

OPTICAL ARRANGEMENT, DEVICE AND NON-INVASIVE METHOD FOR
ANALYZING A SKIN SAMPLE

Cross-Reference To Related Application

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[0001] This application claims the benefit of priority of Singapore patent application No. 10202301934V, filed 6 July 2023, the content of it being hereby incorporated by reference in its entirety for all purposes.

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Technical Field

[0002] Various embodiments relate to an optical arrangement, a device and a non-invasive method for analyzing a skin sample.

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Background

[0003] By 2025, it is estimated that over 1 billion women around the world (constituting 12% of the entire world population) would be experiencing menopause. Menopause is accompanied by several symptoms affecting physical and mental wellness and quality of life (QoL) and is estimated to cost USD 3 billion in annual health expenditure. By 2027, the costs may increase to USD 60 billion in view of a global aging/longevity/silver economy. Symptoms affecting the estrogen-receptor rich areas of women's lower genitourinary tract (LGT) include the Genitourinary Syndrome of Menopause (GSM), affecting at least 84% of menopausal women. The actual prevalence is likely to be higher due to increasing prevalence with aging. GSM refers to oestrogen deficiency associated genital, sexual, and urinary changes in the lower genital tract of menopausal women. Typical symptoms include vulvovaginal dryness, itch, irritation and burning; vaginal discharge; decreased lubrication; painful sex; dysorgasmia; postmenopausal bleeding; urinary frequency, urgency and urge incontinence, dysuria, nocturia and urinary tract infections.

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[0004] Without effective treatment, GSM and postmenopausal complications evolve chronically affecting both QoL as well as the functional and structural aspects of the urogenital tissue. As per a survey, vaginal dryness had a QoL index of 0.566, similar to that of stroke patients and patients with multiple comorbidities.

5 [0005] Diagnosis of GSM is usually clinical, based on medical history and pelvic examination. However, findings at physical examination do not always correlate with the presence or severity of symptoms. Laboratory testing is not typically undertaken, although cultures or biopsies can be performed if the diagnosis is in question, or there is non-responsiveness to treatment. Invasive methods, such as vulva or vaginal biopsy are the gold
10 standard for diagnosis but are least acceptable to patients due to invasiveness, pain, potential complications, and cost. Vaginal Maturation Index (VMI) objectively quantifies the estrogen status of the vaginal epithelium and related structures (vulva, urethra, and bladder). However, it is invasive, requires cytological expertise, is costly and has not gained widespread use beyond research labs. Furthermore, most clinical settings have
15 moved to automation which does not report on cell maturation. Colposcopy just increases magnification without chromophore information and ultrasound is not validated in GSM and unsuitable in those who have not been sexually active. Both require machines that are bulky, costly and not widely available.

[0006] Currently, estrogen therapy is prescribed as “one size fits all” approach for GSM
20 patients, without available objective tech to compare the efficacy of treatment longitudinally, quantify the dosage and inter patient variation. As per studies, 60% of women aged 51-57 years have taken hormone replacement therapy (Br J Gen Pract. 2002; 52:835–837), with 45% having tried it by the time they are 50 (Br J Obstet Gynaecol. 1997; 104:923–933). In the US, about 38% of postmenopausal women take hormone replacement
25 therapy. In 2000, 46 million prescriptions were written for Premarin (conjugated equine estrogens), making it the second most frequently prescribed drug in the United States.

[0007] Both systemic and topical application of estrogen is contraindicated for breast cancer patients. Emerging treatment methods such as moisturizers, laser therapy, ultrasound heating, injection of adipose tissue, amongst others are yet to be fully explored
30 and validated. Their efficacy is yet to be studied extensively, partly due to lack of objective assessment technique.

[0008] There is an unmet need for a device that offers cost effective, objective, non-invasive and timely assessment to track the clinically relevant treatment outcomes and their safety for GSM therapy, thereby addressing at least the problems described above. The proposed technology aims to bring objectivity and personalized assessment and treatment response monitoring for estrogen therapy for menopausal women suffering from GSM.

Summary

[0009] According to an embodiment, an optical arrangement is provided. The optical arrangement may include a first fiber optic probe configured to measure Raman spectra of a skin sample; a second fiber optic probe configured to measure diffuse reflectance spectra of the skin sample; and an imaging camera configured to capture a reflectance image of the skin sample. The first fiber optic probe, at least part of the second fiber optic probe and the imaging camera may be arranged adjacent to one another. The optical arrangement may be configured to acquire at least one selected from the Raman spectra, the diffuse reflectance spectra, or the reflectance image in a location of the skin sample. Based on the at least one selected from the acquired Raman spectra, the acquired diffuse reflectance spectra, or the acquired reflectance image, the optical arrangement may be configured to interrogate a pre-determined depth below a surface of the skin sample at the location, or tissue chromophores of the skin sample at the pre-determined depth, or both.

[0010] According to an embodiment, a device is provided. The device may include an analytical unit; and an optical arrangement in communication with the analytical unit. The optical arrangement may include a first fiber optic probe configured to measure Raman spectra of a skin sample; a second fiber optic probe configured to measure diffuse reflectance spectra of the skin sample; and an imaging camera configured to capture a reflectance image of the skin sample, the first fiber optic probe, at least part of the second fiber optic probe and the imaging camera being arranged adjacent to one another. The optical arrangement may be configured to acquire at least one selected from the Raman spectra, the diffuse reflectance spectra, or the reflectance image in a location of the skin sample. Based on the at least one selected from the acquired Raman spectra, the acquired diffuse reflectance spectra, or the acquired reflectance image, the optical arrangement may

be configured to interrogate a pre-determined depth below a surface of the skin sample at the location, or tissue chromophores of the skin sample at the pre-determined depth, or both. The analytical unit may be configured to assess data including the at least one selected from the acquired Raman spectra, the acquired diffuse reflectance spectra, or the acquired reflectance image, and the interrogated pre-determined depth and the interrogated tissue chromophores to determine a medical status and/or condition based on the skin sample.

[0011] According to an embodiment, a non-invasive method for analyzing a skin sample is provided. The non-invasive method may include acquiring at least one selected from Raman spectra, diffuse reflectance spectra or a reflectance image of the skin sample in a location of the skin sample; based on the at least one selected from the acquired Raman spectra, the acquired diffuse reflectance spectra, and the acquired reflectance image, interrogating a pre-determined depth below a surface of the skin sample at the location, or tissue chromophores of the skin sample at the pre-determined depth, or both; assessing data including the at least one selected from the acquired Raman spectra, the acquired diffuse reflectance spectra, or the acquired reflectance image, and the interrogated pre-determined depth and the interrogated tissue chromophores to determine a medical status and/or condition based on the skin sample.

