

METHOD AND SYSTEM FOR EVALUATING A THERAPEUTIC INTERVENTION

TECHNICAL FIELD

[0001] The present disclosure relates broadly, but not exclusively, to methods and systems for evaluating a therapeutic intervention.

BACKGROUND

[0002] Nonalcoholic fatty liver disease (NAFLD) such as nonalcoholic steatohepatitis (NASH) is a common cause of chronic liver disease worldwide, characterized by fibrosis and/or ballooning and/or inflammation and/or steatosis of the liver. Various therapeutics are being developed for NASH and clinical trials are conducted to assess efficacy of such therapeutics. Histological assessment of liver biopsy remains the basis for diagnosing NASH, grading activity and assessing stage of fibrosis. Clinical trials normally use the NASH Clinical Research Network (CRN) system for semi-quantitative histological assessment of disease severity.

[0003] Figure 1a shows graphical representations of the existing Ishak scoring system for assessing the level of fibrosis where scores range from 0 (no fibrosis) to 6 (cirrhosis). Figure 1b shows a graphical representation of a recently published digital pathology approach to fibrosis assessment. In current literature, natural history of disease development is typically recorded as a single-track process. With reference to Figure 1a, fibrosis progression is conventionally understood to occur from $0 \rightarrow 1 \rightarrow 2 \rightarrow 3 \rightarrow 4 \rightarrow 5 \rightarrow 6$, and it is assumed there is no $1 \rightarrow 3$ without 2. Also, the possibility of something outside these 6 stages is usually ignored. With this background, it is conventionally assumed that the fibrosis reverse/regression is a direct opposite process of progression, meaning it occurs from $6 \rightarrow 5 \rightarrow 4 \rightarrow 3 \rightarrow 2 \rightarrow 1 \rightarrow 0$. Figures 1a and 1b both show a single track by both the conventional NASH-CRN and the recent digital pathology respectively.

[0004] From recent interventional studies, dynamic and heterogenous features of fibrosis have been observed. For example, with reference to the top image in Figure 2, key figures in F0, F1, F2, F3 may all be seen on the same sample before

intervention. In post-intervention samples, if the highest stage feature (F3) is found to disappear, e.g. as shown in the third image in Figure 2, it is clearly a regression case. If a more severe stage feature (F4) appears, e.g. as shown in the second image in Figure 2, it is clearly a progression case. However, most of the patients (>50%) in these studies show similar features only (F0-F3), e.g. as shown in the bottom image in Figure 2, and the level of fibrosis is considered “no change” in these patients. However, it is clear there are many dynamic changes in fibrosis here but cannot be recorded using the conventional staging system.

[0005] A need therefore exists to provide a method and system that can address at least some of the above problems and enable evaluation of a therapeutic intervention for NASH.

SUMMARY

[0006] An aspect of the present disclosure provides a method for evaluating a therapeutic intervention. The method includes receiving a first set of image data indicative of a histopathological feature, the first set of image data comprising data extracted from a first liver biopsy sample of a subject before the therapeutic intervention; receiving a second set of image data indicative of the histopathological feature, the second set of image data comprising data extracted from a second liver biopsy sample of the subject after the therapeutic intervention; quantifying a selected plurality of sub-features of the histopathological feature from each of the first and second sets of image data to form first and second sets of quantified sub-features respectively; and evaluating the therapeutic intervention based on a comparison of the first and second sets of quantified sub-features.

[0007] Evaluating the therapeutic intervention based on the comparison of the first and second sets of quantified sub-features may comprise comparing sums of values in the first and second sets of quantified sub-features.

[0008] Evaluating the therapeutic intervention based on the comparison of the first and second sets of quantified sub-features may further comprise providing a first representation corresponding to the first set of quantified sub-features; and superimposing a second representation corresponding to the second set of quantified sub-features onto the first representation. The first and second representations may comprise first and second radar maps respectively, the radar maps having axes representing the selected plurality of sub-features.

[0009] The histopathological feature may comprise fibrosis, and the selected plurality of sub-features may comprise portal fibrosis, peri portal fibrosis, peri central fibrosis, bridging fibrosis and peri sinusoidal fibrosis.

[0010] Evaluating the therapeutic intervention may comprise determining whether there is a progression or regression of nonalcoholic steatohepatitis (NASH) after the therapeutic intervention.

