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(54) Title: LOW VOLUME ASSAY APPARATUS AND METHOD

(57) Abstract:

# Low Volume Assay Apparatus and Method

The present invention relates to an apparatus and a method for analysing a biological fluid sample to determine a disturbance of haemostasis resulting in a change of viscosity.

More particularly but not exclusively there is disclosed an apparatus and method for measuring the coagulation properties of a fluid sample. In embodiments, the method and apparatus may be used to determine the coagulation or prothrombin time (PT) of a sample of blood or plasma. This may be expressed as an Internationalised Normalised Ratio (INR). Other coagulation properties that may be determined include measurement of the degree of platelet aggregation, the rate or amount of clot formation and/or clot dissolution, the time required for forming a fibrin clot, the activated partial thromboplastin time (APTT), the activated clotting time (ACT), the protein C activation time (PCAT), the Russell's viper venom time (RVVT) and the thrombin time (TT).

Coagulation of blood in a living body, thrombosis, is one of the leading causes of death world-wide. People who suffer from cardiac or vascular diseases and patients that have undergone surgical procedures are at risk of developing blood clots that may result in life-threatening clinical conditions. Such people are often treated with blood-thinning or anticoagulant drugs such as warfarin or aspirin. However, the amount of anticoagulant in the bloodstream must be maintained at the proper level: too little may result in unwanted clotting whilst too much can result in haemorrhaging with life threatening consequences. As a result, routine coagulation screening tests have been developed in order to evaluate the coagulation status of blood or plasma.

Various apparatus' have been developed for use in the laboratory and as point of care testing (POCT). In addition to this, devices have been developed which allow patients to home-monitor their blood coagulation, such as the InRatio™ monitor (Hemosense) and the CoaguChek™ monitor (Roche) which determine prothrombin time (PT). The CoaguChek™ device is suitable for use with capillary blood wherein a test-device designed to receive a sample of capillary blood is inserted into a test meter. The sample of capillary blood may be conveniently obtained by lancing a finger tip with a

lancet.

Many conventional devices for determining a coagulation property of a sample of fluid are large and heavy making them unsuitable to be carried around by the user. A user may be required to test for a clotting time of their own or another's blood on a regular basis in order to ensure good health. Accordingly, there is a need for an apparatus having improved portability.

The rate of coagulation of a sample of fluid is affected by the temperature at which the reaction takes place. A portable device for determining a coagulation property of a sample of fluid may be exposed to a wide range of temperatures thus increasing error in detection of, for example, prothrombin time. For this reason, coagulation devices are provided with a heating means which serve to heat the fluid sample to a particular temperature.

A user may be required to test either themselves or a patient on a regular basis using a lancet to draw capillary blood. Such capillary blood samples are typically taken from a convenient bodily extremity such as a fingertip. However, this is a sensitive area containing many nerve endings and obtaining a large sample of blood, i.e. of the order of 25uL or greater can be painful. Furthermore, it is often difficult to obtain such large quantities without applying significant pressure to the lanced area. This can result in problems such as insufficient quantities of fluid sample being applied to the device requiring the user in many cases to repeat the test. Prior art devices frequently require such significant quantities.

As the measurement of coagulation is often time based, it is important to be able to accurately determine the time at which the coagulation reaction starts and a time when coagulation has been deemed to occur.

Prior art devices typically comprise a disposable device for use with a meter, the user inserting the device into the meter and then applying a sample of fluid to be tested. It is important that the device be properly filled as factors such as underfilling and the presence of air-bubbles may result in measurement errors.

It is an object of the invention to provide an apparatus and method which is able to accurately determine the time at which a coagulation event takes place in a fluid sample.

It is a further object of the invention to provide a device for use with a meter for determining the coagulation time of a fluid wherein the test-device has a low volume requirement.

It is a further object of the invention to provide a meter which is provided with heating means and temperature monitoring means which are able to rapidly heat the fluid sample and to monitor the temperature of the device.

It is a further object of the invention to provide a meter for measuring coagulation times that is easily portable and has a low power requirement.

Together, the device and the meter may make up the apparatus. The meter is provided with means to receive the device, and the device is used in conjunction with the meter in order to carry out the test. The device is typically disposable and the meter designed to be reused. Alternatively the meter and device may be provided as a single integral unit, removing the need to insert and position the device.

The invention is set out in the claims.

According to a first aspect, the invention provides a meter for determining a coagulation property of a sample of fluid, the meter comprising an electromagnetic coil and a device receiving means for receiving a device.

According to a further aspect, the invention provides a meter for determining a coagulation property of a sample of fluid, the meter comprising a single electromagnetic coil having one or more windings defining an internal space. The device receiving means may be arranged such that the device is capable of being positioned at least partially within said internal space.

According to a further aspect, the invention provides a device for use with a meter for

determining the coagulation status of a fluid sample, the device having at least a fluid chamber containing a magnetic body.

According to a further aspect, the invention provides for an apparatus for determining the coagulation status of a liquid, the apparatus comprising a fluid chamber for holding a quantity of said fluid, a magnetic body disposed in the chamber and an electromagnetic coil, the electromagnetic coil co-operating with said magnetic body and being arranged in use to provide a magnetic field which causes the body to move to and fro within the chamber.

According to a further aspect, the invention provides for an electromagnetic coil for use in a meter for determining the coagulation status of a fluid sample, the electromagnetic coil having one or more windings defining an internal space of dimensions such that a device is capable of being positioned at least partially within it.

According to a further aspect of the present invention there is provided a method of determining the coagulation status of a fluid sample comprising the steps of: providing a sample of liquid in a chamber containing a body and applying a magnetic field to the chamber to cause the body to move to and fro within the chamber through the fluid sample.

According to a further aspect, the invention provides for a meter having temperature heating and monitoring means by which to rapidly heat a fluid sample to a particular temperature or temperature range and to accurately monitor the temperature of said sample.

The various aspects of the invention will now be described in more detail.

The device receiving means provided by the meter may be any means which enables the device to be held accurately and reproducibly within or by the meter. The device receiving means may for example be a cavity in which the device may be placed or inserted. Alternative device receiving and holding means may be employed such as a lock and key mechanism wherein a female feature provided by the device may be arranged so as to cooperate and engage with a corresponding male feature on the test-

device and *vice-versa.*

In the case where a meter having a single electromagnetic coil is provided, the cavity may be arranged so as to be at least partially within the internal space as defined by the one or more windings of the coil. .

In the case where an electromagnetic coil having an air core is provided, the electromagnetic coil may be wound about a central axis so as to form an internal air space or air core. The coil may have the form of an open tube. However other forms may be contemplated such as an elongated triangular, ellipsoid, rectangular, square shape and so on, each one defining an internal space.

The device for use with the meter is provided with at least a fluid chamber for receiving a fluid sample. The device may additionally be provided with a fluid application port in fluidic connection with the chamber as well as one of more flow channels in fluidic connection with the fluid application port and chamber. One or more vents may be provided with the device to allow for ingress of fluid sample. The dimensions of the fluid pathways are preferably chosen such that fluid may flow into the chambers under the influenced of capillary force. The dimensions of the chambers may be chosen such that the flow is largely uninfluenced by gravity such that a test may be carried out on a surface that may not be completely horizontal. However, other means of transporting fluid through the device may be contemplated such as electroosmotic flow, magnetic pumping.

Provided within the chamber is a reagent or reagents able to influence the coagulation status of the fluid sample, the nature of which is dependent upon the test to be carried out. For example when the test to be performed is the determination of prothrombin time, the reagent will comprise thromboplastin. Further fluid chambers may be provided containing the same or different reagents which may act as a control to ensure that the test is carried out correctly. Further provided in the or each chamber is a magnetic body. A single magnetic body is preferred although the or each chamber may be provided with one or more magnetic bodies.

The device may have any suitable form. According to an embodiment, the device is

provided in the form of an elongated test-strip. The fluidic pathways will largely be sealed from the environment within the device apart from the sample application port and any air vents. The device may be prepared by lamination of a number of substrates, injection moulding and by other fabrication methods known in the field of microfluidics.

The position of the chamber in relation to the electromagnetic coil is chosen such that in use the magnet passes through a high magnetic field density (i.e. a large number of magnetic field lines) when moving to and fro within the fluid chamber. This creates the highest force on the magnet and therefore gives the best power efficiency

In the case of the electromagnetic coil having a central air core, the chamber is positioned so as to be at least partially within the central cavity defined by the coil so as to correspond to a position having a high field density.

One advantage provided by the use of a hollow electromagnetic coil is that the device may be placed in a region of high magnetic field strength as defined by the electromagnet. Thus the device may be placed either close to or preferably at least partially within the hollow core of the electromagnet itself, the magnetic body of the device effectively acting as the central core of the electromagnet. Placing the device, or more accurately the chamber containing the magnetic body, in a region of high magnetic field strength enables a large perturbation of the magnetic field by the magnetic body of the device which in turn provides a large force to move the magnet. Furthermore the use of a single electromagnet, in particular an electromagnet having a hollow core, reduces the weight, size and power requirements of the device.

Means may be provided to detect movement and/or position of the body within the chamber. Such means preferably comprises a magnetic field sensor such as a Hall Effect sensor, magnetorestrictive sensor, search coil or any other means of detecting a change in magnetic field. In an embodiment at least one sensor is provided, each sensor associated with a respective chamber. In operation the magnetic field measured by the sensor will, amongst other things, be affected by the position of the body relative to the sensor. Thus, the output of a sensor can be used to determine position and/or movement of the body in the chamber. The sensor may also respond to

the rate of change of magnetic field detecting motion.

The magnetic body of the device is preferably chosen to have a high field strength. This enables an electromagnetic coil of low field strength to be used which reduces the power requirements of the device. Furthermore the use of an electromagnetic coil with a low magnetic field strength provides for a low background signal as measured by the magnetic field sensor. Furthermore, subsequent perturbation of magnetic field by the high field strength magnet during measurement provides a large signal to background ratio. Thus to ensure a high signal to background ratio, it is advantageous that the ratio of magnetic field strength of the magnetic body compared to that of the electromagnet is also high. Yet a further advantage provided by this arrangement is that it reduces the need to reproducibly and accurately locate the device with respect to the magnetic field sensor. This in turn allows for a greater tolerance for the device locating means and therefore lower manufacturing cost.

