(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
26 April 2001 (26.04.2001)

PCT

(10) International Publication Number
WO 01/28652 A1

(51) International Patent Classification[7]: B01D 17/12

(21) International Application Number: PCT/US00/28178

(22) International Filing Date: 12 October 2000 (12.10.2000)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
09/419,727 16 October 1999 (16.10.1999) US

(71) Applicant: BAXTER INTERNATIONAL INC. [US/US]; Patricia A. Koppelman - RLP-30, One Baxter Parkway, Deerfield, IL 60015 (US).

(72) Inventors: BROWN, Richard, I.; 23365 Peachtree Lane, Northbrook, IL 60062 (US). FOLEY, John, T.; 455 Stone Place, Wheeling, IL 60090 (US). PATNO, Timothy, J.; 542 Michigan No. 2, Evanston, IL 60202 (US).

(74) Agents: PRICE, Bradford, R, L. et al.; Baxter Healthcare Corporation, Route 120 & Wilson Road, Round Lake, IL 60073 (US).

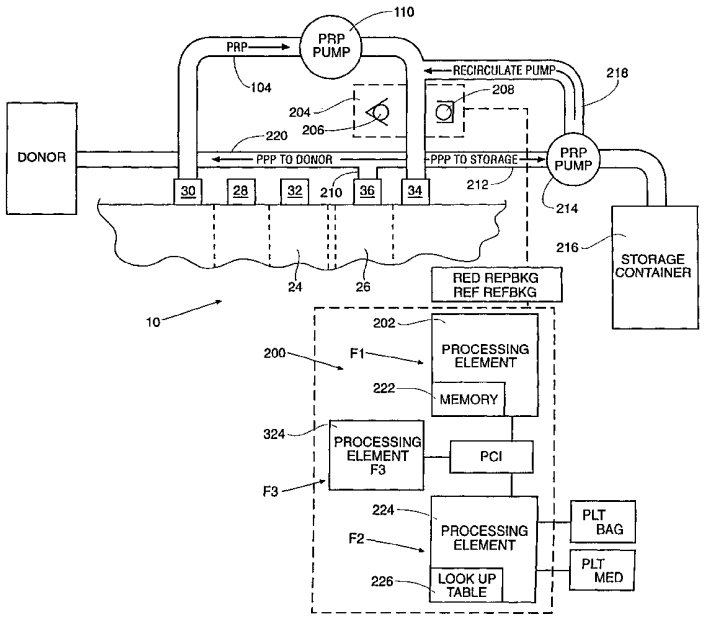
(81) Designated States *(national)*: AU, BR, CA, CN, IN, JP.

(84) Designated States *(regional)*: European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

Published:
— *With international search report.*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: BLOOD PROCESSING SYSTEMS WHICH MONITOR OPTICAL DENSITIES



(57) Abstract: Blood processing systems and methods separate blood into constituents including a plasma constituent that includes a platelet volume. The systems and methods detect the optical density of the plasma constituent and generate a first output indicative of the optical density. A processing element integrates the first output relative to the volume of plasma constituent and generates an integrated output. The integrated output correlates to the platelet volume. A second processing element (324) generates an output based, at least in part, upon the integrated output, which depicts a value indicating a blood volume that needs to be processed to obtain a desired platelet volume.

WO 01/28652 A1

Blood Processing Systems Which Monitor Optical Densities.

RELATED APPLICATION

This application is a continuation-in-part of copending United States Patent Application Serial No. 09/382,893, entitled "Blood Processing Systems and Methods Which Optically Derive the Volume of Platelets Contained in a Plasma Constituent," filed August 25, 1999, which is a continuation in part of United States Patent Application Serial No. 08/807,820, filed February 26, 1997, and entitled "Blood Collection Systems and Methods Which Derive Instantaneous Blood Component Yield Information During Blood Processing," which is a continuation of United States Patent Application Serial No. 08/472,748, filed June 7, 1995 of the same title (now abandoned).

FIELD OF THE INVENTION

The invention relates to centrifugal processing systems and apparatus.

BACKGROUND OF THE INVENTION

Today, people routinely separate whole blood by centrifugation into its various therapeutic components, such as red blood cells, platelets, and plasma.

Certain therapies transfuse large volumes of blood components. For example, some patients undergoing chemotherapy require the transfusion of large numbers of platelets on a routine basis. Manual blood bag systems simply are not an efficient way to collect these large numbers of platelets from individual donors.

On line blood separation systems are today used to collect large numbers of platelets to meet this demand. On line systems perform the separation steps necessary to separate concentration of platelets from whole blood in a sequential process with the donor present. On line systems establish a flow of whole blood from the donor, separate out the desired platelets from the flow, and return the remaining red blood cells and plasma to the donor, all in a sequential flow loop.

Large volumes of whole blood (for example, 2.0 liters) can be processed using an on line system. Due to the large processing volumes, large yields of concentrated platelets (for example, 4 x 10^{11} platelets suspended in 200 ml of fluid) can be collected. Moreover, since the donor's red blood cells are returned, the donor can donate whole blood for on line processing much more frequently than donors for processing in multiple blood bag systems.

Nevertheless, a need still exists for further improved systems and methods for collecting cellular-rich concentrates from blood components in a way that lends itself to use in high volume, on line blood collection environments, where higher yields of critically needed cellular blood components like platelets can be realized.

As the operational and performance demands upon such fluid processing systems become more complex and sophisticated, the need exists for automated process controllers that can gather and generate more detailed information and control signals to aid the operator in maximizing processing and separation efficiencies.

SUMMARY OF THE INVENTION

The invention provides blood processing systems and methods which separate blood into constituents including a plasma constituent having an optical density. The systems and methods convey a volume of the plasma constituent through an outlet path, while detecting the

optical density of the plasma constituent. The systems and methods generate a first output indicative of the detected optical density. The systems and methods integrate the first output relative to the volume of plasma constituent conveyed to generate an integrated output. The integrated output correlates to the platelet volume carried in the plasma constituent and obviates the need to otherwise obtain the platelet volume by off line counting and sizing techniques. The systems and methods generate a second output based, at least in part, upon the integrated opacity value, comprising a value indicating a blood volume that needs be processed to obtain a desired platelet volume.

In a preferred embodiment, the plasma constituent includes a lipid content. In this embodiment, the systems and methods adjust the first output in proportion to the lipid content.

In a preferred embodiment, the systems and methods generate a third output based, at least in part, upon the integrated output. In a preferred embodiment, the third output comprises parameters for storing the platelet volume contained within the plasma constituent. For example, the third output can include a value representing the number of selected storage containers to be used for the platelet volume, or a value representing the recommended volume of storage medium for the platelet volume.

The various aspects of the invention are especially well suited for on line blood separation processes.

Features and advantages of the inventions are set forth in the following Description and Drawings, as well as in the appended Claims.

BRIEF DESCRIPTION OF THE DRAWINGS

Fig. 1 is a side elevation view, with portions

broken away and in section, of a blood processing system comprising a centrifuge with an interface detection system, which embodies features of the invention, the bowl and spool of the centrifuge being shown in their operating position;

Fig. 2 is a side elevation view, with portions broken away and in section, of the centrifuge shown in Fig. 1, with the bowl and spool of the centrifuge shown in their upright position for receiving a blood processing chamber;

Fig. 3 is a top perspective view of the spool of the centrifuge shown in Fig. 2, in its upright position and carrying the blood processing chamber;

Fig. 4 is a plan view of the blood processing chamber shown in Fig. 3, out of association with the spool;

Fig. 5 is an enlarged perspective view of the interface ramp carried by the centrifuge in association with the blood processing chamber, showing the centrifugally separated red blood cell layer, plasma layer, and interface within the chamber when in a desired location on the ramp;

Fig. 6 is an enlarged perspective view of the interface ramp shown in Fig. 5, showing the red blood cell layer and interface at an undesired high location on the ramp;

Fig. 7 is an enlarged perspective view of the interface ramp shown in Fig. 5, showing the red blood cell layer and interface at an undesired low location on the ramp;

Fig. 8 is a side perspective view of the bowl and spool of the centrifuge when in the operating position, showing the viewing head, which forms a part of the interface controller, being carried by the centrifuge to view the interface ramp during rotation of the bowl;

Fig. 9 is a perspective view of the viewing head, with portions broken away and in section, showing the light source and light detector, which are carried by the viewing head, in alignment with the interface ramp, as viewed from within the spool and bowl of the centrifuge;

Fig. 10 is a side section view of the bowl, spool, and viewing head when the viewing head is aligned with the interface ramp;

Fig. 11 is a schematic view of the interface processing element and the interface command element, which form a part of the interface controller;

Fig. 12 is a schematic view of the signal converting element, which forms a part of the interface processing element shown in Fig. 11;

Fig. 13 shows, in its upper portion, a voltage signal generated by the viewing head when passing along the interface ramp and, in its lower portion, a square waveform, which the processing element of the interface controller generates from the voltage signal for the purpose of analyzing the location of the interface on the ramp;

Fig. 14 is a schematic view of the blood calibration element, which forms a part of the interface controller;

Fig. 15 is a schematic view of the first and second utility functions of the processing control application, which forms a part of the blood processing system shown in Fig. 1, as well as the associated monitor which optically monitors the opacity of PRP transported from the separation chamber;

Fig. 16 is a plot showing the fluctuations in the opacity of fluid monitored by the optical monitor shown in Fig. 15, which constitutes an input to the first utility function also shown schematically in Fig. 15;

Fig. 17 is a plot showing the correlation of the

integrated optical density value derived by the first utility function, shown in Fig. 15, to collected platelet volume data;

Fig. 18 is a plot showing the correlation of the integrated optical density value derived by the first utility function, shown in Fig. 15, to platelet yield data;

Fig. 19 is a graph showing the relationship between the partial pressure of oxygen and the permeation of a particular storage container, which the second utility function shown in Fig. 15 takes into account in recommending optimal storage parameters in terms of the number of storage containers; and

Fig. 20 is a graph showing the relationship between the consumption of bicarbonate and storage thrombocytocrit for a particular storage container, which the second utility function shown in Fig. 15 takes into account in recommending optimal storage parameters in terms of the volume of plasma storage medium.

The invention may be embodied in several forms without departing from its spirit or essential characteristics. The scope of the invention is defined in the appended claims, rather than in the specific description preceding them. All embodiments that fall within the meaning and range of equivalency of the claims are therefore intended to be embraced by the claims.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

Figs. 1 and 2 show a blood processing system 10, which incorporates an interface controller 12 that embodies features of the invention. The invention is described in the context of blood processing, because it is well suited for use in this environment. Still, it should be appreciated that use of the invention is not limited to blood processing. The features of the invention can be used in association with any system in which

materials that can be optically differentiated are handled.

A. The Centrifuge

The system 10 includes a centrifuge 14 used to centrifugally separate blood components. In the illustrated embodiment, the centrifuge 14 separates whole blood to harvest red blood cells (RBC), platelet concentrate (PC), and platelet-poor plasma (PPP). The centrifuge 14 can also be used to harvest mononuclear cells and granulocytes from blood.

The centrifuge 14 is of the type shown in United States Patent 5,316,667, which is incorporated herein by reference. The centrifuge comprises a bowl 16 and a spool 18 . The bowl 16 and spool 18 are pivoted on a yoke 20 between an upright position, as Fig. 2 shows, and a suspended position, as Fig. 1 shows.

When upright, the spool 18 can be opened by movement at least partially out of the bowl 16, as Fig. 2 shows. In this position, the operator wraps a flexible blood processing chamber 22 (see Fig. 3) about the spool 18. Closure of the spool 18 and bowl 16 encloses the chamber 22 for processing. When closed, the spool 18 and bowl 16 are pivoted into the suspended position for rotation about an axis.

B. The Blood Processing Chamber

The blood processing chamber 22 can be variously constructed. Fig. 4 shows a representative preferred embodiment.

The chamber 22 shown in Fig. 4 provides multi-stage processing. A first stage 24 separates WB into RBC and platelet-rich plasma (PRP). A second stage 26 separates the PRP into PC and PPP.

As Figs. 3 and 4 best show, a port 28 conveys WB into the first stage 24. Ports 30 and 32, respectively, convey PRP and RBC from the first stage 24. RBC is

returned to the donor. A port 34 conveys PRP into the second stage 26. A port 36 conveys PPP from the second stage 26, leaving PC in the second stage 26 for resuspension and transfer to one or more storage containers. The ports 28, 30, 32, 34, and 36 are arranged side-by-side along the top transverse edge of the chamber 22.

As Figs. 1 and 3 best show, a tubing umbilicus 38 is attached to the ports 28, 30, 32, 34, and 36. The umbilicus 38 interconnects the first and second stages 24 and 26 with each other and with pumps and other stationary components located outside the rotating components of the centrifuge 14 (not shown). As Fig. 1 shows, a non-rotating (zero omega) holder 40 holds the upper portion of the umbilicus 38 in a non-rotating position above the suspended spool 18 and bowl 16. A holder 42 on the yoke 20 rotates the mid-portion of the umbilicus 38 at a first (one omega) speed about the suspended spool 18 and bowl 16. Another holder 44 (see Fig. 2) rotates the lower end of the umbilicus 38 at a second speed twice the one omega speed (the two omega speed), at which the suspended spool 18 and bowl 16 also rotate. This known relative rotation of the umbilicus 38 keeps it untwisted, in this way avoiding the need for rotating seals.

As Fig. 4 shows, a first interior seal 46 is located between the PRP collection port 30 and the WB inlet port 28. A second interior seal 48 is located between the WB inlet port 28 and the RBC collection port 32. The interior seals 46 and 48 form a WB inlet passage 50 and a PRP collection region 52 in the first stage 24. The second seal 48 also forms a RBC collection passage 54 in the first stage 24.

The WB inlet passage 50 channels WB directly into the circumferential flow path immediately next to the PRP collection region 52. As shown in Fig. 5, the WB

separates into an optically dense layer 56 of RBC, which forms as RBC move under the influence of centrifugal force toward the high-G wall 62. The movement of RBC 56 displaces PRP radially toward the low-G wall 64, forming a second, less optically dense layer 58.

Centrifugation of WB also forms an intermediate layer 60, also called the interface, which constitutes the transition between the formed cellular blood components and the liquid plasma component. RBC typically occupy this transition region. White blood cells may also occupy this transition region.

Platelets, too, can leave the PRP layer 58 and settle on the interface 60. This settling action occurs when the radial velocity of the plasma near the interface 60 is not enough to keep the platelets suspended in the PRP layer 58. Lacking sufficient radial flow of plasma, the platelets fall back and settle on the interface 60. Larger platelets (greater than about 30 femtoliters) are particularly subject to settling on the interface 60. However, the closeness of the WB inlet region 50 to the PRP collection region 52 in the chamber 22 shown in Fig. 4 creates strong radial flow of plasma into the PRP collection region 52. The strong radial flow of plasma lifts platelets, large and small, from the interface 60 and into the PRP collection region 52.

Further details of the separation chamber 22 are not material to the invention and can be found in United States Patent No. 5,316,667, previously mentioned.

C. The Interface Controller

As Fig. 5 shows, a ramp 66 extends from the high-G wall 62 of the bowl 16 at an angle across the PRP collection region 52. The angle, measured with respect to the axis of the PRP collection port 30 is preferably about 30°. Fig. 5 shows the orientation of the ramp 66 when viewed from the low-G wall 64 of the spool 18. Fig. 4

shows, in phantom lines, the orientation of the ramp 66 when viewed from the high-G wall 62 of the bowl 16.

Further details of the angled relationship of the ramp 66 and the PRP collection port 30 are not material to the invention. They can be found in copending U.S. Patent Application Serial No. 08/472,561, filed June 7, 1995, and entitled "Enhanced Yield Blood Processing System with Angled Interface Control Surface," which is incorporated herein by reference.

