Detecting Leukaemia (AML) Blood Cells Using Cellular Automata and Heuristic Search

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Abstract. This paper presents a method for the identification of leukaemia cells within images of blood smear microscope slides, which is currently a time consuming manual process. The work presented is the first stage of a procedure aimed at classifying the sub-types of Acute Myeloid Leukaemia. This paper utilises the techniques of Otsu, Cellular Automata and heuristic search and highlights a comparison between random and seeded searches. We present a novel Cellular Automata based technique that helps to remove noise from the images and additionally locates good starting points for candidate white blood cells. Our results are based on real world image data from a Haematology Department, and our analysis shows promising initial results.

Keywords: Otsu, Cellular Automata, Heuristic search, Hill Climbing, Simulation Annealing.

1 Introduction

Haematologists have concluded that the effectiveness of microscope analysis of human blood smears can be vastly improved by the use of techniques such as image segmentation, classification and white blood cell counts, specifically in the pathology of leukaemia [1, 2]. At the same time, there are difficulties in identifying the various types of blast cells because the diagnosis can be either Acute Lymphoblastic Leukaemia (ALL) or Acute Myeloblastic Leukaemia (AML) which indicates different treatment. With AML, there are 8 subtypes, M0 to M7, which can be differentiated on their morphological features. A counting procedure is needed that should cover over 20% of the immature cells (blast cells) in the marrow for the diagnosis of acute leukaemia.

Recently, computer technology has had a big impact on medical imaging technology. Whole slide digital scanners has made research on pathological image analysis more attractive, by enabling quantitative analysis tools to decrease the evaluation time pathologists spend on each slide. This also reduces the variation in decision making processes among different pathologists or institutions and introduces reproducibility [3].

This paper aims to help the medical doctors in the efficient detection of leukaemia cells. We employ new techniques based on Cellular Automata and heuristic search which can reduce the time taken by a haematologist in detecting leukaemia cells.

P.R. Cohen, N.M. Adams, and M.R. Berthold (Eds.): IDA 2010, LNCS 6065, pp. 54–66, 2010.

This paper is organised as follows: in the rest of this section we detail the motivation behind our paper; in section 2 we describe previous work in the area, section 3 details our proposed methodology for identifying leukaemia cells and section 4 explains in detail our methods. The data sets and experiments are presented in section 5 and are followed by section 6 in which we discuss the results. Lastly, in section 7, we draw conclusions and discuss future research.

1.1 Leukaemia

Blood cancer is a condition known as Leukaemia, and is a disease which has no known cause where the bone marrow produces large numbers of abnormal cells [4]. Diagnosis of blood cancer has been determined by observing the image of a blood sample through a microscope. According to [5] the analysis of white blood cell counts through microscope imagery can provide useful information the about patient's health. When viewing the image of white blood cells, especially for the diagnosis of leukaemia, there are problems in identifying the blast cells if the blasts are minimal in number, the staining of the cells is poor, or if the image is being viewed by an inexperienced morphologist, in these cases the diagnosis might be delayed or incorrect. These problems can also lead to fatigue amongst the medical staff involved with this procedure.

There are many types of leukaemia and each of them is classified according to the specified type of cell which is affected by the disease. The types of leukaemia are:

- Acute Lymphocytic Leukaemia (ALL)
- Acute Myeloid Leukaemia (AML)
- Chronic Lymphocytic Leukaemia (CLL)
- Chronic Myeloid Leukaemia (CML)

This research focuses on the detection of white blood cells within Acute Myeloid Leukaemia (AML) which is a serious illness caused by the abnormal growth and development of early granular white blood cells. AML begins with abnormalities in the bone marrow blast cells, the white blood cells that contain small particles, or granules. The AML blasts do not mature, and they become too numerous in the blood and bone marrow. As the cells build up, they hamper the body's ability to fight infection and cause bleeding. Therefore, it is necessary to treat this disease as soon as possible after diagnosis. The recognition of the blast cells in the bone marrow of the patients suffering from myeloid leukaemia is a very important step, it is followed by categorising it into subtypes which will allow the proper treatment of the patients. The clinicians have to identify these abnormal cells under the microscope in order to detect that a patient is suffering from leukaemia, after which they will need a sample from the patient's bone marrow to count the leukaemia cells (blast cells) to confirm the diagnosis [5].