Other or additional detection means for determining the position of the magnetic body may also be provided such as optical, laser, rf.

The invention also provides a device for use with a meter for determining a coagulation property of a sample of fluid, the device containing at least one magnet having a field at the tip greater than 50 mT. When power is applied to the electromagnetic coil, the magnet is caused to move in a reciprocating (to and fro fashion. The higher the energy supplied by the coil, the greater the magnetic field produced thereby. Provision of a magnet having a higher field strength allows for a smaller magnetic field to be generated by the electromagnetic coil of the meter. This further reduces power consumption of the meter.

The invention further provides a device for use with a meter for determining a coagulation property of a sample of fluid, wherein the device operates with a sample of fluid of less than 3 µl. Such a drop may be conveniently obtained from capillaries by use of a lancet.

It is a commonly held belief that there is a lower limit of volume of capillary blood samples that may be used for testing of coagulation time due to the high levels of

interstitial fluid that exist in such samples which in turn gives rise to errors in the measurement of coagulation time. However, surprisingly the red blood cell count of very low volume samples of capillary blood obtained from fingers is not substantially affected and accordingly accurate coagulation measurements may be performed on easily obtained small quantities of blood.

In order to ensure complete filling of a device for use with a device for determining a coagulation property of a sample of fluid, each cavity of the device has at least one fill channel and a plurality of vent channels. A channel may be provided at each corner of the cavity. Placing channels at each corner of the detection chamber ensures complete filling of the detection chamber with reduced likelihood of formation of air gaps; this ensures consistent coagulation detection results.

The invention provides a method for determining a coagulation property of a sample of fluid whereby the magnet is caused to move in a to and fro fashion through the fluid present in the chamber. The amplitude of the signal for example obtained from a Hall effect sensor, is dependent upon the rate of movement of a magnet. As the rate of travel of the magnetic body through the fluid starts to decrease, the amplitude starts to decrease. The coagulation time may be considered as the time for complete cessation of movement of the magnetic body or when the amplitude of the signal has decreased to below a certain threshold.

In addition an initial mixing phase at a first frequency can precede a measuring phase at a second frequency to improve fluid homogeneity.

Furthermore, by causing the magnet to move to a predetermined position once a fluid starts entering the device, consistent filling of the chamber may be achieved by ensuring a defined capillary flow around the magnet.

The energy supplied to the electromagnetic coil may be in the form of pulses, causing the magnet to effectively move within the chamber in the form of small pulsed movements. This has been shown to result in a linear movement of the magnet and helps to prevent twisting of the magnet causing it to stick to or become lodged within the chamber which may occur if larger amounts of energy are supplied to the magnet.

The number of pulses per translation of the magnet (i.e a complete to or fro movement) may be constant or it may vary. For example, once the sensor has detected that the magnet has arrived at the end of the chamber, it may signal the meter to stop delivering energy pulses to the coil, thus reducing the energy requirements of the meter. The polarity of the magnetic coil is thereafter reversed, and electrical pulses are once-more applied to the coil to allow the magnet to travel back through the chamber. A time interval may be applied between each or some of the to and fro movements, namely so that the magnet effectively rests, and this time interval may vary or be constant. A time interval may be useful for example to give the sample an opportunity to develop a clot. The meter may have pre-set time intervals. Alternatively, the duration and number of time intervals might be determined by the measurement process itself, for example by a feature of the measurement signal. As the fluid starts to clot, a larger number of pulses may be required to move the magnet from one end of the chamber to the other. The meter may measure the energy required to move the magnet over a fixed distance or measure the distance moved by application of a pulse of a fixed energy. When carrying out a measurement, the magnet may travel the entire distance of the chamber or a partial distance.

A device for use with a meter for determining a coagulation property of a sample of fluid contains a detection chamber for accepting a fluid sample, the detection chamber also containing a magnet which may be used to stir the fluid sample. If the detection chamber is filled with a substance other than a sample of fluid, or if the fluid sample in the detection chamber contains air, this can have a very detrimental impact on the accuracy of any measurement made. Furthermore, measurement accuracy can be prejudiced by non-homogeneity of the coagulation reagent within the fluid; a mixing phase can advantageously mix the reagent with the fluid sample in the chamber.

In order that the invention may be more clearly understood, embodiments thereof will now be described with reference to the accompanying drawings, of which:

Figure 1 shows a schematic of a device for use with a device;

Figure 2 shows the device in cross section through X-X of figure 1;

Figure 3 shows a meter for use with the device;

Figure 4 shows a cross-section of a device inserted into a meter;

Figure 5 shows two magnets being positioned within the device;

Figure 6 shows a method of power application to the coil of the meter;

Figure 7 shows an output signal from each of two Hall Effect sensors during a clotting test;

Figure 8 shows a control circuit for the meter;

Figure 9 shows a flowchart of a method for operation of the device; and

Figure 10 shows a flowchart of a method for moving the magnet.

A schematic of a device is shown in figure 1. The device preferably comprises a lower layer 12 which is shaped and a lid 13. The lower layer 12 illustrated is 40 mm in length by 8 mm wide with a thickness of 0.8 mm. The lower layer 12 is shaped so as to have a plurality of features present in a face thereof forming a top surface for the assembled device.

By way of example, the features of the lower layer of the schematic device illustrated in figure 1 will now be described. A triangular sample application feature 2 has a depth of 0.3 mm and is joined to at least one, in this example two, inlet channel 3 having a depth of 0.15 mm and a width of 0.3 mm. Each inlet channel 3 is in turn connected to a corner of an entry end of one of two adjacent detection chambers or cavities 4. The detection chamber 4 has a length of 3.5 mm, a width of 1.2 mm and a depth of 0.34 mm. A plurality of vent channels 5, 6 are joined to the detection chamber, the vent channels have a depth of 0.15 mm and a width of 0.15 mm. One vent channel 5 is shown at the entry end of the detection chamber 4 and two vent channels 6 are shown at an exit end of the detection chamber 4 at respective corners, allowing venting of gas traps, wherein said entry end of said detection chamber 4 is opposite the exit end.

Figure 1 shows a device comprising two detection chambers. These detection chambers are separated by 4mm. This separation is important to avoid one magnet signal affecting the other

It should be noted that a channel is proved at each corner of the detection chamber 4 which has a cross section substantially rectangular in shape and has a small but finite depth in a direction perpendicular to the plane of said cross section. It should further be noted that the fill and vent channels have a depth identical to that of the detection

chamber 4. However, the fill and vent channels may have a depth different to that of the detection chamber 4. For example, the fill and vent channels may have a depth between 0.15 mm and 0.1 mm. The depth of the fill and vent channels is preferable consistent along the length of the channel.

A plurality of vents 7, 8 are incorporated into the lower layer, each vent channel 5, 6 being joined to a vent 7, 8 respectively. In the schematic device shown, two vent channels 6 exit a detection chamber 4 and terminate at a common vent 8. The vents 7, 8 comprise circular recesses in the top surface of the lower layer having a diameter of 1mm and a depth of 0.4 mm. The device further comprises a locating hole 9 which passes through the device; this is discussed in more detail below. In addition, capillary breaks are provided at the junction of the vent channel and the vent (not shown). Thus fluid sample is able to pass along the vent channel as far as the capillary break.
One way stop features are provided to ensure that when reagent is placed in the chamber in liquid form it remains within the chamber until it is dried. However when blood is required to flow into the chamber , the stop does not impede its process

The injection moulded lower layer is treated in a plasma chamber so as to produce a hydrophilic layer on the top surface and micro-features of the lower layer. Then a commercially available thromboplastin solution is deposited into each detection chamber 4 of the lower layer. Preferably, each detection chamber 4 contains at least 0.4 µl of thromboplastin solution. The thromboplastin solution is subsequently dried.

The detection chamber is designed to accommodate a fluid sample for testing. The volume of blood required for a test is dependent upon the internal dimensions of the device and the external dimensions of each magnet 10. This volume can be less than 3 µl. In particular it is between 3 µl and 0.1 µl. More preferably, it is between 3 µl and 0.5 µl. Most preferably, it is between 2.75 µl and 0.75 µl. Preferably the volume includes both the volume of the detection chamber and the vent and fill channels.

Each detection chamber 4 of the device contains a neodymium magnet 10. The magnet 10 may comprise $NdFe_3B$. Each neodymium magnet 10 illustrated in figure 1 has dimensions of 3mm by 1mm by 0.25 mm. The detection chamber 4 illustrated in figure 1 has dimensions of 3.5 mm by 1.2 mm by 0.34 mm. Accordingly, the volume

of fluid contained by the detection chamber is 0.7 $mm^3$ or 0.7 µl. The ratio of magnet size to detection chamber size is 0.53.

The magnetic body preferably has a high magnetic field strength. However, it has been found that during manufacture of the device, it is difficult to place and retain such high strength magnets in the chamber. This is particularly so when the device has more than one chamber in close proximity to each other, each containing a magnet, as the magnets have a tendency to jump out and stick together. This problem may be overcome by the steps of placing a metallic body in the chamber, providing a upper laminate to seal the chamber and subsequently magnetising the metallic body to the required field strength *in-situ*. The presence of the upper laminate lid ensures that the magnetic body remains in the chamber and enables chambers to be placed in close proximity to each other. It also provides a convenient method of mass-manufacture of such devices and allows other metallic structures which are capable of attacting the magnetic body to be placed in close proximity to the device. Thus an aspect of the invention provides for a method of manufacturing a device comprising the steps of: providing a metallic body capable of being magnetised within a chamber, causing the movement of the metallic body to be restricted within the chamber and magnetising the metallic body whilst it is present within said chamber.

Each magnet may be chosen of a size such that it substantially fills each detection chamber. This ensures that a high field strength and provides a further advantage that only a small amount of fluid sample is required to fill the chamber. Furthermore substantially all of the fluid in the detection chamber is agitated during testing.

Further, each magnet 10 is sized relative to the detection chamber 4 such that there is a clearance or capillary gap surrounding the magnet when in the detection chamber so as to encourage detection chamber filling and ensure complete filling of the detection chamber. The above dimensions provide a capillary gap of 100 µm around the magnet which is appropriate for this purpose. Similarly, a 500 µm end gap is provided, presenting an optimum value between allowing sufficient magnet movement so as to provide a reasonable signal from the magnetic field sensor 24 yet still allow sufficient capillary effect to ensure filling of the detection chamber without air bubbles. A further advantage is that larger chamber may be employed without

compromising the low volume requirement of the device. Furthermore, provision of a large chamber and a large magnetic body enables the manufacturing process to be carried out more easily.

