MITOS & ATYPIA
Detection of Mitosis and Evaluation of Nuclear Atypia Score in Breast Cancer Histological Images

An ICPR 2014 Contest

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2 General Description of the Problem

Breast cancer is a major cause of death in the world. According to figures published by the International Agency for Research on Cancer in their GLOBOCAN 2012 estimated cancer incidence, mortality and prevalence worldwide in 2012[1], the three most common cancers in the world were lung (1.825 million cases for both sexes, 583.000 cases for women only), breast (1.677 million cases) and colorectal (1.361 million cases for both sexes, 614.000 cases for women only). For women, breast cancer is by far the most frequent cancer worldwide.

To diagnose breast cancer, samples of tissue are removed from breast. From these samples, histology slides are produced. These slides are stained generally with hematoxylin and eosin (H&E). Pathologists analyse breast biopsy slides and give them a grade according to one of two international grading systems:

- The Scarff, Bloom and Richardson grading system.
- The Elston and Ellis grading system [1]. This grading system is a modification of the Scarff, Bloom and Richardson grading system. It is also known as the Nottingham grading system.

The Elston and Ellis grading system is recommended by the World Health Organization [2]. It is derived from the assessment of three morphological features: tubule formation, nuclear pleomorphism and mitotic count. Here is how Elston and Ellis describe mitotic counts [1]:

[1] `http://globocan.iarc.fr/`

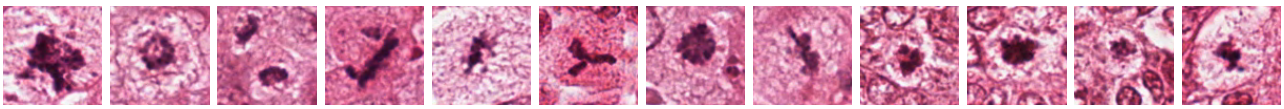


Figure 1: Examples of mitosis.

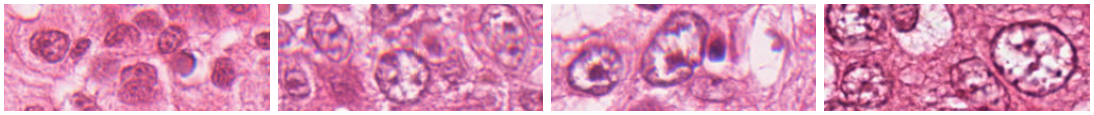


Figure 2: Examples of various degrees of nuclear atypia.

> *"Mitotic activity is best assessed at the periphery of the tumour where active growth is most likely. A minimum of 10 consecutive fields is assessed. Strict criteria for the identification of mitotic figures must be employed, and only nuclei in which clear morphological feature of metaphase, anaphase and telophase are counted. Hyperchromatic[2] and apoptotic[3] nuclei are ignored and care is taken to avoid mistaking lymphocytes within a tumour for mitoses."*

In the same article [1], they describe nuclear pleomorphism as follows:

> *"In this feature both a quantitative and a qualitative judgement is made. When the nuclei are small, with little increase in size in comparison with normal breast epithelial cells, have regular outlines and uniformity of nuclear chromatin and vary little in size, 1 point is appropriate. A score of 2 points is given when the cells appear larger than normal, have open, vesicular nuclei with visible nucleoli, and there is moderate variability in both size and shape. A marked variation is size and shape, especially when large and bizarre nuclei are present, scores 3 points. In this group nuclei are vesicular with prominent, often multiple nucleoli."*

Several studies on automatic tools to process digitized slides have been reported focusing mainly on nuclei or tubule detection. Studies and tools for automatic detection of mitosis on H&E stained biopsies have started to be proposed recently through the availability of datasets proposed during the MITOS contest[4] at ICPR 2012 and the AMIDA13 contest[5] at MICCAI 2013. The novelty of MITOS & ATYPIA 2014 contest is that the opinions of two pathologists (or three in case of disagreement) are given in the dataset, providing to contestants some additional clues about objects that are clearly mitosis (agreement between pathologists) and those that are not so easy to identify (disagreement between pathologists).

