

SYSTEM FOR ORGANIZING MULTIPLE
OBJECTS OF INTEREST IN FIELD OF INTEREST

FIELD OF THE INVENTION

The field of the invention generally relates to systems for analyzing cytological
5 specimens, and more particularly to systems for organizing cellular material within a
field of interest for display to a cytotechnologist.

BACKGROUND OF THE INVENTION

In the medical industry, there is often a need for a laboratory technician, e.g.,
10 a cytotechnologist, to review a cytological specimen for the presence of specified cell
types. For example, there is presently a need to review a cervico-vaginal
Papanicolaou (Pap) smear slides for the presence of malignant or pre-malignant
cells. Since its introduction over fifty years ago, Pap smears have been a powerful
tool for detecting cancerous and precancerous cervical lesions. During that time, the
15 Pap smear has been credited with reducing mortality from cervical cancer by as
much as 70%. This once precipitous drop in the death rate has slowed however,
and the mortality rate in the United States for this preventable disease has remained
virtually constant, at about 5,000 per year since the mid-eighties. Therefore, about
one-third of the 15,000 women diagnosed with cervical cancer annually still die,
20 because the cancer was detected too late. A further cause for concern is National
Cancer Institute data that shows an annual 3% increase in the incidence of invasive
cervical cancer in white women under 50 years of age since 1986.

A number of factors may be contributing to this current threshold, not the least
of which is the fact that many women, particularly in high risk populations, are still

not participating in routine cervical cancer screening. Another contributing factor that has received much attention is the limitation of the traditional Pap smear method.

The reliability and efficacy of a cervical screening method is measured by its ability to diagnose precancerous lesions (sensitivity) while at the same time avoiding
5 false positive diagnosis (specificity). In turn, these criteria are dependent on the accuracy of the cytological interpretation. The conventional Pap smear has false negative rates ranging from 10-50%. This is due in large part to the vast number of cells and objects (typically as many as 100,000 to 200,000) that must be reviewed by a technician to determine the possible existence of a small number of malignant or
10 pre-malignant cells. Thus, Pap smear tests, as well as other tests requiring detailed review of biological material, have suffered from a high false negative rate due to fatigue imposed on the technician.

To facilitate this review process, automated systems have been developed to focus the technician's attention on the most pertinent cells, with a potential to discard
15 the remaining cells from further review. A typical automated system includes an imager and an automated optical microscope. Briefly, the imager can be operated to provide a series of numerous images of a cytological specimen slide, each depicting a different portion of the slide. The imager then processes these images to determine the most pertinent biological objects for review on the slide, and their
20 locations (x-y coordinates) on the slide. This information is then passed onto the microscope, which automatically proceeds to the x-y coordinates and centers on the biological objects for review by the technician. During this review process, the microscope will sequentially step through the x-y coordinates of the biological objects, placing the biological object within the center of its field of view. For
25 example, if the number of pertinent biological objects to be reviewed equals 22, the

technician will review 22 regions on the slide as the microscope automatically or semi-automatically moves the field of view to the defined x-y coordinates of the biological objects. The technician can then mark any objects on the slide that he or she believe require further review by a pathologist, for example, any objects having
5 attributes consistent with malignant or pre-malignant cells.

In general, this automated procedure has proved to be successful, since the technician's attention is focused on a limited number of objects, obviating the need for the technician to review the vast number of objects (biological or not) on the specimen. Because the technician must typically review hundreds of slides per day,
10 however, and thus, tens of thousands of biological objects, the technician may still be subjected to fatigue. In addition, there is also a commercial aspect that must be taken into account. The cost borne by laboratories to review cytological specimens, such as Pap smear specimens, is tied, at least in part, to the time taken for a technician to review each slide. That is, the more time it takes for a technician to
15 review a slide, the more cost in labor the laboratory incurs. Conversely, the less time that it takes for a technician to review a slide, the more money the laboratory can save.

SUMMARY OF THE INVENTION

In one embodiment of the invention, a biological screening system for
20 presenting OOI is provided. The system comprises an imaging station for obtaining images of a specimen slide, and generating image data from the images. The system further comprises at least one processor for filtering and/or processing the image data to obtain OOI, and for assigning one or more OOI to each FOI, at least partially, based on the assignment of OOI to other FOI. Assignment of the OOI to
25 each FOI can be accomplished in the same manner described above. The system

further comprises an automated or semi-automated microscope for scanning a field of view (FOV) relative to each FOI to present the one or more OOs in each FOI.

