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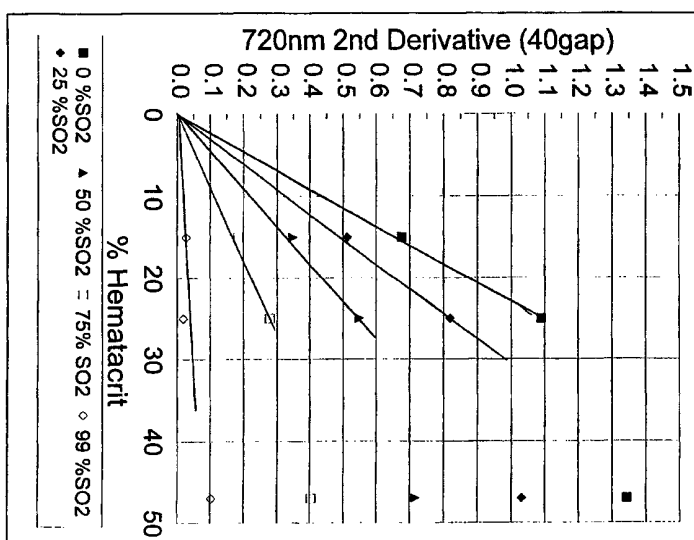
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(54) Title: TOTAL HEMOGLOBIN CONCENTRATION MEASUREMENT



(57) Abstract: A method for operating a spectrophotometric instrument of the type for measuring the oxygenation state of hemoglobin in tissue. The method includes the use of stored hemoglobin concentration relationship data characterizing the relationship between second derivative absorbance values at a hemoglobin-absorbing wavelength and hemoglobin concentration in a tissue as a function of hemoglobin oxygenation state. Data representative of a second derivative absorbance value of tissue being analyzed is received. The hemoglobin oxygenation state of the tissue is determined as a function of the second derivative absorbance value. The hemoglobin concentration in the tissue is then determined as a function of the hemoglobin concentration relationship data, the second derivative absorbance value and the hemoglobin oxygenation state. The accuracy of the hemoglobin oxygenation state can be determined as a function of the hemoglobin concentration value.



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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.

TOTAL HEMOGLOBIN CONCENTRATION MEASUREMENT

BACKGROUND OF THE INVENTION

Spectrophotometric instruments and methods for measuring the amount of a tissue chromophore having a certain functional state (e.g., the percentage of oxidized hemoglobin or StO₂, and the percentage of oxidized cytochrome aa₃) are generally known and disclosed, for example, in the Anderson et al. U.S. Patent 5,879,294, which is hereby incorporated by reference in its entirety. The Anderson et al. patent discloses in particular a measurement algorithm which makes use of scaled second derivative spectrum values.

The Kuestner U.S. Patent 5,377,674 discloses a spectrophotometric instrument and method for measuring the total concentration of a chromophore such as hemoglobin in tissue. The measurement algorithm uses a single term ratio of second derivative absorbance measured at a wavelength at which hemoglobin absorption occurs (analyte wavelength), and a second derivative absorbance measured in a wavelength region where no hemoglobin absorption occurs (reference wavelength) (e.g., 2nd derivative of absorbance at 1740 nm / 2nd derivative of absorbance at 1346 nm).

There remains, however, a continuing need for improved instruments and methods for measuring the total concentration of chromophores such as hemoglobin in tissue.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 is a graph of an example of measured bovine blood second derivative absorbance values as a function of wavelength at a range of conditions of oxyhemoglobin optical density.

Figure 2 is a graph of an example of measured bovine blood second derivative absorbance value data points as a function of hemoglobin oxidation state at hematocrit levels of 47%, 25% and 15%.

Figure 3 is a graph of lines fitted to the data points shown in Figure 2.

Figure 4 is a graph of bovine blood second derivative absorbance values as a function of hematocrit concentrations derived from the data shown in Figure 3 at hemoglobin oxidation (i.e., functional) states of 0%, 25%, 50%, 75% and 99%.

Figure 5 is an example of a lookup table of data derived from the data shown in Figure 4 and describing the relationship between hemoglobin oxidation state and hematocrit levels.

Figure 6 is a graph of data showing the correlation between hematocrit measurements made using the described invention and a reference method by which a centrifuged Wintrobe tube is used to measure the height of packed red blood cells relative to the total sample height (red blood cells and plasma).

Figure 7 is a graph of test data showing the correlation between hematocrit measurements made using the described invention in which hemoglobin oxidation state was varied while hematocrit levels remain constant.

Figure 8 is a graph of an example of measured second derivative absorbance value data points as a function of wavelength at probe send-to-receive fiber spacings of 5 mm, 10 mm, 15 mm and 20 mm.

Figure 9 is a graph of an example of probe scaling factors (PSF) as a function of probe spacing derived from the data shown in Figure 8 and referenced to a spacing of 5 mm.

SUMMARY OF THE INVENTION

A method for measuring the total concentration of a chromophore, such as hemoglobin, in tissue. The method includes providing stored relationship data characterizing the relationship between second derivative absorbance values at a chromophore-absorbing wavelength and the concentration of the chromophore in the tissue. Data representative of a measured second derivative absorbance value from tissue being analyzed is received. Data representative of the chromophore concentration can then be generated as a function of the second derivative absorbance value and the stored relationship data. In one embodiment of the invention, the measured chromophore concentration can be used to evaluate the accuracy of measurements of a functional state of the chromophore (e.g., the oxygenation state of the hemoglobin).

