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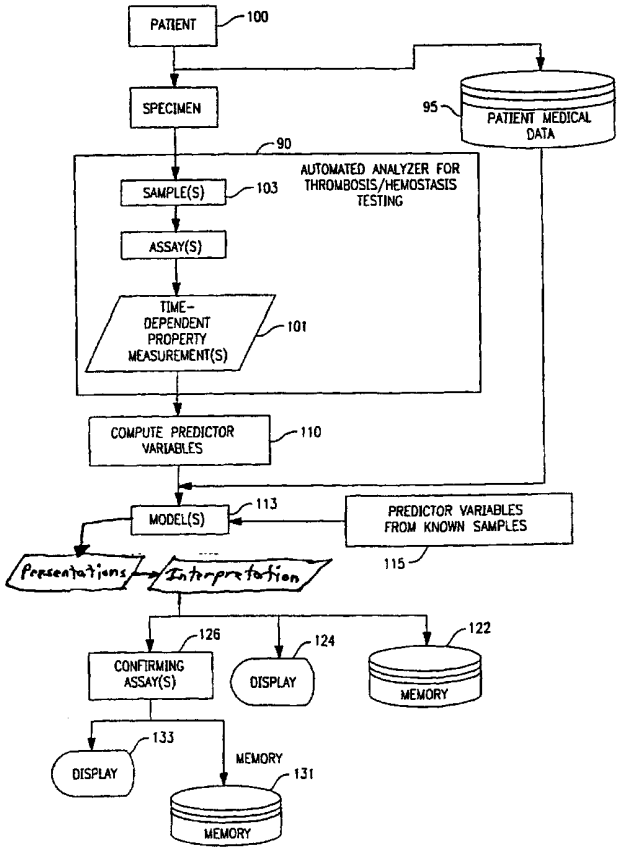
(54) Title: METHOD AND APPARATUS FOR PRESENTING THROMBOSIS AND HEMOSTASIS ASSAY DATA



(57) Abstract: A method is disclosed for presenting data from an assay relating to thrombosis-hemostasis on an unknown sample (103), and data from a plurality of assays relating to thrombosis-hemostasis from known sample populations. Data is provided from at least one time dependent measurement profile for each of a plurality of known blood samples and a respective property over time is measured so as to derive at least one time-dependent measurement (101) for an unknown blood sample (103). Data from these steps are transformed to one or more predictor variables (110) from which a topological feature map (113) is created which has spatial locations that correspond to intrinsic features of the predictor variables (110). A determination is made of the position on the map (113) of the unknown sample (103) corresponding to its set of predictor variables (110) and then a presentation is made of the data from the unknown blood sample time-dependent measurement profile (101) relative to the data from the known blood sample time-dependent measurement profile.

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

Method and Apparatus for Presenting Thrombosis and Hemostasis Assay Data

BACKGROUND OF THE INVENTION

This application is a continuation-in-part of U.S. patent application 09/001,647 to Braun et al., filed December 31, 1997, the subject matter of which is incorporated by reference. This application also relates to U.S. patent 5,646,046 to Fischer et al, the subject matter of which is incorporated herein by reference. This application is further related to the following publications, the subject matter of each also being incorporated herein by reference:

1. B. Pohl, C. Beringer, M. Bomhard, F. Keller, The quick machine - a mathematical model for the extrinsic activation of coagulation, *Haemostasis*, **24**, 325-337 (1994).

2. I. Talstad, Which coagulation factors interfere with the one-stage prothrombin time?, *Haemostasis*, **23**, 19-25 (1993).

3. P. Baumann, T. Jurgensen, C. Heuck, Computerized analysis of the in vitro activation of the plasmatic clotting system, *Haemostasis*, **19**, 309-321 (1989).

4. C. Heuck, P. Baumann, Kinetic analysis of the clotting system in the presence of heparin and depolymerized heparin, *Haemostasis*, **21**, 10-18 (1991).

5. T.Kohonen, The Self-organizing map, *Proc. IEEE*, **78**, 1464-1480 (1990).

6. M. Zweig and G. Campbell, Receiver-operating characteristic (ROC) plots: a fundamental evaluation tool in clinical medicine, *Clinical Chemistry*, 39, 561-577 (1993).

Thrombosis and hemostasis testing involves the in vitro study of the ability of blood to form clots and to dissolve clots in vivo. A variety of coagulation (hemostasis) assays are used to identify congenital or acquired disorders of the coagulation system and to monitor the administration of therapeutic drugs.

Two assays, the PT and APTT, are widely used to screen for abnormalities in the coagulation system, although several other screening assays can be used, e.g. protein C, fibrinogen, protein S and/or thrombin time. These assays usually measure clot time, the time required to initiate clot formation following the addition of a coagulation activating agent to blood or plasma. (Some variations of the PT also use the

amplitude of the change in optical signal to estimate fibrinogen concentration). Automated methods determine clot time based on changes in electromechanical properties, clot elasticity, light scattering, fibrin adhesion, impedance or other properties. For light scattering methods, data is gathered that represents the transmission of light through the specimen as a function of time (one example of an optical time-dependent measurement profile).

Blood coagulation is affected by administration of drugs, in addition to the vast array of internal factors and proteins that normally influence clot formation. For example, heparin is a widely-used therapeutic drug that is used to prevent thrombosis following surgery or under other conditions, or is used to combat existing thrombosis. The administration of heparin is typically monitored using the APTT assay, which gives a prolonged clot time in the presence of heparin. Clot times for PT assays are affected to a much smaller degree since a number of plasma abnormalities or therapeutic conditions may cause a prolonged APTT result, one or several additional tests are needed to isolate the exact source of the abnormality. The ability to discriminate between these effectors from screening assay results

may be clinically significant.

The present invention was conceived of and developed for presenting the relationships between an unknown sample and samples from known populations. The invention is intended to facilitate analysis of information embedded in the data from coagulation assays that is not included in the conventional data analysis for these assays. The additional information can help discriminate between underlying conditions and aid in the identification of otherwise undetected conditions.

