METHOD AND SYSTEM FOR DETERMINING CONCENTRATION OF AN ANALYTE IN A SAMPLE OF A BODILY FLUID, AND METHOD AND SYSTEM FOR GENERATING A SOFTWARE-IMPLEMENTED MODULE

Abstract

A method for generating a module configured to determine concentration of an analyte in a sample of a body fluid is disclosed. The method includes providing a first set of measurement data derived from images of one or more test strips indicating a color transformation in response to a body fluid containing an analyte. The images can be recorded by multiple devices with differing cameras, software and/or hardware device configurations for image recording and image data processing. A neural network model can be generated in a machine learning process applying an artificial neural network and a module configured to determine concentration of an analyte in a second sample of a body fluid can be generated. Further, the present disclosure includes a system for generating the module as well as a method and a system for determining concentration of an analyte in a sample of a bodily fluid.

Inventors: Berg; Max (Mannheim, DE), Hailer; Fredrik (Limburgerhof, DE), Limburg; Bernd (Soergenloch, DE), Sieffert; Daniel (Mannheim, DE), Wieder; Herbert (Lampertheim, DE), Seelig; Peter (Frankfurt am Main, DE), Aysin; Benhur (Fishers, IN), Chittajallu; Siva (Indianapolis, IN)

Applicant: Roche Diabetes Care, Inc. (Indianapolis, IN)

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Background/Summary

RELATED APPLICATIONS [0001] This application is a continuation of U.S. patent application Ser. No. 18/432,427, filed Feb. 5, 2024, which is a continuation of U.S. patent application Ser. No. 17/343,513, filed Jun. 9, 2021, which claims priority to PCT/EP2019/084115, filed Dec. 9, 2019, which claims priority to U.S. Provisional Patent Application No. 62/777,360, filed Dec. 10, 2018 and EP 18 215 541.6, filed Dec. 21, 2018, the entire disclosures of all of which are hereby incorporated herein by reference.

BACKGROUND
[0002] The present disclosure relates to a method for generating a software-implemented module configured to determine concentration of an analyte in a sample of a bodily fluid and a method for determining concentration of an analyte in a sample of a bodily fluid. Further, the present disclosure relates to a system for generating a software-implemented module configured to determine concentration of an analyte in a sample of a bodily fluid and a system for determining concentration of an analyte in a sample of a bodily fluid. Also, a computer program product is disclosed.
[0003] Machine Learning (ML) is a branch of computer science that is used to derive algorithms driven by data. Instead of using explicit formulas, ML algorithms employ real-world training data to generate models that are more accurate and sophisticated than models traditionally conceived by humans. Artificial Neural Networks (ANN) belong to a branch of machine learning and rely on artificial neurons spread over multiple layers. The concept of neural networks has been around for decades, but only lately computational power caught up with the extensive computation needed in order to effectively develop neural network algorithms. Distributed computing capabilities have been enabling developers to distribute the computations over multiple units instead of using super computers. Well-known implementations for distributed computing include Apache Hadoop, Apache Spark, and MapReduce.
[0004] Neural network models are well suited for identifying patterns/non-linear relationships

between an input and output when there is no or a poor direct one-to-one relationship. This is important since the accuracy of a model highly depends on how well the underlying system is characterized and how the relationship between input and output is defined.

[0005] In document US 2006/0008923 A1, systems and methods for medical diagnosis or risk assessment for a patient are provided. These systems and methods are designed to be employed at the point of care, such as in emergency rooms and operating rooms, or in any situation in which a rapid and accurate result is desired. The systems and methods process patient data, particularly data from point of care diagnostic tests or assays, including immunoassays, electrocardiograms, X-rays and other such tests, and provide an indication of a medical condition or risk or absence thereof. The systems include an instrument for reading or evaluating the test data and software for converting the data into diagnostic or risk assessment information. Patient information includes data from physical and biochemical tests, such as immunoassays, and from other procedures. The test is performed on a patient at the point of care and generates data that can be digitized, such as by an electronic reflectance or transmission reader, which generates a data signal. The signal is processed using software employing data reduction and curve fitting algorithms, or a decision support system, such as a trained neural network, or combinations thereof, for converting the signal into data, which is used to aid in diagnosis of a medical condition or determination of a risk of disease. This result may be further entered into a second decision support system, such as a neural net, for refinement or enhancement of the assessment.

[0006] Document WO 2018/0194525 A1 refers to a biochemical analyzing method for quantifying metabolites in a biological sample. The method is based on generating and learning the appearance of a test strip (dipstick) under various conditions to estimate the value/label for an unknown sample image. The method consists of two parts: a training part and a testing part. In the training part, metabolite quantities of a test strip are measured by a biochemistry analyzer. A set of images of the same test strip is captured by a device simulating various ambient lighting conditions. A machine learning model is trained using the images of the test strip and its corresponding metabolite quantities, and the learning model is transferred to a smart device. In the testing part, images of a test strip to be analyzed are captured by the smart device, and the images are processed using the learning model determined in the training part.

[0007] Document US 2018/0211380 A1 refers to a system for imaging biological samples and analyzing images of the biological samples. The system is to automatically analyze images of biological samples for classifying cells of interest using machine learning techniques. In an implementation, diseases associated with specific cell types can be diagnosed.