Each magnet 10 preferably has a field strength greater than 50 mT, more preferably 60 mT at the tip (i.e. at the extremities of the magnet at its respective north and south poles).

Figure 2 shows the completed device in cross section through X-X of figure 1. Each detection chamber 4 of the completed device contains both a reagent 11, for example a clotting agent such as thromboplastin, and a magnet 10. The device 1 is shown as comprising the injection moulded lower layer 12, thromboplastin 11, at least one neodymium magnet 10 and a laminate lid 13 bonded to the lower layer 12.

An electromagnet 20 forming part of a meter for use with device 1 for detecting a clotting event in a sample fluid is shown in figures 3 and 4. The device may be inserted into the hollow core 50 of the electromagnet. When the device is in the use position, each magnet 10 in each detection chamber 4 may be positioned inside the hollow core of the electromagnet 20.

A female feature provided by the device may be arranged so as to cooperate and engage with a corresponding male feature on the meter. Alternatively, a male feature may be provided by the device and arranged so as to cooperate and engage with a corresponding female feature on the meter.

The magnets 10 have a north-south magnetic pole axis which is parallel to the north-south axis of the electomagnet. The magnets 10 are preferably orientated in the detection chamber 4 such that the end having a north pole is arranged at an end of the detection chamber proximal to the fill channel. Accordingly, a known field may be applied to the device in order to move the magnets 10 to a particular end of the detection chambers 4. By magnetising the material in the strip it is further ensured that the magnets move in the same direction when the electromagnet is energised.

Figure 4 shows a cross sectional view of the meter 20 with a device 1 inserted, also in

cross section. The meter 20 comprises a conducting coil 21 at least one Hall Effect sensor 24 arranged to detect the position of a magnet 10 in each detection chamber 4. The meter 20 also comprises at least one optical sensor 22, 23 these optical sensors preferably comprise LED light sources and conventional optical transistors. The use of optical sensors and the operation of the optical sensors is discussed in more detail below.

According to one embodiment, the coil 21 has a direct current resistance of 70 ohms and is driven by a 5 V power supply.

The coil 21 may have the form of an open tube. The coil may have a cross-section of any other shape, such as for example: triangular, ellipsoid, rectangular, square, circular, etc.

In the multi-chamber configuration shown, a Hall Effect sensor 24 is provided for each detection chamber 4. The Hall Effect sensor 24 is preferably positioned such that a mid point of a detection area of the Hall Effect sensor is aligned with one end of the magnet 10 when the magnet is centred in detection chamber 4. In addition, a heater 42 and temperature sensor 45 is provided adjacent the chamber.

The meter comprises first optical sensors positioned so as to detect a sample fluid passing each inlet channel 3 of each detection chamber 4 and second optical sensors positioned so as to detect the sample fluid passing along each vent channel 5 when a device is inserted into the meter. Alternatively, second optical sensors may be positioned so as to detect the sample fluid passing along each vent channel 6.

Typically, the magnetic field strength at the device 1 generated by the coil 21 is approximately 15 mT. This is a smaller field than prior art meters and preferably reduces the power consumption of the device, making the device lighter and cheaper to run.

Figure 8 shows a functional block diagram of a control circuit for meter 20. A microprocessor 40 receives inputs from each Hall Effect sensor 24, each optical sensor 22, and a temperature sensor 45. The microprocessor 40 is connected to

amplifier 43 and 44 which provide power to coil 21 and the heating element 42 respectively. The microprocessor is further connected to display 41, which may be used to indicate a measurement result to a user. The result may be displayed for example as a clotting time or an International Normalized Ratio (INR) value.

The heating element 42 may comprise a resistive coil which generates heat when a current is passed therethrough. The heating element may comprise a ceramic plate with resistive carbon ink printed on top. Such a heating element may have a resistance of 18 ohms. The heating element 42 may alternatively comprise a Peltier device. The peltier device functions as a heat pump and is preferably connected to a heat sink.

The heating element 42 preferably functions to heat the device receiving cavity and device to a predetermined temperature as monitored by temperature sensor 45, prior to the device and meter being used to perform a measurement. Temperature sensor 45 may comprise a conventional thermopile arranged to measure infra red radiation emitted by the device. Accordingly, the thermopile is spaced from the device by an air gap; the air gap may be around 3 mm. The thermopile outputs a voltage signal proportional to the temperature of an infra red source the thermopile is directed towards. Preferably, the temperature sensor 45 is directed towards the device 1, rather than the heating element 42; the temperature sensor thus measures the temperature of the device and not the heating element 42, which may be hotter or cooler than the device 1. This reduces error in the temperature measurement of the device caused by variables such as thermal, lag, contact pressure, flatness of the device and the like and allows an accurate feedback loop to maintain the temperature at a predetermined desired value. This in tun provides for a more accurate determination of the result as the clotting time is temperature dependent.

The meter 20 displays an indication on display 41 when the device and meter reach the predetermined temperature. The indication may be "ready to test". Upon receiving this indication a user may introduce a fluid sample to the device. If an ambient temperature in which the device and meter are being used is greater than the predetermined temperature, then where the heating element 42 is a peltier device, a reverse polarity current may be applied to the peltier device in order to cool the device

and device receiving cavity.

The predetermined temperature will depend upon the nature of the test to be performed. In the case of measurement of prothrombin time, the temperature is chosen to be 37 °C.

The operation of the device and meter will now be described with reference to measuring a coagulation time of a fluid sample. A device is inserted into the device receiving cavity of the meter. A fluid sample is placed at the front of the device at sample application feature 2. The fluid moves by capillary action inside the device. The fluid is taken up from the sample application feature 2, along each inlet channel 3 into each detection chamber 4. The sample fluid continues to flow through each inlet channel 3, filling each respective detection chamber 4 and continues to flow out through vent channels 5 and 6. The sample fluid stops flowing when the fluid in the vent channels 5 and 6 reaches capillary breaks 7 and 8 respectively. Placing channels at each corner of the detection chamber ensures complete filling of the detection chamber with reduced likelihood of formation of air gaps; this contributes to ensuring consistent coagulation detection results.

In a preferred embodiment, the fluid moves through the device by capillary action. However, other standard means of transporting fluid into the device may be contemplated such as electroosmotic flow.

As described above, optical sensors are provided for detecting a sample fluid entry event and/or a detection chamber full event. A sample fluid entry event may be defined as detection of sample fluid in a fill channel of the device. A detection chamber full event may be defined as detection of sample fluid in at least one vent channel of the device.

Upon detecting sample fluid in the inlet channel 3 of the device 1, which defines a fluid entry event, the meter 20 begins timing.

Also, upon detecting a fluid entry event, a fill signal is applied to the coil 21 to create a magnetic field of a fixed polarity such that the magnets 10 in the detection chambers

4 are repelled away from the coil 21 towards the sample application feature 2 of the device 1, as shown in figure 5. This positioning of the magnets during a fill stage ensures reproducible filling of the chamber with fluid sample. Accordingly it is advantageous to fix the magnet in a known position in order to provide consistent fill characteristics for different tests. The fill signal is maintained for 3 seconds after which time the chamber is assumed to be full.

After the fill signal, a mix signal is applied to the coil 21, the mix signal producing oscillating magnetic fields having opposing polarities. The mix signal preferably produces an oscillating magnet field around the coil 21 oscillating at approximately 8 Hz. The mix signal is applied for 5 seconds in order to ensure mixing of the fluid sample and the reagent 11 shown in figure 2.

After the mix signal, a measure signal is applied to the coil 21. The measure signal producing oscillating magnetic fields having opposing polarities and initially oscillating at approximately half the frequency of the mix signal. The mix signal preferably produces an oscillating magnet field around the coil 21 initially oscillating at approximately 4 Hz. During the application of the measure signal, the period of oscillation of the magnetic field around coil 21 is preferably increased by 15 milliseconds per cycle. An example of this method of power application to the coil is shown schematically in figure 6.

The measure signal is applied to the coil 21 until detection of a coagulation event as described in more detail below.

The coil 21 draws a direct current of 71 mA when connected to 5 V power source. In order to reduce power consumption, the coil is operated at a 50% duty cycle at a frequency of 50 Hz. This reduces the average current consumption to around 35 mA. Further, during any one half cycle the magnet may only be powered for a portion of the half cycle. Current is applied having a first polarity during a portion of a first half cycle and then current is applied having a second polarity for a portion of a second half cycle, the second polarity being opposite the first polarity. For example, if the magnet is oscillating at 2Hz, then a half cycle has a 250 ms duration. During a first half cycle a signal of a first polarity is applied to the coil for 100ms, then, during the

second half cycle a signal of a second polarity is applied to the coil for 100ms. Preferably, the signal of a first or second polarity comprises pulsed voltage; the duty cycle of the pulses may be reduced in order to conserve power.

The pulsing of current in opposite directions preferably comprises the application of an alternating voltage source; the alternating voltage source may comprise a square wave signal, a sinusoidal signal, or a triangular waveform signal.

In order to detect movement of the magnet a signal output from each of the Hall Effect sensors 24 of meter 20 is processed as shown in figure 7. A peak amplitude 31 of the signal output from each Hall Effect sensor indicates the motion of the tip of the magnet 10 as it oscillates. The signal output indicates that the magnets perform a reciprocating motion in response to the field applied by the coil 21. As the magnetic body begins to slow indicating that the fluid sample or blood is undergoing a clotting event, the amplitude, and speed of the magnet motion and the corresponding peak amplitude and/or speed of an output signal from the Hall Effect sensor is reduced 32.

Each magnet 10 is magnetised along a longest axis in a direction parallel to a direction in which it reciprocates upon application of the alternating magnetic field by coil 21. Accordingly, the magnetic field measured along the length of the magnet is minimum at the centre and maximum at the ends. As the magnet displacement within the detection chamber 4 varies, the output signal from the Hall Effect sensor varies also. Accordingly, it is possible to calibrate the output signal from the Hall Effect sensor 24 to define an amount of displacement of the magnet within the detection chamber 4. The correlation between Hall Effect sensor output signal and magnet displacement is non linear as the magnet tip moves passed the Hall Effect sensor 24. This non linearity is accounted for during calibration.

