



- (51) **International Patent Classification:**
H04N 7/18 (2006.01)
- (21) **International Application Number:**
PCT/US2012/029391
- (22) **International Filing Date:**
16 March 2012 (16.03.2012)
- (25) **Filing Language:** English
- (26) **Publication Language:** English
- (30) **Priority Data:**
61/453,241 16 March 2011 (16.03.2011) US
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- (81) **Designated States (unless otherwise indicated, for every kind of national protection available):** AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.
- (84) **Designated States (unless otherwise indicated, for every kind of regional protection available):** ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE,

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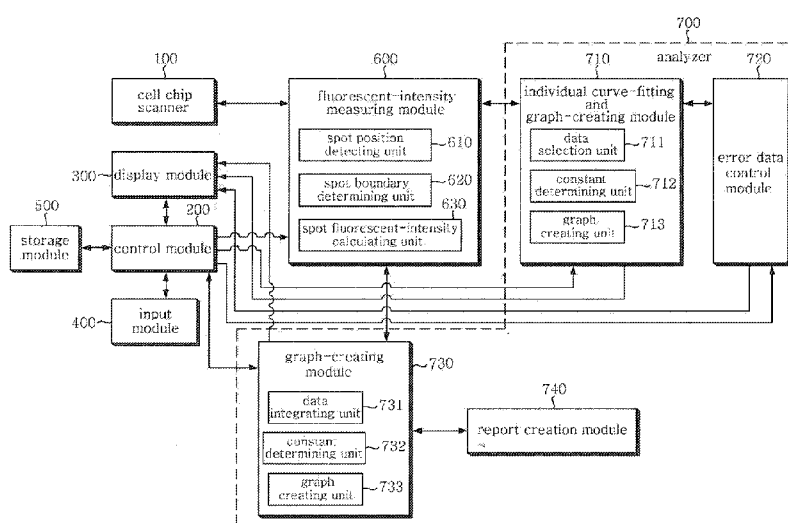
(54) **Title:** APPARATUS AND METHOD FOR ANALYZING DATA OF CELL CHIPS

FIG. 1

(57) **Abstract:** Disclosed herein is an apparatus and method for analyzing data of cell chips. The apparatus includes a cell chip scanner, a fluorescent-intensity measuring module and an analyzer. The cell chip scanner scans cell chips and creates image files. The fluorescent-intensity measuring module measures fluorescent intensities of the spots in the image files created by the cell chip scanner. The analyzer creates graphs in such a way as to individually conduct curve-fitting on the fluorescent intensities of the spots of the blocks that were measured by the fluorescent-intensity measuring module. The analyzer creates an integrated graph in such a way as to integrate pieces of data of the blocks obtained under same test conditions and then conduct curve-fitting on the integrated data.



DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT,
LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE,
SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA,
GN, GQ, GW, ML, MR, NE, SN, TD, TG).

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

Published:

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

APPARATUS AND METHOD FOR ANALYZING DATA OF CELL CHIPS

RELATED APPLICATION

This claims the benefit of U.S. Provisional Application No. 61/453,241, filed on March 16,
5 2011. The entire teachings of the above application are incorporated herein by reference.

BACKGROUND OF THE INVENTION

1. Technical Field

The present invention relates to an apparatus and method for analyzing data of cell chips.
10

2. Description of the Related Art

As is well known to those skilled in the art, "cell chips" refers to chips in which living or
resting cells are placed or maintained on substrates, preferably glass substrates, e.g. under
conditions suitable for conducting one or more cellular reactions.

15 Such cell chips are used in the pharmaceutical field or the cosmetic-related field to test the
reactions of cells to chemicals in order to assess the biological activity, efficacy and/or safety of the
chemicals. Examples include the cell chips described in WO 2007/053561 and USSN 61/381,812,
filed on September 10, 2010, for example, which is incorporated herein by reference in its entirety.

To inspect the efficacy and safety of chemicals by testing the reaction of cells to the
20 chemicals, in pharmaceutical or cosmetic companies, test chemicals are applied to an enzyme-
containing chip that carries out enzymatic reactions. Examples of enzyme-containing chips
include the chips described in US Patent 7,267,958 and USSN 61/381,812, filed on September 10,
2010, for example, which is incorporated herein by reference in its entirety.

Thereafter, the enzyme-containing chip is contacted with the cell chip so that the test
25 compound or test compound that is enzymatically reacted is applied to cells.

The cells are dyed with fluorescent material to facilitate analysis of the reaction of the test compound or enzymatically reacted test compound with the cells. The conditions of the cells are investigated and analyzed by test devices, such as scanners, etc., to determine whether the chemicals are biologically active or toxic.

5 In the conventional art, manual methods are used to carry out the processes of detecting and analyzing the conditions of the cells and determining whether the chemicals are, for example, toxic. Thus, the processes are complex, significant time is required, and the precision of the tests is reduced.

10 SUMMARY OF THE INVENTION

The present invention has been made to provide an apparatus for automatically analyzing data obtained from one or more cell chips, thus simplifying the test process, reducing the required time, and enhancing the precision of the testing process, and a method of analyzing data of cell chips using the apparatus.

15 In an apparatus for analyzing data according to an embodiment of the present invention, a cell chip scanner scans one or more cell chips and creates image files thereof. The cell chips have preferably been subjected to a compound, which upon contact with a cell or a component thereof (e.g., ATP), fluoresces. A fluorescent-intensity measuring module measures fluorescent intensities of the spots in the image files. An analyzer creates graphs in such a way as to individually conduct
20 curve-fitting with respect to the fluorescent intensities of the spots. The analyzer creates an integrated graph in such a way as to integrate pieces of data of the blocks and then conduct curve-fitting on the integrated data.

The apparatus may further include a computer which can accept, analyze, store, and display data provided by the operator relating to the cell chip, the images created by the scanner,
25 and the results created by the analyzer. The apparatus can include a storage module for storing information relating to the cell chips and/or test conditions. A display may provide a data, or test

condition, input window to a tester or operator. A control module may provide the test condition input window on the display. The tester or operator can input data or test conditions relating to the cell chip with an input module, the data then being stored in the storage module. The analyzer may create the graphs in such a way as to individually conduct the curve-fitting with respect to the
5 blocks while referring to the test conditions stored in the storage module.

The analyzer may include an individual curve-fitting and graph-creating module and an integrated curve-fitting and graph-creating module. The individual curve-fitting and graph-creating module may create the graphs in such a way as to individually conduct the curve-fitting with respect to the fluorescent intensities of the spots of the blocks that are measured by the
10 fluorescent-intensity measuring module. For example, where certain spots within a block (a line of spots, for example) differ from one another in test compound concentration (a progression of dilutions of a test compound contacted with the spots, for example), the individual curve-fitting and graph-creating module can create a graph that permits analysis of the fluorescence intensity of those spots as a function of concentration. The integrated curve-fitting and graph-creating module
15 may create the integrated graph in such a way as to integrate the pieces of data of the fluorescent intensities of the spots of the blocks that are measured by the fluorescent-intensity measuring module under the same test conditions and then conduct curve-fitting on the integrated data. One or both of these modules can be incorporated into a single software program to be run by the computer or control module discussed above. In one embodiment, the data received from the
20 operator or tester can be used to identify spots or compositions thereof.

The individual curve-fitting and graph-creating module may include a data selection unit selecting a plurality of fluorescent intensities that were obtained by conducting repetitive tests or replicates in a block or chip. A constant determining unit may determine a constant of a curve equation using the test results. A graph creating unit may create the graph using the constant
25 determined by the constant determining unit. In another embodiment, the software can solve the

equation for a specific value (e.g., an EC50 or IC50) and, optionally, incorporate that solution into a graph, report or other results.

The analyzer may optionally include an integrated curve-fitting and graph-creating module may include a data integrating unit integrating data obtained from a plurality of cell chips. A

5 constant determining unit may determine a constant of a curve equation using the integrated data. A graph creating unit may create the integrated graph.

The analyzer may include an error data control module and a report creation module. The error data control module may classify the data and identify an item to be checked by the tester or operator and, if appropriate, permit the tester to delete the item or erroneous data. The report
10 creation module may classify a result of the curve-fitting with respect to the integrated data and the scanned images, and create a result report, and then output the result report.

The fluorescent-intensity measuring module may include a spot position detecting unit detecting positions of the spots in such a way as to calculate an average of Y-axial fluorescent-intensities and an average of X-axial fluorescent-intensities from the image files created by
15 scanning the cell chips using the cell chip scanner. A spot boundary determining unit may determine boundaries of the spots detected by the spot position detecting unit. A spot fluorescent-intensity calculating unit may calculate a fluorescent-intensity of each of the spots after the boundaries of the spots are determined by the spot boundary determining unit.

In a method of analyzing data of cell chips according to an embodiment of the present
20 invention, image files are created by scanning a plurality of cell chips using a cell chip scanner. Fluorescent intensities of spots are measured by a fluorescent-intensity measuring module in the image files created by the cell chip scanner. Graphs are created in such a way as to individually conduct curve-fitting with respect to the fluorescent intensities of the spots of blocks that are measured by the fluorescent-intensity measuring module. An integrated graph can be created in
25 such a way as to integrate pieces of data that are related to the fluorescent intensities of the spots that are measured by the fluorescent-intensity measuring module under same test conditions and

then conduct curve-fitting with respect to the integrated data.

Each of the cell chips may include blocks. Each of the blocks may have a plurality of spots. The spots can preferably contain cells and one or more compounds to be tested. The compounds added to each spot can be the same or different. In a preferred embodiment, the spots
5 within a block contain the same compound at different concentrations or dilutions. Preferably, the compounds are contacted with an enzyme or enzymes for reaction (e.g., metabolism) and the reaction products (e.g., metabolites) of the compound can then be contacted with the cells in the cell chip. The cells in the cell chip can be contacted with a fluorescent marker that detects, for example, cytotoxicity.

10 In the method, an operator or tester can input data or information relating to the chip and relevant to the test into the apparatus. In one embodiment, a display module can present a test condition input window to a tester, where the tester, using an input module, can input data or information for storage in a storage module.

In the method, integrated results may be classified by an error data control module as
15 above.

In measuring the fluorescent intensities of the spots, positions of the spots may be detected. In one embodiment, the apparatus calculates an average of Y-axial fluorescent-intensities and an average of X-axial fluorescent-intensities from the image files. Boundaries of the spots may be determined by the fluorescent-intensity measuring module. A fluorescent-intensity value for each
20 spot may be calculated after the boundaries of the spots are determined by the fluorescent-intensity measuring module.

In determining the boundaries of the spots, pixels of a predetermined value or more may be connected to each other with lines (or line segments) using the fluorescent-intensity measuring module. In one embodiment, the lines are generated in a specific orientation (e.g., horizontal or
25 vertical, relevant to a boundary of the chip or a block). The lines can be generated in a parallel fashion of a predetermined distance, x , wherein x is less than the predicted radius of a spot and

preferably less than 20%, such as less than 10% of the predicted radius of a spot. Lines may be united, thereby forming a longer line (or line segment), when a distance between the lines is less than a predetermined value, for example, distance y, wherein y is less than the predicted radius of a spot and preferably less than 20%, such as less than 10% of the predicted radius of a spot. A line
5 may be deleted when a length of the line is shorter than a predetermined value, for example distance z, wherein z is less than the predicted radius of a spot and preferably less than 20%, such as less than 10% of the predicted radius of a spot. One or more lines (but preferably less than a majority of the total number of lines drawn) that are spaced apart from a plurality of other lines by a predetermined distance or more (for example, distance v, wherein v is greater than 10%, such as
10 greater than 20% of the predicted radius of the spot) may be deleted. Midpoints of the lines may be determined and the central midpoint may be determined. Using the central midpoint as the center of the spot, the boundary of the spot is calculated using a predetermined radius (e.g., the predicted radius).

In calculating the fluorescent-intensity of each of the spots, an average of absolute
15 intensities of pixels in a spot area may be determined. A central value of pixels in a peripheral area (e.g., an area outside the boundary of any spot) may be determined by the fluorescent-intensity measuring module. The central value of the pixels of the peripheral area may be subtracted from the average of the absolute intensities of the pixels of the spot area, thus attaining the fluorescent-intensity of the spot.

20 In creating the graphs, a plurality of values of fluorescent intensities that are results of various spots on a chip or within a block or repeated tests may be selected by an individual or integrated curve-fitting and graph-creating module. A constant of a curve equation may be determined and/or one or more graphs may be created.