BRIEF DESCRIPTION OF THE DRAWINGS

5 The drawings illustrate the design and utility of embodiment of the invention, in which similar elements are referred to by common reference numerals, and in which:

Fig. 1 is a plan view of a standard microscope slide carrying a biological specimen;

10 Fig. 2 is a plan view of a biological screening system constructed in accordance with one embodiment of the invention;

Fig. 3 is a view of a field of interest (FOI) and marker indicator as shown through a field of view (FOV) of a microscope used in the system of Fig. 2;

Fig. 4 is a flow diagram of process used by an FOI processor of the system of
15 Fig. 2 to assign objects of interest (OOIs) to FOIs;

Fig. 5 is a flow diagram of one process used by the FOI processor to determine if an OOI is collocatable with OOIs previously assigned to an FOI;

Fig. 6 is a diagram of a boundary box expanded to include an OOI;

Fig. 7 is a diagram of the boundary box of Fig. 6 expanded to include another
20 OOI; and

Fig. 8 is a diagram of the boundary box of Fig. 6 expanded to include still another OOI.

DETAILED DESCRIPTION OF ILLUSTRATED EMBODIMENTS

Referring to Fig. 2, a biological screening system 10 constructed in accordance with one embodiment of the invention is described. The system 10 is configured for presenting a biological specimen 12 located on a microscope slide 14 (best shown in Fig. 1) to a technician, such as a cytotechnologist, who can then review objects of interest (OOIs) located in the biological specimen 12. The OOIs are arranged in a number of fields of interest (FOIs) (one of which is illustrated in Fig. 3) that cover portions of the slide 14, so that the cytotechnologist's attention can be subsequently focused on OOIs within the FOIs, rather than slide regions that are not pertinent. The slide 14 is provided with fiducial marks 16, the function of which will be described in further detail below.

Although the system 10 can be used to present any biological specimen (or even a non-biological specimen, such as a computer chip) that requires further review, the system 10 lends itself particularly well to the presentation of cytological cervical or vaginal cellular material, such as that typically found on a Pap smear slide. In this case, the OOIs take the form of individual cells and cell clusters that are reviewed to check for the possible presence of an abnormal condition, such as malignancy or pre-malignancy. The biological specimen 12 will typically be placed on the slide 14 as a thin cytological layer. Preferably, a cover slip (not shown) is adhered to the specimen 12, thereby fixing the specimen 12 in position on the slide 14. The specimen 12 may be stained with any suitable stain, such as a Papanicolaou stain.

The system 10 generally comprises (1) an imaging station 18 for obtaining images of the biological material contained on the slide 14 and generating electronic image data from the images; (2) a server 20 for filtering and processing the image

data to identify OOs, and for assigning one or more of OOs to each FOI; and (3) a plurality of reviewing stations 22 (3 shown), each of which provides a field of view (FOV) (illustrated in Fig. 3) that is scanned relative to each FOI in order to present the OOs for viewing by a cytotechnologist. The system 10 may also comprise a user interface (not shown), including a monitor, keyboard, and mouse (all not shown), so that the cytotechnologist can interact with the system 10.

The imaging station 18 is configured to image the slide 14, which is typically contained within a cassette (not shown) along with other slides. During the imaging process, the slides are removed from the respective cassettes, imaged, and then returned to the cassettes in a serial fashion. In the illustrated embodiment, the imaging station 18 is capable of processing up to 10 cassettes, each holding up to 25 slides, in about 16 hours.

The imaging station 18 comprises a camera 24, a microscope 26, and a motorized stage 28. The camera 24 captures magnified images of the slide 14 through the microscope 26. The camera 24 may be any one of a variety of conventional cameras, such as a charge coupled device (CCD) camera, which alone or in conjunction with other components, such as an analog-to-digital (A/D) converter, can produce a digital output of sufficient resolution to allow processing of the captured images, for example a digital image having a resolution of 640 X 480 pixels. Preferably, each pixel is converted into an eight-bit value (0 to 255) depending on its optical transmittance, with "00000000" being the assigned value for least amount of light passing through the pixel, and "11111111" being the assigned value for a greatest amount of light passing through the pixel.

The slide 14 is mounted on the motorized stage 28, which scans the slide 14 relative to the viewing region of the microscope 26, while the camera 24 captures

images over various regions of the biological specimen 12. The shutter speed of the camera 24 is preferably relatively high, so that the scanning speed and/or number of images taken can be maximized. The motorized stage 28 keeps track of the x-y coordinates of the images as they are captured by the camera 24. For example, encoders (not shown) can be coupled to the respective motors of the motorized stage 28 in order to track the net distance traveled in the x- and y-directions during imaging. These coordinates are measured relative to the fiducial marks 16 affixed to the slide 14 (shown in Fig. 1). As will be described in further detail below, these fiducial marks 16 will also be used by the reviewing station 22 to ensure that the x-y coordinates of the slide 14 during the review process can be correlated to the x-y coordinates of the slide 14 obtained during the imaging process.

Among other processing components that are not immediately pertinent to an understanding of the invention, the server 20 comprises (1) an image processor 30 that is configured to identify OOs from the image data acquired from the camera 24; (2) an FOI processor 32, which is configured to assign OOs to each FOI; (3) a routing processor 34, which is configured to map routing path that the reviewing station 22 will use to scan from one FOI to the next; and (4) a memory 36 configured for storing the OOs and FOIs, the ranking and x-y coordinates of the OOs, and the routing path for the FOIs. It should be appreciated that the functions performed by the respective processors 28, 30, and 32 can be performed by a single processor, or alternatively, performed by more than three processors. Likewise, it can be appreciated that the memory 36 can be divided into several memories.