AML are classified as M0 to M7 according to French-British Group (FAB) classification. The blast cells of these subtypes are different in size, shape, amount of cytoplasm, shape and amount of nucleus and the constituent in the cytoplasm. It is important to identify certain subtypes such as M3 (acute promyelocytic leukaemia) because the treatment is different from other subtypes and it is a good prognosis for the patient. However sometimes morphologists have encountered problems in

classifying this subtype and have resulted in misclassification. Inter-observer variation in classification can lead to improper treatment for the patient, which can affect the survival rate of patients.

2 Previous Work

In this paper, we are using four techniques to detect possible leukaemia cells. We use **Otsu's method, Cellular Automata**, and the heuristic search methods of **Hill Climbing** and **Simulated Annealing**. There are a few papers which have attempted to detect white blood cells but not leukaemia cells. Most of the papers are based on morphological techniques. Previous work in [6] has concentrated on using the nucleus for classification through image segmentation. The sample images are extracted from an accredited image repository, the Atlas of Blood Cells Differentiation, which is highlighted in [6]. The datasets consisted of 113 images that contain 134 expert-labelled leukocytes (white blood cells). In [8] a colour gradient method to smooth the image is employed instead of using gray scale before applying a GVF (Gradient Vector Flow) snake based method. Scale-space filtering and the watershed algorithm were applied to colour images for detecting nuclei in [9]. This paper attempted to locate cell membranes, it required a few steps to apply edge detection but the case studies are different from leukaemia cells because leukaemia cells have different features. Another technique using eigen cells for detecting white blood cells was introduced in [10] but this study had limited success in correctly classify all of the white blood cells. Most of these approaches are based on colour images. However, in the case of overlapping cell there can be some problems. In [7] a histogram of pixel counts focusing on the touching cells was created and an edge cutting algorithm was then applied to separate the cells. This technique can be used for touching cells but not for overlapping cells. The technique is not possible to use in this project because cutting the cells will create different morphological features which might lead to incorrect classification.

Cellular Automata have been used in image processing for removing noise in pictures and modelling the development of tumours. This technique is used to transform one image into another. Cellular Automata models have been developed in three-dimensions to show tumour development. A number of studies involving Cellular Automata and cellular image processing have been in the area of tumour growth prediction via 3D simulation. [11, 12]. Cellular Automata can also reduce the noise in cellular images, e.g. in [13] plasma and red blood cells were removed from images.

Heuristic search and optimisation techniques have been previously applied to microscope imagery and the identification of leukaemia cells. Circle detection has been performed using genetic algorithms and sobel's method in [14] which detected circlers but not morphological features. In [15], they apply seed regions by using heuristic search based on the diameter of the cells which are less than 25um. This technique can be performed if the cells do not overlap or have no neighbours. Particle Swarm Optimization combined with Neural Networks was used to escape from local optimum in an application for detecting the colour nucleus in large-scale image data [16]. These ideas can be used as an extension to our research and can help in the clustering of the different types of leukaemia cells.

Our research uses Cellular Automata to remove noise such as plasma and red blood cells. At the same time, it identifies for each point in the image a representation of the shortest distance that point is away from the background. We use Cellular Automata to find the "best" starting point before proceeding to the heuristic search, which is used to search for the best circular regions representing the Leukaemia cells. For the heuristic search based methods we used the two techniques of Hill Climbing and Simulated Annealing.

3 Work Process

In this paper we present two heuristic search based techniques which are aimed at detecting candidate leukaemia cells within an image of a blood smear microscope slide. The difference between the two types of method is that we use a Cellular Automata to locate good starting points in our "seeded" method. Fig. 1 shows the flowchart consisting of the two methods with seeding shown at the top and random at bottom. In the seeded search, the process involves applying Otsu's method, running the Cellular Automata, detecting the starting coordinates, colour image clustering and coordinate overlap checking. With the random method, we use Otsu's method and then start at a randomly generated set of points. Lastly we use Hill Climbing and Simulated Annealing to find the best candidate leukaemia cells.

