United States Patent

Clifford, Jr. et al.

[15] **3,706,877**

[45] **Dec. 19, 1972**

[54] **DENSITOMETER HAVING AN ANALOG COMPUTER FOR CALCULATING A FRACTION OF THE TOTAL AREA UNDER A CURVE**

[72] Inventors: **George F. Clifford, Jr.; Robert C. Woodward,** both of Natick, Mass.

[73] Assignee: **Clifford Instruments, Inc.,** Natick, Mass.

[22] Filed: **Jan. 18, 1971**

[21] Appl. No.: **107,140**

Related U.S. Application Data

[63] Continuation of Ser. No. 27,067, April 9, 1970.

[52] **U.S. Cl.** ....**235/151.35,** 235/61.6 R, 235/61.6 A, 250/219 QA, 346/29, 346/13, 346/30

[51] **Int. Cl.** **G01d 1/04**

[58] **Field of Search** .346/13, 30; 235/61.6 R, 61.6 A, 235/151.3; 250/219 QA, 222 R, 222 PC

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Primary Examiner—Eugene G. Botz
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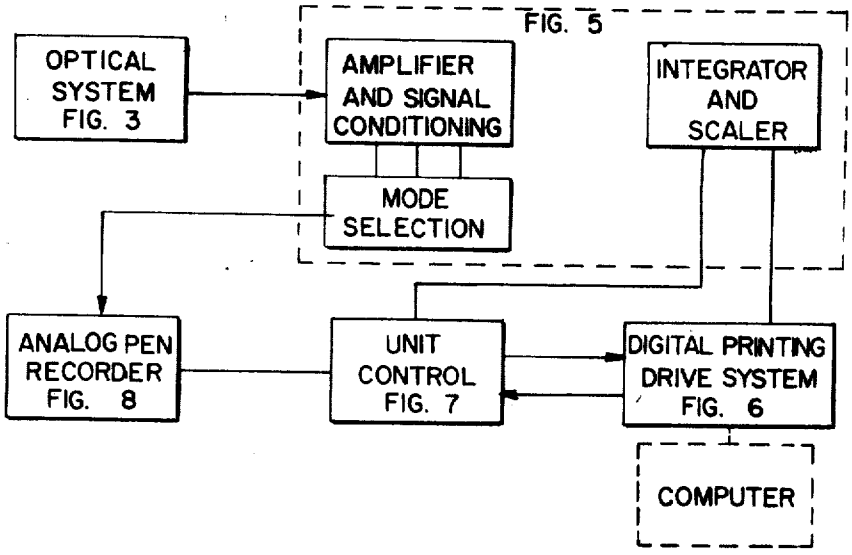
[57] **ABSTRACT**

A densitometer which provides complete electrophoresis results on a single sheet. An electrophoresis sample is scanned by a beam of light energy. The light energy transmitted through the sample is converted to an electrical signal. An analog trace of the density profile is made on a recording chart. At the same time, the total area under the curve is integrated. After the trace and integration have been completed, the portions of the trace from which additional information is required such as area percents and protein levels are marked. The sample is rescanned and reintegrated within the selected portions of the trace. The area percents and protein levels are printed on the recording chart in digital form when the rescanning of the selected portion of the trace has been completed.

27 Claims, 17 Drawing Figures



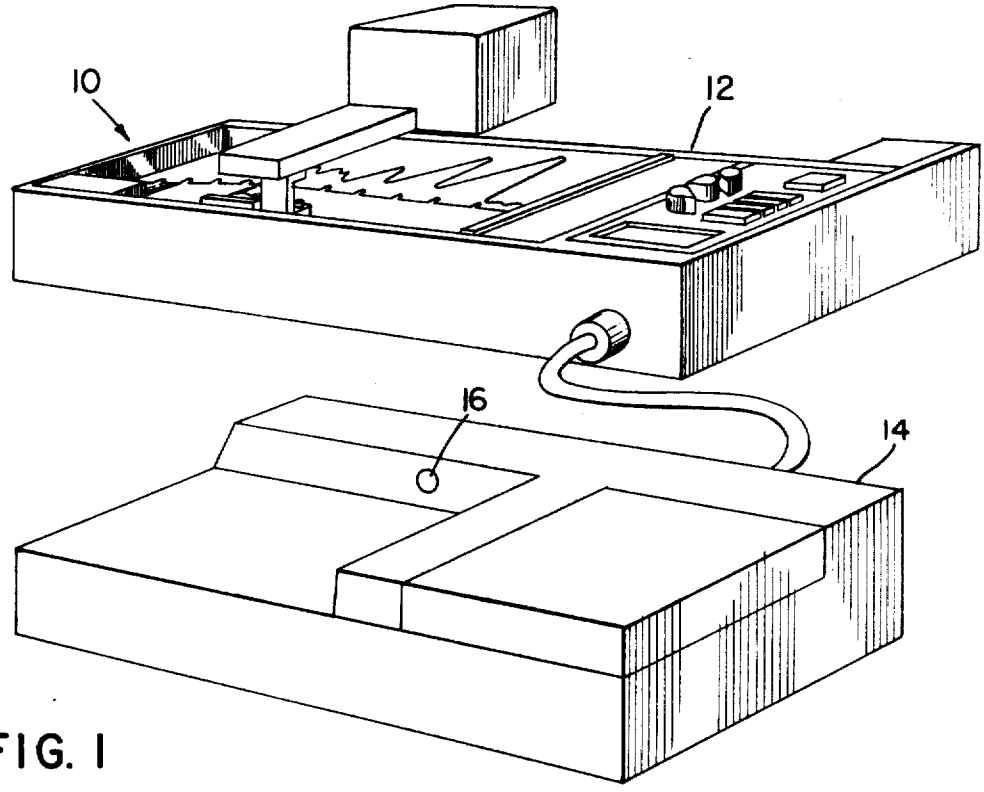


FIG. 1

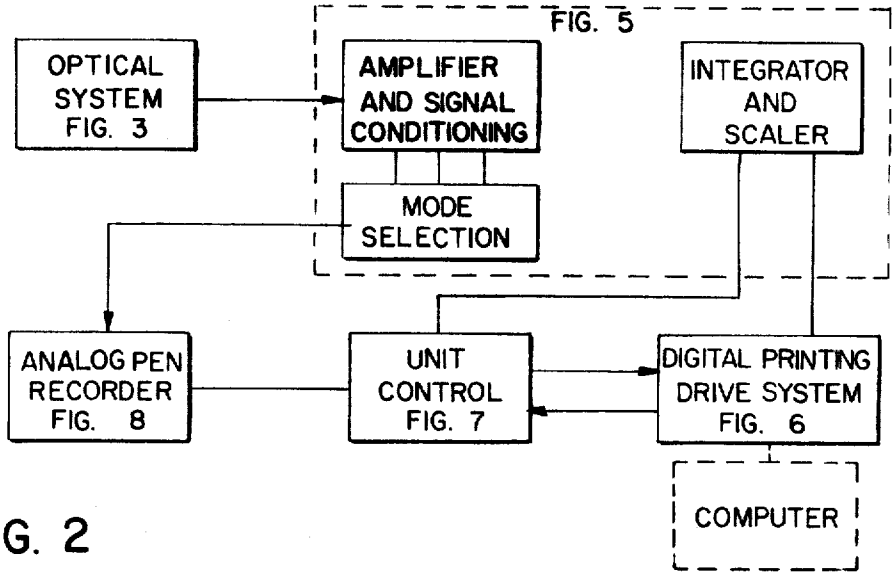


FIG. 2

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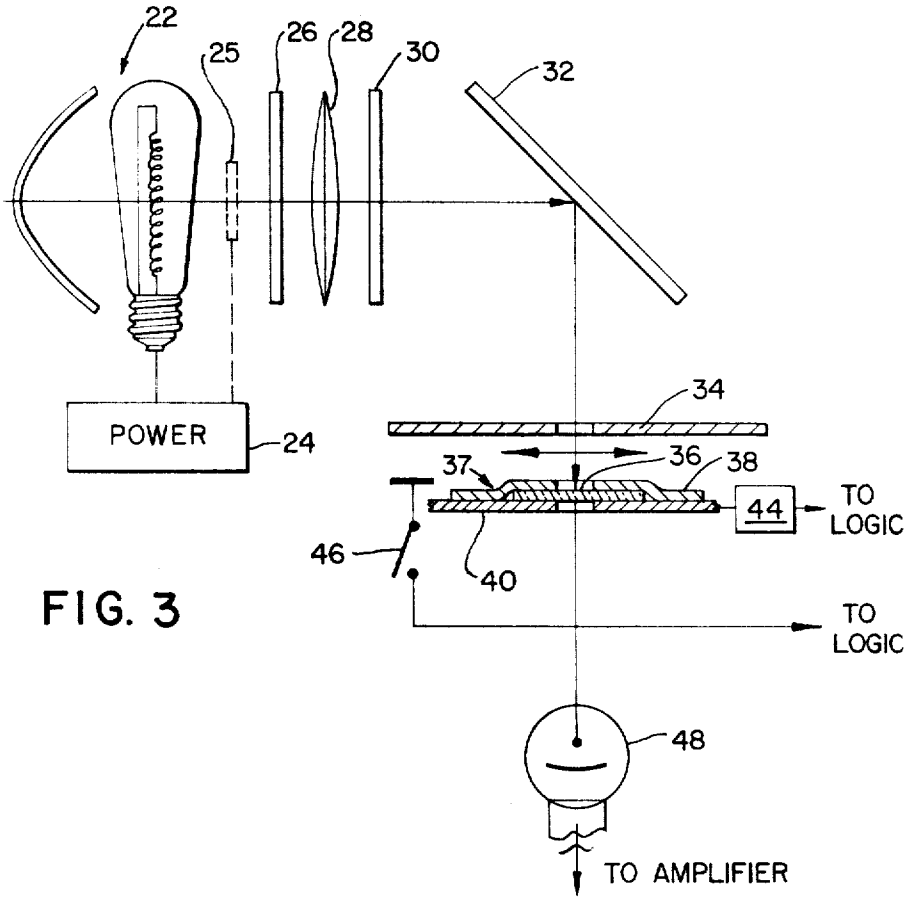

