



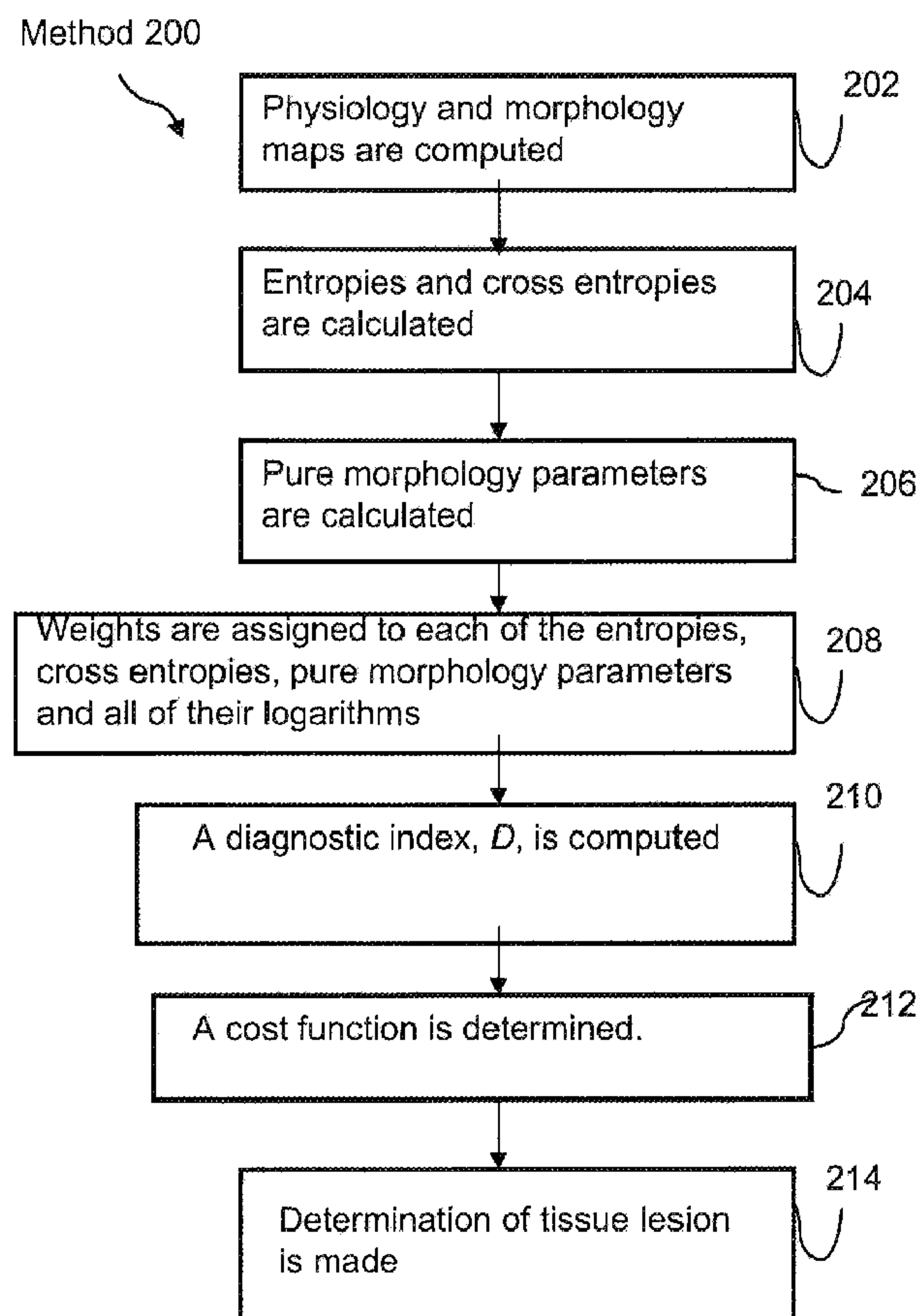
(86) Date de dépôt PCT/PCT Filing Date: 2009/01/26
(87) Date publication PCT/PCT Publication Date: 2009/07/30
(85) Entrée phase nationale/National Entry: 2010/07/23
(86) N° demande PCT/PCT Application No.: US 2009/031969
(87) N° publication PCT/PCT Publication No.: 2009/094623
(30) Priorités/Priorities: 2008/01/24 (US61/023,242);
2008/03/18 (US61/037,503)

(51) Cl.Int./Int.Cl. *G01N 33/483* (2006.01),
G06F 19/00 (2006.01)
(71) Demandeur/Applicant:
BALTER, INC., US
(72) Inventeurs/Inventors:
STAMNES, JAKOB J., NO;
STAMNES, KNUT, US;
RYZHIKOV, GENNADY, NO;
BIRYULINA, MARINA, NO;
HAMRE, BOERGE, NO;
SOMMERSTEN, ENDRE R., NO;
ZHAO, LU, NO
(74) Agent: RIDOUT & MAYBEE LLP

(54) Titre : PROCEDE PERMETTANT DE FAIRE LA DISTINCTION ENTRE DES LESIONS TISSULAIRES MALIGNES ET BENIGNES

(54) Title: METHOD FOR DISCRIMINATING BETWEEN MALIGNANT AND BENIGN TISSUE LESIONS

Figure 2



(57) Abrégé/Abstract:

An embodiment of the present invention includes a method for discriminating between benign and malignant tissue lesions. The method includes the steps of using a plurality of maps of physiology and morphology parameters generated from reflectance



(57) Abrégé(suite)/Abstract(continued):

measurements and pure morphology parameters generated from reflectance measurements. The method also includes calculating entropies and cross entropies of the plurality of maps, and calculating a plurality of pure morphology parameters. Further, the method includes assigning a weight to each entropy and a weight to a logarithm of each entropy, a weight to each cross entropy and a weight to a logarithm of each cross entropy, and a weight to each pure morphology parameter and a weight to a logarithm of each pure morphology parameter. The method further includes computing a diagnostic index, defining a cost function, defining a proper threshold value for a diagnostic index and solving an optimization problem to determine a set of weights from the assigned weights to maximize specificity for 100% sensitivity. Further, the method uses calculations, the cost function and the diagnostic index to determine whether the tissue lesion is benign or malignant.