[0008] Document US 2016/0048739 A1 refers to a diagnostic system for biological samples. The diagnostic system includes a diagnostic instrument, and a portable electronic device. The diagnostic instrument has a reference color bar and a plurality of chemical test pads to receive a biological sample. The portable electronic device includes a digital camera to capture a digital image of the diagnostic instrument in uncontrolled lightning environments, a sensor to capture illuminance of a surface of the diagnostic instrument, a processor coupled to the digital camera and sensor to receive the digital image and the illuminance, and a storage device coupled to the processor. The storage device stores instructions for execution by the processor to process the digital image and the illuminance, to normalize colors of the plurality of chemical test pads and determine diagnostic test results in response to quantification of color changes in the chemical test pads.

SUMMARY

[0009] An improved technology for determining concentration of an analyte in a sample of a bodily fluid is disclosed.

[0010] A method for generating a software-implemented module configured to determine concentration of an analyte in a sample of a bodily fluid is also disclosed. Further, a method for determining concentration of an analyte in a sample of a bodily fluid is disclosed. A system for generating a software-implemented module configured to determine concentration of an analyte in

a sample of a bodily fluid and system for determining concentration of an analyte in a sample of a bodily fluid are also provided. A computer program product is also disclosed.

[0011] According to one aspect, a method for generating a software-implemented module configured to determine concentration of an analyte in a sample of a bodily fluid is provided. The method includes, in one or more data processing devices, providing a first set of measurement data, the first set of measurement data representing first color information derived by image data processing from images for a region of interest of one or more test strips. The images are indicative of a color transformation of the region of interest in response to applying one or more first samples of a bodily fluid containing an analyte to the region of interest, and the images recorded by a plurality of devices each configured for image recording and image data processing for generating the first color information, the plurality of devices provided with different software and/or hardware device configuration applied for image recording and image data processing in the device. The method further includes, in the one or more data processing devices, generating a neural network model in a machine learning process applying an artificial neural network, including providing the neural network model, and training the neural network model by training data selected from the first set of measurement data. A software-implemented module including a first analyzing algorithm representing the neural network model is generated, wherein the software-implemented module is configured to, when loaded into a data processing device having one or more processors, determine concentration of an analyte in a second sample of a bodily fluid from analyzing a second set of measurement data indicative of second color information derived by image processing from images for a region of interest of one or more test strips, the images being indicative of a color transformation of the region of interest in response to applying the second sample of the bodily fluid containing the analyte to the region of interest.

[0012] According to one aspect, a method for determining concentration of an analyte in a sample of a bodily fluid is disclosed. The method includes, in one or more data processing devices: providing a present set of measurement data indicative of present color information derived by image processing from images for a region of interest of a present test strip or stripe, the images being indicative of a color transformation of the region of interest in response to applying a present sample of a bodily fluid containing an analyte to the region of interest; providing a software-implemented module including a first analyzing algorithm representing a neural network model generated in a machine learning process applying an artificial neural network; determining concentration of the analyte in the present sample of the bodily fluid, including analyzing the present set of measurement data by the first analyzing algorithm; and generating concentration data indicative of the concentration of the analyte in the present sample of the bodily fluid. The generating of the neural network model in the machine learning process includes providing a first set of measurement data, the first set of measurement data being indicative of first color information derived by image data processing from images for a region of interest of one or more test strips, the images being indicative of a color transformation of the region of interest in response to applying one or more first samples of a bodily fluid containing an analyte to the region of interest. The first set of measurement data are representing first color information derived from images recorded by a plurality of devices each configured for image recording and image data processing for generating the first color information, the plurality of devices being provided with a different device configuration applied for image recording and image data processing in the device. The neural network model is trained by training data selected from the first set of measurement data.

[0013] According to another aspect, a system for generating a software-implemented module configured to determine concentration of an analyte in a sample of a bodily fluid is provided. The system includes one or more data processing devices, the one or more data processing devices configured to provide a first set of measurement data, the first set of measurement data representing first color information derived by image data processing from images for a region of interest of one

or more test strips. The images are indicative of a color transformation of the region of interest in response to applying one or more first samples of a bodily fluid containing an analyte to the region of interest; and the images are recorded by a plurality of devices each configured for image recording and image data processing for generating the first color information, the plurality of devices provided with different software and/or hardware device configuration applied for image recording and image data processing in the device. The one or more data processing devices can be configured to generate a neural network model in a machine learning process applying an artificial neural network, including providing the neural network model, and training the neural network model by training data selected from the first set of measurement data. Further, the one or more data processing devices can be configured to generate a software-implemented module including a first analyzing algorithm representing the neural network model, wherein the software-implemented module is configured to, when loaded into a data processing device having one or more processors, determine concentration of an analyte in a second sample of a bodily fluid from analyzing a second set of measurement data indicative of second color information derived by image processing from images for a region of interest of one or more test strips, the images being indicative of a color transformation of the region of interest in response to applying the second sample of the bodily fluid containing the analyte to the region of interest.