DETAILED DESCRIPTION OF THE INVENTION

The invention is an instrument and method for using the combination of both a single term ratio of a second derivative absorbance value and a single term non-ratioed second derivative value to measure the volume percentage of a chromophore such as hemoglobin in tissue (a value that directly correlates with hemoglobin concentration). The wavelengths used by the method are all within a region where hemoglobin absorption takes place. There is no requirement for a "reference wavelength" which occurs in a region where hemoglobin absorption does not take place. An advantage of the invention is that the spectral region from 680 nm to 800 nm can be used to measure hemoglobin concentration. In this wavelength region the oxygenation state of hemoglobin (%StO₂) (i.e., a portion of the chromophore having a particular functional state) is a factor which must be considered when making total hemoglobin concentration measurements using derivative spectroscopy. The utilization of both a single term derivative ratio (which varies with %StO₂) and a non-ratioed second derivative term (which varies with %StO₂ and total hemoglobin concentration) provides a means to distinguish hemoglobin concentration separately from the amount of oxidized hemoglobin. The non-ratioed second derivative term (at 720 nm in the embodiment described herein) is also used in the denominator of the ratioed second derivative term. Both hemoglobin oxidation percentage and total hemoglobin concentration percentage can be obtained with a minimum of wavelength specific absorbance measurements (e.g., 4 wavelengths are used in the instrument disclosed in the Anderson et al. patent).

In one configuration the wavelength gap used to calculate the second derivative values (i.e., the interval between adjacent absorbance wavelengths used in the second derivative calculation) is 40 nm. At this gap size only four wavelengths are used to calculate both the percentage of oxidized hemoglobin and the percentage of total hemoglobin in the tissue (% hematocrit). The second derivative absorbance peak at 720 nm (deoxyhemoglobin absorption band of 760 nm) is used to empirically derive the relationship between percent hematocrit and second derivative absorbance. Second derivative gap sizes other than 40 nm can also be used to derive the hematocrit algorithm. Also, other wavelength regions (e.g.,

visible or infrared) corresponding to other oxyhemoglobin or deoxyhemoglobin absorbance maximums could be used.

The total hemoglobin concentration measurements made in accordance with the algorithms described herein can be used by an instrument in connection with tissue recognition algorithms. Inaccurate and/or invalid measurements of %StO₂ or other measured parameters can be displayed by the instrument monitor if the probe is not properly located on the tissue to be measured. The total hemoglobin concentration measurement can be used by the instrument to determine whether the probe is properly positioned and the measurement is accurate. For example, in connection with some or all of the parameter measurements, the instrument can compute the total hemoglobin concentration using the algorithm described herein, and display the parameter measurement as an accurate measurement only if the hemoglobin concentration measurement is representative of a predetermined minimum level. If the hemoglobin concentration measurement is below the predetermined level, the monitor can generate a display indicating that the probe is not properly positioned.

Total hemoglobin concentration measurements in accordance with the invention can be generated as a function of current second derivative spectroscopy values and stored data describing the relationship between the second derivative values and the total hemoglobin concentration. In the embodiment described below, the stored relationship data is data describing a set of lines or slopes (or curves if preferred), each of which is associated with a constant oxidation state of hemoglobin.

During total hemoglobin concentration measurements, the proper stored relationship data can be selected by the instrument on the basis of the measured hemoglobin oxidation state. From this data and the current second derivative spectroscopy value, the total hemoglobin concentration can be computed by the instrument.

Stored second derivative/hemoglobin concentration relationship data can be generated in the following manner. Figure 1 is a graph of measured second derivative (40 nm gap) spectra of bovine blood at a range of conditions of oxyhemoglobin optical density. The shape transformation of the illustrated spectra (e.g., peak height at 720 nm) is influenced by three primary factors (%StO₂, % hematocrit and optical path length). The height of the

second derivative absorbance values shown in Figure 1 varies directly with hemoglobin concentration and inversely with the hemoglobin oxidation state. To determine the % hematocrit from unscaled second derivative features, both the %StO₂ and path length need to be defined.

At multiple levels of hematocrit (HCT), the second derivative spectral features of the blood are recorded at a predetermined (e.g., 5 mm) probe spacing over multiple % StO₂ values within the 0%-100% range as illustrated in Figure 2. For each hematocrit the 720 nm second derivative peak is fitted to a linear equation as is illustrated in Figure 3.

At each constant level of %StO₂, the second derivative 720 nm feature is related to % hematocrit with extrapolation to 0% hematocrit. As illustrated in Figure 4, from this step it is evident that there is a linear relationship between the 720 nm second derivative and hematocrit at hematocrits of about 25% and less.

Using linear extrapolation to 0% hematocrit and empirical measurements at 25% and 15% hematocrit, a lookup table of relationship data which describes the sensitivity of hematocrit to the 720 nm second derivative values (lines of constant %StO₂) can be created as illustrated in Figure 5. The slopes are functionally related to the ratio of the second derivative at 680 nm to the second derivative at 720 nm. Figures 6 and 7 are graphs of several verification exercises (tests) performed for the algorithm described above.

To compensate for measurements made with probe spacings other than that used to generate the relationship data, a probe scaling factor (PSF) which relates the relative change in path length due to probe spacing is used to adjust the 720 nm second derivative values.