FIG. 3

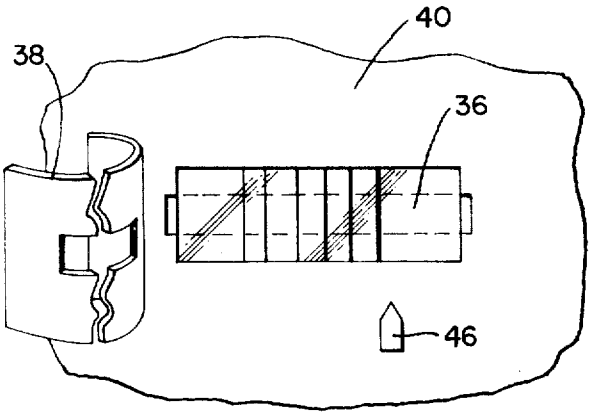

FIG. 4A

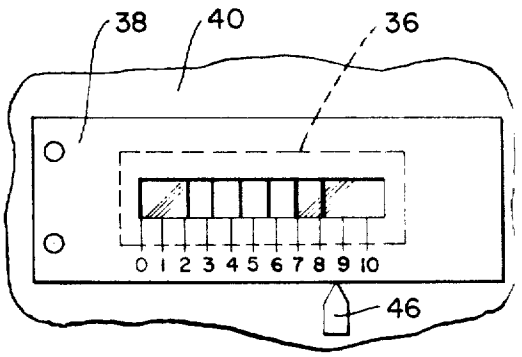

FIG. 4B

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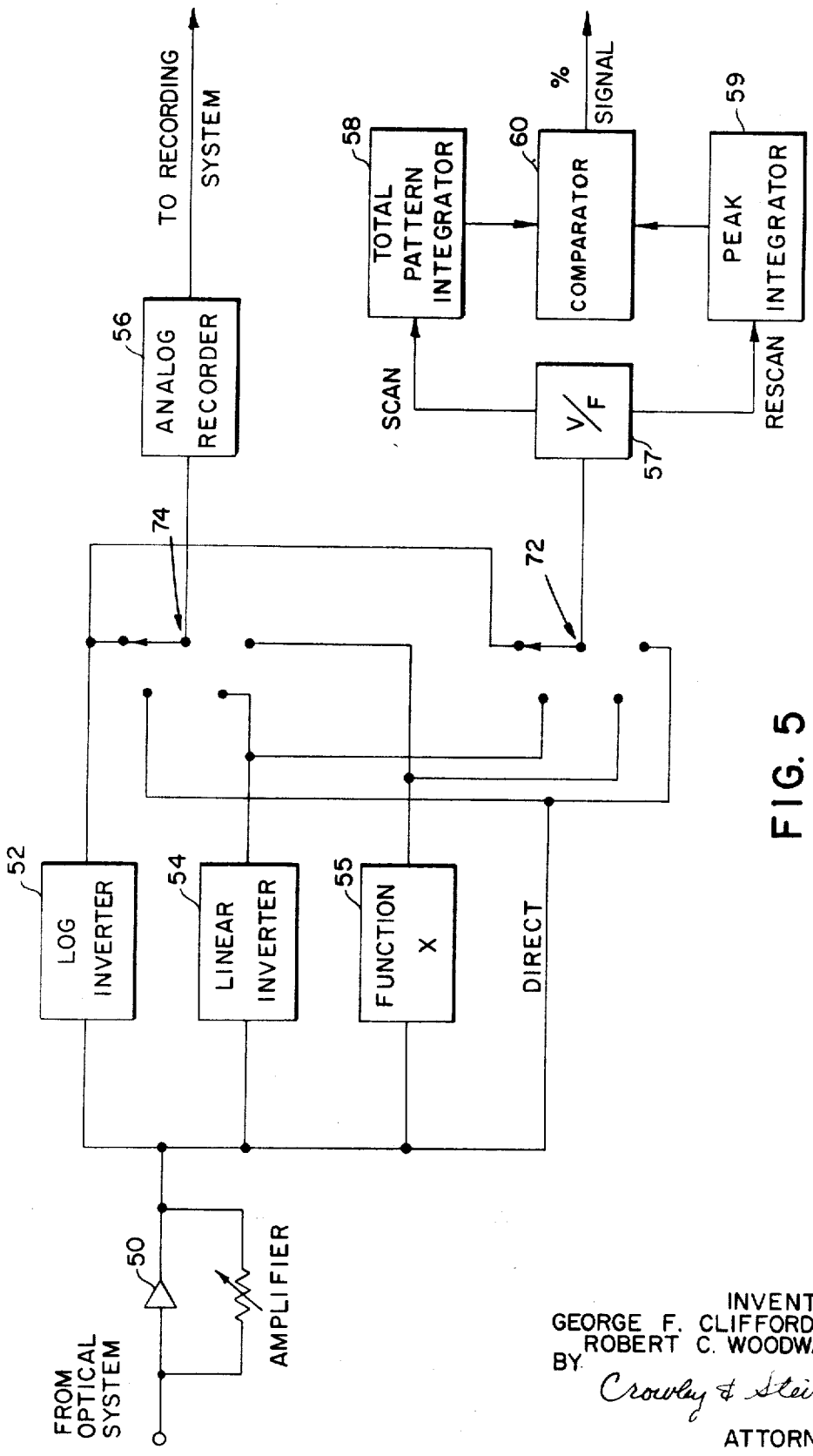

FIG. 5

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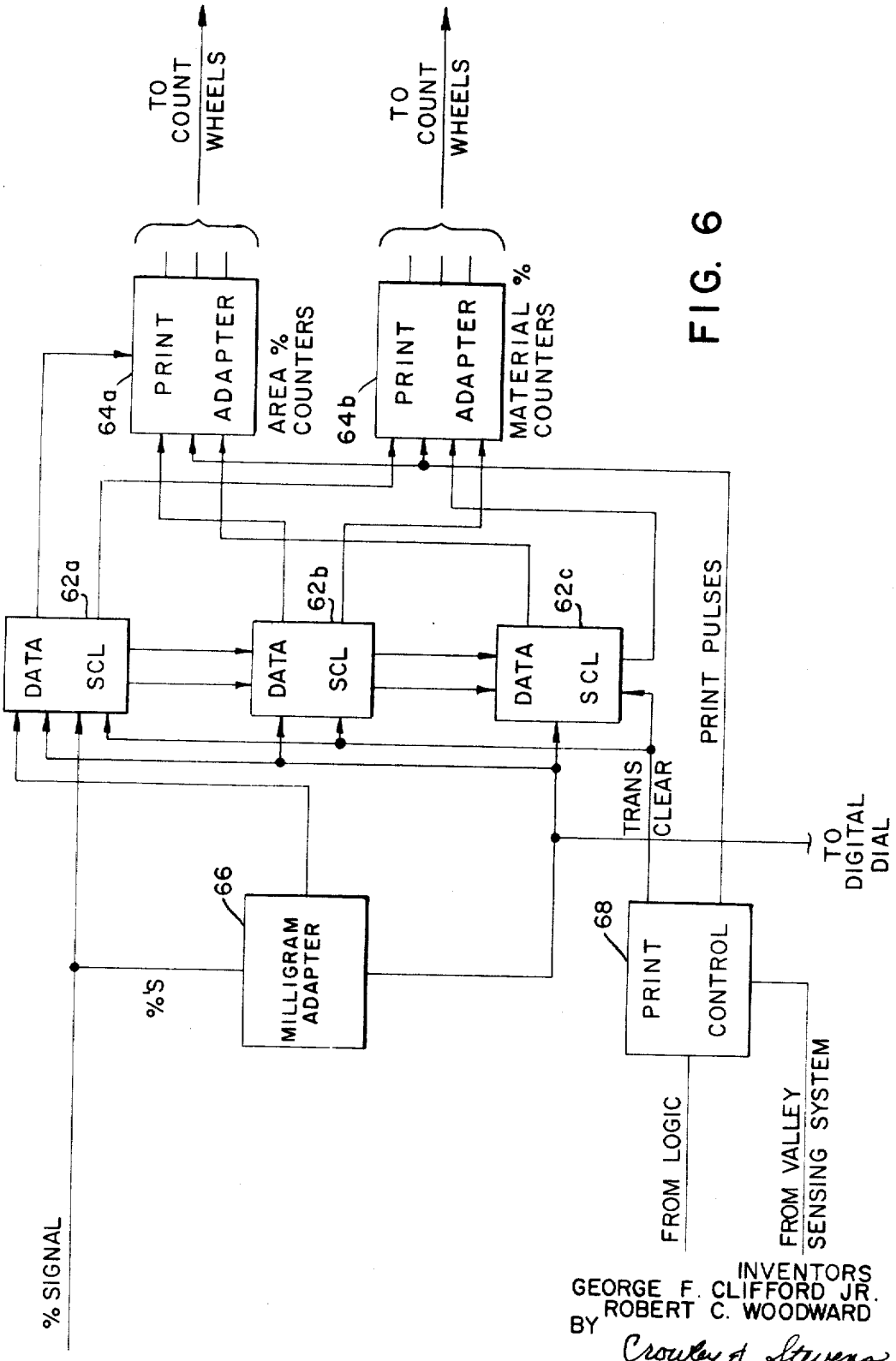

FIG. 6

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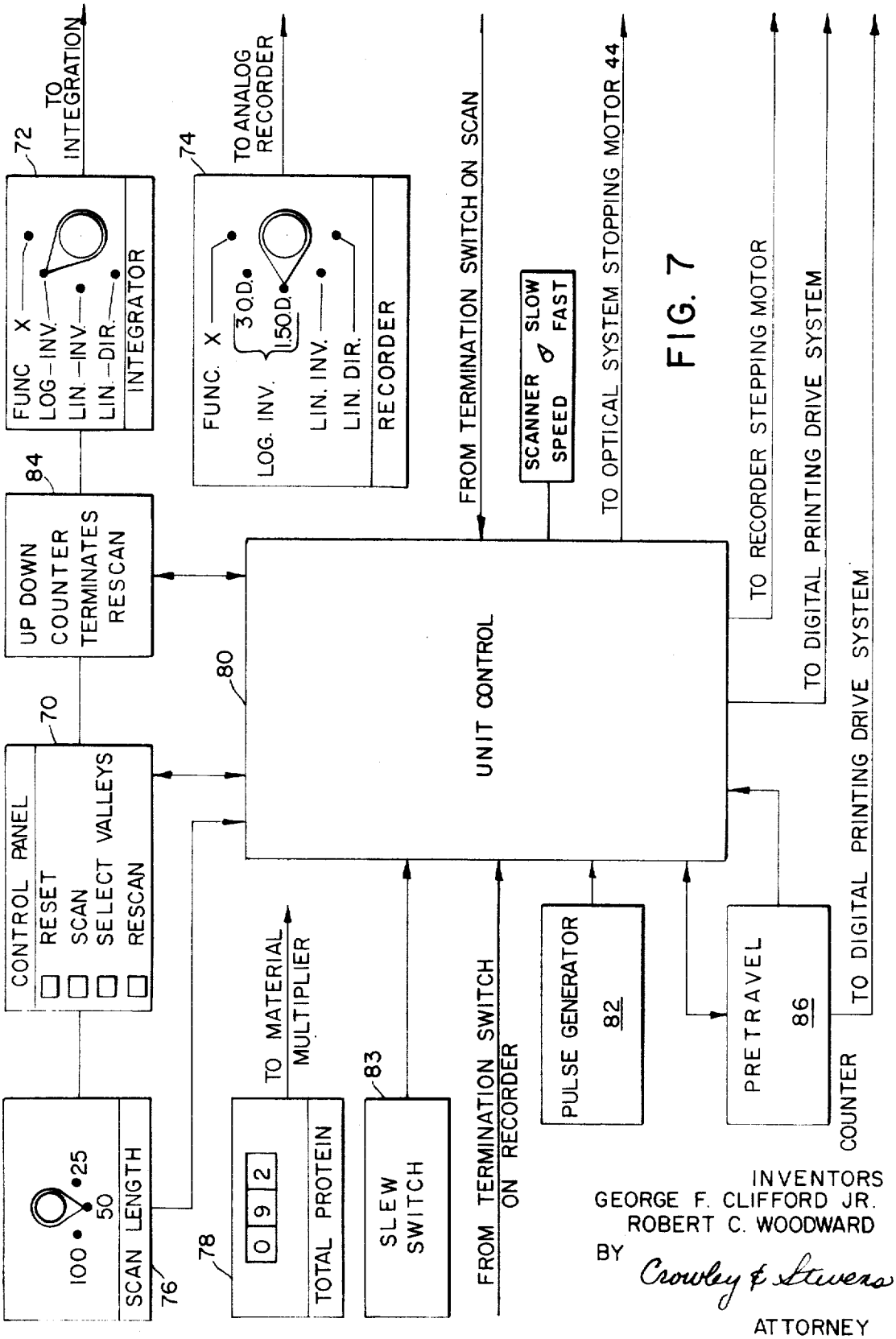