[0014] According to still another aspect, a system for determining concentration of an analyte in a sample of a bodily fluid is disclosed. The system includes one or more data processing devices, the one or more data processing devices can be configured to: provide a present set of measurement data indicative of present color information derived by image processing from images for a region of interest of a present test strip, the images being indicative of a color transformation of the region of interest in response to applying a present sample of a bodily fluid containing an analyte to the region of interest; provide a software-implemented module including a first analyzing algorithm representing a neural network model generated in a machine learning process applying an artificial neural network; determine concentration of the analyte in the present sample of the bodily fluid, including analyzing the present set of measurement data by the first analyzing algorithm; and generate concentration data indicative of the concentration of the analyte in the present sample of the bodily fluid. The generating of the neural network model in the machine learning process includes providing a first set of measurement data, the first set of measurement data being indicative of first color information derived by image data processing from images for a region of interest of one or more test strips, the images being indicative of a color transformation of the region of interest in response to applying one or more first samples of a bodily fluid containing an analyte to the region of interest. The first set of measurement data represents first color information derived from images recorded by a plurality of devices each configured for image recording and image data processing for generating the first color information, the plurality of devices being provided with a different device configuration applied for image recording and image data processing in the device. The neural network model is trained by training data selected from the first set of measurement data.

[0015] Further, a computer program product, including program code configured to, when loaded into a computer having one or more processors, perform the above methods is disclosed.

[0016] The neural network model generated in the machine learning process allows for improved determination of the concentration of the analyte in the (present) sample of the bodily fluid. Having the neural network model generated based on the first set of measurement data representing first color information derived from images recorded by the plurality of different devices each configured for image recording and image data processing for generating the first color information provides for a neural network model which, after training and testing, can be applied or implemented on different devices for determining concentration of an analyte in a sample of a bodily fluid, the different devices having different device configurations applied for image recording and image data processing in the respective device.

[0017] The neural network model generated before is applied for analyzing the present or second set of measurement data indicative of present/second color information derived by image processing from images for a region of interest of the present/second test strip, the images being indicative of a color transformation of the region of interest in response to applying a present/second sample of a bodily fluid of a patient, the sample containing an analyte to the region of interest. In such process, the analyte concentration is determined for the patient for whom the sample is provided.

[0018] The method may include the plurality of devices having at least one of different camera devices and different image processing software applied for image recording and image data processing.

[0019] The images recorded may include images recorded with different optical image recording conditions.

[0020] The method may further include the following: providing a second analyzing algorithm, the second analyzing algorithm being different from the first analyzing algorithm; and determining, for the concentration of the analyte in the present sample of the bodily fluid, a first estimation value by analyzing the present set of measurement data by means of the second analyzing algorithm. The second analyzing algorithm may be a non-machine learning based algorithm such as parametric multivariate linear regression. Such non-machine learning based algorithm may also be referred to as a traditional algorithm for determining analyte concentration. The first estimation value for the analyte concentration may provide for an input to the (further) analysis by means of the neural network model. Alternatively, the result for the concentration derived from the non-machine learning based algorithm may be applied in a failsafe test for the analyte concentration values determined by applying the neural network model.

[0021] The determining may include determining a target range for the concentration of the analyte in the present sample of the bodily fluid. Instead of determining actual values for the analyte concentration or in addition to such determination, the target range for the analyte concentration values may be determined.

[0022] The determining may include determining an averaged concentration by averaging the first estimation value and a concentration value provided by the analyzing of the present set of measurement data by the first analyzing algorithm. Results from the neural network model analysis and the analysis based on the traditional algorithm are combined by determining averaged values.

[0023] In another embodiment, the determining may include determining concentration of blood glucose in the second sample.

[0024] At least one of the first, second and present set of measurement data may be representing first, second, and present color information, respectively, derived by image processing from images recorded over a measurement period of time for the region of interest of the one or more test strips, consecutive images recorded with a time interval from about 0.1 to about 1.5 s.

[0025] The images from which the first set of measurement data is derived may include images of the region of interest prior to applying the one or more first samples of the bodily fluid to the region of interest of the one or more test strips. Similarly, in addition or alternatively, the images from which the present set of measurement data is derived may include images of the region of interest prior to applying the present sample of the bodily fluid to the region of interest of the present test strip.

[0026] In an example, it may be provided that the measurement data are divided into a training data set, a validation data set, and a test data set. For example, about 60% of the measurement data may be used for training (training data set), about 20% for validation (validation data set), and about 20% for testing (test data set). Cross validation techniques such as leave-p-out cross validation or k-fold cross validation can be employed. The training data set may be created by using stratified random sampling of the measurement data. Stratification may be conducted based on at least one of type of device applied for gathering measurement data and type of experiment applied while

collecting the measurement data. The measurement data are divided into separate subpopulations (strata), wherein each stratum may correspond to a different device type and/or different type of experiment. Subsequently, data may be sampled separately for each stratum and then merged in order to create the training data set. Doing so can be applied for assuring that the training data represent essentially the full population of device types and/or experiment types. The validation data set(s) and test data set(s) can be created analogously.

[0027] The embodiments disclosed above with respect to at least one of the methods may apply to one or both systems mutatis mutandis.

Description

BRIEF DESCRIPTION OF THE DRAWINGS

[0028] The above-mentioned aspects of exemplary embodiments will become more apparent and will be better understood by reference to the following description of the embodiments taken in conjunction with the accompanying drawings, wherein:

[0029] FIG. **1** shows a graphical representation of a feed forward artificial neural network (ANN).

[0030] FIG. **2** shows a graphical representation of a method for predicting blood glucose values based on the color change of a dosed test strip.

[0031] FIG. **3** shows a graphical representation of an image of a test strip.

[0032] FIG. **4** shows a graphical representation of the process of creating new features out of features from the feature table by applying a feature transformation.