The ramp 66 forms a tapered wedge that restricts the flow of fluid toward the PRP collection port 30. The top edge of the ramp 66 extends to form a constricted passage 68 along the low-G wall 64. PRP must flow through the constricted passage 68 to reach the PRP collection port 30.

As Fig. 5 shows, the ramp 66 diverts the fluid flow along the high-G wall 62. This flow diversion changes the orientation of the interface 60 between the RBC layer 56 and the PRP layer 58 within the PRP collection region 52. The ramp 66 thereby displays the RBC layer 56, PRP layer 58, and interface 60 for viewing through the low-G wall 64 of the chamber 22.

The interface controller 12 includes a viewing head 70 (see Figs. 1 and 8) carried on the yoke 20. The viewing head 70 is oriented to optically view the transition in optical density between the RBC layer 56 and the PRP layer 58 on the ramp 66. The interface controller 12 also includes a processing element 72 (see Figs. 11 and 13), which analyzes the optical data obtained by the viewing head 70 to derive the location of the interface 60 on the ramp 66 relative to the constricted passage 68.

The location of the interface 60 on the ramp 66 can dynamically shift during blood processing, as Figs. 6 and 7 show. The interface controller 12 includes a command element 74 (see Figs. 11 and 13), which varies the rate at

which PRP is drawn from the chamber 22 to keep the interface 60 at a prescribed location on the ramp 66 (which Fig. 5 shows).

Maintaining the interface 60 at a prescribed location on the ramp 66 is important. If the location of the interface 60 is too high (that is, if it is too close to the constricted passage 68 leading to the PRP collection port 30, as Fig. 6 shows), RBC, and, if present, white blood cells can spill over and into the constricted passage 68, adversely affecting the quality of PRP. On the other hand, if the location of the interface 60 is too low (that is, if it resides too far away from the constricted passage 68, as Fig. 7 shows), the fluid dynamics advantageous to effective platelet separation can be disrupted. Furthermore, as the distance between the interface 60 and the constricted passage 68 increases, the difficulty of drawing larger platelets into the PRP flow increases. As a result, a distant interface location results in collection of only the smallest platelets, and overall platelet yield will, as a consequence, be poor.

(1) The Interface Viewing Head

Referring to Figs. 8 to 10, the viewing head 70, carried by the yoke 20, includes a light source 76, which emits light that is absorbed by RBC. In the illustrated and preferred embodiment, the light source 76 includes a circular array of red light emitting diodes 80. Of course, other wavelengths absorbed by RBC, like green or infrared, could be used.

In the illustrated embodiment, seven light emitting diodes 80 comprise the light source 76. More diodes 80 may be used, or fewer diodes 80 can be used, depending upon the optical characteristics desired.

The viewing head 70 also includes a light detector 78 (see Figs. 9 and 10), which is mounted adjacent to the light source 76. In the illustrated and

preferred embodiment, the light detector 78 comprises a PIN diode detector, which is located generally in the geometric center of the circular array of light emitting diodes 80.

The yoke 20 and viewing head 70 rotate at a one omega speed, as the spool 18 and bowl 16 rotate at a two omega speed. The light source 76 directs light onto the rotating bowl 16. In the illustrated embodiment (see Fig. 8), the bowl 16 is transparent to the light emitted by the source 76 only in the region 82 where the bowl 16 overlies the interface ramp 66. In the illustrated embodiment, the region 82 comprises a window cut out in the bowl 16. The remainder of the bowl 16 that lies in the path of the viewing head 70 comprises a light absorbing material.

The interface ramp 66 is made of a light transmissive material. The light from the source 76 will thereby pass through the transparent region 82 of the bowl 16 and the ramp 66 every time the rotating bowl 16 and viewing head 70 align. The spool 18 may also carry a light reflective material 84 behind the interface ramp 66 to enhance its reflective properties. The spool 18 reflects incoming light received from the source 76 out through the transparent region 82 of the bowl 16, where it is sensed by the detector 78. In the illustrated embodiment, light passing outward from the source 76 and inward toward the detector 78 passes through a focusing lens 120 (shown in Figs. 9 and 10), which forms a part of the viewing head 70.

The arrangement just described optically differentiates the reflective properties of the interface ramp 66 from the remainder of the bowl 16. This objective can be achieved in other ways. For example, the light source 76 could be gated on and off with the arrival and passage of the ramp 66 relative to its line of sight. As another example, the bowl 16 outside the transparent

region 82 could carry a material that reflects light, but at a different intensity than the reflective material 84 behind the interface ramp 66.

As the transparent interface region 82 of the bowl 16 comes into alignment with the viewing head 70, the detector 78 will first sense light reflected through the plasma layer 58 on the ramp 66. Eventually, the RBC layer 56 adjacent the interface 60 on the ramp 66 will enter the optical path of the viewing head 70. The RBC layer 56 absorbs light from the source 76 and thereby reduces the previously sensed intensity of the reflected light. The intensity of the reflected light sensed by the detector 78 represents the amount of light from the source 76 that is not absorbed by the RBC layer 56 adjacent to the interface 60.

(2) The Interface Processing Element

As Fig. 11 shows, the interface processing element 72 includes a signal converting element 112, which converts the sensed light intensity output of the detector 78 (a current) to an amplified voltage signal.

As Fig. 12 shows, the signal converting element 112 includes an inverting current to voltage (I/V) amplifier 114, which converts the relatively low positive current signal from the detector 78 (typically, in μA) to an amplified negative voltage signal. The current-to-voltage gain of the amplifier 114 can vary. In a representative embodiment, the gain is on the order of 58,000, so that current of, for example, 1 μA is converted to a voltage signal of -58 mV. A non-inverting voltage amplifier (V/V) 116 further amplifies the negative voltage signal (in mV) to a negative voltage signal (in V) (i.e., a gain of about 400). This twice amplified negative voltage signal is passed through a buffer 118. The output of the buffer 118 constitutes the output of the signal converting element 112. In the illustrated embodiment,

the total amplification factor (from detector current signal to processed negative voltage signal) is about 23 million.

Fig. 13 shows in solid lines a representative curve (designated V1), which plots representative negative voltage outputs of the signal converting element 112 for light signals detected when a light transmissive liquid, e.g., saline, resides along the entire length of the ramp 66. The curve V1 shows the region 88 where the light signal detected increase, level out, and then decrease, as the transparent region 82 and viewing head 70 pass into and out of alignment. In the illustrated embodiment, the voltage curve V1 is negative-going for increasing light signals, due to processing by the signal converting element 112. It should be appreciated that the light signals could be processed to provide a non-inverted voltage output, so that the voltage curve V1 would be positive-going for increasing light signals.

Referring back to Fig. 11, a waveshaping element 90 converts the amplified voltage signals to a square wave time pulse. In the illustrated embodiment, the element 90 comprises a voltage comparator, which receives as input the amplified voltage signals and a selected threshold value (THRESH). The output of the voltage comparator 88 is one (1) when the voltage signal lies below THRESH (that is, when the voltage signal lies further from zero than THRESH) and zero (0) when the voltage signal lies above THRESH (that is, when the voltage signal lies closer to zero than THRESH).

In the illustrated embodiment, THRESH comprises a digital number between 0 and 4095. The digital number is converted by a 12 bit digital-to-analog converter 120 to a voltage analog value between +10 and -10. For example, a digital number of zero (0) for THRESH represents an analog output of +10V, while a digital

number of 4095 for THRESH represents an analog output of -10V.

Fig. 13 shows in solid lines a representative square wave pulse (designated P1) processed by the comparator 90 from the voltage curve V1, based upon a selected value for THRESH. Negative-going voltage curve V1 varies from zero (0) (when no light is sensed by the detector 70) to -13.5 V (when maximum light is sensed by the detector 70), and THRESH is the digital number 3481, which the converter 120 converts to an analog voltage value of - 7V. The square wave pulse P1 has a width (designated W1 in Fig. 13) expressed in terms of time. The width W1 is proportional to the time that a light signal below THRESH is detected (that is, when the negative voltage signal is farther from zero (0) than analog voltage value of THRESH).

As Fig. 13 shows, maximum light is detected (negative-going voltage signal at - 13.5 V) when the interface viewing region 82 and the viewing head 70 align. When a light transmissive material like saline resides along the entire interface ramp 66, the width W1 of the square wave pulse P1 is proportional to the entire time period that the interface viewing region 82 and viewing head 70 align. Width W1 will also be called the baseline pulse width, or BASE.

When material having a high-relative light absorption properties, such as RBC, occupies a portion of the ramp 66, the profile of the sensed voltages changes. Fig. 13 shows in phantom lines a representative curve (designated V2), which plots representative processed voltage signals detected when RBC occupy about 70% of the length of the ramp 66. Negative-going voltage curve V2 varies from zero (0) (when no light is sensed by the detector 70) to -9.9 V (when maximum light is sensed by the detector 70). The curve V2 follows the path of V1

until the detector 78 senses the plasma layer 58, which is not a transmissive to light as saline. The maximum sensed signal intensity for plasma ($I2_{PLASMA}$) (for example, - 9.9 V) is therefore less than maximum sensed signal intensity for saline ($I1_{SALINE}$) (for example - 13.5 volts). The time period during which $I2_{PLASMA}$ exists is also significantly shorter than the time period which $I1_{SALINE}$ exists. Curve V2 shows the gradual decrease in the sensed voltage signal as the light absorbing RBC layer 56 comes progressively into the field of view of the head 70 (which is generally designated $I2_{RBC}$ in Fig. 13). Curve V2 eventually joins the path of curve V1, as the transparent region 82 and viewing head 70 pass out of alignment.

Fig. 13 also shows in phantom lines that the relative width (W2) of square wave pulse (P2), processed by the comparator 90 using the same THRESH as P1, shortens. The width (W2) diminishes in proportion to the width of the RBC layer 56 relative to the width of the plasma layer 58 on the ramp. As the RBC layer 56 occupies more of the ramp 66, i.e., as the RBC-plasma interface 60 moves closer to the constricted passage 68, the pulse width (W2) shortens relative to the baseline pulse width (W1), and vice versa.

Thus, and by comparing the width of a given pulse wave (such as W2) relative to the baseline pulse width (W1), the interface processing element 72 assesses the relative physical location of the interface 60 on the ramp 66.

As Fig. 11 shows, the interface processing element 72 includes calibration modules 92 and 94 to assure that the optically derived physical location of the interface 66 accurately corresponds with the actual physical location of the interface 66. The first calibration module 92, also called the system calibration module, takes into account the geometry of the spool 18

and ramp 66, as well as operational conditions that can affect the optical acquisition of interface information. The second calibration module 94, also called the blood calibration module, takes into account the physiology of the donor's blood, in terms of the optical density of his or her plasma.

(i) System Calibration Module

The nominal value of the baseline pulse width BASE (expressed in units of time) is selected for a given system. In a representative embodiment, a value of, for example, 640 μsec can be selected for BASE. BASE (in microseconds) is converted to a digital count value (COUNTS), as follows:

$$COUNTS = (\frac{BASE}{PERIOD} * SCALE) + THRESH_{ZERO} \qquad (1)$$

where

SCALE is a selected scale factor (which, in the illustrated embodiment, can be, for example, 80604);

$THRESH_{ZERO}$ is the digital threshold number that represents an analog threshold voltage output of zero (which, in the illustrated embodiment, is 2048); and

PERIOD is the period of rotation of the detector 70, based upon the speed of rotation of the detector 70 ($DETECTOR_{\Omega}$), calculated as follows:

$$PERIOD = (\frac{60}{DECTECTOR_{\Omega}}) \times 10^{6}$$

Once calculated for a given $DETECTOR_{\Omega}$, COUNTS need not be recalculated at different values of $DETECTOR_{\Omega}$, provided BASE is not changed.

The system calibration module 92 derives a

square pulse wave P_{SALINE}, like P1 in Fig. 13, by conveying a light transmissive liquid, such as saline, through the chamber 22, while sampling voltage values along the ramp 66. The voltage value samples are processed by the comparator 90 to create the square wave pulse P_{SALINE}, using an estimated initial threshold value $THRESH_{START}$. The width W_{START} of the pulse P_{SALINE} formed using $THRESH_{START}$ is measured and compared to the baseline width BASE, which is determined according to Equation (1).

Moving THRESH closer to zero than $THRESH_{START}$ will increase the pulse width, and vice versa. When W_{START} does not equal BASE, or, alternatively, if W_{START} falls outside a specified satisfactory range of values for BASE, the system calibration module 92 varies the threshold value from $THRESH_{START}$ to vary the pulse width, until the pulse width of P_{SALINE} meets the target criteria for BASE. The threshold value that achieves the target baseline pulse width BASE becomes the default threshold value $THRESH_{DEFAULT}$ for the system.

Despite the derivation of $THRESH_{DEFAULT}$, variations in sensed pulse width can occur during normal use independent of changes in the actual physical dimension of the interface. For example, sensed voltage signals can change due to changes occurring within the viewing head 70, such as loss of focus, deposition of foreign materials on optical surfaces, shifts in optical alignment, or weakening of the light emitting diodes 80 or detector 78. Sensed voltage signals will change due to degradation of optical performance, independent of and unrelated to changes in the physical dimensions of the interface. When processed by the converter 90 using $THRESH_{DEFAULT}$, the changed voltage signals can result in a reduced or enlarged pulse width, which may no longer accurately reflect the actual state of the interface. Erroneous control signals may result.

In the illustrated and preferred embodiment, the system calibration module 92 includes a set up protocol 96. The protocol 96 sets a threshold value THRESH to obtain the baseline pulse width BASE using actual performance conditions existing at the beginning of each processing cycle.

The set up protocol 96 commands the system to convey saline (or other selected light transmissive material) through the separation chamber 22, as before described in connection with deriving $THRESH_{DEFAULT}$. A representative number of samples (e.g., 10 samples) of pulse widths $W_{DEFAULT\ (1\ to\ n)}$ are obtained based upon sensed voltage values using $THRESH_{DEFAULT}$. The sample pulse widths are averaged $W_{DEFAULT(AVG)}$ and compared to BASE for the system, derived according to Equation (1). If $W_{DEFAULT(AVG)}$ equals BASE, or, alternatively, lies within an acceptable range of values for BASE, THRESH is set at $THRESH_{DEFAULT}$.

In a representative implementation, the protocol 96 uses the following criteria is used to evaluate $THRESH_{DEFAULT}$:

IF

$W_{DEFAULT(AVG)} \geq BASE_{LOWER}$

AND

$W_{DEFAULT(AVG)} \leq BASE_{UPPER}$

THEN

$THRESH = THRESH_{DEFAULT}$

where:

$BASE_{UPPER}$ is a selected maximum value for the baseline pulse width, e.g., BASE times a selected multiplier greater than 1.0, for example 1.0025 ; and

$BASE_{LOWER}$ is a selected minimum value for the baseline pulse width, e.g., BASE times a selected multiplier less than 1.0, for example 0.9975.

If the $W_{DEFAULT(AVG)}$ does not meet the above

criteria, the set up procedure searches for a value for THRESH that brings $W_{DEFAULT(AVG)}$ into compliance with the established criteria for BASE. Various search algorithms can be used for this purpose.

