Cell Volume Estimation from a Sparse Collection of Noisy Confocal Image Slices

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ABSTRACT

Measurement and quantification of the volume of cells are very useful for analyzing and understanding cellular behavior, such as cell growth and differentiation. One popular practice is to use Confocal Laser Scanning Microscopy(CLSM) to image cell slices and then reconstruct the 3-D volume of the cells from these serial optical slices. However, all of the current methods of volume estimation using CLSM imaging require large number of cell slices (i.e. high volume of image data). But in many practical situations, especially in case of CLSM based live cell imaging, such high depth resolution is not feasible in order to avoid photodynamic damage to cells from prolonged exposure to laser. In this work, we have addressed this problem of finding out the volume of a plant cell using CLSM when the amount of data is as limited as two to three slices per cell. We assume an ellipsoid model for a cell and estimate the minimum volume ellipsoid that encloses all three cell slices in the 3D stack. The level set based segmentation often tends to produce cell slice areas less than the actual due to poor signal to noise ratio in images and that is the reason why we choose a Minimum Volume Enclosing Ellipsoid over mean or best-fit ellipsoids. We tested the proposed computational method on time-lapse CLSM images of Shoot Apical Meristem (SAM) cells of model plant *Arabidopsis Thaliana*. The volume estimates of individual cells are reasonably close to what is expected from biological point of view.

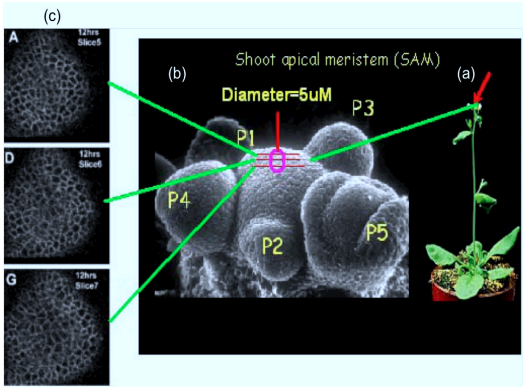

Figure 1: SAM Location and Sample Cell Slices. (a)SAM located at the top of the shoot of Arabidopsis, (b)A detailed surface view of SAM, (c)Three consecutive slices of SAM obtained through CLSM technique

1. INTRODUCTION

Study of cell growth dynamics is one of the major topics of interest in plant and animal developmental biology. Information such as rates and patterns of cell expansion play a critical role in explaining cell growth and deformation dynamics and thereby can be extremely useful in understanding Morphogenesis. The need for quantification of these biological parameters necessitates estimation of individual cell volume with reasonable accuracy. There are several methods for volume estimation of individual cells such as impedance method [12] and light microscopy methods [12, 3, 10].

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But the first method requires the shape of the cell to be near spherical in suspension and the second method has limited spatial resolution. Now-a-days, the most popular practice is to use Confocal Laser Scanning Microscopy (CLSM) to image cell-slices and then reconstruct the 3-D volume of the cell from those serial optical slices which can have high spatial as well as temporal resolution [15, 2].

However, performance of all of the current CLSM imaging based techniques depends heavily on the availability of a large number of very thin optical slices of a cell and the performance rapidly deteriorates in the cases where the number of cell slices becomes limited. This problem is very common especially in CLSM based live cell imaging when the time gap between successive observations is small. In order to keep the cells alive and growing for a longer period of time it is not possible to frequently expose them under laser. As a result, high depth-resolution and time-resolution cannot be achieved simultaneously and hence the number of image slices in which a cell can be present is often really small (e.g. 3 slices/cell). With such a limited amount of image data, the 3-D reconstruction cannot yield a good estimate of cell volume. In the present work we have addressed this problem of estimating volume of a plant cell when the number of image slices per cell is very limited.

We propose an automated and simple method for cell volume estimation which is tested on Shoot Apical Meristem (SAM) cells of model plant *Arabidopsis Thaliana*. We have used CLSM based live imaging set-up to acquire a sequence of time-lapse images forming a 4-D data structure. Each 3-D stack is imaged every third hour and it consists of a series of optical cross sections of SAMs that are separated by approx. 1.5 μm. A standard SAM cell has a diameter of about 5 μm and hence in most cases the imaging process can represent a particular cell only in three consecutive slices. For such sparsity of data we cannot use the existing reconstruction techniques to estimate the volume of a cell.