[0033] FIG. **5**A shows a graphical representation of the correlation behavior of exemplary new features.

[0034] FIG. **5**B shows a further graphical representation of the correlation behavior of exemplary new features.

[0035] FIG. **5**C shows a further graphical representation of the correlation behavior of exemplary new features.

[0036] FIG. **6** shows a graphical representation of an architecture of an ANN model to be trained.

[0037] FIG. **7** shows a Parkes error grid illustrating the performance of the predicted blood glucose values versus actual blood glucose levels.

[0038] FIG. **8** shows another Parkes error grid illustrating the performance of the predicted blood glucose values versus actual blood glucose levels.

[0039] FIG. **9** shows a graphical representation of different types of combinations of traditional algorithms with ANN models.

[0040] FIG. **10** shows a Parkes error grid depicting the predictions of an ANN model which uses traditional algorithm predictions as one of its inputs.

[0041] FIG. **11** shows a graphical representation of another embodiment of a combined traditional and ANN algorithm.

[0042] FIG. **12**A shows a Parkes error grid for a traditional algorithm.

[0043] FIG. **12**B shows a Parkes error grid for an ANN model.

[0044] FIG. **12**C shows a Parkes error grid for an ANN only trained on blood glucose values below 450 mg/dl.

DESCRIPTION

[0045] The embodiments described below are not intended to be exhaustive or to limit the invention to the precise forms disclosed in the following detailed description. Rather, the embodiments are chosen and described so that others skilled in the art may appreciate and understand the principles and practices of this disclosure.

[0046] Following, embodiments for a method for generating a software-implemented module configured to determine concentration of an analyte in a sample of a bodily fluid are disclosed in

further detail. After the software-implemented module has been generated, in a further method, it can be used on different devices such as mobile devices for analyzing experimental results for determining concentration of an analyte in a sample of a bodily fluid applied to a test strip for which a test region will show a color change in response to applying the sample to the test region on the strip.

[0047] The method for generating a software-implemented module is conducted in one or more data processing devices. A first set of measurement data is provided, the first set of measurement data representing first color information derived by image data processing from images for a region of interest of one or more test strips. For example, blood samples may be applied to the test strips, which in response show color change of the region of interest (test region). Such color change may be dependent on a blood glucose concentration in the samples dosed to the test region. The images captured for the region of interest are indicative of a color transformation of the region of interest in response to applying one or more first samples of a bodily fluid containing an analyte to the region of interest. The images are recorded by a plurality of devices, such as mobile devices, e.g., mobile phones or tablet computers. Each device is configured for image recording and image data processing for generating the first color information, the plurality of devices are provided with different software and/or hardware device configurations applied for image recording and image data processing in the device. For example, the devices may be provided with different types of cameras used for capturing the images. Also, different software configuration may be provided for the devices, specifically different software applications applied in the devices for processing the images captured.

[0048] A neural network model is generated in a machine learning process applying an artificial neural network, including providing the neural network model, and training the neural network model by training data selected from the first set of measurement data. The software-implemented module is provided including a first analyzing algorithm representing the neural network model. The software-implemented module is configured to, when loaded into a data processing device having one or more processors, determine concentration of an analyte in a second sample of a bodily fluid from analyzing a second set of measurement data indicative of second color information derived by image processing from images for a region of interest of one or more test strips, the images being indicative of a color transformation of the region of interest in response to applying the second sample of the bodily fluid containing the analyte to the region of interest. Thus, after the neural network model has been generated it is to be applied for analyzing the results for the second sample, which may also be referred to as a present sample and which is a sample of a bodily fluid to be determined by using the neural network model after its generation as explained in further detail in the following. A software application including the software-implemented module is to be loaded to the analysis device such as a mobile phone or other mobile device. The test strip analysis is conducted by running the software application for determining the concentration of the analyte.

[0049] FIG. **1** shows a schematic graphical representation of a feed forward artificial neural network (ANN) **10**. In a typical feed forward ANN, information flows one way. Input features **11**a, **11**b, **11**c, . . . , **11**x are fed to nodes (or artificial neurons) **12**a, **12**b, **12**c, . . . , **12**x of an input layer **12**. The number of the nodes **12**a, **12**b, **12**c, . . . , **12**x should ideally be equal to the number of features in the underlying dataset. The input layer **12** simply receives the input features **11**a, **11**b, **11**c, . . . , **11**x and passes the input features **11**a, **11**b, **11**c, . . . , **11**x via connections **13** to a hidden layer **14**.

[0050] The hidden layer **14** includes nodes **14**a, **14**b, . . . , **14**y. The number of nodes of the hidden layer **14** depends on the number of nodes of the input layer **12** and the output layer **16**. The number of nodes of the input layer **12** and the hidden layer **14** can be equal or unequal. In each node **14**a, **14**b, . . . , **14**y, a transformation is applied to its respective input. Subsequently, the transformed values are passed on via connections **15** to the output layer **16**. As the ANN **10** is trained, nodes

12*a*, **12***b*, **12***c*, . . . , **12***x*, **14***a*, **14***b*, . . . , **14***y* that provide higher predictive value are weighted to a higher extent. The respective connections **13**, **15** receive a higher weight.

[0051] The output layer **16** provides the information that is desired for solving the underlying problem. The number of its nodes **16***a* depends on the problem at hand. If the problem is to, e.g., classify an object into one of four classes, then the output layer **16** will consist of four nodes (not shown). If the problem amounts to a regression, then the output layer **16** will consist of a single node **16***a*.

