 with a plurality of electrodes 302 disposed at a tissue interface portion thereof. The electrodes 302 are arranged in pairs and may, for example, be arranged as an interdigitated array of electrodes 302, although other geometric arrangements are also possible. The array of electrodes 302 is preferably arranged on a surface of the implant device so that they are able to measure the complex impedances of tissue in the vicinity of the implant device.

The implant device may, for example, be an arteriovenous graft, an artificial valve, a vena cava filter, a stent, or an artificial heart pump, or any other implant that is deployable to the vascular system of a patient 100.

The bioelectronics system 300 further comprises an implantable control electronics module 310 that is connected to the array of electrodes 302, e.g., by a tether 303. The control electronics module 310 comprises a microcontroller 312, a multiplexer 314, a power source 316, a wireless communications module 318, and an impedance analyser 320.

The microcontroller 312 comprises a microprocessor and all other necessary circuitry and components required to carry out the complex impedance measurement and analysis operations that the bioelectronics system 300 is configured to carry out.

The multiplexer 314 is connected to the array of electrodes 302 integrated in the implant device and is configured to facilitate the transmission of separate and independent electrical signals across each separate pair of the integrated electrodes 302.

The power source 316 may, for example, be a battery or a rectifier configured to convert received alternating current radio-frequency transmission to a direct current power source, or any other suitable source of power to power the bioelectronics system 300.

The wireless communications module 318 comprises a transmitter to transmit measured complex impedance data (and/or encoded complex impedance information) to a remote unit 330.

The remote unit 330 comprises a receiver 332 configured to receive signals from the wireless communications module 318. In some examples, it may be preferable for the transmitter of the wireless communications module 318 and the receiver 332 of the remote unit 330 to be transceivers to enable two-way communication.

The remote unit 330 may be part of a wearable device such as a smart-watch or may be a smartphone on which an application has been installed to enable the remote unit 330 to communicate with the bioelectronics system 300.

In some examples, the remote unit 330 may be configured for long-range communications with a third-party device 340 – for example a device that is accessible by a doctor or other healthcare professional to analyse collected complex impedance data (and/or encoded complex impedance information).

The impedance analyser 320 is configured to measure complex impedance values between the pairs of electrodes 302.

This measurement may be carried out as follows: Firstly, the wireless communication module 318 may receive instructions from the remote unit 330 to measure complex impedances across a particular part of the implant device. Alternatively, the microcontroller 312 may be configured on a regular, or semi-regular basis, to activate one or more measurement processes of a predefined section (or across all) of the implant device. Based on this, the microcontroller 312 is configured to selectively apply electrical fields across selected pairs of electrodes 302 (via the multiplexer 314) that are arranged at positions across the implant device corresponding to positions at which impedance measurements are desired. Individual pairs of electrodes 302 may have electrical signals applied across them separately, and/or a common electrical signal may be applied across groups of pairs of electrodes 302 according to the instructions received at the multiplexer 314 from the microcontroller 312.

The impedance analyser 320 is configured to analyse the complex impedances associated with each of these electrical signals, for example by taking the complex ratio of the applied voltage to a measured current. By considering the complex ratio, it is possible to determine both the magnitude of the complex impedances, and the phases of the complex impedances relative to the applied voltage.

Based on the measured complex impedances, the microcontroller 312 is configured to encode these measured complex impedances as complex impedance information. The encoded complex impedance information may, for example, take the form of an impedance map (preferably after processing the complex impedance information by a processor configured to execute a program that causes the processor to visualise the complex impedance information as a tissue map). In some examples, the microcontroller may encode the voltage/current and frequency stimulus and the response after stimulation into the complex impedance information. This encoded information may then be transferred to a transceiver for relaying to a base station, said base station having a computing environment configured to implement the necessary visualisation software. The impedance map may be a representation of the spatial distribution of the measured complex impedances. The impedance map may represent the magnitudes and/or the phases of the measured complex impedances. Additionally or alternatively, the encoded complex impedance information may, for example, take the form of a tissue map. The tissue map may represent a spatial distribution of the quantities and/or types of tissue in the vicinity of the implant device.

Figure 5 is a schematic of a bioelectronics system 400 configured to generate and deliver waveform profiles to the vicinity of an implant device 401. The bioelectronics system 400 comprises the implant device with a plurality of electrodes 402 disposed at a tissue interface portion 405 thereof. The electrodes 402 are arranged in pairs and may, for example, be arranged as an interdigitated array of electrodes 402, although other geometric arrangements are also possible. The array of electrodes 402 is preferably arranged on a surface of the implant device so that they are able to deliver electrical signals directly to tissue in the vicinity of the implant device.

The implant device may, for example, be an arteriovenous graft, an artificial valve, a vena cava filter, a stent, or an artificial pump, or any other implant that is deployable to the vascular system of a patient 100.

The bioelectronics system 400 further comprises an implantable control electronics module 410 that is connected to the array of electrodes 402, e.g., via a tether 403. The control electronics module 410 comprises a microcontroller 412, a multiplexer 414, a power source 416, a wireless communications module 418, and a waveform generator 422.

The microcontroller 412 comprises a microprocessor and all other necessary circuitry and components required to carry out the waveform profile generation and delivery operations that the bioelectronics system 400 is configured to carry out.

The multiplexer 414 is connected to the array of electrodes 402 integrated in the implant device and is configured to facilitate the transmission of separate and independent electrical signals across each separate pair of the integrated electrodes 402.

The power source 416 may, for example, be a battery or a rectifier configured to convert received alternating current radio-frequency transmission to a direct current power source, or any other suitable source of power to power the bioelectronics system 400.

The wireless communications module 418 comprises a receiver to receive instructions from a remote unit 430 to generate and deliver waveform profiles.

The remote unit 430 comprises a transmitter 432 configured to transmit signals to the wireless communications module 418. These transmitted signals may include instructions to generate and deliver waveform profiles. Additionally or alternatively, the transmitted signal may include instructions to eliminate, remove, or otherwise destroy tissue contributing to a potential restenosis or thrombosis of the implant device.

In some examples, it may be preferable for the receiver of the wireless communications module 418 and the transmitter 432 of the remote unit 430 to be transceivers to enable two-way communication.

The remote unit 430 may be part of a wearable device such as a smart-watch or may be a smartphone on which an application has been installed to enable the remote unit 430 to communicate with the bioelectronics system 400.

In some examples, the remote unit 430 may be configured for long-range communications with a third-party device 440 – for example a device that is accessible by a doctor or other healthcare professional to

analyse an amount and type of tissue built-up around the vicinity of the implant device and to determine an appropriate sequence of waveform profiles to clear away, eliminate, or otherwise destroy the built-up tissue to prevent or remove a restenosis or thrombosis.

The waveform generator 422 is configured to generate and deliver waveform profiles between the pairs of electrodes 402.

This generation and delivery may be carried out as follows: Firstly, the wireless communication module 418 may receive instructions from the remote unit 430 to clear away, remove, eliminate, or otherwise destroy tissue built up in the vicinity of the implant device. Based on this, the microcontroller 412 is configured to instruct a set of one or more waveform profiles to be generated by the waveform generator 422 and to be selectively delivered therefrom across selected pairs of electrodes 402 (via the multiplexer 414) that are arranged at positions across the implant device corresponding to positions at which the delivery of apoptotic electrical signals is desired. Individual pairs of electrodes 402 may have the generated waveform profiles applied across them separately, and/or a common generated waveform profile may be applied across groups of pairs of electrodes 402 according to the instructions received at the waveform generator 422 and the multiplexer 414 from the microcontroller 412.

As discussed above, in a particular example, the waveform profile may be a sinusoidal waveform having a peak-to-peak voltage of approximately 2 V, a frequency of 40 kHz, and a pulse duration of 2 minutes.

The bioelectronics system may be configured to deliver the waveform repeatedly over the course of a treatment. The treatment may last for between 1 minute and 60 minutes and involve the repeated application of generated waveform profiles. In a particular example, the bioelectronics system may be configured to deliver a treatment by repeatedly delivering a waveform profile having a sinusoidal waveform having a peak-to-peak voltage of approximately 2 V, a frequency of 40 kHz, and a pulse duration of 2 minutes, with a rest-time (i.e., time between successive waveform profiles) of approximately 3 minutes.

The generated waveform profiles may be delivered to induce apoptosis to selectively and controllably kill the cells contributing to (or contributing to a risk of) restenosis and/or thrombosis in the vicinity of the implant device. For example, different waveform profiles may be generated to eliminate soft muscle cells (such as those that could contribute to vascular restenosis) compared to the waveform profiles needed to eliminate clotted blood cells.

The waveform generator 422 may include an amplifier to amplify the generated waveform profiles to a field strength (e.g., on the order of 10-100 kV cm^{-1} peak field strength) that is sufficient to induce apoptosis in the cells of the tissue in the vicinity of the implant device.

Figure 6 is a schematic of a bioelectronics system 500 configured to both measure complex impedance values, and to generate and deliver waveform profiles to the vicinity of an implant device 501. The bioelectronics system 500 comprises the implant device with a plurality of electrodes 502 disposed at a tissue interface portion 505 thereof. The electrodes 502 are arranged in pairs and may, for example, be arranged as an interdigitated array of electrodes 502, although other geometric arrangements are also

possible. The array of electrodes 502 is preferably arranged on a surface of the implant device so that they are able to measure the complex impedances of tissue in the vicinity of the implant device, and deliver electrical signals directly to said tissue.

The implant device may, for example, by an arteriovenous graft, an artificial valve, a vena cava filter, a stent, or an artificial pump, or any other implant that is deployable to the vascular system of a patient 100.

The bioelectronics system 500 further comprises an implantable control electronics module 510 that is connected to the array of electrodes 502. The control electronics module 510 comprises a microcontroller 512, a multiplexer 514, a power source 516, a wireless communications module 518, an impedance analyser 520, and a waveform generator 522.

The microcontroller 512 comprises a microprocessor and all other necessary circuitry and components required to carry out the complex impedance measurement and analysis operations, and waveform profile generation and delivery operations that the bioelectronics system 500 is configured to carry out.

The multiplexer 514 is connected to the array of electrodes 502 integrated in the implant device and is configured to facilitate the transmission of separate and independent electrical signals across each separate pair of the integrated electrodes 502.

The power source may, for example, be a battery or a rectifier configured to convert received alternating current radio-frequency transmission to a direct current power source, or any other suitable source of power to power the bioelectronics system 500.

The wireless communications module 518 comprises a transceiver to both transmit measured complex impedance data (and/or encoded complex impedance information) to a remote unit 530, and to receive instructions to generate and deliver waveform profiles from the remote unit 530.

The remote unit 530 comprises a transceiver 532. The transceiver 532 is configured to receive signals from the wireless communications module 518. The transceiver 532 is further configured to transmit signals to the wireless communications module 518. These transmitted signals may include instructions to generate and deliver waveform profiles. Additionally or alternatively, the transmitted signal may include instructions to eliminate, remove, or otherwise destroy tissue contributing to a potential restenosis or thrombosis of the implant device.

The remote unit 530 may be part of a wearable device such as a smart-watch or may be a smartphone on which an application has been installed to enable the remote unit 530 to communicate with the bioelectronics system 500.

In some examples, the remote unit 530 may be configured for long-range communications with a third-party device 540 – for example, a device that is accessible by a doctor or other healthcare professional. By this third-party device 540, the doctor or other healthcare professional may be able to analyse collected complex impedance data (and/or encoded complex impedance information) so as to determine an amount and type of tissue built-up around the vicinity of the implant device and to determine an

appropriate sequence of waveform profiles to clear away, eliminate, or otherwise destroy the built-up tissue to prevent or remove a restenosis or thrombosis.

The impedance analyser 520 is configured to measure complex impedance values between the pairs of electrodes 502.

The measurement may be carried out as follows: firstly, the wireless communication module 518 may receive instructions from the remote unit 530 to measure complex impedances across a particular part of the implant device. Alternatively, the microcontroller 512 may be configured on a regular, or semi-regular basis, to activate one or more measurement processes of a predefined section (or across all) of the implant device. Based on this, the microcontroller 512 is configured to selectively apply electrical fields across selected pairs of electrodes 502 (via the multiplexer 514) that are arranged at positions across the implant device corresponding to positions at which impedance measurements are desired. Individual pairs of electrodes 502 may have electrical signals applied across them separately, and/or a common electrical signal may be applied across groups of pairs of electrodes 502 according to the instructions received at the multiplexer 514 from the microcontroller 512.

The impedance analyser 520 is configured to analyse the complex impedances associate with each of these electrical signals, for example by taking the complex ratio of the applied voltage to a measured current. By considering the complex ratio, it is possible to determine both the magnitude of the complex impedances, and the phases of the complex impedances relative to the applied voltage.

Based on the measured complex impedances, the microcontroller 512 is configured to encode these measured complex impedances as complex impedance information. The encoded complex impedance information may, for example, take the form of an impedance map. The impedance map may be a representation of the spatial distribution of the measured complex impedances. The impedance map may represent the magnitudes and/or phases of the measured complex impedances. Additionally or alternatively, the encoded complex impedance information may, for example, take the form of a tissue map. The tissue map may represent a spatial distribution of the quantities and/or types of tissue in the vicinity of the implant device.

Figure 7 is a schematic of all the possible pairings of electrodes within an exemplary bioelectronics system superimposed. The pairs of electrodes are arranged in two independent banks of electrodes, denoted ‘A’ and ‘B’ respectively in Figure 7. The electrodes constituting bank ‘A’ are current injection electrodes, while the electrodes constituting bank ‘B’ are the corresponding return electrodes. While Figure 7 depicts 16 electrodes in total with 8 electrodes forming bank ‘A’ (denoted 1A-8A) and 8 electrodes forming bank ‘B’ (denoted 1B-8B), other numbers of electrodes in the bioelectronics system, and in each of banks ‘A’ and ‘B’ are possible. Additionally, banks ‘A’ and ‘B’ may be constituted by the same or respectively different numbers of electrodes.

