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Mitosis detection in breast cancer histological images An ICPR 2012 contest

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Abstract

Introduction: In the framework of the Cognitive Microscope (MICO) project, we have set up a contest about mitosis detection in images of H and E stained slides of breast cancer for the conference ICPR 2012. Mitotic count is an important parameter for the prognosis of breast cancer. However, mitosis detection in digital histopathology is a challenging problem that needs a deeper study. Indeed, mitosis detection is difficult because mitosis are small objects with a large variety of shapes, and they can thus be easily confused with some other objects or artefacts present in the image. We added a further dimension to the contest by using two different slide scanners having different resolutions and producing red-green-blue (RGB) images, and a multi-spectral microscope producing images in 10 different spectral bands and 17 layers Z-stack. 17 teams participated in the study and the best team achieved a recall rate of 0.7 and precision of 0.89. **Context:** Several studies on automatic tools to process digitized slides have been reported focusing mainly on nuclei or tubule detection. Mitosis detection is a challenging problem that has not yet been addressed well in the literature. **Aims:** Mitotic count is an important parameter in breast cancer grading as it gives an evaluation of the aggressiveness of the tumor. However, consistency, reproducibility and agreement on mitotic count for the same slide can vary largely among pathologists. An automatic tool for this task may help for reaching a better consistency, and at the same time reducing the burden of this demanding task for the pathologists. **Subjects and Methods:** Professor Frédérique Capron team of the pathology department at Pitié-Salpêtrière Hospital in Paris, France, has selected a set of five slides of breast cancer. The slides are stained with H and E. They have been scanned by three different equipments: Aperio ScanScope XT slide scanner, Hamamatsu NanoZoomer 2.0-HT slide scanner and 10 bands multispectral microscope. The data set is made up of 50 high power fields (HPF) coming from 5 different slides scanned at ×40 magnification. There are 10 HPFs/slide. The pathologist has annotated all the mitotic cells manually. A HPF has a size of 512 μm × 512 μm (that is an area of 0.262 mm^2, which is a surface equivalent to that of a microscope field diameter of 0.58 mm. These 50 HPFs contain a total of 326 mitotic cells on images of both scanners, and

322 mitotic cells on the multispectral microscope. **Results**: Up to 129 teams have registered to the contest. However, only 17 teams submitted their detection of mitotic cells. The performance of the best team is very promising, with F-measure as high as 0.78. However, the database we provided is by far too small for a good assessment of reliability and robustness of the proposed algorithms. **Conclusions**: Mitotic count is an important criterion in the grading of many types of cancers, however, very little research has been made on automatic mitotic cell detection, mainly because of a lack of available data. A main objective of this contest was to propose a database of mitotic cells on digitized breast cancer histopathology slides to initiate works on automated mitotic cell detection. In the future, we would like to extend this database to have much more images from different patients and also for different types of cancers. In addition, mitotic cells should be annotated by several pathologists to reflect the partial agreement among them.

Key words: Automated mitotic cell detection, breast cancer, H and E stained histological slides

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INTRODUCTION

Nottingham grading system[1] is an international grading system for breast cancer recommended by the World Health Organization. It is derived from the assessment of three morphological features on slides stained with H and E: Tubule formation, nuclear pleomorphism, and mitotic count.

Mitotic count is an important parameter in breast cancer grading as it gives an evaluation of the aggressiveness of the tumor. However, consistency, reproducibility and agreement on mitotic count for the same slide can vary largely among pathologists.[2,3] An automatic tool for this task may help for reaching a better consistency, and at the same time reducing the burden of this demanding task for pathologists.

Detection of mitotic cells is a very challenging task because they are small objects with a large variety of shape configurations and a low frequency of appearance. Some examples of ground truth mitotic cells are shown in Figure 1. The objective of the contest is to encourage works on the detection of mitosis on H and E stained histological images of the breast cancers.