[0052] In the following, examples are disclosed for applying ANNs for determining concentration of an analyte in a sample of a bodily fluid from measurements based on the color change in a test region of a test strip in response to applying the sample of the bodily fluid. For example, a blood glucose level may be determined. FIG. **2** schematically illustrates the steps for an example of the method.

[0053] In the course of the measurement, image series **201** of test strips are captured in a first image data collection step **202** using different devices each device being configured for taking images and processing image data. The devices may be mobile devices such as cell or mobile phone types or tablet computers.

[0054] For taking the images, a sample of a bodily fluid, e.g., a blood sample, is applied to a test region of the test strip. In response to the application of the sample, the test region will show color change which is to be detected by the taking of the image(s). The images are to be processed in an analyzing process for determining concentration of an analyte in the sample of the bodily fluid, such as a blood glucose level.

[0055] While the images are taken for determining the sample of the bodily fluid, different measurement conditions may be present for capturing the images by combinations of, e.g., different temperatures, relative humidity values, illumination values, and/or hematocrit. Other values may also be used. In an example, with respect to different climate conditions, temperature values from 5° C. to 30° C. in steps of, for example, 5° C., and relative humidity values from 15% to 85% in steps of, for example, 10% can be applied. It may be provided that each of the relative humidity values is combined with each of the temperature values in order to form the set of different climate conditions. Alternatively, only certain relative humidity values may be combined with each of the temperature values since certain relative humidity/temperature combinations are less relevant.

[0056] The following measurement conditions may be applied in the data set for temperature and humidity in climate studies:

TABLE-US-00001 Temp (° C.) rel. Humidity (%)   5 45 10 15 10 45 10 85 15 45 25 45 30 45 30 85

[0057] For each test strip, an image series **201** is captured for a measurement period of time. For example, for about 40 seconds an image **30** of the test strip is captured every half second (see FIG. **3** for a graphical representation of image **30**). Each image series **201** per test strip starts with an image of a blank test strip (a test strip without applied blood dose or sample). The subsequent images **30** are captured after applying the blood sample. Thus, the change of color of the test strip is completely captured within each image series **201**. The image series **201** may be saved into a database. An additional time delay between capturing the first and the second image enabling a user to apply a blood dose to the test strip may be provided.

[0058] The images can be captured with a plurality of different cell or mobile phones, each cell phone being provided with an individual camera device and software configuration of image processing parameters RGGB, a color transformation matrix and a tone map curve for capturing the images and processing image data.

[0059] The images taken in the measurements provide for (measured) image data representing color information with respect to the color change of the test region in response to applying the sample(s) of the bodily fluid containing the analyte for which concentration needs to be determined. Following, the image data are used for generating a software-implemented module

configured to determine concentration of the analyte in a present sample. An ANN is provided and trained based on a training data set taken from the measured image data.

[0060] In the next step 203, referring to FIGS. 2 and 3, the image data derived from the image series 201 which may be saved in a database are processed in order to determine an area of interest 31 for each image 30 of the image series 201. The area of interest 31 consists of the part of the image showing the applied sample of the bodily fluid (e.g., blood sample) on a test strip 30a (target field 32) and a square 33 around the target field 32. The space outside the target field 32 and inside the square 33 consisting of four segments is called white field 34. The area of interest (test region) 31 is detected by image processing software by capturing pixel color values for the target field 32 and the white field 34. Each pixel color may, e.g., be RGB encoded. Alternative color spaces and color models such as CIE L*a*b*, CIE 1931 XYZ, CMYK, and HSV can also be employed for encoding the pixel colors. The use of alternative color spaces and color transformations into the alternative color spaces can enhance signal quality, leading to simpler and/or more accurate prediction algorithms.

[0061] The raw pixel data can be transformed in order to improve signal precision. The following types of color transformations, or combinations thereof, can be employed: [0062] Means of the raw R, G, and B channel are calculated from the target field 32 where blood is applied; [0063] R and G channels are normalized by B from the target field 32 (the normalization is performed by dividing each of the R and G channel value by the corresponding B value); [0064] a Delta between R and B channels and a Delta between G and B channels from the target field 32 are calculated; [0065] the R,G,B channels from the target field 32 are normalized by the R,G,B channels from the white field 34; [0066] a ratio between target white normalized R,G,B channels of the target field 32 and white normalized R,G,B channels of a reference field is calculated.

[0067] This list of color transformations is not exhaustive. Further color transformations for different features can be provided.

[0068] For the devices applied for image taking, e.g., a plurality of cell or mobile phones, different methods for calibrating can be employed. Differences in color adjustment schemes among different cell phone types will result in divergent glucose prediction performance if left uncorrected. A variety of approaches can be used in order to generate cellphone type specific calibration curves that will standardize the outputs to a common reference scale. On the one hand, offline calibration can be performed using color reference cards including regions of known chromaticity. Such offline calibration does not need to be carried out before each measurement. It can be provided that the offline calibration is performed once, before any measurement is carried out by a user. Alternatively, the offline calibration can be carried out at periodic time intervals. On the other hand, online calibration using color references can be employed. For this, reference card images are captured along with a test field at a pre-specified time after the test strip has been dosed. Images of the test strip are captured before dosing and after dosing. The test strip may additionally have pre-printed reference fields for online calibration.