The image processor 30 identifies the OOs within the biological specimen 12 by manipulating the digital images received from the camera 24 in a suitable

manner. In the embodiment, the image processor 30 accomplishes this using primary and secondary segmentation operations.

In the primary segmentation operation, the image processor 30 removes artifacts from further consideration. The image processor 30 accomplishes this by
5 masking pixels in the digital image data from further consideration that, by virtue of their lightness, are unlikely to be cell nuclei. The remaining pixels in the digital image form "blobs" having all manner of shapes and sizes. The image processor 30 then performs an erosion process on the blobs in order to remove from further consideration blobs that are only a few pixels in diameter and narrow strands
10 extending from blobs or connecting adjacent blobs. The image processor 30 then determines whether each blob in the image is an individual object or a clustered object, depending on the number of pixels in the blob. For example, a blob having more than 500 pixels might be considered a clustered object, whereas a blob having 500 or less pixels might be considered an individual object. For individual objects,
15 blobs that do not meet certain criteria related to total area, perimeter to area ratio, optical density standard deviation, and grayscale mean pixel value are not considered further.

In the secondary segmentation operation, the image processor 30 removes blobs that are unlikely to be individual cells or clustered cells. For individual objects,
20 the image processor 30 performs a series of erosion operations, which remove small objects and eliminates projections from the remaining blobs, and dilation operations, which remove holes from the remaining blobs. For clustered objects, the image processor 30 sharpens the edges of the object to provide a defined border. From the defined clustered object, the image processor 30 then selects an individual

object or objects having the highest integrated optical density. The individual objects extracted from clusters objects will be flagged as cluster-extracted objects.

In the classification operation, the image processor 30 measures various features for each of the individual objects and clustered objects, and then calculates
5 an object score for each object based on the measured values of these features. Based on this score, the image processor 30 removes individual objects and clustered objects that are likely to be artifacts. Those remaining are considered OOs, with the individual objects representing individual OOs (IOOs), and the clustered objects representing clustered OOs (COOs). The image processor 30
10 then evaluates the OOs for their nuclear integrated or average optical density, and ranks the OOs in accordance with their optical density values. For each digital image, the image processor 30 stores the OOs, along with their relative ranking and coordinates, within the memory 36 as a frame data record (FDR). In the illustrated embodiment, approximately 2000 digital images are obtained for each slide 14, and
15 thus approximately 2000 FDRs will be stored in memory 36 for each slide 14. In the illustrated embodiment, the image processor 30 limits the number of OOs contained in each FDR to 10 for individual OOs and 3 for clustered OOs.

The FOI processor 32 assigns OOs to each FOI based on the ranking of the OOs. Assignment of the OOs is accomplished in a manner that avoids assignment
20 of OOs to an FOI that have already been assigned within another FOI. In this manner, the OOs can be grouped within the FOIs (which in the embodiment, have a fixed number) in a coordinated manner, so that the number of OOs that are included within FOIs can be maximized. Alternatively, if the number of FOIs is not fixed, the number of FOIs required to include all of the OOs can be minimized. In one
25 embodiment, 20 IOOI preferential FOIs and 2 COOI preferential FOIs will be

generated. Thus, it can be ensured that both IOOs and COOs will be included within the FOIs for subsequent review by the cytotechnologist.

Referring now to Fig. 4, the process used by the FOI processor 32 to generate OOI preferential FOIs (in this case, 20) will be discussed in detail. First, the FOI processor 32 accesses the FDRs stored in memory 36 for the current slide 14, and extracts the IOOs and COOs to create an IOOI list and a COOI list (action block 50). Alternatively, the individual and clustered OOs can be combined into a single list. The cluster-extracted IOOs (i.e., the IOOs that were extracted from clusters) will be flagged as such. In one embodiment, the lists contain a predetermined number of OOs, e.g., 100 IOOs and 20 COOs for the respective lists. In this manner, subsequent processing and human reviewing time is minimized by excluding lower risk OOs from further consideration by the FOI processor 32 and cytotechnologist.

The FOI processor 32 then generates the FOIs, which have a predetermined size, by assigning x-y coordinates to them based on the x-y coordinates and rankings of the OOs. Specifically, the FOI processor 32 assigns the top ranked IOOI (i.e., the first IOOI in the list) to the initial FOI (action block 52). The FOI processor 32 then selects the next ranked IOOI (in this case, the second ranked IOOI) as the current IOOI (action block 54), and determines if the current IOOI and the IOOs previously assigned to the initial FOI can be collocated within the initial FOI (decision block 56). Notably, in the first pass, the second ranked IOOI will be the current IOOI, and the previously assigned IOOs will only include the initial (i.e., first ranked) IOOI.