For example, the set up procedure can use a half-step search algorithm, as follows:

where THRESH is the name given to the interface threshold value selected; $THRESH_{UPPER}$ is a set maximum value for THRESH; $THRESH_{LOWER}$ is a set minimum value for THRESH; and $W_{SAMPLE\ (AVG)}$ is an average of pulse widths taken during a set sample period.

set $THRESH_{n-1} = THRESH_{DEFAULT}$
set $THRESH_{UPPER}$
set $THRESH_{LOWER}$
DO n = 2 to 20
IF $W_{SAMPLE(AVG)} > BASE_{UPPER}$ THEN
$THRESH_{LOWER} = THRESH_{n-1}$

$THRESH_n = (THRESH_{LOWER} + THRESH_{UPPER})/2$
ELSEIF $W_{SAMPLE(AVG)} < BASE_{LOWER}$
THEN
$THRESH_{UPPER} = THRESH_{n-1}$

$THRESH_n = (THRESH_{UPPER} + THRESH_{LOWER})/2$
ELSIF
end the search
ENDIF
END DO
IF n = 20 THEN
Activate a Warning Alarm: Interface Detector Problem
ENDIF

The system calibration module 92 thereby assures that the optically derived location of the interface 66 is not skewed based upon operational conditions that can

affect the optical acquisition of interface information.

(ii) Blood Calibration Module

The interface controller 12 can operate on the premise the optical density of the donor's plasma residing on the ramp 66 is substantially equivalent to the optical density of the material (e.g., saline) used by the system calibration module 92 at the outset of a given procedure. Typically, the optical density of normal plasma can be considered equivalent to saline.

However, the optical density of plasma will vary according to the concentration of platelets carried in the plasma. Therefore, plasma particularly rich in platelets, which is a processing goal of the system 10, has a density that differs significantly from saline or normal plasma.

The optical density of plasma will also vary according to the concentration of lipids in the plasma, which depends upon the physiology or morphology of the individual donor. Lipemic plasma has a density that differs significantly from saline or non-lipemic plasma.

The presence of plasma on the ramp 66 carrying high concentrations of platelets or lipids, diminishes the magnitude of the sensed voltage signals, independent of and unrelated to changes in the physical dimensions of the interface. When processed by the converter 90 using THRESH, set by the system calibration module 92 just described, the associated square wave pulses possess a reduced pulse width. The reduced pulse width is caused by the physiology of the donor's blood, and does not accurately reflect the actual state of the interface.

For example, a RBC-plasma interface 60 located at the proper position on the ramp 66 will, in the presence of lipemic plasma or very platelet rich plasma, generate a pulse width, which is otherwise indicative for normal plasma of an RBC-plasma interface 60 that is too close. The artificially reduced pulse width will generate

an error signal, which commands a reduction in the rate at which plasma is conveyed through the port 34. The previously properly positioned interface 60 is needlessly shifted to an out-of-position location down the ramp 66.

The second calibration module 94 adjusts the pulse width in the presence of plasma having an optical density significantly different than saline, to reflect the true position of the interface and thereby avoid blood-related optical distortions. The module 94 includes an optical monitor 98 (see Fig. 14), which senses the optical density of plasma exiting the plasma outlet port 30 or entering the PRP inlet port 34. In the illustrated embodiment shown in Fig. 13, the optical monitor 98 is a conventional hemoglobin detector, used on the Autopheresis-C® blood processing device sold by the Fenwal Division of Baxter Healthcare Corporation. The monitor 98 comprises a red light emitting diode 102, which emits light into the plasma outlet tubing 104. In this arrangement, the wavelength for detecting the optical density of plasma is essentially the same as the wavelength for detecting the location of the interface. Of course, other wavelengths, like green or infrared, could be used. The monitor 98 also includes a PIN diode detector 106 on the opposite side of the tubing 104.

Using the essentially the same wavelength for monitoring the interface and monitoring plasma is a preferred implementation. Using essentially the same wavelengths makes the absorbance spectrum for plasma essentially the same for both detectors. Therefore, there is no need to correlate the absorbance spectrum of the interface detector to the absorbance spectrum of the plasma detector. Of course, different wavelengths can be used, if desired, in which case the absorbance spectrums for plasma of the different wavelengths should be correlated, to achieve accurate calibration results.

The second calibration module 94 also includes a processing element 100, which receives signals from the monitor 98 to compute the optical transmission of the liquid conveyed through the tubing 104, which is called OPTTRANS. Various algorithms can be used by the processing element 100 to compute OPTTRANS. In a representative embodiment, OPTTRANS is derived, as follows:

$$OPTTRANS = \frac{COR(RED\ SPILL)}{CORRREF} \qquad (2)$$

where COR(RED SPILL) is calculated as follows:

$$COR(RED\ SPILL) = RED - REDBKGRD$$

where:

RED is the output of the diode detector when the red light emitting diode is on and the liquid flows through the tubing;

REDBKGRD is the output of the diode detector when the red light emitting diode is off and the liquid flows through the tubing;

and where CORREF is calculated as follows:

$$CORREF = REF - REFBKGRD$$

where:

REF is the output of the red light emitting diode when the diode is on; and

REFBKGRD is the output of the red light emitting diode when the diode is off.

Operating with the system calibration module 92, the processing element 100 obtains data from the monitor 98 and derives the optical transmission of the tubing and

the light transmissive, set up liquid, such as saline. In a preferred embodiment, optical transmission values are calculated at the fastest possible rate during the set up procedure. The values are averaged over the entire set up procedure to derive an optical transmission value for the tubing and setup liquid ($OPTTRANS_{SETUP}$).

After set up is complete, and the system calibration module 92 is no longer operative, the blood calibration module 92 continues during subsequent blood processing to derive the optical transmission of the tubing and plasma using Equation (2). In the preferred embodiment, optical transmission values are calculated by the processing element 100 at the fastest possible rate during the blood processing procedure. The values are periodically averaged at the end of a set sampling interval (for example, every 180 seconds) to derive an optical transmission value for the tubing and plasma ($OPTTRANS_{PLASMA}$).

At the end of each set sampling interval (i.e., every 180 seconds, for example), the processing module 100 determines a new threshold value THRESH, for deriving the pulse width, which varies as a function of OPTRANS, as follows:

$$THRESH = THRESH_n - [\frac{1 - OPTRANS_{PLASMA}}{OPTRANS_{SETUP}}] * MULT \qquad (3)$$

where MULT is a predetermined scale factor from 0 to, for example, 1000. In the illustrated embodiment, MULT can be set at 200.

The foregoing correction of THRESH increases the pulse width in relation to increases in optical density of plasma on the ramp 66. The second calibration module 94 thereby takes into account diminution in voltage signal gain in the presence on the ramp 66 of lipemic plasma or

plasma with very high platelet counts. The second calibration module 94 thereby serves as a gain controller for the interface controller 12, adjusting the width of the pulse to accurately reflect the actual physical location of the interface on the ramp, despite the presence of plasma having greater than normal optical density.

The interface processing element 72 ultimately outputs a signal, which accurately represents the interface location as a function of W. For example, when BASE = 640 μsec, a measured pulse width W indicates that 100% of the ramp 66 is occupied by plasma. A measured pulse width W of 320 μsec indicates that plasma occupies 50% of the ramp 66, while a measured pulse width W of 192 μsec indicates that plasma occupies 30% of the ramp 66 (i.e., RBC occupy 70% of the ramp 66), and so on.

The foregoing description shows the processing element 72 receiving sensed light intensity values from an interface detector 70 that senses light reflected from the interface ramp 66. It should be appreciated that comparable light intensity values can be obtained for processing by the processing element 72 from an interface detector that senses light after transmission through the interface ramp 66, without back reflection. In this alternative embodiment, a light source is carried by the yoke 20 (in the same manner as the optical head 70), and a light detector is carried by the spool 18 behind the interface ramp 66, or vice versa.

(3) Interface Command Element

As Fig. 11 shows, the interface command element 74 receives as input the interface location output of the processing element 72. The command element includes a comparator 108, which compares the interface location output with a desired interface location to generate an error signal (E). The desired interface location is

expressed as a control value consistent with the expression of the interface dimension output.

Generally speaking, for platelet collection, RBC should occupy no more than about 60% to 65% of the ramp 66. This can conversely be expressed in terms of a control value (expressed as a percentage) of between 35% to 40% of BASE, meaning that the measured pulse width W should be 35% to 40% of its maximum value. Alternatively, the control value can be expressed in terms of a number representing a pulse width value (in time units) integrated to a voltage value proportional to the percentage of plasma occupying the ramp 66.

Of course, different control values can be used depending upon the particular blood component collection objectives.

When the control value is expressed in terms of a targeted RBC percentage value, a positive error signal (+E) indicates that the RBC layer 56 on the ramp 66 is too large (as Fig. 6 shows). The interface command element 74 generates a signal to reduce the rate which PRP is removed through port 34. The interface 60 moves away from the constricted passage 68 toward the desired control position (as Fig. 5 shows), where the error signal (E) is zero.

A negative error signal (-E) indicates that the RBC layer 56 on the ramp 66 is too small (as Fig. 7 shows). The interface command element 74 generates a signal to increase the rate at which PRP is removed through the port 34. The interface 60 moves toward the constricted passage 68 toward the desired control position (Fig. 5), where the error signal (E) is again zero.

The interface command element 74 can affect the rate at which plasma is removed through the port 34 by controlling the relative flow rates of WB, the RBC, and the PRP through their respective ports. In a preferred embodiment (as Figs. 11 and 13 show), a pump 110 draws PRP

via the tubing 104 through the port 34. The command element 74 controls the pump rate of the pump 110 to keep the interface 60 at the prescribed location on the ramp 66, away from the constricted passage 68.

D. Optical Derivation of Platelet Volumes

As Fig. 15 shows, the system 10 preferably also includes a processing control application 200, which comprises one or more utility functions, three of which, F1, F2, and F3 are shown. The one or more utility functions F1, F2, and F3 provide processing status and parameter information and generate processing control variables for the system 10. The one or more utility functions F1, F2, and F3 are designed to achieve specified blood processing goals, taking into account the individual morphology of the donor and actual conditions occurring as processing proceeds.

The number and type of utility functions can vary. For example, a particular utility function can derive the yield of platelets during a given processing session, estimate the processing time before commencing a given processing session and while the processing session is underway, or generate control variables that control the rate of citrate anticoagulant infusion during a given processing session. Examples of utility functions are detailed in Brown U.S. Patent 5,639,382, entitled "Systems and Methods for Deriving Recommended Storage Parameters For Collected Blood Components" which is incorporated herein by reference.

In the illustrated embodiment, the processing control application 200 includes at least first, second, and third utility functions F1, F2, and F3. The first utility function F1 generates an optically derived processing value, based upon on line monitoring of the opacity of the donor's platelet-rich plasma (PRP) during processing. The optically derived processing value

correlates with the volume of platelets collected, and thereby obviates the need to calculate the platelet collection volume based upon off line cell counting and sizing techniques. The correlation between the optically derived processing value and the volume of platelets collected also obviates the need for a calibration factor to bring data derived on line into conformance with date derived off line.

The second utility function F2 calculates optimal storage parameters for the platelets collected, based in part upon the processing value optically derived by the first utility function F1. The second utility function F2 specifies these parameters in terms of the number of storage containers and the volume of platelet-poor plasma (PPP) to use as a platelet storage medium.

The third utility function F3 determines the amount of whole blood that needs to be processed to achieve a desired yield of platelets, based in part upon the processing value optically derived by the first utility function F1. F3 calculates this whole blood volume based upon the optical transmission of PRP, which is normalized by a measured transmission of PPP, to take account of the lipid content of the donor's plasma.

(1) The Utility Function F1

The utility function F1 employs a processing element 202 coupled to an optical monitor 204, which is positioned to sense the overall optical transmission of PRP separated from whole blood in the first stage 24 of the chamber 22. This overall optical transmission value for PRP will be called T(PRP).

The processing element 202 calibrates the overall value T(PRP) against a baseline value, which will be called T (PPP). The baseline value T(PPP) reflects the optical transmission of the donor's plasma in the absence of platelets, which also takes into account the lipid

content of the donor's plasma. The processing element 202 also preferably calibrates both T(PRP) and T(PPP) against optical background "noise."

Ultimately, the processing element 202 derives a calibrated opacity value, which reflects the opacity of the PRP due solely to the presence of platelets.

The processing element 202 numerically integrates the calibrated opacity value relative to the plasma volume processed over time, to obtain an integrated value, called PCI. It has been discovered that the magnitude of PCI for a given procedure and donor, using a particular processing system, closely correlates to the platelet yield actually obtained during that procedure (expressed in units x 10^{11}) and the volume of platelets actually collected during the procedure (expressed in ml). As a result, neither of these actual values need be independently calculated by other means.

(i) The Optical Monitor

In the illustrated embodiment (see Fig. 15), the optical monitor 204 is positioned along tubing 104 to sense the optical density of plasma exiting the plasma outlet port 30 of the first stage 24 or entering the PRP inlet port 24 of the second stage 26. In the illustrated embodiment, the monitor 204 is located in line with the tubing 104 downstream of the PRP pump 110, previously described. Alternatively, the monitor 204 could be placed upstream of the PRP pump 110.

The optical monitor 204 can be constructed in various ways. In the illustrated embodiment shown in Fig. 15, the monitor 204 comprises a conventional hemoglobin detector, used, e.g., on the Autopheresis-C® blood processing device sold by the Fenwal Division of Baxter Healthcare Corporation. The monitor 204 comprises a red light emitting diode 206, which emits light into the plasma outlet tubing 104. Other wavelengths, like green or

infrared, could be used.

The monitor 204 also includes a PIN diode detector 208 on the opposite side of the tubing 104.

The wavelength for detecting the optical density of plasma can be essentially the same as the wavelength for detecting the location of the interface, as previously described. In this way, the optical monitor 204 serving the processing element 202 and the optical monitor 98 serving the processing element 100(previously described and shown in Figs. 11 and 14) can comprise the same functional element.

(ii) Deriving a Calibrated Opacity Value

As liquid is conveyed through the tubing 104 from the first stage 24 to the second stage 26, the processing element 202 receives signals from the monitor 204, indicative of the optical transmission of the liquid in the tubing 104. When the liquid is PRP, the signals are indicative of T(PRP), which varies as a function of the number and size of platelets residing in the PRP, as well as any background optical "noise" unrelated to the opacity of the PRP. The processing element 202 takes these factors affecting the opacity signals into account to compute a PRP intensity value T(PRP).

Various algorithms can be used by the processing element to compute T(PRP). In a preferred embodiment, T(PRP) is calculated as follows:

$$T(PRP) = \frac{REDBKG - RED}{REFBKG - REF} \qquad (4)$$

where:

RED represents the output of the diode detector 208 when the red light emitting diode 206 is on and PRP flows through the tubing 104;

REDBKD is the output of the diode detector 208

when the red light emitting diode 206 is off and PRP flows through the tubing 104;

REF is the output of the light emitting diode 206 when the diode 206 is on; and

REFBKG is the output of the light emitting diode 206 when the diode 206 is off.

The values RED, REDBKG, REF, and REFBKG each comprises a digital number between 0 (maximum light transmission) to 2048 (no light transmission). The digital number is obtained by converting the sensed light intensity output of the detector 208 (a current) into a negative voltage signal using an inverting current to voltage (I/V) amplifier. The negative voltage signal is further amplified, buffered, and processed in a conventional manner to provide the digital number output.

In the illustrated and preferred embodiment, the values RED, REDBKG, REF, and REFBKG are obtained by straight through transmission between a single emitter 206 and a single detector 208 and include no side scatter effects.

In the illustrated embodiment, T(PRP) is sampled at a set sample period (the sample rate), e.g., once every five seconds.

(iii) Deriving Baseline T(PPP)

The T(PRP) signals also vary as a function of the lipid content of the donor's plasma, in the manner previously described. In the illustrated embodiment, the processing element 202 takes the affect of the lipid content into account 202 by computing a PPP baseline intensity value T(PPP), to yield a calibrated opacity value.