Brief Description of the Drawings

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[0012] In the drawings, like reference characters generally refer to like parts throughout the different views. The drawings are not necessarily to scale, emphasis instead generally being placed upon illustrating the principles of the invention. In the following description, various embodiments of the invention are described with reference to the following drawings, in which:

[0013] FIG. 1 shows a schematic cross-sectional view of an optical arrangement, according to various embodiments.

[0014] FIG. 2 shows a schematic cross-sectional view of a device for analyzing a skin sample, according to various embodiments.

[0015] FIG. 3 shows a flow chart illustrating a non-invasive method for analyzing a skin sample, according to various embodiments.

[0016] FIG. 4 shows a schematic cross-sectional view of the optical arrangement of FIG. 1 as a single probe, according to one example.

[0017] FIG. 5 shows an isolated view of a first fiber optic probe (e.g. a Raman probe) of FIG. 4.

5 [0018] FIG. 6 shows an isolated view of a second fiber optic probe (e.g. a DRS fiber probe) of FIG. 4.

[0019] FIG. 7 shows an isolated view of a second fiber optic probe, according to different embodiments.

[0020] FIG. 8 shows a photograph of a MFOIS device/system, according to one example.

10 [0021] FIG. 9 shows an expanded view of an integrated probe of the MFOIS device/system of FIG. 8, according to one example.

[0022] FIG. 10 shows a schematic cross-sectional view of the integrated probe of FIG. 9 with DRS, imaging and Raman fiber probe, according to one example.

15 [0023] FIG. 11 shows a plot illustrating the representative data of intervention experiments to capture the changes in blood fraction of human volunteers.

[0024] FIG. 12 shows a plot illustrating the representative data of intervention experiments to capture the changes in sO₂ of the human volunteers.

[0025] FIG. 13 shows a plot illustrating the representative data of intervention experiments to capture the changes in water of the human volunteers.

20 [0026] FIG. 14 shows a plot illustrating the representative data of intervention experiments to capture the changes in lipid content of the human volunteers.

[0027] FIG. 15 shows a plot illustrating the correlation between DRS water index measurement and commercial moisture meter measurement, according to one example.

25 [0028] FIG. 16 shows a plot illustrating average DRS measurement indicating difference in water content among pre-menopausal, peri-menopausal, and post-menopausal women in six locations of the vulva region, according to various examples.

[0029] FIG. 17 shows a plot illustrating average DRS measurement indicating difference in lipid content among pre-menopausal, peri-menopausal, and post-menopausal women in the six locations of the vulva region, according to various examples.

[0030] FIG. 18 shows a plot illustrating average DRS measurement indicating difference in oxygen saturation among pre-menopausal, peri-menopausal, and post-menopausal women in the six locations of the vulva region, according to various examples.

5 [0031] FIG. 19 shows a plot illustrating average DRS measurement indicating difference in blood fraction among pre-menopausal, peri-menopausal, and post-menopausal women in the six locations of the vulva region, according to various examples.

Detailed Description

10 [0032] The following detailed description refers to the accompanying drawings that show, by way of illustration, specific details and embodiments in which the invention may be practiced. These embodiments are described in sufficient detail to enable those skilled in the art to practice the invention. Other embodiments may be utilized and structural, logical, and electrical changes may be made without departing from the scope of the invention. The
15 various embodiments are not necessarily mutually exclusive, as some embodiments can be combined with one or more other embodiments to form new embodiments.

[0033] Embodiments described in the context of one of the methods or devices are analogously valid for the other methods or devices. Similarly, embodiments described in the context of a method are analogously valid for a device, and vice versa.

20 [0034] Features that are described in the context of an embodiment may correspondingly be applicable to the same or similar features in the other embodiments. Features that are described in the context of an embodiment may correspondingly be applicable to the other embodiments, even if not explicitly described in these other embodiments. Furthermore, additions and/or combinations and/or alternatives as described for a feature in the context
25 of an embodiment may correspondingly be applicable to the same or similar feature in the other embodiments.

[0035] In the context of various embodiments, the articles “a”, “an” and “the” as used with regard to a feature or element include a reference to one or more of the features or elements.

30 [0036] In the context of various embodiments, the phrase “substantially” may include “exactly” and a reasonable variance.

[0037] In the context of various embodiments, the term “about” or “approximately” as applied to a numeric value encompasses the exact value and a reasonable variance.

[0038] As used herein, the term “and/or” includes any and all combinations of one or more of the associated listed items.

5 [0039] As used herein, the phrase of the form of “at least one of A or B” may include A or B or both A and B. Correspondingly, the phrase of the form of “at least one of A or B or C”, or including further listed items, may include any and all combinations of one or more of the associated listed items.

[0040] As used herein, the expression “configured to” may mean “constructed to” or
10 “arranged to”.

[0041] Various embodiments may provide an optical spectroscopy device and a method for objective assessment of GSM. The technology may involve a custom designed fiber optic probe and an imaging camera to measure the diffuse reflectance spectroscopy (DRS) and Raman spectroscopy (RS) spectra and high-resolution reflectance image from the
15 vulva/vaginal skin non-invasively. The system employing this technology is named Multifunctional Fiber Optical Imaging and Spectroscopy (MFOIS). These spectral and imaging data may be used to evaluate the relative changes in water, lipid, melanin, oxygen saturation, estrogen content, amongst others in the vulva and vaginal skin. An objective scoring metrics may be developed based on these tissue chromophores.

20 [0042] FIG. 1 shows a schematic cross-sectional view of an optical arrangement 100, according to various embodiments. In FIG. 1, the optical arrangement 100 includes a first fiber optic probe 102 configured to measure Raman spectra of a skin sample (not shown in FIG. 1); a second fiber optic probe 104 configured to measure diffuse reflectance spectra of the skin sample; and an imaging camera 106 configured to capture a reflectance image
25 of the skin sample. The first fiber optic probe 102, at least part of the second fiber optic probe 104 and the imaging camera 106 may be arranged adjacent to one another, as denoted by a dotted circular path 108. Having the first fiber optic probe 102, and the at least part of the second fiber optic probe 104 arranged adjacent to each other may achieve high signal to noise ratio. The order and/or formation shape, in which the first fiber optic probe 102,
30 the at least part of the second fiber optic probe 104 and the imaging camera 106 may be arranged, may vary from that presented in FIG. 1 as long as the first fiber optic probe 102,

the at least part of the second fiber optic probe 104 and the imaging camera 106 may be in close proximity to one another to perform measurements at a location of the skin sample.

[0043] More specifically, the optical arrangement 100 may be configured to acquire at least one selected from the Raman spectra, the diffuse reflectance spectra, or the reflectance image in the location of the skin sample. Based on the at least one selected from the acquired Raman spectra (i.e. the Raman spectra measured by the first fiber optic probe 102), the acquired diffuse reflectance spectra (i.e. the diffuse reflectance spectra measured by the second fiber optic probe 104), or the acquired reflectance image (i.e. the reflectance image captured by the imaging camera 106), the optical arrangement 100 may be configured to interrogate a pre-determined depth below a surface of the skin sample at the location, or tissue chromophores of the skin sample at the pre-determined depth, or both.