25 BRIEF DESCRIPTION OF THE DRAWINGS

The above and other objects, features and advantages of the present invention will be more

clearly understood from the following detailed description taken in conjunction with the accompanying drawings, in which:

FIG. 1 is a diagram showing the construction of an apparatus for analyzing data of cell chips, according to an embodiment of the present invention;

5 FIG. 2 is a view showing one example of a cell chip used in the present invention;

FIG. 3 illustrates one example of a test condition input window used in the present invention;

FIG. 4 is a view illustrating a process of detecting spots using a fluorescent-intensity measuring module according to the present invention;

10 FIGS. 5A, 5B and 6 through 10 are views illustrating a process of determining a boundary of a spot using the fluorescent-intensity measuring module according to the present invention;

FIG. 11 is a view illustrating a process of measuring fluorescent-intensities of the spots using the fluorescent-intensity measuring module according to the present invention;

FIG. 12 is a table of data related to the fluorescent-intensities of one block of an individual
15 cell chip which are obtained by the fluorescent-intensity measuring module according to the present invention;

FIG. 13 is a graph showing the results of testing four kinds of enzymes with respect to the same compound created in an individual curve-fitting and graph-creating module according to the present invention;

20 FIG. 14 is a view showing one example of an image used for sorting out items that can be examined using an error data control module according to the present invention;

FIG. 15 is an example showing an image including scan images and curve-fitting graphs that illustrate in detail the examination-required item sorted out by the error data control module according to the present invention;

25 FIG. 16 is a view showing one example of a report created by a report creation module according to the present invention;

FIG. 17 is a flowchart of a method of analyzing data of cell chips, according to an embodiment of the present invention;

FIG. 18 is a flowchart of a test condition input step of FIG. 17;

FIG. 19 is a flowchart of a spot position detecting step of FIG. 17;

5 FIG. 20 is a flowchart of a spot fluorescent-intensity measuring step of FIG. 17; and

FIG. 21 is a flowchart of an individual curve-fitting and graph creating step of FIG. 17.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

Reference now should be made to the drawings, in which the same reference numerals are
10 used throughout the different drawings to designate the same or similar components. In the following description, when it is determined that the detailed description of the conventional function and conventional structure would confuse the gist of the present invention; such a description may be omitted. Furthermore, the terms and words used in the specification and claims are not necessarily limited to typical or dictionary meanings, but must be understood to
15 indicate concepts selected by the inventor as the best method of illustrating the present invention, and must be interpreted as having had their meanings and concepts adapted to the scope and spirit of the present invention so that the technology of the present invention could be better understood.

Hereinafter, embodiments of the present invention will be described in detail with reference to the attached drawings.

20 FIG. 1 is a diagram showing the construction of an apparatus of analyzing data of cell chips, according to an embodiment of the present invention.

Referring to FIG. 1, the cell-chip data analysis apparatus (hereinafter, referred to as “data analysis apparatus”) according to the embodiment of the present invention includes a cell chip scanner 100, a control module 200, a display module 300, an input module 400, a storage module
25 500, a fluorescent-intensity measuring module 600 and an analyzer 700.

The analyzer 700 includes an individual curve-fitting and graph-creating module 710, an error data control module 720, an integrated curve-fitting and graph-creating module 730 and a report creation module 740.

The fluorescent-intensity measuring module 600 includes a spot position detecting unit 610, a spot boundary determining unit 620 and a spot fluorescent-intensity calculating unit 630.

The individual curve-fitting and graph-creating module 710 of the analyzer 700 includes a data selection unit 711, a constant determining unit 712 and a graph creating unit 713.

The integrated curve-fitting and graph-creating module 730 of the analyzer 700 includes a data integrating unit 731, a constant determining unit 732 and a graph creating unit 733.

In a preferred embodiment, the cell chips receive, for example, from enzyme-containing chips, substances, including products created by reacting enzymes with chemicals in the enzyme-containing chips. The cells on the cell chips can then respond to the substances for a toxic reaction or a biologically active outcome. In one example, a toxic reaction can be cell death or apoptosis. The cell chips can be dyed with a fluorescent material. The cell chip scanner 100 then scans the cell chip(s).

In one example of an enzyme-containing chip, the chip contains enzymes, such as liver enzymes (e.g., human or other animal), placed on a glass substrate under conditions suitable for enzymatic activity. When test chemicals are applied to the enzyme-containing chip, the enzymes can react with the test chemicals and form a product, such as a metabolite.

In a preferred embodiment, the cell chip incorporates human cells, including cells isolated from a human body on a substrate. Cells that can be used, or the tissues/organs they can be derived from, include, but are not limited to bone marrow, skin, cartilage, tendon, bone, muscle (including cardiac muscle), blood vessels, corneal, neural, brain, gastrointestinal, renal, liver, pancreatic (including islet cells), lung, pituitary, thyroid, adrenal, lymphatic, salivary, ovarian, testicular, cervical, bladder, endometrial, prostate, vulval, esophageal, etc. Also included are the various cells of the immune system, such as T lymphocytes, B lymphocytes, polymorphonuclear leukocytes,

macrophages, and dendritic cells. In one embodiment, the cells are normal cells. Alternatively, the cells can be cancerous, derived from a cell line or an immortalized cell. In yet other embodiments, the cells can be bacterial, yeast or derived from a plant.

The cells preferably are placed on a substrate. Examples of preferred substrates include
5 glass substrates. The cells can be encapsulated into or layered over a matrix that can, for example, support growth. Such matrices include alginate or collagen and can include an appropriate cell culture media. The matrices and/or cells can be spotted or placed onto a flat substrate, into wells or upon columns. Preferably, the cells are placed on the substrate in discrete "spots". The spots can be deemed to be discrete if the spots are not touching, in fluid communication or are physically
10 separated.

The cell chip can preferably be organized as a two dimensional array having a plurality of rows and columns. Each cell chip can include a plurality of "blocks." A block is a subarray, section or portion of the array. Each block includes a plurality of spots, preferably arranged in a plurality of columns and rows. In one embodiment, the spots within a block are the same in
15 composition, differing one from another only in the concentrations of one or more components, such as the substance being tested (e.g., a test chemical, enzymatic reaction product or metabolite). In turn, the spots within each block can possess the same composition, differing one from another block only in one component of the composition, such as the substance being tested, an enzyme or the cell. For example, as shown in FIG. 2, the cell chip includes 24 blocks which are formed by a
20 combination of four kinds of enzymes (for the sake of convenience, referred to as A, B, C and D) and six kinds of compounds (for the sake of convenience, referred to as 1, 2, 3, 4, 5 and 6). In this embodiment, the cell can be a constant in all blocks. Alternative configurations of the components can be envisioned and made by the person of skill in the art.

As shown in the enlarged view of FIG. 2, each block includes a matrix with four rows
25 having the same compound concentration and seven columns having different enzyme concentrations (e.g., having dilutions of one-fold, two-fold, three-fold, four-fold, five-fold, six-fold

and seven-fold). The four rows, thereby, provide four replicates of the experiment.

One or more cell chips are scanned in sequence by a scanner, such as the cell chip scanner 100. The results of the scanning can be stored as image files (for example, TIFF files, PDF files, BMP files, etc.) in the storage module 500, which is generally a computer or CPU.

5 The control module 200 controls the operation of the parts of the data analysis apparatus. Particularly, the control module 200 shows the test condition input window on the display module 300 such that a tester (or operator) can input test conditions using the input module 400, which can be, for example, a keyboard. The control module 200 stores test conditions input by the tester in the storage module 500.

10 The display module 300 can display one or more of the image files scanned by the cell chip scanner 100, the test condition input window provided by the control module 200, a table showing fluorescent intensities measured by the fluorescent-intensity measuring module 600, a graph created by the individual curve-fitting and graph-creating module 710 of the analyzer 700, a target item sorted out by the error data control module 720 of the analyzer 700, an integrated graph
15 created by the integrated curve-fitting and graph-creating module 730 of the analyzer 700, or a report created by the report creation module 740 of the analyzer 700.

As shown in the test condition input window of FIG. 3, the test conditions are entered, which can include a project folder title, a chip platform (for example, “672 spot layout”), the number of compound dilution folds (for example, the “4”), a cell type (for example, “Hep3B”) relative to each of slide names (for example, stated as “2010-07-14-M” and “2010-07-14-N”), a
20 unit (for example, a “micro mole”), the compound identifiers (for example, compound designations “AA”, “BB”, “CC”, “DD”, “EE”, “FF”, “GG”, “HH”, “II”, “JJ”, “KK” and “LL”), and the enzymes (for example, designated as “control”, “P450”, “Phase II” and “All mix”).

The fluorescent-intensity measuring module 600 detects spots in the image files created by
25 scanning the cell chips using the cell chip scanner 100, determines boundaries of the spots and then calculates fluorescent-intensities of the spots.

In detail, as shown in FIG. 4, the spot position detecting unit 610 of the fluorescent-intensity measuring module 600 calculates averages of X-axial fluorescent-intensities and averages of Y-axial fluorescent-intensities from the image files created by scanning the cell chips using the cell chip scanner 100. Thereafter, the spot position detecting unit 610 determines junctions of the
5 maximums of the averages of X-axial fluorescent-intensities and the maximums of the averages of Y-axial fluorescent-intensities as approximate positions of the respective spots. With regard to this, FIG. 4 illustrates a process of determining a junction of a first maximum of the X-axial fluorescent-intensity averages and a first maximum of the Y-axial fluorescent-intensity averages as an approximate position of a first spot using the spot position detecting unit 610.

10 The spot boundary determining unit 620 of the fluorescent-intensity measuring module 600 detects an approximate center of each of the spots, determines a precise position of the spot in a predetermined section centered on the approximate center, and determines the boundary of each spot.

To determine the center of each spot, as shown in FIG. 5A, with regard to each spot, the
15 spot boundary determining unit 620 connects pixels of a predetermined value or more (e.g., greater than 30%, preferably greater than 50% of the average of absolute intensities of the pixels in the spot area) to each other with lines. FIG. 5B removes the pixels and retains the drawn lines. As shown in FIG. 6, when a distance between adjacent lines is less than a predetermined value, the lines are united. As shown in FIG. 7, when a length of a line is shorter than a predetermined value,
20 the line is deleted. As shown in FIG. 8, a minor number of lines which are spaced apart from the other lines by a predetermined distance or more are deleted. As shown in FIG. 9, midpoints of the lines are determined. As shown in FIG. 10, an average of the midpoints of the lines is determined and then the average is determined as the center of the spot. The boundary can then be determined by using a predetermined radius measured from the center of the spot.

25 The above-mentioned process can be carried out by the spot boundary determining unit 620 to determine the boundaries of the spots.

The spot fluorescent-intensity calculating unit 630 of the fluorescent-intensity measuring module 600 can calculate the fluorescent-intensity of the spots.

In detail, as shown in FIG. 11, the spot fluorescent-intensity calculating unit 630 determines the average of absolute intensities of pixels in a spot area (e.g., within the boundary of the spot). The unit can, optionally, determine a central value of pixels in a peripheral area (e.g., outside the boundary of the spots), and subtract the central value of the pixels of the peripheral area from the average of the absolute intensities of the pixels of the spot area. Thereby, the fluorescent-intensity of the spot is attained.

The analyzer 700 creates graphs to individually conduct curve-fitting for the fluorescent intensities. The analyzer 700 can also create an integrated graph with data from a plurality cell chips. The analyzer 700 can additionally create and output one or more reports.

During this process, if an error is suspected, for example, with respect to the data related to the fluorescent-intensities, the analyzer 700 can identify potentially erroneous data and enable the tester to delete erroneous data.

In detail, the individual curve-fitting and graph-creating module 710 of the analyzer 700 conducts curve-fitting on the fluorescent intensity of selected spots within each block of the cell chip. For example, spots within a block that differ one from another in the concentrations of a test compound or metabolite can potentially result in differing fluorescent intensities as a function of concentration. The module can analyze the data create a graph resulting from curve-fitting.

The data selection unit 711 of the individual curve-fitting and graph-creating module 710 can select a plurality of fluorescent intensities that have been obtained by repetitive tests with respect to concentrations of compounds of a plurality of blocks. For example, the table of FIG. 12 provides fluorescent intensities resulting from four repetitions with respect to seven dilutions of a compound.

The data selection unit 711 selects the values resulting from the repeated tests. The constant determining unit 712 can determine constants (e.g., d, g and b) of a curve equation (e.g.,

Equation 1) for example, using numerical analysis.

(Equation 1)

$$y=d/(1+\exp((g-x)/b))$$

where y denotes fluorescent intensity, x denotes the number of dilution folds (log
5 concentration), and g denotes an inflection point at which the survival rate of a cell becomes 50%
(that is, the value of g denotes IC50).