The stored relationship data described above is subsequently used during total hemoglobin concentration measurements. Upon measuring %StO₂ (e.g., using conventional algorithms and scaled second derivative values at 680 nm) the corresponding slope value (Mso₂ or hct slope) is found within the lookup table. The predicted hematocrit value is then:

$$\%Hct = Mso_2 \times D720 / PSF$$

Where: D720 is the second derivative at 720 nm using the 40 nm gap

PSF is the relative path length change due to probe spacing

The concentration of tissue hematocrit is generally less than 25%, and is usually in the 1%-10% range. When evaluating probe position on the basis of hemoglobin concentration measurements, relatively high measurement accuracy near the lower end of the range is sufficient. For example, the threshold for determining whether the probe is on or off tissue can be in the range of 1% measured hemoglobin concentration. The linear range of spectral features versus hematocrit concentration (e.g., less than about 25% in Figure 4) need only be used for this application. However, in accordance with the present invention, the measurement accuracy can be extended to greater percentages of hematocrit by redefining the algorithm to account for nonlinearities. The algorithm could, for example, be redefined as a multiple regression algorithm consisting of multiple slope and second derivative transformations (linear transformations). Examples of nonlinear equations include:

$$\%Hct = Mso2_1 \times (D720/PSF) + Mso2_2 \times \text{Log}(D720/PSF)$$

or

$$\%Hct = Mso2_1 \times (D720/PSF) + Mso2_2 \times (D720/PSF)^{1/2} + Mso2_3 \times (D720/PSF)^{1/3} + \dots$$

Where: $Mso2_1, Mso2_2, \dots$ are nonlinear slope value coefficients which can be stored in the lookup table.

The probe scaling factor (PSF) can be empirically determined by collecting second derivative spectral measurements of a chromophore medium, preferably having constant scattering and absorption properties, with optical probes having variable distances between the optical send and receive fibers. The spectral measurements at each probe spacing are then referenced (ratioed) to one of the fixed probe spacing spectral measurements at a particular wavelength of interest. The ratio of one second derivative spectrum value at a probe spacing of interest to the second derivative spectrum value of the reference probe

spacing then reflects the probe scaling factor. Figure 8 is a graph of second derivative spectra measured at 4 different probe spacings. The medium used to obtain the data in Figure 8 was a 2.5% aqueous solution of 1 micron polystyrene microspheres. Figure 9 represents the probe scaling factor measured from the ratio of second derivative spectrum values at approximately 725 nm (the absorbance peak in Figure 8). The following equation represents an example calculation of the probe scaling factor from the spectral information in Figure 9:

$$\text{PSF (20 mm probe)} = \frac{725\text{nm } 2^{\text{nd}} \text{ derivative value (20 mm probe)}}{725\text{nm } 2^{\text{nd}} \text{ derivative value (5 mm probe)}}$$

The denominator in the equation represents the reference probe spacing (the probe spacing used to create the hemoglobin concentration algorithm). This probe scaling factor allows the hemoglobin concentration algorithm to be used with probe designs other than the 5 mm probe for which the algorithm is empirically created.

Although the present invention has been described with reference to preferred embodiments, those skilled in the art will recognize that changes can be made in form and detail without departing from the spirit and scope of the invention.

Claims

1. A method for measuring total concentration of a chromophore in tissue, including:
 - providing stored relationship data characterizing the relationship between second derivative absorbance values at a chromophore-absorbing wavelength and the total concentration of the chromophore;
 - receiving a second derivative absorbance value at the chromophore-absorbing wavelength; and
 - generating data representative of the total concentration of the chromophore as a function of the stored relationship data and the second derivative absorbance value.

2. The method of claim 1, wherein:
 - providing the stored relationship data includes providing stored data representative of lines or curves of constant functional state portions which characterize the relationship between the absorbance values and the total concentration of the chromophore in the tissue;
 - the method further includes receiving functional state value data representative of the value of the functional state portion of the chromophore being measured; and
 - generating data representative of the total concentration of the chromophore includes generating data representative of the total concentration of the chromophore as a function of the line or curve of the constant functional state portion of the chromophore associated with the received functional state value and the second derivative absorbance value.

3. The method of claim 2 for measuring total hemoglobin concentration in tissue, wherein:
 - providing the stored relationship data includes providing data representative of lines of constant %StO₂;

receiving functional state value data includes receiving data representative of the %StO₂ value in the tissue; and

generating data representative of the total concentration of hemoglobin includes generating the data as a function of the line or curve of constant %StO₂ associated with the received %StO₂ value and the second derivative absorbance value.

4. The method of claim 1 wherein the spectrophotometric measurements are all at chromophore-absorbing wavelengths.

5. Determining the accuracy of the functional state value as a function of the data representative of the total concentration value generated by the method of any of claim 2.

6. Providing a display indicating an inaccurate functional state value as a function of the determination of claim 5.

7. A spectrophotometric instrument for generating data representative of the total concentration of a chromophore in accordance with claim 1.

8. A method for operating a spectrophotometric instrument of the type for measuring oxygenation state of hemoglobin in tissue, including:

providing stored hemoglobin concentration relationship data characterizing the relationship between second derivative absorbance values at a hemoglobin-absorbing wavelength and hemoglobin concentration in a tissue as a function of hemoglobin oxygenation state;

receiving data representative of second derivative absorbance value of tissue being analyzed;

determining the hemoglobin oxygenation state of the tissue;

determining the hemoglobin concentration in the tissue as a function of the hemoglobin concentration relationship data, the second derivative absorbance value and the hemoglobin oxygenation state; and
determining the accuracy of the hemoglobin oxygenation state determination as a function of the hemoglobin concentration value.

