International Research Journal of Engineering and Technology (IRJET) e-ISSN: 2395 -0056
Volume: 04 Issue: 01 | Jan -2017 www.irjet.net p-ISSN: 2395-0072

MitoGame: Gamification Method for Detecting Mitosis from Histopathological Images Using Crowdsourcing

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Abstract - *Learning from crowds using Gamification is a novel concept in medical Imaging. Convolution Neural Network can be designed to handle learning from crowds, using additional crowdsourcing layer. In biomedical context, ground truth labeling from non-expert crowd is generated using deep learning. Even though crowdsourcing is used for annotating a large number of online images, their feasibility for application in medical imaging context requires a deep knowledge. Hence Gamification task for detecting breast cancer requires correct instruction and Guidelines for the crowds. Noisy annotations can occur when an expert task like annotating mitosis detection are outsourced to non_expert users like crowds. Gamification in histopathological images is proposed so that complex tasks in biomedical domain in to a game for non experts . Further, analysis of the results from crowd and CNN shows that crowds do not underperform than medical experts.*

Key Words: **Gamification, Crowdsourcing, Mitosis Detection, Histopathological Images, CNN, Deep Learning.**

1.INTRODUCTION

Crowdsourcing is a type of participative online activity in which an individual, an institution, a non-profit organization or a company proposes to a group of individuals of varying knowledge, heterogeneity, and number, via flexible open call, the voluntary undertaking of a task [1]. The definition was made clear by Jeff Howe and Mark Robinson [2]. When new crowdsourcing frameworks were introduced recently IBM, Google and Microsoft are now focusing towards semi-automated computing for gathering ground-truth annotation data on images as well as videos in the medical domain. Recently, Celi et al. [3] conducted challenges, where pathologists, data scientists, and medical universities were invited to address specific tasks . As a part of this competition many new ideas and simulations are introduced.

Deep Learning is a branch of Machine Learning based on a set of algorithms that attempt to model high level abstraction in data by using a deep graph with multiple processing layers , composed of multiple linear and non linear transformation. Widely used algorithm of deep learning in Image context are Convolutional Neural Networks , Since it explicitly implies that input is an image . CNN implementation provides higher accuracy in medical imaging [4]. The problem arises when the accuracy is obtained only when there are large number of training dataset. Since medical images are highly confidential and they are not available to public,obtaining data set has found to be difficult. Hence crowdsourcing platforms will helps the crowd to join with the pathologist and developers for converting problems to new prototype that can be implemented.

1.1 Gamification

Gamification is the application of game design elements and game principles in non-game context. Crowdsourcing methodologies leveraging the contributions of citizen scientists connected via the Internet have recently proved to be of great value to solve certain scientific challenges involving big data analysis that cannot be entirely automated[5]. For example, Fold-It is an online game where players should solve puzzles that are in 3D by folding protein structures. This method should motivate the user to play using attractive graphics. Recent studies shows that 3 billion hours per week are spent by playing games around the globe.

1.2. Breast Cancer Grading

This grading system takes into consideration three important factors which are [6].

- The amount of glandular structure: A score is given to evaluate the level gland structured according to the criteria shown below the amount of Glandular structure: Score 1: 10 percent of tumour area forming glandular structure. Score 2: 10 to 75 percent of tumour area forming glandular structure. Score 3: 75 percent of tumour area forming glandular structure .

- The nuclear pleomorphism index: Nuclear features are measures of the difference in size and shape of nuclei in the tumour cells as compared to normal cells.

- The mitotic index: The pathologist counts how many mitotic cells are seen in 10 High Power Fields (or HPFs, which are regions of interest of the tissue slide examined at high magnification, typically at 40) [7] and score them according to the rules shown below:

Amount of Mitosis:
Score 1 : Upto 7 mitoses per 10 high power fields.
Score 2 : 8-14 mitoses per 10 high power fields.
Score 3 : 15 or more mitoses per 10 high power fields.

Aggressiveness Grade 1 if S is between 3 and 5.
Aggressiveness Grade 2 if S is between 6 and 7.
Aggressiveness Grade 3 if S is between 8 and 9.