A coagulation event may be defined as the time at which the magnet has ceased to move or when it has slowed down to a particular extent. It can readily be determined by measurement of the amplitude of the signal or by the change or rate of change in the signal amplitude. the fluid sample or blood clots, preventing the magnet from moving and can be further defined as a predetermined reduction in Hall Effect sensor output signal amplitude from an average amplitude.

The extent of change in amplitude may be dependent upon factors such as the INR of the blood, the size and shape of the magnet and the ratio or difference of the field strength of the magnet compared to that of the electromagnet. For example, a clotting event may be deemed to have occurred when the signal amplitude is 70 % of the average amplitude signal, the average amplitude signal being the average of all the amplitude measurements measured during the a particular time frame such as first 5 seconds of measurement.

Alternatively a moving average smoothing may be applied to the magnet motion signal and then an amplitude drop measured

Figure 9 shows a flowchart of a method for operation of the apparatus. The method comprises detecting 71 a fluid entry event using the optical sensor 22, 23, which causes the start 72 of a coagulation timer and the application 73 of an initialization signal to the coil 21. The coagulation timer is implemented by microprocessor 40. Upon either: detection 74 of a chamber full signal form another or the same optical sensor 22, 23; or the expiry 75 of a predetermined time out of 3 seconds; the apparatus applies 76 a mix signal to the coil 21 for 5 seconds. After 5 seconds 77 of the mix signal, a measure signal is applied 78 to the coil and the amplitude of the magnet movement is detected 79. A threshold value is calculated 80 from the measured the amplitude of the magnet movement by multiplying the measured value by a fraction such as 70%. The measure signal is applied 78 until the apparatus detects the amplitude of the magnet movement reducing 81 to a value less than the threshold value, which defines the occurrence of a coagulation event. Upon detection of the coagulation event: the coagulation timer is stopped 82; the measure signal is stopped; and the measured coagulation time is output 83 by the apparatus.

Figure 10 shows a flowchart of a method for moving the magnet, said method comprising: moving 91 the magnet; detecting 92 a position of the magnet; determining 93 whether the detected position of the magnet is within a preferred range; and moving 94 the magnet again if the detected position of the magnet is not within a preferred range.

A method of manufacture of the device shown in figure 1 will now be described. The lower layer 1 is preferably formed from polystyrene by injection moulding techniques known in the art. The lower layer illustrated is 40 mm in length by 8 mm wide with a thickness of 0.8 mm. The lower layer is shaped during moulding so as to have the plurality of micro-features present in a top surface.

The injection moulded lower layer is treated in a plasma chamber. The plasma chamber causes a hydrophilic layer to be deposited on the top surface and micro-features of the lower layer.

A commercially available thromboplastin solution is deposited into each detection chamber 4 of the lower layer. The thromboplastin solution may be deposited using a deposition station such as those provided by Horizon Instruments Ltd, UK. Preferably, at least 0.4 µl of thromboplastin solution are deposited in each detection chamber 4. It would be apparent to one skilled in the art that a plurality of other known thromboplastin solutions are appropriate for use in this apparatus.

The deposited thromboplastin solution is dried by passing the lower layer through a heated chamber for 10 min at a temperature of around 65°C for 4 minutes and then a temperature of around 45°C for 6 minutes.

Following the deposition of the thromboplastin solution into each detection chamber 4 of the lower layer and the subsequent drying, a neodymium magnet 10 is placed into each detection chamber 4 in the device 1.

The lid is placed on the lower layer and attached thereto. The lid preferably comprises a polystyrene laminate 125 µm thick and is preferably attached to the lower layer by an adhesive. Alternative methods for attaching the lid to the lower layer are possible.

Once the lid is bonded to the lower layer, a 25 W carbon dioxide laser is used to cut through the lid material laminate to enable excess lid material to be removed from the edges of the lower layer. The 25 W laser is also used to pierce the lid above the vents 7, 8 so as to produce venting holes. In use, the venting holes allow air to escape from

the detection chamber 4 when sample fluid is introduced to the device 1 at the sample application feature 2.

The arrangement set out herein gives rise to a range of advantages. The use of a strong magnetic material such as $NdFe_3B$ for each magnet 10 in the detection chamber 4 is advantageous for various reasons.

Firstly, a smaller magnetic field is required to be produced by the electromagnetic coil 21 in order to produce a particular propulsion force to drive the magnet 10 through the fluid sample in the detection chamber 4. The coil 21 may thus be smaller and will consume less power so the meter 20 may have a smaller power supply. This is particularly advantageous in embodiments where the meter 20 is portable and is powered by batteries.

Second, a stronger magnet 10 produces a higher signal strength at the Hall Effect sensor 24. Accordingly, a signal to noise ratio of the Hall Effect sensor output is reduced allowing for improved accuracy in detection of a coagulation event.

Positioning the Hall Effect sensor 24 such that it is aligned with one end of the magnet 10 when the magnet is centred in detection chamber 4, maximises a change in magnetic field and accordingly output signal from Hall Effect sensor 24 as the magnet moves from one end of the detection chamber 4 to an opposite end. This also advantageously improves the signal to noise ratio of the signal output by each Hall Effect sensor 24.

The two detection chambers shown in figure 1 are separated by 4mm. Positioning of the two chambers near to one another such that the magnets the same axis of magnetic alignment aligned parallel to one another such that the magnets are capable of interacting with one another has been shown advantageously to stabilise the magnets and stop them from twisting in the chamber when subjected to the magnetic fields of the electromagnet.

The output signal from the magnetic field sensor is proportional of the magnetic field strength. Thus, the absolute position and/or rate of movement of the magnet within the chamber may be derived from the output signal from the Hall Effect sensor 24. In

an alternative apparatus, it is thus possible to input only an amount of power into coil 21 required to move the magnet 10 across the detection chamber 4, instead of over driving the coil. The coil 21 is provided with a short duration signal to produce a short duration magnetic field. If the signal output from the Hall Effect sensor does not indicate the magnet is at a measurement extreme, such as at one end of the detection chamber 4, then another short duration signal is applied to the coil 21. If the fluid sample has not coagulated, then the magnet 10 will eventually reach an end of the detection chamber 4 and the process may be repeated with short duration signals applied to coil 21 having an opposite polarity. In this manner only a minimum amount of power is input into the coil 21 to move the magnet 10. This advantageously reduces power consumption of the meter 20. Furthermore such measurement methods may be employed to determine clotting times at high INR's or when the clot is weak. In such circumstances application of a pulse of short duration may may the device more sensitive to detecting a clotting event. Upon coagulation of the fluid sample the magnet 10 is prevented from traversing the detection chamber 4, which is detected by the Hall Effect 24 sensor as described above. Alternatively or additionally the power supplied to the coil may be caused to vary during the measurement.

Applying an excess of power to the electromagnetic coil causes excessive use of energy by the meter. This may cause excessive depletion of any finite power supply such as a battery which can reduce operable life and increase cost of operation. Furthermore, by detecting the position of the magnet during oscillation, only the minimum required energy need be applied to operation, conserving battery power.

In the example described above, the polarity of the magnets 10 is known in respect of their orientation in the detection chamber 4, and accordingly the polarity of field that must be applied to the detection chamber in order to move the magnets into a predetermined position during filling is known. In an alternative, the polarity orientation of the magnets 10 is not known, and so a preliminary fill signal is applied to the coil 21 and the position of the magnet 10 is detected by either hall effect sensors or optical sensors. If the magnet is in a desired predetermined position, the fill signal is maintained as described above. If the magnet is not in a desired predetermined position, the polarity of the fill signal is reversed and the position of the magnet 10 is

again detected. If the meter does not detect the or each magnet 10 being in a desired position, an error signal is produced.

In the above example, means is provided to detect the position of the magnetic body 10 within the detection chamber 4. In an alternative, a means is provided to detect movement of the magnetic body 10. In operation, the movement measured by the sensor will reduce due to a change in viscosity of the fluid sample brought about by a disturbance in haemostasis.

Alternatively still, at least one optical sensor may be used to detect the position of the or each magnet 10. In operation, a reduction in the frequency of changes in the optical transmission properties of the detection chamber 4 indicates a change in viscosity of the fluid sample brought about by a disturbance in haemostasis. The presence or lack thereof of a magnet 10 at a predetermined position of the detection chamber 4 determines the optical transmission properties of the detection chamber 4.

An alternative arrangement of the at least one optical sensor will now be described. An optical sensor may be provided for each detection chamber, the optical sensor positioned to detect the optical transmission, of both inlet channel 3 and vent channel 5. Upon a first transmission reduction event, fluid is detected in inlet channel 3, and upon a second transmission reduction event, fluid is detected in vent channel 5. Accordingly one optical sensor per chamber can be used to detect both a fluid entry event and a chamber full event.

It should be noted that while specific examples of signals applied to the coil 21 have been described above with reference to duty cycle and frequency, these signals are given by way of example only. The duty cycle of pulses applied to the coil must only be greater than 0% and is determined by the coil and power supply used. The frequency of oscillating signals such as the mix signal and the measure signal applied to the coil 21 are preferably between 1Hz and 50Hz.

In the above example, each detection chamber 4 contains a reagent 11. In an alternative, two detection chambers 4 are provided wherein only one detection chamber 4 contains a reagent 11, the other detection chamber 4 acts as a control

during the measurement process.

In the above case, the clotting time may be measured from the detected fluid entry event, which may be defined as time zero. An alternative measure of time zero may be measured by programming the meter 20 with a preset delay to account for filling characteristics of the device 1.

Alternatively, meter 20 may detect both a sample fluid entry event and a detection chamber full event and calculate a time zero according to a predetermined algorithm defined from measured filling characteristics of the device 1. Detection of a chamber full event may be used to trigger a transition from applying a fill signal to the coil 21 to applying a mix signal to coil 21 in lieu of the fixed 3 second time described above.

Further, the given example of reduction in the output signal of Hall Effect sensor 24 to determine cessation of magnet reciprocation is given as an example. Alternative methods for determining the cessation of magnet reciprocation may be applied.

A method for determining a coagulation or a clotting property of a sample of fluid is provided whereby the initial viscosity of the fluid sample is accounted for by measuring the amplitude of movement of a magnet located in the fluid sample prior to coagulation and then detecting a predetermined reduction in this amplitude to determine the occurrence of a coagulation event.

