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Fetner et al.

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[54] **METHOD AND APPARATUS FOR CHROMOSOME DIGITIZING**

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[52] **U.S. Cl.** ..... **235/151.3,** 128/2 R, 340/146.3 R, 340/146.3 AC, 356/39, 178/DIG. 22, 444/1

[51] **Int. Cl.** **G06f 15/42**

[58] **Field of Search** ..... 73/432 PS; 128/1 R, 2 R; 235/151.3; 340/146.3 R, 146.3 AC; 356/39; 178/DIG. 22; 444/1

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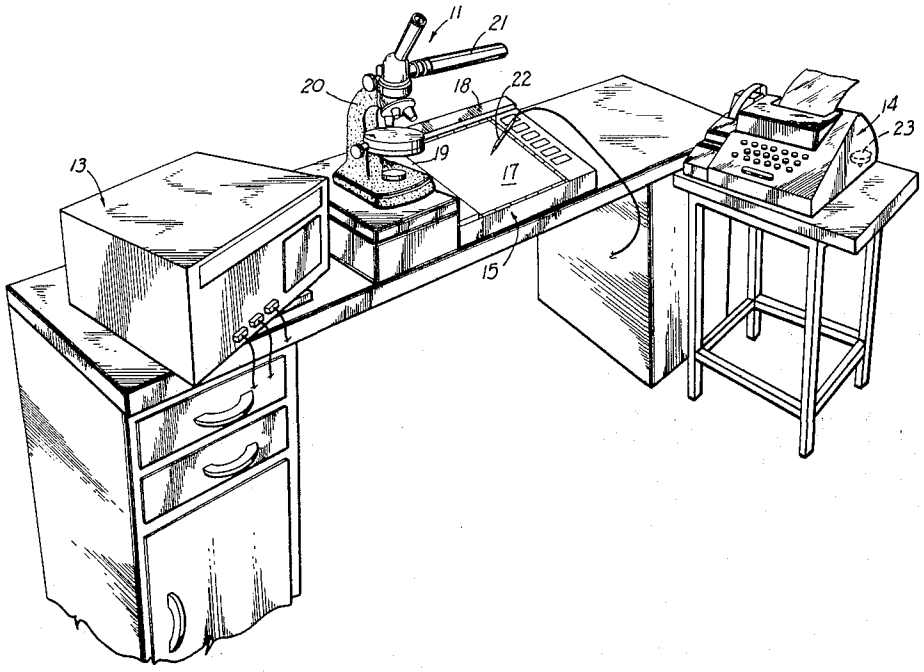
[57] **ABSTRACT**

A chromatizer including an apparatus for and method of effecting the analysis of chromosomes including means for establishing an image of at least one chromosome, means for digitizing the distance each arm of the chromosome is from a preselected reference point, and means for automatically computing a number of quantitative measurements of the chromosome, including the length of each arm and the centromere index. The digitizing means includes means for identifying and recording the location of a plurality of points along each arm of the chromosome relative to the reference point. The establishing means includes means for superimposing the identifying means onto the image of the chromosome. The computing means includes means for displaying the computed quantitative measurements.