In general, each factor is given a score of 1 to 3 (1 being the best and 3 being the worst) and the lowest possible S score (1+1+1=3) represents a well differentiated tumor with well-formed tubules and a low mitotic rate. The highest possible score for S is 9 (3+3+3=9), which indicates a poorly differentiated, high grade tumor. Finally, a group of researchers has also shown that the mitotic rate alone can be as predictive as the three factors combined [8]

2.RELATED WORKS

Mitosis detection is an important area of research, when implementing with Crowdsourcing in a medical domain, only a few literature is available. The related existing methods are discussed below: Malaria Parasite Quantification: An Online Game for Analyzing Images of Infected Thick Blood Smears [9]. This examines an inexperienced player can count count malaria parasites in digitized images of thick blood smears by playing a Web-based game. The experimental system consisted of a Web-based game where online users were given a task for detecting parasites in digitized blood sample images coupled with a decision algorithm that combined the analyses from several players to produce an improved collective detection outcome.

A crowdsourcing implementation with CNN is discussed next. AggNet: Deep Learning From Crowds for Mitosis Detection in Breast Cancer Histology Images [10]. An additional layer in CNN is introduced so that learning from crowd can be implemented. It is a semi automatic system since external help of pathologist is required. An automated method for detecting breast cancer is, Mitosis Detection for Invasive Breast cancer grading in Histopathological Images [11] ,In this paper they extract the red channel Image for preprocessing and then region based segmentation is done. Random forest classifier is used for detecting mitotic and non mitotic cells.

3.METHODOLOGY

CNN is used for aggregating annotations from Gamification in conjunction with learning a model for a challenging classification task. Unlike typical supervised methods, which learn a model from ground truth labeled data, learning from crowd annotations is different in the sense that there may be (possibly noisy) multiple labels for the same sample. The idea is to learn multiple CNN models with the same basic architecture on different image scales , perform mitosis detection using these models and provide the crowds with detected mitosis candidates for annotation . The collected annotations are then passed to the existing CNN to review the models and simultaneously generate a ground-truth. This multi-scale approach ensures that we have redundant responses of the same data instances at different scales, with the goal to increase robustness of both aggregation and classification.

- TRAINING
  Unlabeled data (Histological images) from pathology department is given to pathologist. It is a one time process. Gold standard annotations: Annotations are done by two experts and screened by two observers. Ground truth data is generated using CNN.

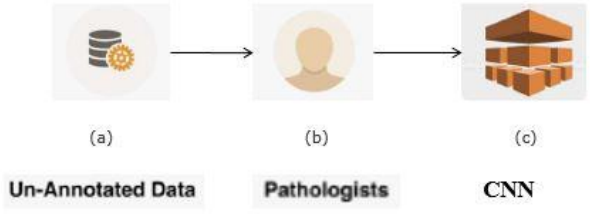

Fig -1: CNN trained from gold standard annotation

- TESTING
  Unlabeled data from pathology department is given to crowd. Crowdsourcing is implemented using Gamification. Crowd votes are collected and compared with the Ground truth .

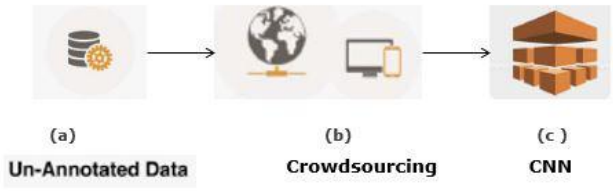

Fig -2: Testing with Gamification

3.1 Game Architecture

Crowds are the players who are supposed to annotate the mitosis based on the instructions given. On the participant side, each user was introduced in brief about the disease and the instructions of the actual task showing some good and bad examples .Then, participants had to conduct a few test questions for quality control purposes. Without being made aware of the quiz mode, each annotator was presented with patches with known labels. Only then, he/she started to annotate the patches presented along with the lterated images. In order to ensure continuous quality control, a few randomly seeded test patches were still shown during the actual annotation .

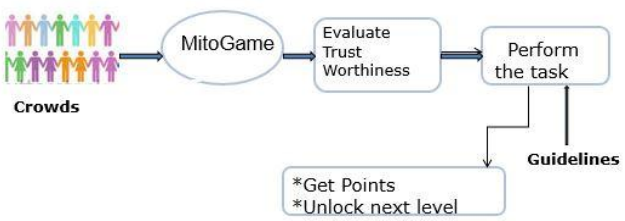

Fig -3: Architecture diagram of MitoGame

• Input for the game is the preprocessed and patched RGB image.

• Before performing actual task trustworthiness T of the user is evaluated .

$$T = \frac{\text{No of correct samples done by the user}}{\text{Total number of annotated samples}}$$

• Introduction about the disease and instructions for performing actual task is given.