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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
30 July 2009 (30.07.2009)



(10) International Publication Number
WO 2009/094623 A3

(51) International Patent Classification:
G01N 33/483 (2006.01) *G06F 19/00* (2006.01)

(21) International Application Number:
PCT/US2009/031969

(22) International Filing Date:
26 January 2009 (26.01.2009)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
61/023,242 24 January 2008 (24.01.2008) US
61/037,503 18 March 2008 (18.03.2008) US

(71) Applicant (for all designated States except US): **BALTER, INC.** [US/US]; 465 Ridgewood Road, Maplewood, NJ 07040 (US).

(72) Inventors; and

(75) Inventors/Applicants (for US only): **STAMNES, Jakob, J.** [NO/NO]; Kvernkalveien 12A, N-0382 Oslo (NO). **STAMNES, Knut** [US/US]; 465 Ridgewood Road, Maplewood, NJ 07040 (US). **RYZHIKOV, Gennady** [NO/NO]; Vestre Vadmyra 35, N-5172 Loddefjord (NO). **BIRYULINA, Marina** [NO/NO]; Vestre Vadmyra 35, N-5172 Loddefjord (NO). **HAMRE, Boerge** [NO/NO];

Aurdalslia 127, N-5253 Sandsli (NO). **SOMMERSTEN, Endre, R.** [NO/NO]; Skjoldber 31, N-5283 Radal (NO). **ZHAO, Lu** [CN/NO]; Fantoft studentboliger, 5075 Bergen (NO).

(74) Agent: **KAUL, Shivani**; Brown Rudnick LLP, One Financial Center, Boston, MA 02111 (US).

(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, SE, SI, SK, TR),

[Continued on next page]

(54) Title: METHOD FOR DISCRIMINATING BETWEEN MALIGNANT AND BENIGN TISSUE LESIONS

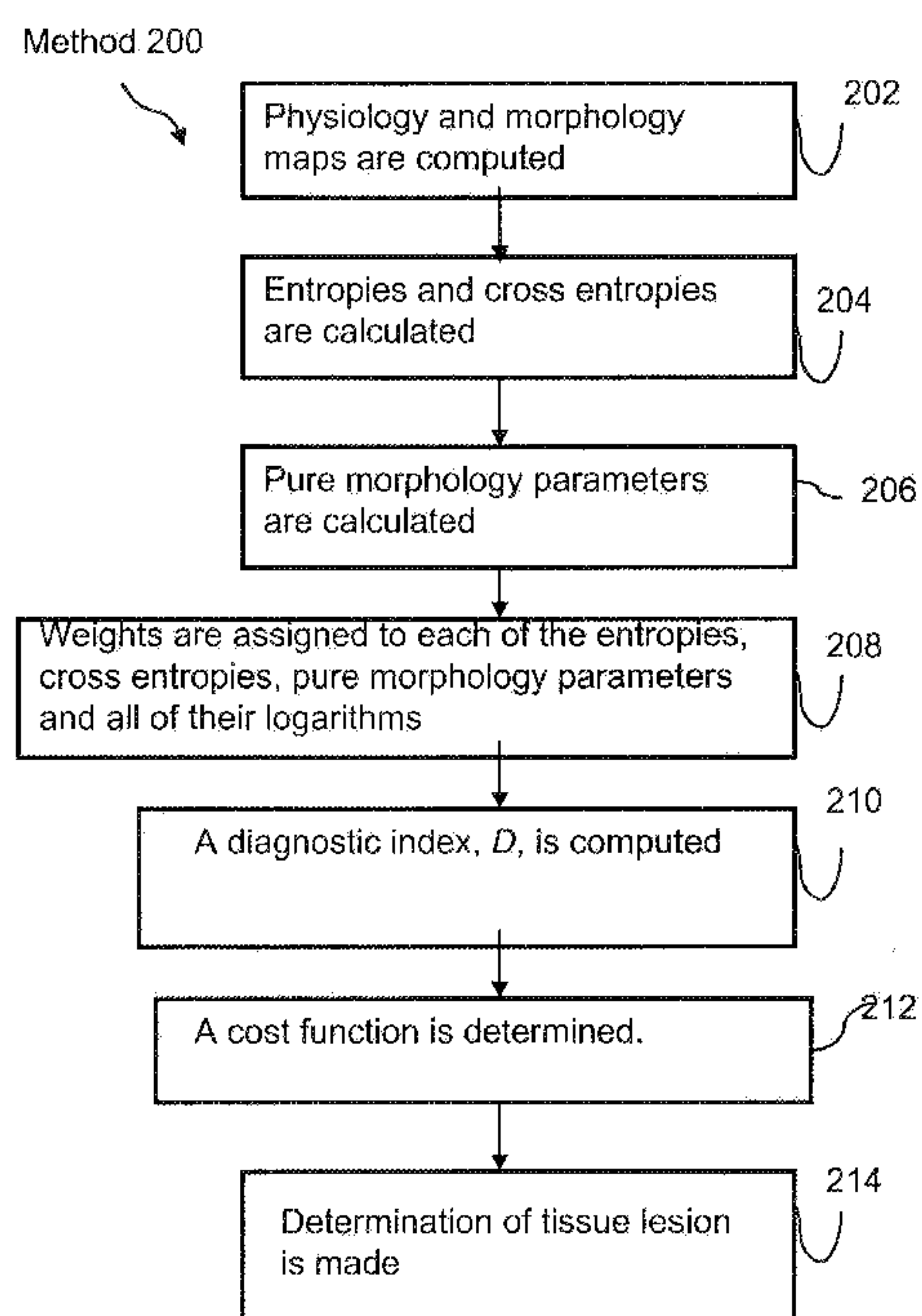


Figure 2

(57) Abstract: An embodiment of the present invention includes a method for discriminating between benign and malignant tissue lesions. The method includes the steps of using a plurality of maps of physiology and morphology parameters generated from reflectance measurements and pure morphology parameters generated from reflectance measurements. The method also includes calculating entropies and cross entropies of the plurality of maps, and calculating a plurality of pure morphology parameters. Further, the method includes assigning a weight to each entropy and a weight to a logarithm of each entropy, a weight to each cross entropy and a weight to a logarithm of each cross entropy, and a weight to each pure morphology parameter and a weight to a logarithm of each pure morphology parameter. The method further includes computing a diagnostic index, defining a cost function, defining a proper threshold value for a diagnostic index and solving an optimization problem to determine a set of weights from the assigned weights to maximize specificity for 100% sensitivity. Further, the method uses calculations, the cost function and the diagnostic index to determine whether the tissue lesion is benign or malignant.