[0011] The first and second sets of image data may comprise data extracted using second harmonic generation (SHG) microscopy and/or two-photon excitation fluorescence (TPEF) microscopy.

[0012] Another aspect of the present disclosure provides a system for evaluating a therapeutic intervention. The system includes a processor and a computer-readable memory coupled to the processor and having instructions stored thereon that are executable by the processor to receive a first set of image data indicative of a histopathological feature, the first set of image data comprising data extracted from a first liver biopsy sample of a subject before the therapeutic intervention; receive a second set of image data indicative of the histopathological feature, the second set of image data comprising data extracted from a second liver biopsy sample of the subject after the therapeutic intervention; quantify a selected plurality of sub-features of the histopathological feature from each of the first and second sets of image data to form first and second sets of quantified sub-features respectively; and evaluate the therapeutic intervention based on a comparison of the first and second sets of quantified sub-features.

[0013] The instructions executable by the processor may further comprise instructions to compare sums of values in the first and second sets of quantified sub-features to evaluate the therapeutic intervention.

[0014] The system may further comprise a display device coupled to the processor. The display device may be configured to display a first representation corresponding to the first set of quantified sub-features and a second representation corresponding to the second set of quantified sub-features, the second representation superimposed onto the first representation, to evaluate the therapeutic intervention. The first and second representations may comprise first and second radar maps

respectively, the radar maps having axes representing the selected plurality of sub-features.

[0015] The histopathological feature may comprise fibrosis, and the selected plurality of sub-features may comprise portal fibrosis, peri portal fibrosis, peri central fibrosis, bridging fibrosis and peri sinusoidal fibrosis.

[0016] The instructions executable by the processor to evaluate the therapeutic intervention may further comprise instructions to determine whether there is a progression or regression of nonalcoholic steatohepatitis (NASH) after the therapeutic intervention.

[0017] The instructions executable by the processor to evaluate the therapeutic intervention may further comprise instructions to determine one or more changes in the sub-features specific to a mechanism of action of the therapeutic intervention.

[0018] The first and second sets of image data may comprise data from a second harmonic generation (SHG) microscope and/or a two-photon excitation fluorescence (TPEF) microscope.

BRIEF DESCRIPTION OF THE DRAWINGS

[0019] Embodiments of the disclosure will be better understood and readily apparent to one of ordinary skill in the art from the following written description, by way of example only, and in conjunction with the drawings, in which:

[0020] Figures 1a and 1b show representations of existing approaches to fibrosis assessment.

[0021] Figure 2 shows images of liver biopsy samples with heterogeneous features of fibrosis.

[0022] Figure 3a shows graphs illustrating correlation between key fibrosis sub-features and fibrosis stages.

[0023] Figure 3b shows a distribution of example fibrosis parameters in different fibrosis stage and in different sample regions.

[0024] Figure 4 shows a flow chart illustrating a method for evaluating a therapeutic intervention according to an example embodiment.

[0025] Figure 5a show a flow diagram illustrating the creation of a trained model for quantitative fibrosis assessment according to an example embodiment.

[0026] Figure 5b provides an evaluation of the model of Figure 5a.

[0027] Figure 5c shows example cut-off values for different fibrosis stage.

[0028] Figure 6 shows some example parameters and definitions of parameters according to an example embodiment.

[0029] Figure 7 shows schematic diagram illustrating the definition of various regions and images illustrating zone 1/2/3 as the definition of “peri” is varied.

[0030] Figure 8 shows how different regions of interest on an image of a sample are detected by the qFibrosis model and the various quantitative values obtained from the image data.

[0031] Figure 9 shows numerical and graphical comparisons of fibrosis values according to an example embodiment.

[0032] Figure 10 shows radar maps of fibrosis values of three patients originally having fibrosis assessed to be “no change”.

[0033] Figure 11 shows radar maps of fibrosis values of four patients given different therapeutic treatments and showing regression of fibrosis.

[0034] Figure 12 shows radar maps of fibrosis values of four patients given placebo and showing regression of fibrosis.

[0035] Figure 13 shows radar maps of fibrosis values of patients showing progression of fibrosis.

[0036] Figure 14 shows a schematic diagram illustrating a computer suitable for carrying out the method of Figure 1.