14 Claims, 8 Drawing Figures



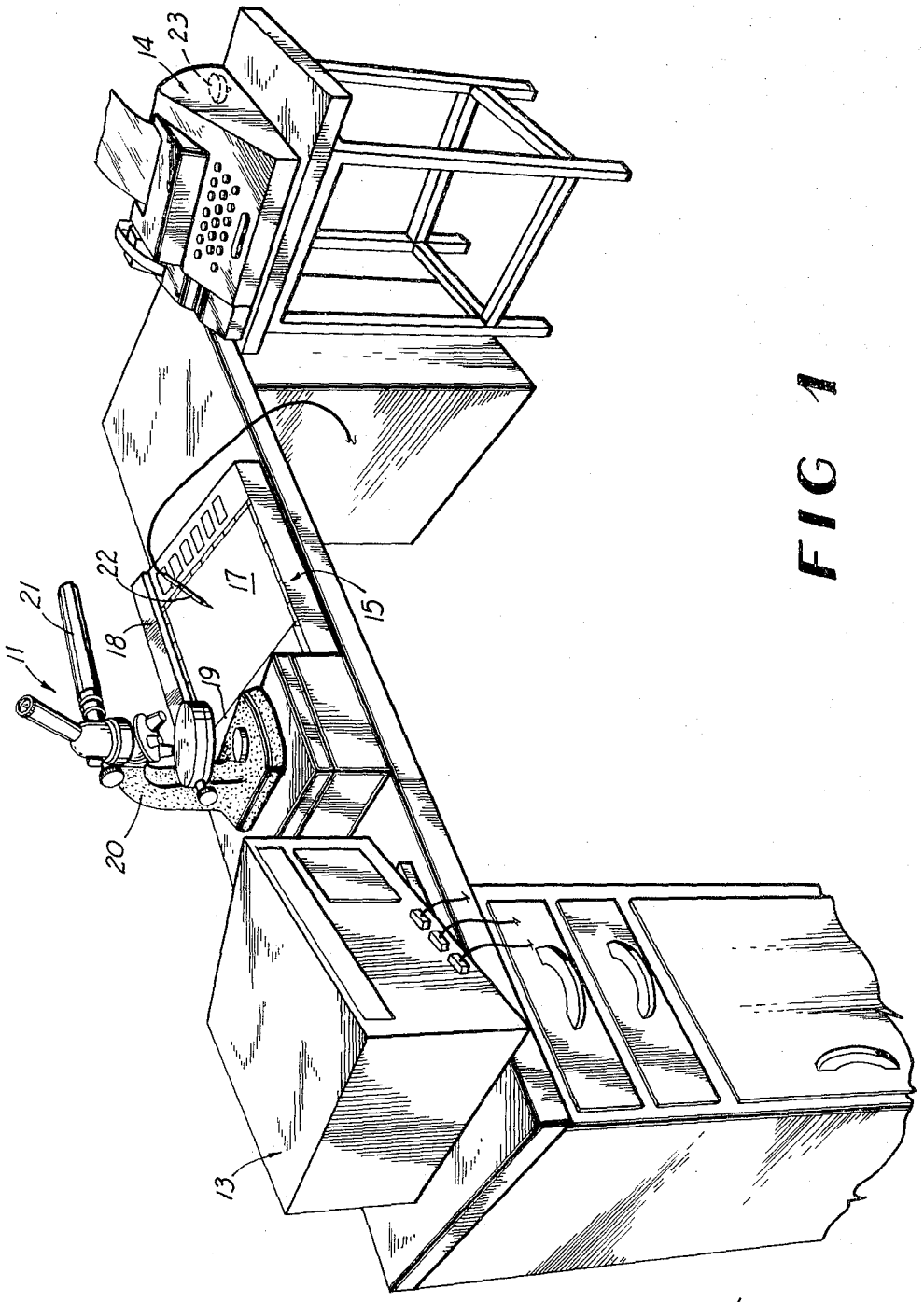


FIG 1

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ATTORNEYS

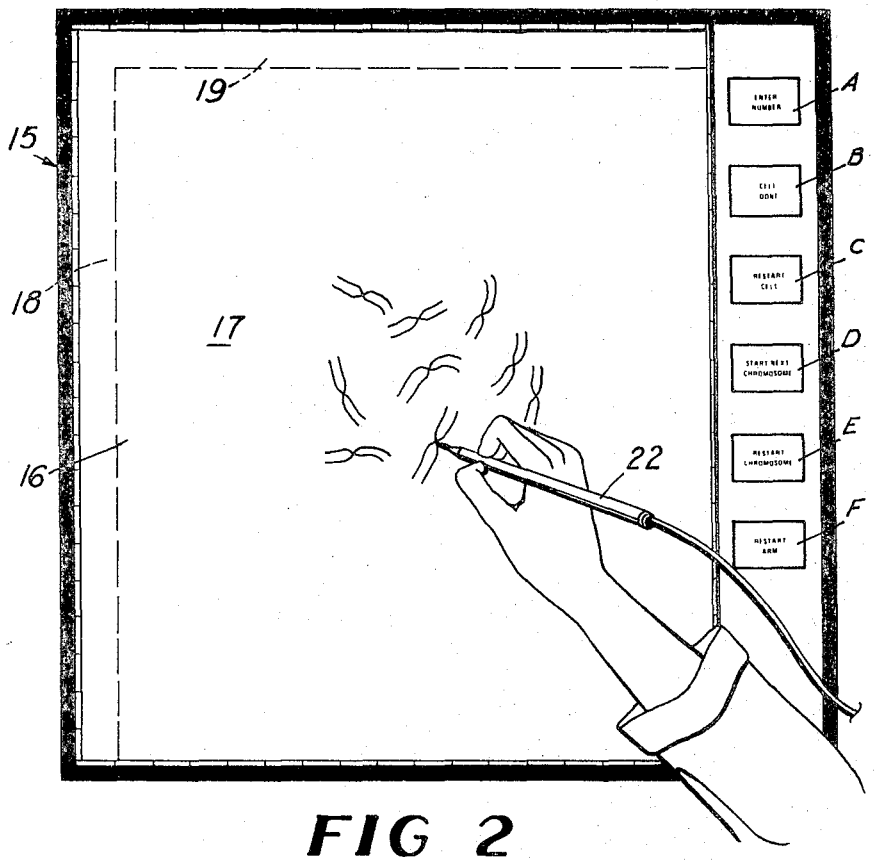
19
15
18
17
16
22
A
B
C
D
E
F

FIG 2

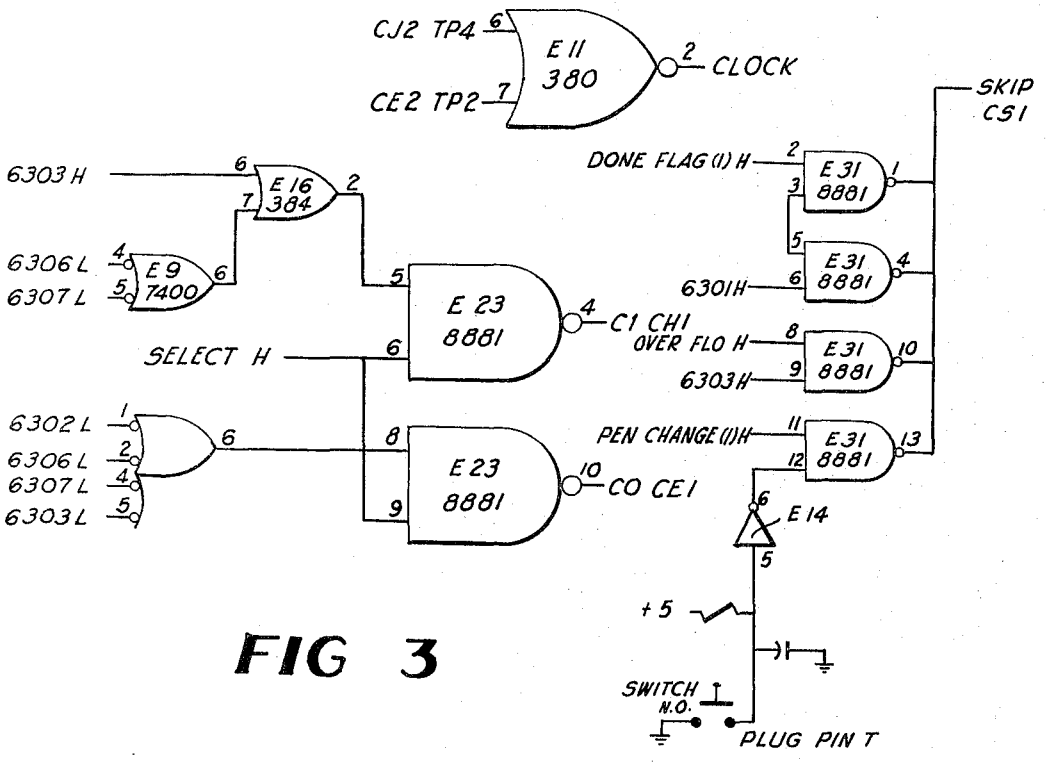
CJ2 TP4
CE2 TP2
E 11
380
CLOCK
SKIP
CS1
6303 H
E 16
384
6306 L
6307 L
E 9
7400
SELECT H
E 23
8881
C1 CHI
DONE FLAG (I) H
E 31
8881
6301H
OVER FLO H
6303H
PEN CHANGE (I) H
6302 L
6306 L
6307 L
6303 L
CO CE1
E 14
+5
SWITCH
N.O.
PLUG PIN T

FIG 3

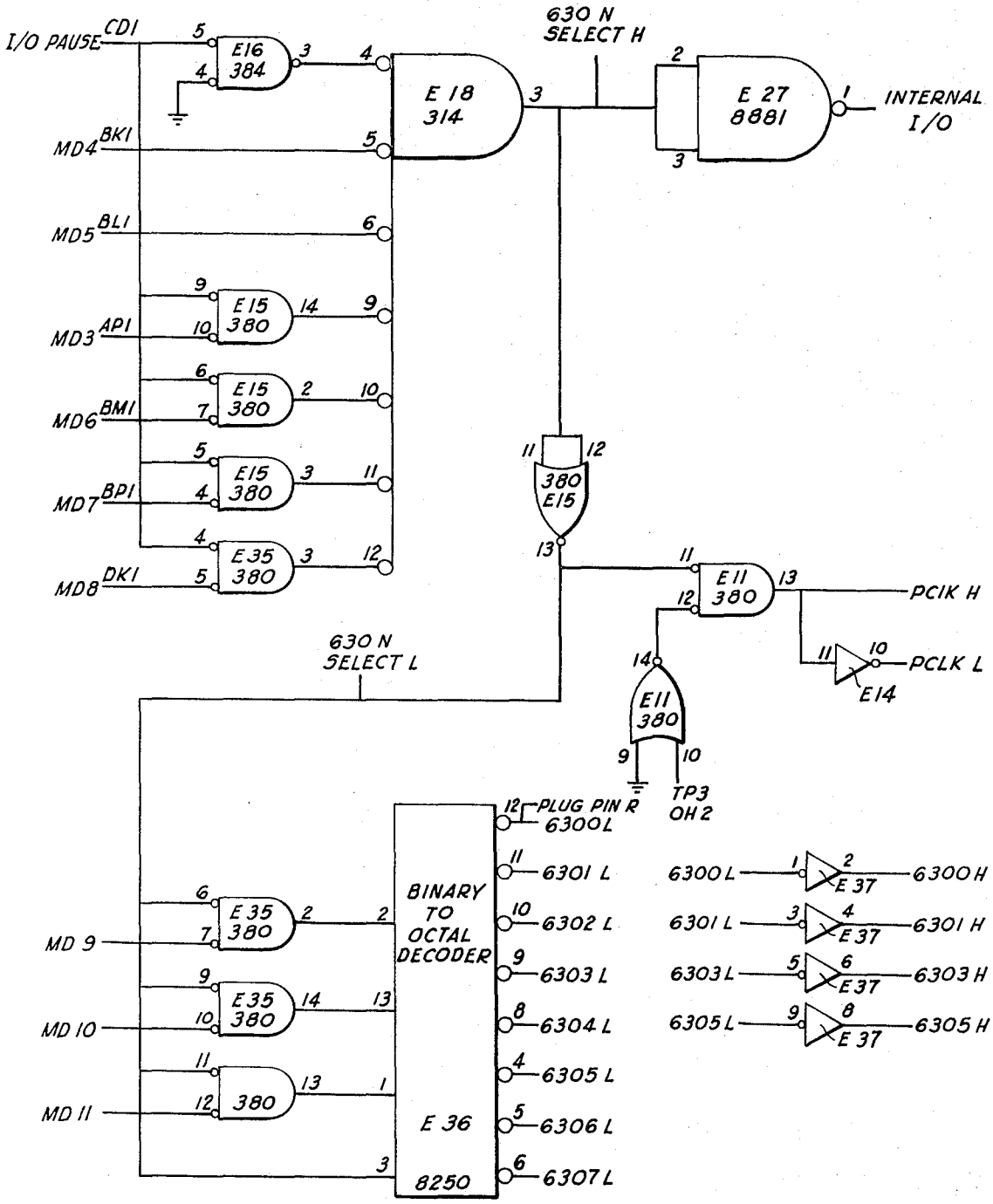
I/O PAUSE
CDI
E16 384
MD4 BKI
MD5 BLI
MD3 API
MD6 BMI
MD7 BPI
MD8 DKI
E 18 314
630 N SELECT H
E 27 8881
INTERNAL I/O
E15 380
E35 380
380 E15
630 N SELECT L
E11 380
PCIK H
PCLK L
E14
TP3 OH2
MD 9
MD 10
MD 11
380
BINARY TO OCTAL DECODER
E 36 8250
PLUG PIN R 6300L
6301 L
6302 L
6303 L
6304 L
6305 L
6306 L
6307 L
6300 L
6300 H
6301 H
6303 H
6305 H
E 37

FIG 4

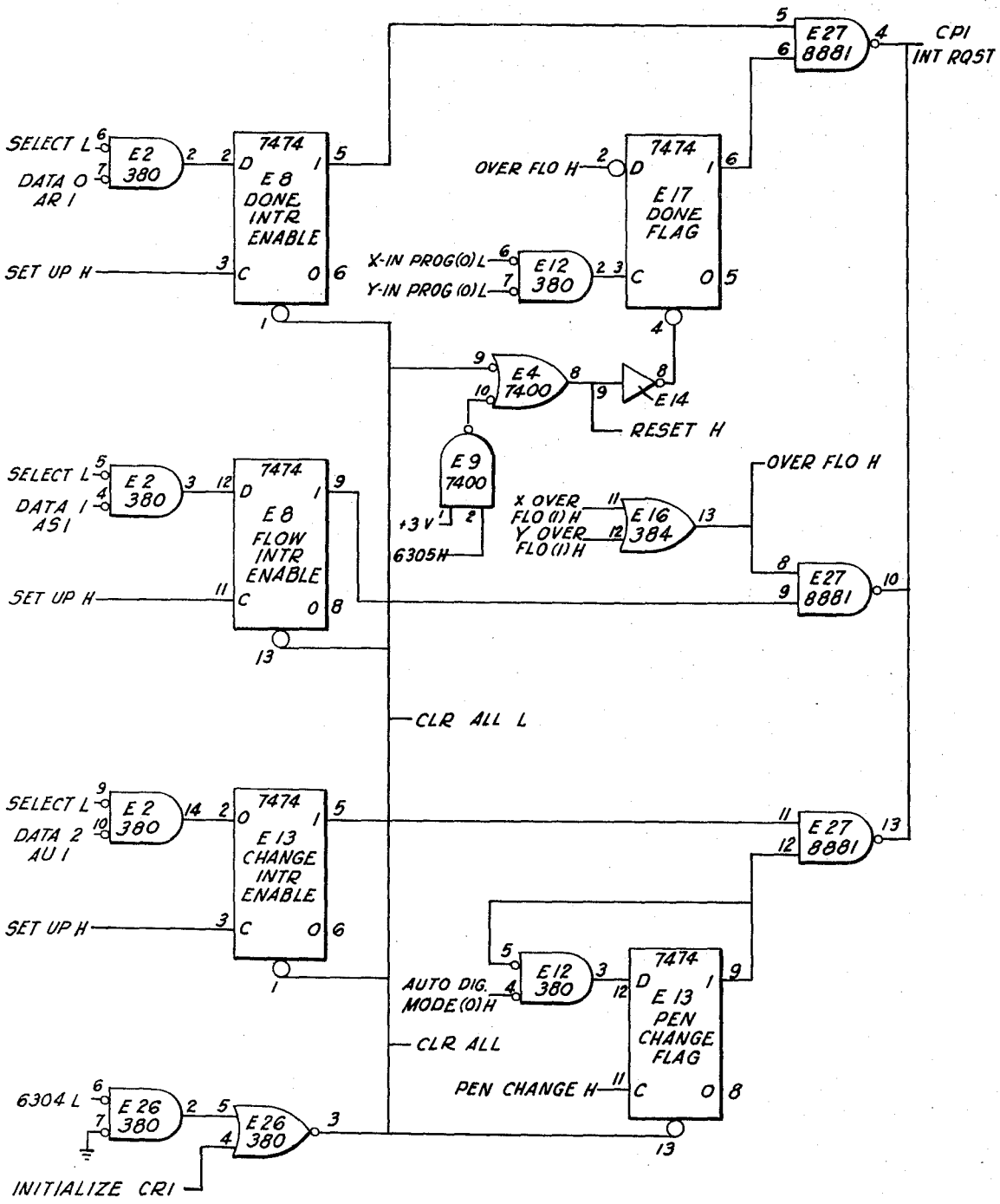
E27 8881
CPI INT RQST
SELECT L
DATA 0 AR I
E2 380
7474
E8 DONE INTR ENABLE
SET UP H
OVER FLO H
E17 DONE FLAG
X-IN PROG(0) L
Y-IN PROG (0) L
E12 380
E4 7400
E14
RESET H
E9 7400
+3V
6305H
SELECT L
DATA 1 AS I
E8 FLOW INTR ENABLE
x OVER FLO (1) H
Y OVER FLO (1) H
E16 384
OVER FLO H
CLR ALL L
SELECT L
DATA 2 AU I
E13 CHANGE INTR ENABLE
AUTO DIG. MODE (0) H
E13 PEN CHANGE FLAG
CLR ALL
PEN CHANGE H
6304 L
E26 380
INITIALIZE CRI