WO 2009/094623 A3



OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML,
MR, NE, SN, TD, TG).

— *before the expiration of the time limit for amending the
claims and to be republished in the event of receipt of
amendments (Rule 48.2(h))*

Published:

— *with international search report (Art. 21(3))*

(88) Date of publication of the international search report:
22 October 2009

METHOD FOR DISCRIMINATING BETWEEN MALIGNANT AND BENIGN TISSUE LESIONS

CROSS-REFERENCE TO RELATED APPLICATIONS

This patent application claims priority to U.S. Provisional Application Serial No. 61/023,242, filed in the U.S. Patent and Trademark Office on January 24, 2008 by Jakob J. Stamnes and Knut Stamnes, and U.S. Provisional Application Serial No. 61/037,503, filed in the U.S. Patent and Trademark Office on March 18, 2008 by Jakob J. Stamnes and Knut Stamnes, and is a continuation-in-part from U.S. Patent Application Serial No. 10/471,111, filed in the U.S. Patent and Trademark Office on October 23, 2003, by Jakob J. Stamnes and Knut Stamnes, the entire contents of these applications being incorporated herein by reference in their entirety.

BACKGROUND

1. Technical Field

The present disclosure relates to a method for discriminating between different types of tissue lesions. In particular, the present disclosure is directed to a method for discriminating between malignant and benign tissue lesions.

2. Description of the Related Art

Malignant melanoma is one of the most rapidly increasing cancers in the world. In the United States alone, the estimated incidence for 2008 is 62,480, which leads to an estimated total of 8,420 deaths per year. Successful treatment of melanoma depends on early detection by clinicians with subsequent surgical removal of tumors. Visual detection has its limitations, even when augmented with dermoscopy, especially with less experienced users. Attempts have thus been made to develop automated devices to assist in the screening of pigmented skin lesions for likelihood of melanoma. Several of these devices

have digitalized dermoscopy-related features analyzed by artificial neural networks or support vector machine learning systems.

SUMMARY

An embodiment of the present invention includes a method for discriminating between benign and malignant tissue lesions. The method includes the steps of using a plurality of maps of physiology and morphology parameters generated from reflectance measurements and pure morphology parameters generated from reflectance measurements. The method also includes calculating entropies and cross entropies of the plurality of maps, and calculating a plurality of pure morphology parameters. Further, the method includes assigning a weight to each entropy and a weight to a logarithm of each entropy, a weight to each cross entropy and a weight to a logarithm of each cross entropy, and a weight to each pure morphology parameter and a weight to a logarithm of each pure morphology parameter. The method further includes computing a diagnostic index, defining a cost function, defining a proper threshold value for a diagnostic index and solving an optimization problem to determine a set of weights from the assigned weights to maximize specificity for 100% sensitivity. Further, the method uses calculations, the cost function and the diagnostic index to determine whether the tissue lesion is benign or malignant.

BRIEF DESCRIPTION OF THE DRAWINGS

The objects and features of the present disclosure, which are believed to be novel, are set forth with particularity in the appended claims. The present disclosure, both as to its organization and manner of operation, together with further objectives and advantages, may be best understood by reference to the following description, taken in connection with the accompanying drawings as set forth below:

Figure 1 is a flow chart illustrating a method in accordance with an embodiment of the present invention; and

Figure 2 is a flow chart illustrating another method in accordance with an embodiment of the present invention.

DETAILED DESCRIPTION OF EXEMPLARY EMBODIMENTS

The following detailed description refers to the accompanying drawings. The same reference numbers in different drawings may identify the same or similar elements. In addition, the following detailed description does not limit the present disclosure.

The present invention relates to a method for discriminating between different types of tissue lesions. In particular, the present invention is directed to a method for discriminating between malignant and benign tissue lesions. In the present invention, a novel melanoma detection method is taught. The method of the present invention uses morphologic and physiologic maps as well as pure morphological parameters generated from spectral reflectance images of melanocytic lesions, and which can be extended to discriminate between benign and malignant tissue lesions, in general.

The present invention uses maps of morphologic and physiologic tissue parameters as well as pure morphologic parameters, which are generated by the Optical Transfer Diagnosis (OTD) method, as described in the patent entitled "Method and an Arrangement for the Determination of the Optical Properties of Multi-Layered Tissue", PCT WO 02/069792 A1.

The OTD device used records 30 spectral reflectance images of a lesion under examination. These 30 reflectance images, which constitute one image set, are recorded at 10 different wavelengths (365-1000 nm) from multiple angles of illumination and detection. One version of the OTD device is a spectral reflectance meter consisting of a measurement head with 12 fixed light-emitting diode (LED) lamps and 3 IEEE (Institute of Electrical and Electronics Engineers) 1394 FireWire cameras. Each LED is placed at a different angle relative to the skin to enhance the ability to retrieve information about the depth of the lesion. The polar angles of the LEDs vary between 30 and 45 degrees, and the relative azimuth angles between 34 and 145 degrees. The polar angles of the detectors

vary between 0 and 45 degrees, and the relative azimuth angles between 0 and 180 degrees. In the current OTD practice, an alcohol-based gel is used as an interface between the measurement probe and the skin, and a selected area of the skin is illuminated and imaged through a 2.2 cm diameter circular sapphire plate. The imaging time is approximately 5 seconds. On the basis of established absorption and transmission spectra for known skin chromophores and mathematical modeling of skin reflectance, the images from each set are used to derive physiology-morphology maps of the lesions for the following 7 parameters (i) percentage of hemoglobin; (ii) percentage of hemoglobin oxygenation; (iii) upper epidermal thickness; (iv) lower epidermal thickness; (v) percentage of upper melanosome concentration; (vi) percentage of lower melanosome concentration; and (vii) percentage of keratin concentration. These parameters vary and are different for normal and malignant tissues.