FIG. 7

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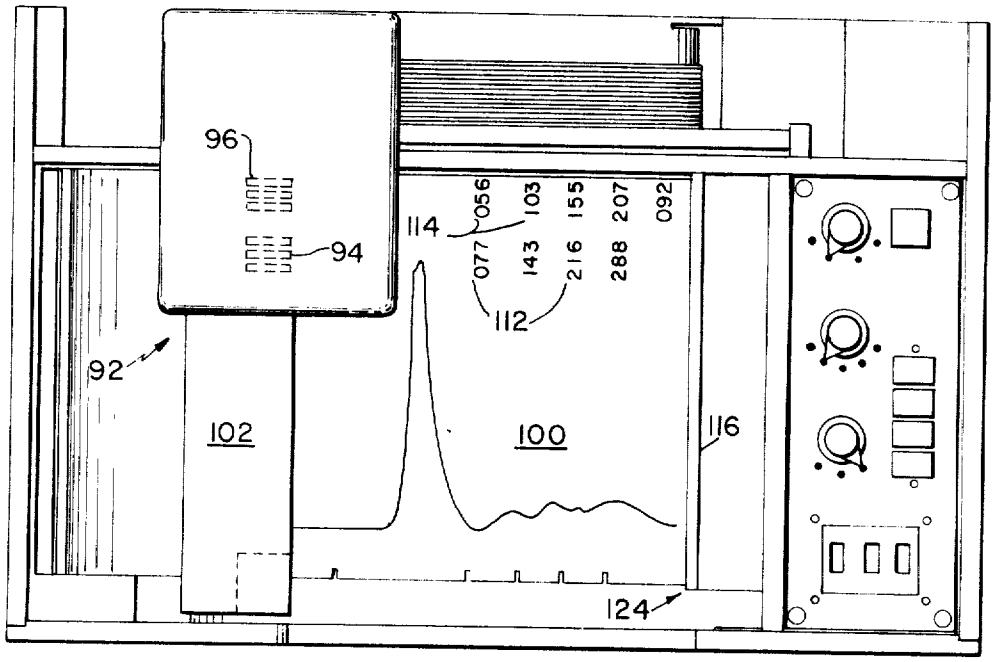

FIG. 8

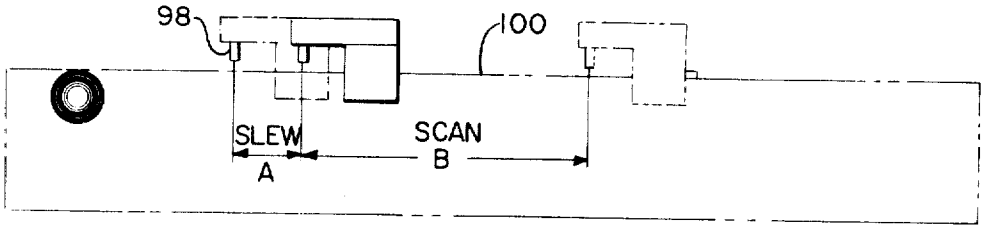

FIG. 9a

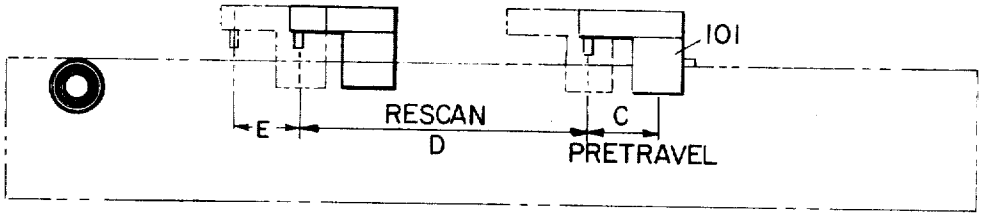

FIG. 9b

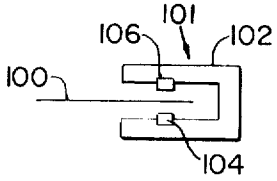

FIG. 10

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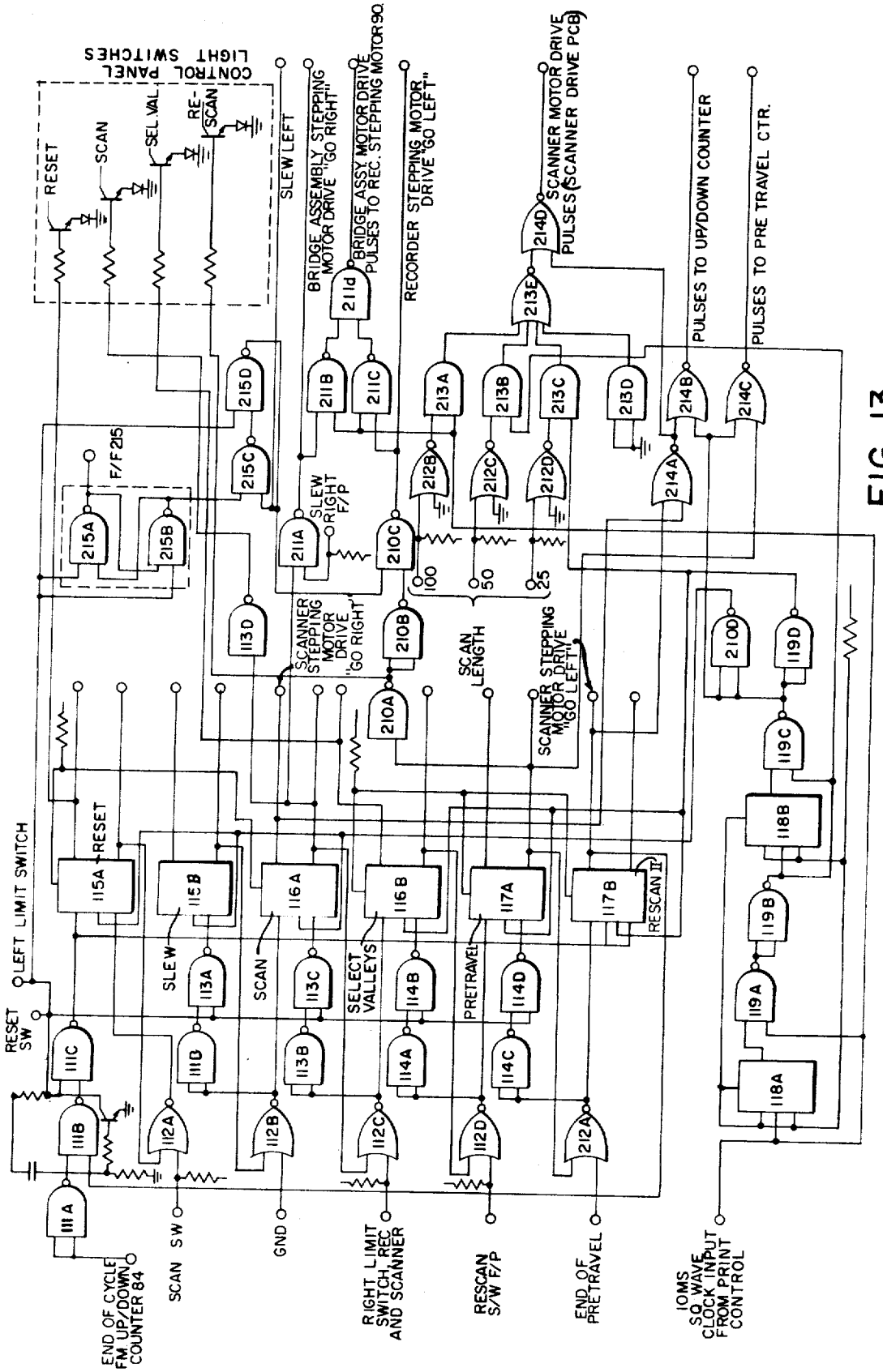
CONTROL PANEL LIGHT SWITCHES
RESET
SCAN
SEL. VAL.
RE-SCAN
SLEW LEFT
BRIDGE ASSEMBLY STEPPING MOTOR DRIVE "GO RIGHT"
BRIDGE ASSY MOTOR DRIVE PULSES TO REC. STEPPING MOTOR 90
RECORDER STEPPING MOTOR DRIVE "GO LEFT"
SCANNER MOTOR DRIVE PULSES (SCANNER DRIVE PCB)
PULSES TO UP/DOWN COUNTER
PULSES TO PRE TRAVEL CTR.
F/F 215
SLEW RIGHT F/P
100
50
25
SCANNER STEPPING MOTOR DRIVE "GO RIGHT"
SCAN LENGTH
SCANNER STEPPING MOTOR DRIVE "GO LEFT"
LEFT LIMIT SWITCH
RESET SW
SLEW
SCAN
SELECT VALLEYS
PRETRAVEL
RESCAN II
END OF CYCLE FM UP/DOWN COUNTER 84
SCAN SW
GND
RIGHT LIMIT SWITCH, REC AND SCANNER
RESCAN S/W F/P
END OF PRETRAVEL
10MS SQ WAVE CLOCK INPUT FROM PRINT CONTROL