[0069] Once the target field 32 is located, RGB pixels values from a region within the target field 32, e.g., a circle with a slightly smaller radius inside the target field 32, are extracted and averaged for each channel, yielding average values for each of the R, G and B channel. Thus, averaging unwanted pixels at the boundary of the target field 32 can be avoided.

[0070] Subsequently, the average values for each color channel are saved into a data table together with further relevant data such as a reference glucose value, an image ID, a study name, error codes, study related information such as temperature, humidity, hematocrit, or device model numbers. The data table can, e.g., be saved as comma separated value (csv) file or MATLAB mat file for further processing.

[0071] For specific modeling purposes, not every column of the data table is relevant. Therefore, a smaller table, the feature table, is generated from the data table by only including the columns that are required for modeling. An exemplary table with four rows for the feature table is depicted in

table 1.

TABLE-US-00002 TABLE 1 Exemplary depiction of a feature table.

sequ. no.	observ. no.	BlankimageName	finalimageName	tfRlin	tfGlin	tfBlin
1	1	R5-W2-07_*_image	R5-W2-07_*_image	129.5	126.74	72.89
2	1	R5-W2-07_*_image	R5-W2-07_*_image	129.6	126.68	73.58
3	1	R5-W2-07_*_image	R5-W2-07_*_image	129.8	126.92	73.35
4	1	R5-W2-07_*_image	R5-W2-07_*_image	129.9	126.95	73.74

sequ. no.	glcCodeValue	wfRlin	wfGlin	wfBlin	Cont	blankValueRtf
1	207.35	206.164	202.28	10.46475029		145.2584534
2	207.16	206.037	201.79	10.11334229		145.2584534
3	207.63	206.186	202.02	10.42901993		145.2584534
4	207.38	206.262	202.08	9.864500046		145.2584534

sequ. no.	blankValueGtf	blankValueBtf	blankValueRwf	blankValueGwf	blankValueBwf
1	143.0743256	73.74324036	209.0067902	207.8676453	204.3337097
2	143.0743256	73.74324036	209.0067902	207.8676453	204.3337097
3	143.0743256	73.74324036	209.0067902	207.8676453	204.3337097
4	143.0743256	73.74324036	209.0067902	207.8676453	204.3337097

[0072] The feature table includes linear average RGB channel values for both the target field (tfRlin, tfGlin, tfBlin) and the white field (wfRlin, wfGlin, wfBlin). The linearization is achieved by setting the tone map curve of a smartphone to a straight 1:1 line. The linearization is necessary for handling different default tone map curves in different smartphone types. Without setting the tone map curve, the relationship between the values would be artificially nonlinear due to the default tone map curves being nonlinear. The averaging is performed for each RGB channel separately by taking the arithmetic average of the channel values of the respective region (target field or white field).

[0073] The feature table further includes linear average RGB channel values for the target field (blank ValueRtf blank ValueGtf, blank ValueBtf) and the white field (blank ValueRwf, blank ValueRwf, blank ValueRwf) before dosing.

[0074] Data can be assessed as invalid if it is determined that the data is very (partly) overexposed, inhomogeneous, included too few pixels, the corresponding image was not sharp enough, or a combination thereof. The invalid data can be removed from the feature table. The feature table does not include information from all the images of the same measurement. In general, for each image series **201**, roughly 80 images **30** are captured, but not all the images **30** are necessary for modeling. It may be sufficient or desirable to employ the data from the final image and from 10 to 19 images preceding the final image for the modeling. In the final images, the slope of R or G channels is close to zero, i.e., color kinetics are stabilized at a certain time after dosing and colors do not change or change only minimally from that point on. Taking images with stationary color kinetics can increase comparability of the images.

[0075] Further referring to FIG. **2**, in step **204**, the data of the feature table are used for feature engineering. One of the aspects of the modeling is to select the proper features for a model. Since the goal is to predict blood glucose values, using features that have a strong correlation with reference blood glucose values is expected to result in better models. The reference blood glucose values have been determined with established blood glucose measuring systems. The linear RGB channels exhibit a certain degree of correlation with the reference glucose values. However, results can still be improved by creating new features having a stronger correlation with the reference glucose values. Creating such new features may moreover be beneficial in that dependencies could be decreased with respect to different cell phone types and measurement conditions such as climate conditions or illumination conditions.

[0076] In this regard, FIG. **4** shows a graphical representation of the process of creating new features **42** out of features **40** from the feature table by applying a feature transformation **41** such as a color transformation to the features **40**. The features **40** may include the linear average RGB channel values for the target field (tfRlin, tfGlin, tfBlin), and/or the white field (wfRlin, wfGlin, wfBlin), and/or the RGB channel values before dosing (blank ValueRtf blank ValueGtf, blank ValueBtf), (blank ValueRwf, blank ValueRwf, blank ValueRwf).

[0077] In FIGS. **5***a* and **5***b*, depictions of the correlation behavior of exemplary new features **42** created by the feature transformation **41** of the features **40** are shown. Graphs **51** to **56** each display the correlation behavior of one of the new features **42** (x-axes) with the reference blood glucose values (y-axes). The feature "GRY" as in graph **52** refers to grayscale color values. The suffix "N" in certain features refers to normalization. In particular, "RGBN" as in graph **53** means "RGB color normalized". Different markers (∘, +, ◇) correspond to different experiment types. The depicted new features **42** exhibit a stronger correlation with reference glucose values than just raw RGB values.