FIG 5

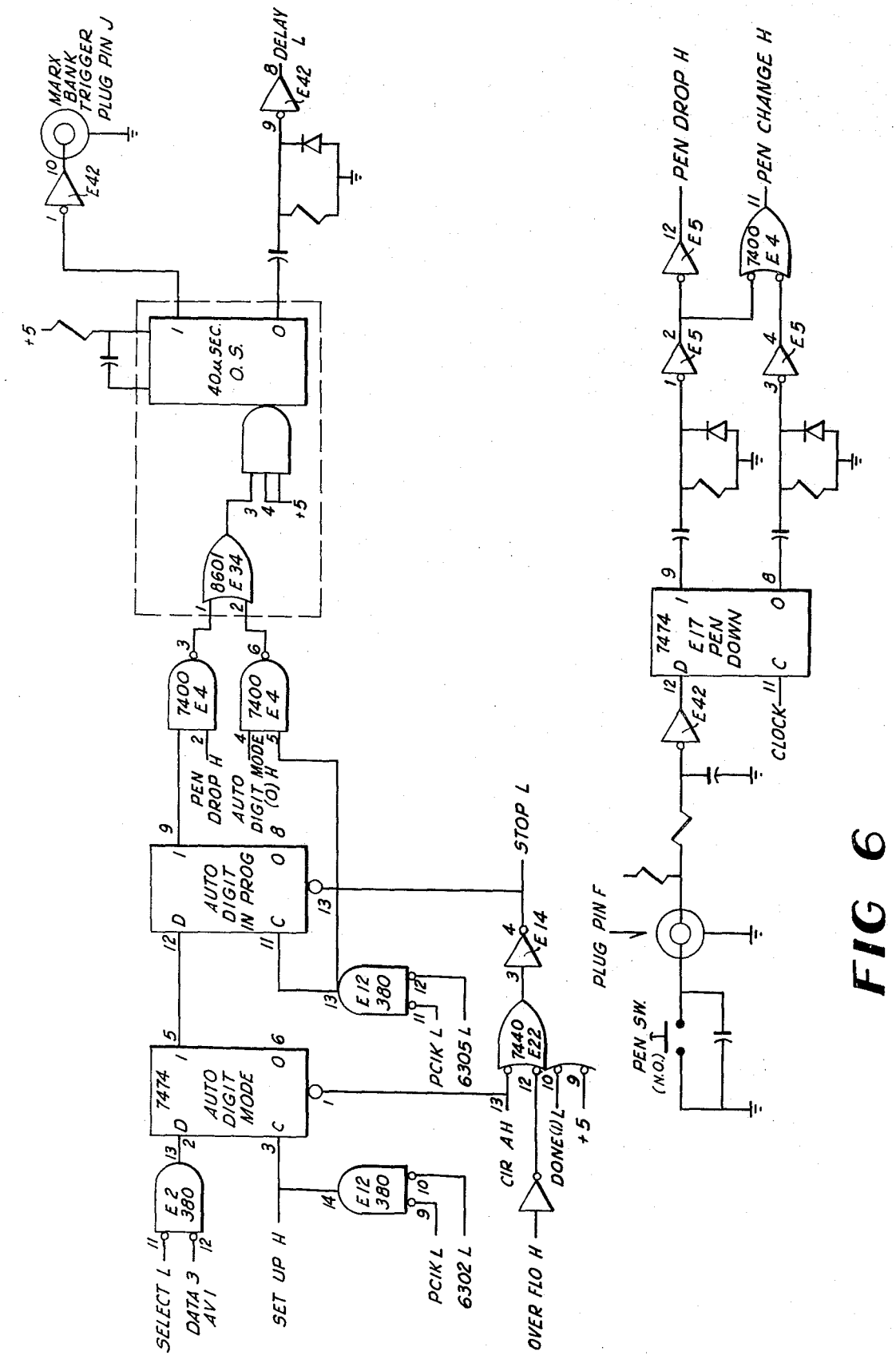
MARK BANK TRIGGER PLUG PIN J
E42
DELAY L
E42
+5
40μ SEC. O.S.
8601 E34
7400 E4
7400 E4
PEN DROP H
AUTO DIGIT (0) H
AUTO DIGIT IN PROG
AUTO DIGIT MODE
7474
E2 380
E12 380
E12 380
SELECT L
DATA 3 AV1
SET UP H
PCIK L
6302 L
PCIK L
6305 L
STOP L
E14
7440 E22
CIR AH
DONE(0) L
OVER FLO H
PLUG PIN F
PEN SW. (N.O.)
PEN DROP H
PEN CHANGE H
E5
E5
7400 E4
E5
7474 E17 PEN DOWN
E42
CLOCK

FIG 6

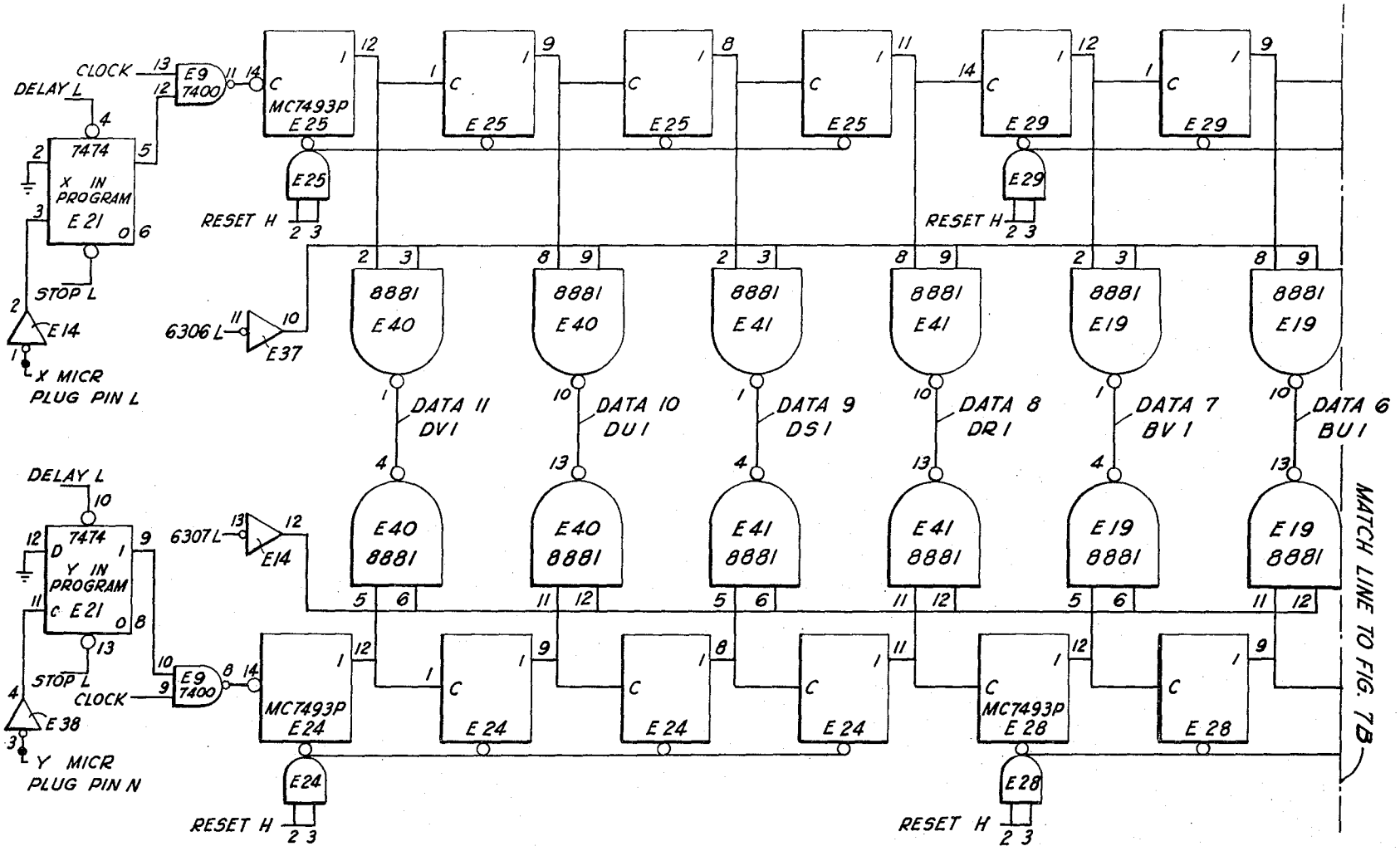
CLOCK
DELAY L
E9 7400
MC7493P E25
E25
E29
7474 X IN PROGRAM E21
RESET H
STOP L
E14
X MICR PLUG PIN L
6306 L
E37
8881 E40
8881 E41
8881 E19
DATA 11 DV1
DATA 10 DU1
DATA 9 DS1
DATA 8 DR1
DATA 7 BV1
DATA 6 BU1
7474 Y IN PROGRAM E21
6307 L
E14
E40 8881
E41 8881
E19 8881
STOP L
CLOCK
E9 7400
E38
Y MICR PLUG PIN N
MC7493P E24
E24
MC7493P E28
E28
RESET H
MATCH LINE TO FIG. 7B