[0037] Skilled artisans will appreciate that elements in the figures are illustrated for simplicity and clarity and have not necessarily been depicted to scale. For example, the dimensions of some of the elements in the illustrations, block diagrams or flowcharts may

be exaggerated in respect to other elements to help to improve understanding of the present embodiments.

DETAILED DESCRIPTION

[0038] Embodiments of the present disclosure make use of a quantitative assessment of NASH features, including fibrosis, that enables the identification of specific sub-features such as portal fibrosis, peri-portal fibrosis, bridging fibrosis, etc. separately and quantitatively. Examples of these key fibrosis sub-features (as described by the NASH-CRN system) from various NASH studies are summarized in Figure 3a where it can be seen that they are correlated to fibrosis stages differently. For example, portal fibrosis and peri portal fibrosis, as represented by lines 302 and 304 respectively, go up from F1. Other sub-features go up at F3 (e.g. bridging fibrosis, represented by line 306) or F4 (e.g. nodule, represented by line 308), which is expected because of their definitions in NASH-CRN systems. On the other hand, a sub-feature like peri-sinusoidal fibrosis, represented by line 310, is observed to go up and down, meaning it goes up at F0 → F3, but disappears at F4. The quantitative fibrosis assessment approach advantageously allows for separate quantifications of the necessary features for assessing multi-dimensional activities therein. Figure 3b provides another representation showing the dynamics of collagen parameters in different regions against NASH CRN staging based on more than 1000 samples. Some parameters show positive correlation with staging, such as parameters in portal tract and peri-PT, while other parameters show different trends.

[0039] Embodiments will be described, by way of example only, with reference to the drawings. Like reference numerals and characters in the drawings refer to like elements or equivalents.

[0040] Some portions of the description which follows are explicitly or implicitly presented in terms of algorithms and functional or symbolic representations of operations on data within a computer memory. These algorithmic descriptions and functional or symbolic representations are the means used by those skilled in the data processing arts to convey most effectively the substance of their work to others skilled in the art. An algorithm is here, and generally, conceived to be a self-consistent sequence of steps leading to a desired result. The steps are those requiring physical manipulations of physical quantities, such as electrical, magnetic or optical signals capable of being stored, transferred, combined, compared, and otherwise manipulated.

[0041] Unless specifically stated otherwise, and as apparent from the following, it will be appreciated that throughout the present specification, discussions utilizing terms such as “scanning”, “calculating”, “determining”, “applying”, “extracting”, “generating”, “initializing”, “outputting”, or the like, refer to the action and processes of a computer system, or similar electronic device, that manipulates and transforms data represented as physical quantities within the computer system into other data similarly represented as physical quantities within the computer system or other information storage, transmission or display devices.

[0042] The present specification also discloses apparatus for performing the operations of the methods. Such apparatus may be specially constructed for the required purposes, or may comprise a computer or other device selectively activated or reconfigured by a computer program stored in the computer. The algorithms and displays presented herein are not inherently related to any particular computer or other apparatus. Various machines may be used with programs in accordance with the teachings herein. Alternatively, the construction of more specialized apparatus to perform the required method steps may be appropriate. The structure of a conventional computer will appear from the description below.

[0043] In addition, the present specification also implicitly discloses a computer program, in that it would be apparent to the person skilled in the art that the individual steps of the method described herein may be put into effect by computer code. The computer program is not intended to be limited to any particular programming language and implementation thereof. It will be appreciated that a variety of programming languages and coding thereof may be used to implement the teachings of the disclosure contained herein. Moreover, the computer program is not intended to be limited to any particular control flow. There are many other variants of the computer program, which can use different control flows without departing from the scope of the disclosure.

[0044] Furthermore, one or more of the steps of the computer program may be performed in parallel rather than sequentially. Such a computer program may be stored on any computer readable medium. The computer readable medium may include storage devices such as magnetic or optical disks, memory chips, or other storage devices suitable for interfacing with a computer. The computer readable medium may also include a hard-wired medium such as exemplified in the Internet system, or wireless medium such as exemplified in the GSM, GPRS, 3G, 4G or 5G mobile telephone

systems, as well as other wireless systems such as Bluetooth, ZigBee, Wi-Fi. The computer program when loaded and executed on such a computer effectively results in an apparatus that implements the steps of the preferred method.