If the current IOOI can be collocated with the previously assigned IOOs, the current IOOI is identified as a collocatable IOOI and is assigned to the initial FOI

(action block 58). If the current IOOI cannot be collocated with the previously assigned IOOIs, the current IOOI is identified as a non-collocatable IOOI and is not assigned to the initial FOI (action block 60). The FOI processor 32 then determines if the current IOOI is the last ranked IOOI (decision block 62). If not, the process
5 goes back to block 54, where the next ranked IOOI is selected as the current IOOI. Thus, it can be appreciated, that the FOI processor 32 will iterate through blocks 54-60 in order to assign all collocatable IOOIs to the initial FOI. The number of iterations will be equal to the number of IOOIs in the list minus one (i.e., minus the initial IOOI), which in this case, will be 99 times.

10 If the current IOOI is the last ranked IOOI, the FOI processor 32 will iterate through the COOI list in order to assign any collocatable COOIs to the initial FOI. Specifically, the FOI processor 32 selects the next ranked COOI as the current COOI (action block 64), and determines if the current COOI can be collocated with the previously assigned IOOIs and COOIs (decision block 66). Of course, if the top
15 ranked COOI is the next ranked COOI, the FOI processor 32 need only determine if the current COOI can be collocated with the previously assigned IOOIs, since there will be no previously assigned COOIs in the initial FOI. In any event, if the current COOI can be collocated with the previously assigned IOOIs, the current COOI is identified as a collocatable IOOI and is assigned to the initial FOI (action block 68).
20 If the current COOI cannot be collocated with the previously assigned IOOIs, the current COOI is identified as a non-collocatable IOOI and is not assigned to the initial FOI (action block 70).

The FOI processor 32 then determines if the current COOI is the last ranked COOI (decision block 72). If not, the process goes back to block 64, where the next
25 ranked COOI is selected as the current COOI. Thus, it can be appreciated, that the

FOI processor 32 will iterate through blocks 64-70 in order to assign all collocatable COOs to the initial FOI. The number of iterations will be equal to the number of COOs in list, which in this case, will be 20 times.

If the current COOI is the last ranked COOI, the initial FOI will be defined by assigning x-y coordinates the initial FOI in a manner that includes all of the collocatable OOs (IOOs and COOs) (action block 74). As will be described in further detail below, the manner in which the x-y coordinates are assigned to the initial FOI will depend, largely in part, upon the manner in which the OOs are determined to be collocatable.

Next, the FOI processor 32 defines the next FOI by assigning previously unassigned collocatable IOOs to the FOI. Specifically, the FOI processor 32 selects the next FOI as the current FOI (action block 76), and assigns the highest ranked previously unassigned IOOI to the current FOI (action block 78). For example, if the first and second ranked IOOs have previously been assigned, but the third ranked IOOI has not, the third ranked IOOI will be assigned to the current FOI. The FOI processor 32 then selects the next ranked previously unassigned IOOI as the current IOOI (action block 80). For example, if the fifth, sixth, and seventh IOOs have previously been assigned, but the eighth ranked IOOI has not, the eighth ranked IOOI will be selected as the current IOOI.

In the same manner described above with respect to the initial FOI, the FOI processor 32 will determine if the current IOOI is collocatable with the IOOs previously assigned to the current FOI (decision block 82). Notably, in the first pass, the previously assigned IOOs will only include the IOOI that was initially assigned to the current FOI. If collocatable, the current IOOI will be assigned to the current FOI (action block 84), and if not, the current IOOI will not be assigned to the current FOI

(action block 86). The FOI processor 32 then determines if the current IOOI is the last ranked previously unassigned IOOI (action block 88). If not, the process goes back to action block 80, where the next ranked previously unassigned IOOI is selected as the current IOOI. Thus, it can be appreciated, that the FOI processor 32 will iterate through blocks 80-86 in order to assign all previously unassigned collocatable IOOIs to the current FOI.

If the current IOOI is the last ranked IOOI, the FOI processor 32 will iterate through the COOI list in order to assign any previously unassigned collocatable COOIs to the current FOI in the same manner described above with respect to the initial FOI. Specifically, the FOI processor 32 selects the next ranked previously unassigned COOI as the current COOI (action block 90), and determines if the current COOI can be colocated with the previously assigned IOOIs and COOIs (decision block 92). Again, if the highest ranked previously unassigned COOI is the next ranked COOI, the FOI processor 32 need only determine if the current COOI can be colocated with the previously assigned IOOIs, since there will be no previously assigned COOIs in the FOI. If collocatable, the current COOI will be assigned to the current FOI (action block 94), and if not, the current COOI will not be assigned to the current FOI (action block 96). The FOI processor 32 then determines if the current COOI is the last ranked previously unassigned COOI (decision block 98). If not, the process goes back to block 90, where the next ranked previously unassigned COOI is selected as the current COOI. Thus, it can be appreciated, that the FOI processor 32 will iterate through blocks 90-96 in order to assign all previously unassigned collocatable COOIs to the current FOI. If the current COOI is the last ranked COOI, the current FOI will be defined by assigning x-

y coordinates to the current FOI in a manner that includes all of the collocatable OOs (IOOs and COOs) (action block 100).