SUMMARY OF THE INVENTION

The present invention is directed to a method for presenting the relationship between data from an assay relating to thrombosis-hemostasis on an unknown sample, and data from a plurality of assays relating to thrombosis-hemostasis from known sample populations, including:

(a) providing data from at least one time-dependent measurement profile for each of a plurality of known blood samples (the blood samples can be whole blood, or a portion thereof such as plasma);

(b) measuring a property over time to derive at least one time-dependent measurement for an unknown blood sample;

(c) transforming data from steps (a) and (b) to a plurality of predictor variables which sufficiently capture the information content of the time-dependent measurements from both the known blood samples and unknown blood sample;

(d) presenting the data from said unknown blood sample time-dependent measurement profile relative to the data from said known blood sample time-dependent measurement profiles using the presentation method of either steps (e), (f) , and (g), or steps (h) and (i);

(e) creating a topological feature map of the sets of predictor variables from step (c) of the known samples in step (a) whose spatial locations within the map correspond to intrinsic features of the sets of predictor variables;

(f) determining the position on the map of the unknown sample corresponding to its set of predictor variables;

(g) presenting the data from said unknown blood sample time-dependent measurement profile relative to the data from said known blood sample time-dependent measurement profiles;

(h) computing the standard deviation for each predictor variable in step (c) of the known samples in step (a);

(i) determining the z-score of the unknown sample in (b) for each predictor variable, and determining if one or more of the z-scores for the unknown sample is greater than a predetermined limit, signifying that the unknown sample is different from the known population represented by the model.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 is an optical profile with first and second derivatives of a normal clotting sample;

Figure 2 is a chart listing examples of predictor variables for use in the present invention;

Figure 3 shows SOM contour plots derived from APTT optical data for six specimen categories; (1) normal donors, (2) heparinized samples, (3) specimens with elevated fibrinogen, (4) specimens with low fibrinogen, (5) specimens from patients receiving oral anticoagulants, and (6) specimens with low factor concentration (Factor II,V,VII,VIII,IX,X,XI, or XII);

Figure 4 shows SOM contour plots derived from PT optical data for six specimen categories (1) normal donors, (2) heparinized samples, (3) specimens with elevated fibrinogen, (4) specimens with low fibrinogen, (5) specimens from patients receiving oral anticoagulants, and (6) specimens with low factor concentration (Factor II,V,VII,VIII,IX,X,XI, or XII)

Figure 5 is an ROC plot for identification of "normal" (negative) and "abnormal" (positive) samples using a PT clot time alone and using all predictor variables (if one or more predictor variables is outside x SD's of the normal range, than the sample is considered "positive", where x is 1sd, 2sd, 3sd, etc).

Figure 6 is an ROC plot for identification of "normal" (negative) and "abnormal" (positive) samples using an APTT clot time alone and using all predictor variables (if one or more predictor variables is outside x SD's of the normal range, than the sample is considered "positive", where x is 1sd, 2sd, 3sd, etc).

Figure 7 is a diagram illustrating key aspects of the present invention.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

In the present invention, both a method and apparatus are provided for presenting data from an unknown specimen as a function of known specimen population or populations. As can be seen in Figure 7, one or more time-dependent measurements (101) are performed on an unknown sample (103). The term "time-dependent measurement" is referred to herein to include (but is not limited to) measurements derived from assays (e.g. PT, APTT, fibrinogen, protein C, protein S, TT, and factor coagulation-based assays).

The term "unknown sample" refers to a sample, such as one from a medical patient (100), where a congenital or acquired imbalance or therapeutic condition associated with thrombosis/hemostasis is not known (or, if suspected, has not been confirmed). In the present invention, a coagulation property is measured over time so as to derive a time-dependent measurement profile. In a preferred embodiment, the time-dependent measurement is an optical measurement for deriving an optical profile corresponding to changes in light scattering and/or light absorption. For example, a PT profile, a fibrinogen profile, a TT profile, an APTT profile and/or variations thereof can be provided where, an unknown sample is analyzed for clot formation based on light transmittance over time through the unknown sample. In another preferred embodiment, optical measurements at two (or more) wavelengths can be taken over time so as to derive multiple optical profiles. In another preferred embodiment, two (or more) optical profiles are provided, such as both a PT profile and an APTT profile.

In one embodiment of the present invention, the method is performed on an automated analyzer (90). The time-dependent measurement profile, such as an optical data profile, can be provided automatically by the automated analyzer, where the unknown sample is

automatically removed by an automated probe from a sample container to a test well, one or more reagents are automatically added to the test well so as to initiate the property changes within the sample which are monitored, and recorded by the analyzer.

After the time-dependent measurement profiles are provided, a set of predictor variables are defined (110) which sufficiently define the data of the time-dependent profiles. In a preferred embodiment, nine predictor variables were used. In this approach, the optical data for a PT or APTT assay was divided into three segments (a pre-coagulation segment, a coagulation segment and a post-coagulation segment) using divisions based on the minimum and maximum value of the second derivative for changes in optical signal with respect to time. Parameters included: 1) the times at which the onset, midpoint and end of the coagulation phase occur; 2) mean slopes for the pre-coagulation phase and the post-coagulation phase and the slope at the mid-point of coagulation; 3) terms for coagulation "acceleration" and "deceleration"; and 4) the magnitude of signal change during coagulation. Figure 1 shows a typical optical profile based on transmittance and the associated derivatives. The parameters are defined in Figure 2.

After defining the set of predictor variables, a model (113) is derived which represents the set of

predictor variables from the known populations of specimens. This model can be derived from a topological feature map in one embodiment of the present invention. In another embodiment, the model is derived via a set of statistical equations.

After deriving the model (113), whether based on topological feature maps or statistical equations, the model is utilized to present (120) the unknown sample's relationship to the known population(s). The user may then interpret these relationships and perform confirming assays (121). The output of the model (120) can be automatically stored in a memory (122) of an automated analyzer and/or displayed relative to one or more known sample populations (124) on the automated analyzer, such as on a computer monitor, or printed out on paper. Also, where the unknown sample is from a medical patient, both the derived model and other patient medical data (95) can be used for generating a model and subsequent relationship to it.

Example: Presentation of Data Using Topological Feature Maps

This example demonstrates how data from known sample populations can be used to generate a topological feature map that can then be used to present the relationships between an unknown sample and known sample

populations for analysis.

Self-organizing feature maps were used to generate the topological feature maps. A self-organizing feature map is a type of neural network that includes an input and output layer of neurons. The network is trained by a competitive learning algorithm where the output neurons compete with one another to be activated and only one output neuron is activated for any given set of inputs. Once trained, the self-organizing map (SOM) algorithm transforms an input vector to an individual output neuron whose location in the output layer, or map, corresponds to features of the input data. These features tend to be spatially correlated in the map. In this example, the presentation of the data from the known specimens was generated in the following steps:

1. PT and APTT assays were performed on an automated analyzer for 765 samples. These samples represented 200 patient specimens that included normal patients, patients with a variety of deficiencies, and patients undergoing heparin or oral anticoagulant therapy.

2. The 200 specimens were also tested to determine the concentration of coagulation factors (FII, FV, FVII, FVIII, FIX, FX, FXI, FXII) heparin, and fibrinogen. The diagnostic cut-off for defining factor deficiencies was set at 30%; that is, specimens with a measured concentration of less that 30% of normal for a specific

factor were defined as deficient and those with greater than 30% activity were defined as non-deficient. Samples were defined as positive for heparin if the measured heparin concentration was greater than 0.05 IU/ml.

3 Time-dependent optical measurements were taken and the data profiles stored for all PT and APTT assays performed in step 1.