FIG 7A

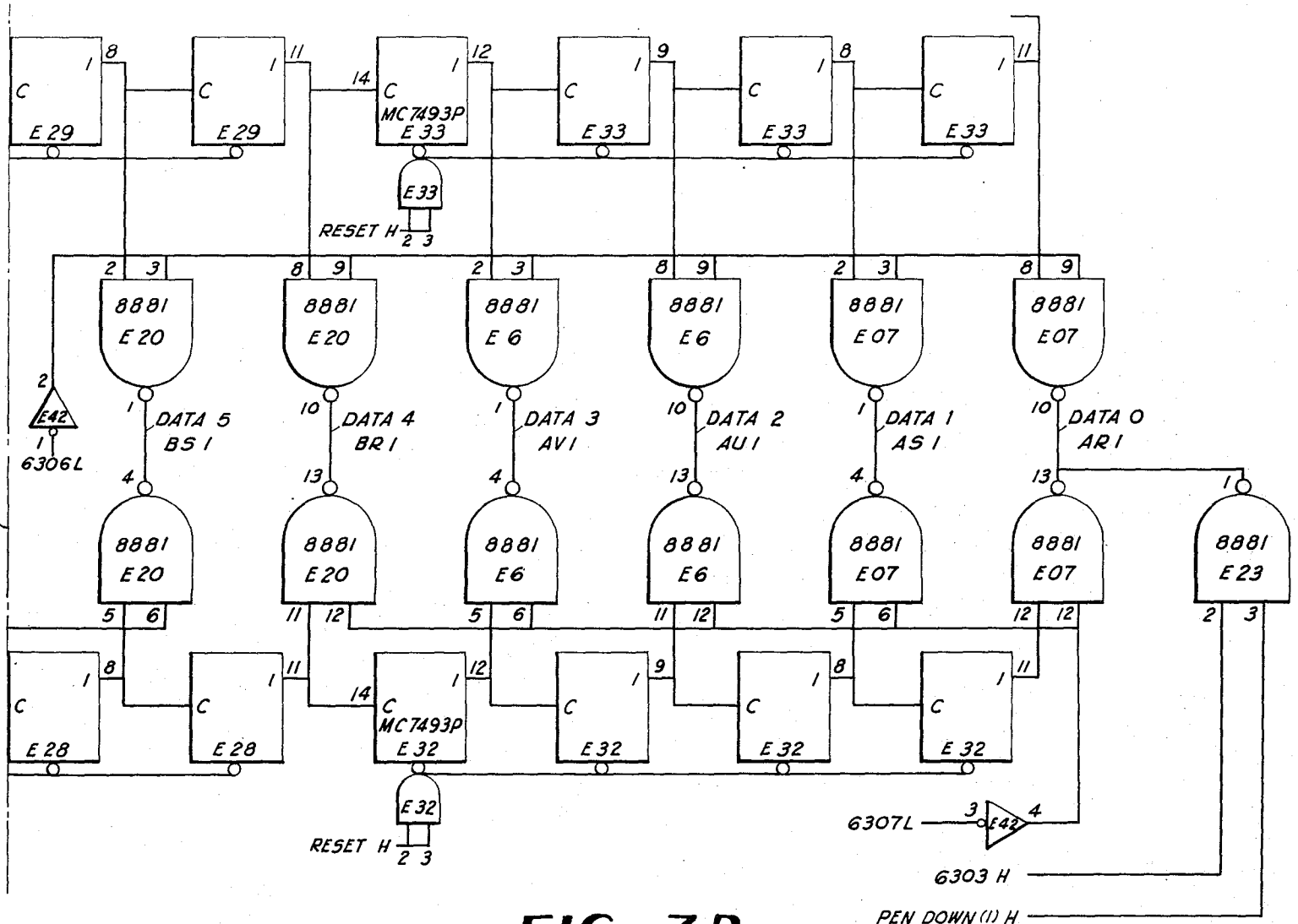
MATCH LINE TO FIG. 7A
E 29
E 29
MC7493P E 33
E 33
E 33
E 33
E33
RESET H
8881 E 20
8881 E 20
8881 E 6
8881 E 6
8881 E 07
8881 E 07
E42
6306L
DATA 5 BS I
DATA 4 BR I
DATA 3 AV I
DATA 2 AU I
DATA 1 AS I
DATA 0 AR I
8881 E 20
8881 E 20
8881 E 6
8881 E 6
8881 E 07
8881 E 07
8881 E 23
E 28
E 28
MC7493P E 32
E 32
E 32
E 32
E32
RESET H
6307L
E42
6303 H
PEN DOWN (I) H

FIG 7B

METHOD AND APPARATUS FOR CHROMOSOME DIGITIZING

BACKGROUND OF THE INVENTION

In the past few years, there has been a dramatic increase in the interest of the medical community with human cytogenetics. This interest has been generated by the demonstrated relationship between chromosome abnormalities and human pathology, and there is the expectation that this discipline will provide an even better understanding of the human organism

At the present state of the art, human cytogenetic studies begin with a karyotype analysis of an individual. The individual chromosomes are characterized primarily by two parameters: length of the individual chromosomes and location of the centromere. The homologous pairs of chromosomes are separated from one another or placed into similar groups on the basis of these two parameters. This analysis sometimes uses other distinguishing chromosome features, such as satellites and secondary constrictions; however, these are either not universally present or may not be distinguishable. The use of radioisotope tagging to determine the time of nucleic acid synthesis, which differs among the chromosomes, and the selective staining of specific parts of different chromosomes with fluorescent compounds are recent developments.

At present, the commonly used distinguishing characteristics of the individual chromosome, length and centromere index, are usually determined qualitatively by visual inspection of chromosome pictures cut from a photographic print. There are a number of shortcomings in such an analysis. It uses photographic prints in which there is a loss in resolution from the original microscope image and, at high magnification, the microscope has a very limited depth of focus. The dependence upon the human eye for quantitative discrimination is another serious fault.

It would be highly desirable to quantitate the chromosome parameters directly under the microscope. This would permit the separation of the chromosomes with greater precision. One of the most useful methods of karyotype analysis is to graph the relative length vs. the centromere index (centromere index, CMI, is the ratio of the length of the short arm to the total length of the chromosome) for all the chormosomes of the karyotype. To accomplish this, it is necessary to measure the lengths of both pairs of arms of each chromosome, from which may be determined:

1. the relative length (i.e., the length of one chromosome relative to that of a female haploid set); and

2. the centromere index. This kind of analysis requires a quantitation of the chromosome arm lengths.

In the past, a common method for measuring chromosome length has been to bend fine wire or string along photographic images of individual chromosomes and then subsequently measure the straightened material. This is obviously a very time consuming process. Other attempts at quantitation have involved area measurements with a planimeter or weighing cut-outs of individual chromosomes from photographic prints.

It is obvious that these relatively unsophisticated methods leave much to be desired for widespread usage. The other extreme in technological sophistication can be seen in a recently developed automated karyotyping system which involves an automated microscope to scan a prepared slide until the technician sees a group of suitable chromosomes and stops the scanner. The system then takes over, automatically sharpening the focus and enlarging the image a great number of times. A special data camera takes a picture of the chromosomes and transfers their nuclear images into a computer. The computer isolates, measures, and rotates each chromosome image until it is erect. The chromosome images are then numbered, classified, paired, and arranged in a customary karyogram. The resulting digital picture inside the computer is transferred to a photographic printer which turns out a picture of the karyogram on paper.

This method of chromosome characterization has attempted to replace the human's pattern recognition facilities with an automatic system which performs the same function. In doing so, the system reduces the chromosome image on the slide to the photographic form so that, as in the previously discussed manual method of chromosome analysis, the accuracy of the analysis is diminished by the loss of resolution in going from the "raw" image of chromosomes on the slide to the photographic image. Also, this automatic karyotyping method, for all its sophistication, does not produce quantitative data, such as the length of the chromosome arm, etc. All the system does is automatically prepare a karyogram. A quantitative measurement of the chromosomes in the karyogram would still have to be manually performed. A final serious drawback to the automatic system is that it is very expensive.

SUMMARY OF THE INVENTION

Briefly described, the present invention includes an apparatus for and a method of characterizing chromosomes which provide means for obtaining an image of at least one chromosome, means for converting the points along each of the arms of the chromosome into data form, and means for automatically computing various quantitative measurements for the chromosome, including the length of each arm and the centromere index.

It is, therefore, a primary object of this invention to provide an apparatus for and a method of effecting the analysis of chromosomes which automatically provide quantitative measurements of the same.

It is a further object of this invention to provide an apparatus for and a method of effecting the analysis of chromosomes which do not require personnel trained in the chromosome art to perform the analysis.

It is another object of this invention to provide an apparatus for the characterization of chromosomes which can be performed from a microscopic image of the chromosome and which does not require a photographic image of the chromosome.

It is still a further object of this invention to provide an apparatus for the rapid analysis of chromosomes that visually displays the computed quantitative measurements of the chromosomes.

Another object of this invention is to provide an apparatus for the analysis of chromosomes which is compact in design, simple in construction and use, economical to manufacture, automatic in its operation, and which is accurate and reliable.

A further object of this invention is to provide a means for automatically determining, from an image of a chromosome, a selected dimension of the chromo-

some by automatically sensing a plurality of points on the chromosome to develope coordinate relationships of the selected dimension.

Still other objects and advantages of the present invention will become apparent after reading the accompanying description of the selected illustrative embodiment of the invention with reference to the attached drawings wherein like reference characters have been used to refer to the like parts throughout the figures of drawings, and wherein:

BRIEF DESCRIPTION OF THE FIGURES OF DRAWINGS

FIG. **1** is a perspective view of the chromosome digitizing apparatus;

FIG. **2** is a top plan view of the digitizing surface;

FIG. **3** is a logic schematic of the skip and data control;

FIG. **4** is a logic schematic of the device selector;

FIG. **5** is a logic schematic of the flags and interrupt enable;

FIG. **6** is a logic schematic of the mode control and initialization;

FIG. 7A is a logic schematic of the X and Y scalers; and

FIG. 7B is a logic schematic of the X and Y scalers taken along the match line in FIG. 7A.

DESCRIPTION OF THE INVENTION

Referring now to the embodiment chosen for the purpose of illustrating the present invention, numeral **10** denotes generally the chromosome digitizing apparatus as depicted in FIG. **1.**

The apparatus **10** is composed of essentially four basic components: chromosome display means **11,** identifying means **12,** control instrument **13,** and an Input-Output (I/O) means **14.**

As shown in FIGS. **1** and **2,** the display means **11** includes a digitizing table **15** which comprises a digitizing tablet **16** having a flat glass surface **17** with at least two sides, a first sensing means **18** adjacent one of the sides and a second sensing means **19** adjacent an adjoining side. The sensing means **18** and **19** are microphones which can detect the sound of a spark generated by the identifying means **12** over the surface **17.** The table **15** also includes means (not shown) for illuminating from below the surface **17.** As seen in FIG. **2,** to the right on surface **17** appear the following labeled squares: ENTER NUMBER, CELL DONE, RESTART CELL, START NEXT CHROMOSOME, RESTART CHROMOSOME and RESTART ARM, numbered A, B, C, D, E and F, respectively.