Any one electrode from bank ‘A’ and any one electrode from bank ‘B’ may be addressed in combination. The full map of each of these possible combinations is shown superimposed in Figure 7. To reduce the

data load, and transfer and micro-processing overheads associated with using the bioelectronics system 300, 400, 500, only one electrode from bank 'A' and one electrode from bank 'B' is addressed at a time.

Figure 8 shows a series of stimulated tissue maps where excitation has been induced across different pairs of electrodes in the presence of blood only, emboli, and occlusive clots.

Panels A-D of Figure 8 show simulated maps in the case where only blood is simulated as being in a blood vessel.

Panels E-H of Figure 8 show simulated maps in the case where a small embolus is simulated as being in the centre of a blood vessel.

Panels I-L of Figure 8 show simulated maps in the case where an occlusive clot is simulated as being in a blood vessel.

In each of panels A-H one electrode from bank 'A' and one electrode from bank 'B' (as depicted in Figure 7) have each been addressed to set up a current and potential difference between the addressed electrodes.

Panels A, E and I show simulated maps where a potential difference of 1 V is established between electrodes 1A and 1B of Figure 7.

Panels B, F and J show simulated maps where a potential difference of 1 V is established between electrodes 1A and 2B of Figure 7.

Panels C, G and K show simulated maps where a potential difference of 1 V is established between electrodes 1A and 3B of Figure 7.

Panels D, H and L show simulated maps where a potential difference of 1 V is established between electrodes 1A and 4B of Figure 7.

The contour lines between the addressed electrodes in each of panels A-L represent electric field lines established between the two electrodes.

As can be seen from panels A-D, when there is no clot or occlusion in the blood vessel, the potential drops smoothly between the addressed electrodes, and the electric field lines take the form of a standard unmodified dipole electric field.

Meanwhile, with a small central embolus, the bath of the electric field lines visibly deviates around the embolus 550 to avoid an area of high resistance within the blood vessel. This makes both the size and position of the embolus 550 readily identifiable from panels E-H.

Similarly, the deviation caused by an occlusive clot 575 can be clearly seen in panels I-L. This deviation to the electric field lines is visibly much larger than the deviation caused by a smaller embolus 550. Further, in panel L, where an electrode (electrode 4B) in contact with the occlusive clot 575 is addressed. As can be seen from panel L, this dramatically alters the change in electric potential across the blood vessel from electrode 1A such that the electric potential across the blood vessel remain substantially constant at approximately 1 V until the electric field lines penetrate the occlusive clot on route to electrode

4B. This effect may be understood as the resistive dissipation of electric potential because, in the case of an occlusive clot 575 and the particular electrode arrangement shown in panel L, the current between the two addressed electrodes (1A and 4B) must pass through the occlusive clot, thereby causing the occlusive clot 575 to function as a resistor. This differs from the other configurations shown panels A-K because, in each of these panels the combination of clear blood/embolus 550/occlusive clot 575 with the respective electrode arrangement provides a clear path for electric current to flow between the pair of addressed electrodes without being forced to pass through a resistive blood clot.

The waveform generator 522 is configured to generate and deliver waveform profiles between the pairs of electrodes 502.

This generation and delivery may be carried out as follows: Firstly, the wireless communication module 518 may receive instructions from the remote unit 530 to clear away, remove, eliminate, or otherwise destroy tissue built up in the vicinity of the implant device. Based on this, the microcontroller 512 is configured to instruct a set of one or more waveform profiles to be generated by the waveform generator 522 and to be selectively delivered therefrom across selected pairs of electrodes 502 (via the multiplexer 514) that are arranged at positions across the implant device corresponding to position at which the delivery of apoptotic electrical signals is desired.

Additionally or alternatively, the microcontroller 512 may be configured to automatically instruct the delivery and generation of a waveform profile by the waveform generator 522 across a pair of the electrodes 502 in response to the impedance analyser 520 measuring a complex impedance across said pair of electrodes 502 that exceeds a predetermined threshold. The predetermined threshold may be selected such that it is indicative of a build-up of tissue that is causing (or risks causing) vascular restenosis or thrombosis.

Individual pairs of electrodes 502 may have the generated waveform profiles applied across them separately, and/or a common generated waveform profile may be applied across groups of pairs of electrodes 502 according to the instructions received at the waveform generator 522 and the multiplexer 514 from the microcontroller 512.

As discussed above, in a particular example, the waveform profile may be a sinusoidal waveform having a peak-to-peak voltage of approximately 2 V, a frequency of 40 kHz, and a pulse duration of 2 minutes.

The bioelectronics system may be configured to deliver the waveform repeatedly over the course of a treatment. The treatment may last for between 1 minute and 60 minutes and involve the repeated application of generated waveform profiles. In a particular example, the bioelectronics system may be configured to deliver a treatment by repeatedly delivering a waveform profile having a sinusoidal waveform having a peak-to-peak voltage of approximately 2 V, a frequency of 40 kHz, and a pulse duration of 2 minutes, with a rest-time (i.e., time between successive waveform profiles) of approximately 3 minutes.

The generated waveform profiles may be delivered to induce apoptosis to selectively and controllably kill the cells contributing to (or contributing to a risk of) restenosis and/or thrombosis in the vicinity of the

implant device. For example, different waveform profiles may be generated to eliminate soft muscle cells (such as those that could contribute to vascular restenosis) compared to the waveform profiles needed to eliminate clotted blood cells.

The waveform generator 522 may include an amplifier to amplify the generated waveform profiles to a field strength (e.g., on the order of 10-100 kV cm^{-1} peak field strength) that is sufficient to induce apoptosis in the cells of the tissue in the vicinity of the implant device.

Figure 9a shows a photograph of an exemplary electrode array 600. The electrode array 600 is arranged as an interdigitated electrode array formed from gold electrodes that are made by applying gold-lithography to a glass substrate using a 10 nm titanium adhesion layer on 100 nm thickness gold. The pictured electrode array 600 comprises two sets of 20 interdigitate gold electrodes. Each electrode has a length of 2 mm, and a separation width of 25 μm between adjacent electrodes.

Figure 9b shows a magnified image of the exemplary array of interdigitated electrodes 600 shown in Figure 9a, zoomed in to clearly highlight the interdigitated arrangement of the electrodes.

Figure 9c shows a blown-up schematic of an individual electrode 610 within the interdigitated electrode array 600. The electrode 610 comprises a plurality of fabrication layers including an outer graft wrap 612, a heat shrink layer 614, an embedding layer 616 with the electrode 610 embedded therein, and an inner graft wrap 618 having an aperture 620 therein aligned with the electrode 610 to facilitate direct contact between the electrode 610 and tissue in the vicinity of the implant device.

The materials from which each of these components are formed may be specifically selected to ensure that the overall structure has the necessary properties to facilitate the bioelectronic system's function.

For example, the outer and inner graft wraps 612, 618 may be formed from a material that is smooth and spongey to cushion the electrode 610, whilst still being sterile. For example, the outer and inner graft wraps 612, 618 may be formed from a material such as expanded polytetrafluorethylene (ePTFE).

The embedding layer 616 may be formed from a material that has a high heat-resistance so that the electrode 610 can be stored securely, whilst ensuring that ohmic heating does not damage the embedding layer 616. The embedding layer 616 may therefore be formed from a thermoplastic such as polyimide, or another similar material.

Figure 10 shows various measured complex impedances, as measured by a bioelectronics system in a demonstrative cellular experiment. The test that yields the data shown in Figure 10 was performed in vitro using monolayers of cultured primary cells. A biocompatible cell chamber was 3D printed and was secured over the electrode sensors of the bioelectronics system. Chambers were seeded with either 150 000 mouse aorta smooth muscle cells (MASMC) or mouse endothelial cells (MECs) and incubated for 24 hours in a DMEM and Hepes buffered culture media. An experimental control of media was used and maintained at 37°C as a comparison.

The MASMC were from an adherent transgenic mouse model, and the MECs, previously immortalised MEC, were incubated at 37°C with 5% carbon dioxide at 95% relative humidity for each experiment.

Dulbeccos Modified Eagles Medium (DMEM) HEPES buffer (Gibco, UK) supplemented with 10% foetal bovine serum, 1 mL per 100 mL penicillin/streptomycin and L-glutamine was used as the control. Each cellular experiment was seeded at 250 000 cells per ml, and a total volume of 2 ml was use for each chamber. The control was 2 ml of media only, with no cells seeded.

Panels A and B show an electrode array in contact with MAMCs stained with a first monolayer. The first monolayer comprises a dye of Calcein Red-Orange, AM (available as C34851 from ThermoFisher), which fluoresces red. The first monolayer was washed with phosphate-buffered saline (PBS) and imaged under an upright microscope. Panel A is imaged at x4 magnification, and panel B shows a single electrode imaged at x10 magnification. Panels A and B clearly show an intact MASMC monolayer observed across the whole sensor.

Meanwhile, panels C and D show an electrode array in contact with MECs stained with a second monolayer. The second monolayer comprises a dye of Calcein, AM (available as C1430 from ThermoFisher), which fluoresces green. Panel C is imaged at x4 magnification, and panel D shows a single electrode imaged at x10 magnification. Panels C and D clearly show an intact MEC monolayer observed across the whole sensor.

Panel E shows the mean electrode impedance across MASMCs, MECs and the control media across a range of frequencies from 1 kHz to 100 kHz. Panel F shows a single frequency comparison of complex impedance measurements for a single frequency of 100 kHz. It can be clearly seen from Panels E and F that both the MASMCs and MECs are distinguishable from the control medium and that the MASMCs and MECs are further distinguishable from one another. MASMCs are equivalent to those cells in a patient 100 that are indicative of blood clotting, while MECs are equivalent to those cells in a patient 100 that are indicative of smooth muscle cell proliferation that could lead to vascular restenosis. Accordingly, it is clearly demonstrated that the bioelectronics system disclosed herein can distinguish between tissue types that contribute to vascular restenosis and/or thrombosis.

Figure 11 shows a comparison of data collected by a bioelectronics system for blood clot and human plaque detection in an arteriovenous graft. Panels A-C shows a comparison of measured complex impedances of heparinised blood versus different blood clots of the same mass across a range of frequencies ranging from 1 to 100 kHz. Panel E clearly shows that it is possible to distinguish between heparinised blood and blood clots, regardless of any variation between different blood clots, taking an example of compared impedances at a frequency of 100 kHz.

Panel D of Figure 11 compares the impedances of a lipid rich region of an explanted carotid artery versus a calcified region of said artery across a range of frequencies from 1 to 100 kHz. It is clear therefore that lipid-rich and calcified tissue can be distinguished by the impedance analyser of the bioelectronics system. Similarly, panel G shows a comparison of these measured complex impedances at a selected frequency of 100 kHz further supporting the distinguishability of lipid-rich and calcified tissue. In this way, it is clear that the bioelectronics module can find applications beyond merely monitoring and maintaining the performance of an implant device such as an arteriovenous graft, but can also be used to monitor and

treat the development of plaque in arteries in the vicinity of e.g., artificial valves, vena cava filters and/or artificial heart pumps.

Figure 12 shows results of impedance measurements from preclinical studies using a bioelectronics system that includes an arteriovenous graft.

Panel A of Figure 12 shows the complex impedances measured across each electrode pair of 32 different electrode pairs in an implanted bioelectronics system when different substances (blood, air, PBS, or emboli) are flowing through the graft. Panel B of Figure 10 shows that the impedance analyser of the bioelectronics system is able to distinguish between blood and emboli in the vicinity of the graft based on the measured complex impedance values.

Panel C of Figure 12 shows how the complex impedance values in the vicinity of the graft increases as the graft clots over a period of 5 minutes. It can be clearly seen that the complex impedance increases as the graft clots. Based on panel C, it is clear that monitoring the complex impedance values measured by the impedance analyser can provides a user with information indicative of the clotting of blood within a graft.

Finally, panel D of Figure 12 clearly shows how liquid blood and blood clots are distinguishable based on the measured complex impedance values.

Figure 13 shows the results of experiments into the effectiveness of inducing apoptosis in cells in the vicinity of an implant device.

Figure 13 shows an impedance trend over a 48-hour time period for various treatment profiles. The complex impedance values were measured at a frequency of 100 kHz. The data tracks the cell growth for 24 hours before delivering an apoptotic electroporation waveform at the 24 hour-time point. Two control curves were measured – a negative control of a sample that includes no cells in the test sample, and an untreated sample of MASMC cells.

As can be seen from Figure 13, the application of a direct current waveform profile (whether wired, or wireless) induces a significant drop in the measured complex impedance values that does not recover. This signal corresponds to a significant drop in population caused by successful apoptosis. Meanwhile, the application of an alternating current waveform profile can be seen to result in a cell population recovery back to basal level within 24 hours of the application of the apoptotic waveform.

From this, it can demonstrably be inferred that it is preferable form the waveform generator of the bioelectronics system to deliver a direct current waveform profile to ensure that any induced apoptosis is permanent (or at least long lasting).

Figure 14 shows the results of experiments illustrating differential cell-killing efficacy in different contexts. In these experiments an alternating current apoptotic waveform profile is applied to both MECs and MASMCs. It can be clearly seen from Figure 14 that alternating current waveform profiles yield a greater proportion of apoptotic cells in MASMC populations 3 hours after treatment, compared to MEC populations. As such it can be seen, based on both Figures 13 and 14, that different qualitative and

quantitative waveform profiles can be selected, generated, and applied to selectively kill either thrombosis-causing cells (corresponding to MASMCs) or restenosis-causing cells (corresponding to MECs).

***

The features disclosed in the foregoing description, or in the following claims, or in the accompanying drawings, expressed in their specific forms or in terms of a means for performing the disclosed function, or a method or process for obtaining the disclosed results, as appropriate, may, separately, or in any combination of such features, be utilised for realising the invention in diverse forms thereof.

While the invention has been described in conjunction with the exemplary embodiments described above, many equivalent modifications and variations will be apparent to those skilled in the art when given this disclosure. Accordingly, the exemplary embodiments of the invention set forth above are considered to be illustrative and not limiting. Various changes to the described embodiments may be made without departing from the spirit and scope of the invention.

For the avoidance of any doubt, any theoretical explanations provided herein are provided for the purposes of improving the understanding of a reader. The inventors do not wish to be bound by any of these theoretical explanations.