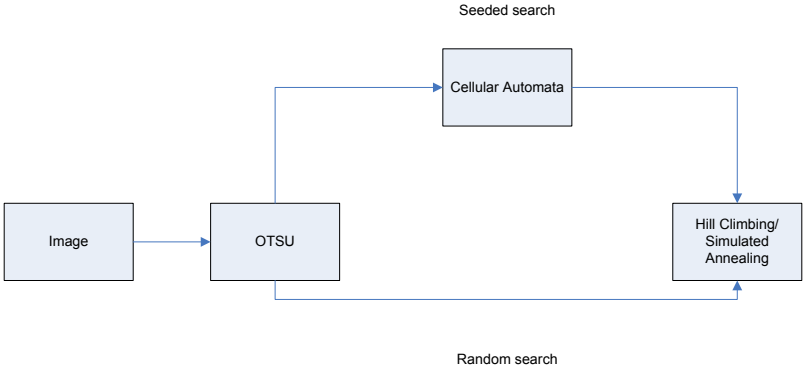

Fig. 1. Research Methodology Flowchart

4 Method

In the following sections we present the methods that we have used in this paper which are Otsu's method, Cellular Automata, coordinate detection, colour image clustering, checking for overlapping coordinates and lastly the heuristic search methods which are Hill Climbing and Simulated Annealing.

4.1 Otsu

We used Otsu's method for extracting objects from their background using the MATLAB image processing toolbox [17]. In applying Otsu's method we use a grey

scale threshold for the separation of the two objects between the foreground and background. The results shown in fig. 3(b) and fig. 4(b) are the image with greyscales after applying Otsu's method.

4.2 Cellular Automata

Cellular Automata (CA) are a type of complex system that have very few parameters and are a development of Conway's game of life [19]. In this paper we use a CA to convert a black and white cell image to a matrix (the same size as the input image) where each point in the matrix represents the shortest distance each point in the image is away from the background. We represent the background as white (or "dead") and the cells body (as identified by Otsu) as black (or "alive"). To create the output "distance" matrix, we initially define $C(0)$ as the input image, we then create a series of matrices $C(i)$ where each $C(i)$ is the CA applied to $C(i\text{-}1)$. The CA itself works by looking at each pixel x,y; if the pixel is already "dead" it stays dead, otherwise its immediate adjoining neighbours (City Block distance of one) are examined. If any neighbours are "dead", the point itself becomes "dead" otherwise it remains "alive". We examine only the neighbours of each point, thus a corner point will only have three neighbours to examine. This process is repeated until all of the points within $C(i)$ are "dead" or white.

Throughout the procedure we maintain another matrix *CP* (the same size as the input matrix), where each x,y element represents the CA iteration that the point "died", i.e. turned from black to white. For example, if after 5 applications of the CA, which has created matrices $C(1)$, $C(2)$, ..., $C(5)$, point 100,200 "dies" (it was "alive" in $C(4)$ but "dead" in $C(5)$, then we set the element 100,200 in matrix *CP* to 5.

We hypothesise that the values in the *CP* matrix represent the shortest path between an "alive" point and a "dead" point. Therefore points within the *CP* matrix with high values represent dense areas of the input image and thus good starting points for locating the largest cells within the input image. An example of the visualisation of matrix *CP* can be seen in figure 3(c).

Once we have the CA image (the visual representation of matrix *CP*), we need to identify points of high value which are located next to each other, e.g. dense spots and areas. We first apply a rudimentary filtering based on the expected size (radius) of the five white blood cells (Neutrophil, Eosinophil, Basophil, Monocyte and Lymphocyte). From the literature, and on consulting expert opinion, we have identified that 8 micrometres is a reasonable demarcation between the size of red and white cells. Due to each image possibly being under varying magnification, we assume that the maximum value in the *CP* matrix corresponds to the size of the largest white cell, and apply a filter accordingly, i.e. we transform the matrix *CP* to a binary image based on this computed threshold, see fig. 3(d) for an example.