4. The nine predictor variables defined in Figure 2 were calculated for all profiles stored in step 3.

5. A 10x10 SOM was trained using the 765 sets of nine PT predictor variables from step 4.

6. A 10x10 SOM was trained using the 765 sets of nine APTT predictor variables from step 4.

7. Contour plots were constructed for six categories of known specimen classifications: normal donors, specimens with heparin > 0.05 IU/ml, fibrinogen >600mg/dl, fibrinogen <200 mg/dl, patients receiving oral anticoagulants, and factor-deficient specimens (specimens with <30% of normal activity for FII, FV, FVII, FVIII, FIX, FX, FXI, or FXII). These contour plots depict the distribution of specimens within a category according to their map coordinates. The shaded areas represent the distribution of output neurons for specific specimen populations within the feature map.

Each contour line represents an incremental step of one test result located at a given set of map coordinates.

Figure 3 shows SOM contour plots derived from APTT optical data. Specimens containing low fibrinogen and high fibrinogen were classified at opposite borders of the SOM with no overlap. Normal populations showed some overlapping with low fibrinogen, factor deficient and oral anticoagulated categories. Overlap between normal specimens and edges of the high and low fibrinogen populations is expected, since some proportion of healthy donors have fibrinogen levels that are lower or higher than normal. Overlap between mapping of normal specimens and factor-deficient plasmas is also not surprising, since APTT tests are sensitive to some factor-deficiencies (but not others), whereas PT assays are sensitive to a separate subset of factor deficiencies. The low fibrinogen category tended to overlap the factor-deficient category, consistent with our observation that many factor-deficient specimens also had reduced fibrinogen levels. The heparin category tended to overlap the high fibrinogen category, again consistent with measured levels of fibrinogen for these specimens. Little or no overlap was observed between normal specimens and specimens containing heparin. Specimens from patients receiving oral anticoagulant therapy show significant overlap with both normal and

heparin populations. This is consistent with known properties of APTT assays, which are sensitive to heparin therapy but relatively insensitive to oral anticoagulant therapy.

Contour plots for self-organizing feature maps trained with PT data are shown in Figure 4. Results are similar to maps from APTT data in several respects: (1) high and low fibrinogen were well resolved at opposite sides of the map; (2) normal specimens were localized in a region that overlapped low fibrinogen specimens slightly; (3) factor-deficient specimens were distributed between non-overlapping regions and regions that overlapped low fibrinogen and normal populations. Overlap was consistent with measured fibrinogen for some specimens, and with poor sensitivity of PT reagents to some factor deficiencies in other cases; (4) oral anticoagulated specimens showed some overlap with both normal and heparin populations; and (5) the heparinized population was distributed over a large portion of the map. Overlap between heparinized specimens and high fibrinogen populations was consistent with measured fibrinogen levels.

These results indicate that self-organizing feature maps are capable of distinguishing differences in optical data parameters from APTT and PT assays even when no information regarding specimen diagnosis is presented to the neural network. Resolution of specimen

populations was variable, depending on reagent properties and sensitivities, and on whether specimens belonged to a given category uniquely or to multiple overlapping categories.

To present the data from an unknown sample, the following additional steps would be taken:

1. Perform a PT and/or APTT assay on the unknown sample.

2. Collect the time-dependent optical data from the assay and store it.

3. Calculate the parameters that comprise the input vector of the trained SOM.

4. Determine the winning output neuron for that particular set of inputs.

5. Display the position of the unknown sample on the contour plots generated in the first part of this example.

Example: Presentation of Data using A Statistical Model

This example demonstrates how data from known sample populations can be used to generate statistical descriptions which can then be used to present the relationships between an unknown sample and known sample

populations for analysis.

The following steps were performed for PT assays (see Figure 5) and then separately for APTT assays (see Figure 6):

1. Mean and standard deviation (SD) were calculated for each of the nine parameters described in figure 2 from assays (PT or APTT) run on aliquots from normal specimens (n=79).

2. Z-scores were calculated for each parameter of each specimen from the normal group (n=79) and abnormal group (n=410). Z-scores are calculated by subtracting the mean of normals from the clot time and then dividing the result by the SD. The group of abnormals included various factor deficiencies, oral-anticoagulated specimens, suspected DIC specimens, and heparinized specimens.

3. Classifying normal samples as negative and all abnormals as positive, the number of true positives, true negatives, false positives and false negatives were determined. If specimens with an absolute value of the z-score greater than x SD (where x=1,2,3,4,5, etc.) for one or more of the parameters, the specimen was called positive.

4. For comparison, steps 1 through 3 were repeated for PT and APTT clot times.

Sensitivity and specificity for non-specific

abnormals as a group is higher when using all parameters rather than the traditional clot time used alone.

It is to be understood that the invention described and illustrated herein is to be taken as a preferred example of the same, and that various changes in the method and apparatus of the invention may be resorted to, without departing from the spirit of the invention or scope of the claims.

WE CLAIM:

1. A method for presenting the relationship between data from an assay relating to thrombosis-hemostasis on an unknown sample, and data from a plurality of assays relating to thrombosis-hemostasis from known sample populations comprising:

(a) providing data from at least one time dependent measurement profile for each of a plurality of known blood samples;

(b) measuring a property over time as to derive at least one time-dependent measurement on an unknown blood sample;

(c) transforming data from steps (a) and (b) to one or more predicator variables which sufficiently captures the information content of both the unknown blood sample's time-dependent measurement profile and the known blood samples' time-dependent measurement profiles;

(e) creating a topological feature map of the sets of predictor variables from step (c) of the known samples in step (a) whose spatial locations within the map correspond to intrinsic features of the sets of predictor variables;

(f) determining the position on the map of the unknown sample corresponding to its set of predictor

variables;

(g) presenting the data from said unknown blood sample time-dependent measurement profile relative to the data from said known blood sample time-dependent measurement profiles.

2. The method according to claim 1, wherein in step (c), data from the time-dependent measurement profiles is transformed into one or more predicator variables that characterize timing, rate and/or magnitude of changes during the time-dependent measurement profile.

3. The method according to claim 2, wherein said set of predictor variables in step (c) includes one or more of: a minimum of the first derivative of the profile, a time index on the minimum of the first derivative, a minimum of the second derivative of the profile, a time index of the minimum of the second derivative, a maximum of the second derivative, a time index of the maximum of the second derivative, an overall change in the coagulation parameter during the time-dependent measurement on the unknown sample, a clotting time, a slope of the profile prior to clot formation, and a slope of the profile after clot formation.

4. The method according to claim 1, wherein

said plurality of known blood samples and said unknown blood sample are samples of whole blood or plasma.

5. The method according to claim 1, wherein said plurality of known blood samples are samples of which information is known relating to one or more intrinsic or extrinsic clotting factors and/or therapeutic agents, or are normal samples.

6. The method according to claim 1, wherein said at least one time-dependent measurement profile comprises a profile from a PT assay.

7. The method according to claim 1, wherein said at least one time-dependent measurement profile comprises a profile from an APTT assay.

8. The method according to claim 1, wherein at least one of said time-dependent measurement profiles consists of optical measurements.

9. The method according to claim 8, wherein said optical measurements correspond to changes in light scattering and or light absorption in the sample.