As such, the graph creating unit 713 can then create graph of the equation. In the
embodiment, FIG. 13 illustrates curve graphs showing results of individual curve-fitting processes
with respect to four kinds of enzymes A, B, C and D. Square marks denote inflection points at
10 which the survival rates of cells become 50%.

The error data control module 720 of the analyzer 700 classifies the result, and if items
required to be checked by the tester are detected, the error data control module 720 sorts out the
items so as to enable the tester to delete erroneous data.

For example, if the IC50 values in repetitive tests are substantially different from each
15 other or if the curve-fitting is defective, the error data control module 720 can indicate this and
cause the data to be displayed and present remove buttons on the display module 300. The
actuation of the remove button can cause the data to be deleted from the storage unit and/or from
data integration.

For example, FIG. 14 shows the case where with regard to the compound AA and the
20 enzyme agent ED of the slide name 2010-07-14-M.tif, the compound BB and the enzyme agent
EC of the slide name 2010-07-M.tif, and the compound CC and the enzyme agent EC of the slide
name 2010-07-14-M.tif, checkboxes are checked to notify the tester if it has to be checked whether
there is data to be excluded or deleted.

Here, as shown in FIG. 15, the error data control module 720 provides the scanned images
25 and the curve-fitting graphs to enable the tester to check in detail whether there is a data error.

Furthermore, when it is necessary to remove data of a desired item from among the items

that require checking, the tester clicks a remove button for the corresponding item. Then, the corresponding data is removed.

The integrated curve-fitting and graph-creating module 730 of the analyzer 700 integrates data from the cell chips (for example, repeat tests) into a single piece of data, and determines
5 constants of the curve equation, and creates an integrated graph, as described above.

The report creation module 740 classifies the results of curve-fitting with respect to the integrated data and the scanned images and outputs a result report.

The result report created by the report creation module 740 is preferably editable. An example of a report is illustrated in FIG. 16. This exemplary report includes a summary, the
10 scanned images and an integrated curve-fitting graph.

FIG. 17 is a flowchart of a method of analyzing the data of cell chips, according to an embodiment of the present invention.

Referring to FIG. 17, the method includes a cell chip scanning step S10, a test condition input step S20, a spot position detecting step S30, a spot fluorescent-intensity measuring step S40,
15 an individual curve-fitting and graph creating step S50, a test result classifying and abnormal item sorting-out step S60, a data error item checking and deletion target data selection step S70, an integrated data curve-fitting and graph creating step S80 and a test result report creating step S90.

At the cell chip scanning step S10, the scanner scans a cell chip that (1) receives, for example, from an enzyme-containing chip, a product (e.g., a metabolite) created by reacting one or
20 more enzymes with chemicals added to the enzyme-containing chip, and (2) carries out a cellular reaction with the product to test for cytotoxicity, and is dyed with fluorescent material to detect cytotoxicity.

The cell chip scanner scans other cell chips in sequence by repeating the above-mentioned process and stores results of the scanning as image files.

25 As shown in FIG. 18, at the test condition input step S20, the control module shows the test condition input window on the display module and the tester appoints a project folder, at step

S21. At step S22, the tester inputs a chip platform. At step S23, the tester inputs the dilutions of the compound or chemical. At step S24, the tester inputs a cell type and other cell information. At step S25, the tester inputs compound information (e.g., compound identifiers). At step S26, the tester inputs enzyme information.

5 In the spot position detecting step S30, as shown in FIG. 19, the fluorescent-intensity measuring module loads images from the project folder, at step S31.

At step S32, the fluorescent-intensity measuring module detects an approximate position of a first spot from the loaded image. At step S33, a precise position of the first spot is determined in a predetermined section centered on the detected approximate position.

10 To detect the approximate position of the first spot, the fluorescent-intensity measuring module uses averages of X-axial fluorescent-intensities and averages of Y-axial fluorescent-intensities. Determining the precise position of a first spot on the chip, block or predetermined section centered on a detected approximate position can include one or more of the following steps: connecting pixels of a predetermined value or more to each other with lines, uniting lines the
15 distance between which is less than a predetermined value, deleting lines that are shorter than a predetermined value, deleting a minor number of lines spaced apart from the other lines by a predetermined distance or more, attaining midpoints of the remaining lines, and then averaging the midpoints of the lines. Additional spots can optionally be detected by these methods or by calculation, using the predicted distance between spots, or be a combination thereof.

20 At step S34, the fluorescent-intensity measuring module determines whether the positions of all spots have been detected. If module detects another spot or concludes that the positions of all the spots have still not been detected, an approximate position of a subsequent spot is detected and the steps are repeated from step S33.

When the fluorescent-intensity measuring module determines that the positions of all the
25 spots have been detected, the center points of the spots are stored, at step S36. At step S37, it is determined whether all the images have been processed. If the module determines that another

image is available for processing, the above steps can be repeated.

In the spot fluorescent-intensity measuring step S40, as shown in FIG. 20, the fluorescent-intensity measuring module loads the images, at step S41.

At step S42, the fluorescent-intensity measuring module attains an average of absolute
5 intensities of pixels in each spot area. At step S43, the fluorescent-intensity measuring module attains a central value of pixels in each peripheral area. At step S44, the fluorescent-intensity measuring module subtracts the central value of the pixels of the peripheral area from the average of the absolute intensities of the pixels of the spot area, thus attaining the fluorescent-intensity of the spot.

10 At step S45, the fluorescent-intensity measuring module determines whether all the spots have been processed. At step S46, if all the spots have still not been processed, the fluorescent-intensity measuring module can process the subsequent spot. At step S47, when all the spots have been processed, the fluorescent-intensity measuring module determines whether all the images are processed. At step S48, the fluorescent-intensity measuring module stores the fluorescent-
15 intensities of the spots.

As shown in FIG. 21, in the individual curve-fitting and graph-creating step S50, the individual curve-fitting and graph-creating module loads information regarding the fluorescent-intensities of the spots, at step S51.

At step S52, the individual curve-fitting and graph-creating module selects data, for
20 example, relating to the compound dilutions or concentrations (x) and the fluorescent-intensity (y) with respect to one test condition, e.g. residing in one block. At step S53, the constants d, g and b of the curve equation are determined.

The individual curve-fitting and graph-creating module conducts numerical analysis, during which it can calculate a numerical formula error with respect to the selected constants d, g
25 and b of the curve equation (at step S54); and, determines whether the error is less than a reference value (at step S54); and step S54 is repeated if the error is not less than the reference value.

At step S56, where the numerical analysis reveals that the error is less than the reference value, the individual curve-fitting and graph-creating module can determine whether all the test conditions (all the blocks) have been processed and repeat the above steps if necessary or desired.

When all the blocks have been processed, the constants d, g and b can be stored and a
5 graph is created and displayed or printed, at step S57.

At the test result classifying and abnormal item sorting-out step S60, the error data control module classifies the results of the tests and sorts out items for checking by the tester.

For example, if the values of IC50 in a repeat experiment are excessively different from each other or curve-fitting is defective, the error data control module indicates this and, optionally,
10 displays a remove button or other method for removing or deleting data on the display module 300.

The error data control module can also display the scanned images and the curve-fitting graphs to facilitate whether the data should be excluded.

At the data error item checking and deletion target data selection step S70, the tester
15 checks target items sorted out by the error data control module. When it is desirable to remove data of an item, the tester can remove the data by, for example, selecting a remove button for the corresponding item.

At the integrated data curve-fitting and graph creating step S80, the integrated curve-fitting and graph-creating module integrates data of the cell chips, determines constants of the curve
20 equation, and creates an integrated graph, as described above, and, if desired, a report of the results. The report is optionally editable.

As described above, the apparatus according to the present invention automatically, efficiently and quickly processes the results of testing cell chips with improved accuracy.

Although the preferred embodiments of the present invention have been disclosed for illustrative
25 purposes, those skilled in the art will appreciate that various modifications, additions and

substitutions are possible, without departing from the scope and spirit of the invention as disclosed in the accompanying claims.

While this invention has been particularly shown and described with references to preferred embodiments thereof, it will be understood by those skilled in the art that various changes in form
5 and details may be made therein without departing from the scope of the invention encompassed by the appended claims.

CLAIMS

What is claimed is:

1. An apparatus for analyzing data of cell chips, comprising:

- 5 a scanner that scans a plurality of cell chips and create a plurality of image files, each of the
cell chips comprising a plurality of blocks, each of the blocks having a plurality of spots;
 a fluorescent-intensity measuring module that measures fluorescent intensities of each spot
in each image file; and
 an analyzer that integrates data relating to the cell chips or one or more blocks thereof,
10 conduct curve-fitting on the integrated data and creates graphs thereof.

2. The apparatus as set forth in claim 1, further comprising:

- a storage module that stores test conditions;
 a display module that provides a test condition input window;
15 a control module that provides the test condition input window to the tester using the
display module and stores input test conditions in the storage module; and
 an input module that receives test conditions input by the tester and provides the input test
conditions to the control module,
 wherein the analyzer creates the graphs in such a way as to individually conduct the curve-
20 fitting with respect to the blocks while referring to the test conditions stored in the storage module.

3. The apparatus as set forth in claim 1, wherein the analyzer comprises:

- an individual curve-fitting and graph-creating module that creates the graphs in such a way
as to individually conduct the curve-fitting with respect to the fluorescent intensities of the spots of
25 the blocks that are measured by the fluorescent-intensity measuring module; and
 an integrated curve-fitting and graph-creating module that creates the integrated graph in

such a way as to integrate the pieces of data of the fluorescent intensities of the spots of the blocks that are measured by the fluorescent-intensity measuring module and then conduct curve-fitting on the integrated data.

- 5 4. The apparatus as set forth in claim 3, wherein the individual curve-fitting and graph-creating module comprises:

a data selection unit that selects a plurality of fluorescent intensities that were obtained by conducting repetitive tests on concentrations of the compounds of each of the blocks;

- 10 a constant determining unit that determines a constant of a curve equation using the test results of the plurality of fluorescent intensities selected by the data selection unit; and

a graph creating unit that creates the graph using the constant determined by the constant determining unit.

- 15 5. The apparatus as set forth in claim 3, wherein the integrated curve-fitting and graph-creating module comprises:

a data integrating unit that integrates the pieces of data of the plurality of cell chips obtained under the same test conditions;

- a constant determining unit that determines a constant of the curve equation using the data of the cell chips integrated by the data integrating unit; and

- 20 a graph creating unit that creates the integrated graph using the constant determined by the constant determining unit.

6. The apparatus as set forth in claim 1, wherein the analyzer comprises:

- 25 an error data control module that classifies the data and sorting out an item required to be checked by the tester so as to enable the tester to delete error data; and

a report creation module that classifies a result of the curve-fitting with respect to the

integrated data and the scanned images, creates a result report, and outputs the result report.

7. The apparatus as set forth in claim 1, wherein the fluorescent-intensity measuring module comprises:

5 a spot position detecting unit that detects positions of the spots in such a way as to calculate an average of Y-axial fluorescent-intensities and an average of X-axial fluorescent-intensities from the image files created by scanning the cell chips using the cell chip scanner;

 a spot boundary determining unit that determines boundaries of the spots detected by the spot position detecting unit; and

10 a spot fluorescent-intensity calculating unit that calculates a fluorescent-intensity of each of the spots after the boundaries of the spots are determined by the spot boundary determining unit.

8. A method of analyzing data of cell chips, comprising:

 creating image files by scanning a plurality of cell chips;

15 measuring fluorescent intensities of spots in the image files;

 creating graphs that individually conduct curve-fitting with respect to the fluorescent intensities of the spots; and

 creating an integrated graph that integrates data related to the fluorescent intensities of the spots under same test conditions and then conduct curve-fitting with respect to the integrated data.

20

9. The method as set forth in claim 8, wherein each of the cell chips comprises a plurality of blocks, each block having a plurality of spots comprising a composition differing in the concentration of a component hereof.

25 10. The method of claim 9, wherein the component is a test compound or a metabolite thereof.

