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Cell tracking in microscopic video using matching and linking of bipartite graphs

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ABSTRACT

Automated visual tracking of cells from video microscopy has many important biomedical applications. In this paper, we track human monocyte cells in a fluorescent microscopic video using matching and linking of bipartite graphs. Tracking of cells over a pair of frames is modeled as a maximum cardinality minimum weight matching problem for a bipartite graph with a novel cost function. The tracking results are further refined using a rank-based filtering mechanism. Linking of cell trajectories over different frames are achieved through composition of bipartite matches. The proposed solution does not require any explicit motion model, is highly scalable, and, can effectively handle the entry and exit of cells. Our tracking accuracy of $(97.97 \pm 0.94)\%$ is superior than several existing methods [$(95.66 \pm 2.39)\%$ [11], $(94.42 \pm 2.08)\%$ [20], $(81.22 \pm 5.75)\%$ [13], $(78.31 \pm 4.70)\%$ [14]] and is highly comparable $(98.20 \pm 1.22)\%$ to a recently published algorithm [26].

1. Introduction

Live-cell imaging experiments provide the scope of computer vision-based identification, tracking, and analysis of cells in video microscopy [1,26,28]. These experiments find application in many diverse branches like biomedicine, material science and organic chemistry. Automated tracking of cell populations *in vitro* in time-lapse microscopy images helps in high-throughput spatiotemporal measurements of a wide variety of cell behaviors, which includes *migration* (translocation), *mitosis* (division), *quiescence* (inactivity) and *apoptosis* (death) in addition to the reconstruction of cell *lineages* (mother–daughter relations) [26]. This capability is of immense value in several areas of biomedical engineering, like, stem cell research, oncological studies, tissue engineering, drug discovery, genomics, and proteomics [2,29]. Automatic cell tracking faces many challenges like poor contrast with high noise levels, irregular cell contours, entry and exit of the cells, and, most importantly, the massive amount of data which needs to be processed [2]. In this paper, we propose a solution that can track a large number of human monocytes in a light microscopic video. A large number of cells with very similar appearance need to be tracked over a period of time. Graph-based methods have already been used for different biomedical segmentation problems [30,31]. This biomedical tracking problem is modeled as a composition of maximum cardinality minimum weight matching of bipartite graphs. A preliminary version of the work, presented in this paper, appears in [3], where

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the tracking of cells was restricted only to pairs of frames using bipartite graph matching with a simple cost function.

The rest of the paper is organized into following sections: in Section 2, we discuss the state-of-the art and highlight our contributions. In Section 3, we provide the outline of the proposed method. In Section 4, we discuss the image pre-processing techniques. In Section 5, we describe bipartite matching for establishing cell correspondences over pairs of frames and further refinements of the match sets using rank-based filtering. In Section 6, we describe how composition of bipartite matches can establish cell trajectories. We provide an analysis of the time-complexity of the proposed method in Section 7. In Section 8, we present the experimental results with necessary comparisons. The paper is concluded in Section 9 with an outline for directions of future research.

2. Literature review

Manual cell tracking approaches can incur tracking errors and can consume lot of time, especially, when large number of cells has to be tracked over a considerable period of time. As a result, semi-automated/automated cell tracking methods have gained widespread popularity. Kanade et al. [15] classified different cell tracking methods into three categories, namely, *sequential tracking*, *model-based tracking* and *detection-based association*. Some important works in each of the above three categories are discussed below.

Within the *sequential tracking* paradigm, use of particle filtering with spatiotemporal information is reported by Smal et al. [4] and Li et al. [5]. Zhou et al. [6] incorporated an orientation adaptive mean shift optimization into particle filter framework in their research on tracking of sperm cells. Ray et al. [7] employed sequential Bayesian framework to establish cell correspondences. Ryoo and Aggarwal [8] proposed a computationally efficient algorithm for multiple-hypotheses-tracking under severe occlusion. For the *model-based* techniques in the area of cell tracking, see the works of Debeir et al. on mean-shift process [9], Dzyubachyk et al., on level sets [10], and Crocker and Grier on non-interacting Brownian particles [11]. Some examples of *detection-based association* approach are the works of Meijering et al. [12], Chetverikov and Veresto'y [13] and Salari and Sethi [14]. Graph-based cell tracking techniques fall under the category of *detection-based association*. Now, we mention certain important works in this area. Padfield et al. [16] extended the standard minimum-cost flow algorithm to account for the entry and exit of cells, by enforcing a coupling of the flow of certain edges. Liu et al. [17] proposed a robust estimation strategy of stem cell lineages using local graph matching techniques. Xie et al. [18] employed a bipartite graph based approach for tracking the centroids of the *E. coli*. The cost function for matching in [18] was developed as a function of the intensity measurements of the target cells, the distance between them, and the smoothness of the velocity (displacement) vector. Mosig et al. [19] used segmented sets to construct a bipartite graph, where the weights were calculated from the relative overlap of the convex hulls of the segments. Sbalzarani and Koumoutsakos [20] defined a cost function in their graph-based tracking paper as the sum of the quadratic distances between the particles and the quadratic differences in the intensity moments of orders 0 and 2. In [26], the authors have modeled the tracking problem as a Linear Assignment Problem. For frame-to-frame particle linking, three types of temporally greedy assignments were considered. The various cost functions used in [26] are based on intensity and distance only. In [27], the authors formulate the problem as a maximum weight path cover for the weighted digraph constructed from all the frames taken together. Their gain function consists of directional coherence and speed consistency.

Many of the sequential tracking methods described above are computationally intensive and hence suffer from the problem of scalability. So, tracking of a large number of cells over long video sequences becomes prohibitive. Furthermore, biological applications often involve tracking where type of motion may not be known explicitly in advance. So, it often gets difficult to successfully apply *sequential methods* and *model-based strategies*. In this paper, we propose a cell tracking method based on matching and linking of bipartite graphs, which falls under the broad category of *detection-based association*. We use a bipartite graph for each pair of consecutive frames only and the proposed cost function is based on the mean motion as well as the past motion of the cells. Furthermore, we establish the links across three frames from a study of the distribution of the match scores and do not employ any greedy strategy. Overall, the proposed framework is quite different from others including the closest matches of [26] and [27]. As mentioned in [26], the cost functions should be based on applications. The proposed simple yet informative cost function works well for the current application. There are several important advantages of the proposed method. Firstly, no explicit model of motion is required as the tracking is essentially based on matching of bipartite graphs with dynamic updates. Secondly, our method can successfully handle the entry and exit of cells at different parts of the video. Thirdly, the proposed method is highly scalable as it utilizes the polynomial time-complexity of bipartite matching. Fourthly, our method requires only a few user inputs. Finally, the proposed algorithm does not take into account any feature other than the position of the cells. So it can effectively handle the challenge of tracking a large number of similar cells with identical characteristics.

3. Proposed method

The input to our problem is an *in vitro* assay of human monocyte cells rolling on human P-selectin obtained through microscopic video. The flow of cells is unidirectional in this *in vitro* data. The average number of cells/frame is 50. Our goal is to reconstruct the trajectories of these cells over various frames constituting the video. A novel cost function is designed for the proposed bipartite graph matching-based cell tracking method. Our method consists of the following four steps:

(i) Image pre-processing to remove background noise and extract cell centroids.