FIG. 13

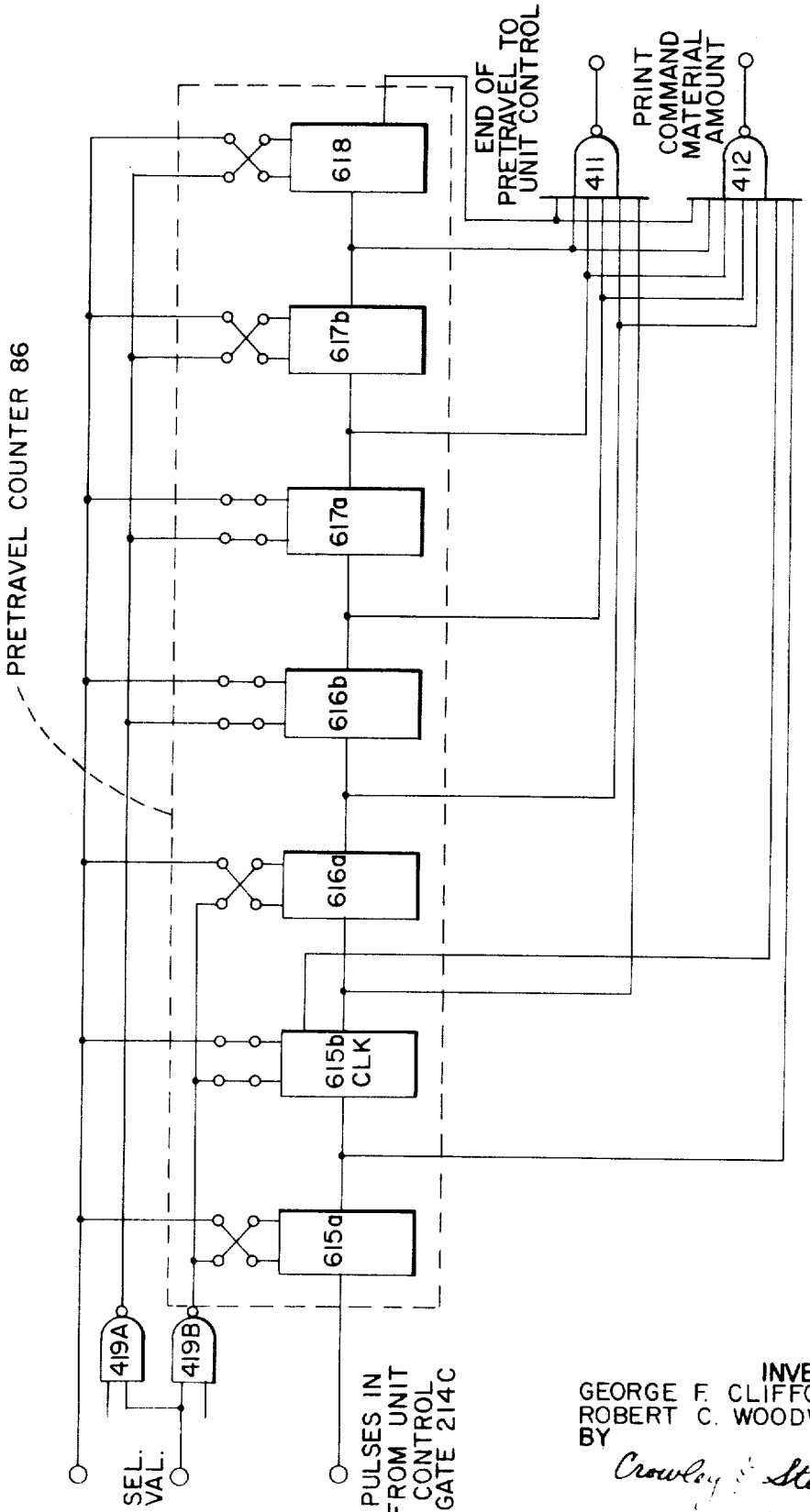

FIG. 14

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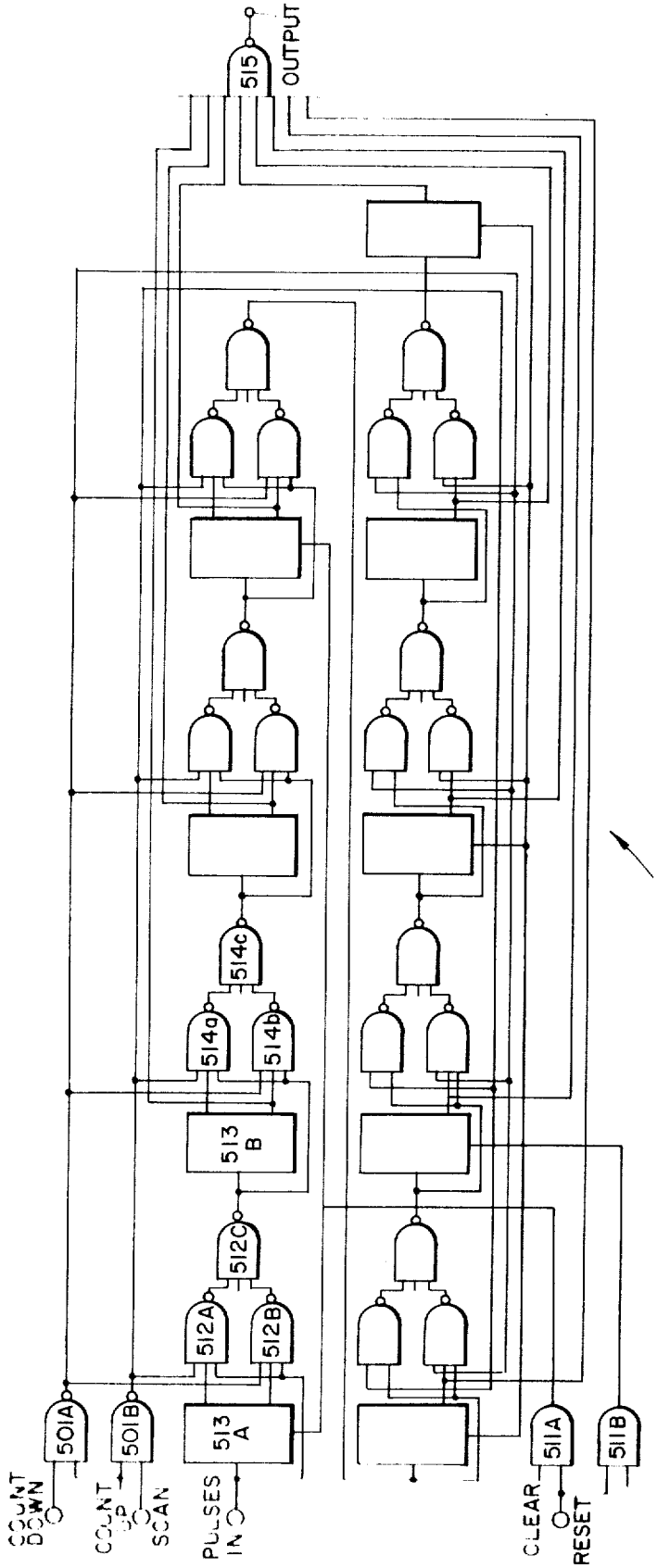

FIG. 15

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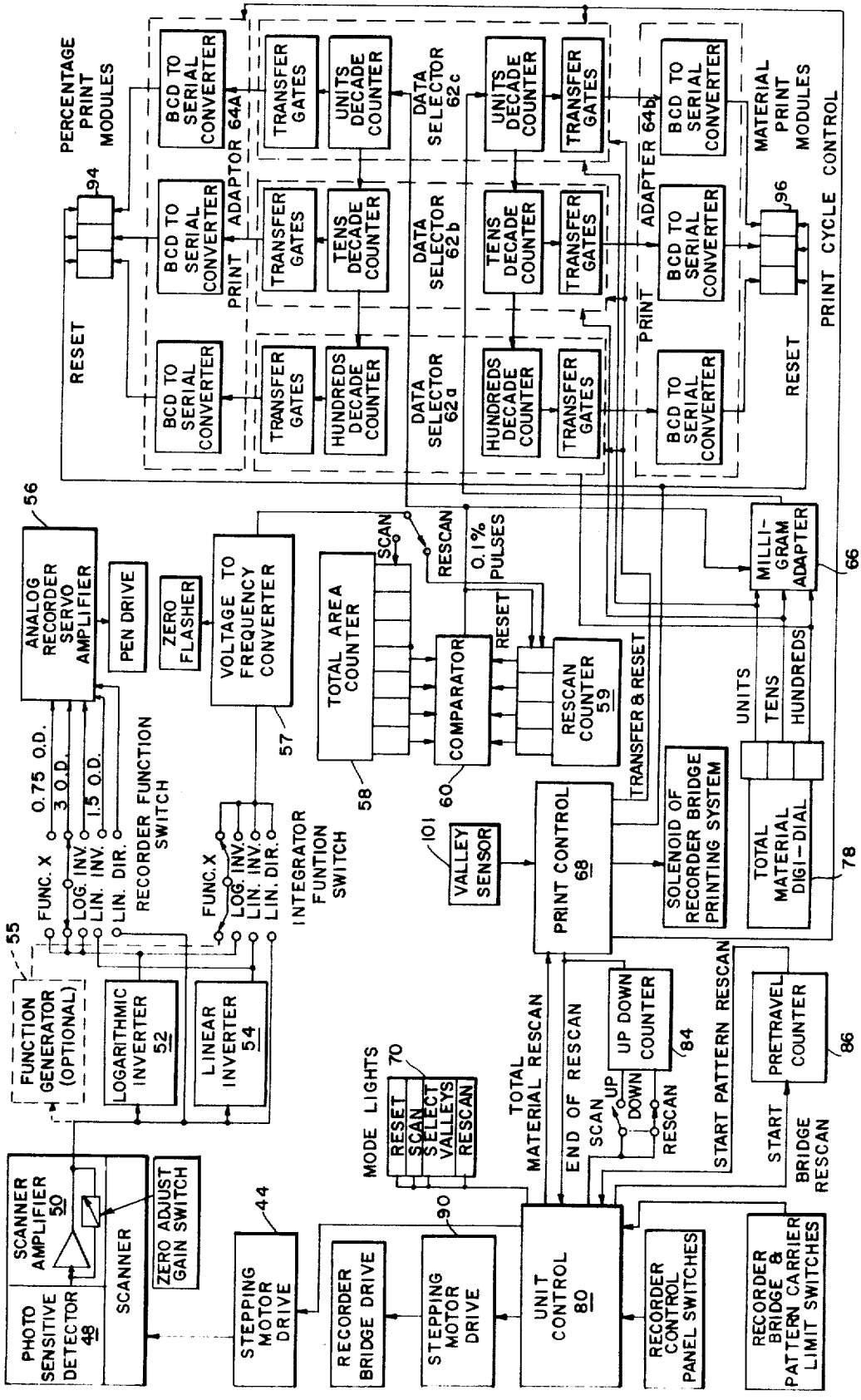
PERCENTAGE PRINT MODULES
94
RESET
BCD TO SERIAL CONVERTER
PRINT ADAPTER 64A
TRANSFER GATES
HUNDREDS DECADE COUNTER
TENS DECADE COUNTER
UNITS DECADE COUNTER
DATA SELECTOR 62a
DATA SELECTOR 62b
DATA SELECTOR 62c
PRINT ADAPTER 64b
MATERIAL PRINT MODULES
96
PRINT CYCLE CONTROL
56
ANALOG RECORDER SERVO AMPLIFIER
PEN DRIVE
ZERO FLASHER
VOLTAGE TO FREQUENCY CONVERTER
57
TOTAL AREA COUNTER
58
SCAN
RESCAN
0.1% PULSES
COMPARATOR
60
RESET
RESCAN COUNTER 59
MILLI-GRAM ADAPTER
66
TRANSFER & RESET
UNITS
TENS
HUNDREDS
0.75 O.D.
3 O.D.
1.5 O.D.
FUNC. X
LOG. INV.
LIN. INV.
LIN. DIR.
RECORDER FUNCTION SWITCH
INTEGRATOR FUNTION SWITCH
55
FUNCTION GENERATOR (OPTIONAL)
LOGARITHMIC INVERTER 52
LINEAR INVERTER 54
101
VALLEY SENSOR
PRINT CONTROL 68
SOLENOID OF RECORDER BRIDGE PRINTING SYSTEM
TOTAL MATERIAL DIGI-DIAL
78
MODE LIGHTS
70
RESET
SCAN
SELECT VALLEYS
RESCAN
TOTAL MATERIAL RESCAN
END OF RESCAN
SCAN
UP
DOWN
RESCAN
UP DOWN COUNTER
84
START PATTERN RESCAN
START
BRIDGE RESCAN
PRETRAVEL COUNTER
86
SCANNER AMPLIFIER 50
ZERO ADJUST GAIN SWITCH
PHOTO SENSITIVE DETECTOR 48
SCANNER
44
STEPPING MOTOR DRIVE
RECORDER BRIDGE DRIVE
90
STEPPING MOTOR DRIVE
UNIT CONTROL 80
RECORDER CONTROL PANEL SWITCHES
RECORDER BRIDGE & PATTERN CARRIER LIMIT SWITCHES