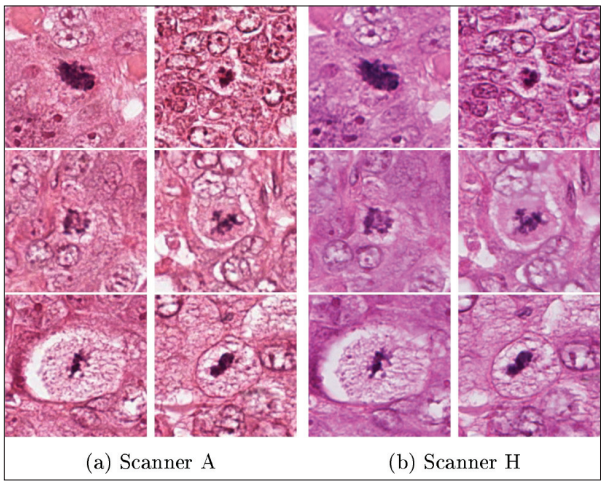

Figure 1: Example of ground truth mitotic cells for scanners

Several studies on automatic tools to process digitized slides have been reported[4] focusing mainly on nuclei or tubule detection. Mitosis detection is a challenging problem that has not yet been addressed well in the literature. Only few works concern detection of mitosis. Beliën *et al.*,[5] counted mitoses on Feulgen stained breast cancer sections. Recently Liu *et al.*,[6] and Huh *et al.*,[7] proposed mitosis detection in time-lapse phase contrast microscopy image sequences of stem cell populations and Schlachter *et al.*[8] performed detection of mitoses in fluorescence staining of colorectal cancer. Roullier *et al.*,[9] propose detection of mitotic cells on breast cancer slides with an immunohistochemical staining that highlights specifically mitosis.

The only work concerning mitosis detection on H and E stained slides is by Malon *et al.*,[10] who propose the use of convolutional neural networks (CNN). Sertel *et al.*,[11] presented a method for the detection of mitosis and karyorrhexis cells (dying cells) without distinction, but for breast cancer grading, only mitotic cells must be counted.

SUBJECTS AND METHODS

Dataset

Professor Frédérique Capron's team of the pathology department at Pitié-Salpêtrière Hospital in Paris, France, has provided a set of five slides of breast cancer. The slides are stained with H and E. They have been scanned by three different equipments:

- Aperio ScanScope XT slide scanner (scanner A);
- Hamamatsu NanoZoomer 2.0-HT slide scanner (scanner H);
- And 10 bands multispectral microscope (microscope M). The spectral bands are all in the

visible spectrum. In addition, for each spectral band, the digitization has been performed at 17 different focus planes (17 layers Z-stack), each consecutive planes being separated from each other by 500 nm.

Ground Truth

The data set is made up of 50 high power fields (HPF) coming from 5 different slides scanned at ×40 magnification. There are 10 HPFs per slide. The pathologist has annotated all the mitotic cells manually. She made the annotations in each selected HPF on the images generated by the scanner A, the scanner H and the multispectral microscope M.

A HPF has a size of 512 μm × 512 μm (that is an area of 0.262 mm^2), which is a surface equivalent to that of a microscope field diameter of 0.58 mm. These 50 HPFs contain a total of 326 mitotic cells on images of both scanners, and 322 mitotic cells on the microscope M.

Table 1 gives the number of mitotic cells in the training data set and in the evaluation data set. There are more mitotic cells on the scanner images as compared to the microscope M images. This discrepancy has its origin in the smaller size of multispectral images as compared to the scanner images. Four multispectral images are needed to cover almost the entire surface of a single scanner HPF. However, small gaps remain between the four multispectral images and the same area of a scanner HPF [Figure 2]. As a result, few mitotic cells visible on the border of scanner HPFs are missing on the multispectral images.

Table 1: Number of HPFs and mitotic cells in training and evaluation data sets

Data sets	Scanners A and H	Microscope M
Training data set: 35 HPFs	226 mitotic cells 69.3% of total	224 mitotic cells 69.6% of total
Evaluation data set: 15 HPFs	100 mitotic cells 30.7% of total	98 mitotic cells 30.4% of total
Total	326 mitotic cells	322 mitotic cells

HPFs: High power fields

Table 2: Resolution of the scanners A and H and the multispectral microscope M

Equipment	Resolution per pixel	Dimension of HPF to cover an area of 512 μm×512 μm
Scanner A	0.2456 μm	2084×2084 pixels
Scanner H	0.2273 μm horizontal 0.22753 μm vertical	2252×2250 pixels
Microscope M	0.185 μm	2767×2767 pixels

HPF: High power field

Resolution of Scanners and Microscope

Scanner A has a resolution of 0.2456 μm/pixel. Scanner H has a slightly better resolution of 0.2273 μm (horizontal) and 0.22753 μm (vertical) per pixel. Note that a pixel of scanner H is not exactly a square. At last, multispectral microscope M has the best resolution of 0.185 μm per pixel. Table 2 shows the resolutions of the different scanners and the microscope. For example, a mitosis having an area of 50 μm^2 will cover about 830 pixels of the image produced by scanner A, about 965 pixels of the image produced by scanner H, and about 1460 pixels of the image produced by multispectral microscope M.