11. The method of claim 10, wherein the composition further comprises an enzyme.
12. The method of claim 11, wherein the enzyme of each spot within a block is the same.
- 5 13. The method of claim 12, wherein the enzyme is a cytochrome p450 isoform.
14. The method as set forth in claim 8, further comprising, the step of providing a test condition input window to a tester using a display module by a control module, and storing test conditions input by an input module in a storage module.
- 10 15. The method as set forth in claim 8, further comprising:
- classifying results using an error data control module and sorting out an item required to be checked by the tester so as to enable the tester to delete error data; and
- classifying a result of the curve-fitting with respect to the integrated data and the scanned
- 15 images using a report creation module, and creating a result report, and then outputting the result report.
16. The method as set forth in claim 8, wherein measuring the fluorescent intensities of the spots comprises:
- 20 detecting positions of the spots wherein an average of Y-axial fluorescent-intensities and an average of X-axial fluorescent-intensities from the image files are calculated;
- determining boundaries of the spots; and
- calculating a fluorescent-intensity of each spot.
- 25 17. The method as set forth in claim 8, wherein determining the boundaries of the spots comprises:
- connecting pixels of a predetermined value or more to each other with lines using the

fluorescent-intensity measuring module;

uniting lines when a distance between the lines is less than a predetermined value using the

fluorescent-intensity measuring module;

deleting a line when a length of the line is shorter than a predetermined value using the

5 fluorescent-intensity measuring module;

deleting a minor number of lines that are spaced apart from the other lines by a

predetermined distance or more using the fluorescent-intensity measuring module; and

determining midpoints of the lines and averaging the midpoints to determine a center of
the lines using the fluorescent-intensity measuring module, and determining a predetermined

10 radius around the center.

18. The method as set forth in claim 16, wherein calculating the fluorescent-intensity of each of the
spots comprises:

determining an average of absolute intensities of pixels in a spot area using the fluorescent-

15 intensity measuring module;

determining a central value of pixels in a peripheral area using the fluorescent-intensity
measuring module; and

subtracting the central value of the pixels of the peripheral area from the average of the
absolute intensities of the pixels of the spot area, thus attaining the fluorescent-intensity of the spot.

20

19. The method as set forth in claim 8, wherein creating the graphs comprises:

selecting a plurality of values of fluorescent intensities that are results of repeated tests with
respect to concentrations of the compounds of each of the blocks using an individual curve-fitting
and graph-creating module;

25 determining a constant of a curve equation using the selected test results by the individual
curve-fitting and graph-creating module; and

creating the graphs using an individual curve-fitting and graph-creating module.

20. The method as set forth in claim 8, wherein creating the integrated graph comprises:

- integrating data obtained from the plurality of cell chips;
- 5 determining a constant of a curve equation; and
- creating an integrated graph.