[0045] The present disclosure may also be implemented as hardware elements. More particularly, in the hardware sense, an element is a functional hardware unit designed for use with other components or elements. For example, an element may be implemented using discrete electronic components, or it can form a portion of an entire electronic circuit such as an Application Specific Integrated Circuit (ASIC) or Field Programmable Gate Array (FPGA). Numerous other possibilities exist. Those skilled in the art will appreciate that the system can also be implemented as a combination of hardware and software elements.

[0046] According to various embodiments, a “circuit” may be understood as any kind of a logic implementing entity, which may be special purpose circuitry or a processor executing software stored in a memory, firmware, or any combination thereof. Thus, in an embodiment, a “circuit” may be a hard-wired logic circuit or a programmable logic circuit such as a programmable processor, e.g. a microprocessor (e.g. a Complex Instruction Set Computer (CISC) processor or a Reduced Instruction Set Computer (RISC) processor). A “circuit” may also be a processor executing software, e.g. any kind of computer program, e.g. a computer program using a virtual machine code such as e.g. Java. Any other kind of implementation of the respective functions which may be described in more detail herein may also be understood as a “circuit” in accordance with an alternative embodiment.

[0047] Figure 4 shows a flow chart 400 illustrating a method for evaluating a therapeutic intervention according to an example embodiment. At step 402, a first set of image data indicative of a histopathological feature, e.g. fibrosis, is received. The first set of image data comprises data extracted from a first liver biopsy sample of a subject before the therapeutic intervention. At step 404, a second set of image data indicative of the histopathological feature is received. The second set of image data comprises data extracted from a second liver biopsy sample of the subject after the therapeutic intervention. At step 406, a selected plurality of sub-features (portal fibrosis, peri portal fibrosis, bridging fibrosis, etc.) of the histopathological feature are quantified from each of the first and second sets of image data to form first and second sets of quantified sub-features respectively. At step 408, the therapeutic intervention is evaluated based on a comparison of the first and second sets of quantified sub-features.

[0048] In example implementations, the first and second sets of image data in steps 402 and 404 may be obtained using second harmonic generation (SHG) microscopy and/or two photon excitation fluorescence (TPEF) microscopy, for example, a Genesis system (Histoindex Pte. Ltd, Singapore), in which SHG microscopy is used to visualize collagen, and the other cell structures are visualized using TPEF microscopy.

[0049] Step 406 of the method in Figure 4 may be carried out using the quantitative approach described in WO 2022/191781, the contents of which are hereby incorporated by reference. Briefly, the approach involves creating a trained model for assessing a selected histopathological feature (e.g. fibrosis) using labelled samples and applying the trained model to assess actual samples. In one non-limiting example, as shown in Figure 5a, 316 labelled samples are divided into a training group and a testing/validation group. A total of 135 collagen parameters are quantified for each sample. Parameter selection is performed to reduce the dimensionality of data by selecting 21 parameters. Based on the selected fibrosis parameters, the quantitative model for fibrosis assessment (qFibrosis) is built by the linear regression method and is validated on the samples in the testing group.

[0050] Figure 5b shows an example graph and table that provide an evaluation of the qFibrosis model as described above with reference to Figure 5a. It has been observed that the model is strongly correlated with the relevant NASH CRN component, with $r = 0.776$. The model is also able to differentiate fibrosis stages, with area under the curve > 0.87 . Figure 5c shows an example scale in which the continuous values calculated by the qFibrosis model can be converted to fibrosis stages (F0-F4), with example cut-off values. In other words, given a value generated by the qFibrosis model, it is possible to determine the fibrosis stage of the liver biopsy sample.

[0051] Figure 6 shows some example parameters and their associated definitions. The parameters are indicative of morphological features and are defined with pathologists' experience and recommendation. The parameters for collagen fibers, such as area, length and width, are determined from the second harmonic generation (SHG)/two photon excitation fluorescence (TPEF) images. The mean septa width and cellular regions are defined as shown in Figure 6.

[0052] The qFibrosis model as described in WO 2022/191781 typically provides a single score or index, which is a continuous value indicative of the fibrosis stage of each sample being assessed, as described above. However, based on the understanding that fibrosis at different regions of the same sample may correlate to the fibrosis stages differently as discussed above with reference to Figure 3, the present embodiments utilize the qFibrosis model to separately determine the scores or values of the different regions. Figure 7 shows a schematic diagram illustrating how the different regions are defined and three images of the same sample illustrating how the sizes of the zones 1/2/3 change as the definition of “peri” is varied.