Any section headings used herein are for organizational purposes only and are not to be construed as limiting the subject matter described.

Throughout this specification, including the claims which follow, unless the context requires otherwise, the word “comprise” and “include”, and variations such as “comprises”, “comprising”, and “including” will be understood to imply the inclusion of a stated integer or step or group of integers or steps but not the exclusion of any other integer or step or group of integers or steps.

It must be noted that, as used in the specification and the appended claims, the singular forms “a,” “an,” and “the” include plural referents unless the context clearly dictates otherwise. Ranges may be expressed herein as from “about” one particular value, and/or to “about” another particular value. When such a range is expressed, another embodiment includes from the one particular value and/or to the other particular value. Similarly, when values are expressed as approximations, by the use of the antecedent “about,” it will be understood that the particular value forms another embodiment. The term “about” in relation to a numerical value is optional and means for example +/- 10%.

Reference Numerals

100	Haemodialysis patient
102	Vascular access region
104a, b	Treatment lines
106	Artery
108	Patient

110	Arteriovenous graft
112	Sutures
114	Smooth muscle cells
116	Tunica media
118	Blood clot
200	Bioelectronics system
202	Arteriovenous graft
204	Artery
206	Vein
208	Electrical impedance spectroscopy electrodes
210	Vascular pathologies
212	Control electronics module
214	Tether
300	Bioelectronics system configured to measure complex impedance values
301	Implant device
302	Electrodes
303	Tether
310	Control electronics module
312	Microcontroller
314	Multiplexer
316	Power source
318	Wireless communications module
320	Impedance analyser
330	Remote unit
332	Receiver/transceiver
340	Third-party device
400	Bioelectronics system configured to generate and deliver waveform profiles to the vicinity of an implant device
402	Electrodes
410	Control electronics module
412	Microcontroller
414	Multiplexer
416	Power source
418	Wireless communications module
422	Waveform generator
430	Remote unit
432	Transmitter/transceiver
440	Third-party device
500	Bioelectronics system configured to measure complex impedance values and to generate and deliver waveform profiles to the vicinity of an implant device
502	electrodes

510	Control electronics module
512	Microcontroller
514	Multiplexer
516	Power source
518	Wireless communications module
520	Impedance analyser
522	Waveform generator
530	Remote unit
532	Transceiver
540	Third-party device
550	Embolus
575	Blood clot
600	Electrode array
610	Electrode
612	Outer graft wrap
614	Heat shrink layer
616	Embedding layer
618	Inner graft wrap
620	Aperture

Claims:

1. A bioelectronics system comprising:

a vascular implant device having a tissue interface portion that has multiple pairs of electrodes disposed therein; and

an implantable control electronics module communicably connectable to the vascular implant device, the control electronics module comprising:

a multiplexer configured to independently address each pair of electrodes;

an impedance analyser connectable with the multiple pairs of electrodes via the multiplexer and configured to measure a respective complex impedance between each pair of electrodes;

a microcontroller configured to encode the measured complex impedances as complex impedance information; and

a wireless communication module configured to transmit the complex impedance information to a remote unit for analysis.

2. The bioelectronics system according to claim 1, wherein the impedance analyser is configured to measure the respective complex impedances over a range of frequencies.

3. The bioelectronics system according to claim 1 or 2, wherein the complex impedance information includes a map of the measured complex impedances based on the positions of each pair of electrodes in the implant device.

4. The bioelectronics system according to any preceding claim, wherein the remote unit is configured to transmit the complex impedance information, and/or analysed complex impedance information to a third-party device.

5. A bioelectronics system comprising:

a vascular implant device having a tissue interface portion that has multiple pairs of electrodes disposed therein; and

an implantable control electronics module communicably connectable to the vascular implant device, the control electronics module comprising:

a multiplexer configured to independently address each pair of electrodes;

a wireless communication module configured to receive instructions to deliver an electrical signal across the multiple pairs of electrodes;

a microcontroller configured to determine a respective waveform profile to be applied across each pair of electrodes based on the received instructions; and

a waveform generator connectable with the multiple pairs of electrodes via the multiplexer and configured to apply the respectively determined waveform profiles across each pair of electrodes.

6. The bioelectronics system according to claim 5, wherein the waveform generator includes an amplifier to amplify the signal to a predetermined voltage.

7. The bioelectronics system according to claim 5 or 6, wherein the one or more waveform profiles are configured to induce apoptosis in cells in the vicinity of the implant device.

8. The bioelectronics system according to any of claims 5 to 7, wherein the implantable control electronics module is a first implantable control electronics module, and the system further comprises a second implantable control electronics module comprising:

a measurement multiplexer configured to independently address each pair of electrodes;

an impedance analyser connectable with the multiple pairs of electrodes via the measurement multiplexer and configured to measure a respective complex impedance between each pair of electrodes;

a microcontroller configured to encode the measured complex impedances as complex impedance information; and

a wireless communication module configured to transmit the complex impedance information to a remote unit for analysis.

9. The bioelectronics system according to claim 8, wherein one or more of:

the multiplexers of the first and second implantable control electronics modules;

the microcontrollers of the first and second implantable control electronics modules; and

the wireless communication modules of the first and second control electronics modules

are common shared components between the first and second control electronics modules.

10. The bioelectronics system according to any one of claims 5 to 7, wherein the control electronics module further comprises an impedance analyser connectable with the multiple pairs of electrodes via the multiplexer and configured to measure a respective complex impedance between each pair of electrodes,

wherein the microcontroller is further configured to encode the measured complex impedances as complex impedance information, and

wherein the wireless communication module is configured to transmit the complex impedance information to a remote unit for analysis.

11. The bioelectronics system according to any one of claims 8 to 10, wherein the impedance analyser is configured to measure the respective complex impedances over a range of frequencies.

12. The bioelectronics system according to any of claims 8 to 11, wherein the complex impedance information includes a map of the measured complex impedances based on the positions of each pair of electrodes in the implant device.

13. The bioelectronics system according to any of claims 8 to 12, wherein the remote unit is configured to transmit the complex impedance information, and/or analysed complex impedance information to a third-party device.

14. The bioelectronics system according to any preceding claim, wherein the implantable control electronics module further comprises a rectifier configured to receive a wireless transmission and convert the wireless transmission to a direct current signal to power said implantable control electronics module.

15. The bioelectronics system according to any preceding claim, wherein the implantable control electronics module is contained within a hermetically sealed housing.

16. The bioelectronics system according to claim 15, wherein the hermetically sealed housing comprises a body made from a radio frequency insulating material, wherein the body comprises a radio frequency window through which signals to or from the wireless communication module are transmissible.

17. The bioelectronics system according to any preceding claim, wherein the multiple pairs of electrodes consist of an array of interdigitated electrodes.

18. The bioelectronics system according to any preceding claim, wherein the implant device is an arteriovenous graft.

19. The bioelectronics system according to any preceding claim, wherein the remote unit is part of a wearable device.

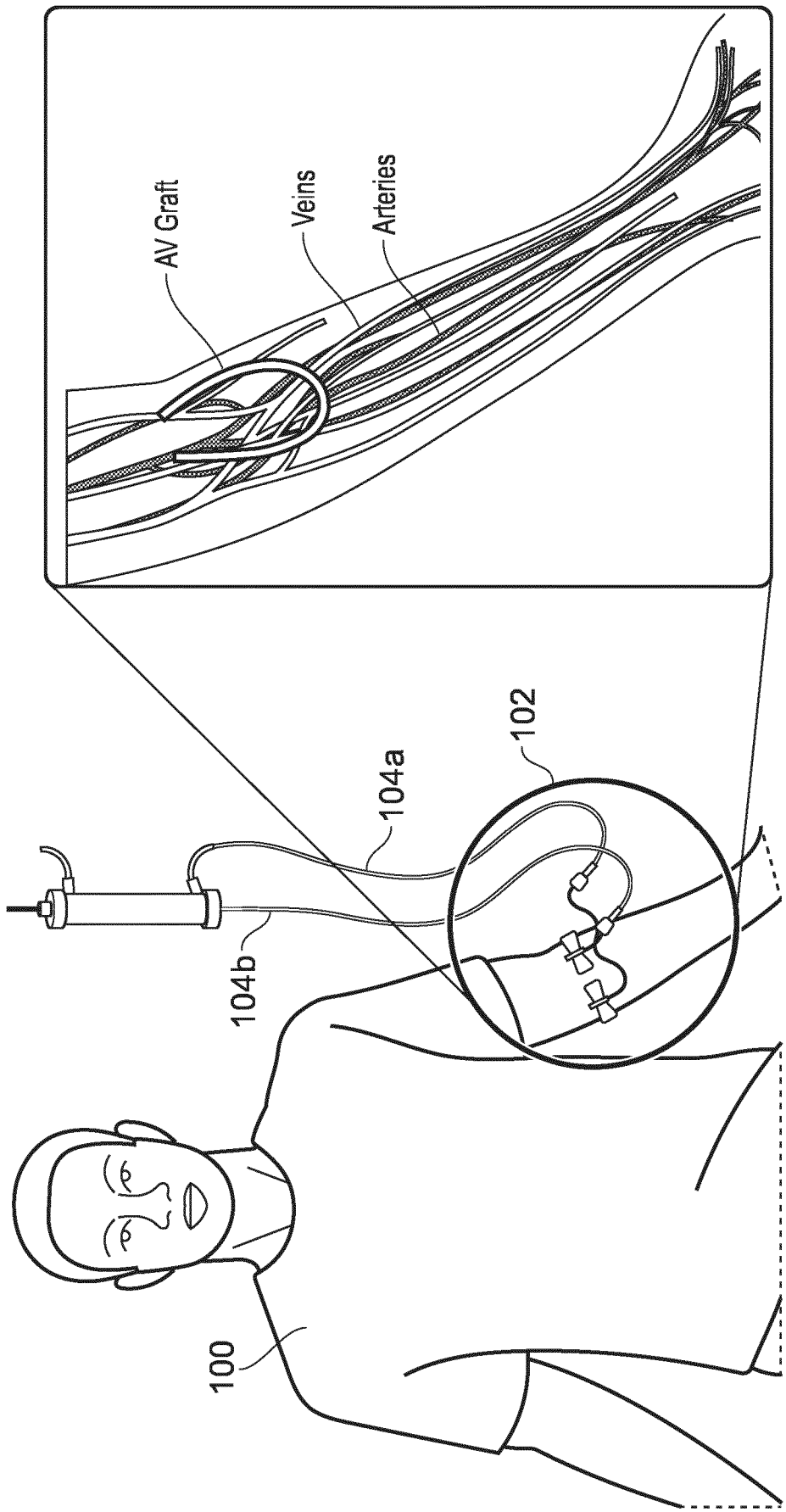


FIG. 1

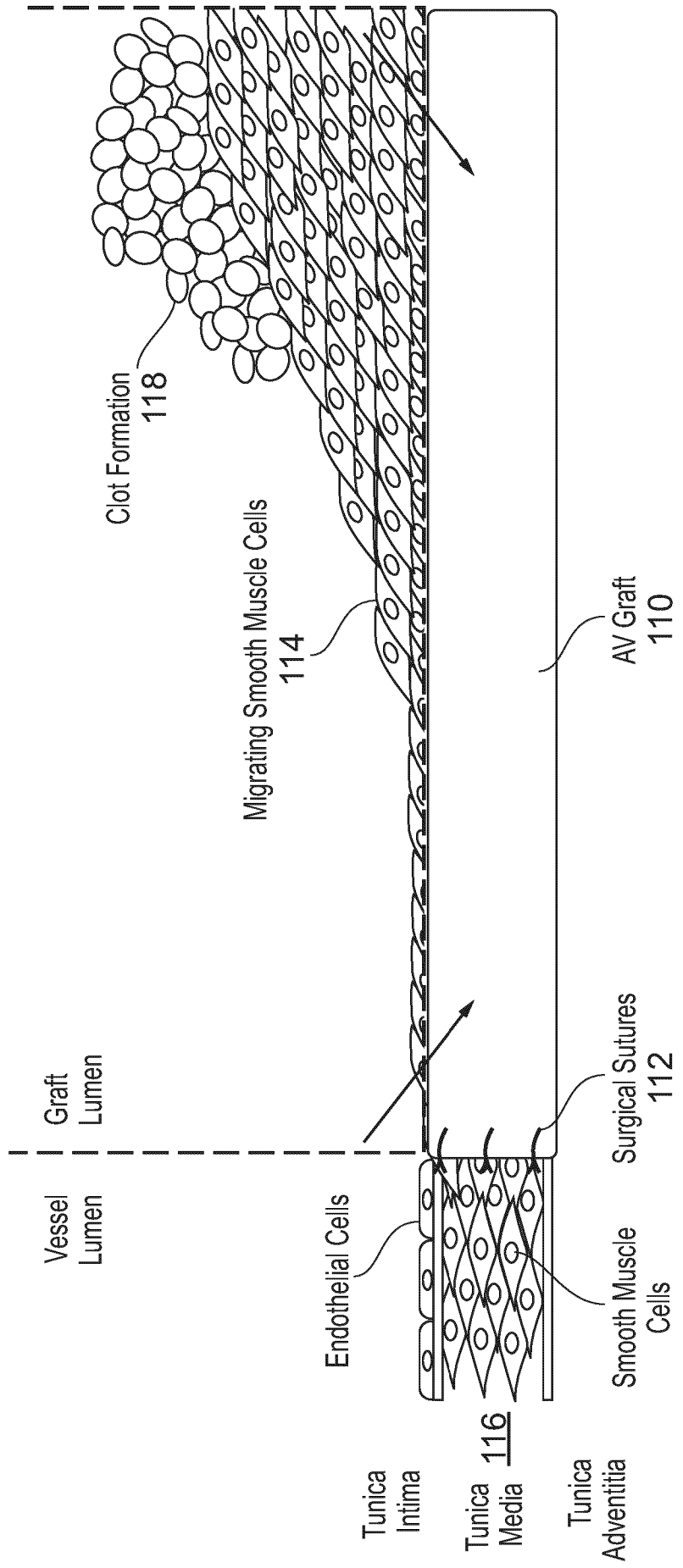

Clot Formation
118
Migrating Smooth Muscle Cells
114
AV Graft
110
Graft
Lumen
Vessel
Lumen
Endothelial Cells
Surgical Sutures
112
Smooth Muscle
Cells
Tunica
Intima
Tunica
Media
116
Tunica
Adventitia