4.3 Detecting Coordinates

Now that we have an indication of where the regions of high density are (as shown in fig. 3(d)) we need to locate the centre of the regions so that they can be used as possible good starting points for locating the white blood cells, i.e. our "seeds". By producing row and column sums over the filtered image, we can define rectangular regions

where horizontal and vertical non-zero totals intersect, as seen in fig. 3(e). Using these regions, we can determine the centre of the candidate dense areas, and thus define an *x*,*y* starting point. The intensity within the *CP* matrix at the point will be used as the starting radius *r*.

4.4 Colour Image Clustering

We now have a candidate list of starting points. We now perform an additional check to identify whether each point is identifying a leukaemia cell. We categorise the cells based on colour, that is how many points are pink i.e. plasma and red blood cells and how many are purple, that is leukaemia cells. Given the colour (three value RGB scale) of a pixel within the circle identified by each potential starting point, we see how close it is (using Euclidean distance) to either a pink or purple vector. Once we have categorised each point, we decide on whether we have a potential leukaemia cell based on whether the pink or purple counts are greater.

4.5 Checking Coordinate Overlap

Once we have detected the starting points, we need to ensure that these starting points do not overlap. Given the centre and radius of two circles, there are three possible states; the circles do not overlap, one circle is contained within another, and the circles overlap. We define a similarity measure which returns a value between 0 (the circles are separate) and 1 (the circles are identical), values in between represent how much of the circles overlap or are contained. We have omitted the derivation of this measure due to space constraints; however we note that it is simple to identify which state (as above) the two circles are in by examining the distance between the centres and comparing this against the two radiuses. The calculation of how much two circles overlap is evaluated by calculating the area of the overlapping segments using Pythagoras's theorem and the circle segment area equation [20]. If two circles overlap then we merge them. We acknowledge that this may not be the correct policy (it is if two circles are contained), but we are leaving this as a task for future work.

4.6 Heuristic Search

We use heuristic search to locate the best position of the required number of circles for each input image. We either have a number of random starting circles, or seeded starting circles depending on if we are using the CA or not. Each circle is represented as an *x*,*y*,*r* triple representing the centre and radius. We use Hill Climbing and Simulated Annealing, which are described in more detail in a later section. We use fitness function number 6 from table 1. The small generator for Hill Climbing and Simulated Annealing are the same, we choose either an *x*,*y* or *r* from one of the circles and randomly add/subtract (equal chance) a value between 1 and 50. Boundary checks are made to ensure that we do not move off the image. The seeded methods can identify the number of circles, however the random methods cannot, hence we set the number of starting circles for the random methods to the same number as the corresponding seeded method.

Table 1. Fitness Function Evaluation

Number	Method	Correlation
1	$F=\sum R(i)((B(i)-W(i))/(B(i)+W(i))$	0.697
2	$F=\sum (B(i)-W(i))/(B(i)+W(i))$	0.782
3	$F=\sum (R(i)B(i))/(B(i)+W(i))$	0.721
4	$F=\sum (R(i)B(i))/W(i)$	0.879
5	$F=\sum B(i)/(B(i)+W(i))$	0.782
6	$F=\sum R(i)(B(i)+1)/(W(i)+1)$	**0.903**
7	$F=\sum B(i)-W(i)$	0.588
8	$F=\sum B(i)$	0.430

4.6.1 Experiments Finding Fitness Function

We tested a number of potential fitness functions methods before finally choosing the most viable fitness function based on 10 test cases that we ranked from worst to best using a single image. The idea is that we rate how good a potential circle is based on the number of valid points (white points from the black and white image) it covers. We performed a simple correlation analysis based on scale 1 to 10 from best to worst, based on a number of potential circles (we created a number of test cases that were easily ranked). We ranked the images by eye, and correlated the rank against image fitness. The aim was to choose a fitness function whose value agreed most with the ranking. Table 1 details the fitness functions we evaluated, the equations are in abbreviated form, the best performing function, and the one we use in this paper, is described fully in equation 1.