Mitotic count is an important parameter in breast cancer grading as it gives an evaluation of the agressiveness of the tumour. Detection of mitosis is a very challenging task since they have a very large variety of shapes (see Figure 1). A mitosis comes through four main phases: prophase, metaphase, anaphase and telophase. The shape of the nucleus is very different depending on the phase of the mitosis. On its last stage, the telophase, a mitotic cell has two distinct nuclei, but they are not yet full individual cells. A mitosis in telophase must be counted as a single mitosis, it should not be miscounted as two mitosis.

A second novelty of MITOS & ATYPIA contest is the introduction of nuclear pleomorphism (or nuclear atypia) scoring, covering a second important criteria necessary for breast cancer grading. Nuclear pleomorphism gives an indication about the stage of evolution of the cancer. Nuclear atypia score is a value, 1, 2 or 3, corresponding to a low, moderate or strong nuclear atpyia respectively. See Figure 2 for a glimpse of nuclear atypia.

The objectives of the contest are therefore twofold:

- to detect mitosis on H&E stained biopsies;
- and to evaluate the score of nuclear atypia.

The contestants are free to work on a single objective or on both of them.

[2] A hyperchromatic nucleus has elevated chromatin, that is there is an abundance of DNA that stains darkly when stained for histological viewing.

[3] Apoptosis is the process of programmed cell death. A cell undergoing apoptosis shows a characteristic morphology, including cell shrinkage and rounding, and chromatin undergoes condensation into compact patches.

[4] `http://ipal.cnrs.fr/ICPR2012/`

[5] `http://amida13.isi.uu.nl/`

3 Dataset

The team of Professor Frédérique Capron, head of the Pathology Department at Pitié-Salpêtrière Hospital in Paris, France, has selected and annotated a set of breast cancer biopsy slides for this contest. The slides are stained with standard H&E dyes and they have been scanned by two slide scanners: Aperio Scanscope XT and Hamamatsu Nanozoomer 2.0-HT.

In each slide, the pathologists selected several frames at ×10 magnification. Each ×10 frame is subdivided into four frames at ×20 magnification. Each ×20 frame is also subdivided into four frames at ×40 magnification (see Figure 3). Information about resolution of both scanners and size of the frames is given in Table 1.

Scanner Aperio has a resolution of 0.2455 μm per pixel. Scanner Hamamatsu has a slightly better resolution of 0.227299 μm (horizontal) and 0.227531 μm (vertical) per pixel, so a pixel of scanner Hamamatsu is not exactly a square. Table 1 shows the resolutions of the two scanners. For example, a mitosis having an area of 30 μm^2 will cover about 500 pixels of the image produced by scanner Aperio and about 580 pixels of the image produced by scanner Hamamatsu.

Scanner	Aperio Scanscope XT	Hamamatsu Nanozoomer 2.0-HT
Resolution at ×40	0.2455 μm per pixel	0.227299 μm per pixel (horizontal) 0.227531 μm per pixel (vertical)
Dimensions of a ×20 frame	1539 × 1376 pixels 755.649 × 675.616 μm^2	1663 × 1485 pixels 755.9965 × 675.7671 μm^2
Dimensions of a ×40 frame	1539 × 1376 pixels 377.8245 × 337.808 μm^2	1663 × 1485 pixels 377.9982 × 337.8835 μm^2

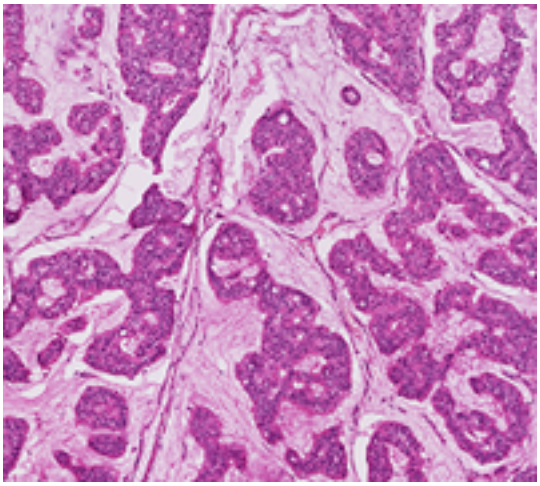
Table 1: Resolution of both scanners and dimensions of frames.

