

CLAIMS:

1. A method for quantifying a biomarker of a tissue, the method comprising:
 - acquiring a plurality of images of the tissue at discrete wavelengths within a main wavelength interval using an imaging sensor;
 - determining, using a processor, at least two spectral sub-intervals in a manner such that combination of the image data in the at least two spectral sub-intervals is correlated with a clinical variable of interest; and
 - calculating a measure of the biomarker of the tissue using the image data in the at least two spectral sub-intervals using the processor;wherein the main wavelength interval is broader than each of the at least two spectral sub-intervals and at least one spectral confounder causing a spectral variability of the acquired image is present in the tissue.
2. A method for quantifying a biomarker of a tissue, the method comprising:
 - determining, using a processor, at least two spectral sub-intervals from a plurality of images of the tissue acquired at discrete wavelengths within a main wavelength interval using an imaging sensor in a manner such that the combination of the image data in the at least two spectral sub-intervals is correlated with a clinical variable of interest;
 - illuminating the tissue using one or more light sources with wavelengths within the at least two spectral sub-intervals;
 - acquiring a measurement of the light reflected by the tissue using an imaging sensor; and
 - calculating a measure of the biomarker of the tissue using the acquired measurement;wherein the main wavelength interval is broader than each of the at least two spectral sub-intervals and at least one spectral confounder causing a spectral variability of the acquired image is present in the tissue.

3. The method of claim 1 or 2, wherein the clinical variable of interest comprises any one or a combination of a disease, a severity or subtype of disease, a known biomarker or a physiological state.
4. The method of any of claims 1 to 3 wherein the main wavelength interval is such that the acquired images represent a hyperspectral or multispectral representation of the tissue.
5. The method of any one of claims 1 to 4, wherein acquiring a plurality of images comprises using one or more cameras operating at different wavelengths.
6. The method of any of claims 1 to 5 comprising extracting a spectral parameter for each of the at least two spectral sub-intervals to form a multispectral representation of the tissue.
7. The method of any of claims 1 to 6 comprising identifying at least one spectral confounder causing a spectral variability in the acquired images.
8. The method of any one of claims 1 to 7, wherein determining at least two spectral sub-intervals is performed in a manner such that the spectral information of the combination of the at least two spectral sub-intervals and the spectral confounder are orthogonal, uncorrelated or independent.
9. The method of any one of claims 1 to 8, wherein determining at least two spectral sub-intervals is performed by applying a band selection method, a machine learning algorithm or an artificial intelligence engine.
10. The method of any one of claims 1 to 10, wherein the variable of interest comprises the amount or distribution of amyloid beta measured in a brain using positron emission tomography (PET), or measured in cerebrospinal fluid (CSF).
11. The method of any one of claims 1 to 10, wherein determining at least two spectral sub-intervals comprises using a multivariate statistics, machine learning or artificial intelligence techniques.
12. The method of any one of claims 1 to 11, wherein calculating a measure of the biomarker uses multivariate statistics, machine learning or artificial intelligence

techniques.

13. The method of claim 12, wherein the multivariate statistics include regression, logistic regression or discrimination.
14. The method of claim 11 or 12, wherein the machine learning or artificial intelligence techniques account for demographic information, clinical information, other variables of interest or multiple regions of interest in the image data.
15. The method of any one of claims 1 to 14, wherein determining at least two spectral sub-intervals is performed by a machine learning algorithm that transforms multispectral data into a score that represents the biomarker.
16. The method of any one of claims 2 to 16, further comprising applying an optical filter to the one or more light sources.
17. The method of claim 16, wherein further comprising applying an optical filter along a light path of the light generated by the one or more light sources.
18. The method of claims 16 or 17, wherein the tissue is the retina of a person and the optical filter is embedded within a contact lens applied on an eye of the person.
19. A system for quantifying a biomarker of a tissue, the system comprising:
 - an optical assembly comprising one or more light sources, the optical assembly being arranged to illuminate a portion of the tissue at wavelengths within at least two predetermined spectral intervals; and
 - an imaging assembly comprising an imaging sensor arranged to receive light reflected from the portion of the tissue and translate the light to digital data;
 - wherein the at least two predetermined spectral sub-intervals are specific to a known variable of interest.
20. The system of claim 19, comprising a biomarker selection assembly arranged to select the at least two light spectral intervals based on a user selected biomarker of a tissue.
21. The system of claims 19 or 20, comprising a processing module arranged to receive

data from the imaging sensor and being configured to:

combine and process the data received from the imaging sensor to extract spectral information and form a multispectral representation of the tissue; and

process the multispectral representation of the tissue to quantify the biomarker.