[0044] In one embodiment, the optical arrangement 100 may be configured to acquire a combination of at least two selected from the Raman spectra, the diffuse reflectance spectra, or the reflectance image sequentially in the location of the skin sample.

[0045] In the context of various embodiments, the term “acquire” may mean measure, obtain, detect, or capture.

[0046] In other words, the optical arrangement 100 may provide integrated optical spectroscopy techniques including reflectance imaging, DRS and/or RS techniques to measure endogenous tissue chromophores (such as water content, lipid, oxygen saturation, melanin, estrogen, amongst others) to objectively track the safety and efficacy of GSM treatment methodology.

[0047] In various embodiments, the first fiber optic probe 102, the second fiber optic probe 104 and the imaging camera 106 may integrally form the optical arrangement 100 in a single probe, which may be interchangeably referred to as a MFOIS probe. FIG. 4 shows a schematic cross-sectional view of the MFOIS probe 400, according to one example. It should be appreciated that other arrangements of the first fiber optic probe 102, the second fiber optic probe 104 and the imaging camera 106 are also possible, although not shown in the figures.

[0048] As shown in FIG. 5, which depicts an isolated view of the first fiber optic probe 102 (e.g. interchangeably referred to as a Raman probe) in FIG. 4, the first fiber optic probe 102 may include a first optical fiber 1022 configured to deliver laser energy to excite the

skin sample; and a first plurality of optical fibers 1024 configured to detect and measure the Raman spectra of the skin sample. The first optical fiber 1022 may be centrally arranged along the first fiber optic probe 102, and the first plurality of optical fibers 1024 may be arranged substantially surrounding the first optical fiber 1022. While such a concentric arrangement is preferred, other arrangements of the first optical fiber 1022 and the first plurality of optical fibers 1024 may also be possible.

[0049] Each optical fiber of the first plurality of optical fibers 1024 may be arranged adjacent to and spaced apart from a neighbouring optical fiber of the first plurality of optical fibers 1024. The arrangement of each optical fiber of the first plurality of optical fibers 1024 may be based on the depth of interrogation.

[0050] In one example, illumination using the first optical fiber 1022 (e.g. interchangeably referred to as a laser source or an illumination source) being a single fiber may be a preference, while the first plurality of optical fibers 1024 (e.g. interchangeably referred to as collection/detection fibers) may be each a single fiber or a single fiber bundle/bunch. In another example, the first optical fiber 1022 may include a first optical fiber bundle, and each optical fiber of the first plurality of optical fibers 1024 may include an optical fiber bundle.

[0051] In various embodiments, the first optical fiber 1022 or each of the first plurality of optical fibers 1024 may include a single mode fiber, or a multimode fiber, or a combination of a single mode fiber and a multimode fiber.

[0052] The first optical fiber 1022 has a core size ranging from 150-800 μm and a cladding size of 160-800 μm .

[0053] The first optical fiber 1022 may have a transmission range of 350 nm to 2400 nm.

[0054] As shown in FIG. 6, which depicts an isolated view of the second fiber optic probe 104 (e.g. interchangeably referred to as a DRS fiber probe) in FIG. 4, the second fiber optic probe 104 may include a second optical fiber 1042 configured to deliver light to the skin sample; and a second plurality of optical fibers 1044 configured to detect and measure the diffuse reflectance spectra of the skin sample. The second optical fiber 1042 may be centrally arranged along the second fiber optic probe 104, and the second plurality of optical fibers 1044 may be arranged substantially surrounding the second optical fiber

1042. While such a concentric arrangement is preferred, other arrangements of the second optical fiber 1042 and the second plurality of optical fibers 1044 may also be possible.

[0055] Each optical fiber of the second plurality of optical fibers 1044 may be arranged adjacent to and spaced apart from a neighbouring optical fiber of the second plurality of optical fibers 1044. The arrangement of each optical fiber of the second plurality of optical fibers 1044 may be based on the depth of interrogation.

[0056] In one example, excitation using the second optical fiber 1042 (e.g. interchangeably referred to as a source fiber or an excitation fiber) being a single fiber may be a preference, while the second plurality of optical fibers 1044 (e.g. interchangeably referred to as DRS collection fibers or DRS detectors) may be each a single fiber or a single fiber bundle/bunch. In another example, the second optical fiber 1042 may include a second optical fiber bundle, and each optical fiber of the second plurality of optical fibers 1044 may include an optical fiber bundle.

[0057] In various embodiments, the second optical fiber 1042 or each of the second plurality of optical fibers 1044 may include a single mode fiber, or a multimode fiber, or a combination of a single mode fiber and a multimode fiber.

[0058] The second optical fiber may have a core size ranging from 150-800 μm and a cladding size of 160-800 μm .

[0059] The second optical fiber may have a transmission range of 350 nm to 2400 nm.

[0060] In some embodiments, each optical fiber of the second plurality of optical fibers 1044 may be arranged at a distance (D1 of FIG. 6) ranging between 500 μm and 1000 μm from the second optical fiber 1042. Such optical arrangement 100 may be configured to interrogate the pre-determined depth below the surface of the skin sample ranging between 250 μm and 2500 μm .

[0061] As shown in FIG. 7, which depicts an isolated view of the second fiber optic probe 104' according to different embodiments, each optical fiber of the second plurality of optical fibers 1044 may be arranged at a distance (D2) ranging between 2700 μm and 6000 μm from the second optical fiber 1042. Such optical arrangement 100 may be configured to interrogate the pre-determined depth below the surface of the skin sample ranging between 1300 μm and 3000 μm .

[0062] Various embodiments may provided the optical arrangement 100 configured to interrogate the pre-determined depth below the surface of the skin sample ranging between 25 μm and 1 mm.

5 [0063] In various embodiments (not shown in figures), the first fiber optic probe 102 and the imaging camera 106 may be integrated into the second fiber optic probe 104 such that the second plurality of optical fibers 1044 may be arranged substantially surrounding the second optical fiber 1042, the first fiber optic probe 102 and the imaging camera 106. Having the first fiber optic probe 102 integrated into the second fiber optic probe 104 may achieve high signal to noise ratio.

10 [0064] The second fiber optic probe 104 may further include a third optical fiber configured to deliver the light to the skin sample, the third optical fiber being arranged offset from the second optical fiber 1042 and substantially surrounded by the second plurality of optical fibers 1044. The third optical fiber may be provided to enhance the excitation.

15 [0065] The first fiber optic probe 102 and the imaging camera 106 may be collectively arranged between the second optical fiber 1042 and the third optical fiber.