[0053] In Figure 7, different regions including portal tract (PT), peri portal, central vein (CV), peri-CV and perisinusoidal fibrosis in zone 1/2/3 are defined and can be detected by the trained model. The bridging regions can be considered ones that connect different zones, and bridging fibrosis is fibrosis connecting across relevant zones, for example, from PT to PT or from PT to CV. The definitions of the regions can be adjusted to meet different needs. For example, the definition of ‘peri’ for zone 1 or zone 3 can be 100 μm , 200 μm or 1400 μm .

[0054] Figure 8 shows how different regions of interest on an image of a sample are detected by the qFibrosis model and the image data is used to determine the various quantitative values. As can be seen in Figure 8, the sample shows a high degree of heterogeneity for fibrosis activities. One can observe features from F1, F2, F3 and F4 stages all from the same sample. The qFibrosis model can provide automated annotation on these features, and quantify these features at the same time. For example, separate scores for fibrosis sub-features of portal fibrosis, peri portal fibrosis, peri central fibrosis, bridging fibrosis and peri sinusoidal fibrosis are determined.

[0055] Figure 9 shows on the top left, images of a liver biopsy sample before treatment and two liver biopsy samples after treatment. For example, the samples after treatment may be taken following different treatment regimes or different therapeutics. By comparing the portal fibrosis, peri portal fibrosis, peri central fibrosis, bridging fibrosis and peri sinusoidal fibrosis values in liver biopsy samples from the same subject taken before treatment and after treatment, it is possible to determine whether the fibrosis has been progressive or regressive, thereby helping to determine the efficacy of the therapeutic intervention. In one implementation, a comparison of the sum of the portal fibrosis, peri portal fibrosis, peri central fibrosis, bridging fibrosis and peri sinusoidal fibrosis values after treatment against a corresponding sum before treatment can provide

an indication of progression or regression. For example, a smaller sum (i.e. a lower total score) may indicate regression while a larger sum (i.e. a higher total score) may indicate progression, as shown in the table at the bottom left of Figure 9. The sum may be a weighted sum and the weights may include negative values.

[0056] Alternatively or in addition, the quantified portal fibrosis, peri portal fibrosis, peri central fibrosis, bridging fibrosis and peri sinusoidal fibrosis values before treatment and after treatment can be graphically represented to provide additional information for visualisation and analysis. Figure 9 shows on the right side, a radar map 902 of the quantified values of the sample before treatment and radar maps 904, 906 of the quantified values of the samples after treatment, using the data in the table at the bottom left of Figure 9. Radar maps 904, 906 are superimposed (i.e. overlap) with radar 902, with the axes of these radar maps representing the portal fibrosis, peri portal fibrosis, peri central fibrosis, bridging fibrosis and peri sinusoidal fibrosis values respectively.

[0057] The method according to the present disclosure can detect changes in fibrosis level more accurately compared to, for example, a manual grading by a pathologist. In one example, three patients are considered to belong to F3 both before treatment and after treatment, i.e. no change, by a human pathologist. However, by using the method as described above, the quantitative changes in fibrosis measurements become apparent. Table 1 provides a summary of the various fibrosis values of the three patients as quantified by the present method, while Figure 10 shows corresponding sets of radar maps.

Table 1

	qFibrosis increased		qFibrosis No-change		qFibrosis decreased	
	Before Treatment	Post Treatment	Before Treatment	Post Treatment	Before Treatment	Post Treatment
Portal Fibrosis	0.35	0.58	0.27	0.23	0.35	0.17
Peri-Portal Fibrosis	0.33	0.47	0.24	0.22	0.62	0.12
Peri-Central Fibrosis	0.11	0.26	0.37	0.25	0.23	0.19
Bridging Fibrosis	0.35	0.74	0.22	0.20	0.25	0.12
Peri-Sinusoidal Fibrosis	0.37	0.62	0.41	0.45	0.81	0.45
Total Weighted Score	1.52	2.67	1.51	1.34	2.26	1.06

[0058] As can be seen from Table 1, while the pathologist's assessment is "no change" for all three patients, at the quantitative level, the present method can provide more precise assessment. For example, the first patient shows an increase in the total score from 1.52 to 2.67, which indicates an increase in fibrosis, i.e. progressive instead of "no change". The second patient shows a small decrease in the total score from 1.51 to 1.34 which may not be sufficient to qualify as a regression, i.e. the same "no change"

assessment as the human pathologist. The third patient shows a decrease in the total score from 1.26 to 1.06, which indicates a decrease in fibrosis, i.e. regressive instead of “no change”. In other words, the assessment is not only more objective, but it also can detect subtle changes even when there is agreement with the human pathologist’s assessment.