10. A method according to claim 1, wherein in addition to the predictor variables in step (c), additional patient medical data associated with each sample is used as the input vector for the map.

11. The method according to claim 1, wherein in

steps (a) and (b), a plurality of one or more coagulation assays are performed to provide said time-dependent measurement profiles.

12. The method according to claim 1, wherein a plurality of maps are provided for presenting said data.

13. A method according to claim 1, wherein said at least one optical profile is provided by an automated analyzer for thrombosis and hemostasis testing.

14. A method according to claim 13, wherein a plurality of optical measurements are made at multiple wavelengths.

15. A method according to claim 13, wherein in steps a) and b) said at least one optical profile is provided automatically by said analyzer, whereby said unknown sample is automatically removed by an automated probe from a sample container to a test well, one or more reagents are automatically added to said test well so as to initiate said property changes within said sample, and the development of said property over time is automatically optically monitored so as to derive said optical data profile.

16. A method according to claim 13, wherein after step f), the position of the unknown sample on

the map(s) is stored in memory of said automated analyzer and/or displayed on said analyzer.

17. A method for presenting the relationship between data from an assay relating to thrombosis-hemostasis on an unknown sample, and data from a plurality of assays relating to thrombosis-hemostasis from known sample populations comprising:

(a) providing data from at least one time dependent measurement profile for each of a plurality of known blood samples;

(b) measuring a respective property over time as to derive at least one time-dependent measurement on an unknown blood sample;

(c) transforming data from steps (a) and (b) to one or more predicator variables which sufficiently captures the information content of both the unknown blood sample's time-dependent measurement profile and the known blood samples' time-dependent measurement profiles;

(d) computing the standard deviation for each predictor variable in step (c) of the known samples in step (a);

(e) determining the z-score of the unknown sample in (b) for each predictor variable, and

determining if one or more of the z-scores for the unknown sample is greater than a predetermined limit, signifying that the unknown sample is different from the known population represented by the model.

18. The method according to claim 17, wherein in step (c), data from the time-dependent measurement profiles is transformed into one or more predicator variables that characterize timing, rate and/or magnitude of changes during the time-dependent measurement profile.

19. The method according to claim 18, wherein said set of predictor variables in step (c) includes one or more of: a minimum of the first derivative of the profile, a time index on the minimum of the first derivative, a minimum of the second derivative of the profile, at time index of the minimum of the second derivative, a maximum of the second derivative, a time index of the maximum of the second derivative, an overall change in the coagulation parameter during the time-dependent measurement on the unknown sample, a clotting time, a slope of the profile prior to clot formation, and a slope of the profile after clot formation.

20. The method according to claim 17, wherein said plurality of known blood samples and said unknown blood sample are samples of whole blood or plasma.

21. The method according to claim 17, wherein said plurality of known blood samples are samples of which information is known relating to one or more intrinsic or extrinsic clotting factors and/or therapeutic agents, or are normal samples.

22. The method according to claim 17, wherein said at least one time-dependent measurement profile comprises a profile from a PT assay.

23. The method according to claim 17, wherein said at least one time-dependent measurement profile comprises a profile from an APTT assay.

24. The method according to claim 17, wherein at least one said time-dependent measurement profiles comprises optical measurements.

25. The method according to claim 24, wherein said optical measurements correspond to changes in light scattering and or light absorption in the sample.

26. The method according to claim 17, wherein in steps (a) and (b), a plurality of one or more coagulation assays are performed to provide said time-dependent measurement profiles.

27. A method according to claim 17, wherein said at least one optical profile is provided by an

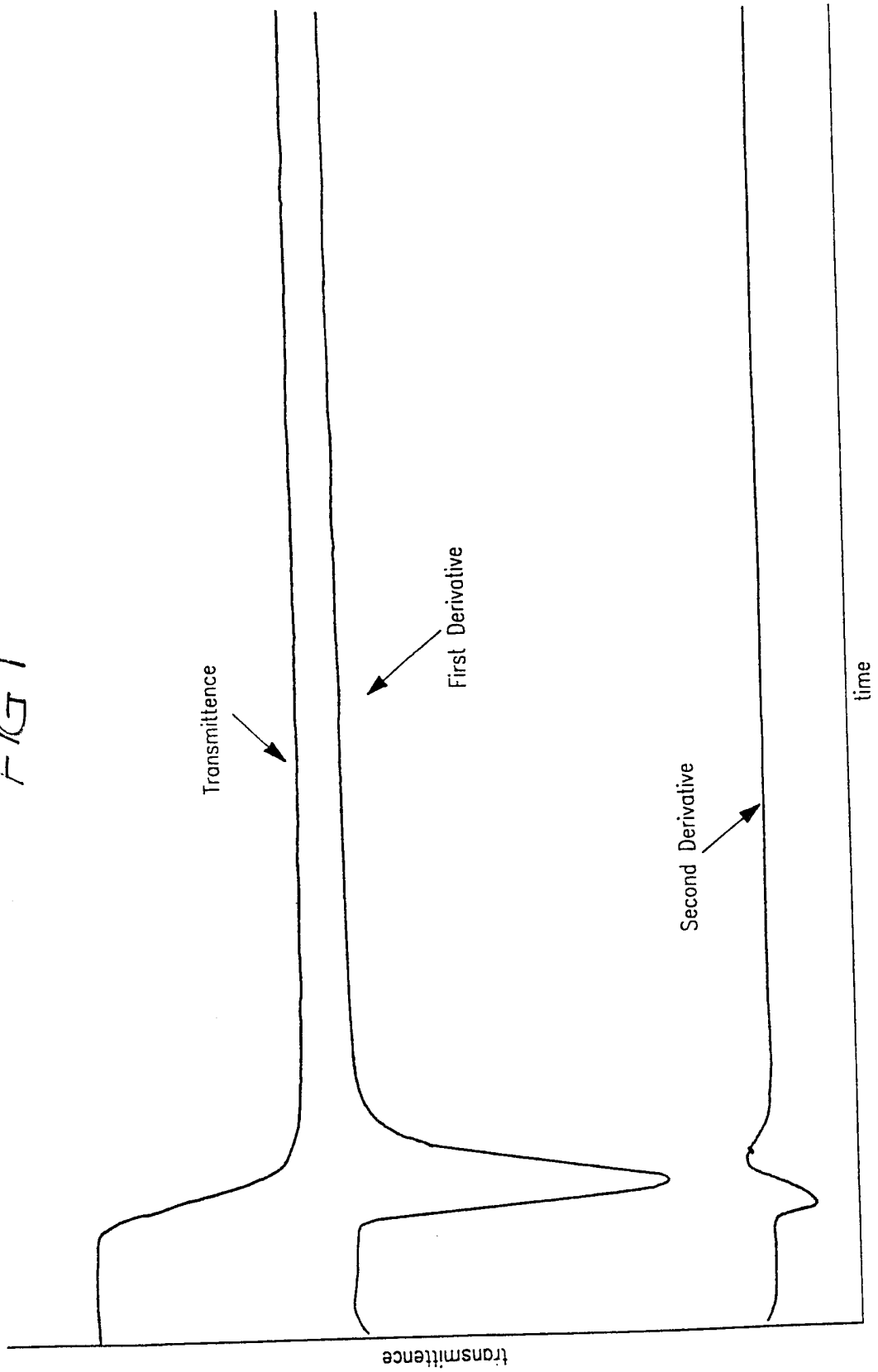
automated analyzer for thrombosis and hemostasis testing.