Within equation 1 and table 1, we define C as our list of circles, C_i as the ith circle and $|C|$ as the number of circles within C. $R(i)$ is the radius of circle i, $B(i)$ is the number of black points within circle i for a given image, $W(i)$ is the number of white points for a given image.

$$F(C) = \frac{R(C_i)\left(\sum_{i=1}^{|C|} B(C_i)+1\right)}{\sum_{i=1}^{|C|} W(C_i)+1} \tag{1}$$

4.6.2 Algorithms

The following sections describe the heuristic search methods of Hill Climbing and Simulated Annealing in more detail.

4.6.2.1 Hill Climbing. Hill Climbing is a local search procedure which utilises the concept of searching the neighbourhood of a solution for a better one. This technique iterates a number of times, each time a new point is selected from the neighbourhood of the current point. If that new point provides a better value of the evaluation

function, the new point becomes the current point. Otherwise other points in the neighbourhood are selected and tested again. The main disadvantage of using Hill Climbing is that it often gets stuck in a local maxima during the search [21]. Below is the algorithm for Hill Climbing used in this paper.

```
Input: Black and White Image BW
       Number of circles N
       Number of iterations ITER
Create C = N circles (using CA or Random)
Let Fit = F(C) applied to BW (equation 1)
For i = 1 to ITER
   Create Cnew from C using change generator
   Let Fnew = F(Cnew) applied to BW
   If Fnew ≥ Fit
      Fit = Fnew, C = Cnew
   End if
End For
Output: Highest Fitness F and circles C
```

4.6.2.2 Simulated Annealing. Simulated Annealing is a heuristic search technique which aims at improving the problems inherent in Hill Climbing. In Simulated Annealing a temperature is maintained which is used to determine the probability of accepting a worse point [21].

```
Input: Black and White Image BW
       Number of circles N
       Number of iterations ITER
       Start and end temperature TZero, TFinal
Define lamda (equation 2)
Create C = N circles (using CA or Random)
Let t = TZero, Let Fit = F(C)
For i = 1 to ITER
   Create Cnew from C using change generator
   Let Fnew = F(Cnew)
   Diff = fnew - fit, P = exp(Diff/t)
   If Fnew ≥  fit
        Fit = Fnew, C = Cnew
   Else
      If random value (0,1) ≤ P
         Fit = Fnew, C = Cnew
      End If
   End If
   t = lamda × t
End For
Output: Highest Fitness F and circles C
```

The parameter λ is calculated based on [18] shown in eqaution 2:

$$\lambda = \frac{\exp((\log(TFinal) - \log(Tzero))}{j} \tag{2}$$

5 Data Sets and Experiments

We used ten images of leukaemia cells (AML). An example image is shown in Fig. 3(a) and Fig. 4(a). The images were 1280 by 960 in size. We executed each of the four algorithms 10 times for 10000 iterations; the repeats were so that any sampling bias is removed from the stochastic nature of the algorithms. We used the image data sets from Hospital University Science Malaysia (USM), Kota Bahru, Kelantan.

6 Results

This section shows all the results for the colour image clustering and heuristic search methods.

6.1 Colour Image Clustering

We clustered the pixels using Euclidean distance as described below. By using Euclidean distance we can determine whether a candidate cell is purple (a leukaemia cell (AML)) or pink (either plasma or red blood cells). We acknowledge that basing the clustering on colour alone is not the best method due to variations between image colourings that will change which can change overtime. The result of our methods is shown in table 2 and represents an overall accuracy of 91.5% by using clustering using colour. The outputs are shown in the fig. 3(f).