For each slide, there is one RGB image produced by scanner A, one RGB image produced by scanner H, and 170 grey scale images for the multispectral microscope M (10 spectral bands and 17 layers Z-stack for each spectral band).

Multispectral Microscope M

The camera attached on top of the microscope generates images of 1360 × 1360 pixels. However, to cover an area of 512 μm × 512 μm, 2767 × 2767 pixels are needed. Therefore, we will use four images to cover the same area as the two scanners. However, these four images do not cover completely the 512 μm × 512 μm area, 47 pixels are missing in width and in height to cover fully the area.

Each image, covering a quarter of a scanner image, is labeled a, b, c or d depending on its position in the scanner image. Figure 2 shows the location of each quarter a, b, c, d. As the quarters do not cover completely the 512 μm × 512 μm area, compared to the scanner images, there is a small gap on the borders, and also a small gap between quarters a, b, c and d.

Figure 3 shows the spectral coverage of each of the 10 spectral bands of the microscope M. All the bands are in the visible spectrum.

Evaluation Metrics

The main goal of the contest is to be able to give the mitotic count on each slide. A segmented mitosis would be counted as correctly detected if its centroid is localized within a range of 8 μm of the centroid of ground truth mitosis. The evaluation metrics are defined as follows:

- TP = number of true positives, that is the number of candidate mitotic cells that are ground truth mitotic

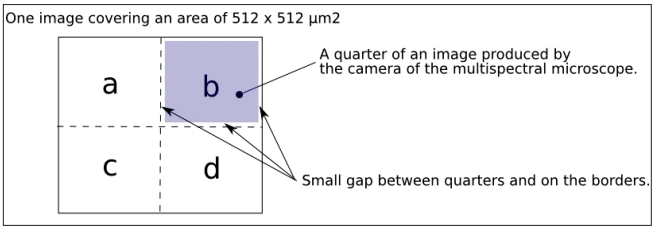

Figure 2: Location of quarters a, b, c and d of multispectral microscope in scanner image

cells.

- FP = number of false positives, that is the number of candidate mitotic cells that are not ground truth mitotic cells.
- FN = number of false negatives, that is the number of ground truth mitotic cells that have not been detected.
- Recall (sensitivity) $= \frac{TP}{TP+FN}$
- Precision (positive predicitive value) $= \frac{TP}{TP+FN}$
- F-measure $= 2 \times \frac{precision \times recall}{precision + recall}$

RESULTS

The ground truth and images of training data set have been provided at the beginning of the contest on November 2011. At the end of the contest, in August 2012, contestants received images of the evaluation data set, but not the corresponding ground truth. All the rankings are made according to F-measure.

Up to 129 teams have registered to the contest. They

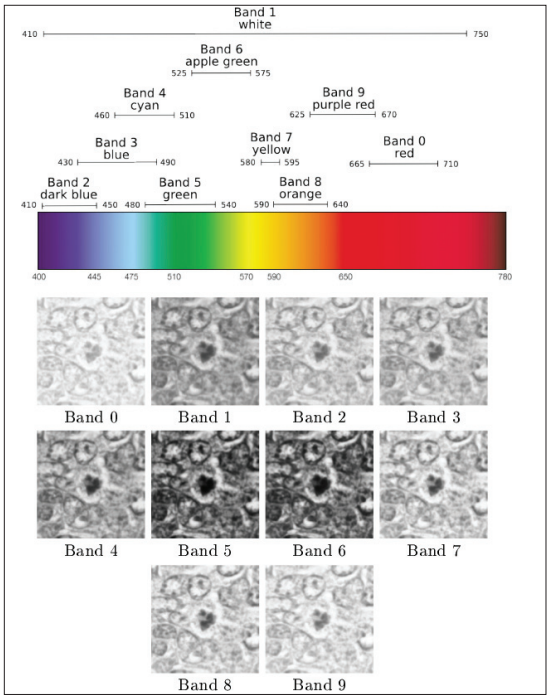

Figure 3: Spectral bands of the multispectral microscope and examples for each band