28. A method according to claim 17, wherein a plurality of optical measurements are made at multiple wavelengths.

29. A method according to claim 17, wherein in steps a) and b) said at least one optical profile is provided automatically by said analyzer, whereby said unknown sample is automatically removed by an automated probe from a sample container to a test well, one or more reagents are automatically added to said test well so as to initiate said property changes within said sample, and the development of said property over time is automatically optically monitored so as to derive said optical data profile.

30. A method according to claim 17, wherein after step f), the z-scores of the unknown sample is stored in memory of said automated analyzer and/or displayed on said analyzer.

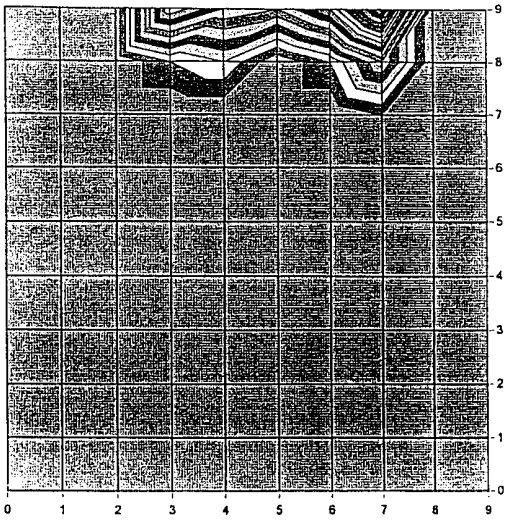
FIG 1


Transmittence
First Derivative
Second Derivative
time
transmittence

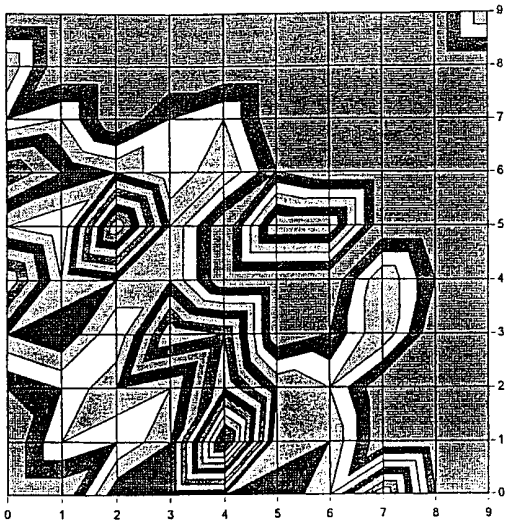
Predictor Variables

Predictor Variable	Description
$pv_{j1} = \left(\frac{dT}{dt}\right)_{\min}$	minimum of the first derivative
$pv_{j2} = t\ at \left(\frac{dT}{dt}\right)_{\min}$	time index of the minimum of the first derivative
$pv_{j3} = \left(\frac{d^2T}{dt^2}\right)_{\min}$	minimum of the second derivative
$pv_{j4} = t\ at \left(\frac{dT^2}{dt^2}\right)_{\min}$	time index of the minimum of the second derivative
$pv_{j5} = \left(\frac{d^2T}{dt^2}\right)_{\max}$	maximum of the second derivative
$pv_{j6} = t\ at \left(\frac{dT^2}{dt^2}\right)_{\max}$	time index of the maximum of the second derivative
$pv_{j7} = T_{t_0} - T_{t_n}$	overall change in transmittance during the reaction
$pv_{j8} = \frac{\left(T_{pv_{j2}} - T_{t_0}\right)}{pv_{j2}}_{t_n}$	pre-coagulation slope
$pv_{j9} = \frac{\left(T_{t_{\max}} - T_{pv_{j5}}\right)}{\left(t_{\max} - pv_{j5}\right)_{t_n}}$	post-coagulation slope