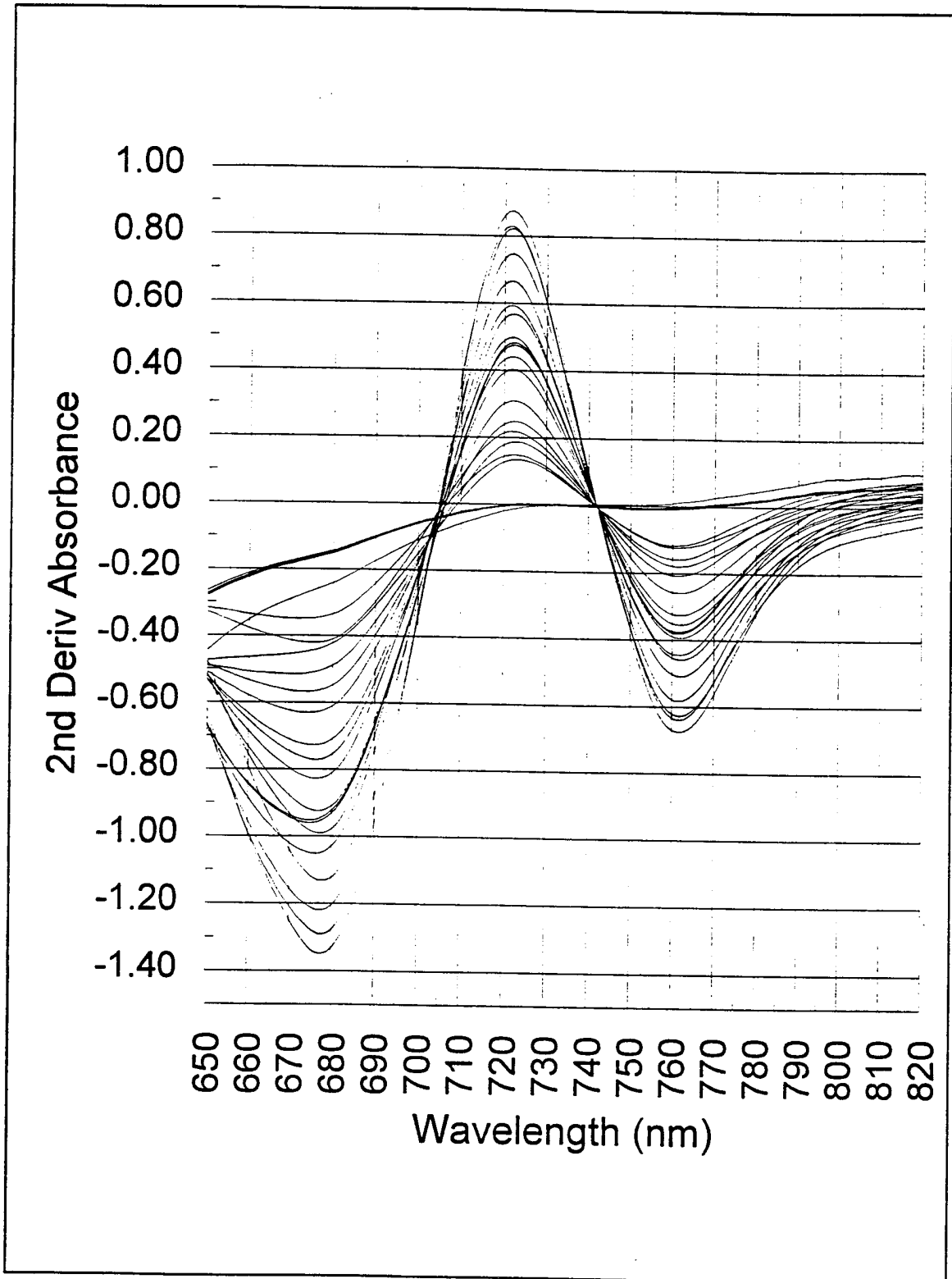


Figure 1

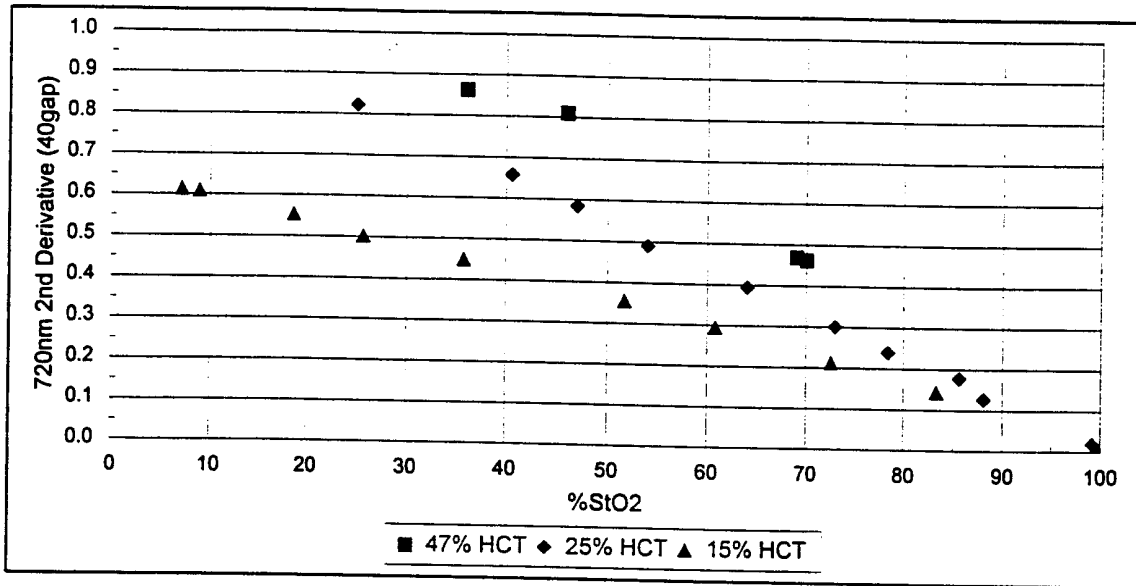


Figure 2

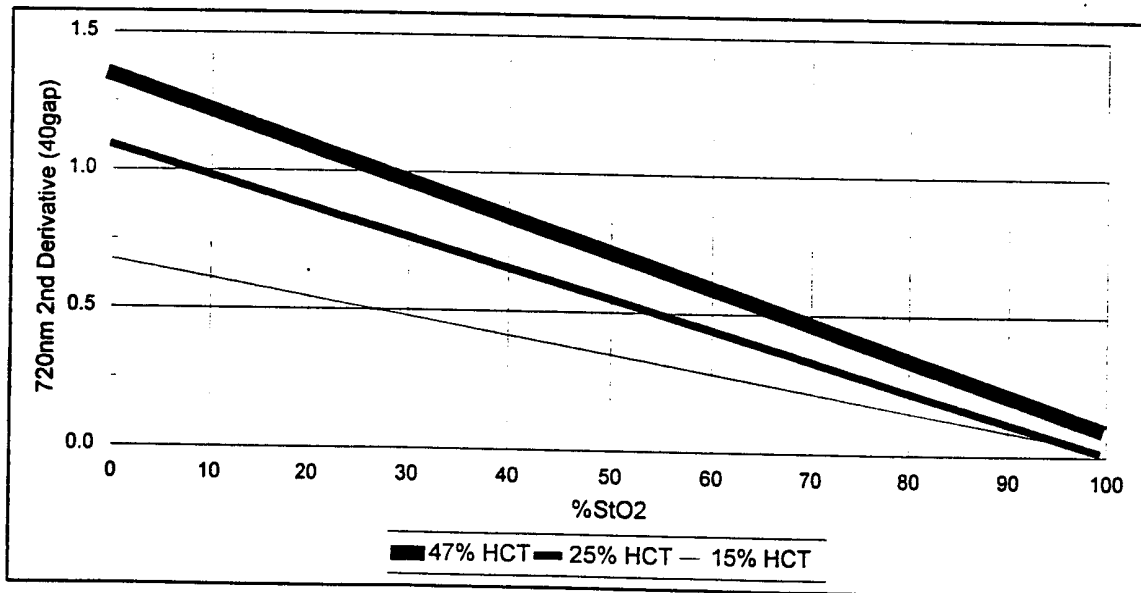


Figure 3

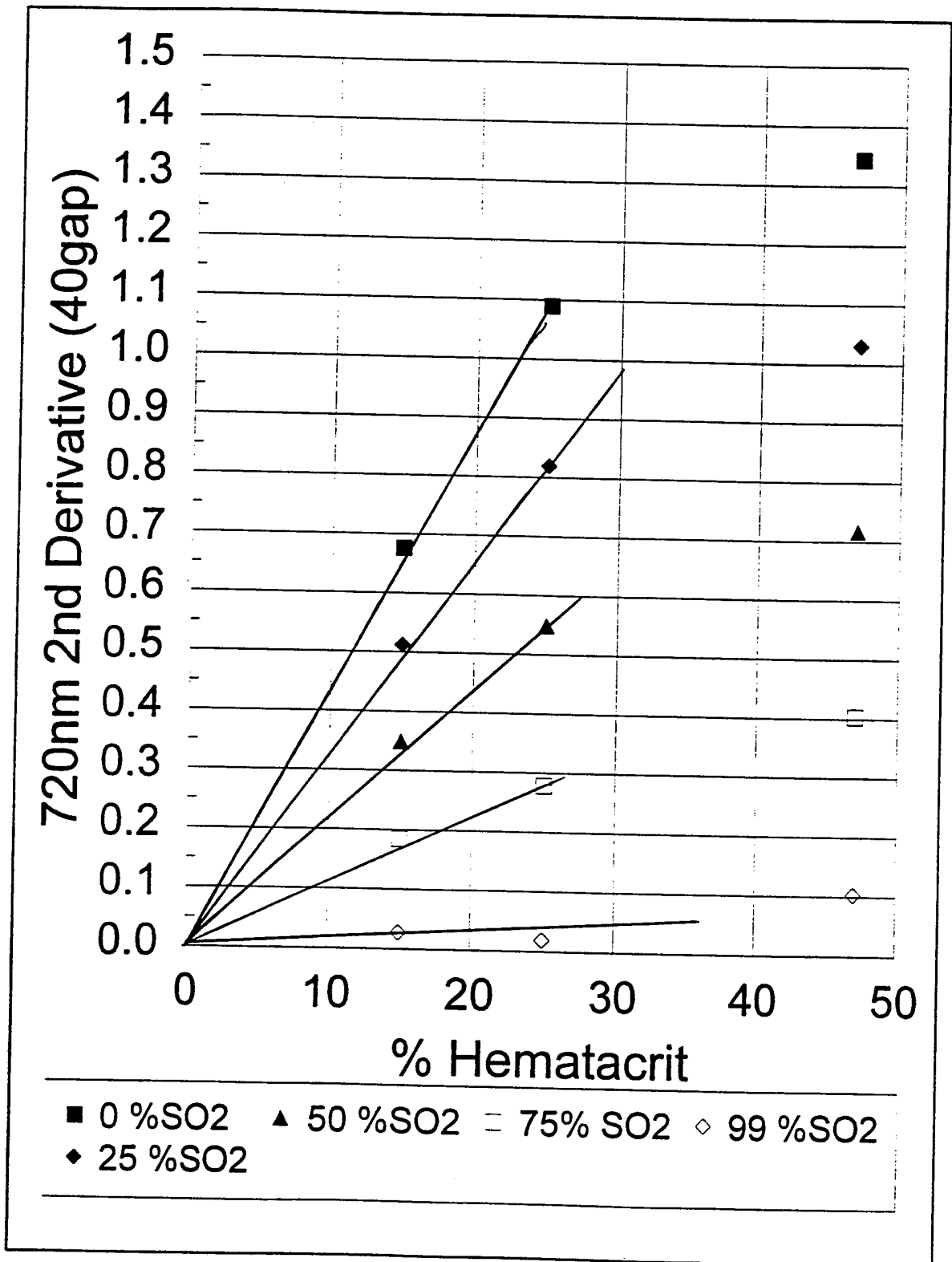


Figure 4

%StO2	2nd680/2nd720	Hct Slope (Mso2)	%StO2	2nd680/2nd720	Hct Slope (Mso2)
0	-1.166	22.56	50	-1.670	44.28
1	-1.175	22.78	51	-1.684	45.15
2	-1.184	23.01	52	-1.699	46.06
3	-1.194	23.24	53	-1.713	47.00
4	-1.203	23.48	54	-1.727	47.98
5	-1.212	23.72	55	-1.741	49.00
6	-1.221	23.97	56	-1.755	50.07
7	-1.230	24.22	57	-1.770	51.19
8	-1.239	24.48	58	-1.784	52.35
9	-1.249	24.75	59	-1.798	53.57
10	-1.258	25.01	60	-1.812	54.85