Table 3: List of contestants

Team	Institute	City and Country
Alberta	Department of Electrical and Computer Engineering, University of Alberta	Edmonton, Canada
BII	BioInformatics Institute	Singapore
Definiens	Definiens	Munich, Germany
Drexel	Center for Integrated Bioinformatics, Drexel University	Philadelphia, USA
ETH-heidelberg	Institute for Biochemistry, ETH Zürich	Zürich, Switzerland
	HCI Heidelberg	Heidelberg, Germany
IDSIA	IDSIA (Dalle Molle Institute for Artificial Intelligence), USI, SUPSI	Lugano, Switzerland
IITG	Indian Institute of Technology, Guwahati	Guwahati, India
IPAL	IPAL, Joseph Fourier University	Grenoble, France
Isik	Department of Computer Engineering, Işık University	Istanbul, Turkey
LNM-IIT	LNM Institute of Information Technology	Jaipur, India
NEC	Department of Machine Learning, NEC America Laboratories	Princeton, USA
NUS	National University of Singapore	Singapore
Okan-IRISA-LIAMA	Okan University	Istanbul, Turkey
	IRISA, University of South Brittany	Vannes, France
	LIAMA	Beijing, China
Qatar	Qatar University	Qatar
SUTECH	Shiraz University of Technology	Shiraz, Iran
Utrecht	Image Sciences Institute-Department of Pathology, University of Medical Center	Utrecht, The Netherlands
Warwick	University of Warwick-University Hospitals Coventry and Warwickshire	Coventry, UK

ETH: Swiss Federal Institute of Technology, IDSIA: Dalle Molle Institute for Artificial Intelligence Research, IPAL: Image & pervasive access lab, LNM: Lakshmi niwas mittal, NEC: NEC Corporation, IRISA: Research Institute in Computer Science and Random Systems, LIAMA: French-Chinese Laboratory in Computer Science, Automatic Control and Applied Mathematics, HCI: Heidelberg collaboratory for image processing, USI: University of Italian Switzerland, SUPSI: University of Applied Sciences and Arts of Southern Switzerland, IITG: Indian institute of technology, IIT: Institute of information technology, SUTECH: Shiraz University of Technology

Table 4: Detection results and rankings for scanner Aperio (rankings are according to F-measure)

Rank	Team	TP	FP	FN	F-measure	Recall	Precision
1	IDSIA	70	9	30	0.7821	0.70	0.89
2	IPAL	74	32	26	0.7184	0.74	0.70
3	SUTECH	72	31	28	0.7094	0.72	0.70
4	NEC	59	20	41	0.6592	0.59	0.75
5	Utrecht	68	65	32	0.5837	0.68	0.51
6	Warwick	57	65	43	0.5135	0.57	0.47
7	NUS	40	23	60	0.4908	0.40	0.63
8	Isik	68	174	32	0.3977	0.68	0.28
9	ETH-heidelberg	80	247	20	0.3747	0.80	0.24
10	Okan-IRISA-LIAMA	22	6	78	0.3438	0.22	0.79
11	IITG	46	214	54	0.2556	0.46	0.18
12	Drexel	21	122	79	0.1728	0.21	0.15
13	BII	32	278	68	0.1561	0.32	0.10
14	Qatar	94	35567	6	0.0053	0.94	0.00

BII: BioInformatics institute, IITG: Indian institute of technology, Guwahati NUS: National university of singapore, SUTECH: Shiraz university of technology, TP: True positives, FP: False positive, FN: False negative, IDSIA: Dalle Molle Institute for Artificial Intelligence Research, IPAL: Image & pervasive access lab, NEC: NEC Corporation, ETH: Swiss Federal Institute of Technology, IRISA: Research Institute in Computer Science and Random Systems, LIAMA: French-Chinese Laboratory in Computer Science, Automatic Control and Applied Mathematics

Table 5: Detection results and rankings for scanner Hamamatsu (rankings are according to F-measure)

Rank	Team	TP	FP	FN	F-measure	Recall	Precision
1	SUTECH	61	13	39	0.7011	0.61	0.82
2	IPAL	71	56	29	0.6256	0.71	0.56
3	NEC	44	14	56	0.5570	0.44	0.76
4	Definiens	30	35	70	0.3636	0.30	0.46

SUTECH: Shiraz university of technology, TP: True positives, FP: False positive, FN: False negative, NEC: NEC Corporation, IPAL: Image & Pervasive access lab