Various algorithms can be used by the processing element to compute T(PPP). In a preferred embodiment, T(PPP) is calculated in the same fashion as T(PRP), namely:

$$T(PPP) = \frac{REDBKG - RED}{REFBKG - REF} \qquad (4A)$$

where:

RED represents the output of the diode detector 208 when the red light emitting diode 206 is on and PPP flows through the tubing 104;

REDBKD is the output of the diode detector 208 when the red light emitting diode 206 is off and PPP flows through the tubing 104;

REF is the output of the light emitting diode 206 when the diode 206 is on; and

REFBKG is the output of the light emitting diode 206 when the diode 206 is off.

In the illustrated embodiment (see Fig. 15), platelet-poor plasma (PPP) is centrifugally separated from PRP in the second stage 26. During processing, PPP is conveyed from the second stage 26 through the port 36, leaving PC in the second stage 26.

Tubing 210 communicates with the PPP port 36. The tubing 210 includes a first branch 212, which leads (via an in line pump 214) to a collection container 216. During the platelet collection stage of processing, a designated volume of the PPP is retained in the container 216 for eventual use as a suspension medium for the PC. Following the platelet-collection stage of the process, a suspension stage is begun, during which all or a portion of the PPP in the container 216 is conveyed back into the second stage 26, via tubing branch 218, to suspend the PC for storage and transfusion.

The tubing 210 also includes a second branch 220, which leads to the donor. The second branch 220 conveys the remaining volume of PPP (i.e., the portion not designated for use as a suspension medium) for return to

the donor during processing.

For a system configured as shown in Fig. 15, the platelet-poor plasma baseline T(PPP) can be derived for the individual donor in various ways.

For example, the value of T(PPP) can be obtained empirically by plotting the fluctuation of T(PRP) over time during a series of processing periods using a given system, and by ascertaining when the value of T(PRP) obtained during the platelet collection stage matches the value of T(PPP) obtained during a suspension stage. Fig. 16 shows a representative plot of the fluctuation of T(PRP) over time during a typical platelet collection stage and suspension stage, using a centrifugal blood collection system of the type previously described and illustrated. In Fig. 16, T(PRP) is expressed as a raw digital number signal from the diode detector 206, so that the digital number increases with sensed opacity (as before described, between 0 and 2048). The value A represents T(SAL) obtained during a set up stage, as described earlier. The opacity is seen to rise as the platelet collection stage progresses, until a desired constituency of PRP is obtained, under the control of the interface controller 12, as previously described. The value B represents a running average of T(PRP) obtained during the platelet collection stage. The value C represents T(PPP) obtained during the suspension stage. Fig. 16 shows that a corresponding value D, essentially equal to T(PPP) is sensed during the early stages (of the platelet collection stage (e.g., after about 3 minutes, as saline is progressively replaced by PRP). Empirical results demonstrate that, for a given procedure on a given system, the value D, corresponding to T(PPP), consistently occurs after the conveyance of a certain volume of PRP from the first stage 24 during the platelet collecting stage (which in Fig. 16, is about 58 ml). Based upon such

empirical data, T(PPP) can be obtained by measuring T(PRP) at a designated point in the platelet collection procedure and assigning T(PPP) its value. It has been empirically determined that the point in the platelet collection procedure where T(PPP) can be accurately obtained in this fashion occurs when priming fluid is first cleared from the first stage 24 and tubing 104, which volume is designated V_{INI}. This initial processing volume V_{INI} is also used in by the processing element 202 in deriving the integrated PCI value, as will be described below.

The intensity value T(PPP) assigned in the above described way can be assumed to remain constant for the remainder of the procedure, unless the donor's plasma carries a very high transient dietary lipid content.

Alternatively, the value of T(PPP) can be obtained or updated during the platelet collection stage by suspending normal PRP processing and circulating a known volume of PPP from the second stage 26 via the pump 214, through the tubing 218, and into tubing 104 upstream of the optical monitor 204. The baseline T(PPP) is then derived according to Equation 4A.

In the illustrated embodiment, T(PPP) is sampled at a set sample rate, e.g., once every five seconds. A series of readings T(PPP) are taken over a set sampling period (e.g., 5 samples) and are averaged to obtain an average T(PPP), which the processing element 202 assigns as the value for T(PPP).

The baseline T(PPP) can be obtained in this fashion at any time during the procedure. However, T(PPP) preferably obtained in this fashion after a sufficient volume of whole blood has been processed to bring the system into a steady state processing condition, e.g., after more than 500 ml of whole blood have been processed. The volume of PPP that needs to be circulated to accurately obtain T(PPP) can be empirically determined.

In the illustrated arrangement, the circulation of about 15 to 20 ml of PPP is required for the optical monitor 204 to reach an optical steady state value for T(PPP).

A value for T(PPP) can be obtained at the outset of processing, when the processed plasma volume reaches V_{INI}, as described above. It can then be updated later in the procedure after steady state processing conditions occur by suspending PRP processing and circulating a volume of PPP past the optical monitor 204, as also described above.

(iv) Deriving Platelet Volume Collected

The processing element 202 numerically integrates the T(PRP) relative to T(PPP) during the processing period relative to the plasma volume V_p processed, to derive the volume of platelets collected, or PCI.

There are various ways in which this numeric integration can be accomplished. In a preferred implementation, the processing element 202 computes PCI as follows:

$$PCI = \sum_{V_{INI}}^{V_{PRP}} [1 - \frac{T(PRP)}{T(PPP)}] \Delta V_{PRP} \qquad (6)$$

where:

V_{INI} represents the volume of plasma that must be processed before priming fluid is cleared from the first stage 24 and tubing 104, earlier described.

V_{PRP} is the total volume of PRP collected during the procedure.

ΔV_{PRP} is the incremental plasma volume (in ml) processed during a sample interval(n). ΔV_{PRP} can be expressed as a function of the sampling rate and plasma pump rate, as follows:

$$\Delta V_{PRP} = Q_{p(n)} \Delta t_{(n)}$$

where:

$Q_{p(n)}$ represents the flow rate of plasma (in ml/min) through the tubing 104 when T(PRP) is measured (which is controlled by the pump 110), and

$\Delta t_{(n)}$ is the period of the sample interval (or the sampling rate), expressed as a fraction of one hour, e.g., a sample period of once every 5 seconds represents the fraction 1/12.

By assuming T(PPP), when ascertained, to be constant through a given procedure, Equation (6) can be reduced to the following expression:

$$PCI = (V_{PRP} - V_{INI}) - \frac{1}{T(PPP)} \sum_{V_{INI}}^{V_{PRP}} T(PRP) \Delta V_{PRP} \quad (6A)$$

Fig. 17 shows a plot of 358 values of PCI derived during blood separation processes of the type previously described, performed by fifteen different centrifuges of the type previously described. The values of PCI are plotted against associated platelet volumes collected (in ml), which are derived by multiplying the number of platelets collected by their mean platelet volume (MPV), as measured by an off line counter. The plot shows a linear distribution having the following relationship:

$$PLT_{vol}(ml) = 0.24 + 0.0070 PCI$$

where 0.24 is the y-intercept, which is only about 6% of the nominal expected collected platelet volume of 4.0×10^{11} ml, and 0.0070 is the slope of the plot. The linear distribution has an r^2 value of 0.75. Fig. 17

demonstrates that a good correlation exists between PCI and collected platelet volume PLT_{Vol}.

Fig. 18 shows a plot of the same 358 values of PCI against associated platelet yields PLT_{Yld} (expressed in units x 10^{11}), which are derived by multiplying the platelet count (measured by an off line counter) by the volume of platelet concentrate. The plot shows a linear distribution having the following relationship:

$$PLT_{Yld}(x10^{11}) = 0.67 + 0.0080PCI$$

where the y-intercept of 0.67 is 17% of the nominal expected collected platelet volume of 4.0 x 10^{11} ml. The linear distribution has an r^2 value of 0.70. Fig. 17 demonstrates that a correlation also exits between PCI and platelet yields, but also illustrates that the quantity PCI is more indicative of platelet volume PLT_{Vol} than the number of platelets collected PLT_{Yld}.

(2) Second Utility Function F2

The second utility function F2 includes a processing element 224 which receives as input the calculation of PCI made by the first utility function F1. Based upon the value of PCI, the processing element 224 derives the optimum storage conditions to sustain the platelet volume collected during the expected storage period. The processing element 224 generates an output reflecting the number of preselected storage containers required for the platelets Plt_{Bag} and the volume of plasma (PPP) Plt_{Med} (in ml) to reside as a storage medium with the platelets.

The optimal storage conditions for platelets depends upon platelet volume desired to be stored Plt_{Vol}. As demonstrated above, the value of PCI (in ml) correlates with Plt_{Vol}. Therefore, the platelet volume Plt_{Vol} can be accurately expressed in terms of PCI, without the need to

know the actual platelet yield or to independently assess platelet cell counts or mean platelet volumes (MPV).

As the value of PCI increases, so too does the platelets' demand for oxygen during the storage period. As the value of PCI increases, the platelets' glucose consumption to support metabolism and the generation of carbon dioxide and lactate as a result of metabolism also increase. The physical characteristics of the storage containers in terms of surface area, thickness, and material are selected to provide a desired degree of gas permeability to allow oxygen to enter and carbon dioxide to escape the container during the storage period.

The plasma storage medium contains bicarbonate HCO_3, which buffers the lactate generated by platelet metabolism, keeping the pH at a level to sustain platelet viability. As the value of PCI increases, the demand for the buffer effect of HCO_3, and thus more plasma volume during storage, also increases.

A. Deriving Plt_{Bag}

The partial pressure of oxygen pO_2 (mmHg) of platelets stored within a storage container having a given permeation decreases in relation to the total platelet volume Plt_{Vol} the container holds. Fig. 19 is a graph based upon test data showing the relationship between pO_2 measured after one day of storage for a storage container of given permeation. The storage container upon which Fig. 19 is based has a surface area of about 54 in^2 and a capacity of 1000 ml. The storage container has a permeability to O_2 of 194 cc/100 in^2/day, and a permeability to CO_2 1282 cc/100 in^2/day.

When the partial pressure pO_2 drops below 20 mmHg, platelets are observed to become anaerobic, and the volume of lactate byproduct increases significantly. Fig. 19 shows that the selected storage container can maintain pO_2 of 40 mmHg (well above the aerobic region) at $Plt_{Vol} \leq$

4.0 ml. On this conservative basis, the 4.0 ml volume is selected as the target volume Plt_{TVol} for this container. Target volumes Plt_{TVol} for other containers can be determined using this same methodology.

The processing element 224 uses the target platelet volume Plt_{TVol} to compute Plt_{Bag} as follows:

$$BAG = \frac{a+bPCI}{Plt_{TVol}} \quad (8)$$

where:

a is the y-intercept and b is the slope of the plot between PLT_{Vol} and PCI derived by linear regression analysis, as previously described and shown in Fig. 17. The values of a and b will change according to the operating parameters of the particular blood processing system. In the illustrated embodiment a = 0.24 and b = 0.0070, and

where Plt_{Bag} is the number of storage containers required, and

Plt_{Bag} = 1 when BAG ≤ 1.0, otherwise

Plt_{Bag} = [BAG + 1], where [BAG + 1] is the integer part of the quantity BAG + 1.

For example, based upon the systems upon which Fig. 17 is derived, given a value of PCI = 400 ml (which correlates to a Plt_{Vol} = 3.8 ml), and given Plt_{TVol} = 4.0 ml, BAG = 0.95, and Plt_{Bag} = 1. Based upon the systems upon which Fig. 17 is derived, if the value of PCI = 600 ml (which correlates to a Plt_{Vol} = 4.4 ml), BAG = 1.1 and Plt_{Bag} = 2.

When Plt_{Bag} > 1, the quantity a + b(PCI) is divided equally among the number of containers called for.

B. Deriving Plt_{Med}

The amount of bicarbonate used each day is a function of the storage thrombocytocrit Tct (%), which can be expressed as follows:

$$Tct = \frac{PLT_{Vol} \times MPV}{Plt_{Med}} \quad (9)$$

The relationship between bicarbonate HCO_3 consumption per day and Tct can be empirically determined for the selected storage container. Fig. 20 shows a graph showing this relationship for the same container that the graph in Fig. 19 is based upon. The y-axis in Fig. 20 shows the empirically measured consumption of bicarbonate per day (in Meq/L) based upon Tct for that container. The processing element 224 includes the data expressed in Fig. 20, for example, in a look-up table 226.

The processing element 224 derives the anticipated decay of bicarbonate per day over the storage period ΔHCO_3 as follows:

$$\Delta HCO_3 = \frac{Don_{HCO_3}}{Stor} \quad (10)$$

where:

Don_{HCO3} is the measured bicarbonate level in the donor's blood (Meq/L), or alternatively, is the bicarbonate level for a typical donor, which is believed to be 19.0 Meq/L ± 1.3, and

Stor is the desired storage interval (in days, typically between 3 to 6 days).

Given ΔHCO_3, the processing element 224 derives Tct from the look-up table 226 for selected storage container. For the storage container upon which Fig. 20 is based, a Tct of about 1.35 to 1.5% is believed to be conservatively appropriate in most instances for a six day storage interval.

Knowing Tct and PCI, the utility function F2 computes Plt_{Med} based upon Eq (8), as follows:

$$Plt_{Med} = \frac{a + bPCI}{\frac{Tct}{100}} \quad (11)$$

where Tct can be a value based upon empirical data for the particular storage container (as just described and shown in Fig. 20), and not requiring off line counting or sizing techniques.

When $Plt_{Bag} > 1$, Plt_{Med} is divided equally among the number of containers called for.

(3) The Third Processing Function (F3)

The third utility function F2 includes a processing element 324 which receives as input the calculation of PCI made by the first utility function F1. Based upon the value of PCI, the processing element 324 derives the amount of whole blood that needs to be processed in order for a the procedure to collect a desired yield of platelets, called WB_To_Process.

The third utility function F3 is activated after the volume of plasma processed equals V_{INI}, earlier described. The third utility function F3 continues to run for the remainder of the process. WB_To_Process can be updated whenever new values of T(PRP) or T(PPP) are acquired to provide an updated PCI or periodically at prescribed processing intervals, e.g., after every 500 ml of whole blood processed.

In the illustrated embodiment, the operator inputs a desired platelet yield, or Plt_{Goal}. The processing element 324 derives a targeted PCI value, called $PCI_{Targeted}$, as a function of Plt_{Goal}. The function is derived empirically based upon a series of blood processing procedures conducted to correlate PCI against actual platelet yields, which have been previously described in terms of the linear regression analyses shown in Figs. 17 or Fig. 18. The function also preferably takes into account a counter calibration factor, which brings the data derived on line during the series of blood processing procedures into conformance with date derived off line by use of a platelet counter. The counter calibration factor

varies according to the type and manufacturer of the particular off line platelet counter used. The operator is given a table of counter calibration factors and instructed to input the factor that corresponds to the off line platelet counter that the operator uses.

In a preferred embodiment, the function relating PCI_{Target} to Plt_{Goal} is expressed as follows:

$$PCI_{Target} = \frac{C_1 Plt_{Goal}}{C_2} \quad (12)$$

where:

C_1 is a factor derived by analysis of blood processing data, as previously described and shown in Fig. 17 or Fig. 18. In a representative implementation, C_1 will typically lay in a numerical range of between 100 and 115, based upon the results of the blood processing procedures upon which the analysis is based. In a current, preferred embodiment using an Amicus™ Blood Processing System (Baxter Healthcare Corporation), $C_1 = 112.5$.

C_2 is the counter calibration factor prescribed for the off-line platelet counter in use.

In the illustrated embodiment, when the processed plasma volume equals V_{INI}, the processing element 324 derives an initial baseline T(PPP), as previously described. The processing element 324 also begins to derive T(PRP) every five seconds, as also previously described. A final baseline T(PPP) is derived later in the procedure, and this value is used throughout subsequent processing as T(PPP).