The above embodiments are described by way of example only, many variations are possible without departing from the invention as defined by the appended claims.

## Claims

1. A device for use with a meter for determining a coagulation property of a sample of fluid, said device having at least one cavity for containing a sample of fluid, the or each cavity containing a magnet for cooperation with the device, wherein the ratio of the volume of the magnet to the volume of the cavity is greater than 0.4.

2. A fluid sample strip as claimed in claim 1, wherein the ratio of the volume of the magnet to the volume of the cavity is greater than 0.5.

3. A fluid sample strip as claimed in claim 1 or 2, wherein the strip is arranged to receive an amount of sample comprising less than 3 μl.

4. A fluid sample strip as claimed in claim 1 or 2, wherein the strip is arranged to receive an amount of sample comprising less than 1 μl.

5. A fluid sample strip as claimed in claim 1 or 2, wherein the strip is arranged to receive an amount of sample comprising 0.7 μl.

6. A fluid sample strip as claimed in claim 1 or 2, wherein the or each cavity is arranged to receive an amount of sample comprising less than 3 μl.

7. A fluid sample strip as claimed in claim 1 or 2, wherein the or each cavity is arranged to receive an amount of sample comprising less than 1 μl.

8. A fluid sample strip as claimed in claim 1 or 2, wherein the or each cavity is arranged to receive an amount of sample comprising 0.7 μl.

9. A fluid sample strip as claimed in any one of claims 1 to 8, wherein the cavity is arranged for movement of the magnet in a movement direction, wherein a clearance or capillary gap between a side of the magnet and a wall of the corresponding cavity is formed in a direction transverse to the movement direction.

10. A fluid sample strip as claimed in claims 1 to 8, wherein the clearance or capillary gap between a side of the magnet and a wall of the corresponding cavity is

between 75 and 125 μm.

11. A fluid sample strip as claimed in claim 9, wherein the clearance or capillary gap is between 95 μm and 105 μm.

12. A fluid sample strip as claimed in claim 9, wherein the clearance or capillary gap is 100 μm.

13. A fluid sample strip as claimed in any one of claims 1 to 12, wherein the cavity is arranged for movement of the magnet in a movement direction, and wherein a movement gap between a side of the magnet and a wall of the corresponding cavity is formed in the movement direction.

14. A fluid sample strip as claimed in claim 13, wherein the movement gap is between 450 and 550 μm.

15. A fluid sample strip as claimed in claim 13, wherein the movement gap is between 490 μm and 510 μm.

16. A fluid sample strip as claimed in claim 13, wherein the movement gap is 500 μm.

17. A fluid sample strip for use with a device for determining a coagulation property of a sample of fluid, said strip having at least one cavity for containing a sample of fluid, the or each cavity containing a magnet for cooperation with the device, the strip being arranged to receive a sample comprising less than 3 μl.

18. A fluid sample strip as claimed in claim 17, wherein the strip is arranged to receive a sample comprising less than 1 μl.

19. A fluid sample strip as claimed in claim 17, wherein the strip is arranged to receive a sample comprising 0.7 μl.

20. A fluid sample strip for use with a device for determining a coagulation

property of a sample of fluid, said strip having at least one cavity for containing a sample of fluid, the or each cavity containing a magnet for cooperation with the device, the or each cavity arranged to receive a sample comprising less than 3 μl.

21. A fluid sample strip as claimed in claim 20, wherein the or each cavity is arranged to receive a sample comprising less than 1 μl.

22. A fluid sample strip as claimed in claim 20, wherein the or each cavity is arranged to receive a sample comprising 0.7 μl.

23. A fluid sample strip for use with a device for determining a coagulation property of a sample of fluid, said strip having at least one cavity for containing a sample of fluid, the or each cavity containing a magnet for cooperation with the device, wherein the cavity is arranged for movement of the magnet in a movement direction, wherein a clearance or capillary gap between a side of the magnet and a wall of the corresponding cavity is formed in a direction transverse to the movement direction.

24. A fluid sample strip as claimed in claim 23, wherein the clearance or capillary gap is between 75 and 125 μm.

25. A fluid sample strip as claimed in claim 24, wherein the clearance or capillary gap is between 95 μm and 105 μm.

26. A fluid sample strip as claimed in claim 23, wherein the clearance or capillary gap is 100 μm.

27. A fluid sample strip for use with a device for determining a coagulation property of a sample of fluid, said strip having at least one cavity for containing a sample of fluid, the or each cavity containing a magnet for cooperation with the device, wherein the cavity is arranged for movement of the magnet in a magnet direction and wherein a movement gap between a side of the magnet and a wall of the corresponding cavity is formed in a direction parallel to the movement direction.

28. A fluid sample strip as claimed in claim 27, wherein the two opposing sides of the magnet are in planes perpendicular to the movement direction.

29. A fluid sample strip as claimed in claim 27 or 28, wherein the movement gap is between 450 and 550 μm.

30. A fluid sample strip as claimed in claim 27 or 28, wherein the movement gap is between 490 μm and 510 μm.

31. A fluid sample strip as claimed in claim 27 or 28, wherein the movement gap is 500 μm.

32. A device for determining a coagulation property of a sample of fluid, the device comprising an electromagnetic coil and a strip receiving cavity for receiving a fluid sample strip, wherein:

at least a portion of the strip receiving cavity is disposed within the electromagnetic coil.

33. A meter for use with a device for determining a coagulation property of a sample of fluid, the meter comprising an electromagnetic coil having a hollow internal core and a device receiving means for receiving a device.

34. A meter according to 33 wherein the device receiving means is located in a position so as to enable the device to be disposed at least partially within the internal space defined by the electromagnetic coil.

35. A device as claimed in 33, wherein said electromagnetic coil has an axis and the strip receiving cavity is provided along said axis.

36. A device as claimed in 33, wherein said electromagnetic coil has a core volume and the strip receiving cavity is provided within the core volume.

37. A meter for determining a coagulation property of a sample of fluid, the device comprising:

a strip receiving cavity for receiving a fluid sample strip,

a heating element for maintaining the strip receiving cavity at a predetermined temperature, and

a temperature sensor for monitoring the temperature of the fluid sample device.

38. A device as claimed in 37, wherein said heating element is a resistive coil.

39. A device as claimed in claim 38, wherein said heating element comprises a printed pattern of resistive carbon ink.

40. A device as claimed in 37, wherein said heating element is a Peltier device arranged to heat said cavity.

41. A device as claimed in 40, wherein a polarity of a voltage applied to the Peltier device may be reversed so as to cool the device receiving cavity to the predetermined temperature.

42. A device as claimed in of claims 37 to 41 wherein the predetermined temperature is 37 °C.

43. A method for determining a coagulation property of a sample of fluid, said method comprising maintaining a sample of fluid in a cavity at a predetermined temperature.

44. A device for use with a meter for determining a coagulation property of a sample of fluid, said device having at least one cavity for containing a sample of fluid, the or each cavity containing a magnet for cooperation with the device, the or each magnet having a minimum field strength at the tip of 50 mT.

45. A strip as claimed in claim 44, wherein the or each magnet has a minimum field strength at the tip of 55 mT to 65 mT.

46. A strip as claimed in claim 44, wherein the or each magnet has a minimum

field strength at the tip of 60 mT.

47. A strip as claimed in any one of claims 44 to 46, wherein said magnet comprises an $NdFe_3B$ magnet.

48. A strip for use with a device for determining a coagulation property of a sample of fluid, said strip having at least one cavity for containing a sample of fluid, the or each cavity containing a magnet for cooperation with the device, the or each cavity further having a plurality of gas trap points, wherein each at least one cavity has a channel connected thereto at each gas trap point.

49. A strip as claimed in claim 48, wherein at least one of said channels is a fill channel.

50. A strip as claimed in claim 48 or 49, wherein at least one of said channels is a vent channel.

51. A strip as claimed in any one of claims 48 to 50, wherein each gas trap point is a corner of the or each cavity.

52. A strip as claimed in any one of claims 48 to 51, wherein the cavity is substantially cuboid in shape.

53. A method for determining a coagulation property of a sample of fluid, wherein a fluid sample strip contains a sample of fluid and at least one magnet arranged to oscillate therein, said method comprising:

causing oscillation of the at least one magnet;

detecting oscillation of the at least one magnet;

determining a coagulation event upon detection of a reduction in an amplitude of oscillation of the at least one magnet to an amplitude below a threshold value, wherein said threshold value is determined by measuring an amplitude of oscillation of the at least one magnet during an initial period of time of said oscillation and defining as the threshold value a predetermined fraction of the measured amplitude average movement.

54. A method as claimed in claim 53, wherein said threshold value is determined by taking an average of a plurality of measurements of an amplitude of oscillation of the at least one magnet during an initial period of time of said oscillation and defining as the threshold value a predetermined fraction of the measured amplitude average movement.

55. A method as claimed in claim 53 or claim 54, wherein the predetermined fraction is between 50 % and 90 %.

56. A method as claimed in claim 53 or claim 54, wherein the predetermined fraction is between 65 % and 75 %.

57. A method for determining a coagulation property of a sample of fluid, comprising causing oscillation of the at least one magnet, wherein said oscillation comprises:

a first oscillation within a first frequency range for a first period of time; and

a second oscillation within a second frequency range for a second period of time.

58. A method as claimed in claim 57, wherein said first frequency is greater than said second frequency.

59. A method as claimed in claim 57 or 58, wherein said method further comprises increasing the period of the second oscillation from an initial second frequency by a fixed time increment per pulse.

60. A method as claimed in claim 59, wherein the fixed time increment per pulse is 0.15 milliseconds.

61. A method as claimed in any one of claims 57 to 60, wherein the first frequency is 8Hz.

62. A method as claimed in any one of claims 57 to 61, wherein the first period of

time is 5 seconds.

63. A method as claimed in any one of claims 57 to 62, wherein the second frequency is 4Hz.

64. A method for determining a coagulation property of a sample of fluid in a device comprising a fluid sample chamber and a magnet moveable therein, said method comprising:

detecting a fluid entry event;

upon detection of a fluid entry event, causing the magnet to move into a predetermined position for a first period of time.