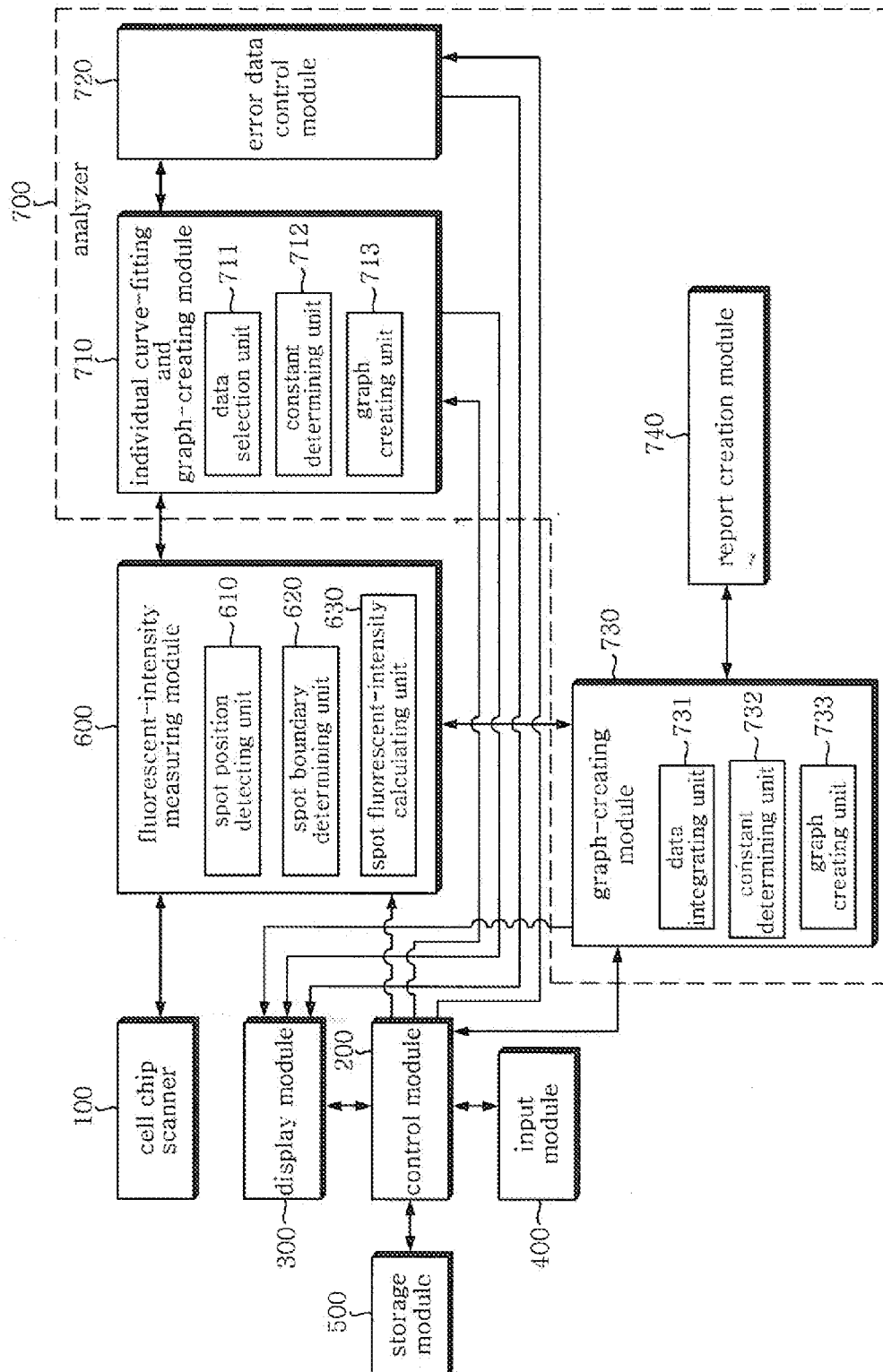


FIG. 1

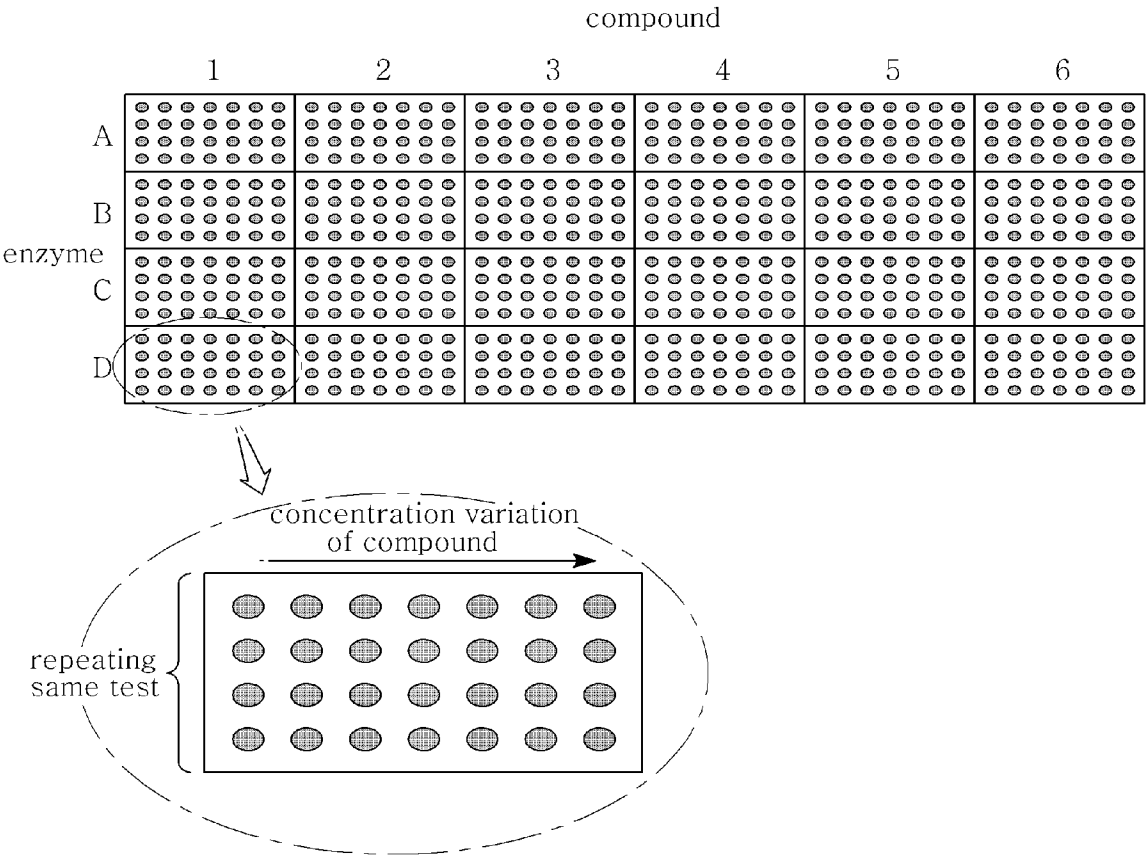


FIG. 2

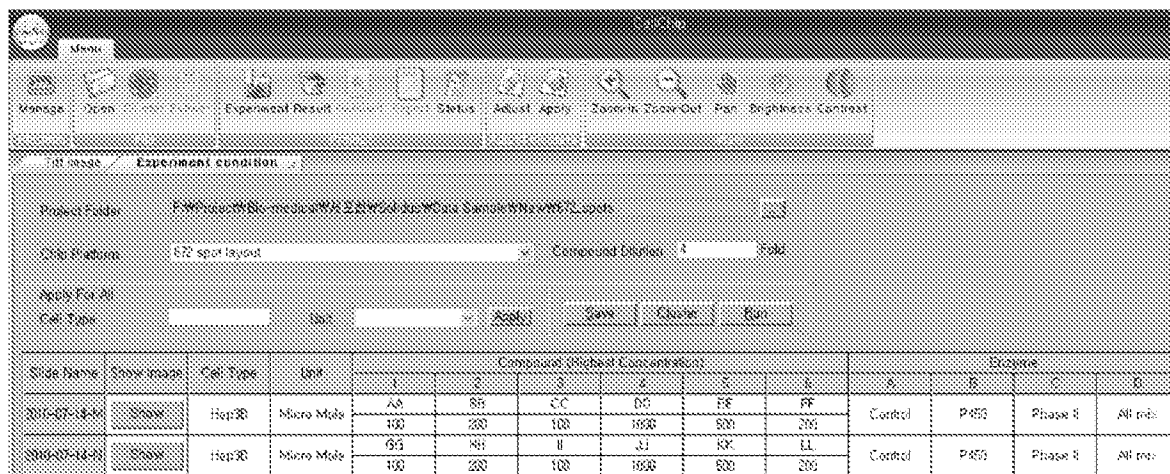


FIG. 3

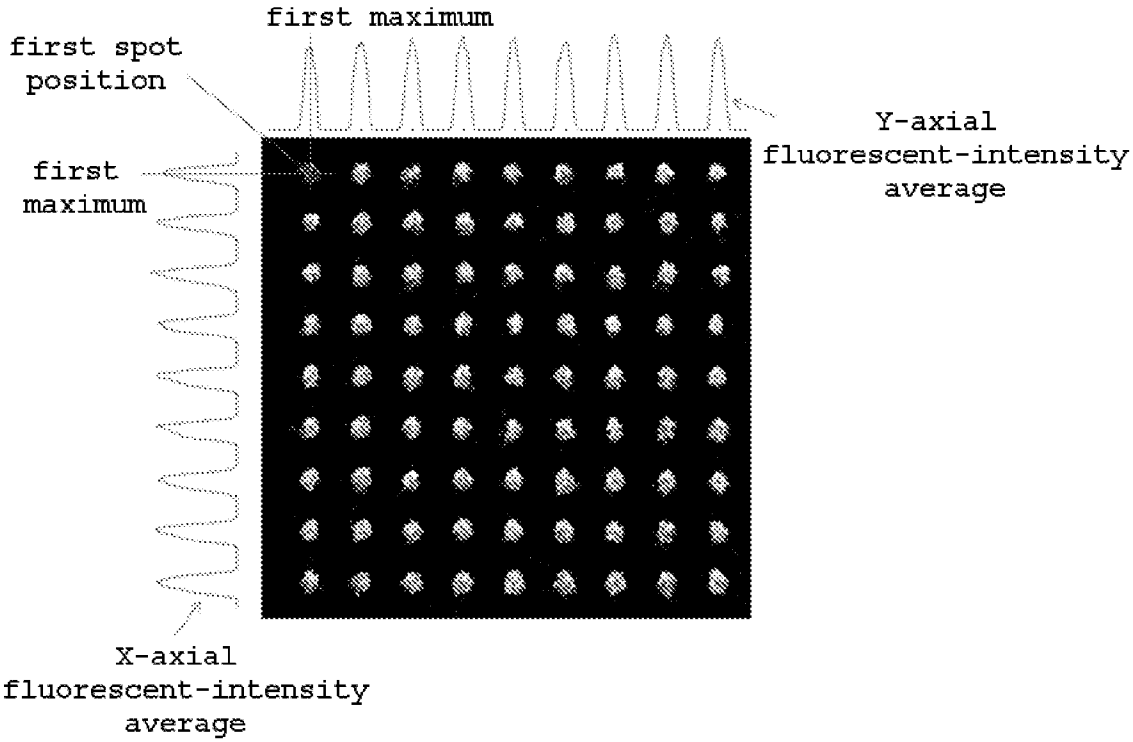


FIG. 4

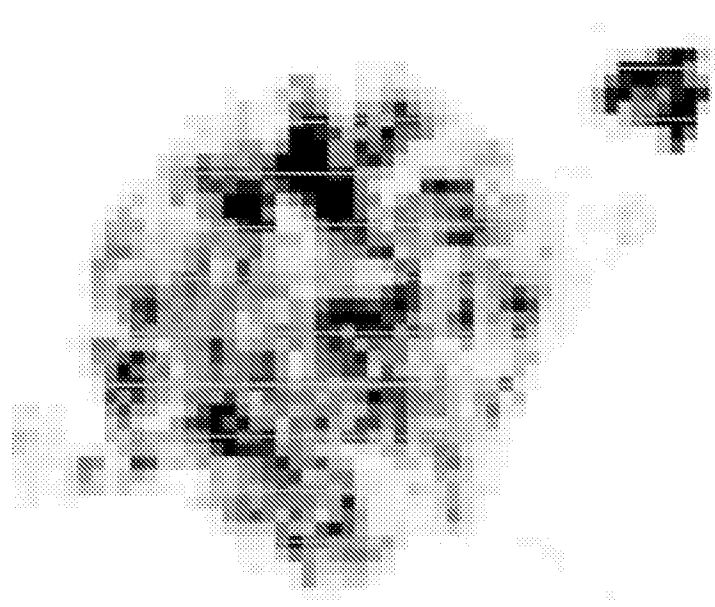


FIG. 5A

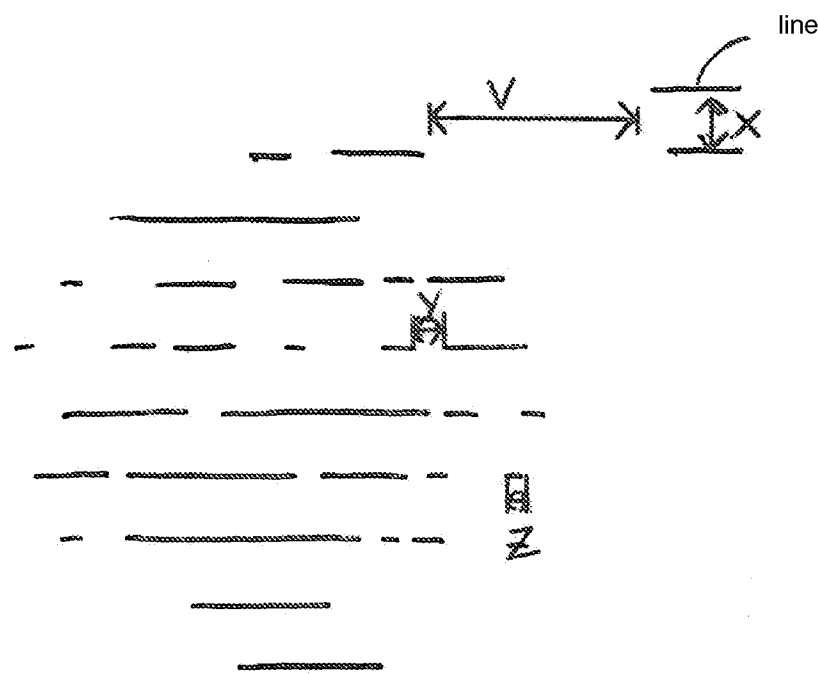


FIG. 5B

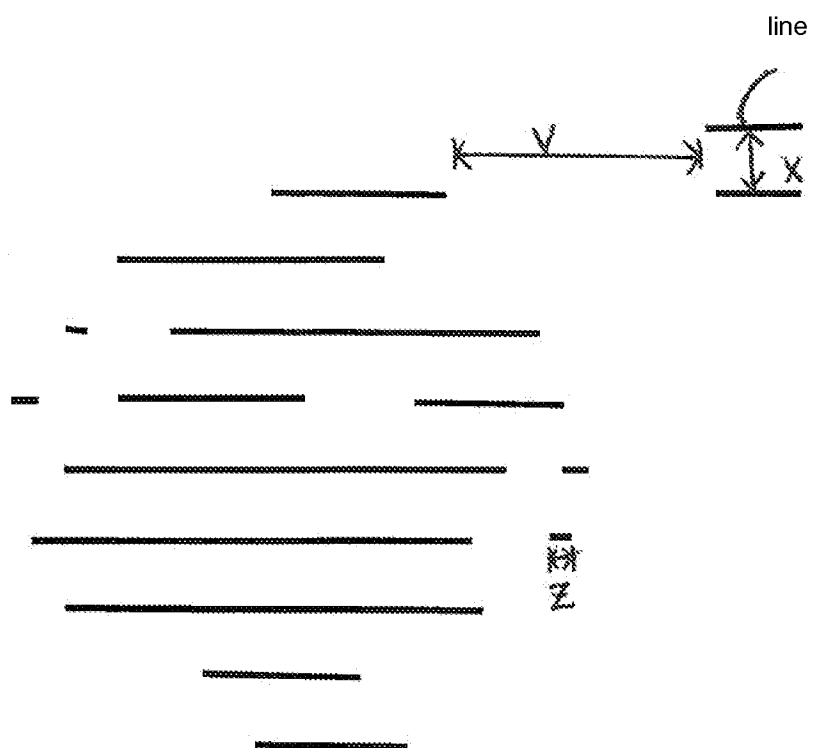


FIG. 6

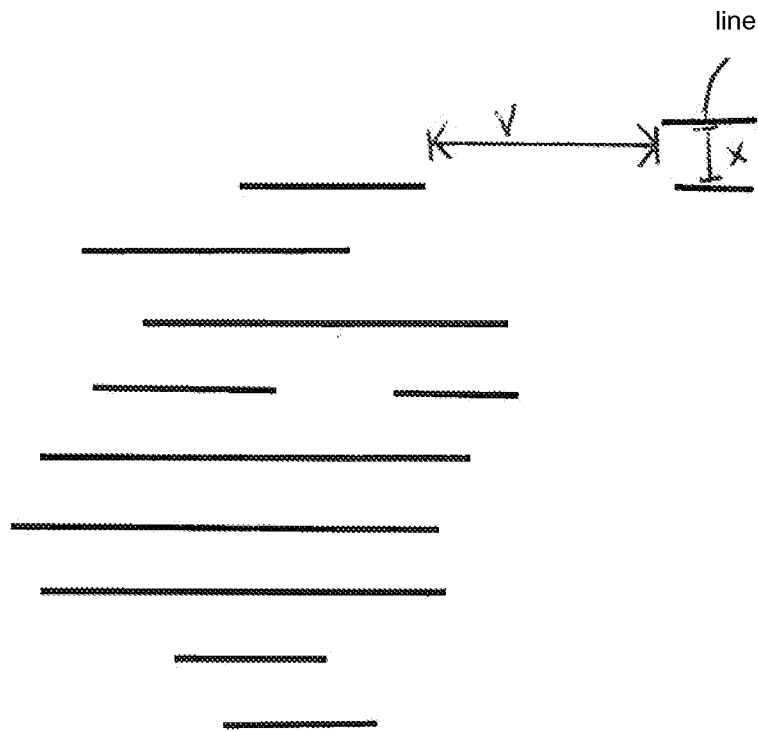


FIG. 7

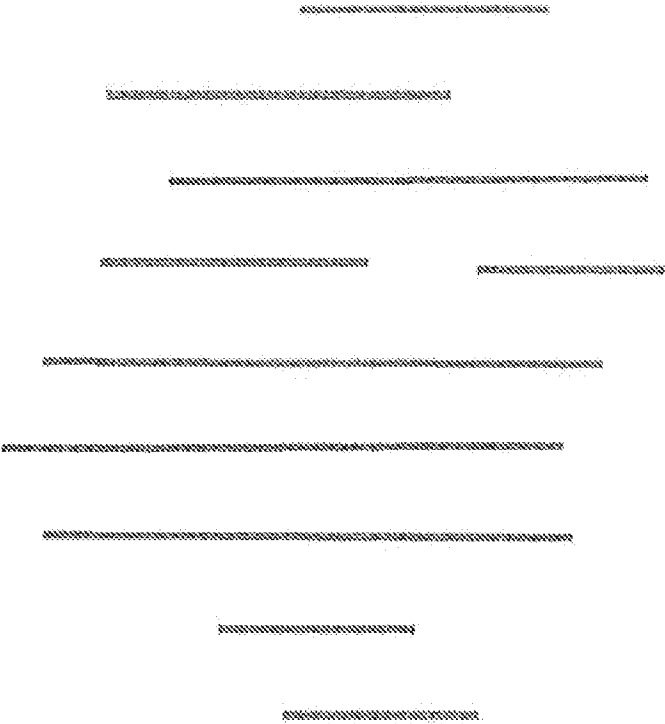


FIG. 8

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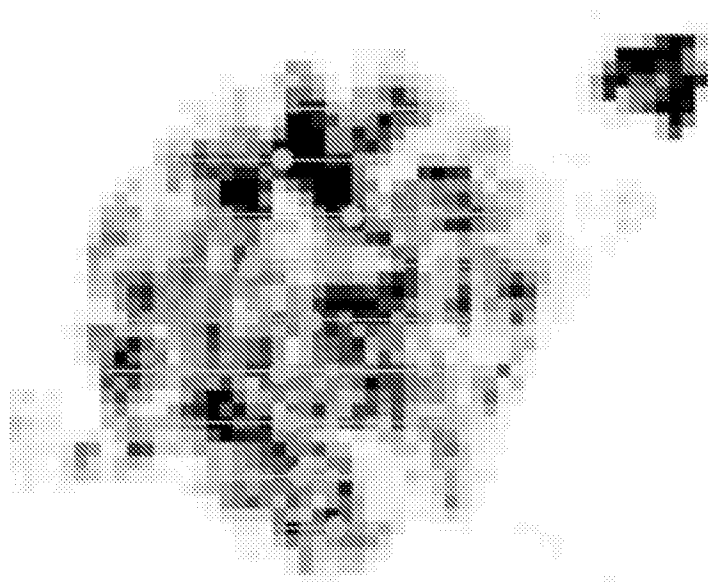


FIG. 9



FIG. 10

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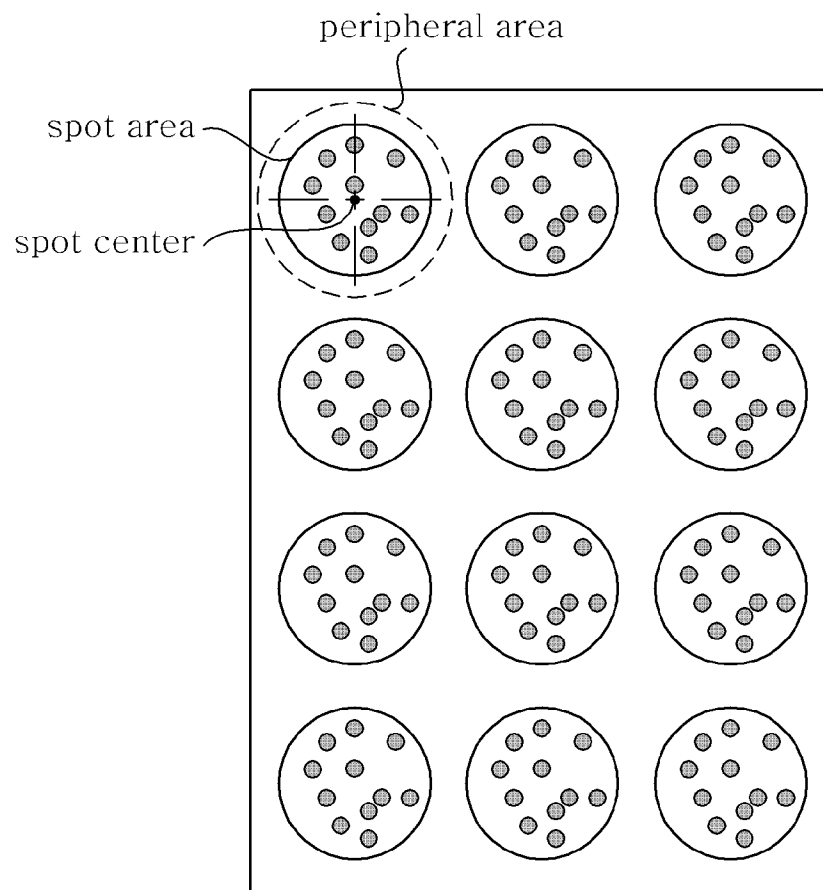