11	-1.267	25.29	61	-1.826	56.19
12	-1.276	25.57	62	-1.841	57.60
13	-1.285	25.86	63	-1.855	59.08
14	-1.294	26.15	64	-1.869	60.64
15	-1.304	26.45	65	-1.883	62.28
16	-1.313	26.76	66	-1.897	64.02
17	-1.322	27.08	67	-1.921	65.85
18	-1.331	27.40	68	-1.932	67.80
19	-1.340	27.73	69	-1.954	69.86
20	-1.349	28.07	70	-1.990	72.05
21	-1.359	28.41	71	-2.050	74.38
22	-1.368	28.77	72	-2.080	76.87
23	-1.377	29.13	73	-2.120	79.54
24	-1.386	29.51	74	-2.150	82.39
25	-1.395	29.89	75	-2.190	85.46
26	-1.404	30.29	76	-2.230	88.76
27	-1.414	30.69	77	-2.270	92.33
28	-1.423	31.10	78	-2.310	96.20
29	-1.432	31.53	79	-2.350	100.42
30	-1.441	31.97	80	-2.400	105.01
31	-1.450	32.42	81	-2.450	110.05
32	-1.459	32.88	82	-2.500	115.60
33	-1.469	33.36	83	-2.550	121.75
34	-1.478	33.85	84	-2.600	128.58
35	-1.487	34.36	85	-2.660	136.24
36	-1.496	34.88	86	-2.730	144.86
37	-1.505	35.42	87	-2.800	154.66
38	-1.514	35.97	88	-2.880	165.90
39	-1.524	36.54	89	-2.960	178.91
40	-1.533	37.13	90	-3.050	194.16
41	-1.542	37.74	91	-3.150	212.28
42	-1.557	38.37	92	-3.270	234.19
43	-1.571	39.02	93	-3.400	261.23
44	-1.585	39.70	94	-3.580	295.49
45	-1.599	40.39	95	-3.750	340.40
46	-1.613	41.12	96	-4.040	402.03
47	-1.628	41.86	97	-4.500	492.44
48	-1.642	42.64	98	-5.510	639.77
49	-1.656	43.45	99	-9.650	931.66