FIG. 11

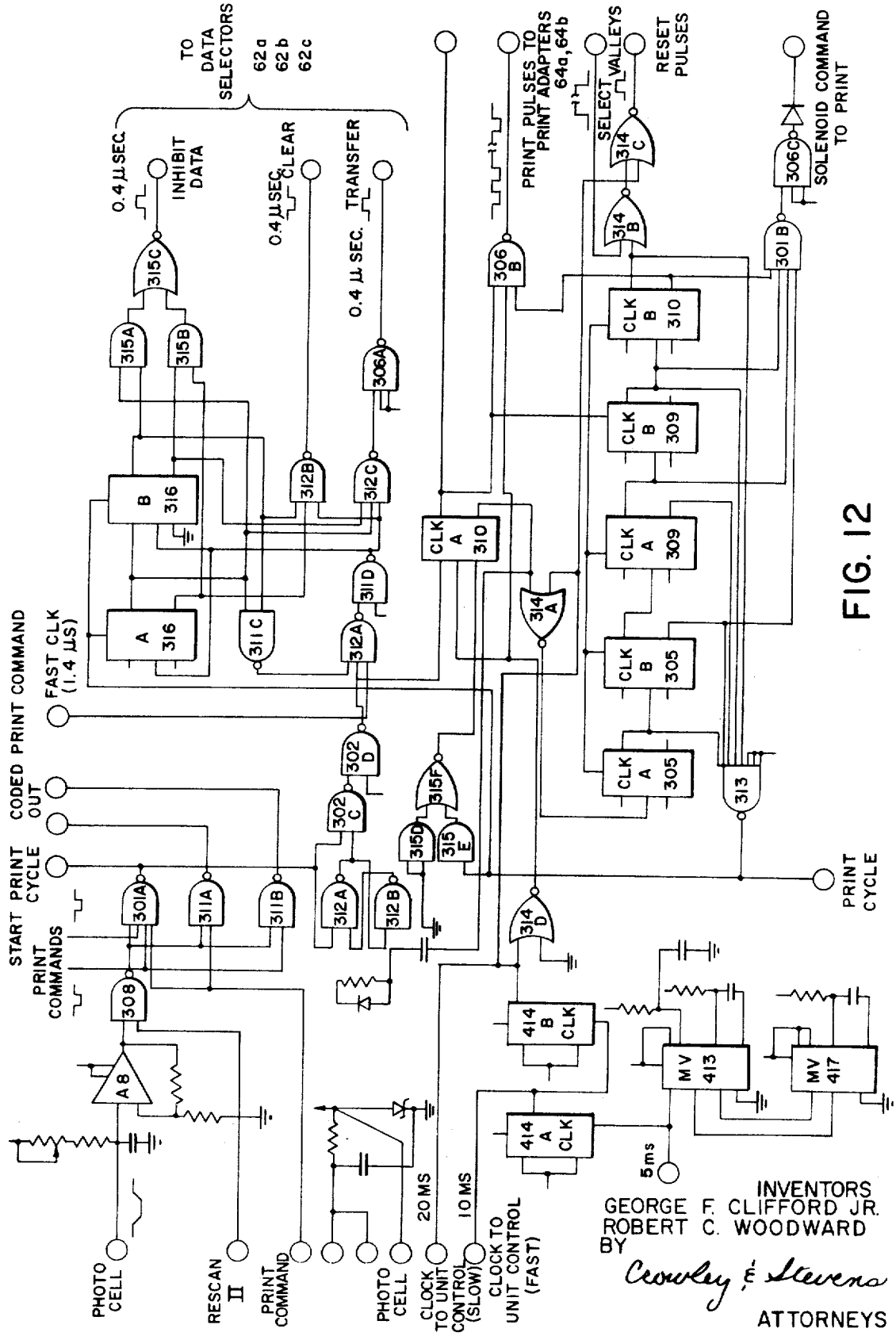

FIG. 12

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DENSITOMETER HAVING AN ANALOG COMPUTER FOR CALCULATING A FRACTION OF THE TOTAL AREA UNDER A CURVE

CROSS-REFERENCE TO RELATED APPLICATIONS

This application is a continuation-in-part of U.S. Ser. No. 27,067, ELECTROPHORESIS DENSITOMETER MODEL 345, filed Apr. 9, 1970.

BACKGROUND OF THE INVENTION

Zone electrophoresis has been used in clinical laboratories and where used, there has always been a need to translate a quantitation of an amount of material such as, for example, dye stained protein to a report form.

Prior methods and equipment used for density determinations of the dyed strip have been unsatisfactory for producing quick and accurate laboratory results. For example, one method which has been used involves cutting strips into different sections and then eluting the dye from each of the sections. After extraction of the dye, the optical density of the eluting solution is measured and the resulting values are plotted on a curve as a function of the distance along the original strip. It is clear that this method is time-consuming and requires many laboratory operations. Another method which has been used for this purpose is to saturate the electrophoresis strip with an oil to make it more transparent. The paper is passed over an illuminated slit and the amount of light passed through the paper is measured by suitable electric means. Again a curve is obtained as a function of distance along the paper strip. This method has the disadvantage that any variation in output of the light source leads to error in determination of the density. Still another method currently employed, see for example, U.S. Pat. No. 2,834,247, employs a mechanical ball and disc integrator which traces a series of pips under the densitometric trace. Each pip represents a defined amount of area under the densitometer profile. The operator then determines where components started and stopped, counts the pips under each peak, totals all the pips, and then calculates an area percent value. A further method employed is to use an electronic voltage-to-frequency converter to activate solenoids which draw area pips under the curve trace. A still further method used is to scan the electrophoresis pattern repetitively sensing the transmitted light and projecting the density profile on a cathode ray tube. The operator adjusts the base line, sets gates to cause a total area integral of the pattern, and adjusts a meter to read **100**. The integration gates are set for individual peaks and the operator reads the area value from the meter. However, with this method no record is made of the decision by the operator on which valleys were selected for the particular area percents. All of the above methods each have distinct disadvantages either by being too time-consuming or too inaccurate and further requiring translation of results to a final report form.

SUMMARY OF THE INVENTION

We have developed a unique apparatus and method whereby complete electrophoresis results can be provided on a single form and which apparatus and method eliminates the necessity of the manual recording of data. In our invention the electrophoresis strip material is scanned and the light transmitted through the sample is received by a photometer. This transmitted signal is generally directly proportional to the amount of the light transmitted through the electrophoresis strip. An analog trace of the pattern is recorded on a chart. At the same time the profile is being recorded, the area under the profile is integrated and this value is stored. The operator through marking the chart on which the profile is recorded selects portions of the profile from which portions the material amount levels and area percents are to be determined. The total material in the sample say for example, the total amount of protein, is stored in a calculation system in the densitometer through a digital dial. The pattern is rescanned and where the markings the operator has made are detected, the area percents and material levels are printed in digital form directly on the chart. After rescan, the operator on one chart or sheet has all the information that is required in final form.

Briefly, our invention comprises a source of radiant energy (wave or particle) such as light energy which may be ultraviolet, infrared, white, and of any wave length which light energy is formed into a beam, such as by passage through a lens system and then focused on the sample and limited as by passage through a slit. The sample to be analyzed which may be transparent, translucent or a semiopaque material containing material to be analyzed quantitatively or qualitatively, which permits variations in passage of the energy through the sample to aid in sample analysis. For example, an electrophoresis strip is exposed to a beam of light energy which may be employed in the sample by reflectance, transmission, fluorescence, or quenching; that is, through an absorbtion of light. The light emerging from the sample is received on a suitable receptor such as a photometer, for example a photocell, photomultiplier, photo-diode, etc., where the signal is converted to an electrical signal. This electrical signal is then transmitted to a function generator which converts the signal from the sample to a level linearly related to the amount of material to be analyzed in the sample. The conversion of the signal from the light receiving means may be linear, logarithmic, log inverse, linear inverse, or some other hybrid function. Other types of samples which themselves provide a source of radiant energy may be successfully used with the invention in which a separate source of energy is not required, such as radioactive samples. For example, materials such as proteins may be tagged with radioactive particles in which case the tagged material itself is the energy source and the slit needs only to reflect or absorb a radioactive material whereby the photomultiplier is only looking at one section of the pattern at any given time. This technique may also be employed with tagged amino acids.

After passing through the function generator, the signal is recorded in the function desired as a profile trace. Simultaneously, with the recording of the profile trace, the signal is converted to a pulse train the frequency of which is related to the signal level and the pulses are accumulated and stored thereby integrating the area under the profile trace. After the density

profile has been traced and the area under the profile integrated, a portion of the trace profile from which additional information is desired, such as the particular area between selected portions, is then marked. The sample is rescanned over the portion scanned previously. The integrated rescan signal is then compared with the accumulated scan signal, the values compared, and the area percents computed as well as the material amounts. Upon command, the desired information is then recorded directly on a medium such as a chart.

Other distinct advantages of our invention are the ability to record the density profile in one function, say for example in linear inverse, and to integrate in another function, say for example log inverse; or to record the trace profile and integrate in the same function. Also, because the printing of the information on rescan is on the same recording form as the indications made by the operator, all pertinent information is directly printed out on the same report form.

Because the majority of clinical laboratories are involved in programs leading to the use of computers for compiling laboratory results by patient, computer compatibility has also been designed into the densitometer. The area percent information and the percent protein values are both held in binary coded decimal (BCD) form. On receiving a pulse from the computer, the information can be transferred to the computer and thence to a memory block to be held until the computer calls for the information on that patient. A minimum of computer memory is required since the need for point-by-point logging of the density profile is completely eliminated.

Further, since the densitometer has its own calculation capability it does not depend upon a computer to derive area percents or percent material values, complete results are obtainable whether or not the computer is in service. Inspection of the chart containing the density profile provides immediate information such as to the identification of albumin and the various globulins. In providing a means for locating fractions along the density profile, the pattern being scanned, the sample, and the recorder are both driven with stepping motors. By counting the steps to each valley, location information is provided which can be used in a simple computer program to identify fractions.

Since most cellulose acetate and gel patterns can be precisely quantitated by integrating in log inverse, this is generally the preferred embodiment or method of operation in the densitometer. However, if the amount of light absorbing material does not increase linearly with optical density, the densitometer is also provided with means to perform the integration linearly in a function such as dye concentration on filter paper or such other function as defined by the user.

In our invention, the analog system of a densitometer has been combined with the digital calculation and printing capabilities of a digital computer to provide on a single report a density profile of the electrophoresis pattern, marks such as by punches or from an electronic valley sensing system indicating how the pattern was divided for calculation purposes, a digital value of area percent printed on the chart for each peak or group of peaks in the pattern, means to enter the total amount of sample material into the densitometer and to print that amount of digital form on the chart, and the capability to multiply area percent times the total material and to print the amount of each fraction selected. Our invention eliminates the necessity of meter reading and interpolation errors as well as transcription errors and combines an analog and digital presentation for obtaining the greater precision of the digital system for calculation of results and further, it is not limited to a certain number of peaks by number of analog memory devices. The marking system employed is advantageous in that it obtains correct results from all serum protein and lipoprotein patterns which often have shoulders and points of inflection which cause an electronic valley sensor to divide patterns into fractions which are not related to the actual material distribution desired.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 is a perspective view of the instrument;

FIG. 2 is a block diagram of the basic sections of the instrument;

FIG. 3 is a partly schematic and partly sectional view of the optical system of the invention;

FIGS. 4*a* and *b* are plan views of the sample holder;

FIG. 5 is a schematic illustration of the amplifier and signal conditioning, mode selection, and integrator and scaler portions of the invention;

FIG. 6 is a schematic illustration of the digital printing drive system of the invention;

FIG. 7 is a partly block diagram and plan view of the control section of the invention;

FIG. 8 is a plan view of the analog pen recorder section of the invention;

FIGS. 9*a* and *b* are schematic illustrations of the movement of the bridge assembly during the slew, scan, pretravel and rescan cycles;

FIG. 10 is a plan view of the valley sensing system;

FIG. 11 is a block diagram of the functional elements of the invention;

FIG. 12 is a circuit diagram of the print control;

FIG. 13 is a circuit diagram of the unit control;

FIG. 14 is a diagram of the pretravel circuit; and

FIG. 15 is a circuit diagram of the up-down counter.

DESCRIPTION OF THE PREFERRED EMBODIMENT(S)

The instrument 10 is shown in FIG. 1 and includes two consoles 12 and 14. The entire system is also shown in block diagram form in FIG. 2. Each major section of the system will be described individually prior to the description of the entire system in a working embodiment.