FIG. 2

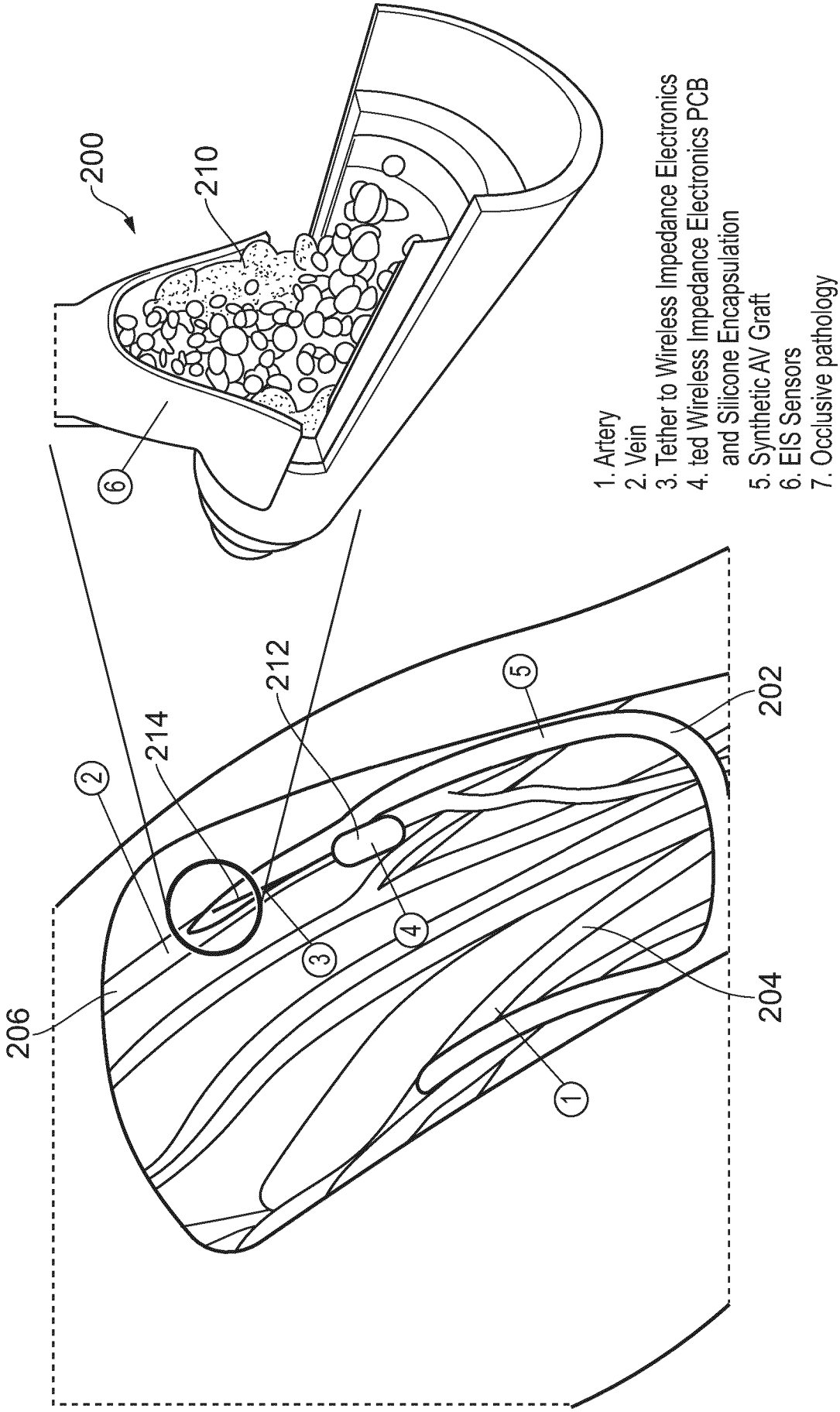

200
210
6
1. Artery
2. Vein
3. Tether to Wireless Impedance Electronics
4. ted Wireless Impedance Electronics PCB and Silicone Encapsulation
5. Synthetic AV Graft
6. EIS Sensors
7. Occlusive pathology
212
214
202
206
204
1
2
3
4
5

FIG. 3

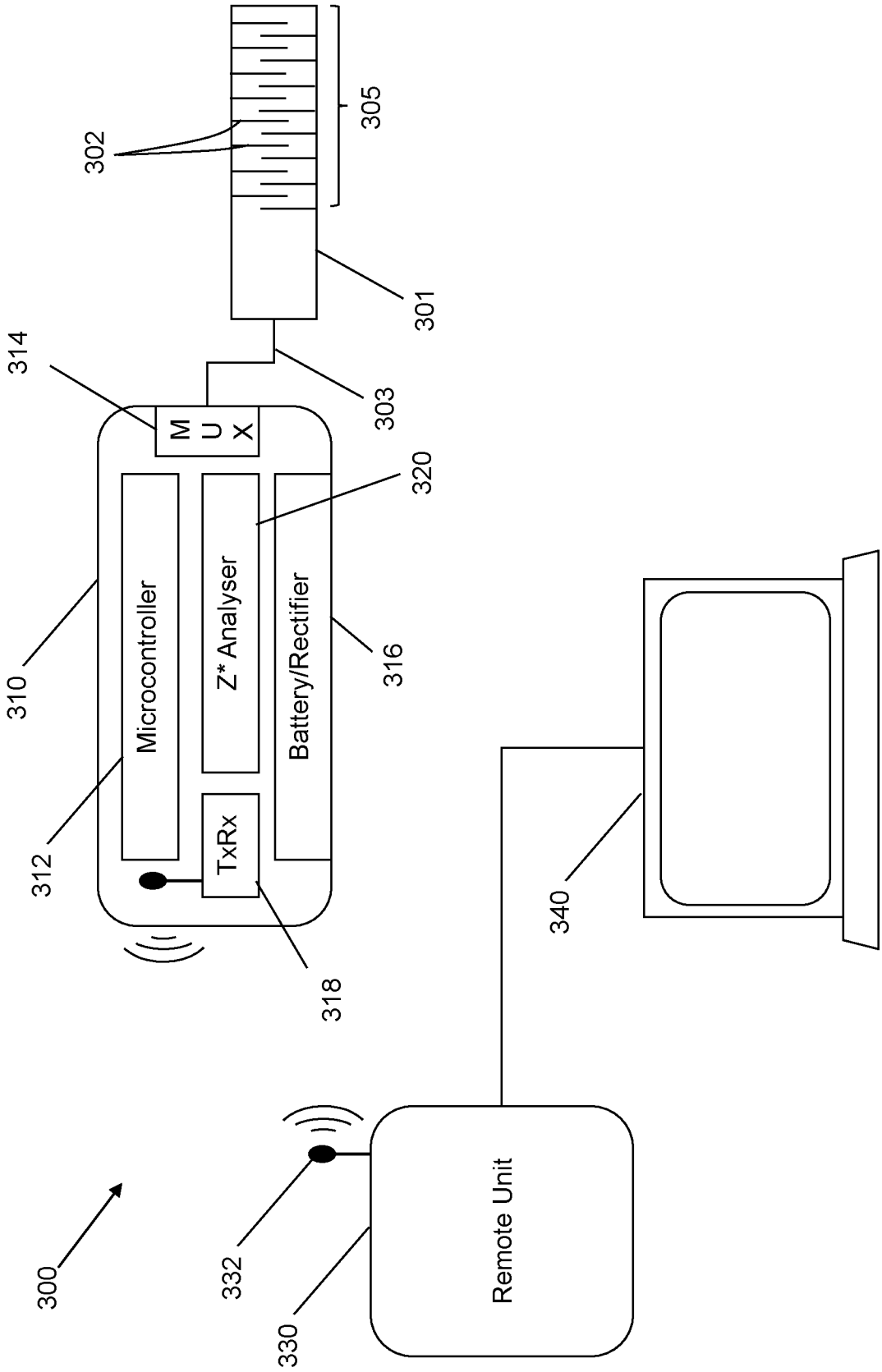

302
305
301
303
314
M
U
X
320
Microcontroller
Z* Analyser
Battery/Rectifier
316
310
312
TxRx
318
340
Remote Unit
332
330
300

Fig. 4

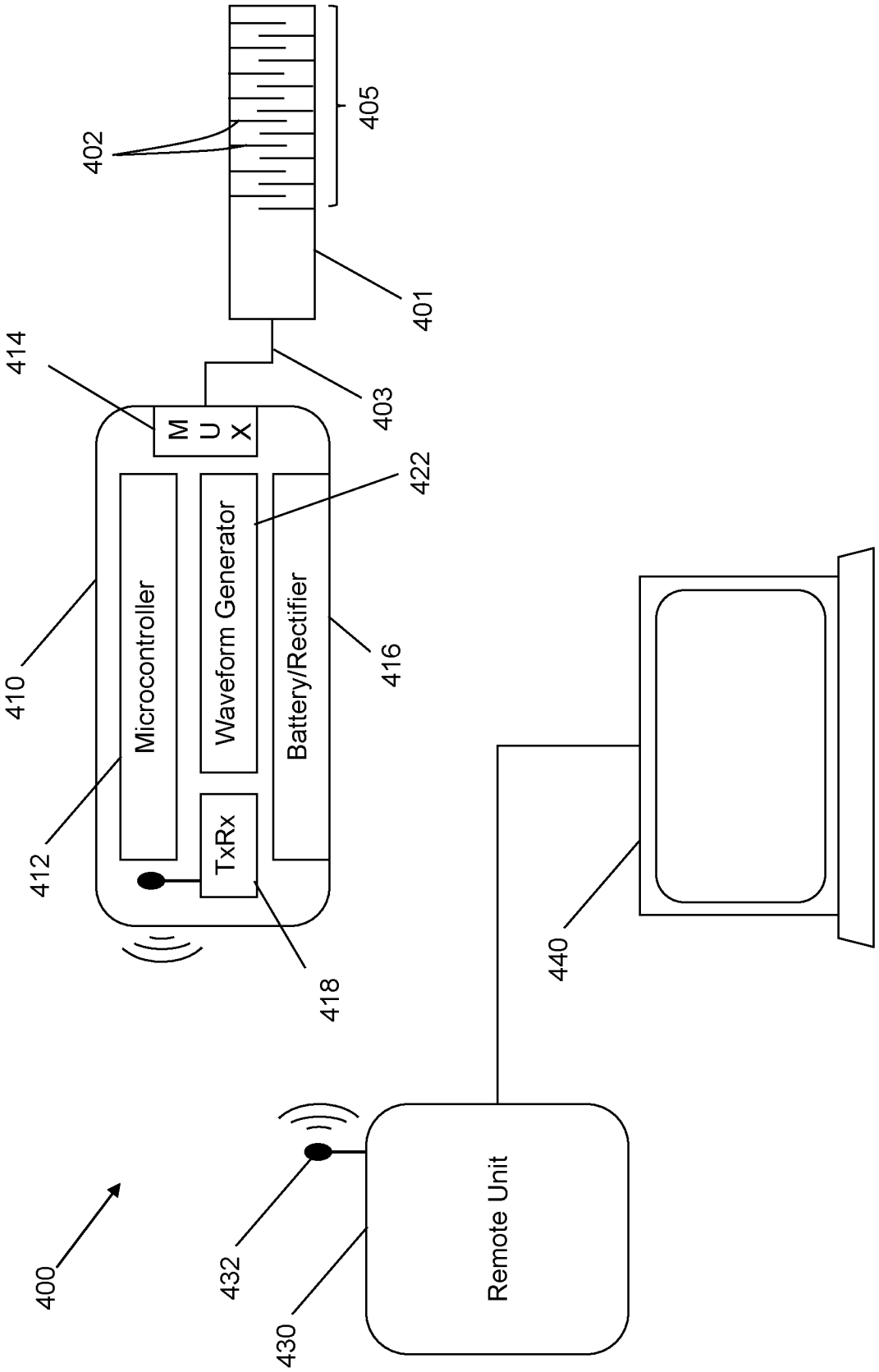

400
402
405
401
403
414
MUX
422
Microcontroller
Waveform Generator
Battery/Rectifier
410
416
412
TxRx
418
440
432
430
Remote Unit