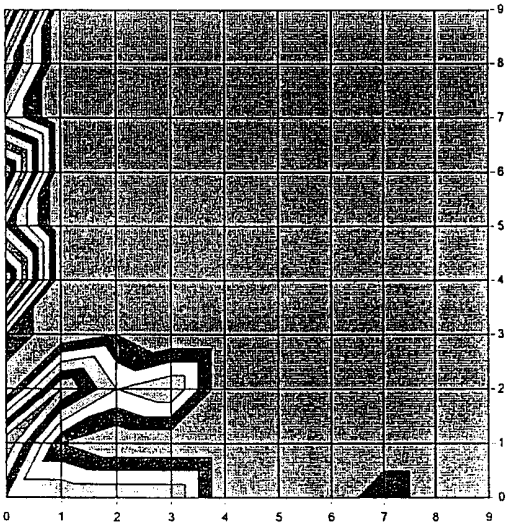
FIG 2



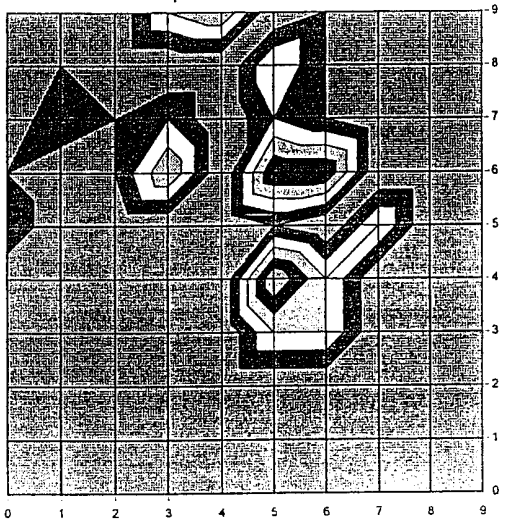
Normal donors



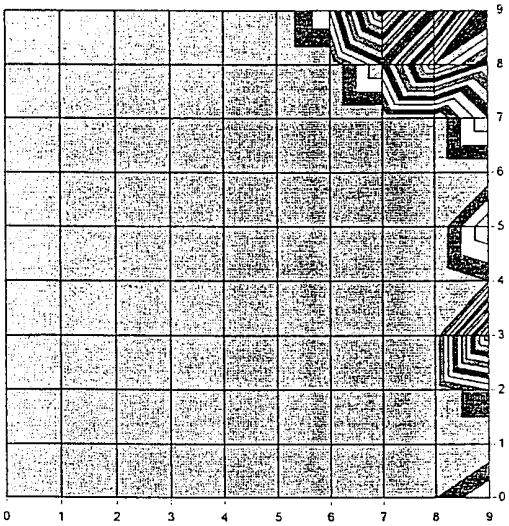
Heparin >0.05IU/ml



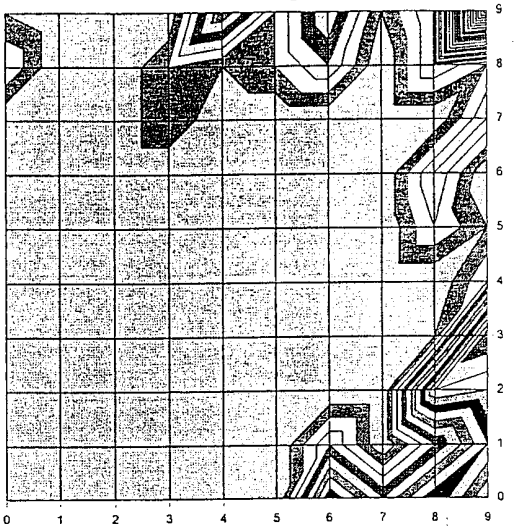
Fibrinogen > 600mg/dl



Oral Anticoagulated

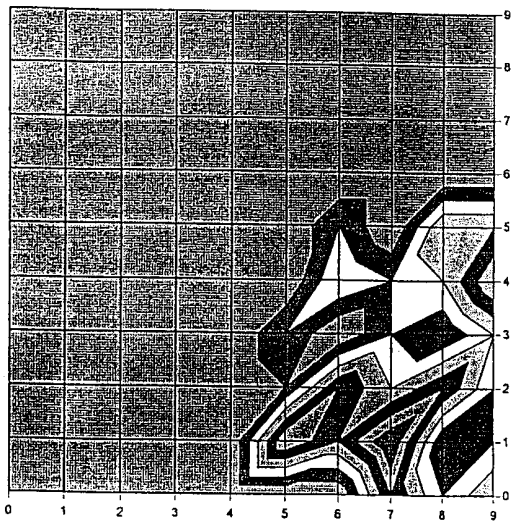


Fibrinogen < 200mg/dl

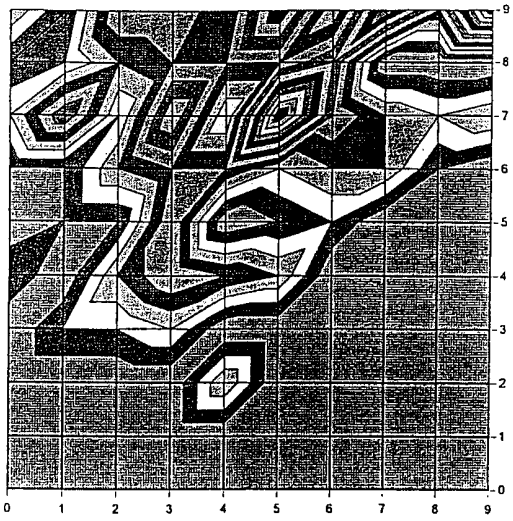


Factor < 30%