From each physiology-morphology map, an entropy value is calculated and the cross entropy values are calculated among different pairs of 2 maps. For example, from the spatial distribution of the melanosome concentration, we compute the entropy of this parameter as the sum of the melanosome concentration multiplied by its logarithm and integrated over the area of the lesion. Simply stated, the entropy provides a measure of the disorder in any one of the maps, and the cross entropy provides a measure of the correlation between two different maps.

In the development of a robust diagnostic procedure, it is important to keep in mind that the final diagnosis to the largest degree possible should be independent of the following:

- The robustness of the measurement probe
- Clinical measurement errors due to: bad contact between the probe and skin, too high or too low pressure between the probe and the skin, or too much or too little gel or oil applied between the probe and the skin
- Azimuth angle between the probe and the lesion (for asymmetric lesions)

- Incorrect exposure time (which may be fixed independent of skin type)
- Location of lesion in the picture frame
- Skin type
- Lesion location on the patient's body
- Changes in the physiological state of the patient due to, for example, but not limited to, jumps in the blood pressure or blood oxygenation

Further, a final diagnosis should be insensitive to errors and assumptions made in the pre-processing of the data.

From a set of digital reflectance images of a lesion generated by the OTD device, the optical properties of a lesion can be determined by the methods of PCT WO 02/069792 A1, and maps of physiology-morphology parameters and pure morphology parameters, can be made in a number of ways, including by the method of US Provisional Patent Application No. 61/037,503.

In an embodiment of the present invention, a method 100, as shown in Figure 1, includes considering a set of physiology-morphology maps, as well as a number of pure morphology parameters, as given quantities. A diagnosis may be made using the following steps. At step 102, for each available measurement, process the measurements in order to obtain a diagnosis. This diagnosis is obtained by using a set of physiology-morphology maps as well as a set of pure morphology parameters derived from reflectance images of the lesion generated by the OTD device. At step 104, compare the diagnosis obtained in step 102 with the pathology results obtained from clinical data. Patients with suspicious lesions are referred for scanning by the OTD device. After scanning, lesions are biopsied for histopathologic examination by dermatopathologists, and a diagnosis is provided. At step 106, a cost function consisting of the following is defined: a master term (including pathology), constraints, regularization, and Occam's rule. The master term is specifically designed to discriminate between malignant and benign lesions. Constraints are used to take advantage of *a priori*

information about the covariance of the measurements, while regularization is used to suppress variations in the measurements, which do not contribute to the correct diagnosis. Some of the physiology-morphology parameters and the pure morphology parameters may not contribute significantly to the diagnosis. Occam's rule is designed to exclude insignificant parameters. At step 108, an optimization procedure is used to derive optimal weights. The optimization is an iterative process in which the weights are adjusted until the number of false positives (diagnosing the lesion as malignant when it actually is benign) becomes as small as possible when at the same time the number of false negatives is zero (no malignant lesions missed by the diagnosis). At step 110, the quality of the optimal weights is analyzed by computing receiver operating characteristic (ROC) curves. A ROC curve is a graphical display of the sensitivity vs. specificity, where the sensitivity is the probability of correctly diagnosing a malignant lesion, and the specificity is the probability of correctly identifying a benign lesion. At step 112, a proper threshold value for the diagnostic index, D , is defined to differentiate between melanomas and non-melanomas. A proper threshold value refers to the desire to discriminate between benign and malignant lesions in such a way that the diagnostic index for malignant lesions is well enough separated from those of benign lesions that inevitable errors in the measurement procedure are properly taken into account. At step 114, the robustness of the diagnosis is analyzed and procedures for cross validation are developed. Given a set of data generated by the OTD device and a corresponding set of pathology results, the method may be used to find optimized weights for the entire data set. But the method may also be used to find optimized weights for a subset of the entire data set obtained by excluding some of the measurements. By creating several such subsets, the robustness of the method can be tested by assessing how well the method works on such subsets. This process is referred to as cross validation.

For the sake of clarity, details of the diagnostic procedure of the method 100 are further explained. In order to facilitate the solution of the global optimization problem involving our entire processing chain, which depends on a

large number of processing parameters, measurements of the maps of the physiology-morphology parameters and the pure morphology parameters obtained using current processing codes should be considered. Further, the maps and pure morphology parameters will be noisy (irreproducible), reflecting both noisy initial digital images of the same lesion and noise arising from the current non-optimal processing.

The diagnostic procedure, when properly optimized, shall give a diagnosis that is insensitive to variations in the input parameters due to experimental factors, such as, but not limited to, camera-tissue interface pressure, lesion-camera angular orientation and positioning. Further, the factors may be dependent on data acquisition and processing. Properly optimized means that variations between different reflectance measurements of the same lesion and corresponding variations in the maps and pure morphology parameters automatically shall be suppressed during the processing going from the maps and pure morphology parameters to the diagnosis. After optimization of the weights, all maps and pure morphology parameters will be processed in an optimal manner.

In order to obtain an optimum diagnosis, another method is shown in Figure 2. The following steps, method 200, are taken for each lesion measurement. At step 202, physiology and morphology maps are computed, including estimated uncertainties. At step 204, entropies and relative entropies are calculated for the probability density function associated with each of the maps. At step 206, pure morphology parameters are calculated from the compressed nadir images for the green and the Near Infrared (NIR) channel. At step 208, weights are assigned to each of the entropies and cross entropies and their logarithms and to each of the pure morphology parameters and their logarithms. For example, there may be 7 physiology and morphology maps, and 10 pure morphology parameters. Therefore, there would be 28 parameters for the entropies and cross entropies, 28 parameters for their logarithms and 10 parameters for the pure morphology parameters and 10 parameters for their logarithms. In this example, 76 weights, w_i , would be assigned. At step 210, a

diagnostic index, D , is computed associated with the diagnosis of melanoma in the following manner: $D = \mathbf{w}^T \mathbf{p}$, where $\mathbf{w}$ is a column vector (the superscript T denotes transpose) consisting of 76 weights w_i (to be optimized as explained below), $\mathbf{p}$ is a column vector of 76 elements or input parameters consisting of 28 entropies and cross entropies and their 28 logarithms together with 10 pure morphology parameters and their 10 logarithms, and D is a value of the diagnostic index computed for every lesion being examined.