OPTICAL SYSTEM

The optical system is shown in greater detail in FIG. 3 and comprises a white light source 22 which is powered by a regulated power supply 24. The light source as shown is a standard lamp operated at a fixed temperature of about 2,700°K. If desired to ensure that the light intensity is constant, a receptor 25 shown in the dotted lines may be utilized to regulate the power supply based on the intensity of the light received. Light energy from the source passes through a heat absorbing or reflecting lens 26, condensing lens 28, filter 30, deflects off a mirror 32 and then passes through an aperture 34.

If desired depending upon the sample being analyzed, energy sources other than white light may be used such as ultraviolet, infrared, etc., and the wave lengths of the incident energy may vary as selected by filters, monochromators, or lenses used. Further, light energy may be measured emerging from the sample by reflectance, transmission, fluorescence, or quenching.

Referring to FIGS. 3, 4*a* and *b*, an electrophoresis sample **36** is placed in a unique holder **37** which employs a flexible magnetic mat **38** such as vinyl ferrite in combination with a magnetizable material **40** such as steel. The holder communicates with a stepping motor **44**, which reciprocates the holder along a fixed path during the scan and rescan cycles. The stepping motor also communicates with the unit control **80** as shown in FIGS. 7, 11, and 13. The use of the magnetic mat to hold the sample in place facilitates insertion and adjustment of the sample in the holder while firmly holding the sample in place during the scanning and rescanning cycles. A termination switch **46** which can be adjusted to coincide with one end of the portion of the sample to be scanned, terminates movement of the sample holder at the end of the scan cycle.

A photocell **48** such as a vacuum photodiode receives the light transmitted through the sample and converts the signal to a current proportional to the energy emerging from the sample being analyzed.

INTEGRATION

Referring now to FIG. 5, the current from the photocell **48** of FIG. 3 is transmitted to an amplifier **50** such as a variable gain amplifier. One of a plurality of function generators such as a log inverter **52**, linear inverter **54**, or a hybrid function **55**, receives the signal from the amplifier **50** and transmits the signal at a different level to an analog recorder **56**, such as a servoamplifier. Simultaneously the signal is also transmitted to a voltage-to-frequency converter **57**. As shown, if desired, a signal may be transmitted directly rather than passing through one of the function generators. A plurality of cascaded binary-coded decimal decade counters within the total pattern integrator **58** or total area counter accumulate, totalize, and store the pulses received from the voltage-to-frequency converter **57** whereby the total area under the density profile trace on the recording chart as shown on FIG. 8 is integrated. Upon rescan, certain selected portions of the density profile trace are selected for analysis and the sample rescanned whereby the area under the selected portion is reintegrated, and the pulses accumulated in the peak integrator **59** or rescan counter. These rescan pulses are compared in the comparator **60** against the pulses stored in the total pattern integrator **58**. The total pulses in the total area counter are digitally divided by **1000** to provide units or values of comparison of 0.1 percent of the total area under the curve. When the rescan pulses reach a predetermined level corresponding to 0.1 percent of the total area, the information is transmitted to the digital printing and drive system shown in FIGS. 6 and 12. After each transmittal of 0.1 percent pulses to the data selectors, the comparator resets the rescan counter **59** and the pulses are again accumulated until they reach a value of 0.1 percent of the total area as determined by the comparator. Again the information is transmitted to the data selectors. This cycle continues throughout rescan while periodically the valley sensing system will command the printing and drive system to print the desired information as will be described later.

As shown in FIG. 7 and FIG. 5, the operator may integrate in one function such as log inverse, and record in another function such as linear inverse, during a scanning cycle, or if desired, through the selection of the appropriate functions the integration and recording may both be accomplished in the same function or either function may be accomplished directly.

DIGITAL PRINTING AND DRIVE SYSTEM

Referring to FIGS. 6 and 11, the digital printing and drive system comprises a plurality of data selector circuits **62***a*, *b*, and *c* which communicate with a plurality of print adapters **64***a* and *b* which transmit the signal received from the data selectors to the count wheels and actuate the count wheels in the recording system. A material multiplier **66** or milligram adapter which comprises a binary coded circuit stores the total amount of protein which value is inserted into the multiplier by the operator through the digital dial **78** shown in FIGS. 7 and 11. The 0.1 percent signals from the comparator flow in two directions, one directly to the data selectors in combination with the print adapter **64***a*, and the second to the milligram adapter **66** and then to the data selectors associated with print adapters **64***b*. The material multiplier digitally multiplies the percent signal times the total material value as dialed-in prior to transmittal to the data selectors.

As will be described in detail, upon receipt of a command from the pretravel circuit shown in FIG, **14**, the stored value of total material is printed on the recording chart prior to rescan. Upon receipt of a command from the valley sensing system, the area percent and the area percent times total material corresponding to the selected portion of the chart is printed on the chart.

The print control circuit **68** is adapted to receive commands from the unit control **80** shown in FIG. 7 and the valley sensing system **101** shown in FIGS. **11**, **12**, and **13**.

UNIT CONTROL

Referring to FIGS. 7, 11, and 13, the unit control **80** comprises a control panel **70** having a series of switches for commencing operation of the instrument and as shown includes the reset, scan and rescan switches and valley selection indicator. An integrator dial **72** and recorder dial **74** select the recording and integration functions as was described for FIG. 5. Also on the front panel, is a scan length switch **76** which determines the ratio of the speed of motion of the pattern to the speed of motion of the bridge in the recorder. This speed ratio controls the amount of total motion of the pattern which corresponds to the bridge moving across the usable portion of the chart, and the scan length switch is calibrated in these distances.

In communication with the control panel is the unit control **80** also shown in greater detail in FIG. 13. A pulse generator **82** which is disposed in the print control **68** communicates with the unit control **80** and provides a pulse train for driving both the stepping motors **44** and **90** shown as drives in FIG. 11 for the scanner and recorder respectively. To ensure that the movement of the bridge carrying the pen, and the holder car-

rying the sample being scanned each move precisely the same distance during scan and rescan, an up-down counter **84** counts the pulses generated during scan and rescan to terminate the rescan mode when the same section of the pattern originally scanned has been rescanned. This ensures that the total area integrated is identical in both scans.

A slew switch **83** moves the recording pen to the starting position prior to the actuation of the scan cycle. A pretravel circuit **86** on rescan moves the bridge carrying the pen recorder, count wheels, and valley sensing system, a predetermined distance prior to actuating rescan of the sample to compensate for a mechanical offset of the pen **98** and valley sensing system **101**. This circuit also controls the print-out of the total amount of material which is stored in the material multiplier.

RECORDING SYSTEM

Referring to FIGS. **8** and **9***a* and *b*, the analog pen recorder comprises a bridge assembly **92** which includes two sets of count wheels **94** and **96** which communicate with the print adapters **64**a and **64**b which wheels record the area percent of selected portions of the density profile trace and the material protein levels. A pen recorder **98** engages a recording chart **100**. The trace of the pen along its *x* axis is controlled by the movement of the bridge driven by the stepping motor **90**. The amplitude or movement of the pen along the *y* axis is controlled by the analog recorder whereby the pen position is directly proportional to the signal selected for recording. The recording pen **98** is slidably engaged within the arm **102** of the bridge assembly **92**.

A valley sensing system **101** as shown in FIG. **10** comprises a light source **104** and a photoresistor **106** disposed within the arm which source and resistor are located on either side of the recording chart **100**. When actuated on rescan, the valley sensing system senses the marks made in the recording chart by the operator and transmits a signal to the digital printing drive system. If desired, in lieu of the light and photoresistor, other valley sensing systems such as an electronic valley sensing system may be used.

FIG. **8** is a top plan view of the travelling bridge and recording chart after scan and rescan. A stepping motor **90** which is preferably driven by the same pulse train as the scanner stepping motor **44** moves the bridge assembly **92** along a fixed path during the scan and rescan periods of travel. The line of digits **112** represent area percent and the line of digits **114** represent the material level accumulated to each mark on the recording chart.

The recording chart **100** is carried in a unique holder **124**. Each end of the recording chart is magnetically held down by magnetic strips **116** which overlay the chart and magnetically engage the steel surface of the holder.

THE OPERATION

The operation of our invention will be described in reference to an analysis of an electrophoresis strip in which various protein fractions of a blood sample are distributed along the strip.

Initially the power of the instrument is activated. Referring to FIGS. **4***a* and *b*, a sample **36** is placed on the steel holder **40** and the magnetic mat is placed over the sample and magnetically secured to the steel plate **40**. The slit **34** through which the light energy passes is adjusted to the desired width. The termination switch **46** shown both in FIGS **4***a* and *b* and FIG. **3** is then set manually to limit the movement of the sample being scanned during the scanning cycle and generally is located about at the end of the protein pattern. The sample holder is adjusted until the slit is under a clear portion of the pattern wherein a maximum amount of transmission of light is passing therethrough. The light energy created by the lamp passes through the various filters and lenses is focused on the pattern and passes through the adjustable slit **34** and received on the phototube **48** which communicates with the amplifier **50**. The variable gain amplifier **50** is adjusted until the pulses received on the voltage-to-frequency converter are as close to zero as possible. This may be determined by visual electrical means such as a flashing lamp **16** which is shown on the console **14** in FIG. **1** and in FIG. **11**. The termination switch for the bridge assembly (not shown) may also be adjusted to limit the movement of the bridge during scan.

A recording chart **100** is secured across a flat surface as shown in FIG. **8** by magnetically engaging the edge of the paper to a holder through the use of a magnetic strip **116** which cooperates with the magnetic holder along the edge of the flat surface.

The function in which the trace is made and in which the area under the profile is integrated is then made. As shown both the integration and the profile trace will be done in log inverse functions. On the recording switch it is possible to vary the amplitude of the trace pattern at a ratio of two to one by selecting the 1.5 or the 3.0 optical density (O.D.) level. That is, if the log inverse function is directed to the 3.0 O.D. level, then the amplitude of the trace on the recording chart will be half than that if the selection had been at the 1.5 O.D. level.

Of course, it should be understood that, if desired, recording in linear inverse would expand the small peaks making it possible for the operator to make better decisions on the proper selection of valleys between peaks while integration may be performed in a log inverse function to correctly quantify material.

Referring to FIG. **7**, the scan length selection switch **76** is set to determine the length of the scan of the trace of the pen in reference to the scan of the sample. The scan length determines the ratio of speeds of the bridge assembly to the sample holder. That is, as shown, it is set at **50** which means that the speed at which the bridge assembly is driven will be four times the speed at which the sample moves from its initial position until the scan cycle is stopped by actuation of the termination switch **46**. The length of the scan of the sample is determined by the location of the termination switch after the sample has been inserted in the holder. The length of the trace across the chart along the x axis is determined by the scan length control which is dependent upon the ratio of speeds between the stepping motor driving the sample scanner and stepping motor driving the bridge assembly. The termination switch **46** for the bridge assembly may be employed in lieu of the termination switch **44**.

The amount of material in a particular sample which in this instance is the total amount of protein in the

sample is then dialed in the digital dial manually **78** and stored in the milligram adapter as shown in FIG. **6**. Referring to FIG. **13**, if the reset lamp is not on, the reset switch (lamp switch) also shown on the control panel **70** in FIG. **7** is actuated and sets flip-flop **115***a* to the one state via gate **111***c*. This energizes the reset lamp on the control panel **70** and holds the instrument in the reset mode. The slew switch **83** is actuated to move the bridge assembly into position as shown in FIG. **9***a* through the slew distance. The zero potentiometer connected with the amplifier **50** is adjusted to bring the light **16** to a flashing condition. Also, when the rescan switch is actuated, all stages of the up-down counter **84** shown in FIG. **15** are set to "0" by gates **511***a* and **511***b*.