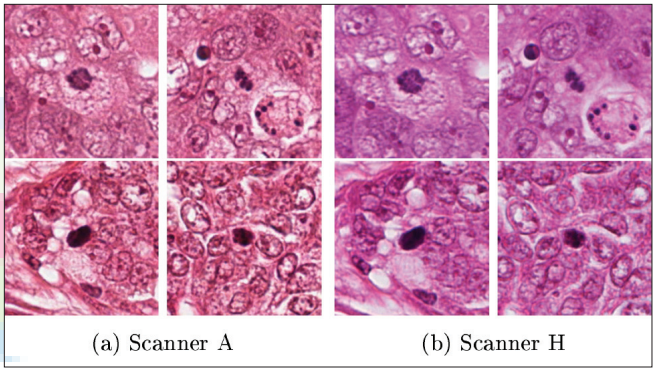

Figure 4: Some examples of false positives. The false mitotic cell objects are located in the center of each image

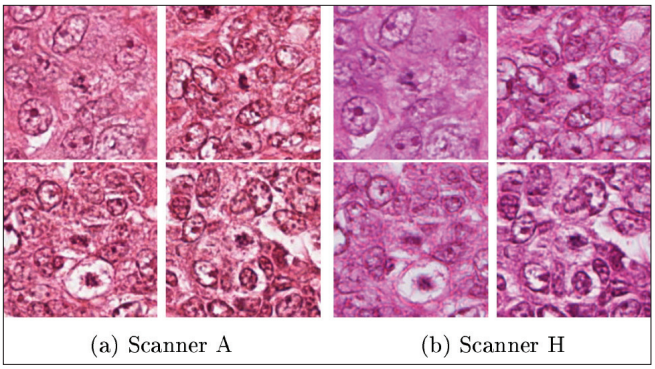

Figure 5: Some examples of false negatives. The not detected mitotic cell objects are located in the center or each image

downloaded and worked on the training data set to prepare and tune their algorithms for detection of mitotic cells. At the end of the contest, they received the evaluation data set. However, only 17 teams submitted their detection of mitotic cells. Team names are listed in Table 3. Detection results and rankings are given in Table 4 for scanner A, Table 5 for scanner H and Table 6 for microscope M.

Overall, detection of mitotic cells is better on scanner A than on scanner H. Detection results on multispectral microscope are very poor as compared to scanners A and H. This is shown by the results of NEC, Shiraz University of Technology (SUTECH) and Image and Pervasive Access Lab (IPAL) teams who had better detection on scanner A respectively with 59, 72 and 74 true positives, whereas these figures are respectively 44, 61 and 71 for scanner H. However, NEC and SUTECH had more false positives on scanner A (respectively 20 and 31) than on scanner H (respectively 14 and 13). Although, IPAL had much more false positives on scanner H (56) than on scanner A (32). A few examples of false positives and false negatives are presented in Figures 4 and 5.

DISCUSSION

The general processing method developed by most teams for detection of mitotic cells is globally made up of four steps.

- Detection of candidate blobs or seed points using

Table 6: Detection results and rankings for multispectral microscope (rankings are according to F-measure)

Rank	Team	TP	FP	FN	F-measure	Recall	Precision
1	NEC	48	17	50	0.5890	0.49	0.74
2	Alberta	71	101	27	0.5259	0.72	0.41
3	LNM-IIT	49	81	49	0.4298	0.50	0.38
4	Okan-IRISA-LIAMA	33	54	65	0.3568	0.34	0.38

IIT: Institute of information technology, TP: True positives, FP: False positive, FN: False negative, NEC: NEC Corporation, LNM: Lakshmi niwas mittal, IRISA: Research Institute in Computer Science and Random Systems, LIAMA: French-Chinese Laboratory in Computer Science, Automatic Control and Applied Mathematics

thresholding and mathematical morphology.
- Blob segmentation with level-set or active contours.
- Computation of features on segmented blobs (radiometry, morphology, texture).
- Classification of candidate blobs as mitosis or non-mitosis object.

For Isik University team, the classifier used was adaboost classifier while for IPAL team, it was a decision tree. IPAL team also used a selection of color channels of different color models (RGB, hue-saturation-value (HSV), Lab, Luv) and computed the features on the selected channels.

NEC team is the only one team who applied their method on all the provided images (both scanners and the multispectral microscope). They used a CNN as classifier. Their method is efficient as they ranked high for both scanners, and first for the multispectral microscope.