Table 2. Calculating the clustering for the 10 images

		Actual		
	Image		**Pink**	**Purple**
Predicted	1	Pink		
		Purple		3
	2	Pink	3	3
		Purple		
	3	Pink		
		Purple		2
	4	Pink		
		Purple		7
	5	Pink		
		Purple		5
	6	Pink		
		Purple		3
	7	Pink	11	3
		Purple		
	8	Pink	13	2
		Purple		
	9	Pink		
		Purple		4
	10	Pink		
		Purple		2

6.2 Check Coordinate Overlap

Hill Climbing and Simulated Annealing cannot be performed if the starting circles overlap. This program checks if the circles overlap based on the equation by [20]. A non-overlapping example is shown in fig. 3(f). If the starting circles are shown in fig 2(a) to overlap, then a new random set are generated as shown in fig 2(b).

6.3 Comparison Random/Seeded Hill Climbing and Simulated Annealing

Table 3 compares our four techniques which are Hill Climbing, Hill Climbing seeded, Simulated Annealing, Simulated Annealing seeded on the 7 images which are image 1, 3, 4, 5, 6, 9, 10. As for images 2, 7 and 8 the colour clustering did not target the leukaemia cells as stated in the Table 2. Overall, Simulated Annealing seeded achieves the highest fitness function value in 4 out of 7 cases.

Although Simulated Annealing random gained the highest fitness value in a number of images, it did not target the correct cells. This indicates that our fitness function probably needs improving upon; however, it does indicate that our seeding strategy works effectively. As shown in the final averages in the results table, Hill Climbing seeded has the highest value of all of the methods. This is a surprising result, since one would expect Simulated Annealing to out perform Hill Climbing. However as we are seeding Simulated Annealing, the search may deviate from the seeded point rapidly in the early stages of the algorithm, where Hill Climbing will always improve upon (or maintain) the fitness of the seeded starting points. The table below states the fitness function on which the equation is based (1).

Table 3. Data from Hill Climbing and Simulated Annealing

Image	HC	HCSeed	SA	SASeed	Max.
1	229796.20	2222000.00	94805.21	**2226000.00**	2226000.00
3	141609.90	1051636.00	**1334923.60**	967496.00	1334923.60
4	951630.35	3422380.00	**5260004.69**	3406880.00	5260004.69
5	784762.14	4174590.00	75808.42	**4239900.00**	4239900.00
6	809407.93	2880000.00	**4378871.82**	2884300.00	4378871.82
9	44192.84	3560000.00	189514.99	**3553350.00**	3560000.00
10	515361.48	2062600.00	905159.28	**2062600.00**	2062600.00
Average	496680.12	2767600.86	1748441.14	2762932.29	N/A