In step 212, a cost function is determined. The cost function, as discussed in method 100, may be defined by a general expression as the following:

$$J(\mathbf{w}) = J_0(\mathbf{w}) + \alpha_1 J_1(\mathbf{w}) + \alpha_2 J_2(\mathbf{w}) + \alpha_3 J_3(\mathbf{w}),$$

where α_1 , α_2 and α_3 are coefficients to be determined, and $J_0(\mathbf{w})$ is called the master term of the cost function, $J_1(\mathbf{w})$ represents constraints of the cost function, $J_2(\mathbf{w})$ represents self-adaptive regularization of the cost function, and $J_3(\mathbf{w})$ is called Occam's rule.

For exemplary purposes, an example of how the diagnostic procedure may be implemented is shown using a special case of discrimination between benign pigmented lesions and malignant melanomas. The total set of obtained measurements under consideration is divided into two subsets. One subset consists of all non-melanomas, and the other subset consists of all melanomas, the total number of the latter being N . For any chosen weight vector $\mathbf{w}$, the distribution of the diagnostic indices is calculated for the set of *non-melanomas* being considered. The average value of this distribution is $\mu(\mathbf{w})$, and the standard deviation squared is $\sigma^2(\mathbf{w})$. The master term of the cost function may be given by:

$$J_0(\mathbf{w}) = -\frac{1}{N} \sum_{n=1}^N \frac{D_n^M(\mathbf{w}) - \mu(\mathbf{w})}{\sigma(\mathbf{w})} \left[1 + \tanh\left(-\beta \frac{D_n^M(\mathbf{w}) - \mu(\mathbf{w})}{\sigma(\mathbf{w})}\right) \right]$$

where $D_n^M(\mathbf{w})$ is the diagnostic index for melanoma number n as determined by pathology, and β is a penalizing factor, which must be positive. Here, the difference $D_n^M(\mathbf{w}) - \mu(\mathbf{w})$ should be positive and as large as possible in order to

minimize the value of the master term $J_0(\mathbf{w})$. The master term of the cost function is designed to be quadratic around its minimum value so that it works well with standard optimization methods based on quadratic forms. It is also designed to penalize low $D_n^M(\mathbf{w})$ values. Thus, a master term of the cost function is created that pushes all differences $D_n^M(\mathbf{w}) - \mu(\mathbf{w})$ for melanomas towards higher values, while pushing corresponding differences for non-melanomas towards lower values.

Multiplication of the weight vector by any positive constant, will not change the distribution of the diagnostic indices. Thus, the length of $\mathbf{w}$ may be constrained by the second term in the following equation:

$$J(\mathbf{w}) = J_0(\mathbf{w}) + \alpha_1(\mathbf{w}^* \mathbf{w} - \mathbf{w}_0^* \mathbf{w}_0)^2 + \alpha_2 J_2(\mathbf{w}) + \alpha_3 J_3(\mathbf{w}),$$

where $\mathbf{w}_0$ is the initial guess for the weight vector. The second term in the equation above constrains the end points of the weight vectors $\mathbf{w}$ to lie on the surface of a hypersphere in 76 (per the earlier example) dimensions of radius $\mathbf{w}_0$. If the end point of the weight vector $\mathbf{w}$ lies outside or inside the surface of the hypersphere, its length will be longer or shorter than the length of the vector $\mathbf{w}_0$, which is the radius of hypersphere. The constraint term $\alpha_1(\mathbf{w}^* \mathbf{w} - \mathbf{w}_0^* \mathbf{w}_0)^2$ will be non-negative, and will increase the further away from the surface of the hypersphere the end point of the weight vector $\mathbf{w}$ lies. Thus, by adding the constraint term with positive value of the coefficient α_1 to the cost function, which is to be minimized, the optimization routine is constrained to look for solutions $\mathbf{w}$ that have end points close to the surface of the hypersphere of radius $|\mathbf{w}_0|$.

Probabilistic (soft) constraints on the weight vector $\mathbf{w}$ will be required to get a well-posed optimization problem. Such constraints should include *a priori* information about the covariance. A self-adaptive regularization, which exploits the use of a specific function associated with Fisher's information operator may be used. This kind of regularization allows for automatic suppression of variations in those elements of $\mathbf{w}$, which do not contribute to the correct diagnosis.

It is possible that some of the 28 physiology-morphology parameters and the 10 pure morphology parameters may not be vital for the diagnosis. In order to

exclude insignificant parameters, the fourth term $J_3(\mathbf{w})$ in the cost function equation is included. Thus, the fourth term of the cost function in terms of Shannon's entropy is:

$$J_3(\mathbf{w}) = -\mathbf{s}(\mathbf{w}) \cdot \ln \mathbf{s}(\mathbf{w}),$$

where $\mathbf{s}(\mathbf{w})$ is the probability density vector function of the weight vector $\mathbf{w}$, with components given by

$$s_i = |w_i| / \sum_{i=1}^{76} |w_i| \quad ; \quad \sum_{i=1}^{76} s_i = 1$$

and where $\ln \mathbf{s}(\mathbf{w})$ is a vector with components $(\ln s_1, \ln s_2, \dots, \ln s_{76})$.

Note that $J_3(\mathbf{w})$ is non-negative, and that its smallest value of zero occurs if all weights are zero, except for one of them. Since the goal is to minimize the cost function, the Shannon entropy should be as small as possible, *i.e.* as many weights as possible should be zero, so that the corresponding physiology/morphology or pure morphology parameters from the input parameter vector $\mathbf{p}$ can be excluded. For this reason the term involving $J_3(\mathbf{w})$ is called Occam's rule.