The FOI processor 32 will then determine whether the current FOI is the last IOO preferential FOI (in this case, the 20th FOI) (decision block 102). If not, the process returns to block 76 where the next FOI is selected as the current FOI, and then the previously unassigned collocatable IOOs and COOs are assigned to it.

If the current FOI is the last IOO preferential FOI, the process ends (action block 104), and then the FOI processor 32 will generate COO preferential FOIs (in this case, the final 2 FOIs) in a manner similar to that used to generate FOIs set out in blocks 76-100. The significant difference is that the previously unassigned collocatable COOs will be assigned to the FOIs before the previously unassigned collocatable IOOs are. Another difference stems from the fact that there may be less than 2 previously unassigned COOs left after the 20 IOO preferential FOIs are generated, and thus, at least one of the COO preferential FOIs cannot be initialized with a COO. In this case, the FOI processor 32 will attempt assign previously unassigned cluster-extracted IOOs (i.e., IOOs that have been flagged as being extracted from clusters) to the FOI(s). If there are not enough previously unassigned cluster-extracted IOOs, the FOI processor 32 will assign previously unassigned IOOs that were not extracted from clusters to the FOI(s).

As briefly mentioned above, the manner in which the OOs are determined to be collocatable, and the manner in which the x-y coordinates are assigned to the FOIs are interrelated. For example, if the x-y coordinates are assigned to the FOI, such that it is centered over the initial OO assigned to it, the FOI will be fixed in position, and OOs falling within the borders of this fixed FOI will simply be considered collocatable, while the OOs falling outside of the borders of the fixed FOI

will simply be considered non-collocatable. If x-y coordinates are assigned to the FOI, such that it is ultimately centered over a group of OOI, and thus is allowed to move from the initially assigned OOI, an OOI falling within the borders of the dynamically movable FOI (assuming that the FOI is moved to accommodate the OOI and the current collocatable OOIs), without causing a currently collocatable OOI to fall outside of the borders of the FOI, will be considered collocatable, while an OOI either falling outside of the borders of the dynamically movable FOI or causing a currently collocatable to fall outside of the borders of the FOI, will be considered non-collocatable. The later method is preferred over the former, since it will generally allow more OOIs to be collocated within a given FOI.

A FOI can be conveniently centered over a group of collocatable OOIs (either or both IOOIs and COOIs) by using an expandable bounding box. Specifically, and with reference to Figs. 5-8, the use of an expandable bounding box 150 to iteratively determine whether FOIs are collocatable is described. First, the bounding box 150, which will start off as a point, will be initialized by making the x-y coordinates of the bounding box 150 equal to the coordinates of the initial OOI (shown as OOI_0 in Fig. 6) (action block 160). The next OOI (shown as OOI_1 in Fig. 6) is identified as the current OOI (action block 162), and the bounding box 150 is then expanded to include the current OOI (action block 164).

Significantly, only the sides of the bounding box 150 necessary to include the current OOI are expanded. In other words, if the x-coordinate of the current OOI is less than the minimum x coordinate of the bounding box 150, the left side of the bounding box 150 will be expanded, such that the minimum x-coordinate of the bounding box 150 matches the x-coordinate of the current OOI. Similarly, if the y-coordinate of the current OOI is less than the minimum y-coordinate of the bounding

box 150, the bottom side of the bounding box 150 will be expanded, such that the minimum y-coordinate of the bounding box 150 matches the y-coordinate of the current OOI. If the x-coordinate of the current OOI is greater than the maximum x-coordinate of the bounding box 150, the right side of the bounding box 150 will be expanded, such that the maximum x-coordinate of the bounding box 150 matches the x-coordinate of the current OOI. If the y-coordinate of the current OOI is greater than the maximum y-coordinate of the bounding box 150, the top side of the bounding box 150 will be expanded, such that the maximum y-coordinate of the bounding box 150 matches the y-coordinate of the current OOI.

In the exemplary case illustrated in Fig. 6, the x-coordinate of OOI_1 is less than the minimum x-coordinate of the bounding box 150 (which is essentially a point), and thus the left side of the bounding box 150 is expanded outward, so that the minimum x-coordinate of the bounding box 150 matches the x-coordinate of OOI_1 . The y-coordinate of OOI_1 is also greater than the maximum y-coordinate of the bounding box 150, and thus the top side of the bounding box 150 is expanded outward, so that the maximum y-coordinate of the bounding box 150 matches the y-coordinate of OOI_1 .