The processing element 324 derives a quantity called Sigma, where:

$$Sigma = T(PRP) * Q_P \Delta t \quad (13)$$

where

T(PRP) is the transmission of PRP

measured by the optical detector measured at the end of a sample interval (n),

Q_p represents the flow rate of plasma (in ml/min) through the tubing 104 when T(PRP) is obtained, and

Δt is the period of the sample interval (or the sampling rate), expressed as a fraction of one hour, e.g., a sample period of once every 5 seconds represents the fraction 1/12.

The processing element 324 initializes Sigma at zero, $Sigma_{old}$. Once the amount of plasma processed equals V_{INI}, the processing element 324 measures T(PRP)and derives a current Sigma at the prescribed sampling rate. For each sampling period, the new value for Sigma is added to the old value of Sigma, to yield an integrated current value for Sigma ($Sigma_{Current}$)

At the end of each sampling period, the processing element 324 derives a current PCI value ($PCI_{Current}$), as follows:

$$PCI_{Current} = (V_{PRP(Current)} - V_{INI}) - (\frac{1}{T(PPP)} * Sigma_{Current})$$

where:

$V_{PRP(Current)}$ is the current cumulative volume of PRP processed at the end of the given sampling period.

At the end of each sampling period, the processing element 324 also derives a current value for WB_To_Process as follows:

$$WB\_To\_\mathrm{Process} = (WB\_\mathrm{Processed} - V_{\mathrm{Prime}}) * \left[\frac{PCI_{Target}}{PCI_{Current}}\right] + V_{\mathrm{Prime}} \quad (14)$$

where:

WB_Processed is the volume of whole blood that has been processed up to the present point of the process, and

V_{Prime} is the priming volume of the blood processing flow path.

The WB_To_Process is preferably displayed for viewing by the operator on an appropriate user interface screen (not show). The displayed WB_To_Process value can be updated periodically, e.g., for every 100 ml of whole blood processed. The operator can be given the option of altering the WB_To_Process value in real time during the course of a given procedure. In this circumstance, the altered value is accepted and corrected to get the desired platelet yield.

Various features of the inventions are set forth in the following claims.

CLAIMS

We claim:

1. A blood processing system comprising

an input to receive a value indicating a desired platelet volume,

a separation chamber assembly operating to separate blood into constituents including a plasma constituent containing platelets and having an optical density,

an outlet path for conveying a volume of the plasma constituent from the separation chamber during a processing period, the volume of plasma constituent containing a platelet volume,

a sensor assembly operating to detect the optical density of the plasma constituent in the outlet path during several sample intervals within the processing period and generate for each sample interval a sampled opacity value expressing the detected optical density as a function of incremental plasma volume processed during the respective sample interval,

a first processing element coupled to the sensor including an element that is operable to sum the sampled opacity values over the processing period and generate an integrated opacity value, and

a second processing element which receives as input the integrated opacity value and generates a second output based, at least in part, upon the integrated opacity value, comprising a value indicating a blood volume that needs be processed to obtain the desired platelet volume.

2. A system according to claim 1

wherein the processing element includes an output that expresses the platelet volume based upon the integrated opacity value.

3. A system according to claim 1

wherein the separation chamber further separates the plasma constituent into a platelet-poor plasma constituent and a platelet concentrate comprising the platelet volume, the platelet-poor plasma constituent including an optical density that varies with lipid content,

further including a sensor to detect the optical density of the platelet-poor plasma constituent and generate a baseline optical density value, and

wherein the processing element includes a calibration element that calibrates the integrated opacity value against the baseline optical density value.

4. A system according to claim 1

and further including a third processing element which receives as input the integrated opacity value and generates a third output, different than the second output, based, at least in part, upon the integrated opacity value.

5. A system according to claim 4

wherein the third output comprises a parameter for storing the platelet volume.

6. A system according to claim 4

wherein the third output includes a value representing the number of selected storage containers to be used for the platelet volume.

7. A system according to claim 4

wherein the third output includes a value representing the recommended volume of storage medium for the platelet volume.

8. A system according to claim 1

wherein the sensor includes an emitter of a selected wavelength of light energy and a detector of the selected wavelength.

9. A system according to claim 8

wherein the first output is free of side scatter

effects.

10. A blood processing method comprising

defining a desired platelet volume,

separating blood into constituents including a plasma constituent containing platelets and having an optical density,

conveying in an outlet path a volume of the separated plasma constituent during a processing period, the volume of separated plasma constituent containing a platelet volume,

detecting the optical density of the plasma constituent in the outlet path during several sample intervals within the processing period,

generating for each sample interval a sampled opacity value expressing the detected optical density as a function of incremental plasma volume processed during the respective sample interval,

generating an integrated opacity value by summing the sampled opacity values over the processing period,

generating an output based, at least in part, upon the integrated opacity output, comprising a value indicating a blood volume that needs be processed to obtain the desired platelet volume.

11. A method according to claim 10

further including expressing the platelet volume based upon the integrated opacity value.

12. A method according to claim 10

wherein the separating step provides a platelet-poor plasma constituent which includes an optical density that varies with lipid content,

further including the steps of detecting the optical density of the platelet-poor plasma constituent and generate a baseline optical density value and calibrating the integrated opacity value against the

baseline optical density value.

13. A method according to claim 10

and further including the step of generating another output based, at least in part, upon the integrated opacity output.

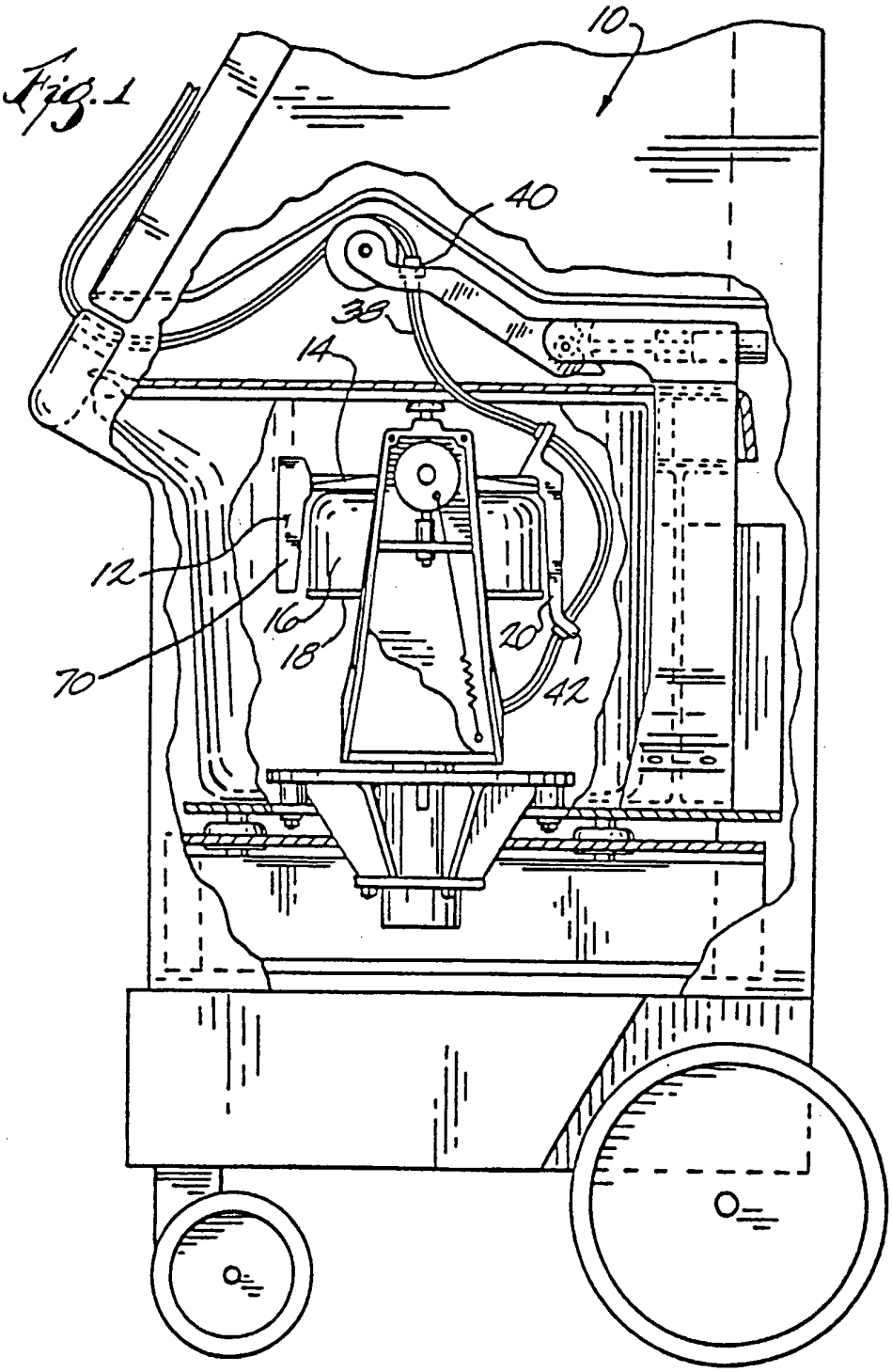
14. A method according to claim 13

wherein the other output comprises a parameter for storing the platelet volume.

15. A method according to claim 10

wherein the step of generating the sampled opacity values is free of side optical scatter effects.