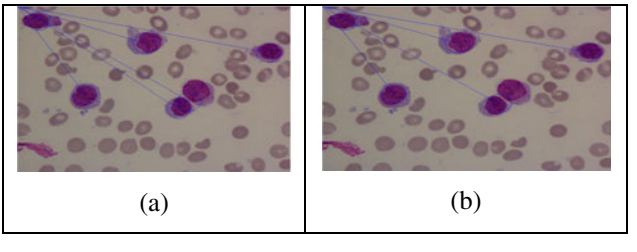

Fig. 2. Finding the new coordinate if the starting point circle are overlap

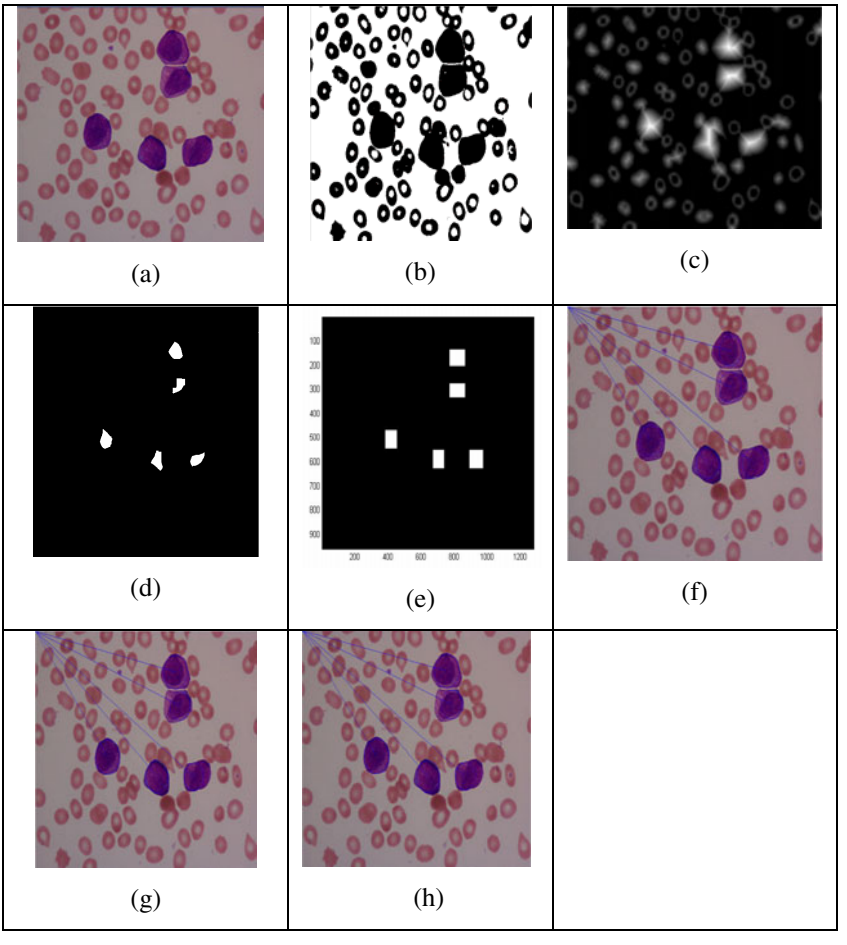

Fig. 3. The seeded search process for Hill Climbing and Simulated Annealing from colour image until detecting the leukaemia cell seeded

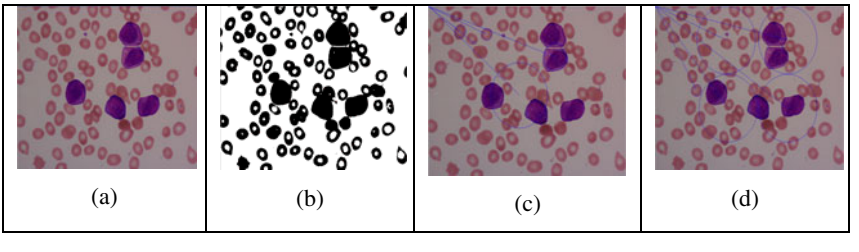

Fig. 4. Example Images from Stages within the Proposed Methodology, (a) Input Image, (b) After the Application of Otsu, (c) After the Application of Random Hill Climbing, (d) After the Application of Random Simulated Annealing

7 Conclusion

In this paper we have presented a comparison between random and seeded search for the location of potential leukaemia cells. With the random search methods, there were only three steps which consist of Otsu's method, random coordinate generation and the application of a heuristic search. The seeded method consists of more steps, which are Otsu's, Cellular Automata seed generation, coordinate location, colour image clustering, and heuristic search.

The Cellular Automata correctly identified good starting points for 7 images after filtering based on the minimum and maximum sizes of white blood cells. These preliminary methods need refining for the other images, and may have failed to work due to the quality of the images. On the 7 images that we applied our work to, an overall accuracy of 91.5% was attained. Our research has identified that the Cellular Automata approach produces excellent starting positions, and that Heuristic search can refine the positions, however, we need to improve our fitness function. Additionally our approach has some limitations when applied to images that contain overlapping cells. These two issues will be the focus of future work. Additionally, we will look into using the circle similarity metric to rate the repeatability of our experiments.

The Heuristic Search method of Simulated Annealing seems to achieve the best overall result but is more variable than Hill Climbing, thus Hill Climbing seeded tends to have a better average.

This research project is still in its infancy, with the overall goal being to identify the individual AML subtypes M0 to M7 using classification techniques such as Neural Networks (as in [6]) applied to the results generated by this paper.

Acknowledgments. We would like to thank the Islamic Science University of Malaysia and the Ministry of Higher Education, Malaysia for supporting this research and providing the scholarship.

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