[0059] The graphical representations provided by the radar maps also show the quantitative changes. For example, the radar maps for the first patient, on the left of Figure 10, shows a significant enlargement in the total area after treatment, as compared to before treatment, with increase occurring on every axis. The radar maps for the second patient, in the middle of Figure 10, shows a small reduction in size, which may not be sufficient to warrant a regression assessment. The radar maps for the third patient, on the right of Figure 10, shows a significant shrink in the total area after treatment as compared to before treatment, with biggest decreases occurring in peri sinusoidal fibrosis and peri portal fibrosis.

[0060] Further, the graphical representations provided by the radar maps can reveal mechanism of action-specific changes from various therapeutic interventions. Figure 11 shows radar maps of four patients each provided with a different therapeutic intervention, but all patients are assessed to have fibrosis at F3 stage before treatment and F2 stage after treatment by a human pathologist, i.e. a regression in fibrosis. From the radar maps, all four patients show similar effects, i.e. a reduction following treatment, and further details can be analysed. For example, patients treated with drugs 2 and 4 show similar regression patterns with clear reduction in portal fibrosis, peri portal fibrosis and bridging fibrosis, but different effects in peri sinusoidal fibrosis and peri central fibrosis. For patients treated with drugs 3 and 5, only portal and peri-portal fibrosis show reductions, but not peri-central, peri-sinusoidal and bridging fibrosis. It can then be inferred that drugs 2 and 4 have similar mechanism of actions, while drugs 3 and 5 have similar mechanism of actions.

[0061] In contrast, for patients who are under placebo and assessed to have fibrosis at F3 stage before treatment and F2 stage after treatment by a human pathologist, the patterns of change are different from those observed in patents who are given therapeutic treatment. Figure 12 shows radar maps of patients who are given placebo, with no common or similar regression pattern being observe..

[0062] Likewise, a progression can be observed using the radar maps. For example, Figure 13 shows radar maps for patients who are assessed to have fibrosis at F2 stage

before treatment and F3 stage after treatment. Here, no pattern can be observed and patients treated with therapeutics cannot be distinguished from patients given placebo.

[0063] As described, the present method is capable of measuring all fibrosis parameters simultaneously and quantitatively. The method comprises using radar map to view a number of selected fibrosis parameters based on the NASH-CRN system, and by overlapping the representations of the pre- and post- treatment samples. This visualisation tool advantageously allows for assessing the mechanism of action-specific changes for multi-dimensional fibrosis activities in livers.

[0064] Figure 14 depicts an exemplary computing device 1400, hereinafter interchangeably referred to as a computer system 1400, where one or more such computing devices 1400 may be used for implementing the method as described above. The following description of the computing device 1400 is provided by way of example only and is not intended to be limiting.

[0065] As shown in Figure 14, the example computing device 1400 includes a processor 1404 for executing software routines. Although a single processor is shown for the sake of clarity, the computing device 1400 may also include a multi-processor system. The processor 1404 is connected to a communication infrastructure 1406 for communication with other components of the computing device 1400. The communication infrastructure 1406 may include, for example, a communications bus, cross-bar, or network.

[0066] The computing device 1400 further includes a main memory 1408, such as a random access memory (RAM), and a secondary memory 1410. The secondary memory 1410 may include, for example, a hard disk drive 1412 and/or a removable storage drive 1414, which may include a floppy disk drive, a magnetic tape drive, an optical disk drive, or the like. The removable storage drive 1414 reads from and/or writes to a removable storage unit 1418 in a well-known manner. The removable storage unit 1418 may include a floppy disk, magnetic tape, optical disk, or the like, which is read by and written to by removable storage drive 1414. As will be appreciated by persons skilled in the relevant art(s), the removable storage unit 1418 includes a computer readable storage medium having stored therein computer executable program code instructions and/or data.