65. A method as claimed in claim 64, wherein said step of causing the magnet to move into a predetermined position for a first period of time comprises applying a signal of a first polarity to an electromagnetic coil.

66. A method as claimed in claim 64 or 65, wherein the first period of time is 3 seconds.

67. A method as claimed in claim 64 or 65, wherein the first period of time is terminated upon detection of a chamber full event.

68. A method for determining a coagulation property of a sample of fluid in a device comprising a fluid sample chamber and a magnet moveable therein, said method comprising:

moving the or each magnet;

detecting a position of the or each magnet; and

moving the magnet again dependent upon the result of the detecting step.

69. A method for determining a coagulation property of a sample of fluid in a device comprising a fluid sample chamber and a magnet moveable therein, said method comprising causing the magnet to oscillate between two preferred ranges by:

moving the magnet;

detecting a position of the magnet;

determining whether the detected position of the magnet is within one of the two preferred ranges;

if the magnet is not within a desired one of the two preferred ranges, then moving the magnet again;

if the magnet is within a desired one of the two preferred ranges, waiting for a predetermined time period to elapse before moving the magnet again.

70. A method for determining a coagulation property of a sample of fluid in a device comprising a fluid sample chamber and a magnet moveable therein, said method comprising:

moving the or each magnet;

detecting a position of the or each magnet;

determining whether the detected position of the or each magnet is within a preferred range; and

moving the magnet again dependent upon the result of the determining step.

71. A method for determining a coagulation property of a sample of fluid, comprising causing oscillation of the at least one magnet, wherein said oscillation comprises:

a first oscillation within a first frequency range for a first period of time.

72. A device for determining a coagulation property of a sample of fluid, the device comprising one optical sensor for detecting both a first event and a second event.

73. A device as claimed in claim 72, wherein the first event is a fluid entry event.

74. A device as claimed in claim 73 or claim 74, wherein the second event is a chamber full event.

75. A device as claimed in any one of claims 72 to 74, wherein the optical sensor is arranged to interrogate both a fill channel and a vent channel of a chamber.

76. A device as claimed in claim 75, wherein the optical sensor is arranged to

detect a change in transmission characteristics of the fill channel and the vent channel.

77. A device as claimed in claim 75, wherein the optical sensor is arranged to detect a reduction in transmission characteristics of the fill channel and the vent channel caused by fluid entering each of said channels.

78. A fluid sample strip for use with a device for determining a coagulation property of a sample of fluid, said strip having at least one locating feature arranged to interact with a corresponding locating component of the device.

79. A fluid sample strip as claimed in claim 78, wherein the locating feature is a recess in a surface of the fluid sample strip.

80. A fluid sample strip as claimed in claim 78, wherein the locating feature is a hole in the fluid sample strip.

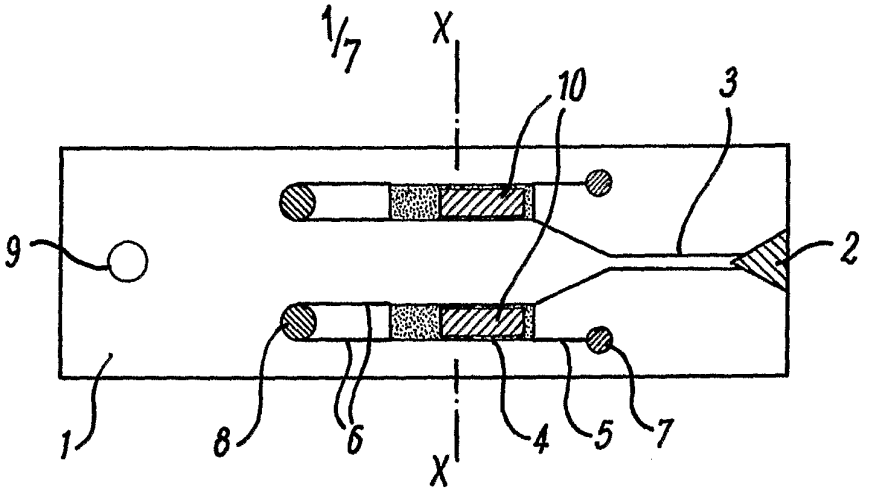



FIG. 1

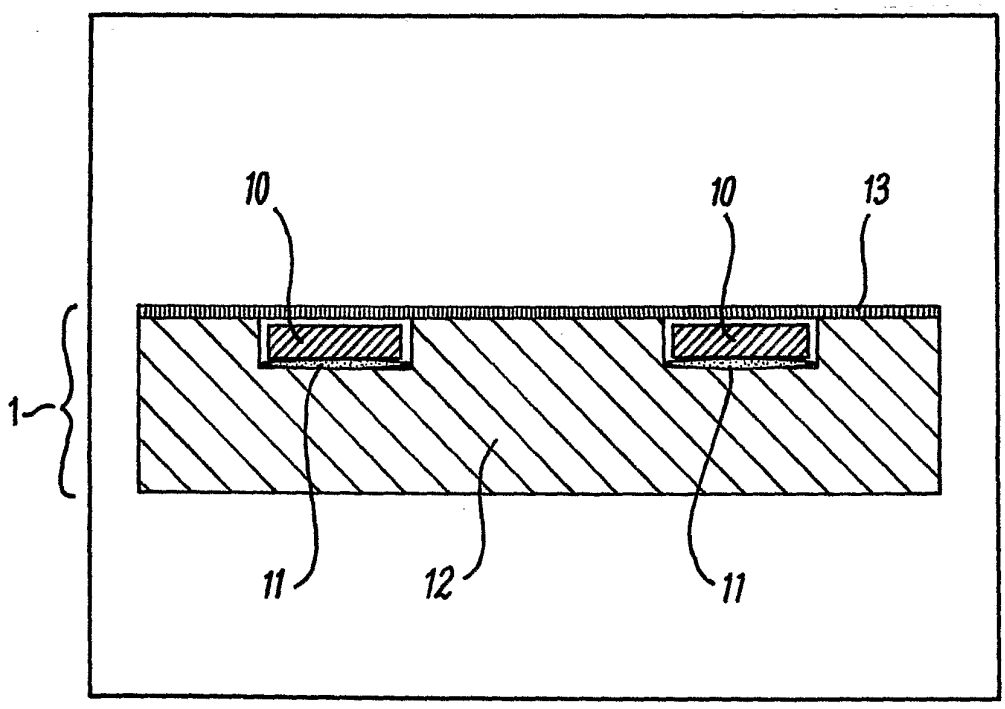



FIG. 2

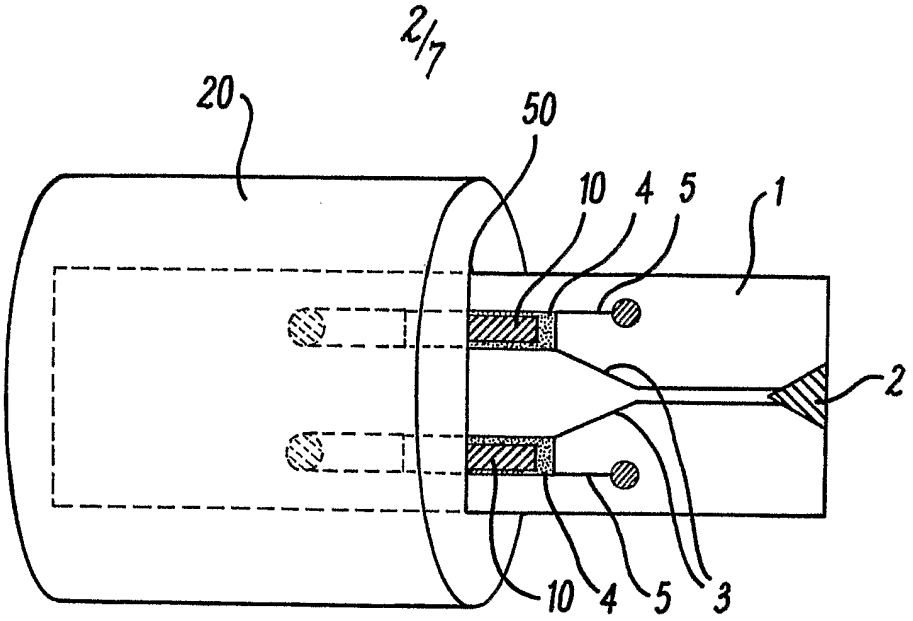



FIG. 3

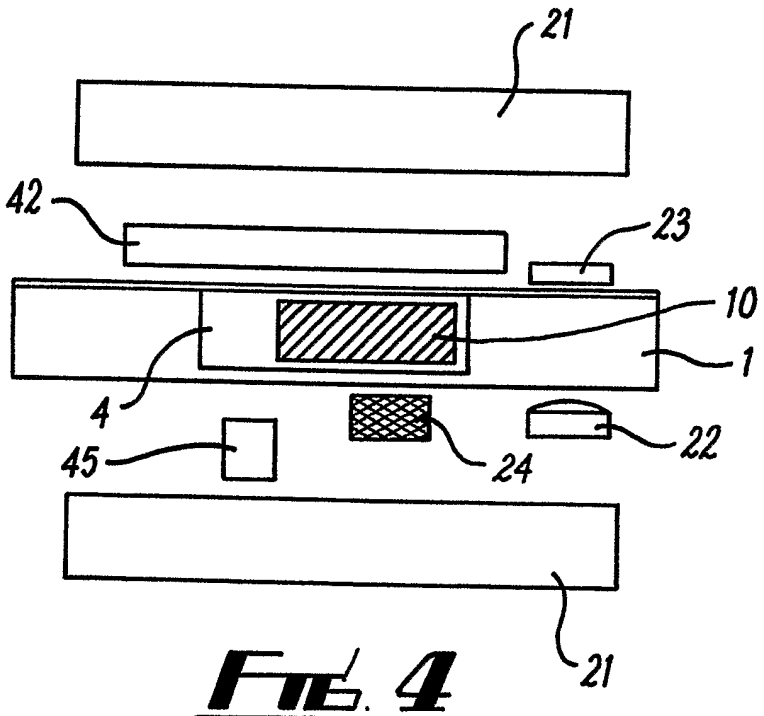



FIG. 4

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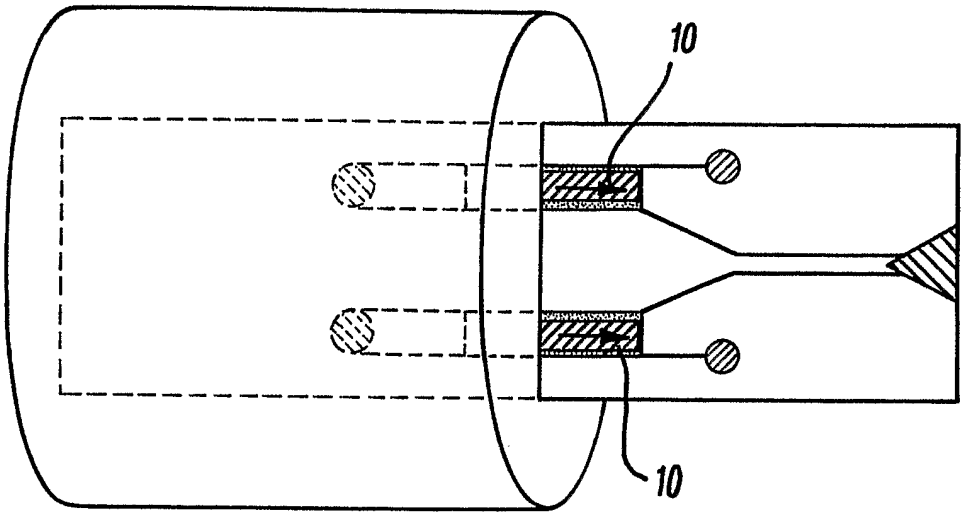