A determination is then made as to whether any dimension of the bounding box 150, after expansion, exceeds a dimension of the current FOI (decision block 166). If not, the current OOI is identified as being collocatable (action block 168), and the expanded boundary box will be set as the new boundary box for the next iteration (action block 172). In contrast, if the bounding box 150, after expansion, exceeds the dimensions of the current FOI, the current OOI is identified as being non-collocatable (action block 170), and the expanded boundary box will revert back to the previous boundary box (i.e., the previous boundary box will remain the new

boundary box for the next iteration) (action block 174). In the exemplary case, the dimension of the boundary box, when expanded to include OOI_1 , is $200\ \mu\text{m} \times 100\ \mu\text{m}$. Assuming that the FOI has a predefined dimension of $400\ \mu\text{m} \times 400\ \mu\text{m}$, both dimensions of the boundary box are less than the dimensions of the current FOI, and thus, OOI_1 will be identified as being collocatable, and the expanded boundary box will be set as the new boundary box for the next iteration.

A determination is then made as to whether the current OOI is the last OOI assigned to the FOI (decision block 176). If so, the process ends (action block 178). If not, the process will then return to action block 162 in order to determine if the next OOI (shown as OOI_2 in Fig. 7) is collocatable. For example, in the exemplary case illustrated in Fig. 7, the x-coordinate of OOI_2 is less than the minimum x-coordinate of the new bounding box 150, and thus the left side of the bounding box 150 is expanded outward, so that the minimum x-coordinate of the bounding box 150 matches the x-coordinate of OOI_2 . The y-coordinate of OOI_2 is less than the minimum y-coordinate of the bounding box 150, and thus the bottom side of the new bounding box 150 is expanded outward, so that the minimum y-coordinate of the bounding box 150 matches the y-coordinate of OOI_2 . As illustrated in Fig. 7, the dimension of the new boundary box, when expanded to include OOI_2 , is $600\ \mu\text{m} \times 350\ \mu\text{m}$. In this case, the x-dimension of the boundary box is greater than the x-dimension of the current FOI. Thus, OOI_2 will be identified as being non-collocatable, and the previous boundary box will remain the new boundary box for the next iteration.

In the exemplary case illustrated in Fig. 8, the next OOI is shown as OOI_3 . The x-coordinate of OOI_3 is greater than the maximum x-coordinate of the new bounding box 150, and thus the right side of the bounding box 150 is expanded

outward, so that the maximum x-coordinate of the bounding box 150 matches the x-coordinate of OOI₃. As illustrated in Fig. 8, the dimension of the new boundary box, when expanded to include OOI₃, is 300 μ m x 100 μ m. In this case, both dimensions of the boundary box are less than the dimensions of the current FOI, and thus, OOI₃ will be identified as being collocatable, and the expanded boundary box will be set as the new boundary box for the next iteration. It should be noted that, once the bounding box has been finally set, the FOI processor 32 can easily center the FOI over the collocated OOIs by assigning an x-coordinate to the FOI equal to the average of the minimum and maximum x-coordinates of the bounding box 150, and likewise assigning a y-coordinate to the FOI equal to the average of the minimum and maximum y-coordinates of the bounding box 150.

After all 22 FOIs have been generated, the FOI processor 32 stores the x-y coordinates of all of the FOIs in memory 36 for later use by the routing processor 34. Specifically, the routing processor 34 maps the x-y coordinates of the FOIs using a suitable routing algorithm, such as a modified "traveling salesman" algorithm, which determines the most efficient viewing route for presenting the FOIs in the reviewing station 22. The routing processor 34 then stores the x-y coordinates of the FOIs, along with the routing plan (which in the illustrated embodiment, is accomplished by simply placing the FOIs in a list in the order that they will be reviewed), in memory 36 for subsequent access by the reviewing station 22.

Referring back to Fig. 2, in one embodiment, a total of three reviewing stations 20 are shown coupled to the server 20, so that up to three cytotechnologists have simultaneous access to the pertinent information stored in the server 20. Notably, the system 10 can typically process the slides 12 much quicker than a cytotechnologist can review them. Even if the specimen processing speed of the

system 10 is slower than the specimen review speed of a cytotechnologist, the system 10 can generally be operated 24 hours a day, whereas the typical cytotechnologist will only work 8 hours a day. Thus, the bottleneck in the screening process occurs at the human level, i.e., the detailed review of the biological material contained on the slides 12. Thus, it can be appreciated that the use of multiple reviewing stations 20 alleviates this bottleneck, thereby providing for a much more efficient process.