A means for obtaining or forming the image of at least one chromosome includes an ordinary high power microscope **20** preferably a phase-contrast microscope into which is inserted a prepared slide containing the particular chromosome or chromosomes to be analyzed. Typically, magnifications of 1,500 diameters are required to amplify the images to visual size.

The preferred method of displaying the chromosome image is to superimpose the surface **17** and the identifying means **12** onto the plane of the chromosome image within the microscope. This is accomplished by such devices as a drawing tube or a camera ludica attachment **21** to the microscope **20.**

Also, the chromosome analysis accomplished by the apparatus **10** could be performed just as well from a negative or a microphotograph of the chromosomes which was placed on the surface **17** and illuminated from below. However, some resolution is lost in the transfer of the optical image to the photographic form, but the ease of the analysis is increased with the photomicrograph as compared to the use of the optical image because the need for superimposing the chromosome image in the microscope is eliminated and the operator does not have to manipulate a microscope **20** to observe the image.

Another method of displaying the chromosome image is to substitute a television camera for the eyepiece of the microscope **20.** The image will then be shown or displayed on a television monitor, the screen surface of which can be utilized as a digitizing surface by the placement of two adjoining microphones on the sides of the monitor screen.

Whatever display method is employed, the basic concept is the overlaying of the image of the chromosome with the identifying means **12.**

The identifying means **12** has two major functions:

1. to select an action to be undertaken by the control instrument **13** (via the labeled squares on surface **17**); and
2. to select and digitize the coordinate position of a chromosome and the length of its arms. The identifying means **12** includes a pen **22** which is capable of producing a spark when applied to surface **17.** The combination of the pen **22** and the tablet **15** form a spacial coordinate measuring means. A switch contact closure (not shown) within the body of the pen **22** is connected to the control instrument **13** so that each depression of the pen **22** upon the surface **17** is recognized and detected by the control instrument **13.**

The control instrument **13** is used for data acquisition and reduction and is essentially divided into three main components: the pen digitizer, the interface and the computer. The pen digitizer is the means for digitizing points along the chromatid arm, recording the position of the points relative to a reference point and converting this analog data to digital form.

The interface allows the computer to control the digitization process and read data from it. The interface is highly dependent upon both the characteristics of the pen **22** and the computer. It is preferable to make the interface and much of the electronics involved in the pen digitizer as a plug-in module to be installed in the computer mainframe.

The computer controls the pen digitizer and performs calculations on the data acquired by the digitizer. It also prepares the data output for the operator.

The I/O device **14** is depcited in FIG. **1** as a Teletype, a registered trademark of the Teletype Corporation machine which is connected to the control instrument **13.** A bell **23** is in the housing of the device **14.** The I/O device **14** is used by the operator to control the instrument **13** and is used by the control instrument **13** to signal an output data to the operator.

OPERATION

The first step in the operation of the apparatus **10** is that the power switch on the I/O device **14** be placed in the "Line" position and that the control instrument **13** have its power switch in the "On" position. The I/O device **14** will then type out a number of line-feeds, a page origin (two dashes), some more line-feeds, fol-

lowed by the message "PRESS RED AND BEGIN" and a carriage return. The message will be described hereinafter.

The next step of the chromosome digitizing procedure is to form an image of the chromosome or chromosomes. A human blood cell with 46 chromosomes will be used in this description, but it is understood, of course, that the method and apparatus of the present invention can be effectively utilized for the analysis of any type of chromosome.

The chromosome image is usually formed in a microscope **20,** as shown in FIG. **1.** This image is viewed as a superimposition of the image of the digitizing means **17** on the plane of the chromosome image within the microscope **20.**

To have the surface **17** superimposed on the plane of the image within microscope **20,** the operator peers through the eyepiece while having one hand holding the pen **22** poised over the surface **17.** The image of the tablet **16,** including surface **17** and the labeled squares A–F, plus the operator's hand holding pen **22** are superimposed onto the chromosome image by means of attachment **21.** Thus, the operator will see essentially the same view as FIG. **2** when looking through the eyepiece. Surface **17** and the pen **22** then appear as superimposed on the chromosome image. Since the lettering within the squares labeled ENTER NUMBER, etc. will be too small to be read through the microscope optical system, each labeled square is of a different color, thus providing a visual clue for the selection of the appropriately labeled square. The RESTART CELL square is colored red so that the initial message typed by the I/O device **14** ("PRESS RED AND BEGIN") is designed to tell the operator that the apparatus **10** is ready to start its measurement cycle upon his depression of pen **22** in the red or RESTART CELL square. This square will initialize the system to accept the beginning measurements of a cell.

If the image is superimposed on the surface **17,** external to the microscope, the operator does not have to be concerned any further with the microscope **20.** Regardless of how the image appears, though, the operator must adjust the image so that the individual chromosomes do not appear within the marked-off squares on the surface **17.**

After the "red" square has been depressed, the operator should then select a chromosome from the spread under the microscope **20.** The scheme for selecting chromosomes in a systematic way will vary with the particular operator, but one popular scheme is to measure from the top left-hand corner of the spread toward the right-hand corner (similar to the way the eye reads a book). The order really doesn't matter as long as it is consistent within a single cell and each chromosome is measured once and only once.

In order to measure the length of the chromosome arms, some reference point is determined. The preferred reference point is the centromere, with all other points on the chromosome being measured relative to that point.

Once the image is in position, the actual measurement of an individual chromosome is initiated by touching the pen **23** to the centromere of that chromosome. An audible spark is produced by the pen **22** which is picked up by the microphones **18** and **19.** The switch contact closure in the pen **22** informs the control instrument **13** that the pen **22** is depressed on surface **17.** The control instrument **13,** having detected the pen-down condition, causes the pen digitizer to record the X and Y coordinates as indicated. Since the speed of sound through air is known, the microphones **18** and **19** sense how long it takes for the sound of the spark to travel through the air from the point of the pen depression. The pen digitizer is then able to convert this time into X and Y coordinates relative to the edges of the surface **17** where the microphones **18** and **19** are located.

The control instrument **13** acknowledges the initial point by signaling the operator. This signaling can be accomplished by a visual signal, such as a flashing light, or an audible signal, such as bell **23** in the I/O device **14.** It is preferred that the signal be audible so that the operator does not have to look up from the chromosome image to see if the initial point and subsequent points were registered which is desired for rapid operation. When the centromere is touched by the pen **22,** the bell **23** in the I/O device **14** will ring twice and then print three sets of numbers, being, respectively, the chromosome number, the X-axis centromere coordinate and the Y-axis centromere coordinate. A chromosome number is assigned by the I/O device **14** to each chromosome measured. The X and Y axis coordinates are in arbitrary "tablet" units, and are provided mainly so that the operator can check that a chromosome is not being measured twice, since these two coordinates will be unique for each chromosome of the spread (provided that the relative position of the surface **17** and the microscope **20** are not changed during the measurement process).

Starting at the distal point of one chromatid arm, the pen **22** is moved point-by-point along the arm toward the centromere. Thus, the operator may plot straight line segments along the observed "middle" of the chromosome arm being measured, and the control instrument **13** will be able to read the X and Y coordinate of each of the points indicated by depression of the pen **22.** The bell is sounded once as each point is accepted by the control instrument **13.** The computer is provided with means for storing the location of the points relative to the reference point, the centromere. The distance between the points is accumulated as the length along the chromatid arm, until the operator comes within the "radius of closure" around the centromere (as it was originally defined), at which time bell **23** will ring twice informing the operator that the effective length of the chromatid arm has been measured. The value of the centromere point is used in computing the distance from the next-to-last point on the chromosome arm, so that the operator does not need to "find" the centromere exactly in order to obtain an accurate measurement. The sum of the distance between the points over the length of an arm is the "arm length," and the I/O device **14** will print out this length in arbitrary tablet units.

The sister chromatid arm (i.e. the arm that is most like the one just measured) is measured in the same fashion as above (starting at the distal point and moving the pen **23** along the arm until the centromere is reached). The other two arms are measured with the I/O device **14** printing out the length of the arm after each measurement.

When all four arms have been measured, the I/O device **14** will print the sum of the lengths of the arms as measured and the message "NEXT TASK" and wait

for the operator to select a labeled square on surface **17.** At this time, the operator should inspect the numbers printed on this line, which would look something like this:

1	490	1099	66	65	57	51	239	NEXT TASK
(chromosome number)	(X axis cent. coord.)	(Y axis cent. coord.)	(1st arm)	(2nd arm)	(3rd arm)	(4th arm)	(Sum of lengths)	

If these arm lengths appear to be reasonable (i.e. the first two arms nearly alike and the second two arms nearly alike), then the operator would select the square labeled START NEXT CHROMOSOME. This would cause the message "OK" to be printed indicating the operator's acceptance of the data so far and that the next chromosome is ready to be measured. The number for the next chromosome will be advanced automatically by the depression of the START NEXT CHROMOSOME square so that the operator will not have to specify the chromosome number explicitly.

When the final chromosome within the spread has been measured, the operator should depress the CELL DONE square with the pen **22,** which will cause the stored data to be printed out in the following summary format:

NO CMI RL

"NO" is the chromosome number, "CMI" is the centromere index (the ratio of the length of the shortest arm of a chromosome to the sum of the length of all the arms for that chromosome), and "RL" is the ratio of the relative length of each chromosome to the length of the longest chromosome (in percent). The CMI ranges from 0.5 to 1.0 and the longest chromosome will have a "RL" of 100.0.

This table of data is then followed by a data-plot, which uses the teletype as a crude (but effective) grahpical plotter. The X-axis is the "CMI" and the Y-axis is the "RL." The character "1" is printed for each chromosome in this plot, except when more than one point may lie "on top" of each other, in which case the character "2" or "3" will be printed, indicating the situation. Note that the axes are labeled in the same units as the listing of the summary data above, so it is easy to locate a particular chromosome in the data-aquisition listing (generated when the measurements were made), in the data-summary, and in the data plot. Thus, the operator can check the quality of the measurements by inspecting the printout from the I/O device **14.** This permanent record may then be removed from the I/O device **14** and used for subsequent analysis of possible genetic abnormalities.

A further step that may be accomplished by the I/O device **14** is the computation of the errors in measurement of the chromosomes and the fitting of the position of the chromosomes to the known positions within groups, thus producing a graph with all of the "normal" chromosomes removed, and only the abnormal ones remaining. This would be particularly useful in mass chromosome genetic studies undertaken on the general populace.