To overcome this problem, assumption of a 3-D model is necessary and for plant cells *ellipsoid* is a reasonable model. But, images obtained from live imaging can be noisy due to poor signal-to-noise ratio and hence the segmentation error is often substantial. More specifically, the commonly used level set based segmentation technique relies on a stopping criterion and for cell images with low SNR the segmented area of a cell is often less than the actual area. To mitigate this problem we chose to estimate the minimum volume ellipsoid which encloses all the pixels of the three cell slices(MVEE) instead of estimating the mean or best fit ellipsoid.

The rest of the paper is organized as follows. Section 2 describes the overview of our approach. The theory behind Minimum Volume Enclosing Ellipsoid(MVEE) is presented in section 3. We have shown experimental results and validation of our approach in section 4 followed by concluding discussion and future work in section 5.

2. OVERVIEW OF THE METHOD

The Confocal Laser Scanning Microscopy (CLSM) is now being widely used to obtain cross sectional optical slices of varied biological specimens - from cellular to organism level. By changing the depth of focal plane, CLSM can provide in-focus images from various depths of the specimen. Generally, fluorescent dyes are used to make objects visible under laser. The set of images obtained constitute a 3-D stack, also known as a 'Z-Stack'. If there is any minor shift in the alignment of the images in the 3-D stack, various image registration techniques like [14, 9] can be employed to register the images in a stack.

We are interested in computing volume of each cell in a colony of cells and hence we need to segment out all the cells in each slice. One of the most well known approaches is the level set segmentation [1]. A level set is a collection of points over which a function takes on a constant value. Every cell is represented by a separate level set function, wherein every level set function behaves like an active contour which gradually evolves towards the boundary of the cells. We have adopted this method for segmenting cells.

Next step is to find corresponding cells in consecutive slices and a tracking method is required to achieve that. Some popular tracking methods are the multiple level set approach of simultaneous segmentation and tracking [7], the local graph matching approach [8] etc. In our experiments with SAM cells of Arabidopsis we use the latter one because of its robustness.

Given the segmented contours of each of the cells in multiple slices, our objective is to find out the best possible estimates of the volumes of these cells. But we are considering those cases where the number of slices in which a particular cell is present is very less (e.g. 2 - 4 slices/cell). Typically, this is commonplace in live imaging when we have to sacrifice the depth resolution in imaging in order to have more frequent observations. For such cases, we need to adopt a 3-D model for each cell. Now, for most of the plant cells, an ellipsoid can be a reasonable model.

But due to the imaging process, as we go deeper inside the z-stack, the signal-to-noise ratio deteriorates and the level set segmentation tends to yield a segmented cell contour with area less than the actual one. So the ellipsoid we estimate can not be a mean ellipsoid because its volume will be heavily affected by the poorly segmented cell slice. Instead, we can estimate an ellipsoid which encloses all the points on the three cell slices and has the minimum volume amongst all such enclosing ellipsoids. There is a clear advantage of estimating this Minimum Volume Enclosing Ellipsoid (MVEE) over all other ellipsoids. Even if we have a poorly segmented slice of a cell and the other slices are properly segmented, the volume of the ellipsoid will be affected more by those better slices and hence the estimate of the volume will be less erroneous. In the next section, we pose the problem of estimating an MVEE as a convex optimization problem and describe how to solve this problem to estimate the volumes of the cells.