3.1 File Naming and Slide Directory Organisation

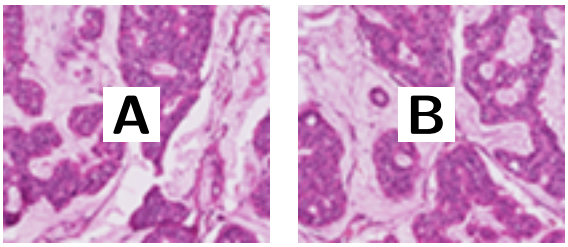
Files of scanner Aperio are prefixed by capital letter A, and files of scanner Hamamatsu are prefixed by capital letter H. Frames are identified hierarchically according to their magnification level as shown in Figure 3.

For each slide, several files are provided. For example, for slide H03, the list of files and subdirectories is as follows:

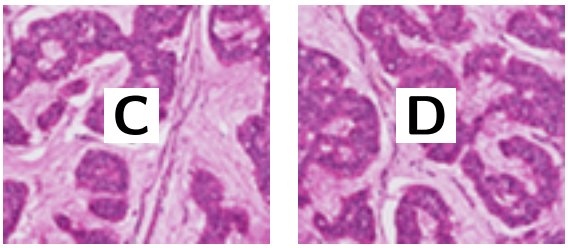
```
H03
├── H03.txt ..... Resolution of the scanner, number of mitosis and number of frames
├── atypia
│   ├── x20
│   │   ├── H03_00A_cna_score_all.csv ..... List of scores given the the two or three pathologists for frame 00A
│   │   ├── H03_00A_cna_score_decision.csv ..... Score selected for frame 00A (majority of scores given by pathologists)
│   │   ├── H03_00B_cna_score_all.csv ..... List of scores given the the two or three pathologists for frame 00B
│   │   ├── H03_00B_cna_score_decision.csv ..... Score selected for frame 00B (majority of scores given by pathologists)
│   │   └── ...
│   └── x40
│       ├── H03_00Aa_cna_criteria.csv. List of values given by three pathologists to the 6 atypia criteria for frame 00Aa
│       ├── H03_00Ab_cna_criteria.csv. List of values given by three pathologists to the 6 atypia criteria for frame 00Aa
│       └── ...
└── frames
    ├── x10
    │   ├── H03_00.tiff ..... Image file of frame 00
    │   ├── H03_01.tiff ..... Image file of frame 01
    │   └── ...
    ├── x20
    │   ├── H03_00A.tiff ..... Image file of frame 00A
    │   ├── H03_00B.tiff ..... Image file of frame 00A
    │   └── ...
    └── x40
        ├── H03_00Aa.tiff ..... Image file of frame 00Aa
```