FIG. 11

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dilution ▼	value ▼	concentration ▼	logconc ▼
1	3069	0.02	-1.61
1	3557	0.02	-1.61
1	4582	0.02	-1.61
1	5389	0.02	-1.61
2	3131	0.1	-1.01
2	3011	0.1	-1.01
2	4324	0.1	-1.01
2	5159	0.1	-1.01
3	3964	0.39	-0.41
3	3922	0.39	-0.41
3	4982	0.39	-0.41
3	3963	0.39	-0.41
4	2973	1.56	0.19
4	3286	1.56	0.19
4	3450	1.56	0.19
4	3693	1.56	0.19
5	1467	6.25	0.8
5	2054	6.25	0.8
5	2111	6.25	0.8
5	1879	6.25	0.8
6	63	25	1.4
6	55	25	1.4
6	64	25	1.4
6	116	25	1.4
7	46	100	2
7	49	100	2
7	76	100	2
7	82	100	2

FIG. 12

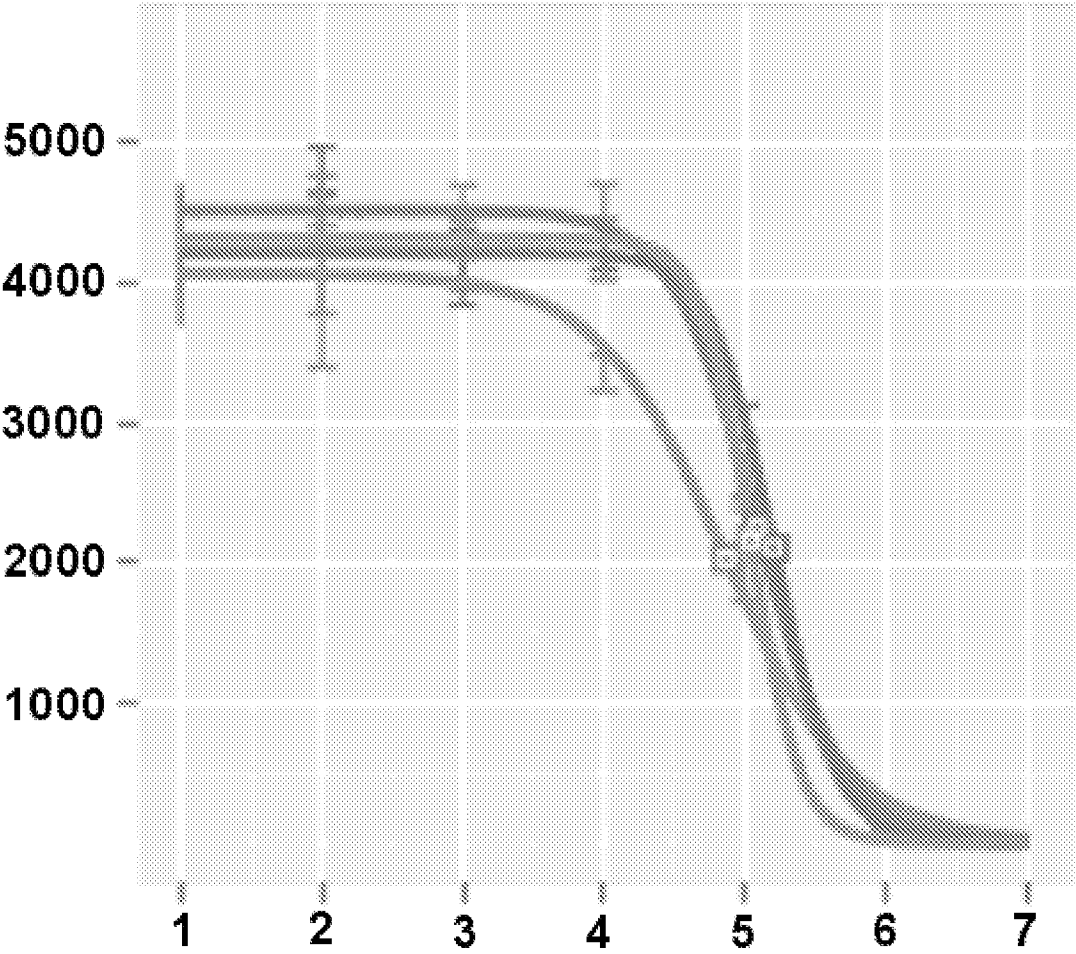
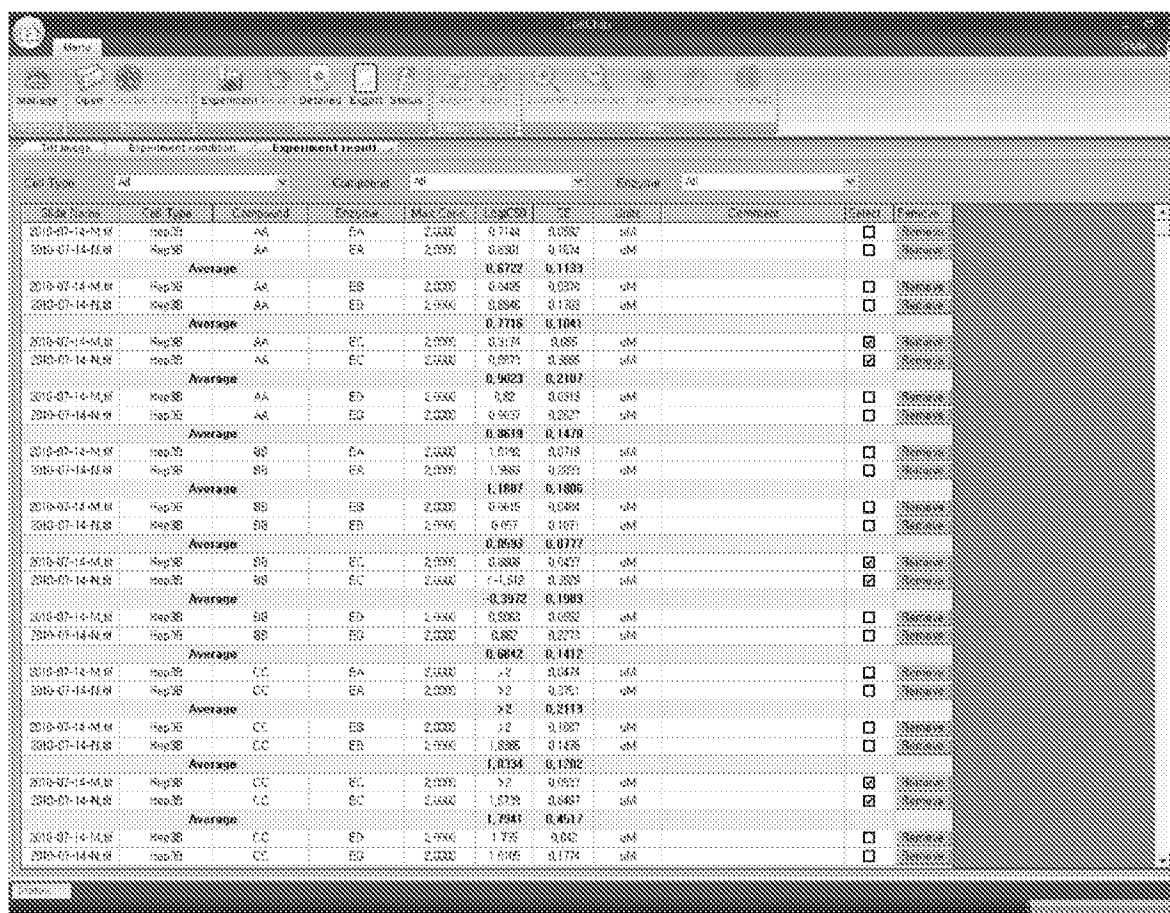


FIG. 13

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Date Range	Cell Type	Compound	Enzyme	Max Conc	LogIC50	IC	Units	Comments	Used	Reviewed
2010-07-14-M-S	Rep 30	AA	EA	2.0000	0.7144	0.0582	uM		☐	Reviewed
2010-07-14-F-S	Rep 30	AA	EA	2.0000	0.0301	0.1574	uM		☐	Reviewed
	Average				0.6722	0.1133				
2010-07-14-M-S	Rep 30	AA	EB	2.0000	0.0495	0.0576	uM		☐	Reviewed
2010-07-14-F-S	Rep 30	AA	EB	2.0000	0.0546	0.1382	uM		☐	Reviewed
	Average				0.0771	0.1041				
2010-07-14-M-S	Rep 30	AA	EC	2.0000	0.3174	0.055	uM		☒	Reviewed
2010-07-14-F-S	Rep 30	AA	EC	2.0000	0.0571	0.3686	uM		☒	Reviewed
	Average				0.9023	0.2107				
2010-07-14-M-S	Rep 30	AA	ED	2.0000	0.32	0.0513	uM		☐	Reviewed
2010-07-14-F-S	Rep 30	AA	ED	2.0000	0.0637	0.2527	uM		☐	Reviewed
	Average				0.3819	0.1479				
2010-07-14-M-S	Rep 30	BB	EA	2.0000	1.0742	0.0719	uM		☐	Reviewed
2010-07-14-F-S	Rep 30	BB	EA	2.0000	1.0863	0.0551	uM		☐	Reviewed
	Average				1.1807	0.1006				
2010-07-14-M-S	Rep 30	BB	EB	2.0000	0.0615	0.0494	uM		☐	Reviewed
2010-07-14-F-S	Rep 30	BB	EB	2.0000	0.057	0.1071	uM		☐	Reviewed
	Average				0.0593	0.0777				
2010-07-14-M-S	Rep 30	BB	EC	2.0000	0.0808	0.0427	uM		☒	Reviewed
2010-07-14-F-S	Rep 30	BB	EC	2.0000	1.1512	0.2029	uM		☒	Reviewed
	Average				0.3972	0.1983				
2010-07-14-M-S	Rep 30	BB	ED	2.0000	0.0363	0.0552	uM		☐	Reviewed
2010-07-14-F-S	Rep 30	BB	ED	2.0000	0.052	0.2773	uM		☐	Reviewed
	Average				0.0842	0.1412				
2010-07-14-M-S	Rep 30	CC	EA	2.0000	>2	0.0474	uM		☐	Reviewed
2010-07-14-F-S	Rep 30	CC	EA	2.0000	>2	0.0751	uM		☐	Reviewed
	Average				>2	0.2113				
2010-07-14-M-S	Rep 30	CC	EB	2.0000	>2	0.1057	uM		☐	Reviewed
2010-07-14-F-S	Rep 30	CC	EB	2.0000	1.0386	0.1436	uM		☐	Reviewed
	Average				1.0134	0.1202				
2010-07-14-M-S	Rep 30	CC	EC	2.0000	>2	0.0527	uM		☒	Reviewed
2010-07-14-F-S	Rep 30	CC	EC	2.0000	1.0739	0.0467	uM		☒	Reviewed
	Average				1.0941	0.0517				
2010-07-14-M-S	Rep 30	CC	ED	2.0000	1.735	0.042	uM		☐	Reviewed
2010-07-14-F-S	Rep 30	CC	ED	2.0000	1.0105	0.1774	uM		☐	Reviewed