[0067] In an alternative implementation, the secondary memory 1410 may additionally or alternatively include other similar means for allowing computer programs or other instructions to be loaded into the computing device 1400. Such means can include, for example, a removable storage unit 1422 and an interface 1420. Examples of a

removable storage unit 1422 and interface 1420 include a program cartridge and cartridge interface (such as that found in video game console devices), a removable memory chip (such as an EPROM or PROM) and associated socket, and other removable storage units 1422 and interfaces 1420 which allow software and data to be transferred from the removable storage unit 1422 to the computer system 1400.

[0068] The computing device 1400 also includes at least one communication interface 1424. The communication interface 1424 allows software and data to be transferred between computing device 1400 and external devices via a communication path 1426. In various embodiments of the disclosure, the communication interface 1424 permits data to be transferred between the computing device 1400 and a data communication network, such as a public data or private data communication network. The communication interface 1424 may be used to exchange data between different computing devices 1400 which such computing devices 1400 form part an interconnected computer network. Examples of a communication interface 1424 can include a modem, a network interface (such as an Ethernet card), a communication port, an antenna with associated circuitry and the like. The communication interface 1424 may be wired or may be wireless. Software and data transferred via the communication interface 1424 are in the form of signals which can be electronic, electromagnetic, optical or other signals capable of being received by communication interface 1424. These signals are provided to the communication interface via the communication path 1426.

[0069] As shown in Figure 14, the computing device 1400 further includes a display interface 1402 which performs operations for rendering images to an associated display 1430 and an audio interface 1432 for performing operations for playing audio content via associated speaker(s) 1434.

[0070] As used herein, the term "computer program product" may refer, in part, to removable storage unit 1418, removable storage unit 1422, a hard disk installed in hard disk drive 1412, or a carrier wave carrying software over communication path 1426 (wireless link or cable) to communication interface 1424. Computer readable storage media refers to any non-transitory tangible storage medium that provides recorded instructions and/or data to the computing device 1400 for execution and/or processing. Examples of such storage media include floppy disks, magnetic tape, CD-ROM, DVD, Blu-ray™ Disc, a hard disk drive, a ROM or integrated circuit, USB memory, a magneto-optical disk, or a computer readable card such as a PCMCIA card and the like, whether or not such devices are internal or external of the computing device 1400. Examples of

transitory or non-tangible computer readable transmission media that may also participate in the provision of software, application programs, instructions and/or data to the computing device 1400 include radio or infra-red transmission channels as well as a network connection to another computer or networked device, and the Internet or Intranets including e-mail transmissions and information recorded on Websites and the like.

[0071] The computer programs (also called computer program code) are stored in main memory 1408 and/or secondary memory 1410. Computer programs can also be received via the communication interface 1424. Such computer programs, when executed, enable the computing device 1400 to perform one or more features of embodiments discussed herein. In various embodiments, the computer programs, when executed, enable the processor 1404 to perform features of the above-described embodiments. Accordingly, such computer programs represent controllers of the computer system 1400.

[0072] Software may be stored in a computer program product and loaded into the computing device 1400 using the removable storage drive 1414, the hard disk drive 1412, or the interface 1420. Alternatively, the computer program product may be downloaded to the computer system 1400 over the communications path 1426. The software, when executed by the processor 1404, causes the computing device 1400 to perform functions of embodiments described herein.

[0073] It is to be understood that the embodiment of Figure 4 is presented merely by way of example. Therefore, in some embodiments one or more features of the computing device 1400 may be omitted. Also, in some embodiments, one or more features of the computing device 1400 may be combined together. Additionally, in some embodiments, one or more features of the computing device 1400 may be split into one or more component parts.

[0074] It will be appreciated that the elements illustrated in Figure 4 function to provide means for performing the various functions and operations of the servers as described in the above embodiments.

[0075] In an implementation, a server may be generally described as a physical device comprising at least one processor and at least one memory including computer program code. The at least one memory and the computer program code are configured to, with the at least one processor, cause the physical device to perform the requisite operations.

[0076] It will be appreciated by a person skilled in the art that numerous variations and/or modifications may be made to the present disclosure as shown in the specific embodiments without departing from the scope of the disclosure as broadly described. The present embodiments are, therefore, to be considered in all respects to be illustrative and not restrictive.