Fig. 5

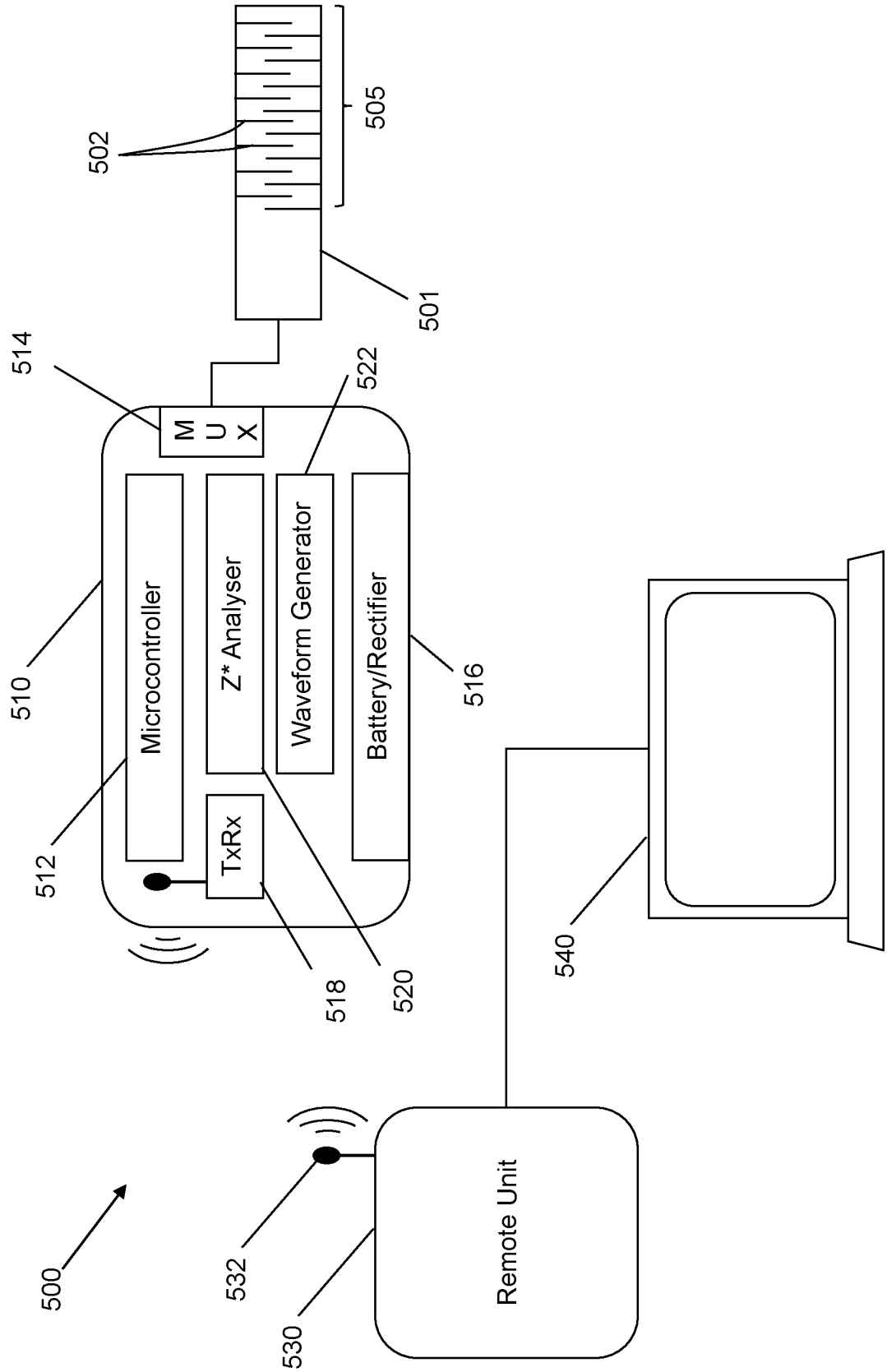

502
505
501
514
522
M
U
X
Microcontroller
Z* Analyser
Waveform Generator
Battery/Rectifier
TxRx
510
512
516
518
520
540
500
532
530
Remote Unit

Fig. 6

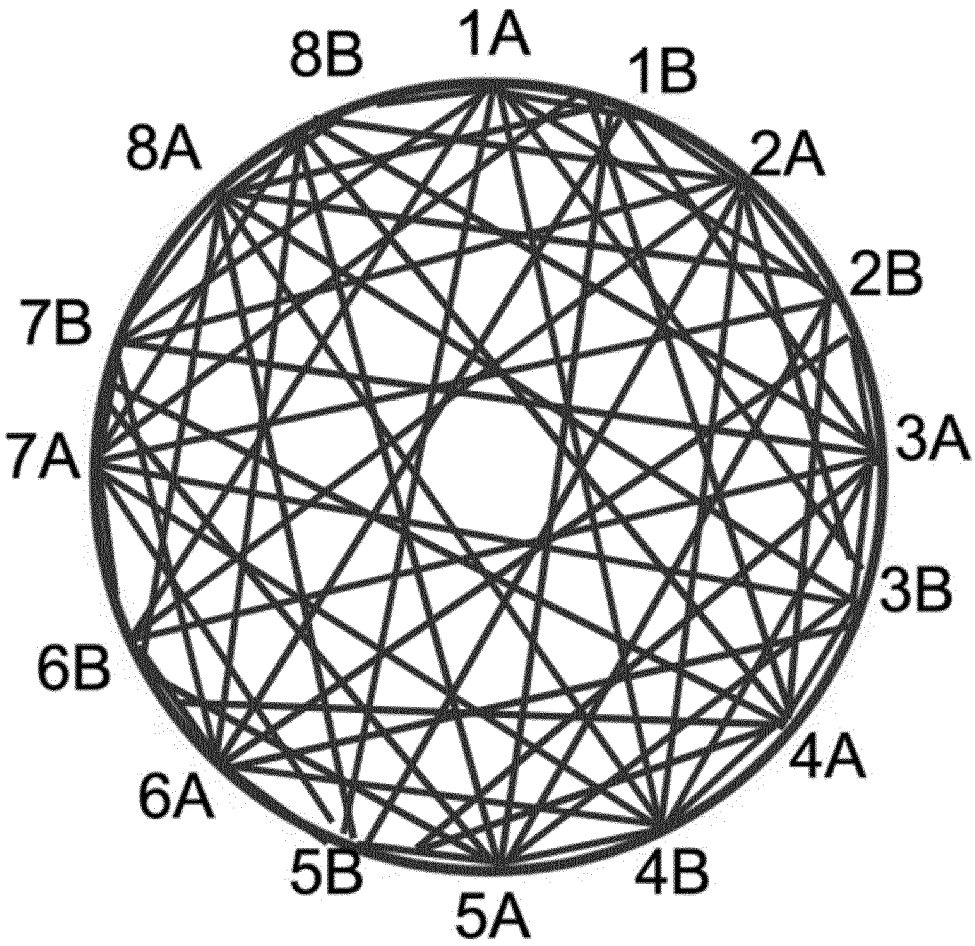


Fig. 7

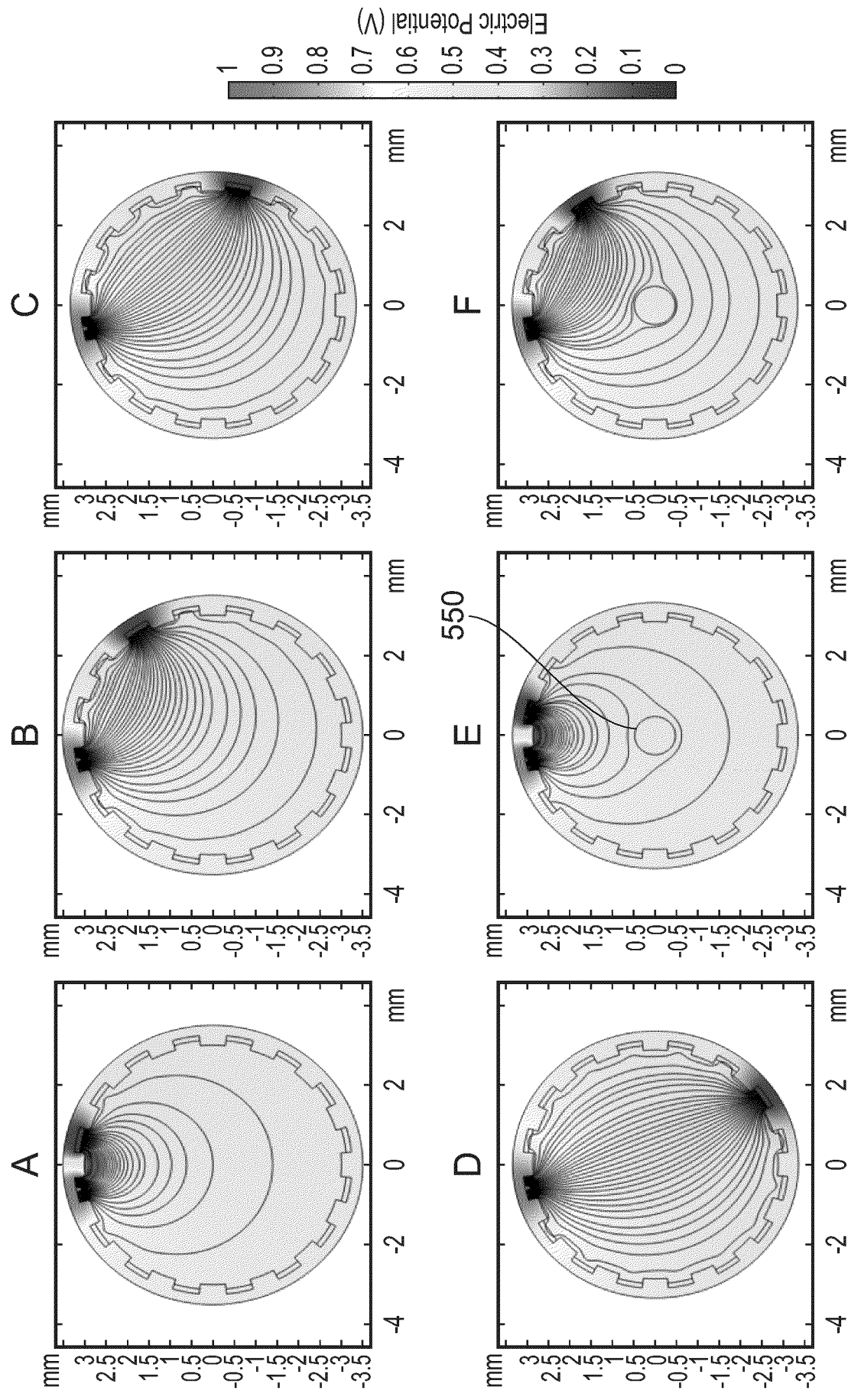

Electric Potential (V)
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
A
B
C
D
E
F
550
mm
3
2.5
2
1.5
1
0.5
0
-0.5
-1
-1.5
-2
-2.5
-3
-3.5
-4
-2
0
2
mm

FIG. 8

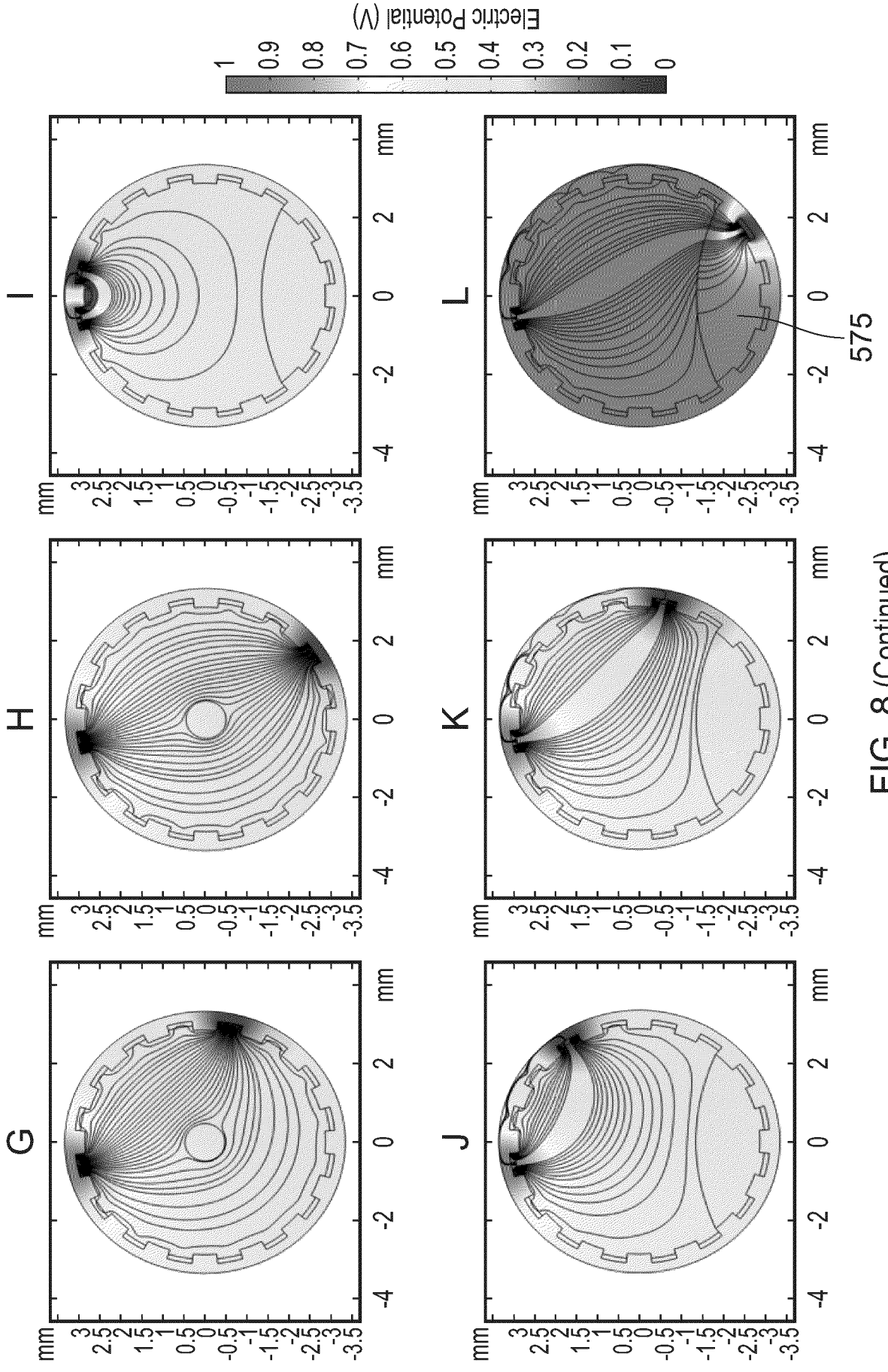


FIG. 8 (Continued)