22. The system of any of claims 19 to 21, wherein the tissue is a portion of the retina and the biomarker is a measure of amyloid beta (AB) for predicting/stratifying risk, screening or diagnosing Alzheimer's disease and the at least two spectral intervals consist of three wavebands located within about 100 nm of 475 nm, within about 100 nm of 545 nm, and within about 100 nm of 725 nm, and each with a bandwidth under about 200 nm.
23. The system of any of claims 19 to 22, wherein the optical assembly is arranged to generate light with a spectrum within the at least two spectral intervals.
24. The system of any of claims 19 to 23, wherein the illumination assembly comprises optical filters arranged to filter the generated light path or the reflected light path within the at least two sub-spectral intervals.
25. The system of any one of claims 19 to 24, wherein the tissue is a portion of the retina and the variable of interest is brain or cerebrospinal fluid amyloid beta level related to Alzheimer's disease and the at least two spectral intervals consist of three wavebands located within about 100 nm of 475 nm, within about 100 nm of 545 nm, and within about 100 nm of 725 nm, and each with a bandwidth under about 200 nm.
26. A method for quantifying a biomarker of a tissue, the method comprising:
 - acquiring a hyperspectral image of the tissue using an imaging sensor within a contiguous wavelength interval;
 - identifying at least one spectral confounder causing a spectral variability of the hyperspectral image;

deriving a spectral model of the tissue in a manner such that the correlation of the spectral model and the identified spectral confounder is minimized; and

calculating a measure of the biomarker of the tissue using the derived spectral model.

27. The method of claim 26, wherein the spectral model of the tissue is derived to be orthogonal, uncorrelated or independent to the identified spectral confounder.
28. The method of claims 26 or 27, wherein the spectral model is derived from the main spectral difference between two groups, each group having a distinct amount of the variable of interest.
29. The method of any of claims 26 to 28, wherein deriving a spectral model of the tissue comprises deriving a clean hyperspectral representation of the tissue by processing the hyperspectral representation of the tissue and a spectral signature of the at least one spectral confounder in a manner such that the clean hyperspectral representation of the tissue has reduced variability caused by the spectral signature of the at least one spectral confounder.
30. The method of any one of claims 26 to 29, wherein acquiring an hyperspectral image of the tissue comprises sequentially illuminating the tissue, using one or more light sources, with monochromatic or narrow bandwidth light within a contiguous predetermined range of wavelengths and, for each wavelength, using the imaging sensor to acquire a measurement of the light reflected by the tissue.
31. The method of any of claims 26 to 30, wherein identifying at least one spectral confounder comprises reading from a spectral database one or more spectral profiles of spectral confounders and processing the spectral information from the hyperspectral image and the one or more spectral profile.
32. The method of any of claims 26 to 31, wherein deriving a clean hyperspectral representation comprises removing, from the spectral information, a spectral variability caused by the spectral profile of the at least one spectral confounder.
33. The method of any one of claims 26 to 32 wherein identifying at least one spectral

confounder comprises using a specific spectral confounder as a reference cofounder and calculating a delta hyperspectral image which represents a pixel-by-pixel and wavelength-by-wavelength difference between two hyperspectral images.

34. The method of any one of claims 26 to 33, wherein the spectral information is processed in accordance with the following steps:

computing the inter-class spectral variability between groups that differ with respect to the variable of interest;

extracting a first set of principal eigenvectors of the intra-class spectral database; and

removing one or more eigenvectors using an orthogonal projection to produce an intermediate dataset in which the intra-class variability is substantially removed;

wherein the biomarker is quantified using a spectral dimension reduction based on the clean spectral representation of the tissue.

35. The method of any one of claims 26 to 34, wherein the spectral information is processed in accordance with the following steps:

computing the inter-class spectral variability between distinct groups of the spectral database;

extracting a first set of principal eigenvectors of the inter-class variability between the distinct groups;

removing the inter-class variability using an orthogonal projection based on the first set of principal eigenvectors from a combination of the distinct groups to produce an intermediate dataset in which the inter-class variability is substantially removed;

computing intra-class variability within the intermediate dataset; extracting a second set of principal eigenvectors of the intra-class variability of the intermediate dataset; and

extracting a third set of principal eigenvectors of a plurality of clean spectral presentations in the statistical database;

wherein removing, from the interim spectral information, the spectral variability caused by the at least one non-specific confounder comprises removing, from the interim spectral information, the intra-class variability using an orthogonal projection based on the second set of principal eigenvectors to create the clean spectral representation of the tissue; and

wherein the biomarker is quantified using a projection based on the third set of principal eigenvectors on the clean spectral representation of the tissue.

36. The method of claim 35, wherein the at least one spectral confounder comprises at least one ocular confounder and the quantified biomarker indicates the presence or absence of a variable of interest in the retina of the person.
37. The method of claim 36, wherein the at least one ocular spectral confounder is comprised of variations in melanin content, cataract, discolouration of the lens, hemoglobin content, retinopathy, retinal pigment epithelial thickness or density, RNFL thickness, choroidal thickness, macular pigment content and/or a combination thereof.
38. A system for quantifying a biomarker of a tissue, the system comprising:
 - an illumination assembly arranged to successively illuminate a portion of a tissue with monochromatic light within a contiguous range of wavelengths;
 - an imaging assembly comprising an imaging sensor arranged to receive light reflected by the portion of the tissue and translate the light to digital data; and
 - a processing module and a memory module arranged to receive data from the imaging sensor and being configured to execute instructions to perform a method in accordance with anyone of claims 27 to 38.