[0066] According to various embodiments, when in operation, the optical arrangement 100 (or the MFOIS probe) may acquire DRS spectra only, or Raman spectra only, or a reflectance image only, or any combinations thereof, at a location of a sample area, depending on the applications and the requirements. In the event where the combinations involve any two of the DRS spectra, the Raman spectra, or the reflectance image to be acquired, or all three of the DRS spectra, the Raman spectra, and the reflectance image to be acquired, the acquisitions may be performed in a sequential manner at a same location of the sample area.

25 [0067] State-of-the-art devices including at least one optical fiber probe have been demonstrated for determining one or more tissue parameters. For example, a prior publication discloses a device capable of capturing digital images of a sample area using a CCD camera while measuring Raman, reflectance and/or fluorescence spectra mainly for skin assessment, specifically for lesions.

30 [0068] Various embodiments of the present invention may be vastly different as compared to state-of-the-art devices at least in the following aspects:

- A multifunctional probe configured to interrogate various depths of the skin, specifically to capture tissue features of vulva/vaginal skin at various depths (from about 25 microns to about 1mm) is proposed. This may only be achieved by customizing and optimizing the source-detector fiber separation, size of the fiber, numerical aperture of the fiber, and collection features.
- The probe may achieve reflectance imaging and sequential Raman spectroscopy measurement, and more specifically, may achieve spectral data from specific depth of skin.
- The probe may be a handheld probe.
- Further acquiring Raman signal from various depth in superficial layers (about 50 microns) requires new design of light collection geometry.
- It is proposed for quantitative detection of tissue features such as water, lipid, oxygenation, estrogen etc. and formation of totally new 'objective index' using these tissue parameters to evaluate the severity of GSM and its treatment monitoring.
- A device and probe may be customized to interrogate the vulva/vaginal skin to evaluate the GSM condition. To the best of the inventors' knowledge, there are no prior reports on using integrated DRS and Raman probe to evaluate the vulva/vaginal skin for GSM applications.
- The Raman probe may include an excitation fiber and a plurality of collection fibers, wherein the plurality of collection fibers may be arranged surrounding the excitation fiber in a concentric manner.
- The DRS probe may include an illumination fiber and a plurality of collection fibers, wherein the plurality of collection fibers may be arranged surrounding the illumination fiber in a concentric manner.
- It should be noted that a general skin specific fiber optic probe is not suitable for GSM application as the vulva/vaginal skin is thin (much smaller epidermal thickness) and less affected by Melanin. Thus, signal collection and interpretation throw totally different challenges if a general skin specific fiber optic probe is used.
- It is also proposed for detection of estrogen, specific for GSM in the vulva vaginal skin.

- The proposed design does not involve any revolving assembly, mainly for the orientation of the polarizing beam splitter and related lens system to center in the optical axis with a high degree of reproducibility. Such a configuration makes data collection prone for subtle movement. Instead, it is proposed for stable optical collection assemble and polarization independent measurements to be used.
- It is further proposed for novel spectral unmixing of DRS and Raman data to deduce the relative change in tissue chromophores and estrogen. Analytics according to the present invention may quantify the lipid and oxygen saturation at various skin depths other than standard water measurements.
- The diffused reflectance spectra in the present invention cover near-infrared regions up to 2000 nm, which are more effective for lipid, water analysis.

[0069] FIG. 2 shows a schematic cross-sectional view of a device 220, according to various embodiments. In FIG. 2, the device 220 may include an analytical unit 222; and an optical arrangement 100 in communication with the analytical unit 222, as denoted by a line 224. The optical arrangement 100 may include a first fiber optic probe 102 configured to measure Raman spectra of a skin sample; a second fiber optic probe 104 configured to measure diffuse reflectance spectra of the skin sample; and an imaging camera 106 configured to capture a reflectance image of the skin sample, wherein the first fiber optic probe 102, at least part of the second fiber optic probe 104 and the imaging camera 106 may be arranged adjacent to one another. The optical arrangement 100 may be configured to acquire at least one selected from the Raman spectra, the diffuse reflectance spectra, or the reflectance image in a location of the skin sample. Based on the at least one selected from the acquired Raman spectra, the acquired diffuse reflectance spectra, or the acquired reflectance image, the optical arrangement 100 may be configured to interrogate a pre-determined depth below a surface of the skin sample at the location, or tissue chromophores of the skin sample at the pre-determined depth, or both.

[0070] In various embodiments, the optical arrangement 100 may be configured to acquire a combination of at least two selected from the Raman spectra, the diffuse reflectance spectra, or the reflectance image sequentially in the location of the skin sample.

[0071] The optical arrangement 100 may include the optical arrangement 100 of FIG. 1. More specifically, the optical arrangement 100 of FIG. 2 may include the same or like elements or components as those of the optical arrangement 100 of FIG. 1, and as such, the same numerals are assigned and the like elements may be as described in the context of the optical arrangement 100 of FIG. 1, and therefore the corresponding descriptions are omitted here.

[0072] The analytical unit 222 may be configured to assess data including the at least one selected from the acquired Raman spectra, the acquired diffuse reflectance spectra, or the acquired reflectance image, and the interrogated pre-determined depth and the interrogated tissue chromophores to determine a medical status and/or condition based on the skin sample. The skin sample may be a vulva/vagina skin sample. The medical status and/or condition may be associated with Genitourinary Syndrome of Menopause of a female subject providing the skin sample.

[0073] In various embodiments, analytical unit 222 may include a receiving unit 226 configured to receive the data; a processor 228 configured to unmix the interrogated tissue chromophores and determine relative changes of tissue chromophores of the skin sample; and an output unit 230 configured to provide information based on the determined relative changes of tissue chromophores. The receiving unit 226 may be in communication with the processor 228, as denoted by a dotted line 232, while the processor 228 may be in communication with the output unit 230, as denoted by a dotted line 234.

[0074] In the context of various embodiments, the phrase “in communication” may refer to direct connection or indirect connection, wired communication or wireless communication. The term “assess” may mean analyze, examine, or calculate.

[0075] The processor 228 may further be configured to generate an objective index based on the determined relative changes of tissue chromophores, the objective index being used to monitor an efficacy of a course of treatment on the medical status and/or condition.

[0076] In other words, the device 220 may be for analyzing a skin sample and may be a multi-well surface-enhanced infrared spectroscopy (SEIRA) sensor chip that may include a custom designed portable multifunctional fiber optic probe capable of acquiring the reflectance image, DRS and RS sequentially e.g. in less than 1 minute in the location of the tissue; and interrogating the various depth in the skin to accurately deduce the

concentration of tissue chromophores such as water, lipid, melanin, oxygen saturation, estrogen, amongst others. The custom designed MFOIS point of care device may demonstrate associated data analytics for the objective assessment of the severity of GSM and way to monitor the effectiveness and dosage of their course of treatment, eventually
5 leading to safer and improved result. For example, the MFOIS may measure the endogenous tissue parameters (tissue chromophores) non-invasively (via non-contact) and objectively from LGT of woman undergoing GSM treatment, and may provide custom designed spectral/data analytics capable of spectrally unmix various tissue chromophores and estimate their relative changes in the vulva/vaginal skin. A new 'objective index', and
10 optionally using tissue markers, may be developed based on the tissue chromophores to provide objective assessment of the severity of GSM, as well as objectively track treatment outcome and efficacy.