CLAIMS

1. A method for evaluating a therapeutic intervention, the method comprising:
 - receiving a first set of image data indicative of a histopathological feature, the first set of image data comprising data extracted from a first liver biopsy sample of a subject before the therapeutic intervention;
 - receiving a second set of image data indicative of the histopathological feature, the second set of image data comprising data extracted from a second liver biopsy sample of the subject after the therapeutic intervention;
 - quantifying a selected plurality of sub-features of the histopathological feature from each of the first and second sets of image data to form first and second sets of quantified sub-features respectively; and
 - evaluating the therapeutic intervention based on a comparison of the first and second sets of quantified sub-features.
2. The method as claimed in claim 1, wherein evaluating the therapeutic intervention based on the comparison of the first and second sets of quantified sub-features comprises comparing sums of values in the first and second sets of quantified sub-features.
3. The method as claimed in claim 1 or 2, wherein evaluating the therapeutic intervention based on the comparison of the first and second sets of quantified sub-features further comprises:
 - providing a first representation corresponding to the first set of quantified sub-features; and
 - superimposing a second representation corresponding to the second set of quantified sub-features onto the first representation.
4. The method as claimed in claim 3, wherein the first and second representations comprise first and second radar maps respectively, the radar maps having axes representing the selected plurality of sub-features.
5. The method as claimed in any one of the preceding claims, wherein the histopathological feature comprises fibrosis, and wherein the selected plurality of sub-features comprise portal fibrosis, peri portal fibrosis, peri central fibrosis, bridging fibrosis and peri sinusoidal fibrosis.

6. The method as claimed in any one of the preceding claims, wherein evaluating the therapeutic intervention comprises determining whether there is a progression or regression of nonalcoholic steatohepatitis (NASH) after the therapeutic intervention.
7. The method as claimed in any one of the preceding claims, wherein evaluating the therapeutic intervention comprises determining one or more changes in the sub-features specific to a mechanism of action of the therapeutic intervention.
8. The method as claimed in any one of the preceding claims, wherein the first and second sets of image data comprises data extracted using second harmonic generation (SHG) microscopy and/or two-photon excitation fluorescence (TPEF) microscopy.
9. A system for evaluating a therapeutic intervention, the system comprising:
 - a processor; and
 - a computer-readable memory coupled to the processor and having instructions stored thereon that are executable by the processor to:
 - receive a first set of image data indicative of a histopathological feature, the first set of image data comprising data extracted from a first liver biopsy sample of a subject before the therapeutic intervention;
 - receive a second set of image data indicative of the histopathological feature, the second set of image data comprising data extracted from a second liver biopsy sample of the subject after the therapeutic intervention;
 - quantify a selected plurality of sub-features of the histopathological feature from each of the first and second sets of image data to form first and second sets of quantified sub-features respectively; and
 - evaluate the therapeutic intervention based on a comparison of the first and second sets of quantified sub-features.
10. The system as claimed in claim 9, wherein the instructions executable by the processor further comprise instructions to compare sums of values in the first and second sets of quantified sub-features to evaluate the therapeutic intervention.
11. The system as claimed in claim 9 or 10, further comprising a display device coupled to the processor, wherein the display device is configured to display a first representation corresponding to the first set of quantified sub-features and a second

representation corresponding to the second set of quantified sub-features, the second representation superimposed onto the first representation, to evaluate the therapeutic intervention.

12. The system as claimed in claim 11, wherein the first and second representations comprise first and second radar maps respectively, the radar maps having axes representing the selected plurality of sub-features.

13. The system as claimed in any one of claims 9 to 12, wherein the histopathological feature comprises fibrosis, and wherein the selected plurality of sub-features comprise portal fibrosis, peri portal fibrosis, peri central fibrosis, bridging fibrosis and peri sinusoidal fibrosis.

14. The system as claimed in any one of claims 9 to 13, wherein the instructions executable by the processor to evaluate the therapeutic intervention further comprise instructions to determine whether there is a progression or regression of nonalcoholic steatohepatitis (NASH) after the therapeutic intervention.

15. The system as claimed in any one of claims 9 to 14, wherein the instructions executable by the processor to evaluate the therapeutic intervention further comprise instructions to determine one or more changes in the sub-features specific to a mechanism of action of the therapeutic intervention.

16. The system as claimed in any one of claims 9 to 15, wherein the first and second sets of image data comprise data from a second harmonic generation (SHG) microscope and/or a two-photon excitation fluorescence (TPEF) microscope.