Frame at ×10 magnification: `H11_01`

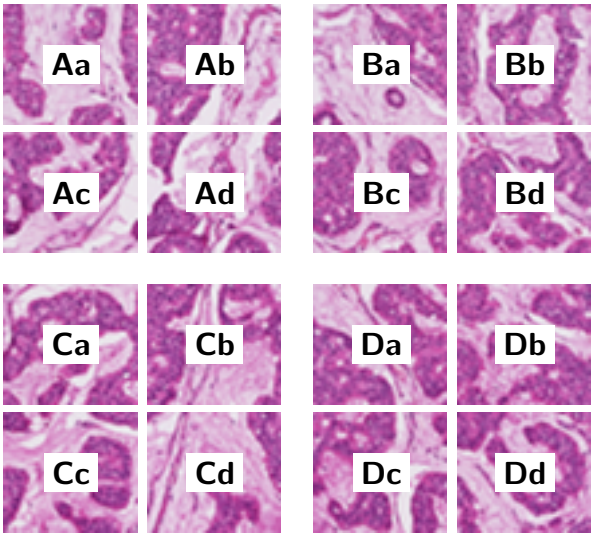


4 frames at ×20 magnification:
`H11_01A`, `H11_01B`, `H11_01C`, `H11_01D`



Information available at ×20 magnification:

- Score of nuclear atypia



16 frames at ×40 magnification:
`H11_01Aa`, `H11_01Ab`, `H11_01Ac`, `H11_01Ad`
`H11_01Ba`, `H11_01Bb`, `H11_01Bc`, `H11_01Bd`
`H11_01Ca`, `H11_01Cb`, `H11_01Cc`, `H11_01Cd`
`H11_01Da`, `H11_01Db`, `H11_01Dc`, `H11_01Dd`

Information available at ×40 magnification:

- Values for the 6 criteria related to nuclear atypia
- Location of mitosis and NOT mitosis

Figure 3: Hierarchical organisation and naming of frames at different magnification levels.

Size of nuclei	1	0 to 30% of tumour nuclei are bigger than normal nuclei
	2	30 to 60% of tumour nuclei are bigger than normal nuclei
	3	more than 60% of tumour nuclei are bigger than normal nuclei
Size of nucleoli	1	0 to 30% of tumour cells have nucleoli size bigger than nucleoli of normal cells
	2	30 to 60% of tumour cells have nucleoli size bigger than nucleoli of normal cells
	3	more than 60% of tumour cells have nucleoli size bigger than nucleoli of normal cells
Density of chromatin	1	0 to 30% of tumour cells have chromatin density higher than normal cells
	2	30 to 60% of tumour cells have chromatin density higher than normal cells
	3	more than 60% of tumour cells have chromatin density higher than normal cells
Thickness of nuclear membrane	1	0 to 30% of tumour cells have nuclear membrane thickness higher than normal cells
	2	30 to 60% of tumour cells have nuclear membrane thickness higher than normal cells
	3	more than 60% of tumour cells have nuclear membrane thickness higher than normal cells
Regularity of nuclear contour	1	0 to 30% of tumour cells have nuclear contour more irregular than normal cells
	2	30 to 60% of tumour cells have nuclear contour more irregular than normal cells
	3	more than 60% of tumour cells have nuclear contour more irregular than normal cells
Anisonucleosis (size variation within a population of nuclei)	1	within the population of tumour cells, all nuclei are regular and/or nuclei size is not bigger than twice the size of normal epithelial cell nuclei
	2	for cases that are not fitting neither with case 1 nor with case 3
	3	within the population of tumour cells, either nuclei size are irregular or nuclei size is bigger than 3 times the size of normal epithelial cell nuclei

Table 2: The six criteria to evaluate nuclear atypia

```
    ├── H03_00Ab.tiff ..... Image file of frame 00Ab
    └── ...
└── mitosis
    ├── H03_00Aa_mitosis.csv ..... List of true mitosis annotated in frame 00Aa
    ├── H03_00Aa_mitosis.jpg ..... Image file showing location of true mitosis on frame 00Aa
    ├── H03_00Aa_not_mitosis.csv ..... List of objects similar to mitosis but that are NOT mitosis in frame 00Aa
    └── H03_00Aa_not_mitosis.jpg ..... Image file showing location of NOT mitosis on frame 00Aa
```

3.2 Training Dataset for Nuclear Atypia

Score for nuclear atypia requires a wide area to be able to evaluate shape and size of a large population of nuclei. For this task, the pathologists have worked at $\times 20$ magnification. The score is given by two experienced senior pathologists. When pathologists disagree about the score to be given to a frame, the opinion of a third pathologist has been requested. In that case, the final score for this frame is the score having the majority among the three pathologists.