Fig. 1



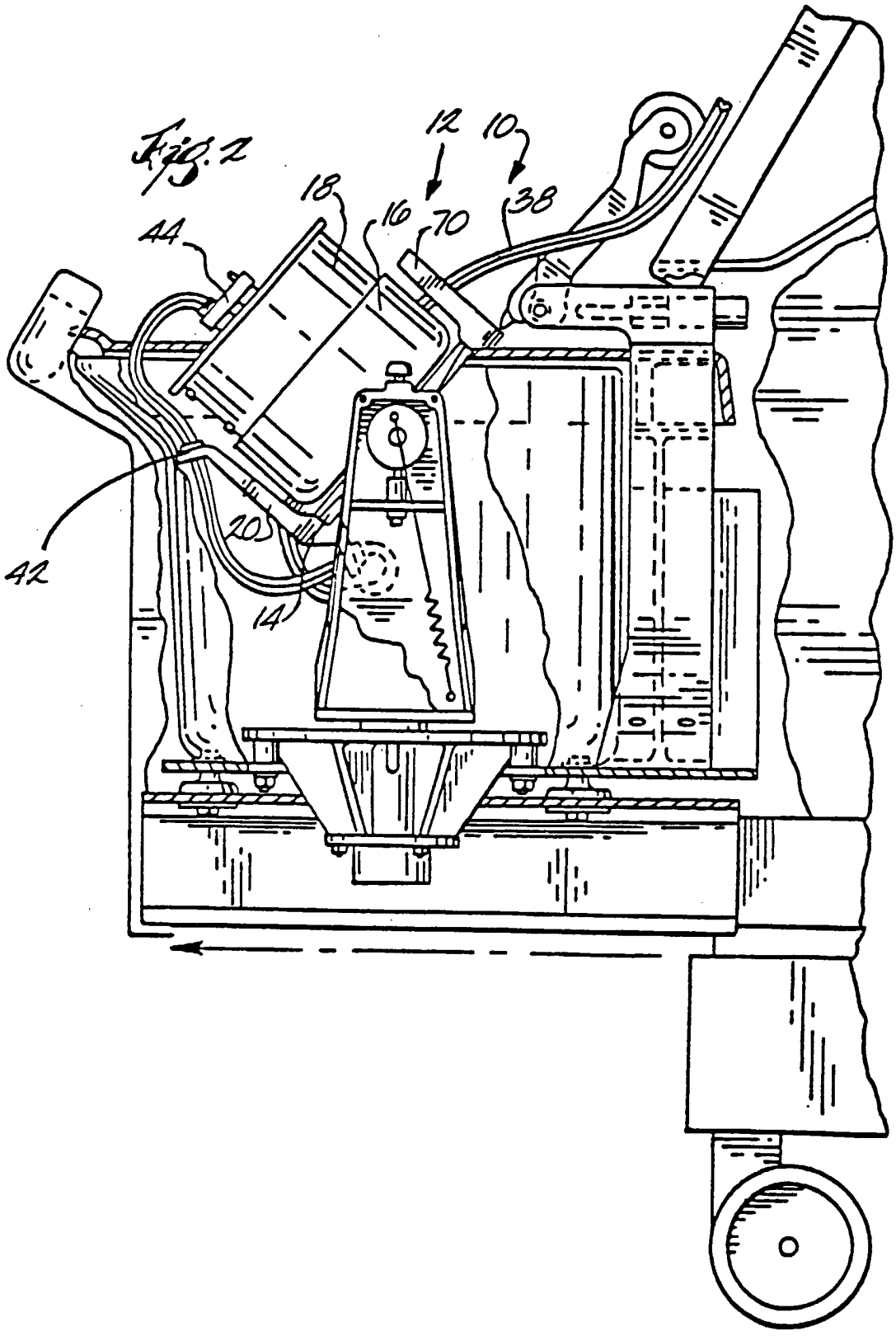


Fig. 2
12
10
18
16
70
38
44
42
20
14

Fig. 3

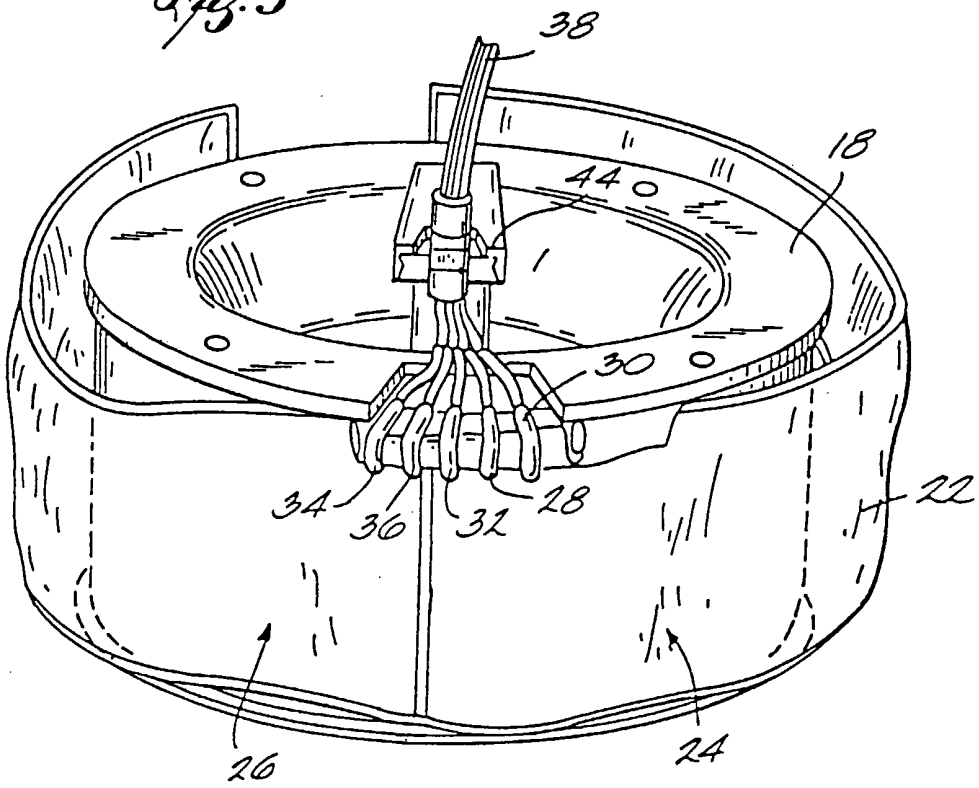

38
18
44
30
34
36
32
28
22
26
24

Fig. 4

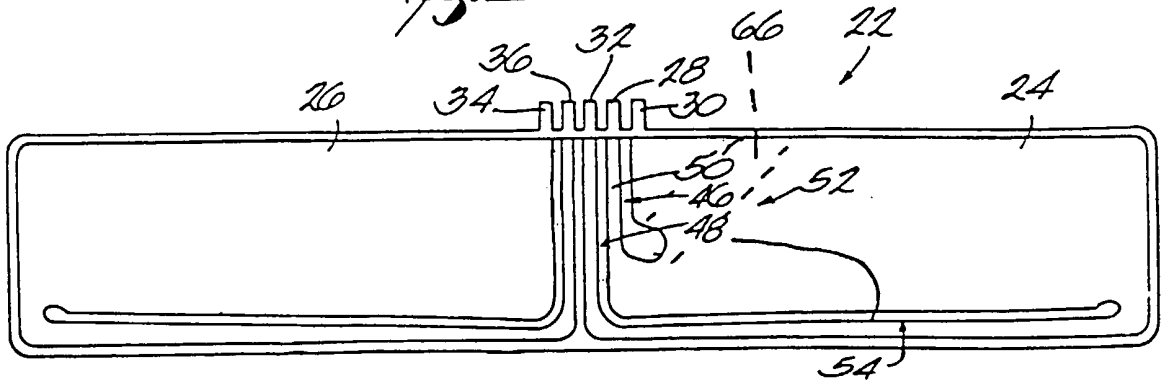

66
22
36
32
28
26
34
30
24
50
52
46
48
54

Fig. 6

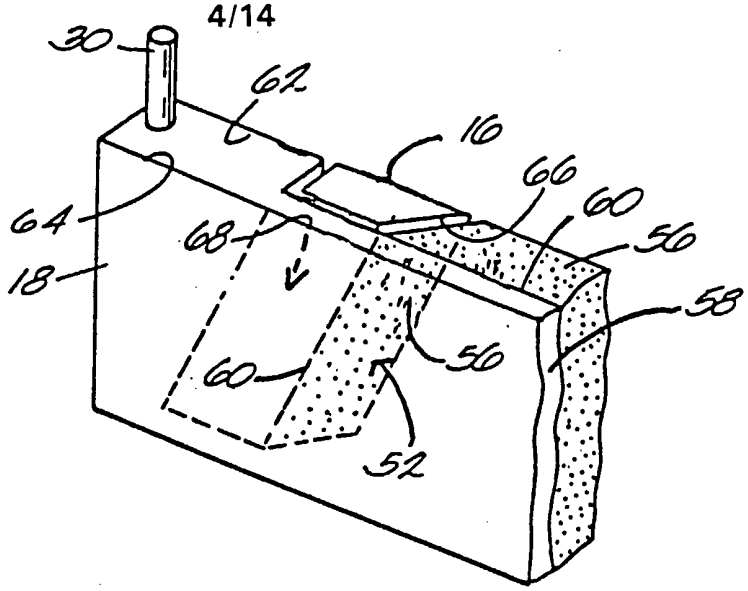


Fig. 5

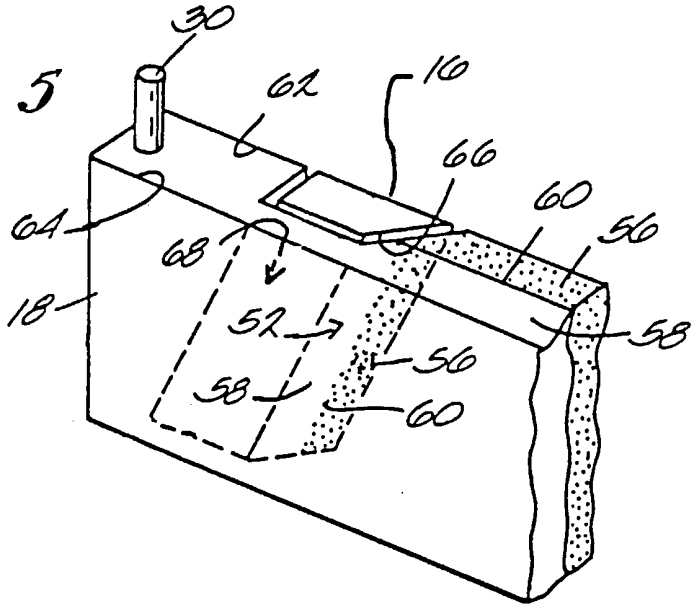


Fig. 7

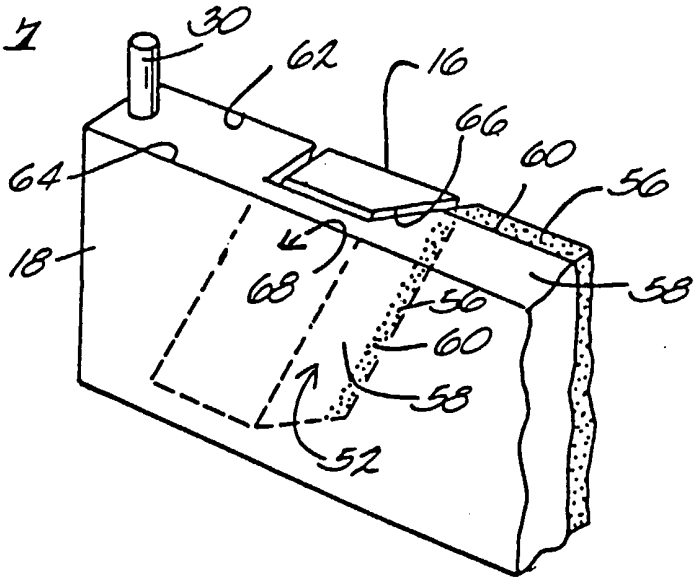


Fig. 8

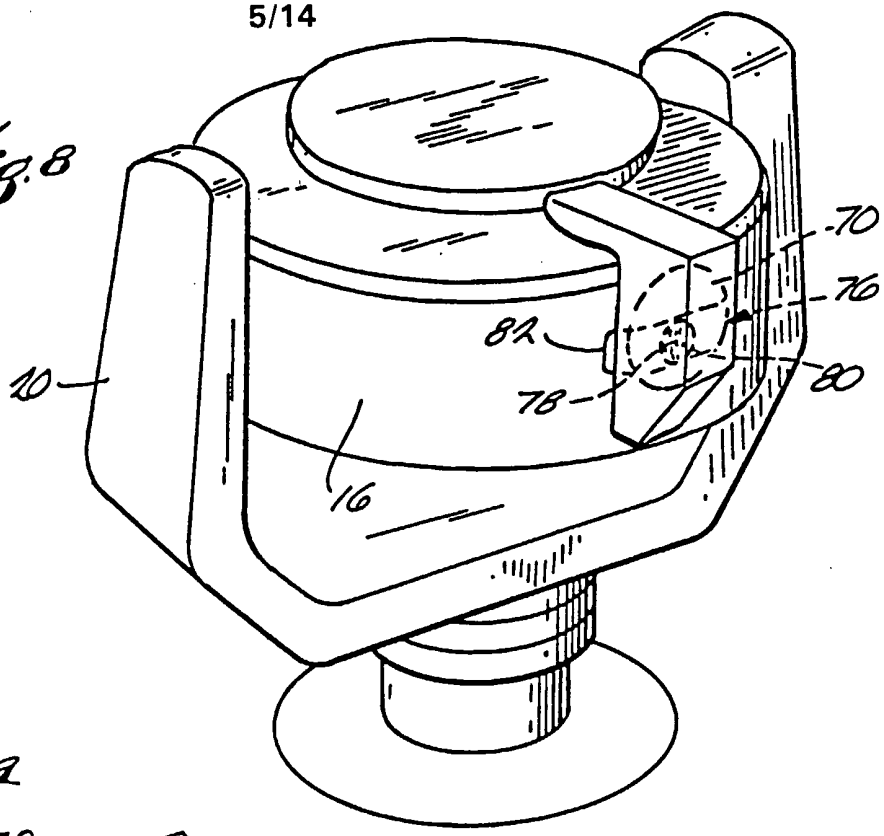


Fig. 9

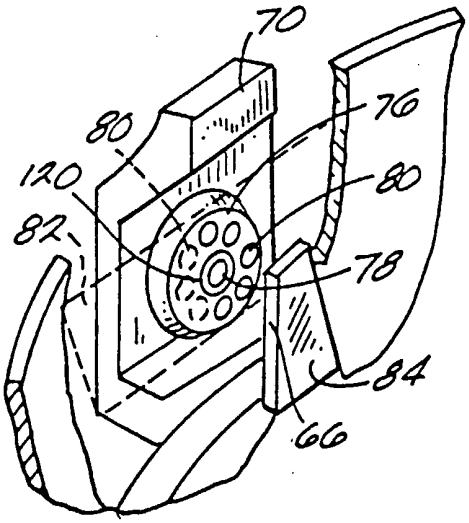
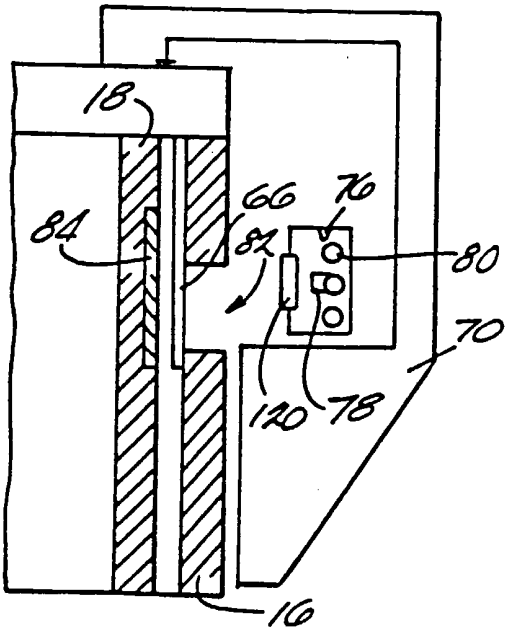


Fig. 10



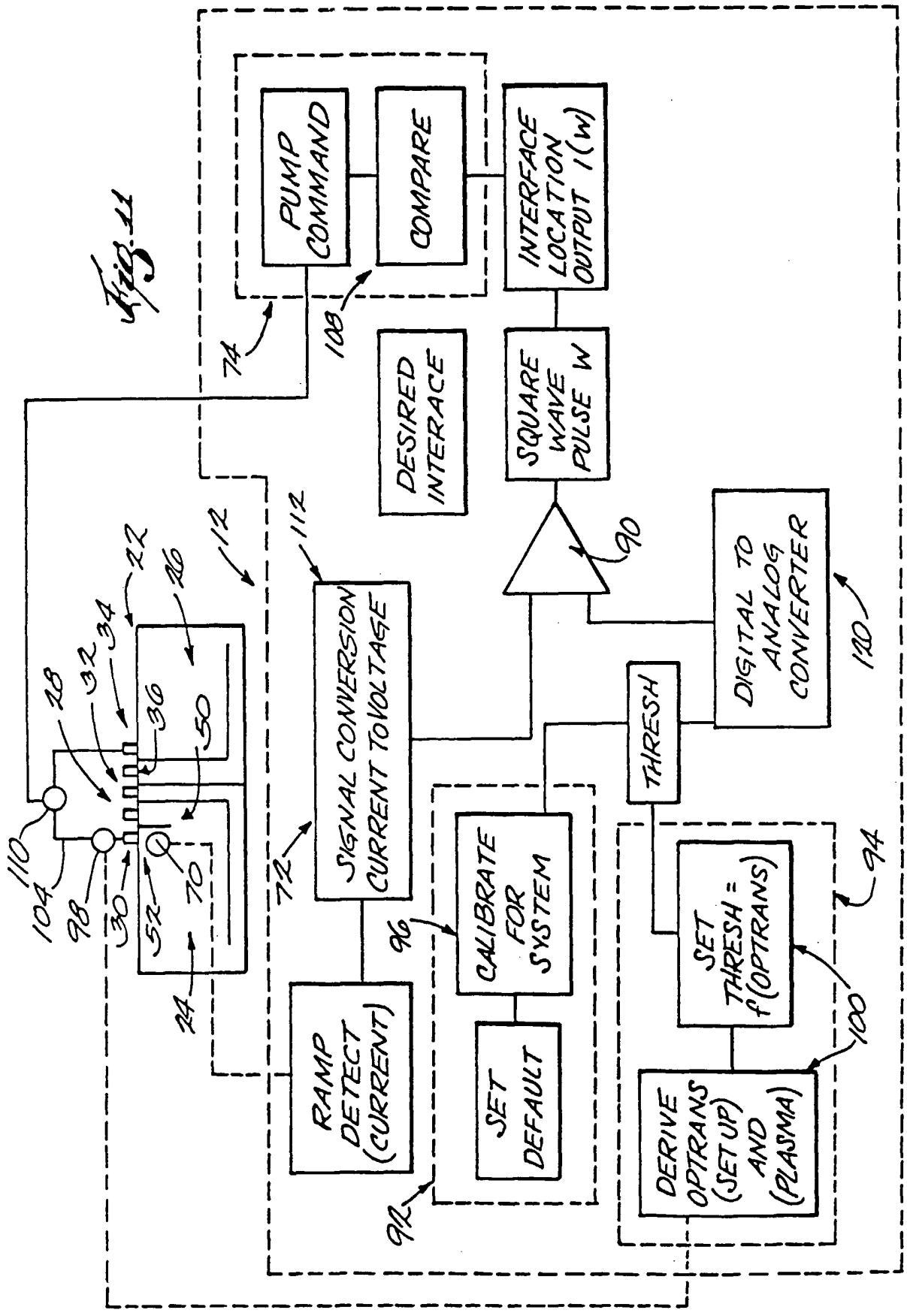

PUMP COMMAND
COMPARE
INTERFACE LOCATION OUTPUT I(w)
74
109
DESIRED INTERACE
SQUARE WAVE PULSE W
90
DIGITAL TO ANALOG CONVERTER
120
112
SIGNAL CONVERSION CURRENT TO VOLTAGE
72
THRESH
CALIBRATE FOR SYSTEM
96
SET THRESH = f(OPTRANS)
94
RAMP DETECT (CURRENT)
SET DEFAULT
92
DERIVE OPTRANS (SET UP) AND (PLASMA)
100
110
104
28
32
34
22
26
36
50
98
30
52
70
24