[0077] The device 220 and the methodology which will be further explained below may be suitable for in situ measurements and close to real-time continuous monitoring.

15 [0078] FIG. 3 shows a flow chart illustrating a non-invasive method 340 for analyzing a skin sample, according to various embodiments. At Step 342, at least one selected from Raman spectra, diffuse reflectance spectra or a reflectance image of the skin sample may be acquired in a location of the skin sample. At Step 344, based on the at least one selected from the acquired Raman spectra, the acquired diffuse reflectance spectra, and the acquired
20 reflectance image, a pre-determined depth below a surface of the skin sample at the location, or tissue chromophores of the skin sample at the pre-determined depth, or both may be interrogated. At Step 346, data including the at least one selected from the acquired Raman spectra, the acquired diffuse reflectance spectra, or the acquired reflectance image, and the interrogated pre-determined depth and the interrogated tissue chromophores may
25 be assessed to determine a medical status and/or condition based on the skin sample.

[0079] The pre-determined depth may be ranged between 25 μm and 1 mm, or between 1300 μm and 3000 μm , or between 250 μm and 2500 μm . The skin sample may be a vulva/vagina skin sample.

30 [0080] The non-invasive method 340 may be performed by an optical arrangement 100 of FIG. 1 or a device 220 of FIG. 2. Since the optical arrangement 100 or the device 220 used in the non-invasive method 340 may include the same or like elements or components as

those of the optical arrangement 100 of FIG. 1 or the device 220 of FIG. 2, the same numerals are assigned and the like elements may be as described in the context of the optical arrangement 100 of FIG. 1 or the device 220 of FIG. 2, and therefore the corresponding descriptions are omitted here.

5 [0081] In one embodiment, Step 342 of acquiring the at least one selected from the Raman spectra, the diffuse reflectance spectra or the reflectance image of the skin sample may include acquiring a combination of at least two selected from the Raman spectra, the diffuse reflectance spectra or the reflectance image of the skin sample sequentially in the location of the skin sample. The step of acquiring the combination of the at least two selected from
10 the Raman spectra, the diffuse reflectance spectra, or the reflectance image of the skin sample sequentially in the location of the skin sample may include at least two correspondingly selected from: delivering laser energy to excite the skin sample, and sequentially measuring the Raman spectra using a first fiber optic probe 102; delivering light to illuminate the skin sample, and sequentially measuring the diffuse reflectance spectra using a second fiber optic probe 104; or sequentially capturing the reflectance
15 image using an imaging camera 106. For example, acquiring the combination of the at least two selected from the Raman spectra, the diffuse reflectance spectra or the reflectance image of the skin sample sequentially in the location of the skin sample may include acquiring the at least two selected from the Raman spectra, the diffuse reflectance spectra or the reflectance image of the skin sample sequentially in less than 1 minute in the location
20 of the skin sample.

[0082] In another embodiment, Step 342 of acquiring the at least one selected from the Raman spectra, the diffuse reflectance spectra or the reflectance image of the skin sample may include acquiring the Raman spectra, the diffuse reflectance spectra and the
25 reflectance image of the skin sample sequentially in the location of the skin sample. The step of acquiring the Raman spectra, the diffuse reflectance spectra, and the reflectance image of the skin sample sequentially in the location of the skin sample may include: delivering laser energy to excite the skin sample, and measuring the Raman spectra using a first fiber optic probe 102; delivering light to illuminate the skin sample, and sequentially
30 measuring the diffuse reflectance spectra using a second fiber optic probe 104; and sequentially capturing the reflectance image using an imaging camera 106. For example,

acquiring the Raman spectra, the diffuse reflectance spectra, and the reflectance image of the skin sample sequentially in the location of the skin sample may include acquiring the Raman spectra, the diffuse reflectance spectra and the reflectance image of the skin sample sequentially in less than 1 minute in the location of the skin sample.

5 [0083] The laser energy may be emitted from a laser operable in a wavelength range of 500 nm to 950 nm. The laser may include a single wavelength laser or a tunable laser.

[0084] The light may have a wavelength in a range of 300 nm to 2500 nm.

[0085] The first fiber optic probe 102, the second fiber optic probe 104 and the imaging camera 106 form a stable and non-revolving optical collection assemble.

10 [0086] In various embodiments, each of the Raman spectra, the diffuse reflectance spectra and the reflectance image may be polarization-independent.

[0087] Step 346 of assessing the data may include receiving the data, unmixing the interrogated tissue chromophores, determining relative changes of tissue chromophores of the skin sample, and providing information based on the determined relative changes of
15 tissue chromophores.

[0088] In various embodiments, the non-invasive method 340 may further include generating an objective index based on the determined relative changes of tissue chromophores, wherein the objective index may be used to monitor an efficacy of a course of treatment on the medical status and/or condition.

20 [0089] The tissue chromophores may include endogenous tissue chromophores. The tissue chromophores may include at least one of water contents, lipid contents, melanin contents, oxygen saturation levels, estrogen levels, and blood fraction levels.

[0090] The medical status and/or condition may be associated with Genitourinary Syndrome of Menopause of a female subject providing the skin sample. The non-invasive
25 method 340 may further be configured to assess a severity of the Genitourinary Syndrome of Menopause of the female subject. The non-invasive method 340 may include an in situ non-invasive method conducted on the female subject.

[0091] In various embodiments, the non-invasive method 340 may be performed in substantially real-time to provide continuous monitoring of the medical status and/or
30 condition.

[0092] While the method described above is illustrated and described as a series of steps or events, it will be appreciated that any ordering of such steps or events are not to be interpreted in a limiting sense. For example, some steps may occur in different orders and/or concurrently with other steps or events apart from those illustrated and/or described herein. In addition, not all illustrated steps may be required to implement one or more aspects or embodiments described herein. Also, one or more of the steps depicted herein may be carried out in one or more separate acts and/or phases.

[0093] Examples of the device 220 in the form of a MFOIS device/system and its employment in a pilot clinical study will be described as follows.

[0094] FIG. 8 shows a photograph of a MFOIS device/system 820, and FIG. 9 shows an expanded view of an integrated probe 800 of the MFOIS device/system 820, according to one example. FIG. 10 shows a schematic cross-sectional view of the integrated probe 800 with DRS 804, imaging 806 and Raman 802 fiber probe.

[0095] The MFOIS device/system 820 and the integrated probe 800 may include the same or like elements or components as those of the device 220 of FIG. 2 and the optical arrangement 100 of FIG. 1, respectively, and thus, the same ending numerals are assigned and the like elements may be as described in the context of the device 220 of FIG. 2 and the optical arrangement 100 of FIG. 1, respectively, and therefore the corresponding descriptions are omitted here.