When the slew switch **83** is actuated, the bridge assembly or recorder moves the slew distance A as shown in FIG. **9**. Referring to FIG. **13**, gate **211***a* is enabled by the actuation by the slew switch **83** on the control panel to manually position the recording assembly to the right as shown in FIG. **9***a*.

The scan switch on the control panel **70** is then actuated and since the switches on the control panel are light switches, the actuation of the switch is indicated by the light as shown in FIG. **13**.

Actuation of the scan switch on the control panel after the bridge assembly has moved its "slew" distance with flip-flop **115***a* in the one state sets flip-flop **115***b* to its one state and resets flip-flop **115***a* to its zero state through gate **112***a*. Flip-flop **115***b* enables flip-flop **116***a* to be set to its one state through gate **112***b* immediately after flip-flop **115***b* has been set. The output of gate **112***b* also resets flip-flop **115***b* through gates **111***d* and **113***a*. When either flip-flops **115***b* or **116***a* are in the one state the scan lamp is energized via gate **113***d*. Flip-flop **116***a* thus holds the instrument in the scan mode until it is reset by a signal from the scanner termination switch **46**.

The logic level generated by gate **211***a* controls the direction of rotation of the stepping motor **90** to drive the bridge assembly. The bridge assembly stepping motor drive signal which is a 10Ms square wave is obtained from gate **211***d*. The logic levels generated by gates **211***a* and **210***c* control the direction of rotation of the stepping motor **90** via logic circuitry in the stepping motor drive unit. The motor drive signal is derived from the square wave clock located in the print control unit through gates **211***b* or **211***c*. During the scan cycle, gate **211***b* is enabled through gate **211***a* by flip-flop **116***a* which is in its one state. Gate **211***a* generates a "go right" command. As shown in FIG. **9***a*, this would move the bridge assembly to the right through its scan cycle.

The scanner drive motor or stepping motor **44** is controlled in similar fashion when the instrument is in the scan mode. Flip-flop **116***a* commands the scanner holding the sample to "go right" during the scan mode (flip-flop **117***b* commands the scanner to "go left" during the rescan mode) via logic circuits the same as those employed for the bridge assembly stepping motor drive and generally located in the stepping motor drive unit **44**. The period of the scanner motor drive pulses **44** is manually selectable in order to provide three scan langths: 25 centimeters, 50 centimeters, and 100 centimeters as shown in FIG. **7**. The scan length switch **76** on the control panel and as shown in FIG. **13** selects gates **213***a*, **213***b*, or **213***c* (via inverters **212***b*, **212***c*, and **212***d*) for the appropriate scanner motor drive signal. The three available signals are derived from the 10Ms clock and the outputs of the two-stage counter flip-flop **118***a* and flip-flop **118***b* which provides square waves of 20Ms and 40Ms. The outputs of gates **213***a*, **213***b*, and **213***c* are applied to gate **214***d* which during the scan cycle is enabled by flip-flop **116***a*. (During the rescan cycle, gate **214***d* is enabled by flip-flop **117***b*.)

When the scan switch is actuated, the stepping motors **44** and **90** are driven by the pulse generator **82** whereby the stepping motors move the scanner holder **40** transversely to the beam of light passing through the slit **34** and move the bridge assembly **92** along the *x* axis of the recording chart **100**. The variations in light transmitted through the sample are received by the photometer **48** and transmitted to the amplifier **50**. The signal is converted to a selected integrator function log inverse as shown and simultaneously converted to a selected analog recorder function, log inverse as shown. The density profile trace of the sample being scanned is recorded on the recording chart **100** by the pen recorder **98**. The pulses from the voltage-to-frequency converter are serially accumulated in the cascaded binary coded decimal counters in the total pattern integrator **58** and totalized while the sample is being scanned. When the sample holder **40** actuates the termination switch **46**, a signal is transmitted to the unit control **80**.

During the scan cycle, 40Ms clock pulses are applied to the up-down counter **84** and during this cycle flip-flop **116***a* commands the up-down counter **84** to count up. The pulses during scan are accumulated to some arbitrary count depending upon the scan period. Referring to FIG. **15**, flip-flop **116***a* of unit control through gates **214***a* and **214***b* enables gate **512***b* and gate **512***a* is disabled via gates **501***a* and **501***b* respectively. When flip-flop **513***a* responsive to 40Ms pulses from the unit control changes from its "1" to its "0" state, a carry pulse is transmitted through gates **512***b* and **512***c* to the input of flip-flop **513***b*. In a like manner each of the nine stages as shown receives an input pulse from the preceding stage when the latter goes from "1" to "0". This results in an up-counting mode. Also, during the scan cycle, the pretravel counter **86** receives 40Ms pulses from gate **214***c* which is enabled by flip-flop **417***a*.

Referring to FIG. **13**, the termination switch **46** signals through gates **112***c*, **113***b*, and **113***c* that the scanner has reached the end of travel in the scan direction. The output of gate **112***c* sets flip-flop **116***b* to its one state and thus establishes the select valleys mode and terminates the scan mode. Although the scanner limitation or termination switch has been shown, a similar termination switch which may be physically adjusted to limit the travel of the bridge assembly rather than the scanner may be employed in this instrument which bridge assembly termination switch would be responsive to engagement by any desired portion of the bridge assembly. As shown in FIG. **13**, the termination switch (recorder or scanner) is designed so that a switch may be employed as shown for the scanner or for the bridge assembly or for both and the unit control would be responsive to the first received signal. The output of gate **112c** also sets flip-flop **116***b*

to its one state which establishes the select valley mode and resets flip-flop **116***a*.

The select valleys indicator or light on the control panel is actuated and the operator at this time selects the valleys on the profile trace between which valleys the area percent and protein levels are to be determined. As shown in FIG. **8**, these valleys are selected by physically punching slots in the edge of the recording chart **100**. The select valleys lamp is controlled by flip-flop **116***b*.

The pretravel counter **86** which is shown in schematic form in FIG. **14** is preset to a determined number (determined during final tests) via gates **419***a* and **419***b* by a signal from the unit control when the select valleys switch is actuated. The preset number is determined by wiring jumpers to the terminals as shown. During rescan **1** or pretravel, clock pulses from the unit control are applied to the input of the counter. The counter is wired to count down from the preset number. At the count of 010000 (i.e., decimal 2) gate **412** generates the command which causes the value of the material amount level which was stored by the digi-switch to be printed on the recording chart. At the count of 1000000 (decimal 1) gate **411** generates the end of pretravel signal which signal initiates the rescan 2 mode and terminates the pretravel or rescan 1 mode.

After the indications have been made on the recording chart **100** selecting the valleys to be examined, the rescan switch is actuated whereby flip-flop **117***a* is set to its one state via gate **112***d*. The actuation also resets flip-flop **116***b* to its zero state. Flip-flop **117***a* establishes the pretravel or rescan **1** mode. Referring to FIG. **9***b*, this moves the bridge assembly **101** the pretravel distance C while the scanner remains stationary. That is, the stepping motor **90** drives the bridge assembly. The pretravel counter which previously received pulses from gate **214***c* which was enabled by flip-flop **117***a* is designed to count down a predetermined number of pulses during this pretravel cycle to control the movement of the bridge assembly the distance C shown in FIG. **9***b*. As previously described, flip-flop **215** is set to its one state by flip-flop **117***a* which causes gate **210***c* to generate a "go left" command and also enables gate **211**c to provide the motor drive pulses. When the rescan switch is actuated, the print control **68** receives print commands from the pretravel counter **86**, for example, the total material amount in the total material digi-dial **78** upon command from the pretravel counter, the value stored in the digi-dial **78** is transferred to the decade counters in the data selectors **62***a*, *b*, and *c* in combination with the print adapter **64***b*. The command from the pretravel counter enables gate **312**a of FIG. **12** to trigger the circuitry which transfers the data to be printed from the data selectors to the print adapters. Flip-flop **310***a* enables gate **306***b* to transmit print pulses to the printer adapters to the count wheels, and then to the printer solenoid command at the appropriate time. This particular circuitry will be described in detail during the rescan 2 cycle of the instrument.

The amount of material in the digi-dial is printed as shown on FIG. **8** by the count wheels **96**. Upon completion of the pretravel cycle when the pretravel counter has counted down to zero or decimal one, a signal from gate **411**, FIG. **14**, is gated to gate **212**a of the unit control. This sets F/F **117***b* to its one state and causes the scanner motor drive to generate a "go left" command. Also, through gates **214***a* and **214***b* it causes the updown counter **82** to count down at the termination of the pretravel. The bridge assembly continues to move and the updown counter commences to count down and simultaneously the stepping motor **44** is actuated and the sample rescanned and curve reintegrated as described during the scanning cycle.

Referring to FIG. **15**, gate **512***a* is enabled from gate **214***b* and gate **512***b* is disabled whereby flip-flop **513**b receives an input pulse when F/F **513**a goes from "0" to "1" and similarly for other stages. In this mode the counter counts down from the count which was accumulated in scan. When the count reaches zero, gate **515** produces an output to the unit control to gates **111***a*, **111***b*, and **111***c* which sets flip-flop **115***a* to "one," its reset condition, and resets flip-flop **117***b* to its zero state to terminate the drive of the stepping motor **44** and to end rescan two. This stops scanning motor **44** and reintegration of the sample. The bridge assembly continues moving the distance E shown in FIG. **9***b* until it strikes the "left" termination switch after moving the slew distance.

On rescan, the pulses received on reintegration are transmitted to the rescan counter and accumulated. Referring to FIG. **11**, the pulses from the voltage-to-frequency converter received on rescan are accumulated in the rescan counter **59**. These pulses are continuously accumulated and compared in the comparator **60** against the total accumulated pulses and in total area counter **58**. The pulses initially received in the total area counter are divided by 1,000 to produce 0.1 percent pulse values. Each time the rescan counter **59** counts pulses corresponding to 0.1 percent pulses as determined by the comparator **60** this information is transmitted directly to the decade counters in the data selectors **62***a*, **62***b*, and **62***c*.

As shown most clearly in FIG. **11**, the pulses are serially accumulated in the decade counters of the print modules directly from the comparator. The same signal or value from the comparator each time the 0.1 percent pulse level is reached is transferred directly to the milligram adapter **66**. The milligram adapter multiplies the percentage of each signal received by the total amount of protein which was dialed in by the digi-dial **78** and serially transfers this information to the decade counters associated with the data selectors of the material print modules. After each transfer of the 0.1 percent pulse to the appropriate data selectors, the rescan counter is automatically reset by the comparator. In the rescan mode the transfer of information to the data selectors continues and is accumulated in both sets of the decade counters until such time as the first mark made on the recording chart **100** is sensed by the photocell of the valley sensing system. When the photocell **106** in the valley sensing system which is contained within the arm of the bridge assembly **92** senses the first mark by the operator, the information is printed directly on the recording chart **100** by the count wheels **94** and **96**.

Referring to FIG. **12**, the signal from the photocell which senses the mark which was punched by the operator to select the valleys is applied to amplifier A8. When the punch mark is sent, the output of A8 sets

flip-flop **310***a* to its one state via gates **308**, **301***a*, **302***c* and **302***d*. Gates **312***a* and **312***b* as shown form a pulse-shaping network. The output of gate **302***d* also enables the gate **312***a* to trigger the circuitry which transfers data to be printed from the data selectors to the print adapters. This circuitry which comprises flip-flops **316***a*, **316***b*, and gates **312***a*, **312***b*, **312***c*, **311***c*, **311***d*, **306***a*, **315***a*, **315***b*, and **315***c* develops a 0.4 microsecond transfer command to the data selectors followed by a 0.4 microsecond clear command. The data input lines to the data selectors are inhibited during the clear and transfer period.