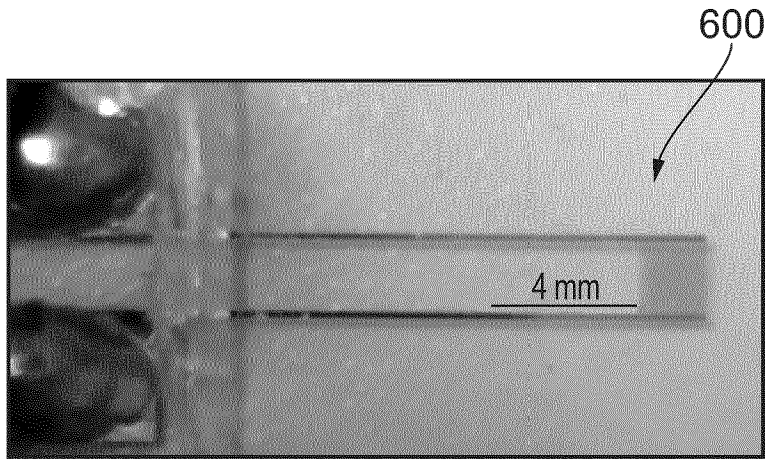


FIG. 9a

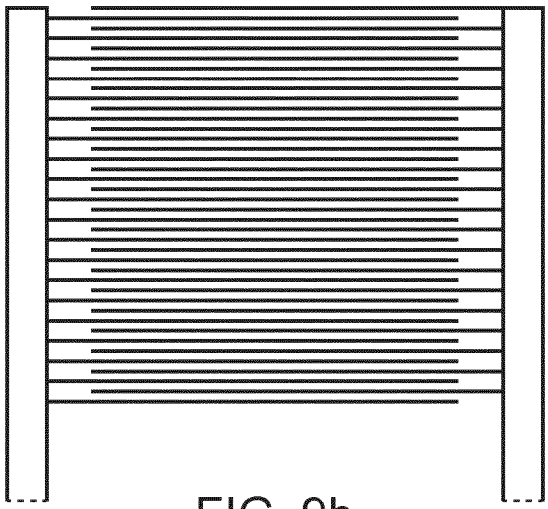


FIG. 9b

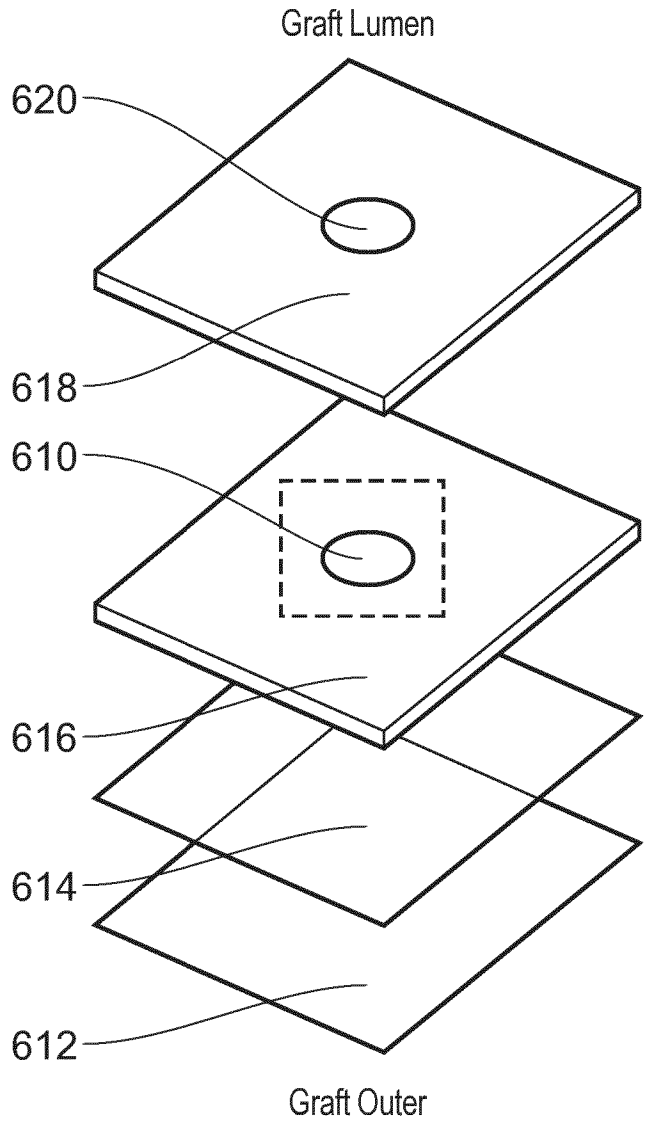


FIG. 9c

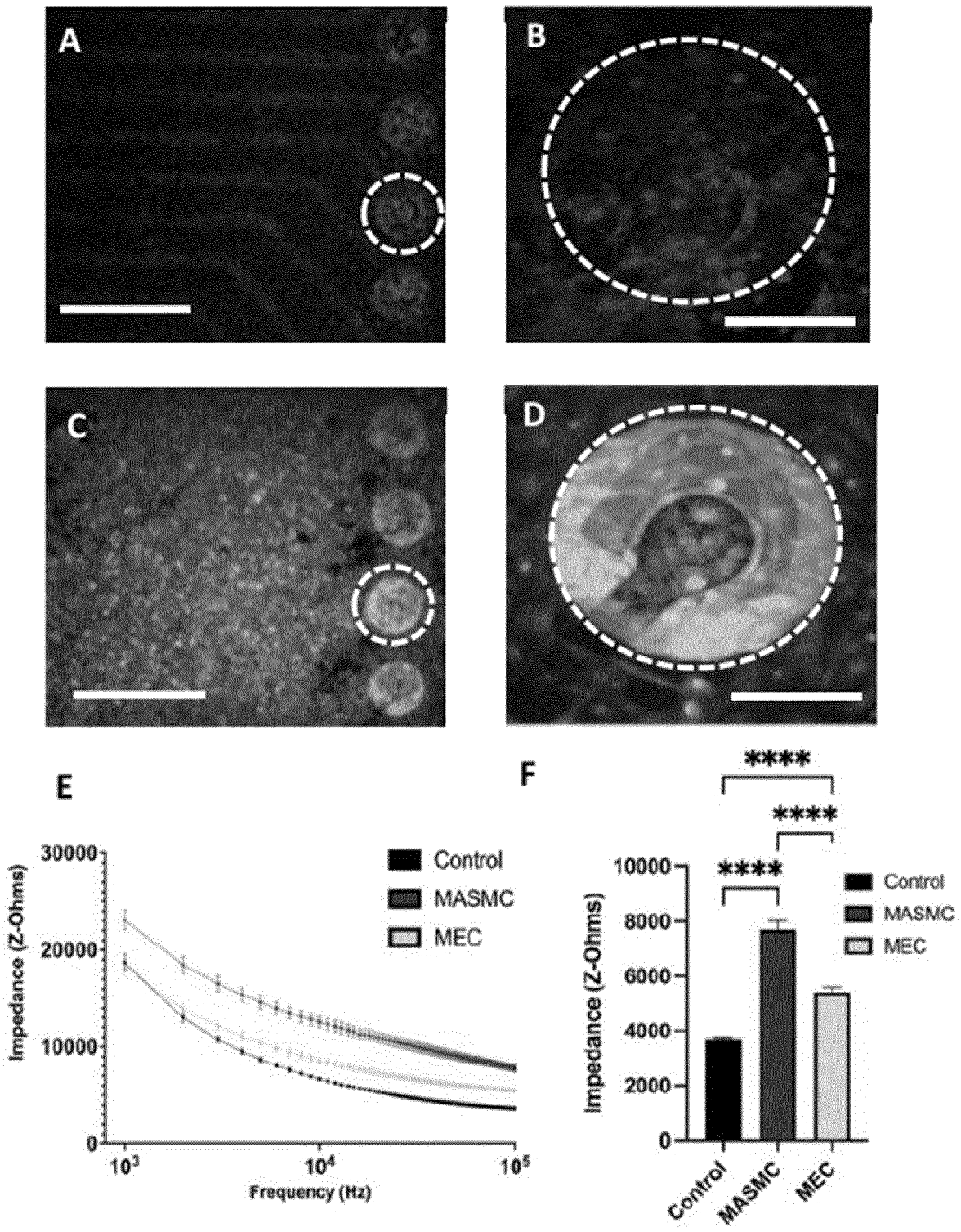


Fig. 10

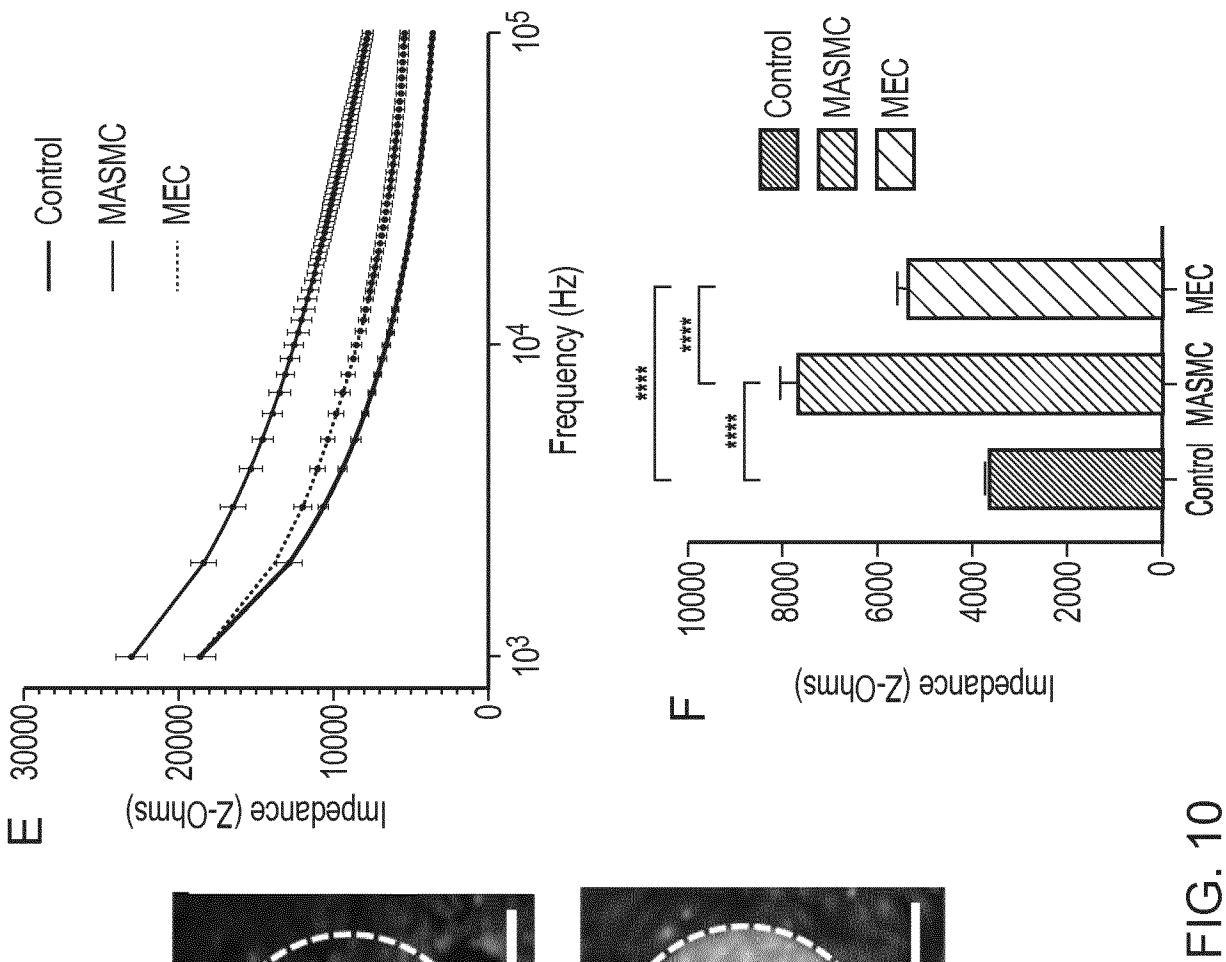

E
Impedance (Z-Ohms)
30000
20000
10000
0
10^3
10^4
10^5
Frequency (Hz)
Control
MASMC
MEC
F
Impedance (Z-Ohms)
10000
8000
6000
4000
2000
0
****
****
****
Control
MASMC
MEC
A
B
C
D

FIG. 10

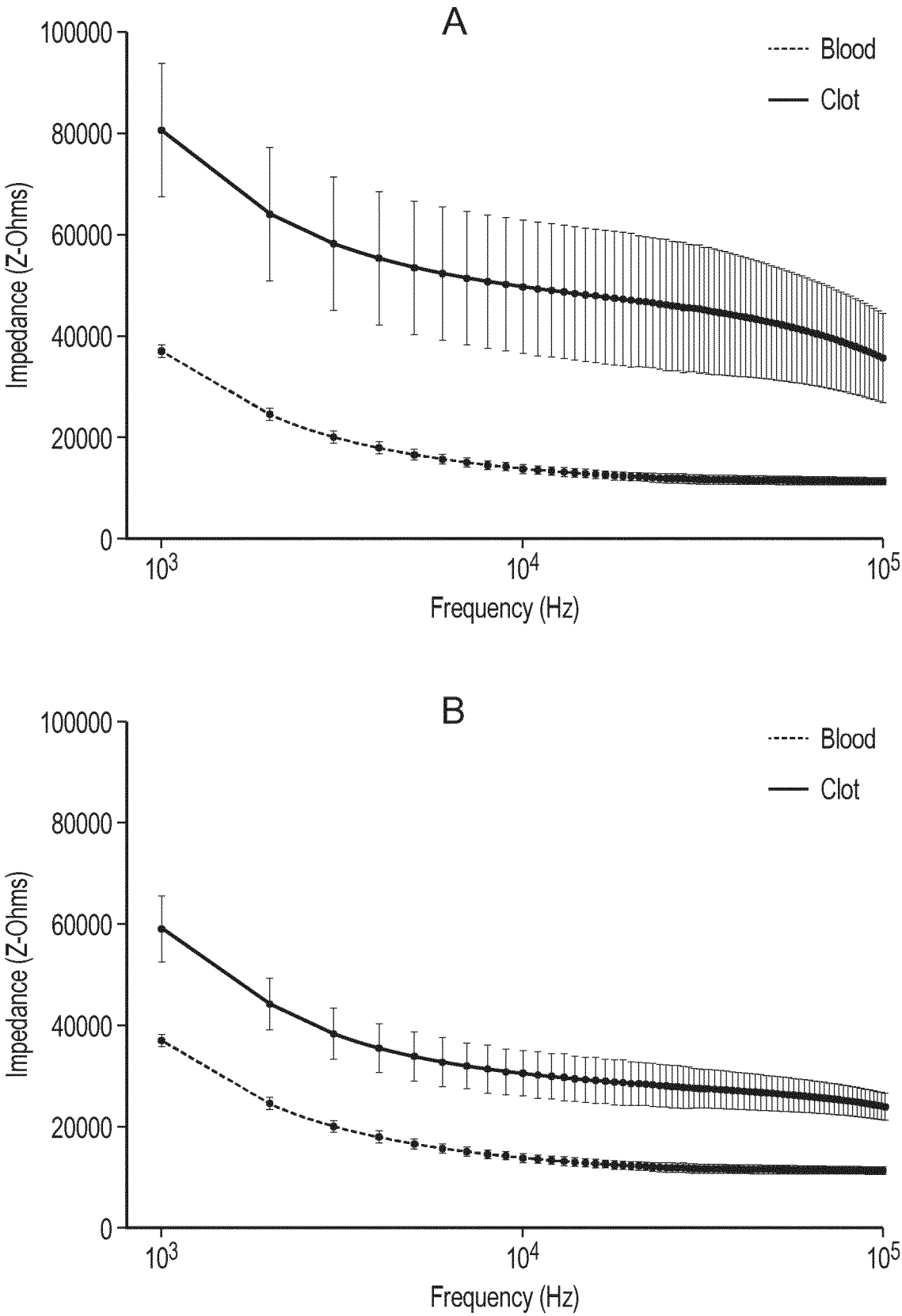

A
Blood
Clot
100000
80000
60000
40000
20000
0
Impedance (Z-Ohms)
10^3
10^4
10^5
Frequency (Hz)
B
Blood
Clot
100000
80000
60000
40000
20000
0
Impedance (Z-Ohms)
10^3
10^4
10^5
Frequency (Hz)