ERROR RECOVERY PROCEDURES

Much of the utility of the approach to measurements of chromosome morphology of the present invention lies in the interactive ability of the operator to correct his mistakes before they are propogated into other forms. Thus, most of the squares on the surface **17** are associated with correction of operator-detected errors in the measurement process. The apparatus **10** makes essentially no checks on the data as acquired, but provides the operator with very complete information on the process of measurements as they are made.

It is helpful to consider errors of the most common variety first. Usually, the operator will find that he has made some sort of error in "picking" a point along the chromosome arm as he moves the pen **22** toward the centromere. This is easily corrected by depressing the square marked RESTART ARM with the pen **22.** This will cause the control instrument **13** to cancel any of the points measured so far along the present arm. The I/O **14** will retype the information up to the end of the measurement of the previous arm on the next line, and wait for the operator to again select the distal end of the present arm, moving back along it toward the centromere as he goes. Note that the RESTART ARM square works even after the operator has "found" the centromere at the end of measuring the current arm. Thus, it is possible to correct a measurement of an arm if an error has been detected, at any time up to the time the next arm is selected (by picking its distal point).

The next most common error for the operator to find some error in the results after an entire chromosome has been measured and is waiting for instructions (NEXT TASK message has been printed). The operator can simply pick the RESTART CHROMOSOME square to cause the present chromosome measurement to be aborted. The control instrument **13** is now ready to re-define the centromere. Note that the RESTART CHROMOSOME square may be selected at any time during a chromosome measurement.

Usually, the operator will detect errors in measuring the chromosome before he goes to the next chromosome. However, the apparatus **10** does allow the operator to remeasure any chromosome(s) at random. This feature is selected by picking the ENTER NUMBER square on the surface **17.** The user must then type in on the keyboard of I/O **14** the number of the chromosome to be measured (restricted to 1–50), followed by striking the "return" key. At this time, the instrument **13** is setup to measure the specific chromosome (or remeasure it, if required) via the definition of the centromere by the operator. Note that the centromere definition coordinates are helpful in determining the chromosome to be re-measured in the spread. If the operator makes a typing error before striking the "return" key, he may delete all that has been typed by holding the key marked "CTRL" down, and pressing the "O" (letter **0**) key, which will cause a backarrow (←) to be printed.

Also note that the ENTER NUMBER square selects the chromosome to be re-measured strictly by user-provided number. The user should return to the sequence of measurements via the ENTER NUMBER square, when finished correcting the chromosomes that were just re-measured.

The rare situation will sometimes exist in which a chromosome will have one or more arms completely missing. In this situation, the operator can just pick the centromere immediately which will indicate to the instrument **13** a zero length for that arm. Thus, regardless of whether one or more arms is missing, the centromere must be picked four times for each chromosome measured.

Sometimes the operator will determine that the whole measurement process needs to be restarted (for example, a cell has been selected for measurement that is not suitable). In this case depressing the RESTART CELL square will abort the measurements so far recorded for that cell and allow the operator to restart on a new cell.

There are a number of I/O devices **14** that can be utilized to improve the operation of the system, but they are not essential and are of the nature of frills. The first is an oscilloscope which could be used to display the points and straight line segments between them as they are plotted by the operator. The face of the scope could also be used in place of surface **17** and thus could be superimposed upon the chromosome image which would facilitate the measurement process considerably. This feature is one that would be considered for systems where precision performance is of the utmost importance, and the cost is secondary.

A further embodiment of the display means **11** would be to replace the eyepiece of microscope **20** with a television camera. The image would be viewed on the screen of a television monitor, the screen surface serving as a digitizing surface by the placement of microphones (such as microphones **18** & **19**) on adjacent sides of the screen. The operator would then not have to peer through the microscope and there would be no need for the superimposing of any images.

Another I/O device **14** which could be used is a digital (or analog) plotter which could considerably improve the appearance of the output graph, but it would not increase the precision of the plotting, since the data limits the precision.

Another extra item could be additional storage means (such as magnetic tape) for the computer which would make further analysis and comparisons of measurements much easier, since the data would then be stored in a form convenient for calculation.

The most important feature of the present invention is that the operator is called upon to make all of the decisions concerning the measurements. The apparatus **10** is designed to relieve the operator of the tedium of the measurement process, but it does not make any decision as to what is being measured. The apparatus **10** is unique both in its reliance upon the operator's ability to recognize the chromosome patterns and its extremely low cost. In essence, the apparatus **10** provides the quantative ability, while the operator provides the qualitative ability, and together they make a team with high performance and low cost which is feasible to introduce into the laboratory. The process of measuring the chromosomes is not radically different from the present laboratory procedures, and thus the training and familiarization cost for user personnel is also minimized.

DETAILED DESCRIPTION OF CHROMATIZING APPARATUS

The following is a detailed description of the various elements of the chromatizing apparatus **10**, including the computer, the interface, and the computer program. The brand name, the model number and manufacturer source for these particular elements are mentioned in the following as the operation of apparatus **10** is highly dependent upon what type of components are utilized therein.

COMPUTER

The computer used in this embodiment is a Digital Equipment Corporation (D.E.C.) PDP8/E-AA with teletype and teletype control module, hardward boot strap module and chromosome digitizer interface module. The chromosome digitizer interface module plugs into the omnibus of the PDP8/E-AA exactly like all of the other omnibus processor options made by D.E.C. The omnibus is fully explained in the 1971 edition of the "Small Computer Handbook," published by D.E.C.

The preamplifier for microphones and Marx-Bank spark generator are purchased items from Science Accessories Corp. and are mounted on a plate in place of the second omnibus inside the PDP8/E-AA processor, and derive power from the PDP8/E-AA power supply.

Front Panel

The front panel for the instrument **13** has two controls and a light. The controls are a three position key-operated master power switch. The left OFF position of this switch disables all power to the computer. The middle POWER ON position enables power to the power ON-OFF switch, the right position enables computer power and automatically starts the hardward boot strap loader into operation for loading program tapes via the teletype paper tape reader. There is another switch labeled "Power-on-off" which is used by the operators. In normal operation, it is in series with the center and right position of the master keylock power switch. In the ON position, the computer power is enabled; in the OFF position, the computer powers down for later turn-on.

When the computer power is removed by either of the power switches, or external events, the hardware power fail option of the precessor detects the power "low" condition, and saves the contents of the active registers in magnetic core (which is non-volatile) for later restoration when the power is restored. The two-position toggle-type power switch will normally be operated by users to turn the unit ON and OFF. When the unit is turned ON, the program will take action to reinitialize the system for normal operation. When the power is enabled, a power light on the front panel is illuminated.

CONNECTORS

Teletype

The teletype connector is brought to the rear panel of the chromatizer so that the Teletype may be easily disconnected when moving the instrument. In normal operation, this connector MUST be connected to the teletype.

Marx-Bank Connector

This rear-panel connector is the one used for the pen and carries the signals from the Marx-Bank high-voltage generator to the spark gap of the pen and from the pen microswitch back through the Marx-Band unit to the chromatizer interface.

Microphone Connector

This is a twin co-ax connector which connects the output of the "X" and "Y" microphones to the input of the "X" and "Y" microphone connectors. This connector is also mounted on the rear panel of the chromatizer.

MARX-BANK GENERATOR

This unit contains a 500 volt power supply and five stage Marx-Bank voltage multiplier which is used to generate the very high voltage (but very low energy) spark utilized by the graph pen as a sound source for locating the coordinants of the pen. This unit is manufactured by the Science Accessories Corporation and is a standard card with a number of silicon controlled rectifiers and a proprietary (with SAC) control circuit. Input to this card is 380 volts a.c. RMS but very low current is required. The Marx-Bank is triggered by the negative transition of the Marx-Bank trigger from the chromatizer interface. The maximum rate of this device is 100 pulses per second.

X and Y MICROPHONE PREAMPLIFIERS

The sound pressure wave from the spark is amplified and turned into a negative pulse by the "X" and "Y" microphone preamplifiers. The circuitry in this unit is proprietary to the Science Accessories Corporation, and the unit is a standard production item from them. The outputs of these two preamplifiers clear the "X" and "Y" IN-PROGRESS flip-flops at the end of the digitization cycle.

GRAF-PEN TABLET

The Graf-pen, a registered trademark of the Science Accessories Corporation tablet consists of a **14"** square glass surface, two linear microphones along the top and lefthanded edges of the tablet, and the pen containing the spark gap, pen microswitch, and ballpoint pen. These items are catalog items from the Science Accessories Corporation,

W966 PDP8/E INTERFACE BOARD

It is a single module and contains **40** integrated circuits. Referring to FIGS. **3–7B**, the interface basically consists of two 12 bit scalers, device selection logic, a four bit command register and the appropriate control circuitry for controlling the digitization process.

Command Structure

The device code 630X where "X" ranges from **0–7,** the code used to control the chromatizer interface. The device codes are assigned as follows:

I.O.T.	MNEMONIC	FUNCTION
6300	GPMS	Skip if maintenance switch enabled
6301	GPSF	Skip if done or overflow
6302	GPCR	Function main command register AC0 (1) Enable interrupt on "Done" AC1 (1) Enable interrupt on "Overflow" AC2 (1) Enable interrupt on "pen change" AC3 (1) Enable Auto Digit Mode
6303	GPSP	Skip if Pen Changed If Pen Up, Acc = ϕ If Pen Down, Acc = 4000
6304	GPCL	Clear All
6305	PPST	Start Digitization
6303	GPRX	Read "X" register
6307	GPRY	Read "Y" register

The maintenance switch is mounted on the interface board and is used to enable program modifications by maintenance personnel.