Before discussing the details of the reviewing stations 20, reference is made to Fig. 3, which illustrates an exemplary FOV that each reviewing station centers over a FOI. In the illustrated embodiment, the FOV has a diameter of 2.2 mm, and the FOI is defined by a 0.4 mm x 0.4 mm square circumscribed by the FOV. In the actual embodiment, the borders of the FOI are imaginary and cannot be seen, so that the cytotechnologist's view of any OOIs is not obstructed. In order to more quickly direct the cytotechnologist's attention to the FOI and to provide a reference that generally indicates the exact region bound by the imaginary borders of the FOI, an L-shaped mark indicator 152 is provided. The mark indicator 152 captures the FOI (i.e., an open square portion 154 of the mark indicator 152 borders the left and bottom sides of the FOI). A 0.05 mm margin is provided between the mark indicator 152 borders and the imaginary borders of the FOI, so that the portions of OOIs extending outside of the left and bottom borders of the FOI (resulting from an OOI that is included within the FOI, but centered near the left or bottom border of the FOI) will not be obstructed by the mark indicator 152. The mark indicator 152 also serves to provide a means for the cytotechnologist to electronically mark the FOI (e.g., by pushing a button that electronically colors the mark indicator 52) as requiring further review by a pathologist (e.g., if an OOI has malignant or pre-malignant attributes).

Referring back to Fig. 2, each reviewing station 20 comprises a microscope 38 and a motorized stage 40. The slide 14 (after image processing) is mounted on the motorized stage 40, which moves the slide 14 relative to the viewing region of the microscope 38 based on the routing plan and a transformation of the x-y coordinates of the FOIs obtained from memory 36. Specifically, these x-y coordinates, which were acquired relative to the x-y coordinate system of the imaging station 18, will be transformed into the x-y coordinate system of the reviewing station 20 using the fiducial marks 16 affixed to the slide 14 (shown in Fig. 1). Thus, it is ensured that the x-y coordinates of the slide 14 during the reviewing process are correlated to the x-y coordinates of the slide 14 during the imaging process. The motorized stage 40 will then move in accordance with the transformed x-y coordinates of the FOIs, as dictated by the routing plan.

In the illustrated embodiment, to advance from one FOI to another, the cytotechnologist presses an activation switch (not shown). In this sense, the reviewing station 20 is semi-automatic. Alternatively, the FOIs are automatically advanced from one to the next. In this case, the motorized stage 40 may optionally pause for a predetermined amount of time for each FOI. In this sense, the reviewing station 20 is fully automatic.

As the selected FOIs are presented in the FOV of the microscope 38, the cytotechnologist reviews the FOIs and makes decisions about the level of cell abnormality, if any. The cytotechnologist will electronically mark any FOIs that are suspect. The cytotechnologist is capable of returning to a previously viewed FOI, and manually moving to (and viewing) locations on the slide not encompassed by FOIs. Following review of the slide 14, if any FOIs have been marked by the cytotechnologist, the reviewing station 22 preferably automatically scans the entire

biological specimen 12, so that 100% viewing coverage is ensured. The cytotechnologist is able to pause the autoscan and to move the stage 40 in order to reposition and access locations on the slide 14, as desired.

CLAIMS

1. A biological screening system for presenting objects of interest (OOIs) located on a microscope slide within fields of interest (FOIs) covering portions of the slide, comprising:

5 an imaging station for obtaining scanned images of the slide, and generating image data from the scanned images;

at least one processor for filtering the image data to obtain OOIs, and for assigning one or more OOIs to each FOI, at least partially, based on the assignment of OOIs to other FOIs; and

10 an automated or semi-automated microscope for scanning a field of view (FOV) relative to each FOI to present the one or more OOIs in each FOI.

2. The biological screening system of claim 1, wherein the at least one processor assigns one or more OOIs to each FOI by:

sequentially selecting OOIs that have not been assigned to any FOI;

15 assigning an initially selected OOI to the FOI;

determining if each subsequently selected OOI can be collocated with OOIs previously assigned to the FOI; and

identifying each subsequently selected OOI as a collocatable OOI based on the determination.

20 3. The biological screening system of claim 1, wherein the FOIs have predetermined dimensions.

4. The biological screening system of claim 1, wherein the number of FOIs is fixed.

25 5. The biological screening system of claim 1, wherein the at least one processor is further for centering each FOI over an initially assigned OOI.

6. The biological screening system of claim 1, wherein the at least one processor is further for centering each FOI over a group of collocated OOI.

7. The biological screening system of claim 1, wherein the OOIs are cells.

8. The biological screening system of claim 2, wherein the at least
5 processor is further for ranking the OOIs, wherein the OOIs are selected in accordance with the ranking of the OOIs.

9. The biological screening system of claim 8, wherein the OOIs are cells.

10. The biological screening system of claim 9, wherein the cells are ranked in accordance with the likelihood that the cells are at risk of having an
10 abnormal condition.

11. The biological screening system of claim 9, wherein the abnormal condition is malignancy or pre-malignancy.

12. The biological screening system of claim 2, wherein the at least one processor determines if each subsequently selected OOI can be collocated with
15 OOIs previously assigned to the FOI by:

initially defining a current boundary that includes the initially selected OOI, wherein the boundary is geometrically similar to the FOI; and

for each subsequently selected OOI, expanding the current boundary to include the subsequently selected OOI, and if each dimension of the expanded
20 boundary is the same or smaller than a corresponding dimension of the FOI, identifying the subsequently selected OOI as collocatable and setting the expanded boundary as a new current boundary.