FIG. 11

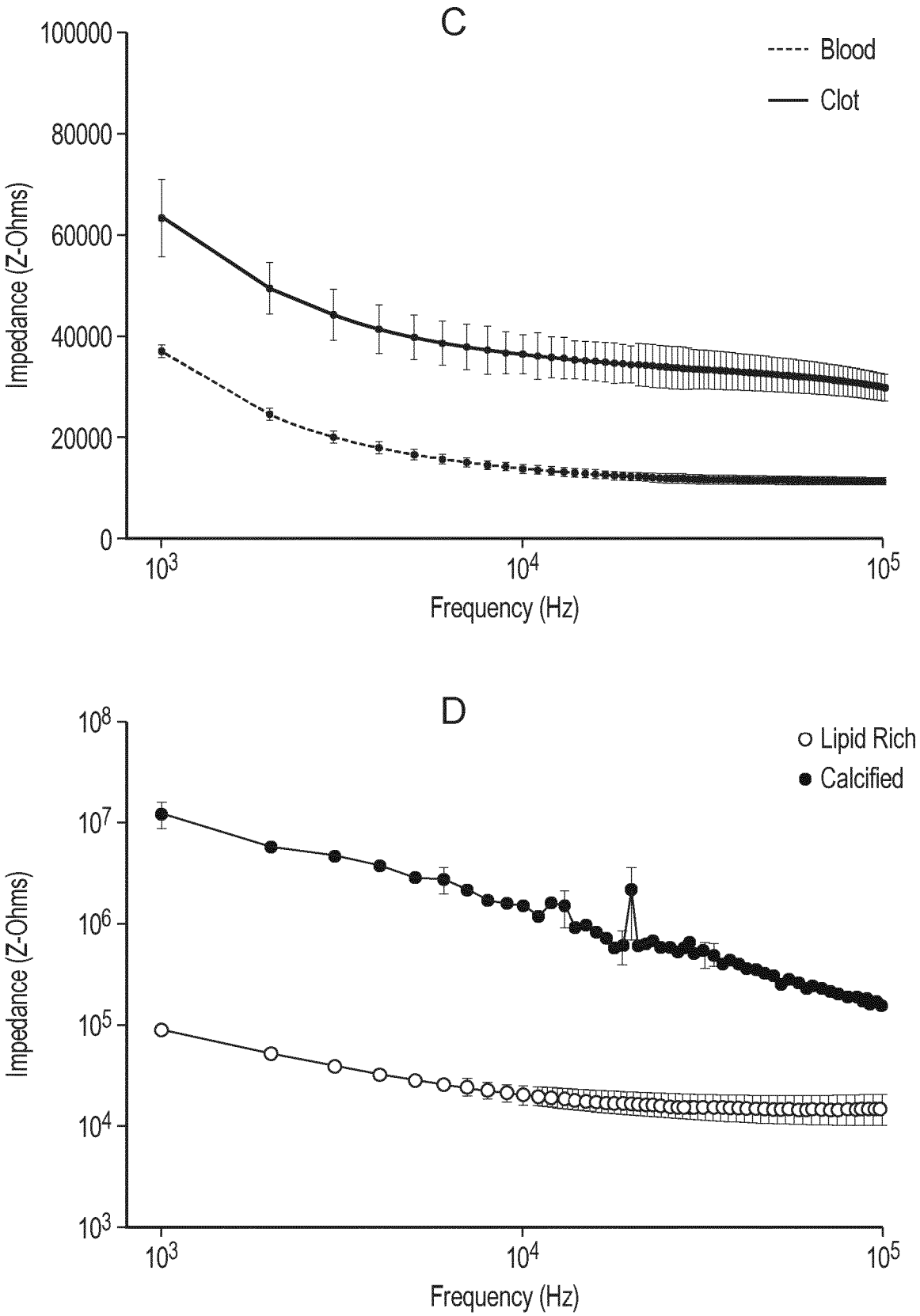


FIG. 11 (Continued)

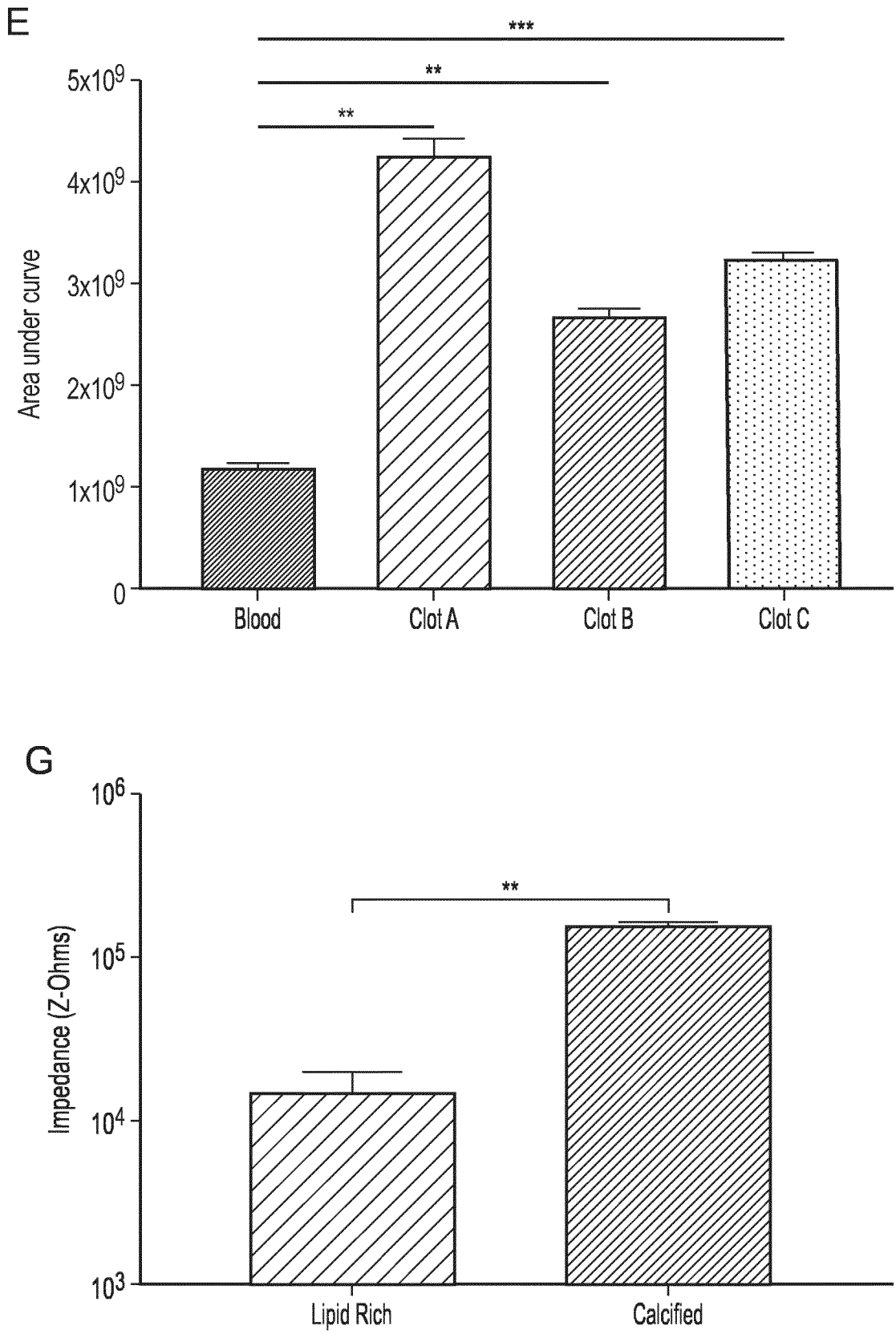


FIG. 11 (Continued)

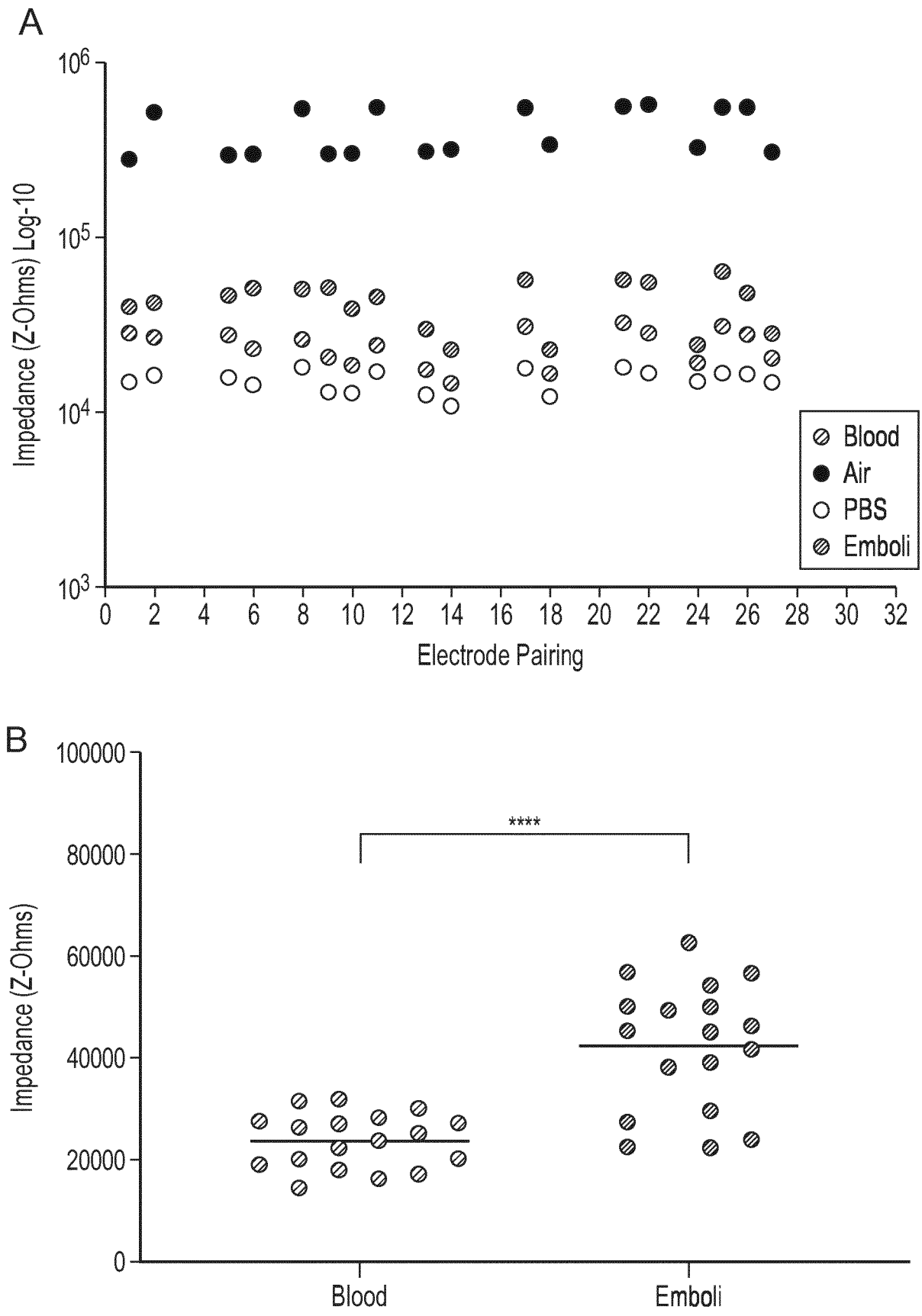
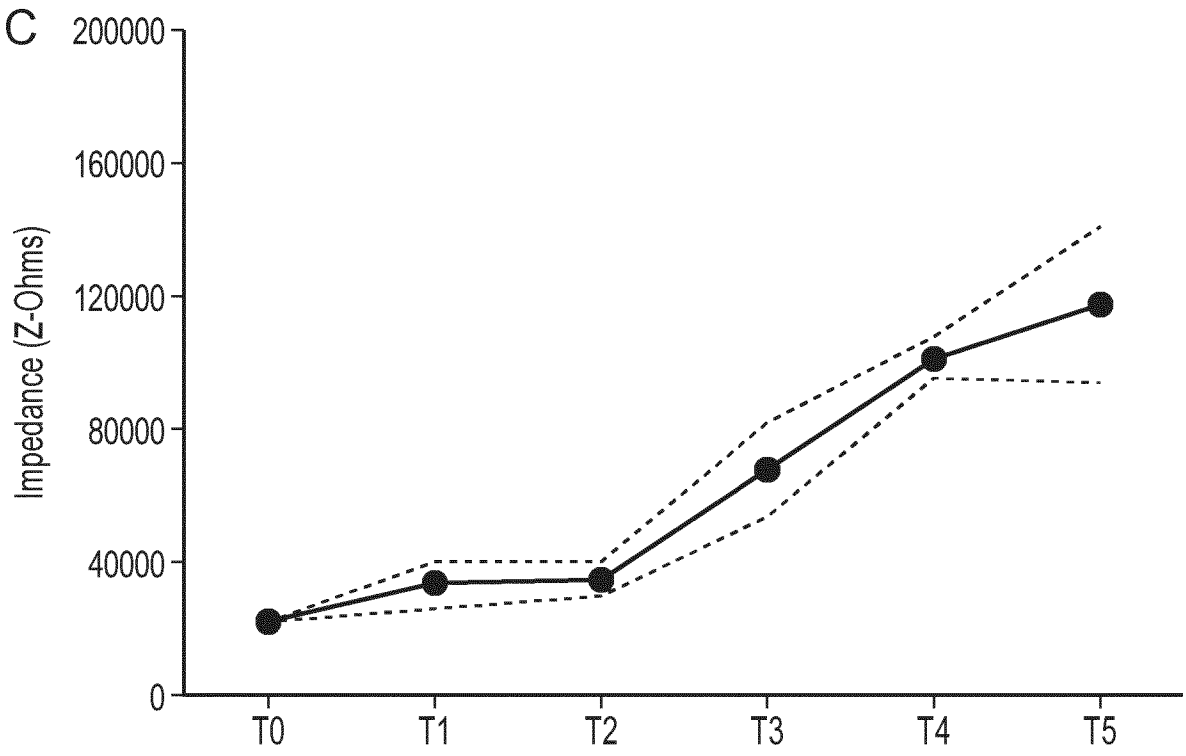