Fig. 11

FIG. 12

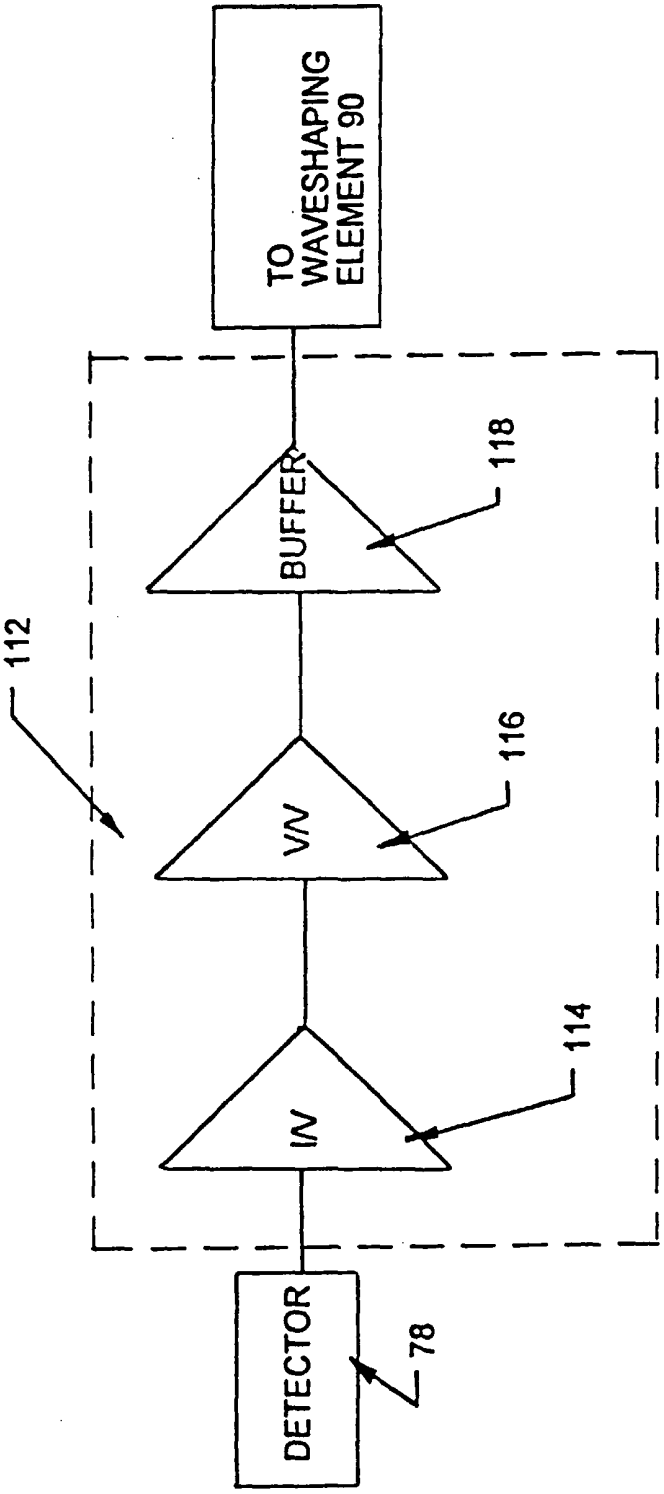

TO WAVESHAPING ELEMENT 90
BUFFER
118
112
V/V
116
I/V
114
DETECTOR
78

FIG. 13

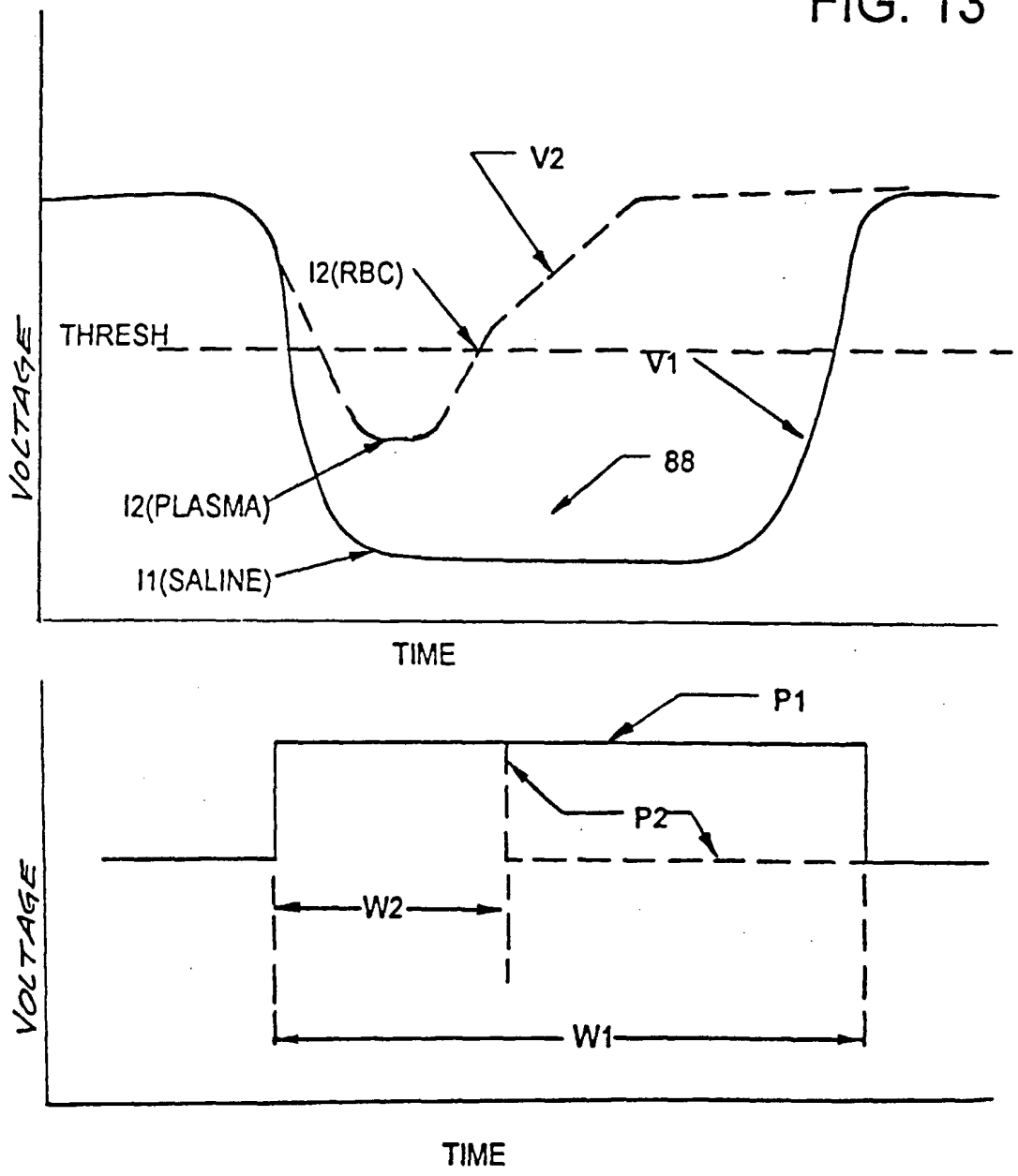
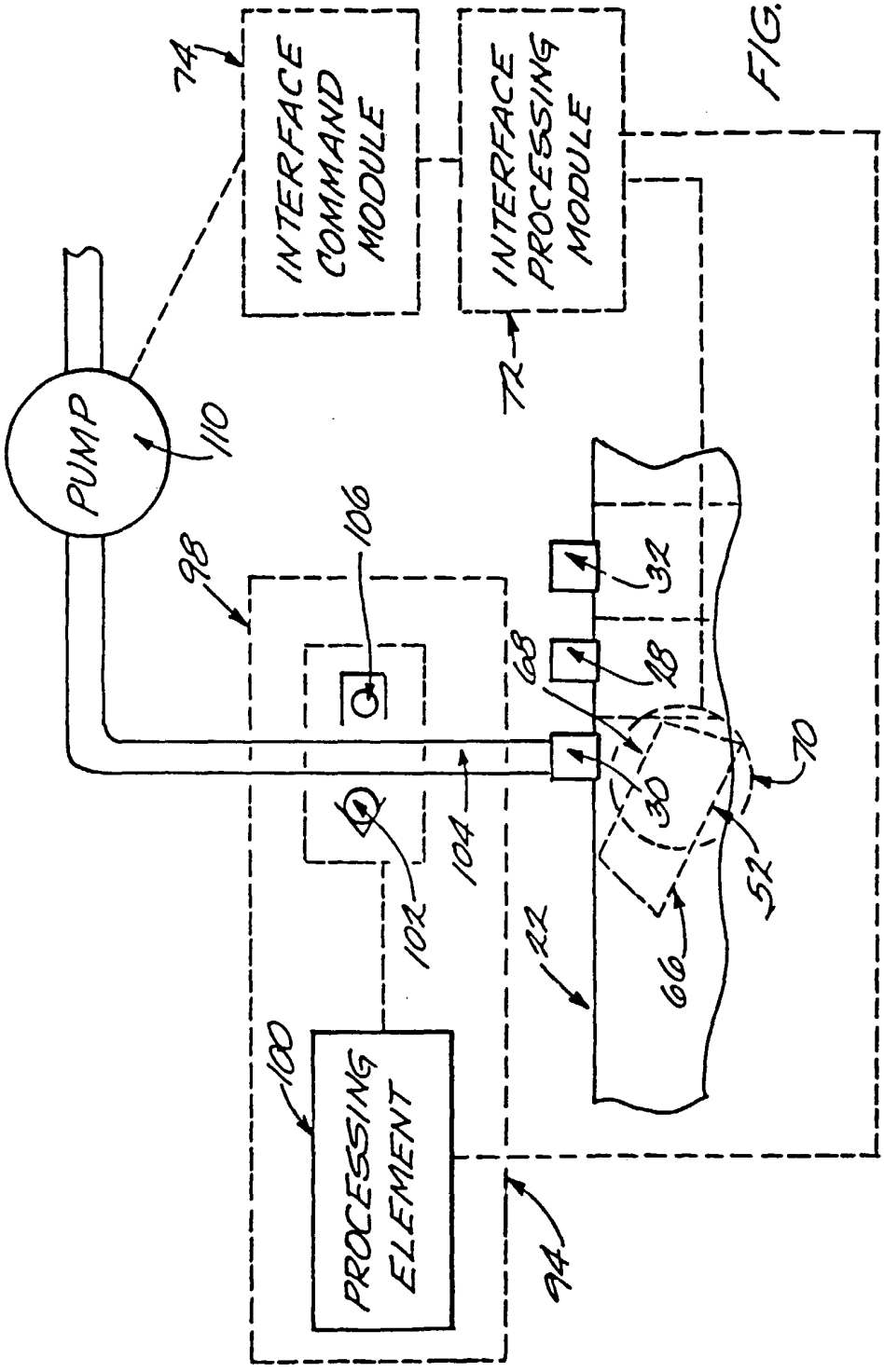

V2
I2(RBC)
THRESH
V1
88
I2(PLASMA)
I1(SALINE)
VOLTAGE
TIME
P1
P2
W2
W1
VOLTAGE
TIME

FIG. 14


INTERFACE COMMAND MODULE
INTERFACE PROCESSING MODULE
74
72
PUMP
110
98
106
32
68
18
70
30
52
66
104
102
22
100
PROCESSING ELEMENT
94

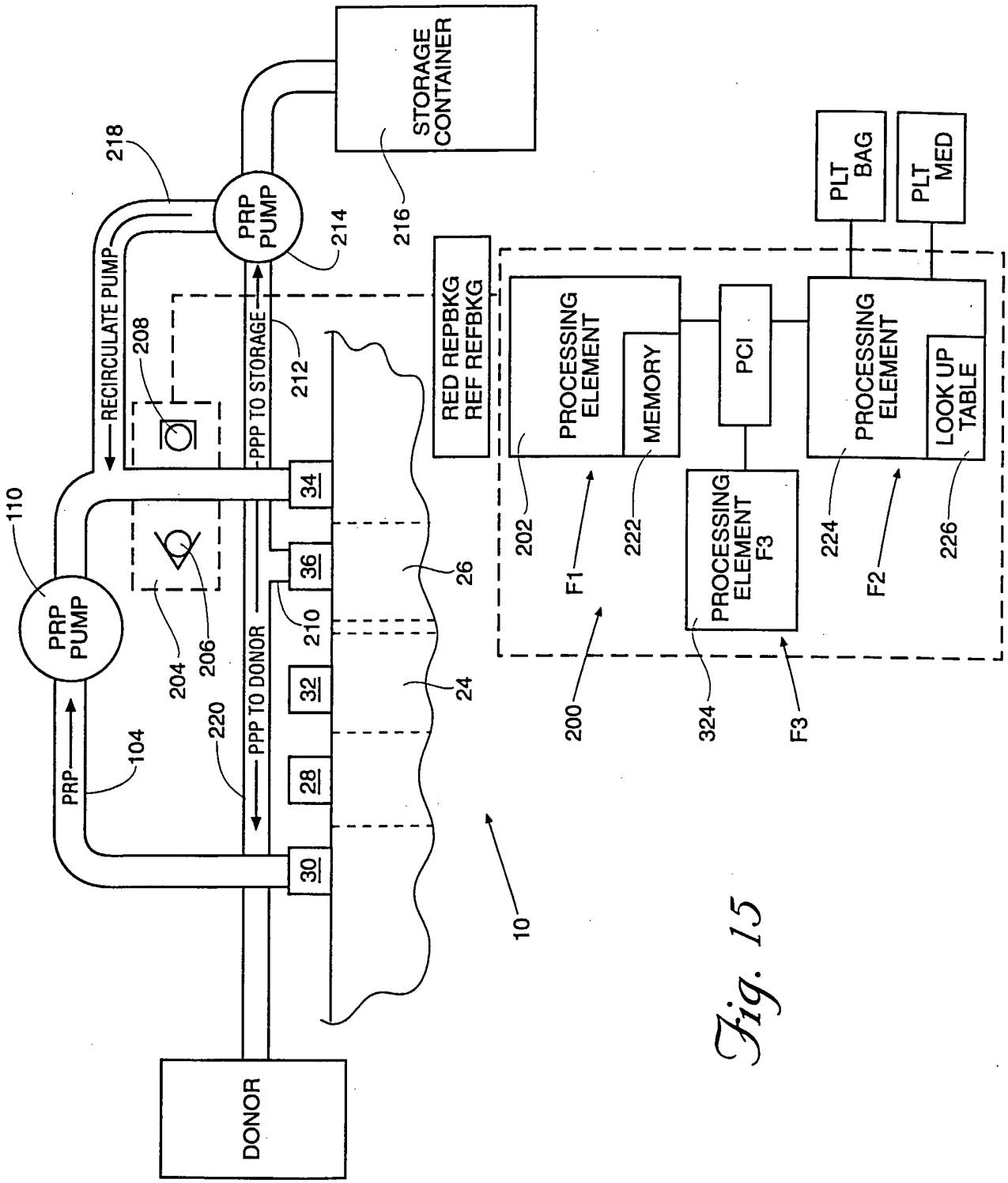

STORAGE CONTAINER
216
218
PRP PUMP
214
RECIRCULATE PUMP
208
PPP TO STORAGE
212
RED REPBKG REF REFBKG
PROCESSING ELEMENT
MEMORY
PCI
PROCESSING ELEMENT
LOOK UP TABLE
PLT BAG
PLT MED
202
F1
222
PROCESSING ELEMENT F3
224
F2
226
200
324
F3
110
PRP PUMP
204
206
220
PPP TO DONOR
210
34
36
32
28
30
26
24
PRP
104
DONOR
10