FIG. 14

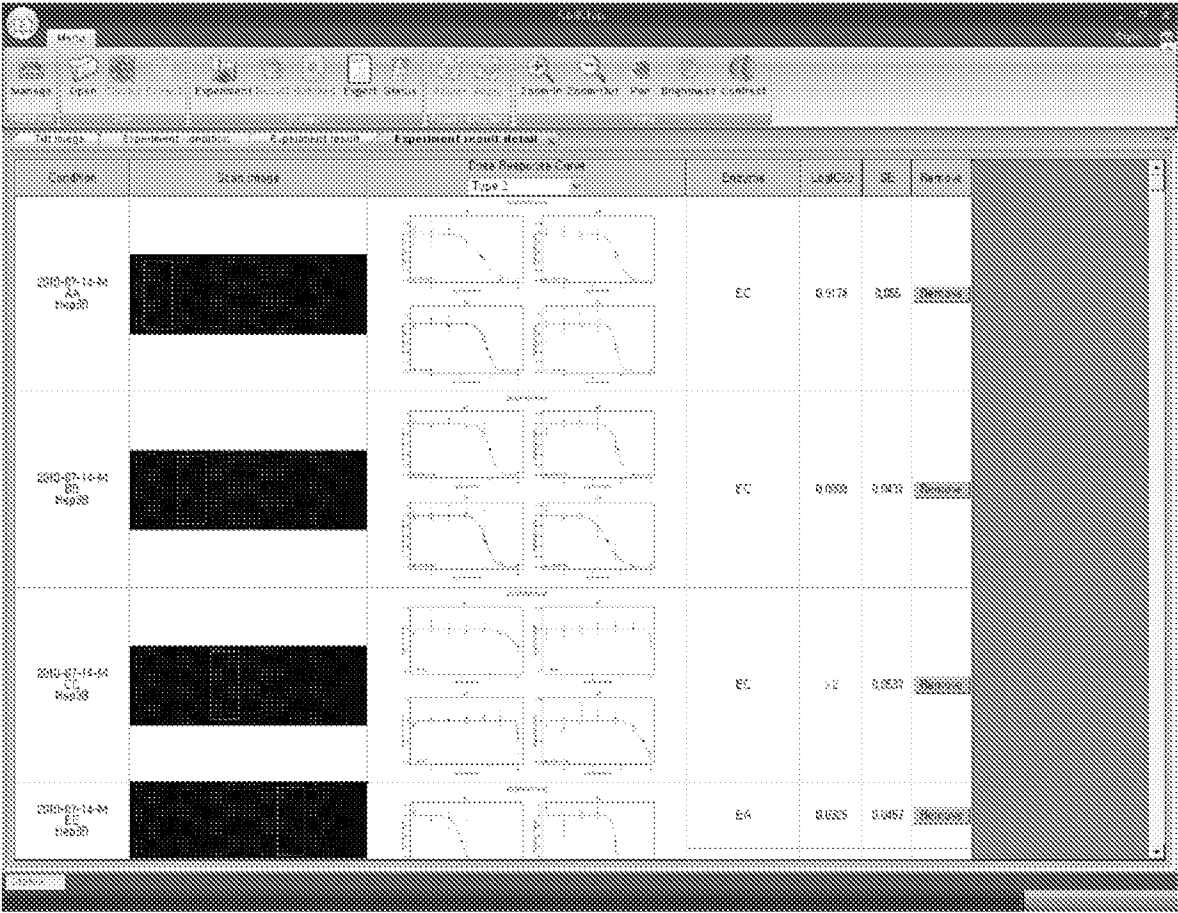


FIG. 15

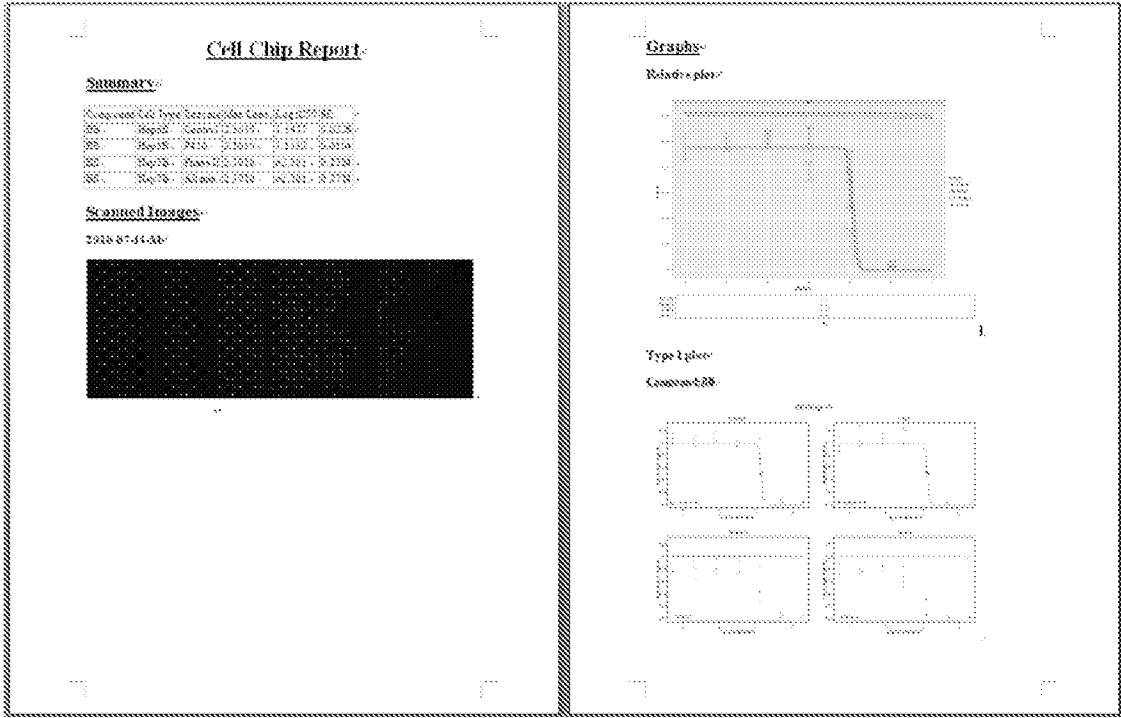


FIG. 16

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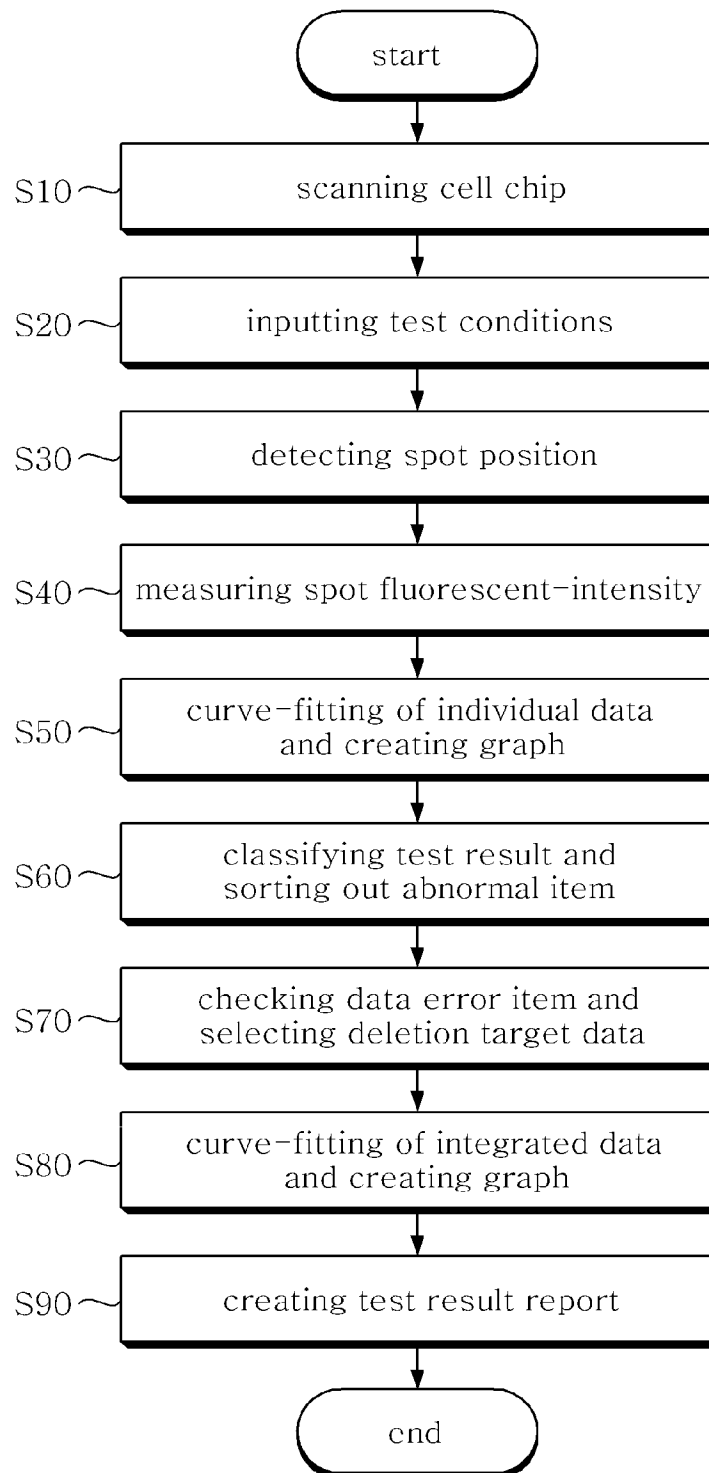


FIG. 17

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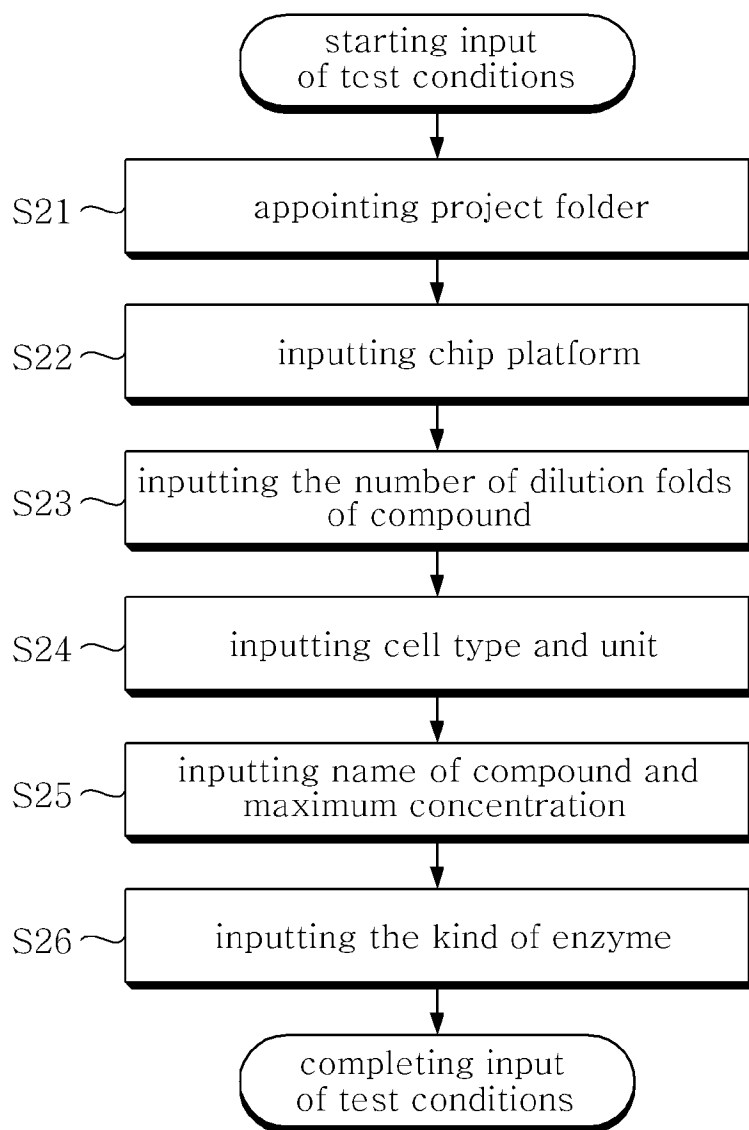