Warwick team introduced a tumor segmentation to discard non-tumor areas from the images as these areas are full of lymphoid, inflammatory or apoptotic cells, which are not relevant for cancer grading. Hence mitosis detection is performed only on tumor areas. They made statistical modeling of mitotic cells from their grey level intensities. To match the distribution of grey level intensities of each class (mitotic cell/background), they used a Gamma distribution for mitotic cells and a Gaussian distribution for background.

Istituto Dalle Molle di Studi sull'Intelligenza Artificiale (IDSIA) team approach relies on a single step processing: The use of a CNN to compute a map of probabilities of mitosis over the whole image. Their CNN has been trained with the ground truth mitosis provided in the training data set. Their approach proved to be very efficient as they clearly had the best F-measure on scanner images, and a very low number of false positives as compared to their immediate competitors.

An improved version of this successful challenge will involve a much larger number of mitosis, images from more slides and multiple pathologists' collaborative/cooperative annotations. Besides, some slides will be dedicated to test only without any HPF of these slides included in the training data set.

CONCLUSION

Mitotic count is an important criterion in the grading of many types of cancers; however, very little research has been made on automatic mitotic cell detection, mainly because of a lack of available data. A main objective of this contest was to propose a database of mitotic cells on digitized breast cancer histopathology slides to initiate works on automated mitotic cell detection.

Up to 129 teams have registered to the contest and downloaded the training data set. In the end, 17 of them submitted their detection results on the evaluation data set. The performance of the best team is very promising, with F-measure as high as 0.78. However, the database we provided is by far too small for a good assessment of reliability and robustness of the proposed algorithms.

In the future, we would like to extend this database to have much more images from different patients and also for different types of cancers. In addition, mitotic cells should be annotated by several pathologists to reflect the partial agreement among them.

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REFERENCES

1. Elston C, Ellis I. Pathological pronostic factors in breast cancer. I. The value of histological grade in breast cancer: Experience from a large study with long-term follow-up. Histopathology 1997;28:135-40.
2. Gurcan MN, Boucheron LE, Can A, Madabhushi A, Rajpoot NM, Yener B. Histopathological image analysis: A review. IEEE Rev Biomed Eng 2009;2:147-71.
3. Beliën JA, Baak JP, van Diest PJ, van Ginkel AH. Counting mitoses by image processing in Feulgen stained breast cancer sections: The influence of resolution. Cytometry 1997;28:135-40.
4. Liu AA, Li K, Kanade T. A semi-Markov model for mitosis segmentation in time-lapse phase contrast microscopy image sequences of stem cell populations. IEEE Trans Med Imaging 2012;31:359-69.
5. Huh S, Ker DF, Bise R, Chen M, Kanade T. Automated mitosis detection of stem cell populations in phase-contrast microscopy images. IEEE Trans Med Imaging 2011;30:586-96.
6. Schlachter M, Reisert M, Herz C, Schlürmann F, Lassmann S, Werner M, *et al*. Harmonic filters for 3D multichannel data: Rotation invariant detection of mitoses in colorectal cancer. IEEE Trans Med Imaging 2010;29:1485-95.
7. Roullier V, Lézoray O, Ta VT, Elmoataz A. Multi-resolution graph-based analysis of histopathological whole slide images: Application to mitotic cell

extraction and visualization. Comput Med Imaging Graph 2011;35:603-15.
8. Malon C, Miller M, Burger HC, Cosatto E, Graf HP. Identifying histological elements with convolutional neural networks. Proceedings of the International Conference on Soft Computing as Transdisciplinary Science and Technology; 2008 Oct. Cergy-Pontoise, France.
9. Sertel O, Catalyurek UV, Shimada H, Gurcan MN. Computer-aided prognosis of neuroblastoma: Detection of mitosis and karyorrhexis cells in digitized histological images. Conf Proc IEEE Eng Med Biol Soc 2009;2009:1433-6.
10. Meyer JS, Alvarez C, Milikowski C, Olson N, Russo I, Russo J, *et al*. Breast carcinoma malignancy grading by Bloom-Richardson system vs proliferation index: Reproducibility of grade and advantages of proliferation index. Mod Pathol 2005;18:1067-78.
11. Malon C, Brachtel E, Cosatto E, Graf HP, Kurata A, Kuroda M, *et al*. Mitotic figure recognition: Agreement among pathologists and computerized detector. Anal Cell Pathol (Amst) 2012;35:97-100.