In the dataset, two files are provided for each frame ($\times 20$ magnification):

- `XXX_cna_score_all.csv`: list of the scores given by the two (or three) pathologists for frame XXX
- `XXX_cna_score_decision.csv`: final score decided for frame XXX (this score is the majority of the different scores given by the pathologists for this frame)

If the frame does not contain enough relevant nuclei, the pathologists did not provide a score for the frame. In that case, both CSV files related to this frame are empty.

In addition to the score, six criteria related to nuclear atypia are provided. The six criteria have been given by three pathologists as a number 1, 2 or 3. The list of six criteria together with the signification of values 1, 2 and 3 for each criterion are given in table 2. As these criteria require a detailed analysis of the nuclei shape and size, they are given at $\times 40$ magnification. The values given by the three pathologists for the six criteria for frame XXX can be found in file `XXX_cna_criteria.csv`

Please take note that these six criteria are provided only as hints for nuclear atypia scoring. You are free to use one, several or none of them for scoring nuclear atypia. You may also design you own personal criteria.

3.3 Training Dataset for Mitosis

The mitosis have been annotated by two pathologists using three possible values:

Pathologists Opinions	Class of Object	Confidence Degree
all “mitosis”	true mitosis	1.0
majority of “mitosis”	true mitosis	0.8
all “probably a mitosis” or majority of “probably a mitosis”	true mitosis	0.65
majority of “not a mitosis”	NOT mitosis	0.2
all “not a mitosis”	NOT mitosis	0.0

Table 3: The confidence degree given to mitosis and NOT mitosis

- true mitosis
- probably a mitosis
- not a mitosis

In case the pathologists disagree, a third expert pathologist have been requested to give his opinion using the same convention (true mitosis, probably a mitosis, not a mitosis). The annotated objects have then been put in two separate classes:

- class mitosis for objects having a majority of votes as “mitosis” or “probably a mitosis” (file `XXX_mitosis,csv`)
- class NOT mitosis for objects having a majority of votes as “not a mitosis” (file `XXX_not_mitosis,csv`)

Each frame at $\times 40$ magnification comes with two ground truth text files (CSV type), which indicate the approximative center of each single mitosis or NOT mitosis. Organisation of a coordinates CSV text file (see Figure 4):

- the file has no header
- one line gives the approximative center of a mitosis (respectively NOT mitosis) in this order: x location, y location (the origin of the image is its top left corner (coordinates 0,0))
- the coordinates of the center are followed by a confidence degree (the confidence degree reflects the majority of the opinions (see Table 3)