13. The biological screening system of claim 1, wherein the FOIs are divided into primary FOIs and secondary FOIs, and the OOIs are divided into primary
25 OOIs and secondary OOIs, and the at least one processor is for assigning one or

more primary OOs to each primary FOI, at least partially, based on the assignment of primary OOs to other primary FOIs, and for assigning one or more secondary OOs to each secondary FOI, at least partially, based on the assignment of secondary OOs to other secondary FOIs.

5 14. The biological screening system of claim 13, wherein the at least one processor:

 assigns one or more primary OOs to each primary FOI by:

 sequentially selecting primary OOs that have not been assigned to any primary FOI;

10 assigning an initially selected primary OO to the primary FOI;

 determining if each subsequently selected primary OO can be collocated with primary OOs previously assigned to the primary FOI; and

15 identifying each subsequently selected primary OO as a collocatable primary OO based on the determination; and

 assigning each primary collocatable OO to the primary FOI; and

 assigns one or more secondary OOs to each secondary FOI by:

 sequentially selecting secondary OOs that have not been assigned to any secondary FOI;

20 assigning an initially selected secondary OO to the secondary FOI;

 determining if each subsequently selected secondary OO can be collocated with secondary OOs previously assigned to the FOI;

 identifying each subsequently selected secondary OO as a collocatable secondary OO based on the determination; and

25 assigning each secondary collocatable OO to the secondary FOI.

15. The biological screening system of claim 13, wherein the at least one processor is further for assigning one or more secondary OOs to each primary FOI, at least partially, based on the assignment of secondary OOs to other primary FOIs and secondary FOIs.

5 16. The biological screening system of claim 15, wherein the at least one processor:

 assigns one or more primary OOs to each primary FOI by:

 sequentially selecting primary OOs that have not been assigned to any primary FOI;

10 assigning an initially selected primary OO to the primary FOI;

 determining if each subsequently selected primary OO can be collocated with primary OOs previously assigned to the primary FOI; and

 identifying each subsequently selected primary OO as a collocatable primary OO based on the determination; and

15 assigning each primary collocatable OO to the primary FOI;

 assigns one or more secondary OOs to each secondary FOI by:

 sequentially selecting secondary OOs that have not been assigned to any secondary FOI;

20 assigning an initially selected secondary OO to the secondary FOI;

 determining if each subsequently selected secondary OO can be collocated with secondary OOs previously assigned to the FOI;

 identifying each subsequently selected secondary OO as a collocatable secondary OO based on the determination; and

25 assigning each secondary collocatable OO to the secondary FOI; and

.assigns one or more secondary OOs to each primary FOI by:

sequentially selecting secondary OOs that have not been assigned to any primary or secondary FOI, the secondary OOs being selected after the primary OOs;

5 determining if each subsequently selected secondary OO can be collocated with primary or secondary OOs previously assigned to the primary FOI;

identifying each selected secondary OO as a secondary collocatable OO based on this determination; and

10 assigning each secondary collocatable OO to the primary FOI.

17. The biological screening system of claim 13, wherein the at least one processor is further for assigning one or more primary OOs to each secondary FOI, at least partially, based on the assignment of primary OOs to primary FOIs and other secondary FOIs.

15 18. The biological screening system of claim 17, wherein the at least one processor:

assigns one or more primary OOs to each primary FOI by:

sequentially selecting primary OOs that have not been assigned to any primary FOI;

20 assigning an initially selected primary OO to the primary FOI;

determining if each subsequently selected primary OO can be collocated with primary OOs previously assigned to the primary FOI; and

25 identifying each subsequently selected primary OO as a collocatable primary OO based on the determination; and

assigning each primary collocatable OOI to the primary FOI;

assigns one or more secondary OOIs to each secondary FOI by:

sequentially selecting secondary OOIs that have not been assigned to any secondary FOI;

5 assigning an initially selected secondary OOI to the secondary FOI;

determining if each subsequently selected secondary OOI can be collocated with secondary OOIs previously assigned to the FOI;

identifying each subsequently selected secondary OOI as a collocatable secondary OOI based on the determination; and

10 assigning each secondary collocatable OOI to the secondary FOI;

assigns one or more secondary OOIs to each primary FOI by:

sequentially selecting primary OOIs that have not been assigned to any primary or secondary FOI, the primary OOIs being selected after the secondary OOIs;

15 determining if each subsequently selected primary OOI can be collocated with primary or secondary OOIs previously assigned to the secondary FOI;

identifying each selected primary OOI as a primary collocatable OOI based on the determination; and

20 assigning each primary collocatable OOI to the secondary FOI.

19. The biological screening system of claim 13, wherein the primary OOIs are individual cells, and the secondary OOIs are cell clusters.