[0096] Referring to FIGS. 8 to 10, the MFOIS system 820 includes special fiber optic probe (integrated probe 800) integrated for reflectance imaging, DRS and RS measurement. The integrated probe 800 includes a Raman probe 802 (e.g. as described in similar context to the first fiber optic probe 102 of FIG. 5) arranged adjacent to a high-resolution reflectance imaging camera 806 and two separate optical fibers 8042 (e.g. each described in similar context to the second optical fiber 1042 of FIGS. 6 and 7) arranged between the Raman probe 802 and the imaging camera 806, where both the Raman probe 802 and the imaging camera 806 are arranged within a DRS probe 804. More specifically, a plurality of DRS collection fibers 8044 (e.g. as described in similar context to the second plurality of optical fibers 1044 of FIGS. 6 and 7) substantially surrounds the Raman probe 802, the imaging camera 806 and the two separate optical fibers 8042. For example, each DRS collection fiber 8044 may be spaced apart from a neighbouring DRS collection fiber 8044 to encircle

the Raman probe 802, the imaging camera 806 and the two separate optical fibers 8042. The DRS collection fiber 8044 (source detector) separation in the fiber 804a may be optimized to interrogate at various depth (~25 microns to ~1 mm) below the skin surface of vulva and vaginal skin. One of the two separate optical fibers 8042 may be located
 5 opposite to the other separate optical fiber 8042 and both 8042 being strategically positioned to optimize illumination/excitation with respect to the imaging camera 806 and the plurality of DRS collection fibers 8044.

Preliminary data on human volunteers

10 [0097] The efficacy of a generation 1 probe (e.g. integrated probe 800) for evaluating the changes in water, lipid, and oxygen saturation in the skin upon various intervention in human volunteers is studied.

[0098] To demonstrate the applicability of MFOIS on human skin to measure tissue oxygenation (sO_2), blood fraction, moisture and lipid content, several preliminary
 15 experiments were conducted on volunteers. Firstly, to monitor the tissue oxygenation and blood fraction changes, a blood pressure cuff was placed around the right upper arm of each volunteer. The spectra on each volunteer's thumb were measured pre-, during and post-occlusion (represented by pre intervention, during intervention and post intervention reflected in FIGS. 11 to 14).

20 [0099] FIG. 11 shows a plot 1101 illustrating the representative data of intervention experiments to capture the changes in blood fraction. FIG. 12 shows a plot 1201 illustrating the representative data of intervention experiments to capture the changes in sO_2 . FIG. 13 shows a plot 1301 illustrating the representative data of intervention experiments to capture the changes in water. FIG. 14 shows a plot 1401 illustrating the representative data of
 25 intervention experiments to capture the changes in lipid content.

[0100] Unmixed result in visible region can be seen from FIGS. 11 and 12, where blood fraction increased about 96% during occlusion. After releasing, it decreased reaching values closer to baseline. sO_2 decreased to about 42% during occlusion and recovered to a higher value after release. This may be because venous outflow was blocked while the
 30 arterial inflow remained unaltered.

[0101] Secondly, moisturizing gel was applied on volunteers' thenar eminence and the water content was investigated by applying a moisturizing gel (pre intervention and during intervention respectively). After that, excessive gel was removed by alcohol wipe and measured again (post intervention). The results are shown in FIG. 13. There was a significant increase (about 8.6%) in water content when the gel was applied and significant drop after wiping it away.

[0102] Thirdly, pork oil was applied on volunteers' arm and wiped away using alcohol to capture the changes in lipid quantity pre, during intervention and post intervention (FIG. 14). There was about 2.5-fold increasing in lipid after applying the pork oil on skin surface. After alcohol wiping, the value dropped closer to pre intervention values.

[0103] DRS measurements of water content on volunteers were also validated using MoistureMeterSC (Delfin), which is used in dermatology clinics to measure skin moisture levels. FIG. 15 shows a plot 1501 illustrating the correlation between DRS water index measurement 1503 and commercial moisture meter measurement 1505.

Preliminary results from pre-menopausal and post-menopausal women

[0104] In a pilot clinical study involving pre-menopausal and post-menopausal women, it has been demonstrated that there is a change in water, lipid, and oxygen saturation levels, which can be used a marker for evaluating the severity of GSM and also to track the efficacy of the treatment response.

[0105] FIGS. 16 to 19 show the relative change in water content, lipid content, oxygen saturation, and blood fraction measured at the vulva skin of pre-menopausal, peri-menopausal (reflected as "menopausal transition"), and post-menopausal women using DRS. More specifically, FIG. 16 shows a plot 1601 illustrating average DRS measurement indicating difference in water content among pre-menopausal, peri-menopausal, and post-menopausal women in six locations of the vulva region. FIG. 17 shows a plot 1701 illustrating average DRS measurement indicating difference in lipid content among pre-menopausal, peri-menopausal, and post-menopausal women in the six locations of the vulva region. FIG. 18 shows a plot 1801 illustrating average DRS measurement indicating difference in oxygen saturation among pre-menopausal, peri-menopausal, and post-menopausal women in the six locations of the vulva region. FIG. 19 shows a plot 1901

illustrating average DRS measurement indicating difference in blood fraction among pre-menopausal, peri-menopausal, and post-menopausal women in the six locations of the vulva region.

[0106] FIG. 16 depicts that there is significant increase in the water content of post-menopausal women compared to pre-menopausal women. This could be due to different skin layer being examined with the 1.3 mm DRS probe i.e. epidermis in pre-menopausal and peri-menopausal women, and dermis in post-menopausal women. In FIG. 17, post-menopausal women appear to have higher lipid content possibly indicating lipid and accumulation which occurs during estrogen deficiency. FIGS. 18 and 19 respectively depict a slight decrease in oxygen saturation and a decrease in blood fraction of post-menopausal women which may stem from estrogen deficiency leading to vaginal atrophy.

[0107] MFOIS scan may be performed on site for the objective assessment of treatment monitoring and risk evaluation of therapy of GSM as a companion diagnostics device.

[0108] The technology brought about by the MFOIS system significantly and advantageously impacts the pharmaceutical and medtech industry in terms of:-

- cost effectiveness,
- assessments of emerging drugs and therapy,
- advancements in drug and medical device development,
- provision of gold standard for assessment/regulatory approval (e.g. FDA),
- assessments of objective therapeutic efficacy and monitoring safety of usage,
- precision medicine, dosing, delivery, frequency.

[0109] While the invention has been particularly shown and described with reference to specific embodiments, it should be understood by those skilled in the art that various changes in form and detail may be made therein without departing from the spirit and scope of the invention as defined by the appended claims. The scope of the invention is thus indicated by the appended claims and all changes which come within the meaning and range of equivalency of the claims are therefore intended to be embraced.