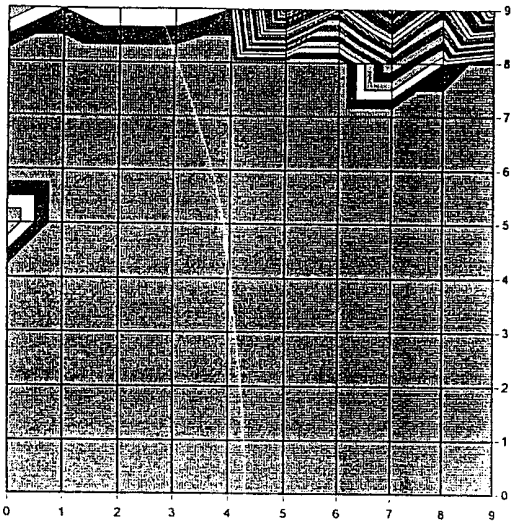
FIGURE 3



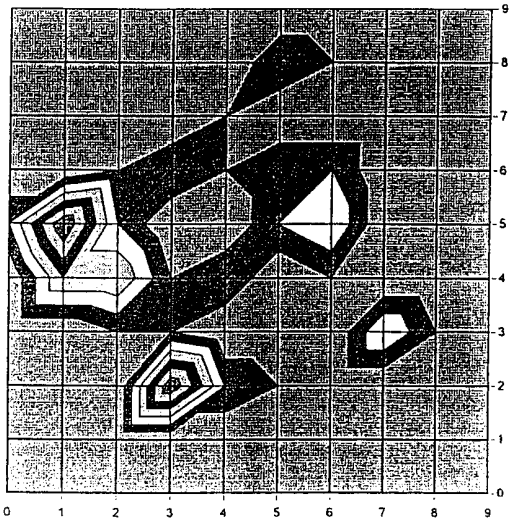
Normal donors



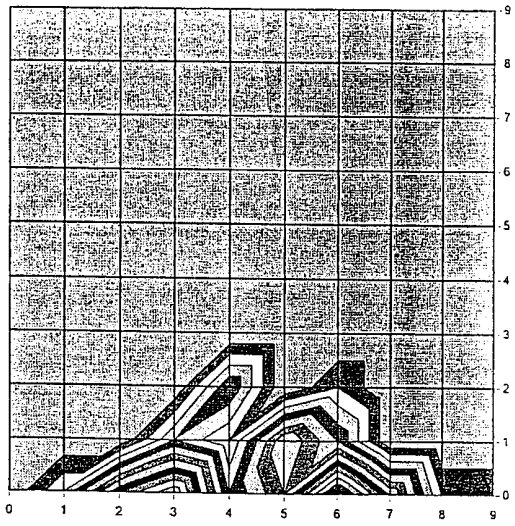
Heparin > 0.05IU/nl



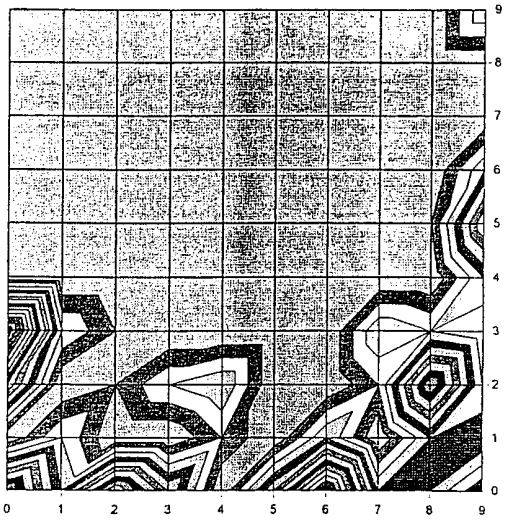
Fibrinogen >600 mg/dl



Oral Anticoagulated



Fibrinogen < 200 mg/dl



Factor < 30%

Figure 4

Fig 5

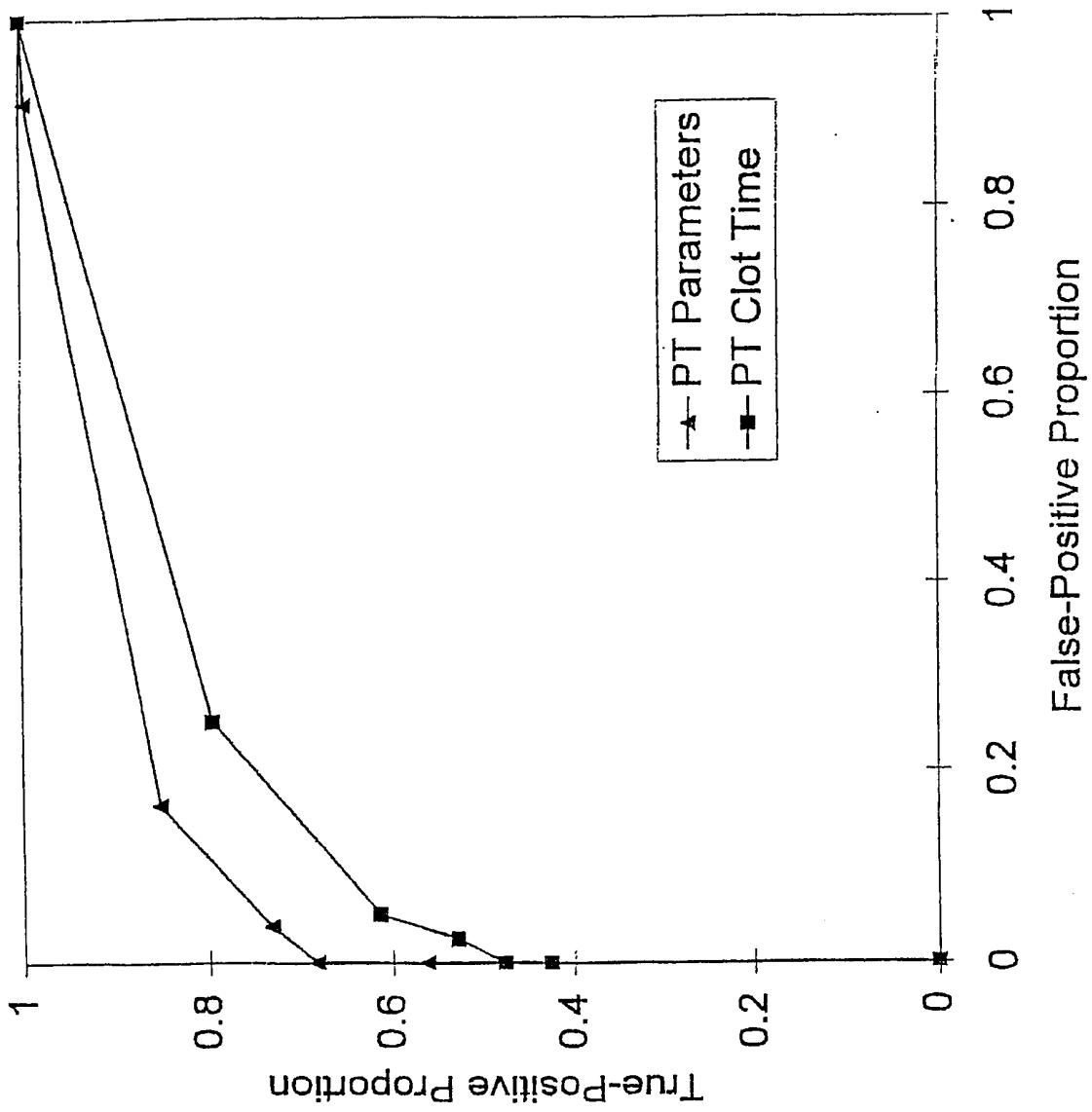
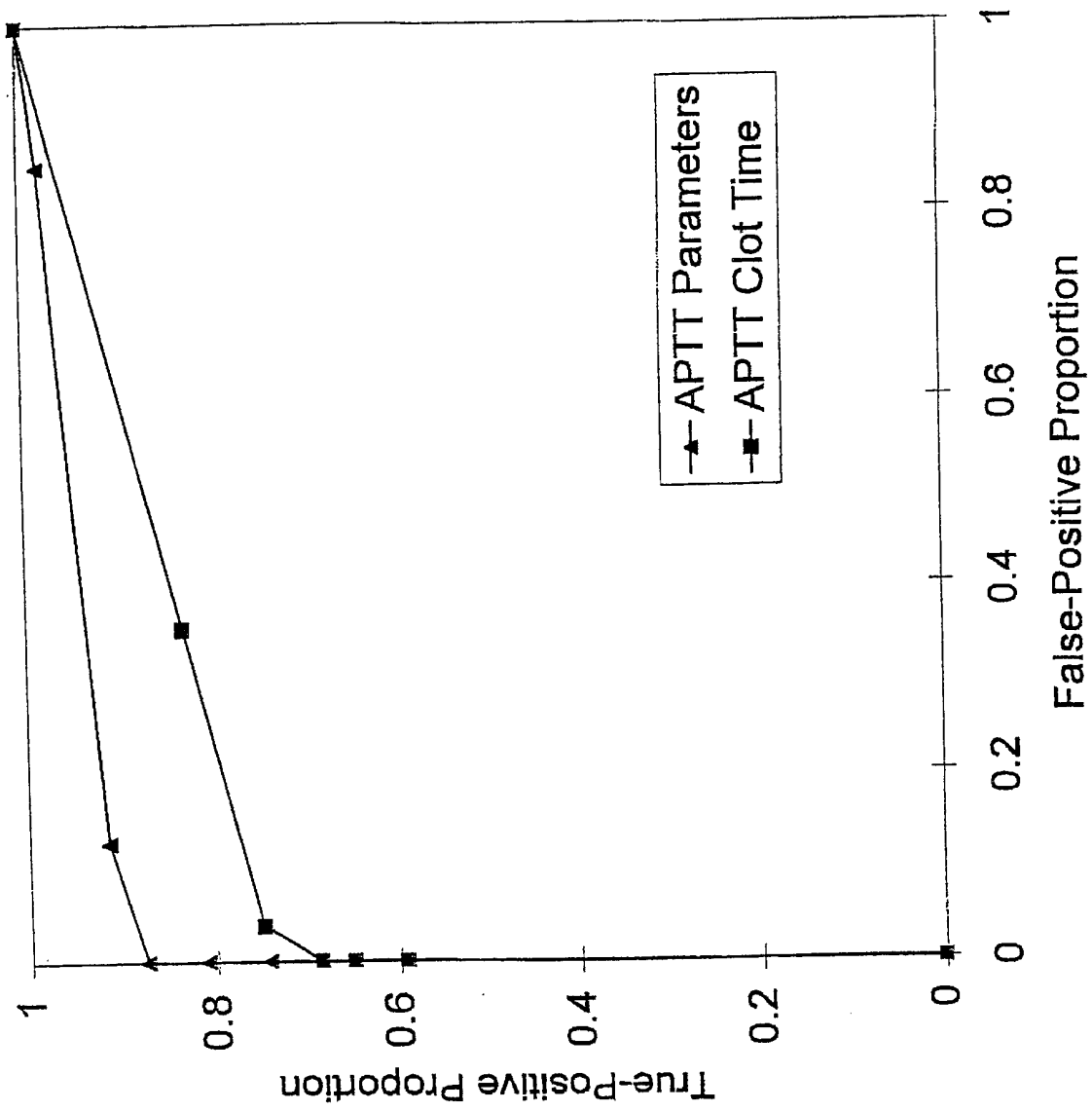