• In addition to this, Good and Bad Examples are also provided with Tips They are given before performing the tasks:

Example: -Mitotic figures look more irregular than non-mitotic cells -Mitotic cells are darker than non-mitotic cells -In blue ratio representation, mitotic figures have very bright spots Fig 4,5

3.2 Description of Features

Intensity feature of histological images are considered for the detection of mitosis. It is based on the fact that, at the starting of mitosis, the chromosomes condenses. Even though the shape of nuclei varies, intensity consistency remains the same throughout the all four phases of mitosis. The player can easily distinguish between mitotic cell and non-mitotic cell based on intensity. Examples:

• Mitotic Cells (fig-4) : First row shows the histological image of mitotic cells .Second row shows the corresponding preprocessed image ie blue-ratio representation with bright spots .

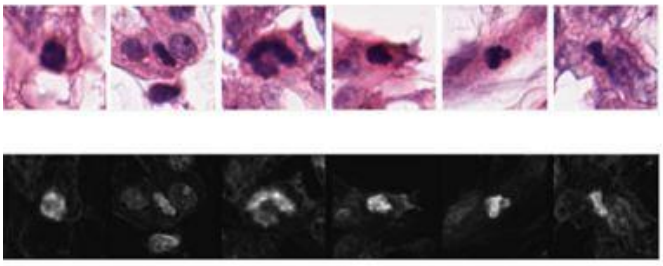

Fig -4: Mitotic cell (Good Example)

• Non-Mitotic Cells (fig-5) : First row shows the histological image of non-mitotic cells. Second row shows the corresponding preprocessed image that is, blue-ratio representation. They have less bright spots compared to mitotic figure.

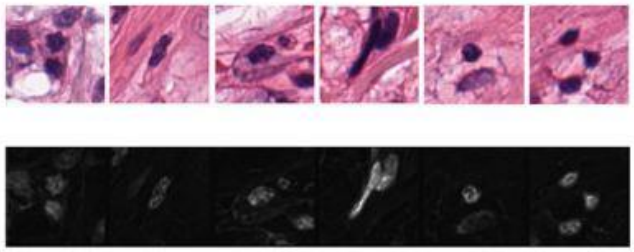

Fig -5: Non-Mitotic cell (Bad Example)

3.3 Dataset

Proposed methodology can be implemented on a publicly available MICCAI AMIDA13 challenge dataset. It contains annotated histology images of a many patients, who have gone through biopsy for detecting breast cancer. AMIDA13 dataset is very trustworthy since the annotation was done by two pathologist. Similar annotations are taken as ground truth where as dissimilar ones are given to another observers for annotation.

3.4 Implementation Requirements

Neural Network: CNN can be implemented in MATLAB with ConvNet, for this we requires,Parallel Computing Toolbox and a CUDA-enabled NVIDIA GPU with compute capability 3.0 or higher. Network parameters like learning rate can be set to 0.001, for dataset7 in CNN,this can be changed during training process for different dataset.

Image Processing : Preprocessing is done by staining appearance normalization[12]. Images are patched. Blue ratio is extracted for providing it to the user. Classification is done by the player. Then the performance between result from player and ground truth can be done .

Crowdsourcing: Gamification implemented with the help of crowdsourcing. A crowdsourcing platform called crowdflower can be used, but its limitation leads to the use of Annot8 world wide. In this the user can create and upload images as well as whole datasets. After tagging images from Annot8, it is easy to transfer annotated dataset to crowdflower.

4. CONCLUSIONS

MitoGame is proposed to classify mitotic and non mitotic cells using Crowdsourcing.. In this methodology, trustworthiness measure can be calculated as an accuracy score that each player should possess for qualifying. Raykar et al. [13] recommend such score for calculating the sensitivity and specific nature of the crowd. The user who annotate less sample is more trusted that a person who wrongly annotate large number of images. Gamification methodology can also handle missing Labels. When users fails to annotate certain samples parameters in [13] remains unknown.In future this can be implemented as an mobile game and results can be submitted in one of the relevant medical imaging challenges.

ACKNOWLEDGEMENT

We would like to thank our Principal Dr. Sudha Venugopal, Head of the Department,Prof. Sunitha C ,our co-ordinator Asst. Prof. Beena M.V and my guide Asst. Prof Nitha KP for their valuable advice and technical assistance.

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BIOGRAPHIES

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