CLAIMS

1. An optical arrangement comprising:
 - a first fiber optic probe configured to measure Raman spectra of a skin sample;
 - 5 a second fiber optic probe configured to measure diffuse reflectance spectra of the skin sample; and
 - an imaging camera configured to capture a reflectance image of the skin sample, wherein the first fiber optic probe, at least part of the second fiber optic probe and the imaging camera are arranged adjacent to one another,
 - 10 the optical arrangement is configured to acquire at least one selected from the Raman spectra, the diffuse reflectance spectra, or the reflectance image in a location of the skin sample, and
 - based on the at least one selected from the acquired Raman spectra, the acquired diffuse reflectance spectra, or the acquired reflectance image, the optical arrangement is
 - 15 configured to interrogate a pre-determined depth below a surface of the skin sample at the location, or tissue chromophores of the skin sample at the pre-determined depth, or both.
2. The optical arrangement according to Claim 1, where the optical arrangement is configured to acquire a combination of at least two selected from the Raman spectra, the
- 20 diffuse reflectance spectra, or the reflectance image sequentially in the location of the skin sample.
3. The optical arrangement according to Claim 1 or 2, wherein the first fiber optic probe, the second fiber optic probe and the imaging camera integrally form the optical
- 25 arrangement in a single probe.
4. The optical arrangement according to any one of Claims 1 to 3, wherein the first fiber optic probe comprises a first optical fiber configured to deliver laser energy to excite the skin sample; and a first plurality of optical fibers configured to detect and measure the
- 30 Raman spectra of the skin sample.

5. The optical arrangement according to Claim 4, wherein the first optical fiber is centrally arranged along the first fiber optic probe, and the first plurality of optical fibers is arranged substantially surrounding the first optical fiber.
- 5 6. The optical arrangement according to Claim 4 or 5, wherein each optical fiber of the first plurality of optical fibers is arranged adjacent to and spaced apart from a neighbouring optical fiber of the first plurality of optical fibers.
7. The optical arrangement according to any one of Claims 4 to 6, wherein the first
10 optical fiber comprises a first optical fiber bundle, and each optical fiber of the first plurality of optical fibers comprises an optical fiber bundle.
8. The optical arrangement according to any one of Claims 4 to 7, wherein the first
15 optical fiber or each of the first plurality of optical fibers includes a single mode fiber, or a multimode fiber, or a combination of a single mode fiber and a multimode fiber.
9. The optical arrangement according to any one of Claims 4 to 8, wherein the first optical fiber has a core size ranging from 150-800 μm and a cladding size of 160-800 μm .
- 20 10. The optical arrangement according to any one of Claims 4 to 9, wherein the first optical fiber has a transmission range of 350 nm to 2400 nm.
11. The optical arrangement according to any one of Claims 1 to 10, wherein the second
25 fiber optic probe comprises a second optical fiber configured to deliver light to the skin sample; and a second plurality of optical fibers configured to detect and measure the diffuse reflectance spectra of the skin sample.
12. The optical arrangement according to Claim 11, wherein the second optical fiber is
30 centrally arranged along the second fiber optic probe, and the second plurality of optical fibers is arranged substantially surrounding the second optical fiber.

13. The optical arrangement according to Claim 11 or 12, wherein each optical fiber of the second plurality of optical fibers is arranged adjacent to and spaced apart from a neighbouring optical fiber of the second plurality of optical fibers.
- 5 14. The optical arrangement according to any one of Claims 11 to 13, wherein the second optical fiber comprises a second optical fiber bundle, and each optical fiber of the second plurality of optical fibers comprises an optical fiber bundle.
- 10 15. The optical arrangement according to any one of Claims 11 to 14, wherein the second optical fiber or each of the second plurality of optical fibers includes a single mode fiber, or a multimode fiber, or a combination of a single mode fiber and a multimode fiber.
- 15 16. The optical arrangement according to any one of Claims 11 to 15, wherein the second optical fiber has a core size ranging from 150-800 μm and a cladding size of 160-800 μm .
17. The optical arrangement according to any one of Claims 11 to 16, wherein the second optical fiber has a transmission range of 350 nm to 2400 nm.
- 20 18. The optical arrangement according to any one of Claims 11 to 17, wherein each optical fiber of the second plurality of optical fibers is arranged at a distance ranging between 2700 μm and 6000 μm from the second optical fiber.
- 25 19. The optical arrangement according to Claim 18, wherein the optical arrangement is configured to interrogate the pre-determined depth below the surface of the skin sample ranging between 1300 μm and 3000 μm .
- 30 20. The optical arrangement according to any one of Claims 11 to 17, wherein each optical fiber of the second plurality of optical fibers is arranged at a distance ranging between 500 μm and 1000 μm from the second optical fiber.

21. The optical arrangement according to Claim 20, wherein the optical arrangement is configured to interrogate the pre-determined depth below the surface of the skin sample ranging between 250 μm and 2500 μm .
- 5 22. The optical arrangement according to any one of Claims 11 to 17, wherein the optical arrangement is configured to interrogate the pre-determined depth below the surface of the skin sample ranging between 25 μm and 1 mm.
23. The optical arrangement according to any one of Claims 11 to 22, wherein the first
10 fiber optic probe and the imaging camera are integrated into the second fiber optic probe such that the second plurality of optical fibers is arranged substantially surrounding the second optical fiber, the first fiber optic probe and the imaging camera.
24. The optical arrangement according to any one of Claims 11 to 23, wherein the
15 second fiber optic probe further comprises a third optical fiber configured to deliver the light to the skin sample, the third optical fiber being arranged offset from the second optical fiber and substantially surrounded by the second plurality of optical fibers.
25. The optical arrangement according to Claim 24, wherein the first fiber optic probe
20 and the imaging camera are collectively arranged between the second optical fiber and the third optical fiber.
26. A device comprising:
an analytical unit; and
25 an optical arrangement in communication with the analytical unit,
wherein
the optical arrangement comprises:
a first fiber optic probe configured to measure Raman spectra of a skin sample;
a second fiber optic probe configured to measure diffuse reflectance spectra of the
30 skin sample; and
an imaging camera configured to capture a reflectance image of the skin sample,

the first fiber optic probe, at least part of the second fiber optic probe and the imaging camera being arranged adjacent to one another,

the optical arrangement is configured to acquire at least one selected from the Raman spectra, the diffuse reflectance spectra, or the reflectance image in a location of the skin sample,

based on the at least one selected from the acquired Raman spectra, the acquired diffuse reflectance spectra, or the acquired reflectance image, the optical arrangement is configured to interrogate a pre-determined depth below a surface of the skin sample at the location, or tissue chromophores of the skin sample at the pre-determined depth, or both, and

wherein the analytical unit is configured to assess data including the at least one selected from the acquired Raman spectra, the acquired diffuse reflectance spectra, or the acquired reflectance image, and the interrogated pre-determined depth and the interrogated tissue chromophores to determine a medical status and/or condition based on the skin sample.