Occam's rule may not be sufficient in order to exclude insignificant parameters. Therefore, the 76-element weight vector may be a sum of the initial weight vector $\mathbf{w}_0$ and a superposition of certain basis vectors $\mathbf{v}_j$ with coefficients a_j :

$$\mathbf{w} = \mathbf{w}_0 + \mathbf{V} \mathbf{a}$$

where $\mathbf{V}$ is a $76 \times L$ matrix, composed of $L < 76$ basis vectors (column vectors: $\mathbf{v}_1, \mathbf{v}_2, \mathbf{v}_3, \dots, \mathbf{v}_L$), each having 76 components, and $\mathbf{a}$ is a column vector with L components a_j ($j = 1, 2, \dots, L$). Further, the number L is determined through the use of an information operator. Also, the basis vectors $\mathbf{v}_1, \mathbf{v}_2, \mathbf{v}_3, \dots, \mathbf{v}_L$, and the coefficients a_j of interest may be determined. An information operator $\mathbf{H}_0^*$ is defined as follows:

$$\mathbf{H}_0^* = \mathbf{H}_0 \mathbf{C}_U^{-1} \mathbf{C}_p \mathbf{C}_p \mathbf{C}_U^{-1} \mathbf{H}_0,$$

where $\mathbf{H}_0$ is the Hessian matrix associated with the master term of the cost function, *i.e.*

$$\mathbf{H}_0(\mathbf{w}) = \left[\frac{\partial^2}{\partial \mathbf{w}^2} J_0(\mathbf{w}) \right]_{\mathbf{w}_0}.$$

Here $\mathbf{w}_0$ is the initial value of $\mathbf{w}$. $\mathbf{C}_p$ is the covariance matrix of the input parameter vectors $\mathbf{p}$ for all measurements:

$$\mathbf{C}_p = \langle (\mathbf{p} - \langle \mathbf{p} \rangle)(\mathbf{p} - \langle \mathbf{p} \rangle)^T \rangle$$

and $\mathbf{C}_U$ is the covariance matrix of the measurement errors:

$$\mathbf{C}_U = \mathbf{C}_U^* + k\mathbf{I}$$

where $\mathbf{I}$ is the unity matrix, k is a regularization factor to ensure the invertibility of $\mathbf{C}_U$, and $\mathbf{C}_U^*$ is given by

$$\mathbf{C}_U^* = \langle \langle (\mathbf{p}_{lesion} - \langle \mathbf{p}_{lesion} \rangle)(\mathbf{p}_{lesion} - \langle \mathbf{p}_{lesion} \rangle)^T \rangle \rangle = \langle (\mathbf{C}_p)_{lesion} \rangle$$

where $(\mathbf{C}_p)_{lesion}$ is the covariance matrix for all measurements performed on one lesion, and where the final averaging is over all lesions.

Note that the information operator contains all pathological information as well as information about measurement uncertainties and the ranges of variation of the input parameters. The expression for the information operator can be interpreted as follows. The larger the value of $\mathbf{H}_0^*$, the smaller the measurement errors (represented by $\mathbf{C}_0$), the wider the range of the input parameters (represented by $\mathbf{C}_p$), the more information we can obtain for diagnostic purposes.

Next, the eigenvalue problem for the information operator

$$\mathbf{H}_0^* \mathbf{v}^{(0)} = \lambda^{(0)} \mathbf{v}^{(0)}$$

where $\mathbf{v}^{(0)}$ is an eigenvector that depends on the initial weight vector $\mathbf{w}_0$, and $\lambda^{(0)}$ is the eigenvalue. However, the tangential projection $\mathbf{e}$ of the eigenvector is

$$\mathbf{e} = (\mathbf{I} - \mathbf{w}_0 \mathbf{w}_0^T) \mathbf{v}^{(0)}$$

where $\mathbf{w}_0$ is the initial weight vector. The vectors $\mathbf{e}$, which are not orthonormal, but which satisfy the constraint that the end point of the weight vector should lie on the hypersphere, will be used as basis vectors to represent $\mathbf{w}$.

Next, the set of eigenvectors is ordered according to the magnitude of the product I_i of the eigenvalue λ_i and the length squared of the tangential projection $\mathbf{e}_i$ ($I_i = |\lambda_i| |\mathbf{e}_i|^2$), and then only those tangential projections $\mathbf{e}_i$ of the eigenvector are considered that satisfy the inequality

$$I_i = |\lambda_i| |\mathbf{e}_i|^2 > \alpha \{(|\lambda| |\mathbf{e}|)^2\}_{max}$$

where α is a threshold value to be determined that is positive and less than a certain pre-selected value, currently set to 0.01. The larger the value of I_i , the larger the information content associated with the corresponding basis vector $\mathbf{e}_i$.

Now the weight vector is defined by replacing $\mathbf{V}$ by $\mathbf{E}$ in the previous expression for $\mathbf{w}$:

$$\mathbf{w} = \mathbf{w}_0 + \mathbf{E} \mathbf{a}$$

where $\mathbf{E}$ is a $76 \times L$ matrix, composed of L basis vectors (column vectors: $\mathbf{e}_1, \mathbf{e}_2, \mathbf{e}_3, \dots, \mathbf{e}_L$), each having 76 components, and $\mathbf{a}$ is a column vector with L components, the number L being the maximum value of i . The vector $\mathbf{a}$ will be determined by the optimization.

Using the representation above for $\mathbf{w}$, we redefine the cost function as follows:

$$J^*(\mathbf{a}) = J_0^*(\mathbf{a}) + \alpha_1 J_1^*(\mathbf{a}) + \alpha_2 \underbrace{[\mathbf{a}^T(\mathbf{R}\mathbf{a})]}_{J_2(\mathbf{w})} + \alpha_3 J_3^*(\mathbf{a})$$

where

$$J^*(\mathbf{a}) = J(\mathbf{w}) = J(\mathbf{w}_0 + \mathbf{E} \mathbf{a}); J_n^*(\mathbf{a}) = J_n(\mathbf{w}) = J_n(\mathbf{w}_0 + \mathbf{E} \mathbf{a}); (n = 0, 1, 2, 3).$$

The regularization term $\mathbf{a}^T(\mathbf{R}\mathbf{a})$ contains the diagonal matrix $\mathbf{R}$ with elements $(I_1^{-1}, I_2^{-1}, \dots, I_L^{-1})$, where $I_i = \|\lambda_i \mathbf{e}_i\|^2$, and L is the maximum value of i .

The regularization term is constructed such that the smaller the information content in a certain direction, the shorter the step taken in that direction.