Fig. 15

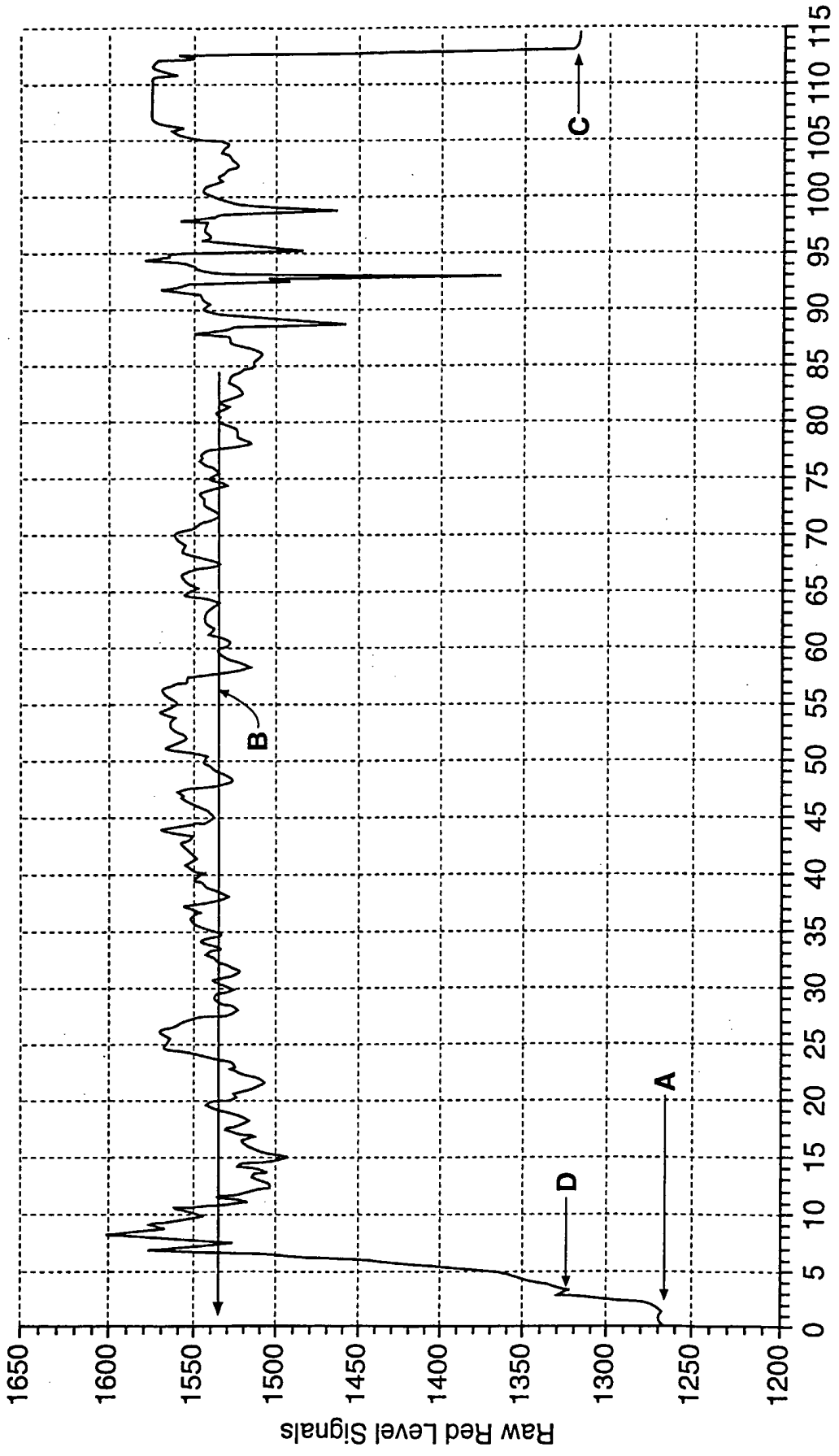

Raw Red Level Signals
1650
1600
1550
1500
1450
1400
1350
1300
1250
1200
Time (Minutes)
0 5 10 15 20 25 30 35 40 45 50 55 60 65 70 75 80 85 90 95 100 105 110 115
A
B
C
D

Fig. 16

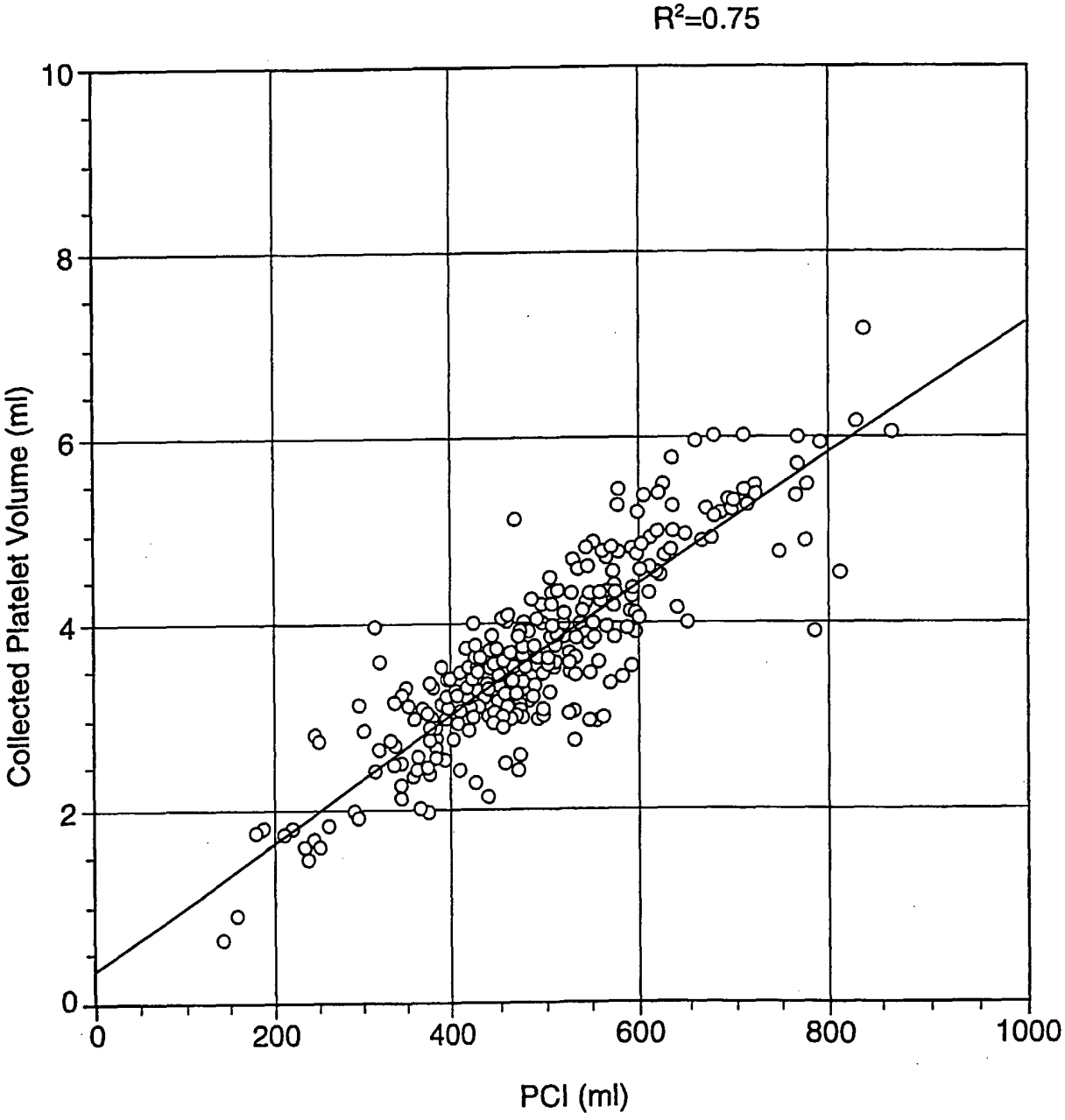

R²=0.75
Collected Platelet Volume (ml)
PCI (ml)
0
2
4
6
8
10
0
200
400
600
800
1000

Fig. 17

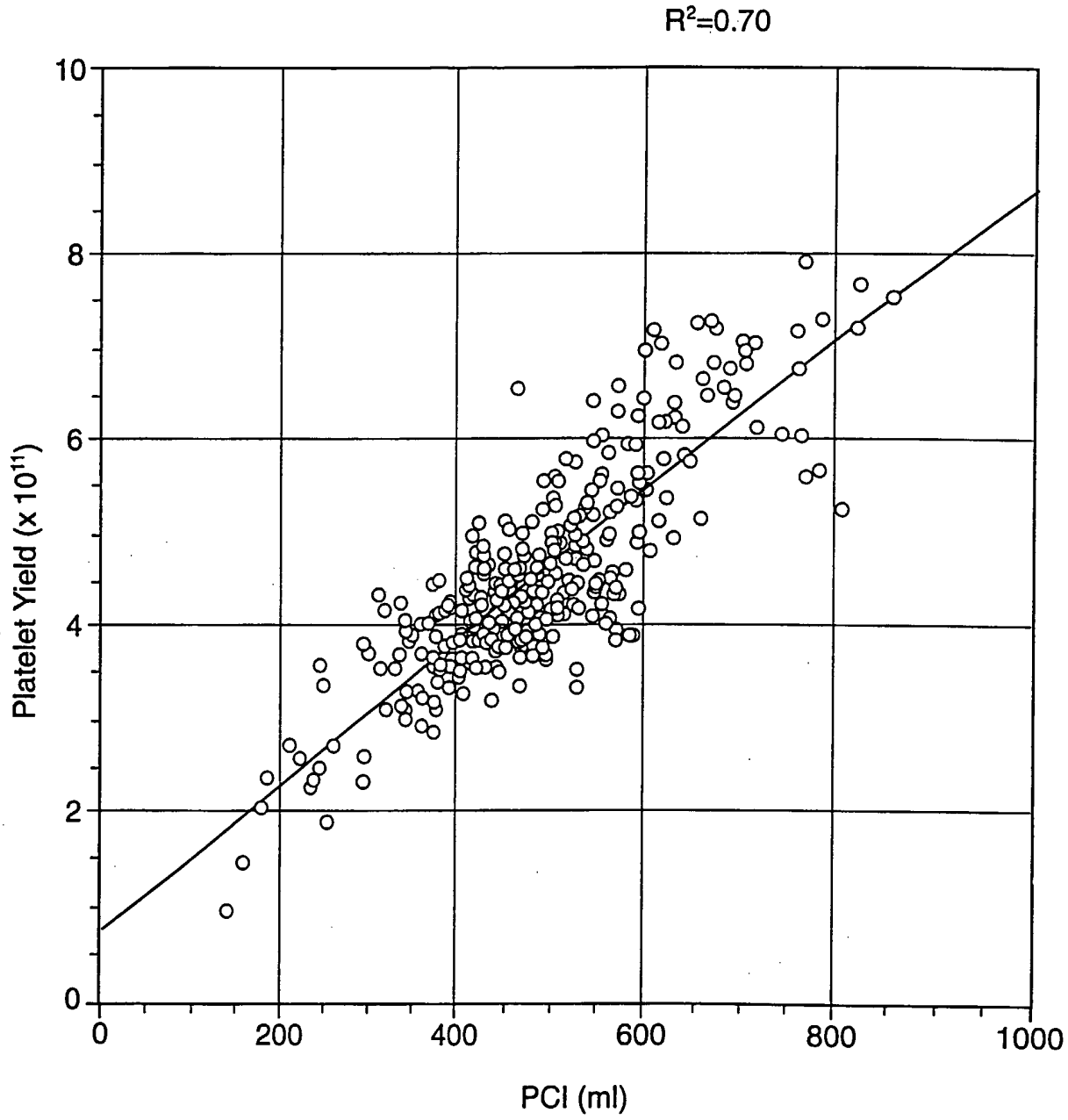

R²=0.70
Platelet Yield (x 10¹¹)
PCI (ml)
0
2
4
6
8
10
0
200
400
600
800
1000

Fig. 18

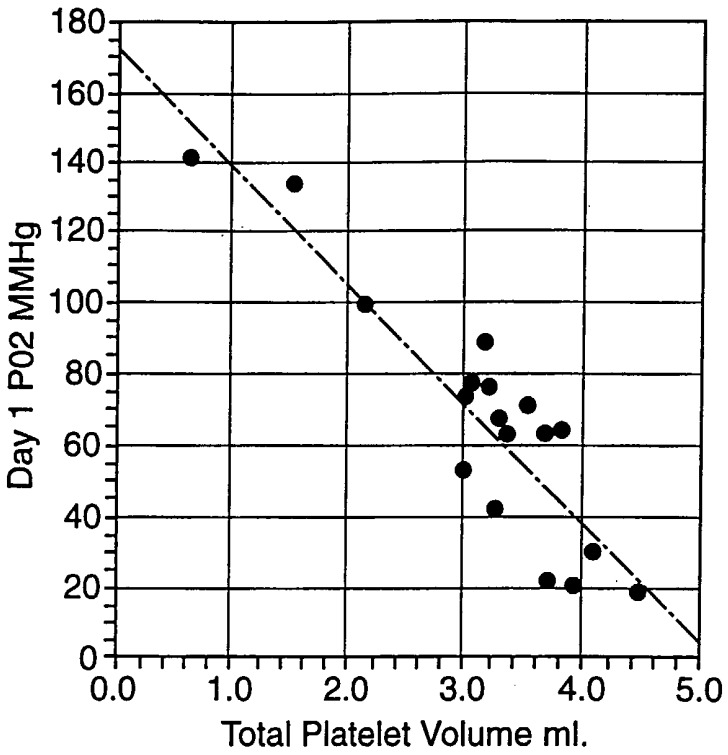

Day 1 P02 MMHg
180
160
140
120
100
80
60
40
20
0
0.0
1.0
2.0
3.0
4.0
5.0
Total Platelet Volume ml.

Fig. 19

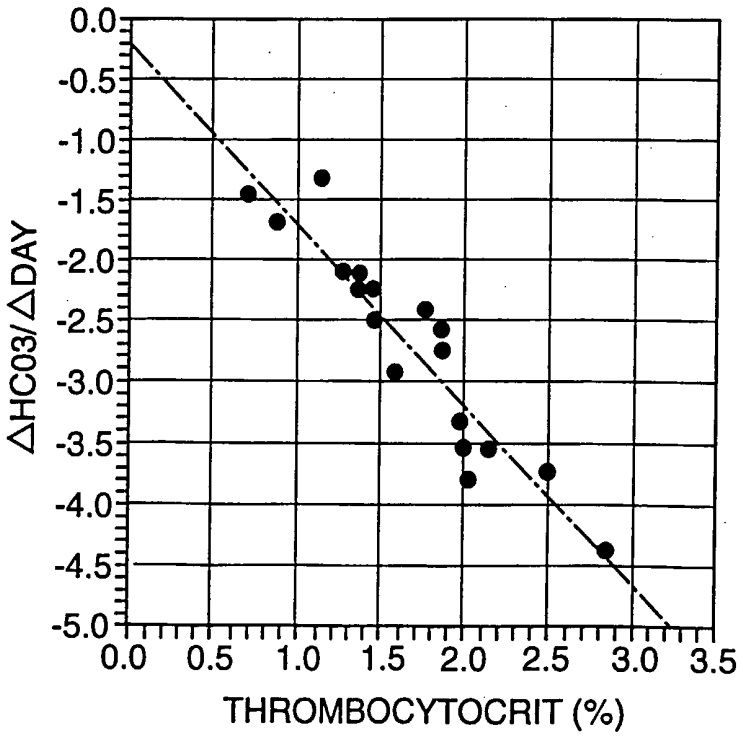

ΔHC03/ΔDAY
0.0
-0.5
-1.0
-1.5
-2.0
-2.5
-3.0
-3.5
-4.0
-4.5
-5.0
0.0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
THROMBOCYTOCRIT (%)

Fig. 20

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US00/28178

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) :B01D 17/12
US CL :210/745
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)

U.S. : 210/745, 87, 94, 96.143, 257.1, 512.1, 645, 739, 745, 767, 787, 789; 604/4.01, 5.01; 356/39; 494/1, 10, 37

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)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5,658,240 A (URDAHL) 19 August, 1997, see entire document	1-15
A	US 5,637,082 A (PAGES) 10 June 1997, see entire document	1-15
A	US 4,828,716 A (MCEWEN et al) 09 May 1989, see entire document	1-15

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

*	Special categories of cited documents:	"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
"A"	document defining the general state of the art which is not considered to be of particular relevance	"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
"E"	earlier document published on or after the international filing date	"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
"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)	"&"	document member of the same patent family
"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		

Date of the actual completion of the international search 11 DECEMBER 2000	Date of mailing of the international search report 23 JAN 2001
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer JOSEPH DRODGE Telephone No. (703)-308-0661

Form PCT/ISA/210 (second sheet) (July 1998)★