Device Selection Logic (Refer to Logic Schematic, FIGS. **3–7B**)

The device code selection is accomplished by four SP380, one SP384 and one SP314 gates. They are wired to decode device 630X and when that code is detected by the device selection circuitry, 630N SELECT H is generated. **630N** SELECT H will enable the INTERNAL IOT level via the gate at **E27. 630N** SELECT H is inverted by the gate at E-**15** to create **630** N SELECT L which enables MD**9, 10** and **11** to select the correct IOT code via the binary-to-octal decoder at E-**36.** E-**36** has eight outputs, each of which are asserted at ground. The device selection code **630N** SELECT L is ANDed with an inverted version of TP **3** to create PC1K H and, through an inverter, PCLCK L. These pulses are used elsewhere in the circuitry to enable IOT's. Note that the binary-to-octal decoder is enabled only when **630N** SELECT L is true, this inhibits all eight outputs when IOT **630N** is not being generated. In order to properly condition lines C-O and C-**1,** of the OMNIBUS in the PDP**8**/E it is necessary to select C-O to ground for some of the IOT's used by this device. C-O is grounded when either **6302**L, **6306**L, **6307**L or **6303**L are asserted to gate E-**22.** C-**1,** is grounded when **6303**L or **6306**L or **6307**L are asserted. The GRAF-PEN Command Register are coded from bits **0, 1, 2** and **3** of the accumulator. Bit **0,** enables an interrupt upon completion of the digitization operation (DONE FF = 1). Bit 1, enables INTERUPT-IF-OVERFLOW [either X-OVERFLOW = (1) or Y-OVERFLOW = (1)] occurs and bit **2,** enables an interrupt if the pen changes state. (raise or lower) Bit 3, when set, enables the autodigitization mode (see below). The command register is loaded by GPCR (IOT-**6302**)

When the AUTO-DIGITIZER-MODE flip-flop at (E-**3**) is not set, the interface is in so-called normal mode. In the normal mode, the start-digitization-signal (IOT **6303**) will immediately begin a digitization cycle which consists of a 40 micro-second delay (from E–**34**) at the end of which the X-IN-PROGRESS and Y-IN-PROGRESS flip-flops are set. Simultaneously, with the start of the initial delay, the spark is generated by the Marx-Bank generator. When pulses arrive from the "X" and "Y" microphone preamplifiers, these flip-flops will be cleared and the "DONE" flag will be set. If either microphone does not recieve a pulse, then over flow (for either "X" or "Y") is detected in which case the "DONE" flag is inhibited but the "OVERFLOW" flag is set. This normal mode of operation may be used for both point-plotting and continuous-curve-following. This mode of operation is not used in the current version of the chromatize but is available in the interface for later usage if required.

Auto-Digitize Mode

When AC Bit **3** and IOT **6302** is generated the autodigitize mode is enabled. In this mode the start of a digitization cycle is inhibited until the user depresses the pen against the tablet at which time the delay is started, the spark is generated, and the digitization cycle is entered. At the end of the digitization cycle "DONE" or "OVERFLOW" will create an interrupt if the appropriate bit of the GPCR is enabled (bits 0 & 1 of the GPCR). When the AUTO-DIGITIZE-MODE is enabled the pen change flag is inhibited (Bit 2 of the GPCR).

Maintenance Switch

IOT, **6300** is used to test the state of a switch labeled MS, this switch is installed in the module containing the digitizer interface. When the switch is closed IOT **6300** will cause a skip. When this switch is enabled the maintenance mode is available to the programmer which means that programs may be changed by striking control "O" on the teletype keyboard. The normal users of this equipment will not have the maintenance switch available to them which means that they cannot make program modifications or changes, a desirable feature in order to prevent mistakes. The pen microswitch is brought onto the interface board via I/O connector Pen "P." After going through a suitable switch filter it comes to the D-gate of the "PEN-DOWN" flip-flop. The "PEN-DOWN" flip-flop is clocked (at the C input) every clock cycle. Thus, the first clock cycle after the pen is depressed against the glass will cause a transistion from 0 to +3 volts at "PEN DOWN" (1). A differentiator (consisting of a 0.0022 micro-farad compacitor and a 350 ohm resistor) will create a pulse at E-**5,** pin **2,** (negative going) at the time the pen is depressed against the glass. "PEN-DROP" H is the inversion of this signal and is used in auto-digitization mode to start a digitization cycle. When the pen rises, another differentiator similar to the one mentioned above, generates a negative going pulse at E-**5** pin-**4.** The negative going pulse at E-**5,** pin **4** or E-**5,** pin **5** generates a position going pulse labeled "PEN-CHANGE" H at E-**4,** pin-**11.** This is used to clock the "PEN-CHANGE FLAG" to a 1, if it is already in an "0" state, and the auto-digitiz mode is not enabled. Thus, in normal mode the "PEN-CHANGE FLAG" will be set everytime the pen changes from either pen-down, or pen-up state. This flag may create an interrupt if its interrupt is enabled by the flip-flop which may be set by AC Bit 2, and **6302** IOT. Thus, the programmer who is using normal mode can raise an interrupt when the pen changes state and make use of this fact in his program.

Clear All

The "CLEAR ALL" may be generated by INITIALIZE from the OMINBUS or IOT **6304** L. "CLEAR-ALL" clears the three interrupt enable flip-flops, the "PEN-CHANGE FLAG," the "DONE FLAG," the X and Y scalers, the OR GATE at E-**22-13** clears the auto-digitize mode, AUTO-DIGITIZATION-IN-PROGRESS and the "X" and "Y" IN-PROGRESS flip-flops. "CLEAR-ALL" may be used at any time to abort and/or inhibit operations of the chromatizer interface.

Skip Line Requests

Skips are requested by DONE-FLAG on a (1) or OVERFLOW H ANDed with **6301** H thus, the IOT-**6301** is effectively skip on done or overflow. The skip is also requested for **6303** H and "pen-change" flag on a (1). Skip is also requested for **6300** H and maintenance switch enabled. The four gates that can create the skip condition R on E-**31.**

Done Flag

The "DONE-FLAG" is set at the end of a digitization operation by the transition of both "X" and "Y" "in-progress" to the zero "0" state. The OVERFLOW H into the D-input of E-**17** ("done-flag") will clear the "DONE-FLAG" rather than set it, but an interrupt may still occur if the overflow interrupt is enabled. "OVERFLOW" H is generated at E/**16-13** by the condition of either "X" overflow on a (1) H or a "Y" overflow on a (1) H. The done flag is cleared either by "CLEAR-ALL" or IOT **6305** (start digitization mode). If the "done-flag" is up and the done interrupt is enabled (E-**18** and **5**) then an interrupt request will appear at the omnibus.

Pen-in-Progress Flip-Flops

There are two logically similar flips-flops IN-PROGRESS and Y-IN PROGRESS, these flip-flops are cleared by STOP L which is CLEAR ALL or OVERFLOW HIGH or DONE on a (1) low. They are set at the end of the 40 micro-second delay at the beginning of a digitization cycle. When these flip-flops are set clock pulses accumulate in the 12 Bit "X" and "Y" scalers which continue to accumulate clock pulses until the "X" microphone of "Y" microphone preamplifiers deliver a ground going pulse to the input to the inverters at E-**14,,** pin **1,** and E-**38,** pin **3.** If more than 2048_{10} pulses arrive for either "X" or the "Y" scaler, the "X" OVERFLOW on a (1) high or the "Y" OVERFLOW on a (1) high levels will be asserted, which will cause "OVERFLOW" H which will generate "STOP" L via the four input NOR gate at E-**22.** STOP will clear "X" and "Y" IN-PROGRESS and strobe the inversion of "OVERFLOW" H into the "DONE-FLAG". Thus, the largest number that either the "X" or "Y" scalers may accumulate is 4000_8. "OVERFLOW" H is normally an error condition and the users program will normally test the content of the "X" and "Y" registers to determine if overflow has occurred.

"X" and "Y" Registers

The "X" and "Y" registers are identical 12 Bit scalers as mentioned above which are reset by RESET HIGH and read into the PDP **08**/E accumulator by **6306** L (in the case of the "X" register) or **6307** L (in the case of the "Y" register).

Clock

Since the PDP-8E timing is derived from a 20MHZ crystal clock, TP2 and TP4 are used as the clock for the interface. SP**380** at E-**11** generates CLOCK whenever TP2 and TP4 is generated by the processor. This has an interesting implication in that when the processor is halted TP2 and TP4 are inhibited and thus, the clock pulses are not generated when the processor is stopped.

Testing the Pen State

The pen microswitch may be tested (at any time) by use of the IOT **6303,** which will set AC Bit zero "0" of the accumulator if the pen is down and clear all the other bits of the accumulator is up.

Marx-Bank Trigger

The Marx-Bank trigger is derived from the leading edge of the 40 microsecond initial delay. This delay is used to inhibit the circuitry during the initial Marx-Bank pulse time since the pulse generates large transients in the signals into the interface, which might cause spurious conditions to be detected. It is the negative going transition of the Marx-Bank trigger pulse that creates the spark. At the end of the 40 microsecond delay the pulse at E-**46-8** called "DELAY" L is generated which sets the "X" IN-PROGRESS" and "Y" IN-PROGRESS" flip-flops.

Simulation Using IOT **6300**

IOT **6300** L is brought to pin R of the I/O plug. This pulse may be umpered to either pin L or pin N of that plug when the normal connection to the "X" and "Y" microphone preamplifier is not made. Thus, the processor may create a dummy "X" and "Y" microphone preamplifier signal which can be used for maintenance

purposes. This feature is especially useful when testing the various bits of the "X" and "Y" scaler.

CHROMATIZER PROGRAM

The program for the control instrument **13** consists of 3968 octal numbers, which must be core-resident in a Digital Equipment Corporation PDP8/E-AA. The following "core-dump" is the listing of the numbers in octal format. The leftmost column is the address (also in octal) of the location whose contents is in the second column from the left, and each column from the left is the contents of the next location in core. Any user of a PDP8 could easily devise a program to accept the numbers from the I/O device **14** and place them in the corresponding core locations.