In order to investigate the accuracy and robustness of the method, an example is to apply the method to a clinical data set that had been performed on

pigmented lesions on 100 different patients. The total number of lesions was 125, and three OTD measurements (each consisting of 30 images) were taken of each lesion, making the total number of measurements $125 \times 3 = 375$. But some of the measurements were discarded because of measurement errors, reducing the total number of useful measurements to 342.

A receiver operating characteristic (ROC) curve (as defined here) is a graphical plot of sensitivity vs. specificity. By applying the method of the present invention to the clinical data set described above, the sensitivity was found to be 1 (*i.e.* 100%) for any specificity below 0.914 (*i.e.* 91.4%). The area underneath the ROC curve should be equal to 1 in order to have a sensitivity of 100% for a specificity of 100%. The application to clinical data just mentioned showed that a reduction of the value of the master term of the cost function is highly correlated to an increase in the area underneath the ROC curve.

The optimization may be performed in accordance with the described procedure. The optimization is an iterative process, where the optimized weight vector from a given iteration is used as the input weight vector to the next iteration. For example, a total of 8 iterations may be used for each optimization, and the weights for each of the iterations may be stored. The optimization may be performed on any subset. In this example, the criterion used for accepting a weight vector was that it should give a specificity value larger than 90% at 100% sensitivity for all subsets.

The described method may be used to find optimized weights for a few different subsets of the entire data set. The subsets were created by starting from the entire set of all clinical measurements (342) and excluding some of the measurements. One subset was created by dividing the total set into three equal parts, each consisting of every third measurement, and then excluding one third of the total subset, so that the remaining subset contained two thirds of the entire data set. In the current data set there are a total of eleven melanomas. Nine different subsets were created by excluding all measurements that had been performed on one of the eleven lesions being a melanoma according to the pathology report.

Covariance matrices are used in the information operator and Occam's rule is used in the cost function, in order to suppress insignificant weights (and corresponding input parameters). In the clinical data described above, several weights were found to be very small and were set equal to zero. The new weight vector with fewer non-zero weights was tested for acceptance. With a correct selection of insignificant weights, the specificity at 100% sensitivity for all subsets did not change noticeably. With the present invention, weights optimized using several different subsets were found to be acceptable with as many as 26 of the 76 weights set equal to zero.

No element, act, or instruction used in the present disclosure should be construed as critical or essential unless explicitly described as such. In addition, as used herein, the article "a" is intended to include one or more items. Where only one item is intended, the term "one" or similar language is used.

It will be understood that various modifications may be made to the embodiments disclosed herein. Therefore, the above description should not be construed as limiting, but merely as exemplifications of the various embodiments of the present disclosure. Those skilled in the art will envision other modifications within the scope and spirit of the claims appended hereto.

WHAT IS CLAIMED IS:

1. A method for discriminating between benign and malignant tissue lesions, the method comprising the steps of:
 - using a plurality of maps of physiology and morphology parameters generated from reflectance measurements;
 - using a plurality of pure morphology parameters generated from reflectance measurements;
 - calculating entropies and cross entropies of said plurality of maps;
 - calculating a plurality of pure morphology parameters;
 - assigning a weight to each said entropy and a weight to a logarithm of each said entropy;
 - assigning a weight to each said cross entropy and a weight to a logarithm of each said cross entropy;
 - assigning a weight to each said pure morphology parameter and a weight to a logarithm of each said pure morphology parameter;
 - computing a diagnostic index;
 - defining a cost function;
 - defining a proper threshold value for a diagnostic index;
 - solving an optimization problem to determine a set of weights from said assigned weights to maximize specificity for 100% sensitivity; and
 - using calculations, said cost function and the diagnostic index to determine whether said tissue lesion is benign or malignant.
2. The method of claim 1, wherein the diagnostic index is computed by using said entropies, cross entropies, said pure morphology parameters and said plurality of logarithms.
3. The method of claim 1, wherein the cost function includes a master term with pathology information from a plurality of investigated lesions.

4. The method of claim 1, wherein the proper threshold value for said diagnostic index is used to differentiate between benign and malignant tissue lesions.
5. The method of claim 1, wherein the method is used to discriminate between benign pigmented lesions and malignant melanoma.
6. The method of claim 1, wherein the method is used to discriminate between benign tissue and basal cell carcinoma.
7. The method of claim 1, wherein the method is used to discriminate between benign tissue and squamous cell carcinoma.
8. The method of claim 1, wherein the method is used for beauty care.
9. The method of claim 1, wherein the method is used for forensic medicine.
10. The method of claim 1, wherein the method is used to monitor efficacies of different kinds of treatment.