FIG. 5

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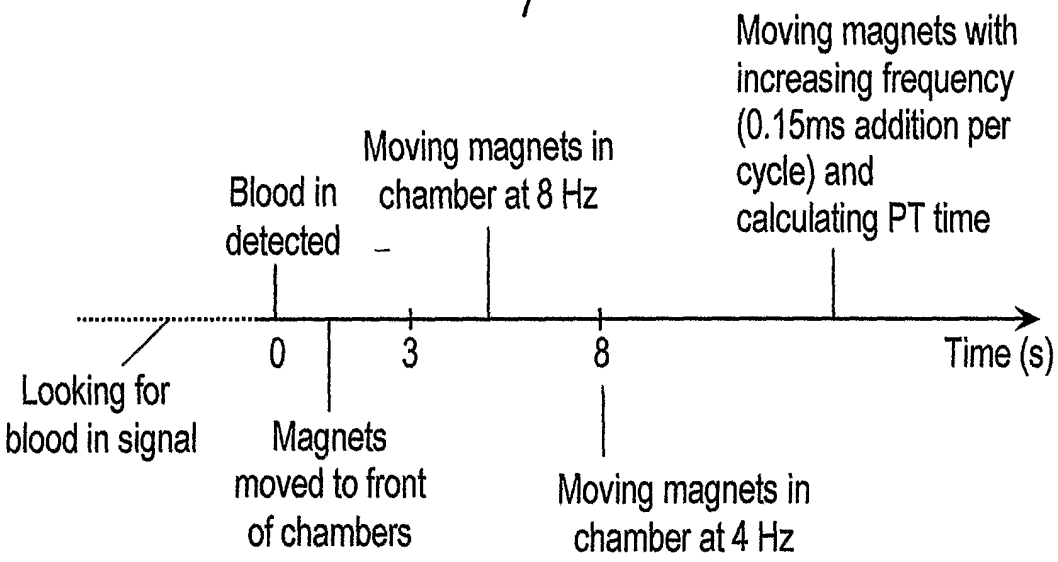

Moving magnets with increasing frequency (0.15ms addition per cycle) and calculating PT time
Moving magnets in chamber at 8 Hz
Blood in detected
0
3
8
Time (s)
Looking for blood in signal
Magnets moved to front of chambers
Moving magnets in chamber at 4 Hz

FIG. 6

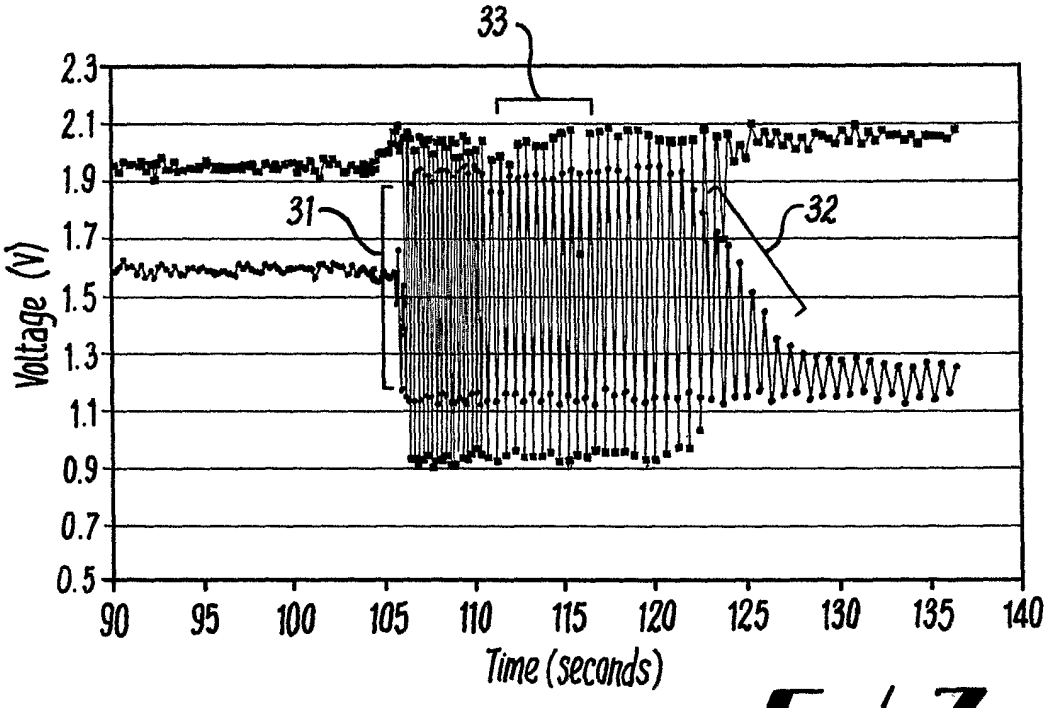

33
31
32
Voltage (V)
2.3
2.1
1.9
1.7
1.5
1.3
1.1
0.9
0.7
0.5
90
95
100
105
110
115
120
125
130
135
140
Time (seconds)

FIG. 7

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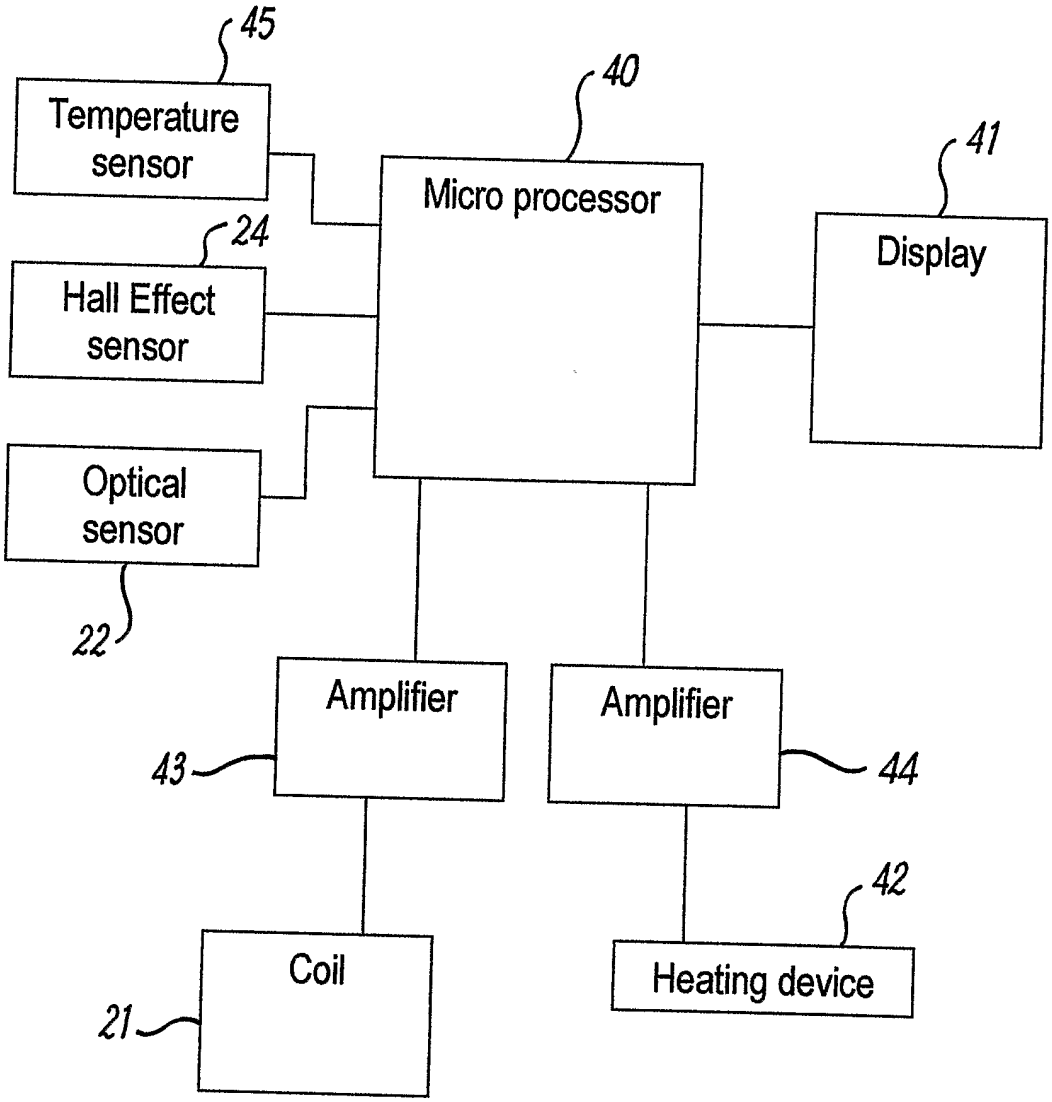