A
Impedance (Z-Ohms) Log-10
10^6
10^5
10^4
10^3
0 2 4 6 8 10 12 14 16 18 20 22 24 26 28 30 32
Electrode Pairing
Blood
Air
PBS
Emboli
B
Impedance (Z-Ohms)
100000
80000
60000
40000
20000
0
****
Blood
Emboli

FIG. 12



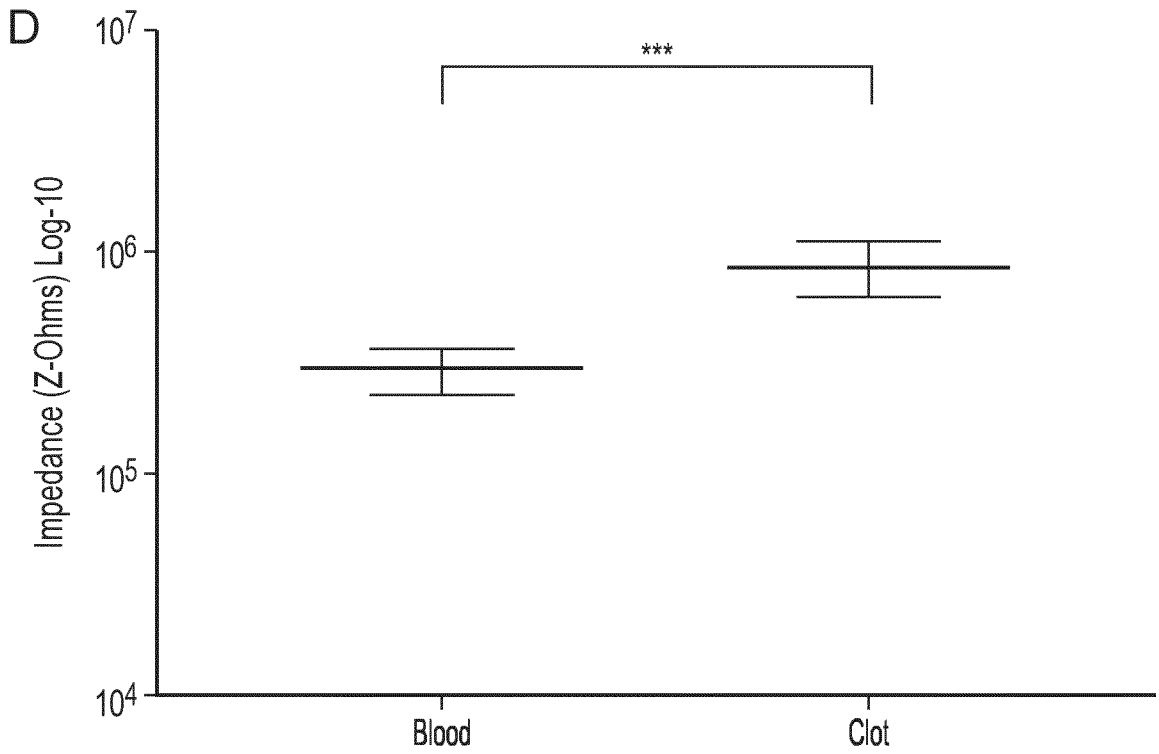


FIG. 12 (Continued)

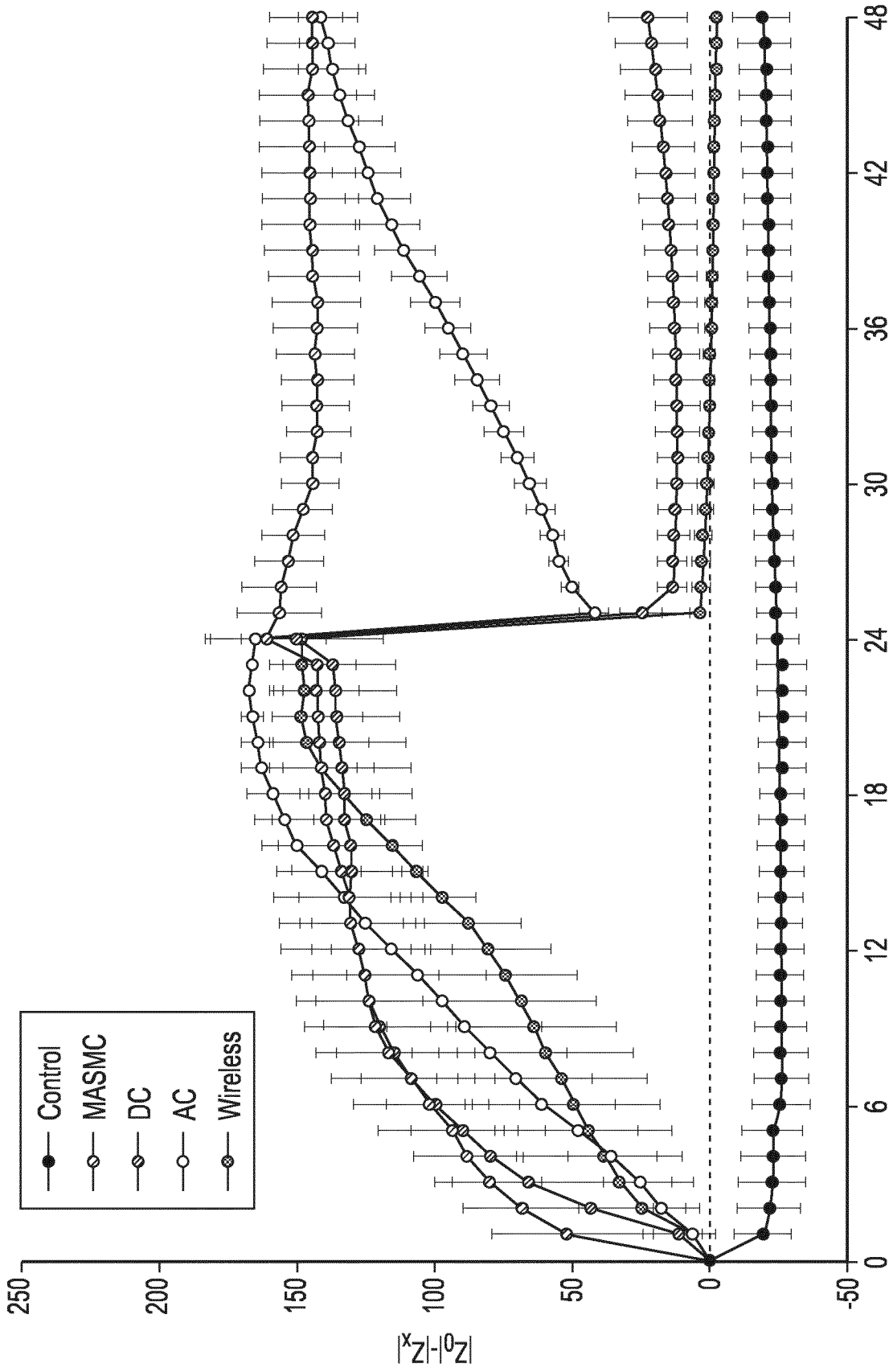

Control
MASMC
DC
AC
Wireless
250
200
150
100
50
0
-50
0
6
12
18
24
30
36
42
48
Time (Hours)
|Z0|-|Zx|

FIG. 13

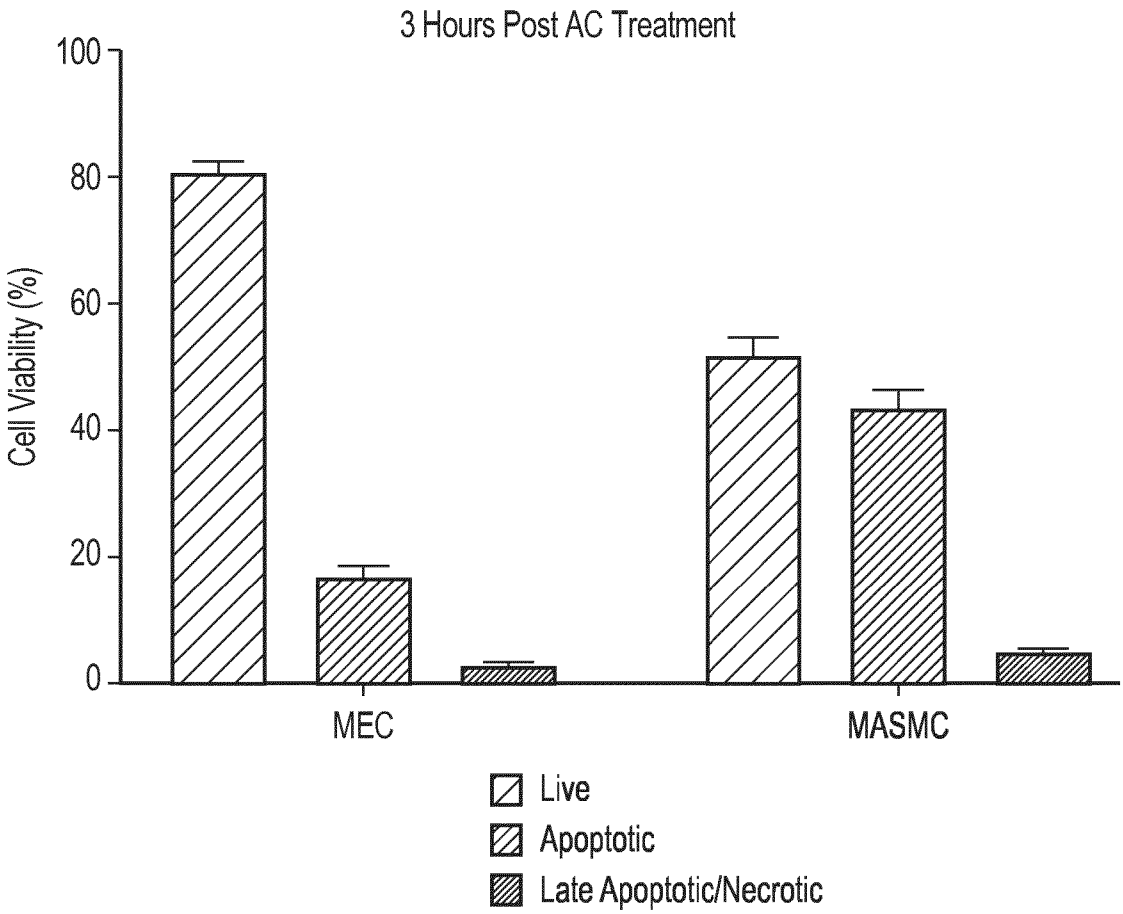

3 Hours Post AC Treatment
Cell Viability (%)
100
80
60
40
20
0
MEC
MASMC
Live
Apoptotic
Late Apoptotic/Necrotic

FIG. 14

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2024/067665

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61B5/00 A61B5/0537 A61B5/0538 A61N1/375
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61B A61N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2023/023897 A1 (MERCER JOHN RICHARD [GB] ET AL) 26 January 2023 (2023-01-26) paragraphs [0027], [0034] - [0039], [0059] - [0061]	1-15, 17-19
X	WO 02/058549 A1 (FRAUNHOFER GES FORSCHUNG [DE]; THIELECKE HAGEN [DE] ET AL.) 1 August 2002 (2002-08-01)	1,2,4,5, 14,15
A	pages 16-18; figures 1-4	6-10
X	US 2020/129087 A1 (SWEENEY FIACHRA M [IE] ET AL) 30 April 2020 (2020-04-30)	1,2,4,5, 14-16
A	paragraphs [0079], [0105], [0143], [0184], [0195] - [0220], [0267]; figures 2-4	6-10
X	US 2007/083239 A1 (DEMARAIS DENISE [US] ET AL) 12 April 2007 (2007-04-12)	1,3,5-9
A	paragraphs [0052], [0084] - [0087]	12

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance;; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance;; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
19 September 2024	08/10/2024

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Dydenko, Igor

1

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2024/067665

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 2023023897 A1	26-01-2023	NONE	
WO 02058549 A1	01-08-2002	DE 10103503 A1	14-08-2002
		WO 02058549 A1	01-08-2002
US 2020129087 A1	30-04-2020	EP 3629921 A1	08-04-2020
		US 2020129087 A1	30-04-2020
		US 2023414124 A1	28-12-2023
		WO 2018220146 A1	06-12-2018
US 2007083239 A1	12-04-2007	NONE	