27. The device according to Claim 26, where the optical arrangement is configured to acquire a combination of at least two selected from the Raman spectra, the diffuse reflectance spectra, or the reflectance image sequentially in the location of the skin sample.

28. The device according to Claim 26 or 27, wherein the analytical unit comprises:
a receiving unit configured to receive the data;

a processor configured to unmix the interrogated tissue chromophores and determine relative changes of tissue chromophores of the skin sample; and

an output unit configured to provide information based on the determined relative changes of tissue chromophores.

29. The device according to Claim 28, wherein the processor is further configured to generate an objective index based on the determined relative changes of tissue chromophores, the objective index being used to monitor an efficacy of a course of treatment on the medical status and/or condition.

30. The device according to any one of Claims 26 to 29, wherein the optical arrangement comprises the optical arrangement according to any one of Claims 1 to 25.

5 31. The device according to any one of Claims 26 to 30, wherein the skin sample is a vulva/vagina skin sample.

32. The device according to any one of Claims 26 to 31, wherein the medical status and/or condition is associated with Genitourinary Syndrome of Menopause of a female
10 subject providing the skin sample.

33. A non-invasive method for analyzing a skin sample, the non-invasive method comprises:

acquiring at least one selected from Raman spectra, diffuse reflectance spectra or a
15 reflectance image of the skin sample in a location of the skin sample;

based on the at least one selected from the acquired Raman spectra, the acquired diffuse reflectance spectra, and the acquired reflectance image, interrogating a pre-determined depth below a surface of the skin sample at the location, or tissue chromophores of the skin sample at the pre-determined depth, or both; and

20 assessing data including the at least one selected from the acquired Raman spectra, the acquired diffuse reflectance spectra, or the acquired reflectance image, and the interrogated pre-determined depth and the interrogated tissue chromophores to determine a medical status and/or condition based on the skin sample.

25 34. The non-invasive method according to Claim 33, wherein acquiring the at least one selected from the Raman spectra, the diffuse reflectance spectra or the reflectance image of the skin sample comprises acquiring a combination of at least two selected from the Raman spectra, the diffuse reflectance spectra or the reflectance image of the skin sample sequentially in the location of the skin sample.

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35. The non-invasive method according to Claim 34, wherein acquiring the combination of the at least two selected from the Raman spectra, the diffuse reflectance spectra, or the reflectance image of the skin sample sequentially in the location of the skin sample comprises at least two correspondingly selected from:

5 delivering laser energy to excite the skin sample, and sequentially measuring the Raman spectra using a first fiber optic probe;

delivering light to illuminate the skin sample, and sequentially measuring the diffuse reflectance spectra using a second fiber optic probe; or

sequentially capturing the reflectance image using an imaging camera.

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36. The non-invasive method according to Claim 33, wherein acquiring the at least one selected from the Raman spectra, the diffuse reflectance spectra or the reflectance image of the skin sample comprises acquiring the Raman spectra, the diffuse reflectance spectra and the reflectance image of the skin sample sequentially in the location of the skin sample.

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37. The non-invasive method according to Claim 36, wherein acquiring the Raman spectra, the diffuse reflectance spectra, and the reflectance image of the skin sample sequentially in the location of the skin sample comprises:

20 delivering laser energy to excite the skin sample, and measuring the Raman spectra using a first fiber optic probe;

delivering light to illuminate the skin sample, and sequentially measuring the diffuse reflectance spectra using a second fiber optic probe; and

sequentially capturing the reflectance image using an imaging camera.

25 38. The non-invasive method according to Claim 35 or 37, wherein the laser energy is emitted from a laser operable in a wavelength range of 500 nm to 950 nm.

39. The non-invasive method according to Claim 38, wherein the laser includes a single wavelength laser or a tunable laser.

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40. The non-invasive method according to Claim 35 or 37, wherein the light has a wavelength in a range of 300 nm to 2500 nm.
41. The non-invasive method according to Claim 35 or 37, wherein the first fiber optic probe, the second fiber optic probe and the imaging camera form a stable and non-revolving optical collection assemble.
42. The non-invasive method according to Claim 34 or 35, wherein acquiring the combination of the at least two selected from the Raman spectra, the diffuse reflectance spectra or the reflectance image of the skin sample sequentially in the location of the skin sample comprises acquiring the at least two selected from the Raman spectra, the diffuse reflectance spectra or the reflectance image of the skin sample sequentially in less than 1 minute in the location of the skin sample.
43. The non-invasive method according to any one of Claims 33 to 42, wherein each of the Raman spectra, the diffuse reflectance spectra and the reflectance image is polarization-independent.
44. The non-invasive method according to any one of Claims 33 to 43, wherein assessing the data comprises receiving the data, unmixing the interrogated tissue chromophores, determining relative changes of tissue chromophores of the skin sample, and providing information based on the determined relative changes of tissue chromophores.
45. The non-invasive method according to Claim 44, further comprising generating an objective index based on the determined relative changes of tissue chromophores, wherein the objective index is used to monitor an efficacy of a course of treatment on the medical status and/or condition.
46. The non-invasive method according to any one of Claims 33 to 45, wherein the pre-determined depth is ranged between 25 μm and 1 mm.

47. The non-invasive method according to any one of Claims 33 to 45, wherein the pre-determined depth is ranged between 1300 μm and 3000 μm .
- 5 48. The non-invasive method according to any one of Claims 33 to 45, wherein the pre-determined depth is ranged between 250 μm and 2500 μm .
49. The non-invasive method according to any one of Claims 33 to 48, wherein the tissue chromophores comprise endogenous tissue chromophores.
- 10 50. The non-invasive method according to any one of Claims 33 to 49, wherein the tissue chromophores comprise at least one of water contents, lipid contents, melanin contents, oxygen saturation levels, estrogen levels, and blood fraction levels.
- 15 51. The non-invasive method according to any one of Claims 33 to 50, wherein the skin sample is a vulva/vagina skin sample.
52. The non-invasive method according to any one of Claims 33 to 51, wherein the medical status and/or condition is associated with Genitourinary Syndrome of Menopause
- 20 of a female subject providing the skin sample.
53. The non-invasive method according to Claim 52, further configured to assess a severity of the Genitourinary Syndrome of Menopause of the female subject.
- 25 54. The non-invasive method according to Claim 52 or 53, comprising an in situ non-invasive method conducted on the female subject.
55. The non-invasive method according to any one of Claims 33 to 54, being performed in substantially real-time to provide continuous monitoring of the medical status and/or
- 30 condition.

56. The non-invasive method according to any one of Claims 33 to 55, being performed by an optical arrangement according to any one of Claims 1 to 25 or a device according to any one of Claims 26 to 32.