3. MINIMUM VOLUME ENCLOSING ELLIPSOID

3.1 Problem Formulation

After segmentation and identification of a cell in multiple slices in the 3-D stack, we can define a co-ordinate system with origin at the centroid of either of the 3 cell slices and get (X, Y, Z) co-ordinates of a set of 'n' points on the perimeter of the segmented cell slices (Using the knowledge that the slices are 1.5 μm apart along the Z-axis). Suppose, this set of points is $\mathcal{P} = \{p_1, p_2, \cdots p_n\} \in \mathbb{R}^3$. We have to estimate the minimum volume ellipsoid which encloses all these 'n' points in $\mathbb{R}^3$ and we denote that with MVEE($\mathcal{P}$). Now, an

ellipsoid in its center form is represented by

$$\mathcal{E} = \{p \in \mathbb{R}^3 \mid (p-c)^T \Sigma (p-c) \leq 1\}$$

where $c \in \mathbb{R}^3$ is the center of the ellipsoid $\mathcal{E}$ and $\Sigma \in \mathbb{R}^{3\times 3}$. Since all the points in $\mathcal{P}$ must reside inside $\mathcal{E}$

$$(p_i - c)^T \Sigma (p_i - c) \leq 1 \text{ for } i \ = \ 1, 2, \cdots n$$

and the volume of this ellipsoid is

$$Vol(\mathcal{E}) \ = \ \frac{4}{3}\pi \{det(\Sigma)\}^{-\frac{1}{2}}$$

Therefore, the problem of finding the Minimum Volume Enclosing Ellipsoid (MVEE) for the set of points $\mathcal{P}$ can be posed as

$$\begin{aligned} \min_{\Sigma, c} \quad & - log\ det(\Sigma) \\ \text{s.t.} \quad & (p_i - c)^T \Sigma (p_i - c) \leq 1 \quad \text{for } i \ = \ 1, 2, \cdots n \\ & \Sigma > 0 \end{aligned} \tag{1}$$

Problem(1) is clearly not a convex optimization problem. The primal problem, hence, is converted into its dual problem and the dual is easy to solve. A detailed analysis on the problem formulation and its solution can be found in [5, 6, 13, 11]. We shall describe the main steps which lead to the final estimate of the volume.

3.2 Solution

We define a 'lifting' from $\mathcal{P} \in \mathbb{R}^3$ to $\mathbb{R}^4$ via

$$\mathcal{P}^{'} \ = \ \{\pm q_1, \ \pm q_2, \ \cdots \ \pm q_n\}$$

where $q_i = [p_i, 1]^T, \ i = 1, 2, \cdots n$. Now, we define a hyperplane $\mathcal{H} = \left\{(p, \ p_4) \in \mathbb{R}^4 : p_4 = 1\right\}$ such that

$$MVEE(\mathcal{P}) \ = \ MVEE(\mathcal{P}^{'}) \ \cap \ \mathcal{H} \tag{2}$$

MVEE($\mathcal{P}^{'}$) is centered at origin and this helps us in changing the problem in (1) as a convex optimization problem for MVEE($\mathcal{P}^{'}$). Once this problem is solved we can find out MVEE($\mathcal{P}$) using Relation (2). Now, the lifted problem is

$$\begin{aligned} \min_{A} \quad & -log\ det(A) \\ \text{s.t.} \quad & {q_i}^T A q_i \leq 1 \text{ for } i = 1, 2, \cdots n \\ & A \text{ is a } 4 \times 4 \text{ positive definite symmetric matrix} \end{aligned} \tag{3}$$

The Lagrangian dual problem of the above can be shown to be

$$\begin{aligned} \max_{u} \quad & log\ det\ F(u) \\ \text{s.t.} \quad & \underline{1}^T u = 1 \\ & u \geq 0 \end{aligned} \tag{4}$$

where $u \in \mathbb{R}^n$ is the decision variable and $'F'$ is a linear operator such that

$$F(u) = \sum_{i=1}^{n} u_i q_i {q_i}^T \tag{5}$$

Problem(4) is a concave optimization problem which can be solved by an ascent method. Based on the work by L.G. Khachiyan in [5], a conditional gradient ascent method [6] can be employed to solve this optimization problem. [13] provides with a detailed analysis on improvements over [5].