FIG. 18

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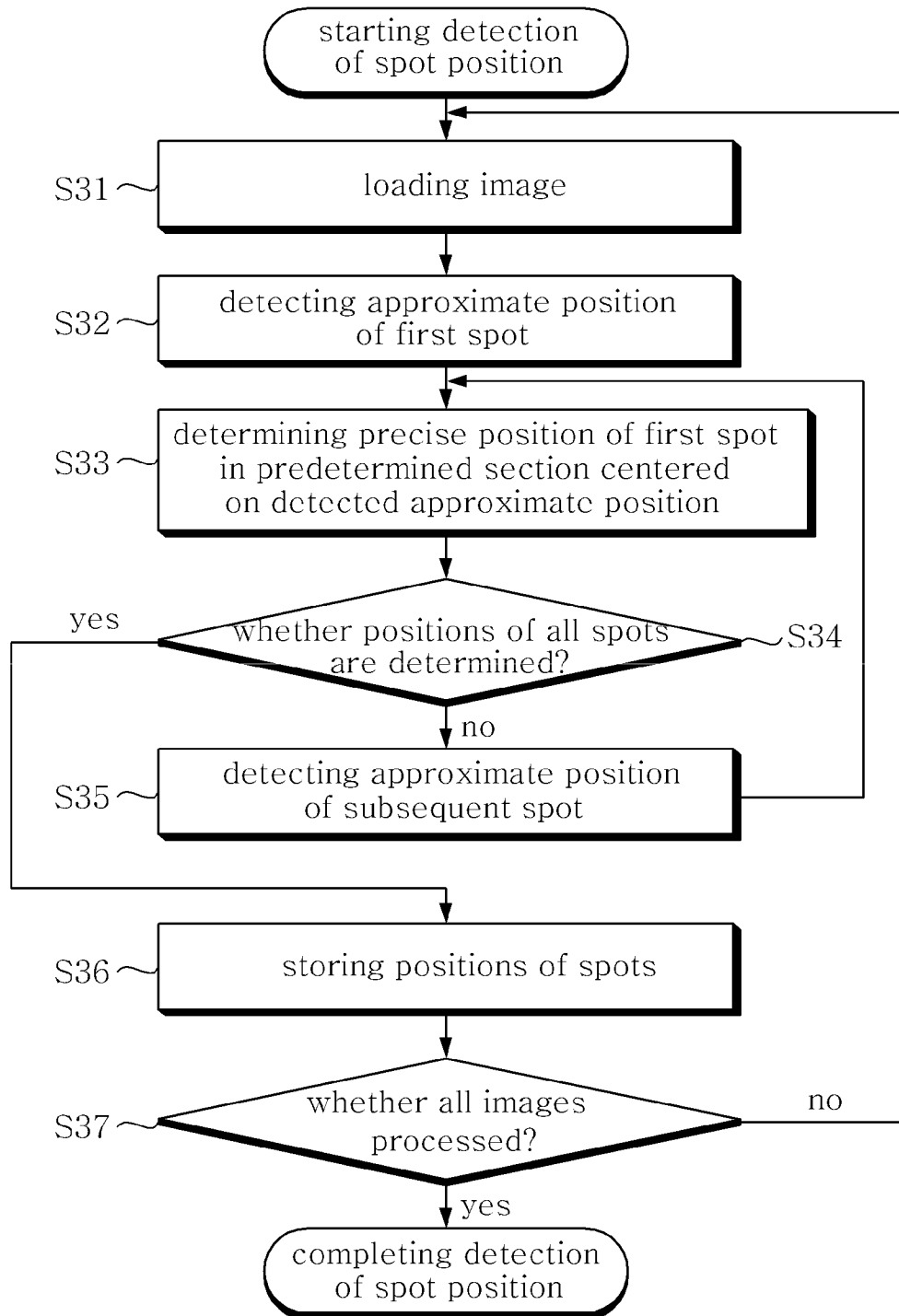


FIG. 19

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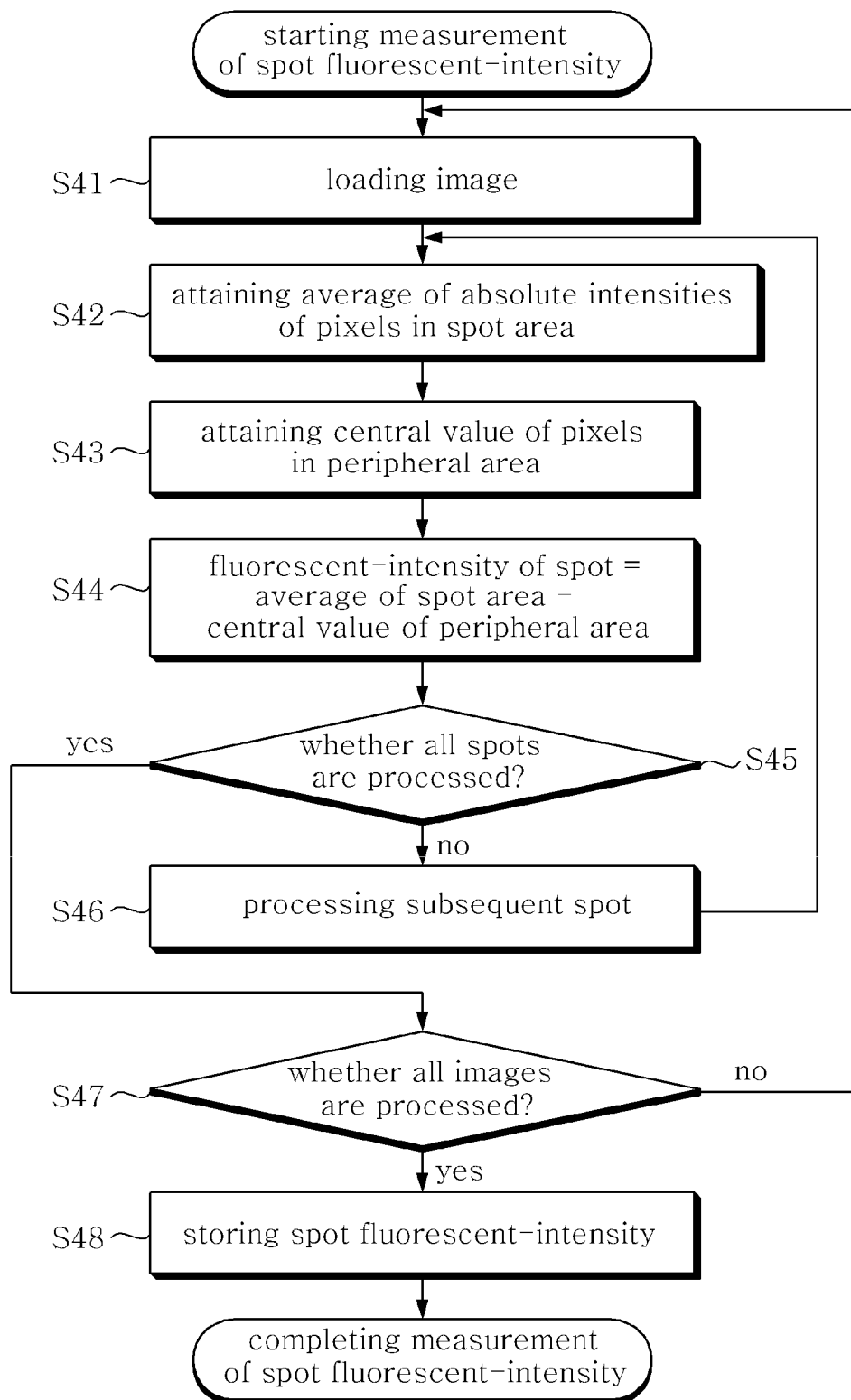


FIG. 20

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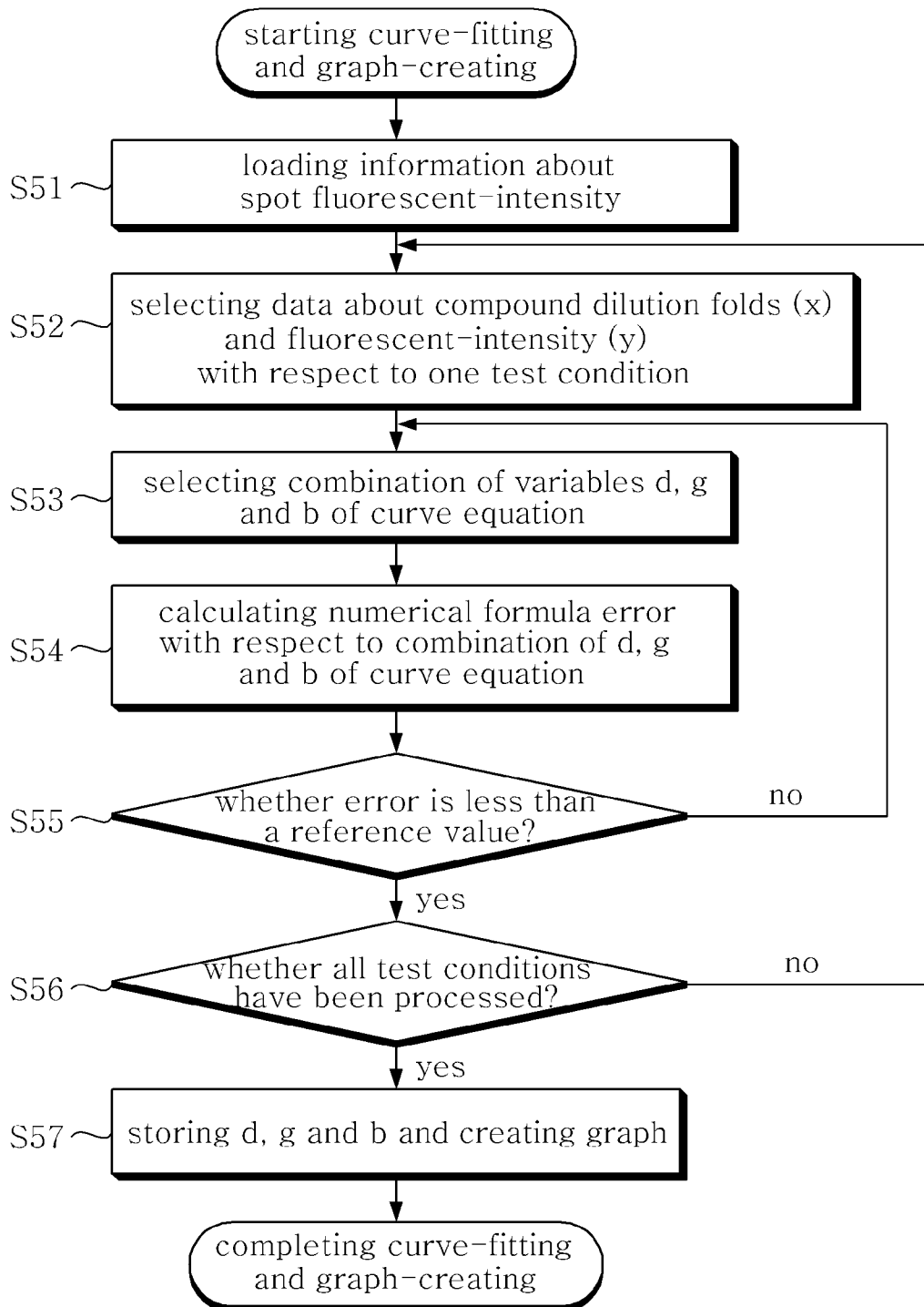


FIG. 21

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 12/29391

A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - H04N 7/18 (2012.01)

USPC - 348/126

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

USPC: 348/126

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
 IPC(8): H04N 7/18 (2012.01); USPC: 348/87, 126, 127; 382/141; 204/400, 403.01, 403.03; 356/ 39, 246,
 (keyword limited; terms below)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

PubWEST(USPT,PGPB,EPAB,JPAB); Google Scholar

Search Terms: cell, chip, scanner, intensity, window, graph, spot, boundary, store, position, image, pixel, distance, integration, fluorescent, line, connect, midpoint, intensity, concentration, display, equation, test, center, enzyme, metabolite, curve, image, error, fill.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X --- Y	US 2009/0055147 A1 (MIYAKE et al.) 26 February 2009 (26.02.2009), entire document, especially; para [0049], [0050], [0177], [0305], [0400], [0417], [0424], [0432], [0433]-[0435], [0442], [0443]-[0445], [0447]-[0453], [0457], [0498], [0499], [0502]-[0504], [0514], [0520], [0521], [0534], [0535], [0573], [0574], [0593], [0624], [0676], [0898], [0903], [1029].	1-6, 8-12, 14, 15, 19, 20 ----- 7, 13, 16-18
Y	US 2011/0007178 A1 (KAHLMAN) 13 January 2011 (13.01.2011), entire document, especially; para [0001], [0011], [0014], [0019], [0023], [0052]-[0054], [0092], [0101], [0121].	7, 16-18
Y	US 2009/0221441 A1 (LEE et al.) 03 September 2009 (03.09.2009), entire document, especially; para [0013], [0014], [0132]-[0134].	13
A	US 2005/0014201 A1 (DEUTHSCH) 20 January 2005 (20.01.2005), entire document.	1-20
A	US 6,977,722 B2 (WOHLSTADTER et al.) 20 December 2005 (20.12.2005), entire document.	1-20



Further documents are listed in the continuation of Box C.



* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

26 June 2012 (26.06.2012)

Date of mailing of the international search report

11 JUL 2012

Name and mailing address of the ISA/US

Mail Stop PCT, Attn: ISA/US, Commissioner for Patents
P.O. Box 1450, Alexandria, Virginia 22313-1450

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