[0078] In contrast, FIG. **5***c* shows depictions of the correlation behavior of raw RGB channel values with the reference blood glucose values. Graph **57** shows the linear average R channel value for the target field tfRlin. Graph **58** shows the linear average G channel value for the target field tfGlin. The graphs **57** and **58** show a larger scattering of the values and hence a weaker correlation with the reference blood glucose values than the new features **42** depicted in FIGS. **5***a* and **5***b*.

[0079] Referring again to FIG. **2**, in a subsequent step **206**, training, validation, and test sets can be created from the data in the feature table before an ANN model can be trained. It may be provided that the data are divided into a training, a validation, and a test set. 60% of the data are used for training, 20% for validation, and 20% for testing. Cross validation techniques such as leave-p-out cross validation or k-fold cross validation can also be employed. The training set is created using stratified random sampling of the data. Stratification can be conducted based on smartphone types and experiment types. As in, the data can be divided into separate subpopulations (strata), wherein each stratum corresponds to a different smartphone type and experiment type. Subsequently, data can be sampled separately for each stratum and then merged in order to create the training data. Doing so assures that the training data still represent the full population of smartphone and experiment types. The validation sets and test sets can be created analogously.

[0080] The validation set is used in order to prevent overtraining/overfitting, while the test set is used for an independent evaluation of the model during the training. A column is added to an input dataset to indicate which data is used for training, testing and validation. The added column is to identify proper subsets when training the ANN.

[0081] In step **207**, the ANN is trained. The ANN is trained with different measurement conditions such that the different measurement conditions are represented in the training set and can be included in the model. It can also be provided that different smartphone types are included in the modelling. The training of the ANN can be performed in numerical computing environments such as MATLAB. For increased performance, compiled programming languages can also be employed. FIG. **6** shows a graphical representation of an exemplary architecture of an ANN model **60** to be trained. The architecture in FIG. **6** includes two hidden layers **62**, **63**. Alternatively, a single hidden layer of more than two hidden layers can be employed (not shown) depending on the complexity of the problem. Input values **61** are passed to the hidden layer **62**. The output of the hidden layer **62** is passed to the hidden layer **63**. The output of the hidden layer **63** in turn is passed to an output layer **64**, resulting in an output value **65**. The output value **65** corresponds to a predicted blood glucose value. Weight coefficients **62***a*, **62***b*, **63***a*, **63***b*, **64***a*, and **64***b* are optimized during the training for the proper blood glucose model.

[0082] Regularization methods such as early stopping can be used to prevent overtraining. For example, it can be provided that a maximum of 12 iterations is allowed for training the model **60**. The maximum number of epochs can be set to 1000, for example. Multiple models **60** with different initialization points are trained and their performance metrics saved into a table file, such as a csv file, for later model selection. Once all the models **60** are created and performance metrics are evaluated, a best performing model is selected as the final trained model.

[0083] Referring back to FIG. **2**, in step **208**, the trained model is established using a neural network formula consisting of linear combination of hyperbolic tangents of features with optimized coefficients obtained from the trained ANN. By use of the trained neural network model, blood

glucose values are determined (step **209**). Subsequently, the determined blood glucose values are output for further processing (step **210**).

[0084] FIGS. **7** and **8** each show a Parkes error grid illustrating the performance of the determined blood glucose values versus actual blood glucose values on the full dataset. Parkes error grids (consensus error grids) are well-known graphical tools for comparing different data in quantitative diagnostics (Parkes et al., *Diabetes Care* 23:1143-1148, 2000). Each y-axis corresponds to the predicted blood glucose values; each x-axis corresponds to the actual blood glucose values. Each error grid is divided into different zones A to D, corresponding to different error regions. Deviations from the bisecting lines **71**, **81** within zone A correspond to low errors. It is desirable that most values are within zone A. Zone B corresponds to moderate errors, zone C to unacceptably large errors for the treatment of patients, and zone D to excessively large errors. In FIG. **7**, different markers correspond to different experiment types; in FIG. **8**, different markers correspond to different smartphone types. As can be seen from the FIGS. **7** and **8**, the predicted blood glucose values correspond to the actual blood glucose values reasonably well for both different cell phone types and different experiment types.

[0085] Table 2 shows one example of how often blood glucose values fall into different Parkes error grid zones A to E for a traditional or non-ANN algorithm (parametric multivariate linear regression) in comparison with the ANN model approach. Values within the zones A and B are considered acceptable, values within the zones C to E unacceptable to critical. Both the traditional algorithm and the ANN model can be trained with coding datasets M1 and M2. Subsequently, unknown cell phone types (coding datasets M4, M5, and M6) can be assessed. The coding datasets M1 to M5 in this example stem from lab data determined under standard conditions (T=24° C., Hum=45%) at a standard measuring station and including a Hexokinase Glucose reference value. Environmental and handling effects can be minimized. Five different types of cell phones can be employed per coding dataset. Hence, training can be performed by use of 10 different cell phone types. The thus generated algorithms can be subsequently provided with unknown data of 3×5=15 different cell phone types.