45
Temperature sensor
40
Micro processor
41
Display
24
Hall Effect sensor
Optical sensor
22
Amplifier
43
Amplifier
44
42
Coil
21
Heating device

FIG. 8

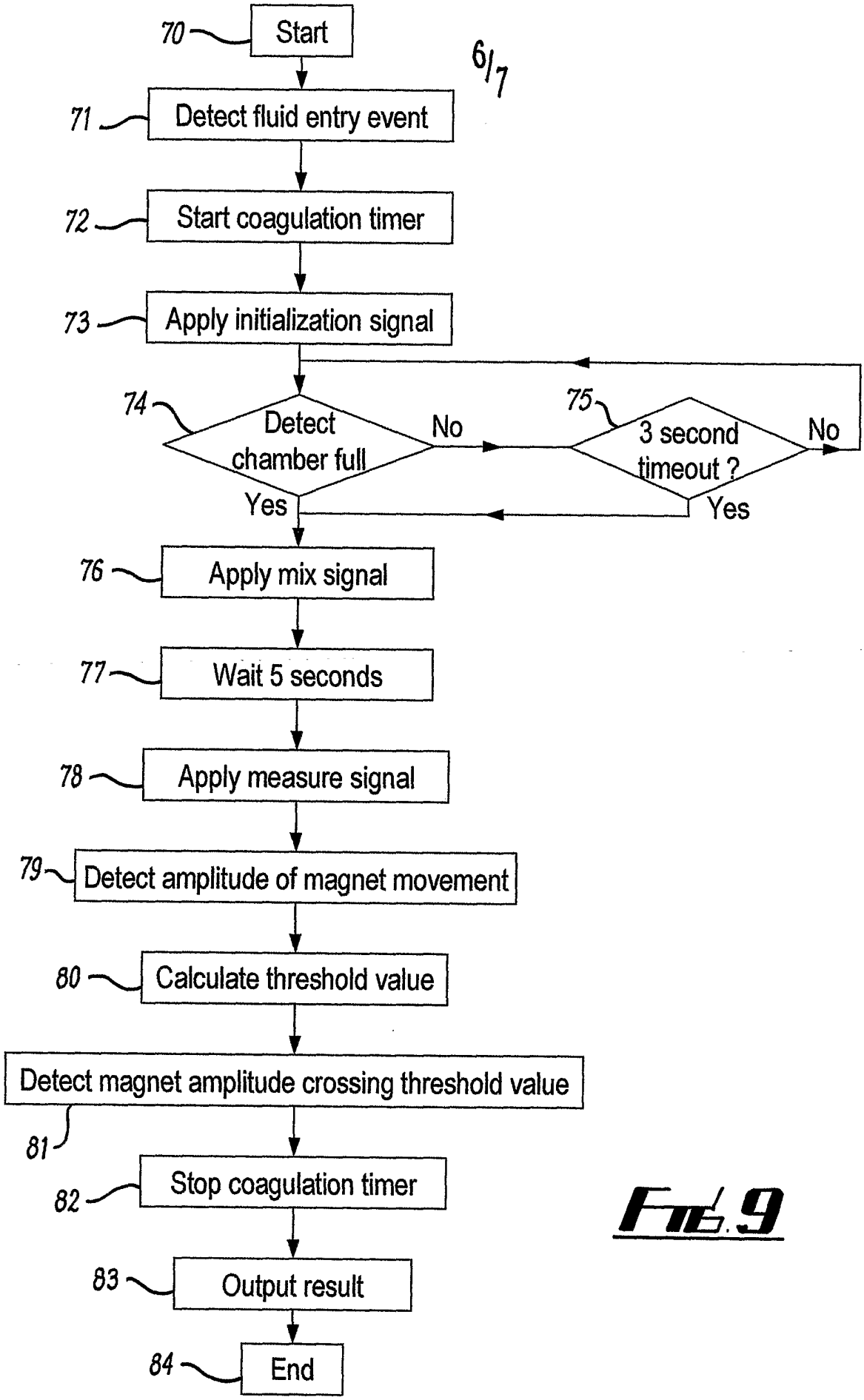

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70
Start
71
Detect fluid entry event
72
Start coagulation timer
73
Apply initialization signal
74
Detect chamber full
No
Yes
75
3 second timeout ?
No
Yes
76
Apply mix signal
77
Wait 5 seconds
78
Apply measure signal
79
Detect amplitude of magnet movement
80
Calculate threshold value
Detect magnet amplitude crossing threshold value
81
82
Stop coagulation timer
83
Output result
84
End

FIG. 9

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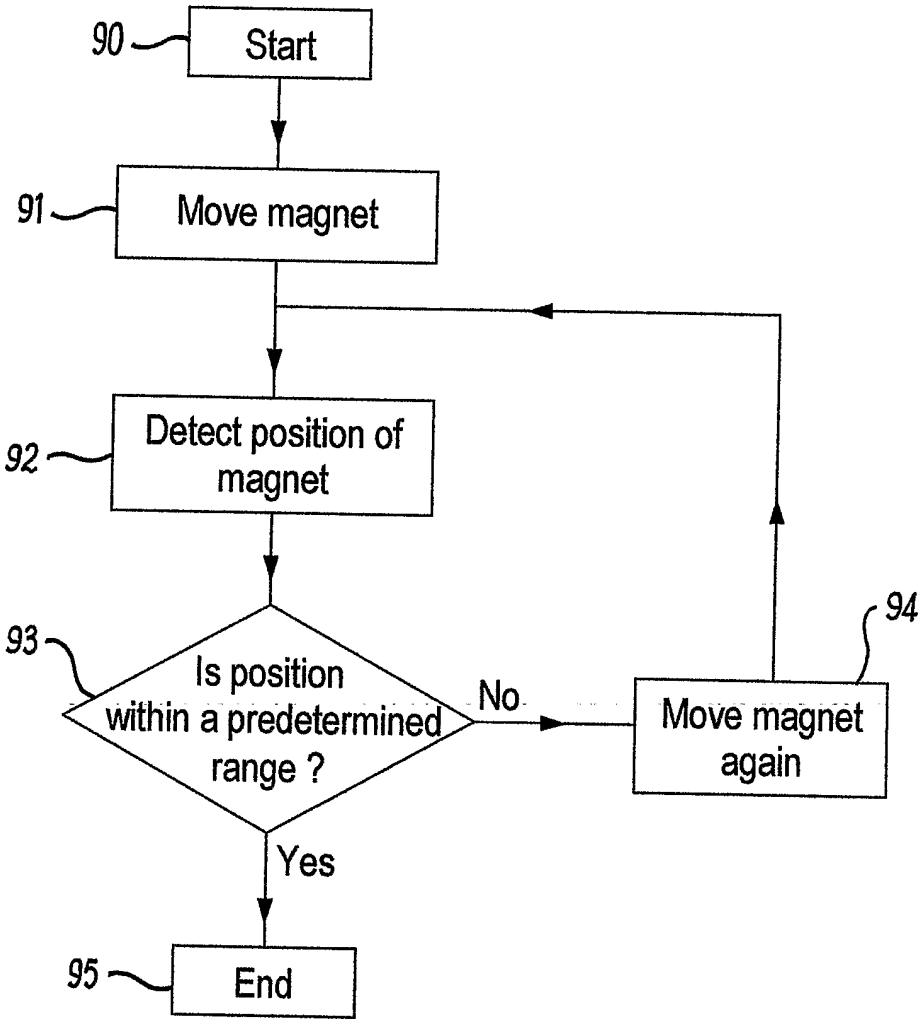

90
Start
91
Move magnet
92
Detect position of magnet
93
Is position within a predetermined range ?
No
94
Move magnet again
Yes
95
End

FIG. 10

# PATENT COOPERATION TREATY

# PCT

DECLARATION OF NON-ESTABLISHMENT OF INTERNATIONAL SEARCH REPORT

(PCT Article 17(2)(a), Rules 13*ter*.1(c) and Rule 39)

| Applicant's or agent's file reference | IMPORTANT DECLARATION | Date of mailing *(day/month/year)* |
|---|---|---|
| P/32508.WO | | 17/07/2006 |
| International application No. | International filing date *(day/month/year)* | (Earliest) Priority date *(day/month/year)* |
| PCT/GB2006/000964 | 16/03/2006 | 19/03/2005 |
| International Patent Classification (IPC) or both national classification and IPC | | |
| G01N33/49 G01N11/16 | | |
| Applicant | | |
| IVMD (UK) LIMITED | | |

This International Searching Authority hereby declares, according to Article 17(2)(a), that **no international search report will be established** on the international application for the reasons indicated below

1. ☐ The subject matter of the international application relates to:
   - a. ☐ scientific theories
   - b. ☐ mathematical theories
   - c. ☐ plant varieties
   - d. ☐ animal varieties
   - e. ☐ essentially biological processes for the production of plants and animals, other than microbiological processes and the products of such processes
   - f. ☐ schemes, rules or methods of doing business
   - g. ☐ schemes, rules or methods of performing purely mental acts
   - h. ☐ schemes, rules or methods of playing games
   - i. ☐ methods for treatment of the human body by surgery or therapy
   - j. ☐ methods for treatment of the animal body by surgery or therapy
   - k. ☐ diagnostic methods practised on the human or animal body
   - l. ☐ mere presentations of information
   - m. ☐ computer programs for which this International Searching Authority is not equipped to search prior art
2. ☒ The failure of the following parts of the international application to comply with prescribed requirements prevents a meaningful search from being carried out:
   ☒ the description ☒ the claims ☐ the drawings
3. ☐ A meaningful search could not be carried out without the sequence listing; the applicant did not, within the prescribed time limit:
   - ☐ furnish a sequence listing on paper complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.
   - ☐ furnish a sequence listing in electronic form complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.
   - ☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rule 13*ter*.1(a) or (b).
4. ☐ A meaningful search could not be carried out without the tables related to the sequence listings; the applicant did not, within the prescribed time limit, furnish such tables in electronic form complying with the technical requirements provided for in Annex *C-bis* of the Administrative Instructions, and such tables were not available to the International Searching Authority in a form and manner acceptable to it.
5. Further comments:

| Name and mailing address of the International Searching Authority | Authorized officer |
|---|---|
| European Patent Office, P.B. 5818 Patentlaan 2<br>NL-2280 HV Rijswijk<br>Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,<br>Fax: (+31-70) 340-3016 | Anne Witzig |