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Phase classification of mitotic events using selective dictionary learning for stem cell populations☆

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ABSTRACT

Nowadays, thanks to the use of advanced technological tools, stem cell studies which play an important role in regenerative medicine and cancer studies have increased considerably. In this study, selective dictionary learning method is presented for detecting mitotic event phases in stem cells using phase contrast time-lapse microscopy images. In the proposed method, three phases are defined for representation of mitotic events. Creating a dictionary that represents these phases with a single feature space restricts the success. For this reason, three dictionaries with different features are created. Although the multiplication of image alpha values with all generated dictionaries is quite suitable for determining the lowest error value, this process is time consuming. For this reason, a selective dictionary approach based on the automatic selection of the best values with a cooperation between the dictionaries has been proposed. In this way, the high success rate is maintained and the processing time is significantly reduced. The proposed method gives better results than other state-of-art studies in terms of computational efficiency and accuracy in experiments with C2C12 and BAEC datasets.

1. Introduction

Stem cells are divided cells that are found in multicellular organisms and play important roles in the repair of the body, the healing of wounds and the growth. Also, they play an important role in the treatment of some diseases such as heart diseases, tissue regeneration, and cancer. Many scientists from different fields have carried out studies on this issue. These studies are of great importance for the protection and improvement of human health and for the pharmaceutical sector. However, many of the methods are detrimental to cell and cell tissue. For this reason, cell behavior cannot be fully assessed. Experiments performed in the laboratory require more effective and reliable results in order to produce the same effect under real conditions [1]. For this reason, the cells should not be exposed to external factors in the laboratory environment. Light microscopes are a non-destructive examination method that does not involve the above-mentioned destructive factors used to monitor and analyze cell populations. The use of these instruments in studying cell movements and division behaviors has been useful for cell research. Moreover, it is useful for continuous monitoring of cell samples and for the capture of image samples. However, images taken with microscopes have large dimensions and complicated texture. For this reason, the evaluation of these images takes a long time and expert knowledge is required. In addition, the interpretation of these

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images depends on the experience of the expert and is subjective. In most cases, the same images are interpreted differently by different experts. Automated and reliable results should be obtained using computerized techniques to overcome this confusion. Computer aided diagnosis (CAD) techniques are used to make more objective assessments [2]. These systems usually consist of three basic parts: image segmentation, feature extraction and classification [3]. In complex applications such as breast cancer [4], bone metastasis [5], liver tumors [6], colonoscopy [7], lung cancer [8], CAD systems are preferred because of their ability to make decisions faster and to be able to make objective assessments.

Time-lapse phase contrast microscopy is currently used for monitoring cell populations [9]. Images obtained with phase contrast microscopy have high resolution. So, it is very difficult for standard image processing algorithms to deal with these images. It is difficult to separate the cells and background parts from each other in these images, due to shade-off effects. Also, the sudden change in brightness value that occurs in the pixels around some cells creates complexity. Since these effects inhibit the desired success when examined by traditional methods, several approaches to detect and track mitotic events have been proposed in the literature. These methods are divided into three categories that are namely tracking-based, tracking-free and hybrid methods according to cell behavior [10]. When examined according to image characteristics, they are divided into two categories as spatial feature based and sequential feature based methods [11]. Tracking based techniques examine the sequential variations of cells in time-lapse images. This approach examines the cell properties of each scene in the time-lapse images and observes the movements of mother and daughter cells in the time-lapse image sequences. Some successful tracking-based methods are; the mean-shift based tracking method [12], multi-grained random fields [13], and using convolutional neural networks [14]. Tracking-free techniques use a single image to detect mitotic events without using sequential images. Hybrid methods aim to overcome many problems by using various image processing methods such as feature extraction, preprocessing, classification by looking at a wider scale. In these methods, information can be obtained from a single image or sequential images according to the behavior of the algorithm [1,15]. In a spatial-feature based approach, spatial features within a single image are examined [16]. In sequential-feature based methods, an examination is carried out depending on the change of features in sequential images [17]. Both algorithms show similarity when considering the classification methods of mitosis detection algorithms. Sequential approaches and tracking based approaches are similar, and spatial approaches and tracking free approaches are similar. In order to evaluate the success rates and problems of mitosis studies, it may be more understandable to examine important studies in the literature one by one. Liu et al. [10] proposed a semi-Markov model for the detection of image patches containing mitosis. In this study, the mitotic division is examined with respect to four separate frames and a three-step image analysis algorithm is proposed. Finally, manually-segmented images are used for the semi-Markov model. Zhang et al. [18] used the circle scanning algorithm to detect round objects in images. However, the cell shapes are not round in the later stages of mitosis division. In the method proposed by Nie et al. [14], auto-learned features are used instead of handcrafted features. In this method, the use of suitable images for network training is very effective. Huh et al. [1] proposed a study on the capture of mitotic events from sequential image patches with conditional random field algorithm. In this study, mitosis candidate cells are determined and birth events are detected by extracting their characteristics. Xie et al. [19] conducted a study using convolutional regression networks and used synthetic data in the training process. During the test, both synthetic and biologic data were used. But, the noise ratio of real images is higher than the synthetic data. Wan et al. [20] examined wavelet-based non-Gaussian modeling method for the mitotic division of breast cancer. Liu et al. [13] proposed a multi-grained random field model to overcome the hidden state constraint in the mitotic sequential structure model. Hao et al [21] proposed an adaptive support vector machine. Farina et al. [22] used FPGA to classify cells. They used DCT and neural networks.

Mitosis is the division of a cell into two identical cells for renewal of worn-out cells. It usually provides the fulfillment of body functions such as growth, wound healing etc. Many mitotic event detection algorithms are influenced by the background characteristics and morphological features of the cells are being investigated. Even though the use of morphological features is a very simple method, the ever-changing cell stages reduce the success of these approaches. Euclidean distance, which is the source of inspiration for many daughter cell detection studies in the beginning, cannot detect a large number of mitosis events, although it seems quite logical. In the methods in which the hand-crafted features are used, expertise is required to determine appropriate features. Extracted features are very influential on the success of the method. Models produced with synthetic data cannot achieve the expected success in real images.

In this paper, a dictionary learning model that automatically detects mitotic phases for time-lapse phase contrast microscopy images is presented. The proposed method is a fast and effective method which the finding of three mitosis phases and to find a selective dictionary by using the most successful class components. The proposed method is based on the training of three dictionaries and the use of the most successful class components. Each dictionary can identify one phase with high success. Other dictionaries are used for detection of other phases. According to this approach, there are three classes in each dictionary, and in each dictionary only one class of success is the foreground, but they can detect other phases. Thanks to this feature, a selective dictionary structure has been introduced. The selective dictionary structure creates a single matrix for each class using atoms representing the same class in different dictionaries. Atom selection operation is done using the smallest reconstruction error for this operation. Classification success is increasing, because the most successful atoms for each class are selected by interclass and in-class selection. In our study, mitotic events are divided into three classes; undivided, the start of mitosis and separation of daughter cells. When these phases are examined, it is seen that cell structures are very close to each other. This would lead to very little difference between the classes in the dictionaries, so the risk of misclassification is high. For this reason, three separate dictionaries have been created using features that can make each stage more foreground than others. In the first dictionary, the class of the undivided phase is different from other classes.