Figure 1

Method 100

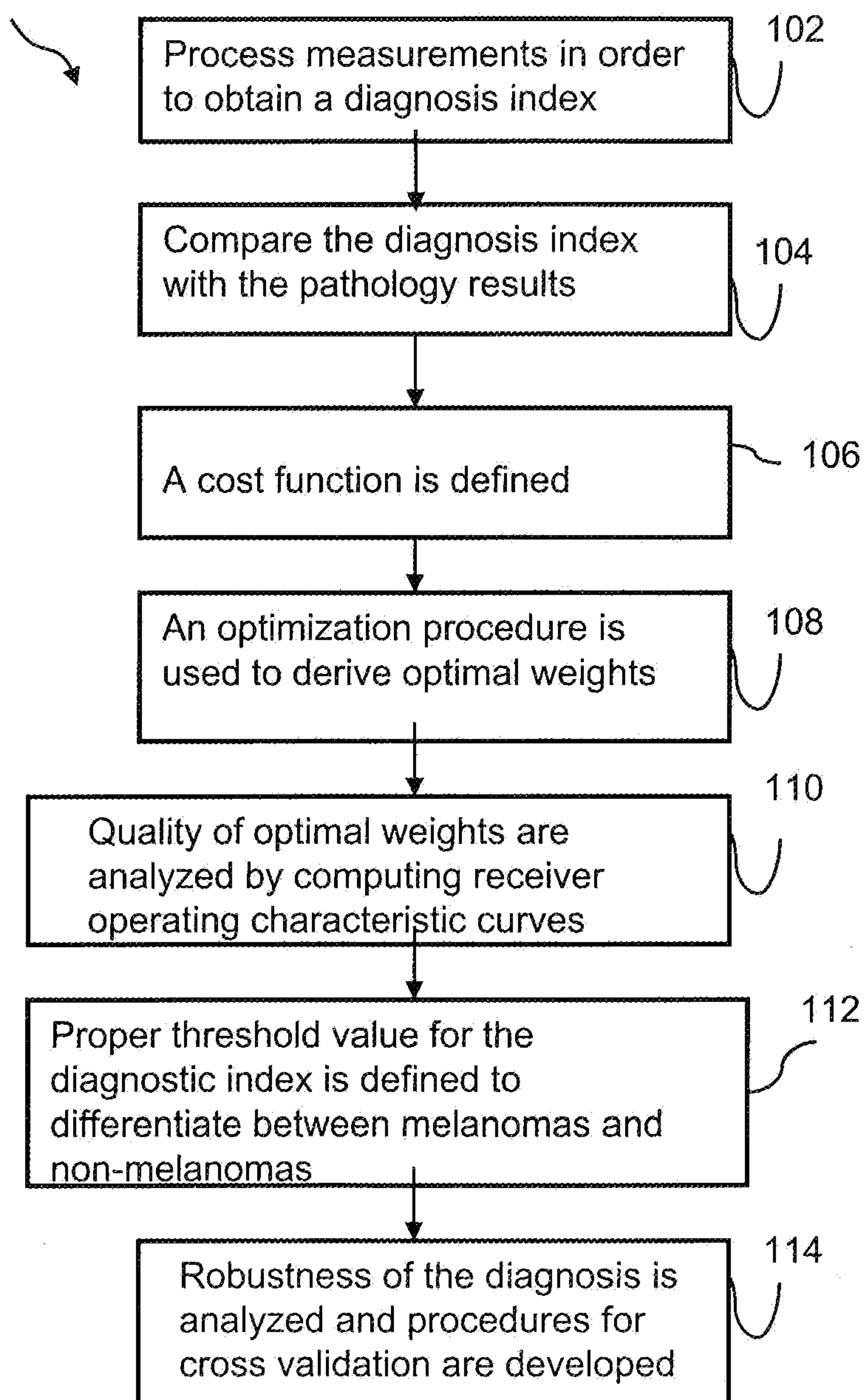
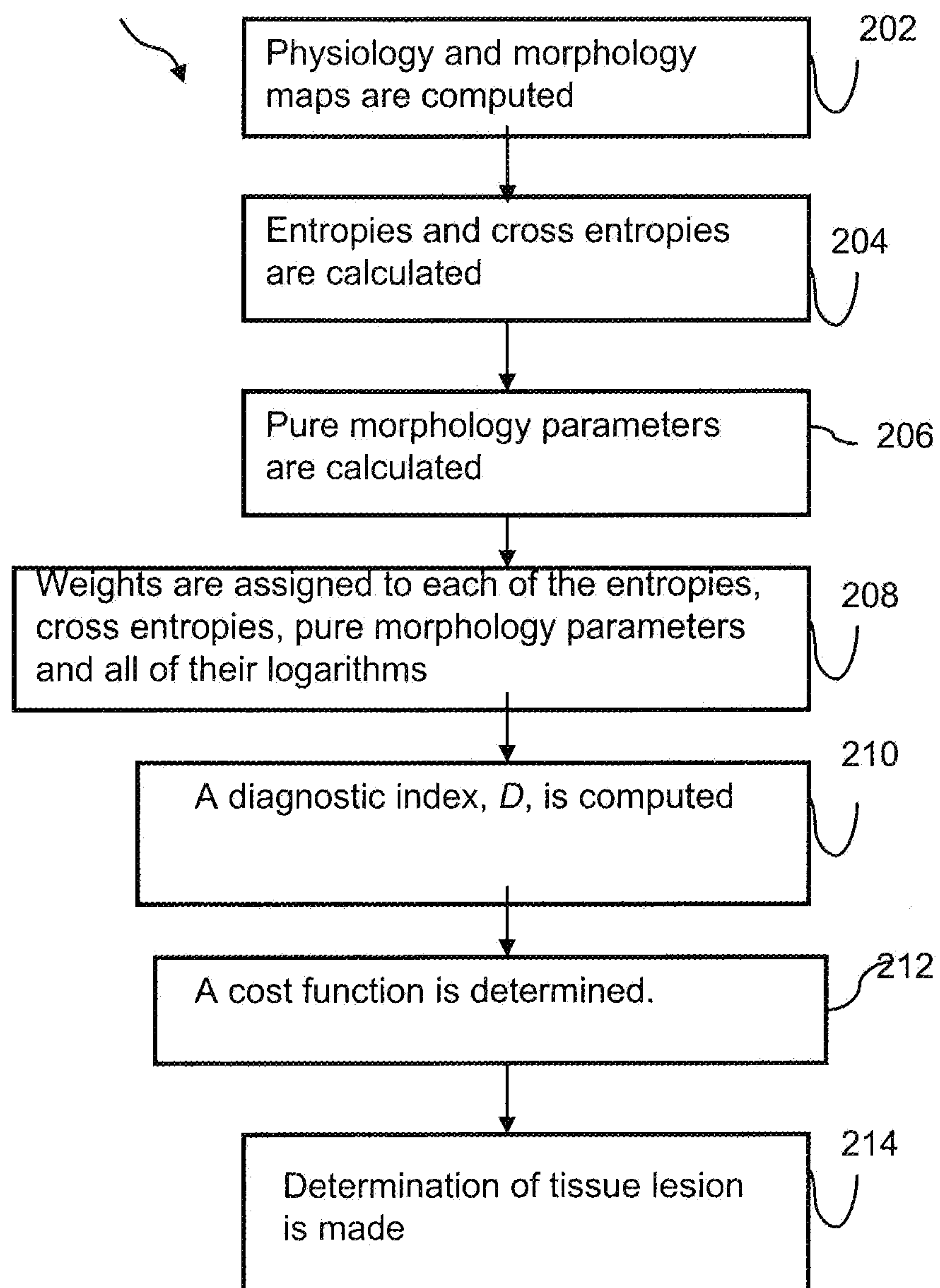


Figure 2

Method 200



Method 200

Figure 2