TABLE-US-00003 TABLE 2 Comparison of traditional and ANN approaches for blood glucose prediction. n A B C D E Traditional algorithm Coding set   371   338   33 0 0 0 M1 (91.11%) (8.89%) Coding set   470   405   65 0 0 0 M2 (86.17%) (13.83%) Coding sets 1429 1159 263 2 5 0 M4, M5, M6 (81.11%) (18.40%) (0.14%) (0.35%) ANN model Coding set   371   362   9 0 0 0 M1 (97.57%)   (2.43%) Coding set   470   435   35 0 0 0 M2 (92.55%)   (7.45%) Coding sets 1429 1106 323 0 0 0 M4, M5, M6 (77.40%) (22.60%)

[0086] As can be seen from table 2, the ANN model performs better in estimating blood glucose values for unknown cell phone types than the traditional algorithm. Importantly, no values from the ANN model are within the unacceptable zones C to E, corresponding to gross misclassifications of the blood glucose levels.

[0087] In further examples for blood glucose prediction, a traditional algorithm **91** such as, e.g., polynomial fits can be used in combination with ANN models **92**. FIG. **9** shows a graphical representation of different types of combinations that can be used: [0088] a) Predictions **93** from a traditional algorithm **91** can be used as an input (feature) to the ANN model **92**; [0089] b) predictions **94** from an ANN model **92** can be used as an input to a traditional algorithm **91**; and [0090] c) Both a traditional algorithm **91** and an ANN model **92** can be used and differences in the predictions **93**, **94** from both algorithms can be used as a failsafe to eliminate incorrect predictions.

[0091] FIG. **10** shows a Parkes error grid depicting the predictions of the ANN model which uses traditional algorithm predictions as one of its inputs.

[0092] FIG. **11** shows a graphical representation of another embodiment of a combined traditional and ANN model algorithm **110**. Out of the image series **201**, including at least two images, certain features can be extracted (step **111**). These features can then be monitored and a dry (blank) value and a final value can be determined using a kinetic algorithm (step **112**).

[0093] The features are then processed in a traditional algorithm (step **113**) and an ANN model (step **114**) in parallel, resulting in blood glucose value predictions (step **115**). Error flags can also be provided if applicable.

[0094] FIGS. **12**A, **12**B and **12**C show three Parkes error grids **120**, **121**, **122**, respectively, for comparing the performance of traditional and ANN model approaches. For error grid **120**, depicted in FIG. **12**A, only a traditional algorithm was employed; for error grid **121**, depicted in FIG. **12**B, only an ANN model was employed. As can be seen in error grids **120** and **121**, the measurement performance for the feature based ANN model is better than the one for the traditional algorithm. Error grid **122**, depicted in FIG. **12**C, demonstrates why not to only rely on ANN models. Here, as a showcase, the ANN was only trained on blood glucose values below 450 mg/dl. Therefore, samples **122***a*, **122***b* out of the training scope are severely misclassified. To protect against any unexpected input data entered into the ANN leading to wrong blood glucose results, the traditionally determined blood glucose values could be used as a failsafe for the ANN blood glucose results.

[0095] While exemplary embodiments have been disclosed hereinabove, the present invention is not limited to the disclosed embodiments. Instead, this application is intended to cover any variations, uses, or adaptations of this disclosure using its general principles. Further, this application is intended to cover such departures from the present disclosure as come within known or customary practice in the art to which this invention pertains and which fall within the limits of the appended claims.

Claims

1. A system for determining concentration of an analyte in a sample of a body fluid, comprising: a software-implemented module having a first analyzing algorithm generated by: deriving a first set of color information from images recorded by a plurality of devices, wherein the images depict a color transformation on a first test strip in response to a body fluid containing an analyte, and training a neural network model using training data selected from the first set of color information; and a processor configured to: receive second color information derived from images of a present test strip indicating a color transformation in response to a present sample of a body fluid containing an analyte, and use the first analyzing algorithm to determine concentration of the analyte in the present sample of the body fluid.

2. The system according to claim 1, wherein at least some software and/or hardware configurations are different among the plurality of devices.

3. The system according to claim 1, wherein generating the first analyzing algorithm further includes generating a neural network model in a machine learning process applying an artificial neural network.

4. The system according to claim 1, wherein the processor is configured to use a second analyzing algorithm to determine a first estimation value of the concentration of the analyte on the present test strip.

5. The system according to claim 4, wherein the first estimation value comprises a target range for the concentration of the analyte on the present test strip.

6. The system according to claim 4, wherein the concentration of the analyte on the present test strip is determined by averaging the first estimation value and a concentration value determined by the neural network model.

7. The method according to claim 1, wherein the first and/or second set of measurement data includes color information derived from consecutive images recorded over a measurement period of time for the region of interest of the first and/or present test strip.

8. The system according to claim 7, wherein the measurement period of time is from about 0.1 to about 1.5 s.

9. The system of claim 7, wherein the measurement period of time begins before the body fluid sample is applied to the test strip and ends after completion of the color change reaction.

10. The system according to claim 1, wherein the plurality of devices have different cameras and/or different image processing software.

11. The system according to claim 1, wherein the recorded images of the color transformation of the region of interest of the first test strip comprise images recorded with different optical image recording conditions.

12. The system according to claim 1, wherein the recorded images comprise images of the region of interest prior to applying the fluid containing an analyte to the region of interest.

13. The system according to claim 1, further comprising extracting image data from the recorded images for a blank region of the first test strip where no color transformation occurs.

14. The system according to claim 13, wherein the image data from the blank region of the first test strip is used to train the neural network model.