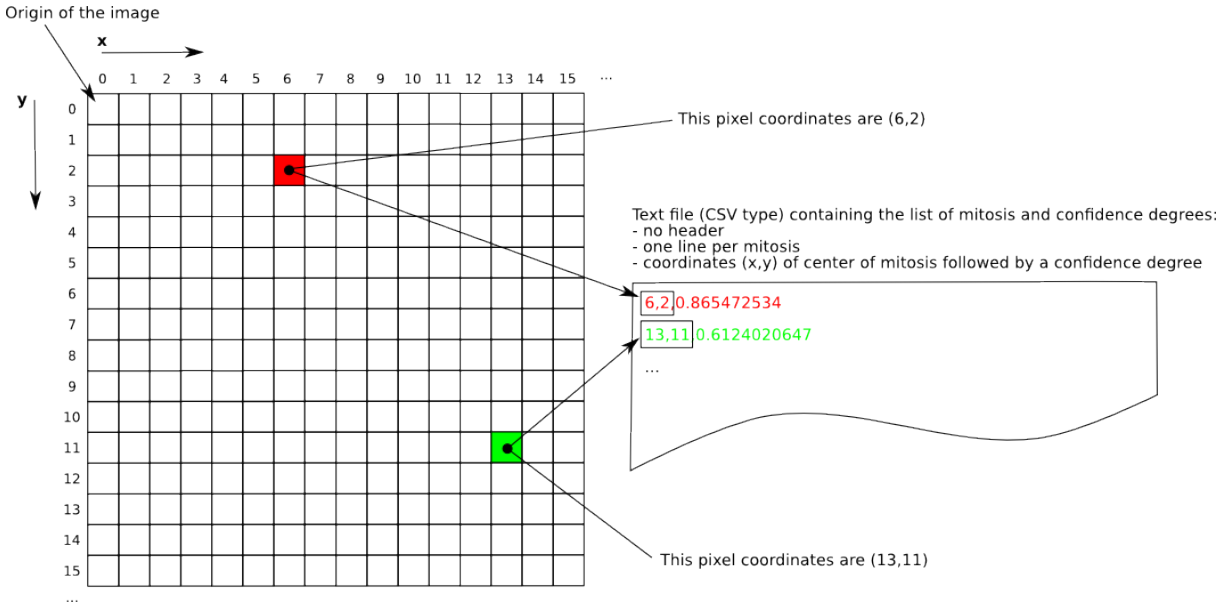


Figure 4: Organisation of a text file containing the list of mitosis located in a frame.

4 Description of the Competition Tasks

For nuclear atypia, the competition consists in giving the correct score for frames at $\times 20$ magnification. The result scores should be written in a separate text file (CSV type) for each input frame.

For mitosis, the competition consists in giving the location of all mitosis on frames at $\times 40$ magnification. The coordinates of the center of each detected mitosis together with a confidence degree should be written in a text file (CSV type), one line per mitosis and one file per input frame. The origin point of an image is at the top left corner of the image (see Figure 4).

5 Evaluation Metrics

The contestants have to provide their results (scores for nuclear atypia or list of detected mitosis with their confidence degree) in the same format as the training data, that is one CSV text file for each frame at $\times 20$ magnification for nuclear atypia and one CSV text file for each frame at $\times 40$ magnification for mitosis (CSV text file format for mitosis must be as described in Figure 4).

5.1 Evaluation Metric for Nuclear Atypia

Only the nuclear pleomorphism score for frames at $\times 20$ magnification will be considered (this score is given in files `XXX_cna_score_decision.csv`).

- Score identical to ground truth score will give one point.
- Score different by one unit from ground truth score will give zero point. Example: proposed score is 1 but ground truth score is 2.
- Score different by two units from ground truth score will give a negative point of -1. Example: proposed score is 1 but ground truth score is 3.

The contestants will be ranked according to the sum of their points, biggest number being ranked first.

5.2 Evaluation Metrics for Mitosis

A detected mitosis would be counted as correct if its centre point is localised within a range of 8 μm of the centre point of a ground truth mitosis (true mitosis are listed in files `XXX_mitosis.csv`).

- D = number of detected mitosis.
- `TP` = number of True Positives, that is the number of mitosis that are ground truth mitosis among the D detected mitosis
- `FP` = number of False Positives, that is the number of mitosis that are not ground truth mitosis among the D detected mitosis
- `FN` = number of False Negatives, that is the number of ground truth mitosis that have not been detected
- recall (sensitivity) = $\frac{\texttt{TP}}{\texttt{TP}+\texttt{FN}}$
- precision (positive predictive value) = $\frac{\texttt{TP}}{\texttt{TP}+\texttt{FP}}$
- F-measure = $2 \times \frac{\text{precision} \times \text{recall}}{\text{precision} + \text{recall}}$

The contestants will be ranked according to the F-measure, highest F-measure being ranked first.

Acknowledgement

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References

[1] C.W. Elston and I.O. Ellis. 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*, 19:403–410, 1991.

[2] Fattaneh A. Tavassoli and Peter Devilee, editors. *Tumours of the Breast and Female Genital Organs*. World Health Organization Classification of Tumours. Pathology & Genetics. International Agency for Research on Cancer, September 2003.