0000	3507	5473	7000	7000	7000	0013	0100	6600	5332	5273
0012	6535	5576	3117	0000	0000	5333	0000	7715	2415	5272
0024	0000	5272	0000	5332	0000	5576	0006	0261	0000	5576
0036	0000	0215	0000	0000	0000	0000	0000	0000	0000	0024
0050	0000	7003	2004	7124	7735	0000	0000	0000	5332	0000
0062	0000	2676	3477	4000	0215	5050	0005	0215	6541	2603
0074	0215	6536	7700	0256	7701	7600	7760	0177	0017	0277
0106	7776	7477	0260	7540	7522	7563	7775	7773	7767	0077
0120	0200	4000	2031	2156	6115	6200	6400	3140	3664	3664
0132	2020	2415	0501	0540	0511	0543	0555	2264	2473	1323
0144	0727	3307	2156	2433	0301	2232	2351	1562	1531	1540
0156	2036	0752	0706	2063	2726	0523	0000	3046	1170	5564
0170	7620	2556	4533	4545	0754	0000	2741	7610	5576	1133
0202	3022	7001	3475	3026	1031	3013	1225	4545	1060	3010
0214	3062	1060	3027	4546	4543	6531	2041	4542	5217	0252
0226	4542	4542	1060	3017	3020	4541	1031	3013	4554	4555
0240	5361	5270	2026	4550	1121	1065	7640	4562	1060	3010
0252	3062	1067	3410	4554	7410	4541	4542	1066	1113	7640
0264	5257	4561	4552	5177	5671	3165	1422	7450	5177	3022
0276	1022	7001	5231	0244	4554	4555	7410	5770	7200	3036
0310	4771	1047	0372	1046	7640	4562	1047	4553	7004	3067
0322	4555	4541	4555	5337	5351	1054	7106	1054	7004	1067
0334	3067	4541	4555	4562	5351	1054	1067	3067	4541	4555
0346	5337	7410	4562	7100	1067	0101	7640	7020	1067	0103
0360	7460	4562	7640	1373	7020	7004	3065	5701	3246	6000
0372	7740	2000	3516	3547	2015	2011	3226	3400	3644	3641
0404	3557	0240	0240	0240	0240	0240	0531	7240	1013	0534
0416	7240	1013	3013	5615	4550	1022	4536	4537	0017	4537
0430	0065	1065	7710	5265	4551	7000	1023	3011	1411	4557
0442	4562	4534	0613	4540	0065	1422	7450	5273	7001	3030
0454	1065	7740	5262	1430	4557	5273	1430	3067	5227	4551
0466	4562	4534	0615	4540	0065	4540	0017	4563	3022	5700
0500	0616	0272	6201	7301	1301	4536	1701	5341	3154	0272
0512	6201	3413	6201	1031	7141	1013	7630	4562	5711	0541
0524	3311	4215	6201	1413	6201	1311	3311	4215	1311	5723
0536	1133	3022	4563	3301	5701	0000	7240	1743	3011	2343
0550	4710	1411	4536	4772	5743	0000	7301	1755	3011	2355
0562	4710	4563	3411	7344	1011	3011	4772	5755	3160	2740
0574	0212	0217	0226	1112	1153	1153	2725	1102	0615	0615
0606	0621	7472	4550	4551	4562	1023	3022	4541	1066	1113
0620	7650	5535	4544	1401	5215	1066	0242	4536	4541	4544
0632	1401	7410	5230	4563	4543	1002	0163	4562	0337	4550
0644	2026	4551	5275	1067	7640	4547	4541	4545	1066	1113
0656	7640	5252	1423	7450	5277	7001	3030	1065	7700	1430
0670	4557	5301	1430	3067	5245	1023	5261	3026	5535	1065
0702	7750	5277	4545	5272	2373	4554	4544	1767	5706	1066
0714	2306	1207	7650	5325	4555	5706	7410	5706	2306	2306
0726	5706	2164	1727	3012	1412	7510	5346	7041	1066	7640

0740	5332	1727	7040	1012	3054	7410	2327	2327	7300	5727
0752	0000	0101	7041	3071	1067	0101	1071	7650	2352	5752
0764	6046	1036	7640	5372	4541	5764	4546	4543	7176	3210
0776	5764	1046	0615	0615	0621	0323	0306	0311	0304	0307
1010	0303	0301	0324	0314	0305	0327	0315	0321	0322	0212
1022	0302	0317	4560	4651	5356	4652	1106	3032	1045	7510
1034	2032	7750	2032	7410	5650	4543	1402	7374	4541	5241
1046	4541	5236	6515	1601	2050	4534	1407	4554	1066	1365
1060	7440	4562	1030	7000	7000	4536	4534	1612	4563	3030
1072	4407	6430	0000	7000	4543	1402	7200	4562	1030	4536
1104	4534	1612	4543	1402	7174	4562	4537	2031	4534	1612
1116	4537	2031	4537	0017	4534	0615	4540	0017	4540	2031
1130	4540	3175	4563	3030	4407	0430	1751	6430	2522	0000
1142	7000	1045	7740	5535	1030	4536	4537	3175	5316	4537
1154	2413	5316	4563	7300	5227	7000	7000	7000	7000	7503
1166	1053	1053	6512	0422	0610	0621	1207	1210	2725	2367
1200	0643	1265	0177	0536	2725	2725	6511	7240	3056	3026
1212	4543	1374	0172	2056	5235	4534	1407	1066	4536	1264
1224	4545	2036	7001	4526	7000	4563	3066	5207	7000	4534
1236	1613	4525	5210	2026	4541	4543	1407	0775	4545	5242
1250	4541	4550	1067	3052	5211	1074	4463	7040	1074	4545
1262	4541	5211	0272	4550	4551	4562	1060	3010	3062	1067
1274	3410	1010	3027	4464	3475	2026	4541	4545	4543	6534
1306	2636	4542	5302	1060	7001	3010	3062	4546	4543	6527
1320	2636	4542	5315	0222	7450	1066	7041	3071	1723	2323
1332	3012	1412	7510	5347	1071	7640	5333	1012	1723	3071
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6604	1600	7450	5600	3262	1262	0120	7650	5216	1101	0200
6616	3040	1103	0262	1040	3040	1263	0262	7650	5231	1440
6630	3040	2200	7040	1040	3015	1262	7106	7006	0104	7450
6642	5267	1264	3262	1662	7450	5265	3262	1304	3014	1114
6654	3057	1415	3414	2057	5255	5662	0000	0400	6773	1303
6666	5273	1303	3015	7040	1040	3014	1114	3057	1414	3415
6700	2057	5276	5201	0043	0037	4765	4770	5201	4772	4771
6712	4773	4767	5201	1045	7640	5325	3044	3045	3046	3047
6724	5201	4537	0044	4537	0040	4540	0044	4453	7510	5342
6736	7040	3262	3043	1045	7640	4562	4537	2413	4540	0044
6750	4540	3175	5360	4537	3175	4540	0040	4766	2262	5353
6762	5201	4766	5201	7353	7204	7535	7023	6154	7157	6133
6774	6706	6705	7307	6763	6715	0000	6713	0000	7300	1047
7006	7041	3047	1046	7040	7430	7101	3046	1045	7040	7430
7020	7101	3045	5603	0000	1045	7450	1046	7650	5311	1041
7032	7450	1042	7450	1043	7650	5623	1040	7041	1044	7450
7044	5273	3203	1203	7500	7041	3322	1322	1336	7710	5275
7056	1203	7700	5265	4357	2322	5261	5273	7040	1040	3040
7070	4723	2322	5270	2223	5623	1040	7700	5304	1044	7700
7102	5623	5306	1044	7700	1203	7740	5623	1040	3044	1041
7114	3045	1042	3046	1043	3047	5623	0000	6154	0000	4751
7126	1044	7750	5353	7001	3043	1350	3040	4223	0027	2047
7140	5344	2046	7410	2045	3047	4752	1046	5724	0027	5771
7152	7373	3044	3045	3046	5344	0000	7300	1045	7510	7020
7164	7010	3045	1046	7010	3046	1047	7010	3047	2044	5757
7176	5757	0337	0377	0212	0375	7777	0000	7001	1040	4324
7210	7710	4353	3301	3300	3277	3276	1045	3751	1041	4752
7222	0002	1042	4752	0003	1046	3751	1041	4752	0003	1042
7234	4752	0004	5263	3274	1043	3751	1045	4752	0004	1046
7246	4752	0005	1047	3751	1041	4752	0004	1042	4752	0005
7260	1043	4752	0006	1301	3045	1300	3046	1277	3047	4301
7272	3047	5604	7004	1045	1041	7420	5304	0000	2050	4451
7304	4747	2047	5701	1041	7650	4562	1040	7041	7001	4324
7316	7700	4353	4750	4301	5723	6601	0000	1044	3044	1121
7330	0045	1041	7700	7040	3050	1045	7450	5746	7710	4451
7342	1041	7450	5746	5724	6720	7535	7461	7456	7400	0000
7354	7300	1043	7041	3043	1042	7040	7430	7101	3042	1041
7366	7040	7430	7101	3041	5753	0000	1050	7710	4451	5773

7400	0000	7450	5600	3254	3253	1257	3255	7100	1254	7010
7412	3254	1253	7420	5220	7100	1256	7010	3253	2255	5210
7424	1254	7010	3255	1600	7041	1252	3254	1255	7100	1654
7436	3654	2254	7004	1253	1654	3654	7420	5600	2254	2654
7450	5600	5246	7302	0000	0000	0000	0000	7764	7751	0000
7462	3200	3254	1260	3255	7410	4524	7100	1042	1046	3256
7474	7004	1045	1041	7420	5304	3045	1256	3046	7200	1254
7506	7004	3254	1200	7004	3200	2255	5267	1254	3046	1200
7520	3045	5661	7004	3335	2255	5267	1335	3045	1200	3046
7532	1254	3047	5661	0000	4775	4366	1045	7450	1047	7450
7544	1046	7650	5363	1045	7104	7710	5360	4524	7140	1044
7556	3044	5347	4776	4366	5735	3044	5735	7157	0000	1045
7570	7510	7041	7710	4765	5766	5771	7373	7000		

It is obvious that one skilled in the art may make modifications in the details of construction without departing from the spirit of the invention which is set out in varying scope in the appended claims.

We claim:

1. A method for the automatic characterization of chromosomes, comprising the steps of:

a. displaying an image of a chromosome;

b. locating a reference point on said chromosome;

c. registering the location of said reference point;

d. advancing an identifying means from the distal end of each of the arms of said chromosome to approximate engagement with said reference point; and

e. computing the effective length of each of said arms.

2. A method as described in claim **1,** including the step of superimposing said identifying means onto said image.

3. A method as described in claim **1,** including the step of detecting a plurality of points along said arm.

4. A method as described in claim **3,** including the step of recording the location of said points relative to said reference point.

5. A method as described in claim **4,** including the step of converting said points into coordinate pairs.

6. A method as described in claim **5,** including the step of computing the centromere index for said chromosome.

7. A method as described in claim **6,** wherein said image includes a plurality of chromosomes of a particular cell.

8. A method as described in claim **7,** including the step of computing the arm ratio and the length ratio of said chromosomes.

9. A method as described in claim **8,** including the step of plotting said arm ratio versus said length ratio.

10. A method as described in claim **9,** including the step of recording said effective length, said arm ratio, said length ratio, and said centromere index.

11. An apparatus for the automatic characterization of chromosomes, comprising in combination:

means for displaying an image of a chromosome;

manual selection means for selective registration with discrete points of said image;

means for identifying a plurality of points selected by said manual selection means along the length of each of the arms of said chromosomes relative to a reference point on said chromosome; and

means for computing the effective length of each of said arms from said plurality of points identified with respect to said reference point.

12. An apparatus as described in claim **11** wherein said image is a microscopic image.

13. An apparatus as described in claim **11** wherein said image is a photographic image.

14. An apparatus as described in claim **11** wherein said reference point is the centromere of said chromosome.

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