Figure 5

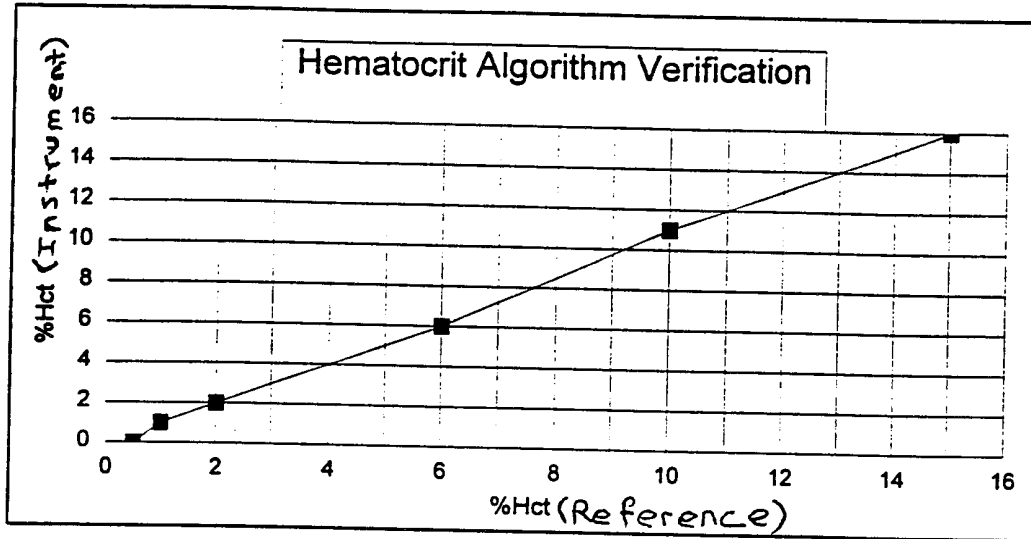


Figure 6

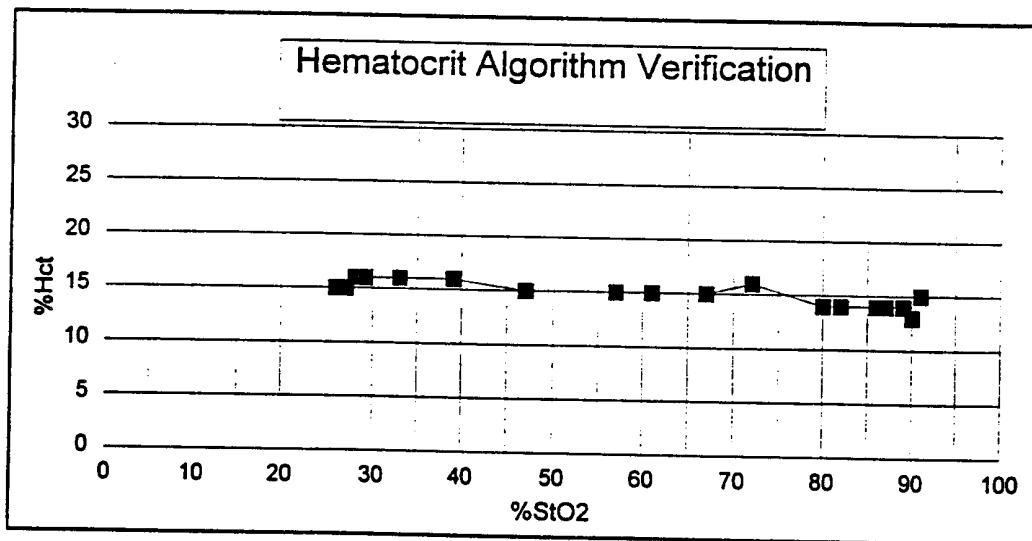


Figure 7

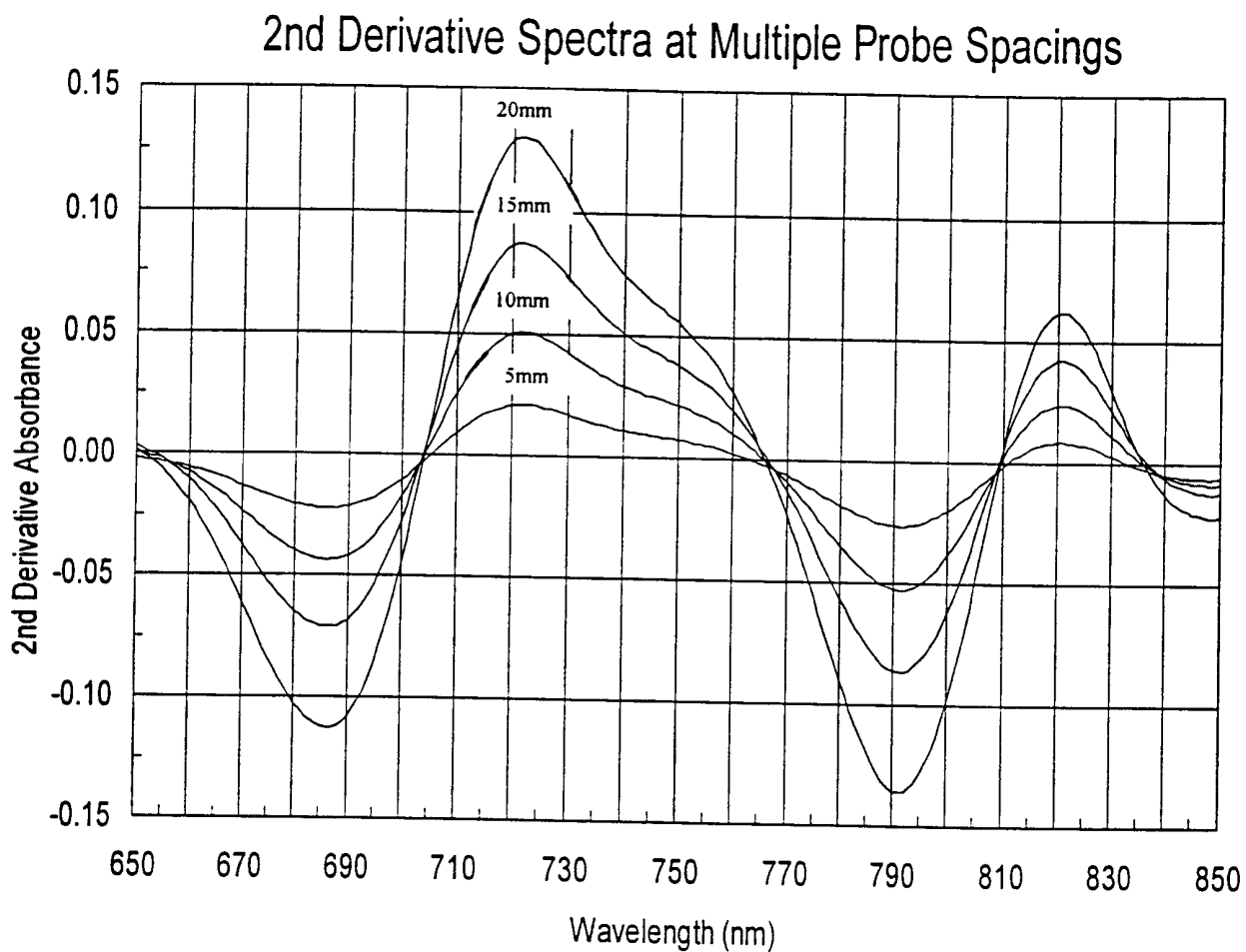


Figure 8

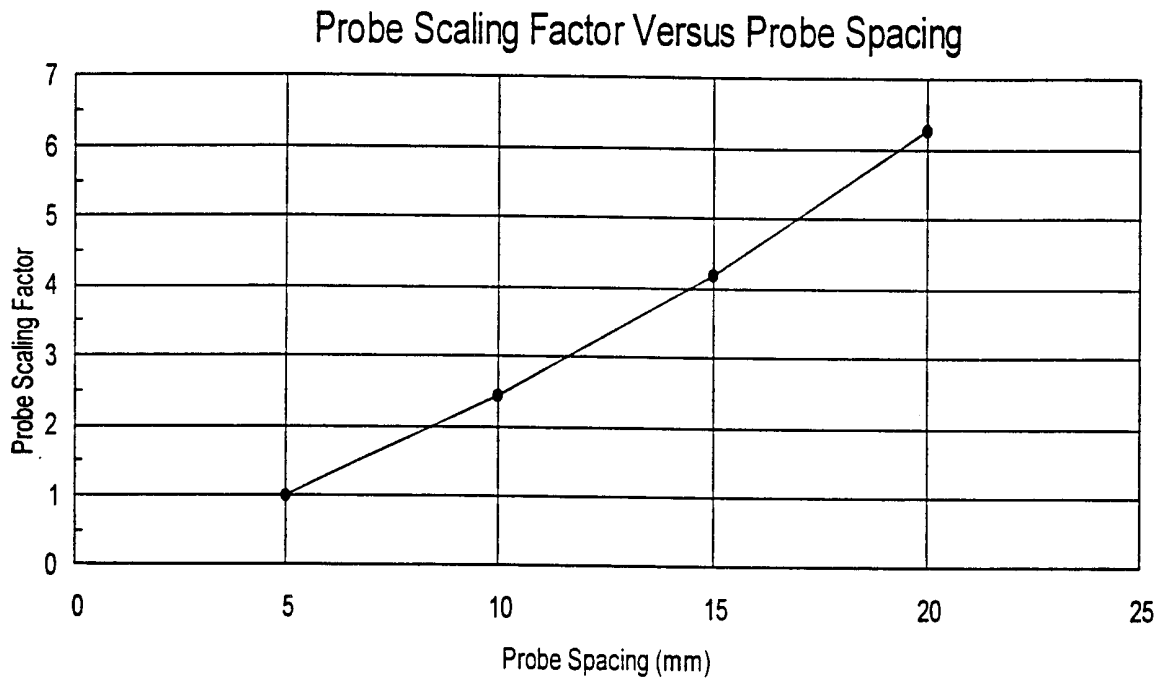


Figure 9

INTERNATIONAL SEARCH REPORT

Int: National Application No

PCT/US 00/16589

A. CLASSIFICATION OF SUBJECT MATTER
 IPC 7 G01N21/35 G01J3/433 A61B5/00

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)
 IPC 7 G01N G01J A61B

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

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

EPO-Internal, WPI Data, PAJ, COMPENDEX, BIOSIS, INSPEC

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 729 333 A (CARIM HATIM M ET AL) 17 March 1998 (1998-03-17)	1,2,7
Y	column 9, line 3 -column 10, line 27	5,8
A	column 14, line 1 - line 13 column 15, line 9 -column 16, line 27; figures 2,10,11	3,4
X	EP 0 816 829 A (HUTCHINSON TECHNOLOGY) 7 January 1998 (1998-01-07)	1,7
Y	page 12, line 27 -page 15, line 28	5,8
A	claim 11	2-4
A	US 5 308 982 A (IVALDI JUAN ET AL) 3 May 1994 (1994-05-03) claims 1,3,10	1,7,8
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Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

* Special categories of cited documents :

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Date of the actual completion of the international search

Date of mailing of the international search report

22 September 2000

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Name and mailing address of the ISA

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Authorized officer

Stuebner, B

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 00/16589

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>US 5 377 674 A (KUESTNER J TODD) 3 January 1995 (1995-01-03) cited in the application column 3, line 14 - line 20 column 4, line 14 - line 33 -----</p>	1,7,8

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No PCT/US 00/16589

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