Referring to FIG. **11**, when the output from gate **302***d* enables gate **312***a* to trigger the circuitry as described, referring to the data selectors **62***a*, **62***b*, and **62***c*, the information accumulated in the decade counters is allowed to pass through the transfer gates and into the binary coded decimal to serial converters which comprise the print adapters. Specifically, for the 0.1 percent pulses transmitted directly to the percent print modules, the information accumulated on the decade counters flows through the transfer gates and into the serial converters or print adapters **64***a*. Similarly, the same occurence takes place at print adapters **64***b* where the information which was multiplied in the milligram adapter and accumulated on the decade counters in transferred to the serial converters of the print adapters **64***b*.

Flip-flop **310***a* enables gate **306***b* to transmit print pulses to the print adapters. Flip-flop **310***a* also enables gate **314***a* to transmit clock pulses to the input of a five-stage counter which comprises flip-flops **305***a*, **305***b*, **309***a*, **309***b*, and **310***b*. The fivestage counter controls the time interval during which the print pulses and reset pulses are applied to the print adapters. This counter also generates the print or solenoid command at the appropriate time. In the select valleys mode reset pulses are generated on command from the unit control via gate **314***d*. At the conclusion of the print cycle, flip-flop **316***a*, **316***b* and **310***a* are reset to zero by a signal from gate **313** through gates **315***d*, **315***e*, and **315***f*. Flip-flop **310a** then resets the five-stage counter. The print control is then ready to receive the next command. During the rescan mode, the print commands from the valley sense circuit are accepted only during this mode and this feature is controlled by gate **308**. The print command output code is a two-bit code generated by gates **311***a* and **311***b*. Therefore, gate **306***b* in timed relationship transmits print pulses to the print adapters **64***a* and **64***b*. This information is transferred to the count wheels where the count wheels are rotated to the proper position. Subsequently, upon command from the counter, the print or solenoid command is made whereby the information is printed in digital form on the recording chart **100** as shown in FIG. **8**.

This rescan mode is continued and each time the valley sensing system senses the mark made by the operator, the accumulated information in the decade counters is transferred to the print adapters and then printed on the recording chart. The rescan and reintegration of the sample and the movement of the bridge assembly is continued until the movement of the scanner drive ceases when the counter **84** has counted down. The bridge continues travel on rescan whereby a left recorder limit switch (not shown), which is physically set to engage the bridge assembly at the end of the slew distance, resets flip-flop **215** comprised of gates **215***a* and **215***b*. This in turn inhibits the recorder motor drive pulses through gates **215***c*, **215***d*, **210***c*, **211***c*, and **211***d*. The recorder stepping motor drive signal which is a 10Ms square wave is obtained from gate **211***d*. As mentioned above, in the rescan mode flip-flop **215** of the unit control is set to its one state by flip-flop **117***a*. This causes gate **210***c* to generate a "go left" command and also enables gate **211***c* to provide the motor drive pulses.

Similarly, the scanner drive stepping motor **44** is controlled in similar fashion. Flip-flop **117***b* commands the scanner to "go left" during the rescan mode via the logic circuits located in the stepping motor drive unit **44**. Referring to FIG. **9b**, the bridge assembly is now in the position indicated by the dotted line and prior to analyzing the next sample, the slew switch is actuated to bring the bridge assembly and pen back to the beginning of the scan cycle.

Having described our invention, what we now claim is:

1. A densitometer which comprises in combination:
   a. a source of energy;
   b. means to expose a sample to be analyzed to said energy;
   c. means to cause the scanning of the sample by relative movement between the sample and said energy;
   d. means to convert the energy emerging from the sample to an electrical signal;
   e. means to display a selected signal in analog form;
   f. means to integrate a selected signal;
   g. means to select a portion of the analog form from which additional information is desired;
   h. means to cause the rescanning of the sample and to integrate the signal received;
   i. means to compare the integrated rescan signal with the integrated scan signal; and
   j. means to record the compared signals in digital form.

2. The densitometer of claim **1** wherein the source of energy is light energy and which includes means to focus said light energy as a beam, the means to expose the sample to the beam of light energy includes an aperture therein whereby the sample may be placed on a support means and the beam of light energy adapted to pass through said aperture, and wherein the means to scan the sample includes means to drive the support means along a predetermined path.

3. The densitometer of claim **2** wherein the support means includes a holding means having a flat surface thereon, said surface being characterized by a slot therein and being formed of a magnetizable material, and further wherein a magnetic mat having an aperture slit therein is secured to the flat surface of the holding means whereby the sample is placed on the flat surface of the holding means and the magnetic mat engages the magnetizable material thereby holding the sample firmly in place.

4. The densitometer of claim **2** wherein the means to drive the support means includes a motor means adapted to operate at a selected constant speed which reciprocates the support means between preselected positions.

5. The densitometer of claim 1 wherein the means to convert the light energy to an electrical signal includes a photometer whereby the energy is converted to current and said current is transmitted to an amplifier whose output signal is voltage,

wherein the means to display in analog form includes a servomechanism in combination with a recording stylus adapted to trace a profile,

wherein the means to integrate includes a voltage-to-frequency converter and a plurality of BCD cascade counters,

wherein the means to select portions of the profile trace to be integrated on rescan includes means to mark a medium on which the density profile trace is formed, and

which includes means to control the scan and rescan cycles.

6. The densitometer of claim 1 wherein the means to rescan the sample includes holding means and drive means to move the holding means along a predetermined path;

wherein the means to integrate the signal during rescan includes means to accumulate a plurality of pulses on BCD cascade counters,

wherein the means to compare the rescan signal with the total accumulated signal includes means to calculate the percent of rescan signals compared against the total accumulated signal, and

wherein the means to record the signal in digital form includes print means.

7. The densitometer of claim 6 wherein the means to calculate the area percent includes a digital divider.

8. The densitometer of claim 1 wherein the sample being analyzed is a thin layer chromatography plate.

9. The densitometer of claim 1 which includes means to define preselected areas of the analog trace.

10. An improved densitometer which comprises in combination:

a. a source of light energy;

b. means to form a beam of said light energy;

c. means to expose a sample to be analyzed to the beam of light energy;

d. means to scan the sample with the beam of light energy;

e. means to convert the light energy transmitted through the sample to an electrical signal;

f. function generator means to convert the signal from the sample to a level related to the amount of material to be analyzed in the sample;

g. means to record the signal in analog form as a profile trace on a recording medium;

h. means to integrate the selected signal with the recording of the selected signal in analog form in communication with the function generator means;

i. means to select a portion of the analog profile trace from which additional information is desired;

j. means to rescan the sample and to integrate the signal received;

k. means to compare the integrated rescan signal of the selected portion of the analog profile trace with the total accumulated scan signal whereby on comparison the pulses are discharged; and

l. means to record the compared signals in digital form on the medium.

11. The densitometer of claim 10 wherein the function generator means includes a linear inverse converter, a log inverse converter, function of x converter, and further includes the means to record in one of said functions and integrate in that or another of said functions as desired,

wherein the medium includes chart recording means, and

wherein the means to record in digital form includes:

1. housing means,

2. bridge means secured to the housing means and extending across the chart recording means,

3. sensing means adapted to indicate when the rescan of a selected portion of the analog trace has been completed and pen means disposed in the bridge means, and

wherein the chart recording means includes a chart which is magnetically secured to a support means,

wherein the digital printing means are disposed within the housing of the bridge assembly and axially aligned with and spaced apart from the sensing means along the y axis of the recording chart.

12. The densitometer of claim 11 wherein the means to compare the integrated rescan signal against the total accumulated scan signal includes means to calculate percents.

13. The densitometer of claim 12 wherein the means to calculate includes:

means to store a number representing the total amount of material;

means to control the movement of the holding means and bridge assembly means;

means to control the selection of the information transmitted to the digital printing means in the bridge assembly means;

means to multiply percent times the total amount of material; and

means to print the percent and the material amount for the selected portion of the analog trace upon the receipt of a command from the sensing means.

14. The densitometer of claim 10 wherein the sample being analyzed is an electrophoresis strip.

15. The densitometer of claim 11 wherein the bridge assembly means and the holding means for the sample are each driven by stepping motors which stepping motors are driven by pulses derived from the same pulse train.

16. A method of scanning a sample and recording the results of said scan therefrom which comprises:

a. creating a source of light energy;

b. exposing a sample to be analyzed to the beam of light energy;

c. receiving a portion of said beam of light energy emerging from the sample on a receptor;

d. converting the light energy emerging from the sample to an electrical signal;

e. integrating the electrical signal transmitted from the receptor;

f. recording the signal from the receptor as an analog profile trace on a medium;

g. selecting a portion of the profile trace from which desired information is required;

h. rescanning and integrating the sample over the desired portion from which information is desired;

i. comparing the integrated rescan signal against the total integrated scan signal;

j. providing a value representative of a comparison between the rescan signal against the total scan signal; and

k. recording said value in digital form on the medium.

17. The method of claim 16 which includes converting the light energy emerging from the sample into an electrical signal by transmitting said signal to a photometer;

integrating said signal by converting the signal to a plurality of pulses and accumulating the pulses.

18. The method of claim 16 which includes recording the signal from the photometer as an analog profile trace by tracing said signal on a recording medium, and further which includes selecting the desired portion of the profile trace from which additional information is desired by marking the medium.

19. The method of claim 16 which includes converting the signal received on rescan into pulses and totalizing the pulses received and further which includes dividing digitally the pulses received on rescan by the pulses previously accumulated during scan in a digital divider.

20. The method of claim 16 which includes printing the calculated value in digital form on the medium, and further which includes storing a material amount level, multiplying the value times said material amount level and recording said calculations in digital form on the medium.

21. The method of claim 16 which includes:

transmitting the electrical signal to one of a plurality of function generators,

selecting the function in which the analog trace is to be recorded, and

selecting the function in which the integration is made.

22. The method of claim 21 wherein the function generators include a log inverter, a linear inverter, and a function of x converter.

23. The method of claim 16 wherein the sample to be analyzed is an electrophoresis sample.

24. A modular computer for calculating a fraction of a total area under a curve which comprises:

a. means to receive signals representative of variations in composition of a scanned sample from a source;

b. means to display said signals in analog form;

c. means to integrate said signals;

d. means to select a portion of the analog form from which additional information is desired;

e. means to receive and integrate signals representative of variations in composition of the sample rescanned;

f. means to compare the integrated rescanned signal with the integrated scanned signal; and

g. means to record the compared signals in digital form.

25. The computer of claim 24 wherein means to integrate the signals received includes means to accumulate a plurality of pulses on BCD cascade counters and wherein the means to compare the rescan signal with the total accumulated scan signal includes means to calculate the percent of rescan signals compared against the total accumulated signal.

26. The computer of claim 24 wherein the means to display in analog form includes a seryomechanism in combination with a recording stylus adapted to trace a profile, wherein the means to integrate includes a voltage-to-frequency converter and a plurality of BCD cascade counters, and wherein the means to select portions of the profile trace includes means to mark a medium on which the analog trace is formed.

27. The computer of claim 24 which includes:

a. function generator means to convert the signals received to a level related to the amount of material to be analyzed in the sample;

b. means to record the signals in analog form as a profile trace on a recording medium;

c. means to integrate the selected signals with the recording of the selected signals in analog form in communication with the function generator means;

d. means to select a portion of the analog profile from which additional information is desired;

e. means to compare the integrated rescan signals of the selected portion of the analog profile trace with the total accumulated scan signals whereby on comparison the pulses are discharged; and

f. means to record the compared signals in digital form on the medium.

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