True-Positive Proportion
False-Positive Proportion
PT Parameters
PT Clot Time
0
0.2
0.4
0.6
0.8
1

FIG 6


APTT Parameters
APTT Clot Time
True-Positive Proportion
False-Positive Proportion
0
0.2
0.4
0.6
0.8
1

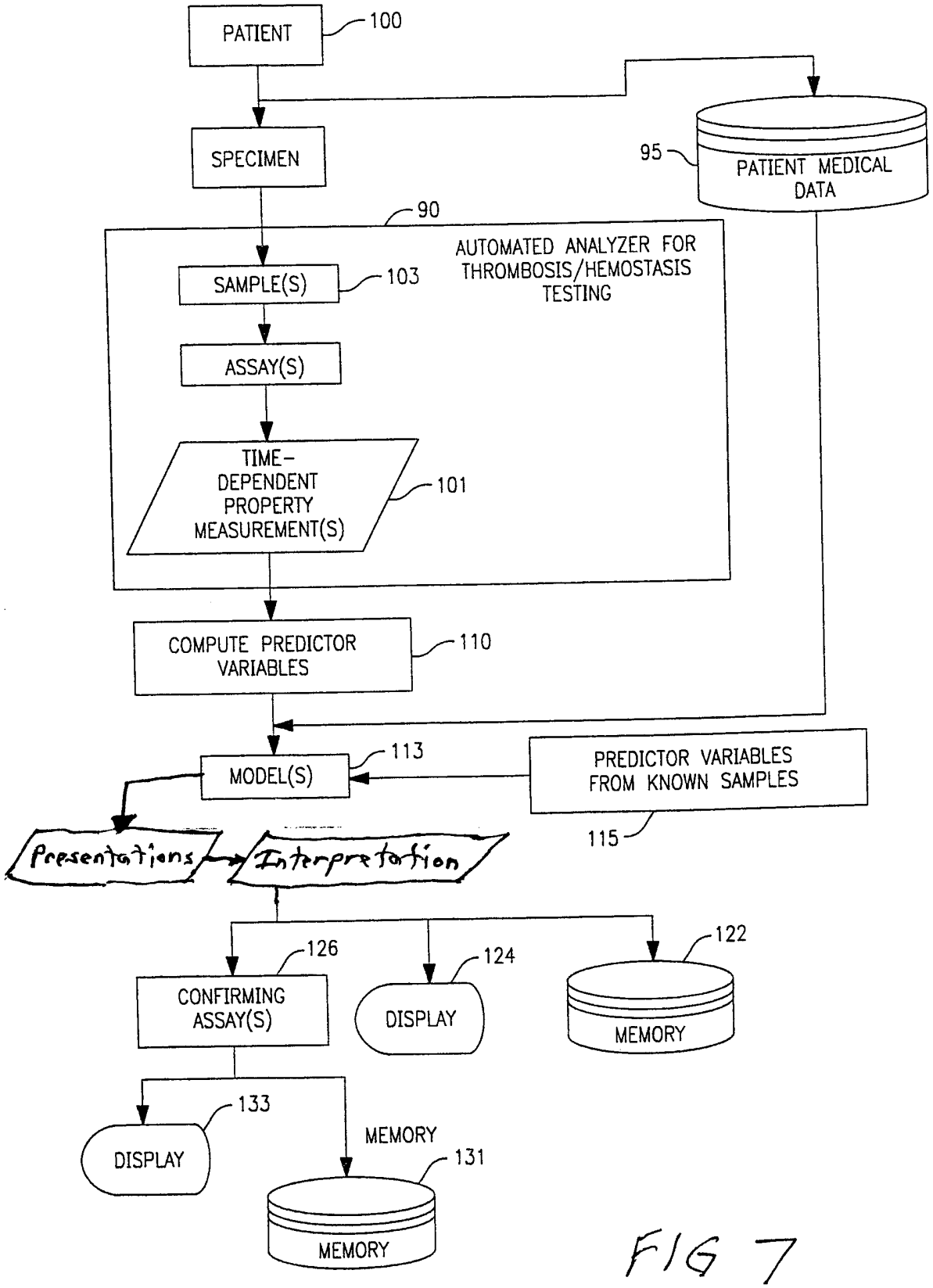

PATIENT
100
SPECIMEN
95
PATIENT MEDICAL DATA
90
AUTOMATED ANALYZER FOR THROMBOSIS/HEMOSTASIS TESTING
SAMPLE(S)
103
ASSAY(S)
TIME-DEPENDENT PROPERTY MEASUREMENT(S)
101
COMPUTE PREDICTOR VARIABLES
110
MODEL(S)
113
PREDICTOR VARIABLES FROM KNOWN SAMPLES
115
Presentations
Interpretation
126
CONFIRMING ASSAY(S)
124
DISPLAY
122
MEMORY
133
DISPLAY
MEMORY
131
MEMORY

FIG 7

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US00/18310

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) :G01N 33/86
US CL :702/22, 28, 30, 32; 703/11

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : Please See Extra Sheet.

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

NONE

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

EAST
search terms: feature, topological, predictor, score, predicting, map, blood

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5,834,223 A (GRIFFIN et al) 10 November 1998, (10/11/98) abstract, col. 12, lines 12-37.	1, 17
A	US 5,715,821 A (FAUPEL) 10 February 1998, (10/02/98) abstract, col. 14, lines 2-31.	1, 17
A	US 5,856,114 A (MANN et al) 05 January 1999, (05/01/99) abstract, col. 21, lines 2-13.	1, 17

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

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search	Date of mailing of the international search report
24 AUGUST 2000	06 SEP 2000
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer HAL D. WACHSMAN Telephone No. (703) 305-9788

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

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US00/18310

B. FIELDS SEARCHED
Minimum documentation searched
Classification System: U.S.

702/22, 28, 30, 32, 23, 27, 29, 31, 128, 131, 139, 179, 180, 183, FOR 115 - FOR 119, FOR 170, FOR 171, FOR 131; 703/11, 6, 9, 12; 700/266, 268; 73/64.43; 436/66, 43, 47-50, 54, 55, 69, 174, 164, 171, 180, 805; 422/50, 61-67, 68.1, 73, 82.05; 382/133, 134, 156-159; 356/39, 40, 42; 706/924, 21, 20; 435/13; 377/10, 11