Let $\hat{u} \in \mathbb{R}^n$ be the solution to the concave optimization problem (4). Now, $\hat{u}$ is an optimal solution to the optimization problem along with the dual solutions $\hat{s} \in \mathbb{R}^n$ and $\hat{\lambda} \in \mathbb{R}$ if and only if the following conditions are satisfied [6]

$${q_i}^T F(\hat{u})^{-1} q_i + \hat{s_i} = \hat{\lambda} \text{ for } i = 1, 2, \cdots n \tag{6}$$

$$\underline{1}^T \hat{u} = 1 \tag{7}$$

and

$$\hat{u_i}\hat{s_i} = 0 \text{ for } i = 1, 2, \cdots n \tag{8}$$

where $\hat{u}, \ \hat{s} > 0$. Then, multiplying both sides of (6) by $\hat{u_i}$ and summing up over all i gives

$$\sum_{i=1}^{n} \hat{u_i} {q_i}^T F(\hat{u})^{-1} q_i = \text{Trace} \left[F(\hat{u})^{-1} \left(\sum_{i=1}^{n} \hat{u_i} q_i {q_i}^T \right) \right] = \text{Trace(I)}$$

Now I is a 4×4 matrix and hence Trace(I)=4. This implies $\hat{\lambda} = 4$. Consequently, a feasible solution for (3) is

$$A = \frac{1}{4} F(\hat{u})^{-1} \tag{9}$$

Combining (2), (3) and (9), the MVEE can be computed as

$$MVEE(\mathcal{P}) = \{p \in \mathbb{R}^3 \mid \frac{1}{4} \begin{bmatrix} p^T & 1 \end{bmatrix} F(\hat{u})^{-1} \begin{bmatrix} p \\ 1 \end{bmatrix} \leq 1\} \tag{10}$$

Now, let $\mathrm{P} \in \mathbb{R}^{3\times n}$ such that the i'th column of P is p_i. Then, $F(\hat{u})$ from Equation(5) can be alternatively expressed in a matrix form in terms of P -

$$F(\hat{u}) = \begin{bmatrix} \mathrm{P}\hat{\mathrm{U}}\mathrm{P}^T & \mathrm{P}\hat{u} \\ (\mathrm{P}\hat{u})^T & 1 \end{bmatrix}$$

where, $\mathrm{U} = \text{diagonal}(u) \in \mathbb{R}^{n\times n}$. Upon inversion,

$$F(\hat{u})^{-1} = \begin{bmatrix} \mathrm{I} & 0 \\ (-\mathrm{P}\hat{u})^T & 1 \end{bmatrix} \begin{bmatrix} (\mathrm{P}\hat{\mathrm{U}}\mathrm{P}^T - \mathrm{P}\hat{u}(\mathrm{P}\hat{u})^T)^{-1} & 0 \\ 0 & 1 \end{bmatrix} \begin{bmatrix} \mathrm{I} & -\mathrm{P}\hat{u} \\ 0 & 1 \end{bmatrix}$$

Plugging this value of $F(\hat{u})^{-1}$ into (10), we get $MVEE(\mathcal{P})$ as

$$\{p \in \mathbb{R}^3 \mid (p - \mathrm{P}\hat{u})^T \frac{1}{3} (\mathrm{P}\hat{\mathrm{U}}\mathrm{P}^T - \mathrm{P}\hat{u}(\mathrm{P}\hat{u})^T)^{-1} (p - \mathrm{P}\hat{u}) \leq 1\} \tag{11}$$

Comparing Expression(11) with the standard ellipsoid equation, we deduce the parameters of the $MVEE(\mathcal{P})$ as

$$\hat{\Sigma} = \frac{1}{3} (\mathrm{P}\hat{\mathrm{U}}\mathrm{P}^T - \mathrm{P}\hat{u}(\mathrm{P}\hat{u})^T)^{-1} \text{ and } \hat{c} = \mathrm{P}\hat{u} \tag{12}$$

Finally, with these estimated parameters we compute the volume of the MVEE as

$$Vol(\mathcal{E}) \ = \ \frac{4}{3}\pi \{det(\hat{\Sigma})\}^{-\frac{1}{2}} \tag{13}$$

4. EXPERIMENTS AND RESULTS

4.1 Experimental Methodology

We have tested the proposed approach on a collection of around one hundred cells in shoot apical meristem (SAM) of Arabidopsis Thaliana. To visualize cell boundaries of all the cells in the SAM, plasma membrane-localized Yellow Fluorescent Protein(YFP) is used. We have used confocal laser

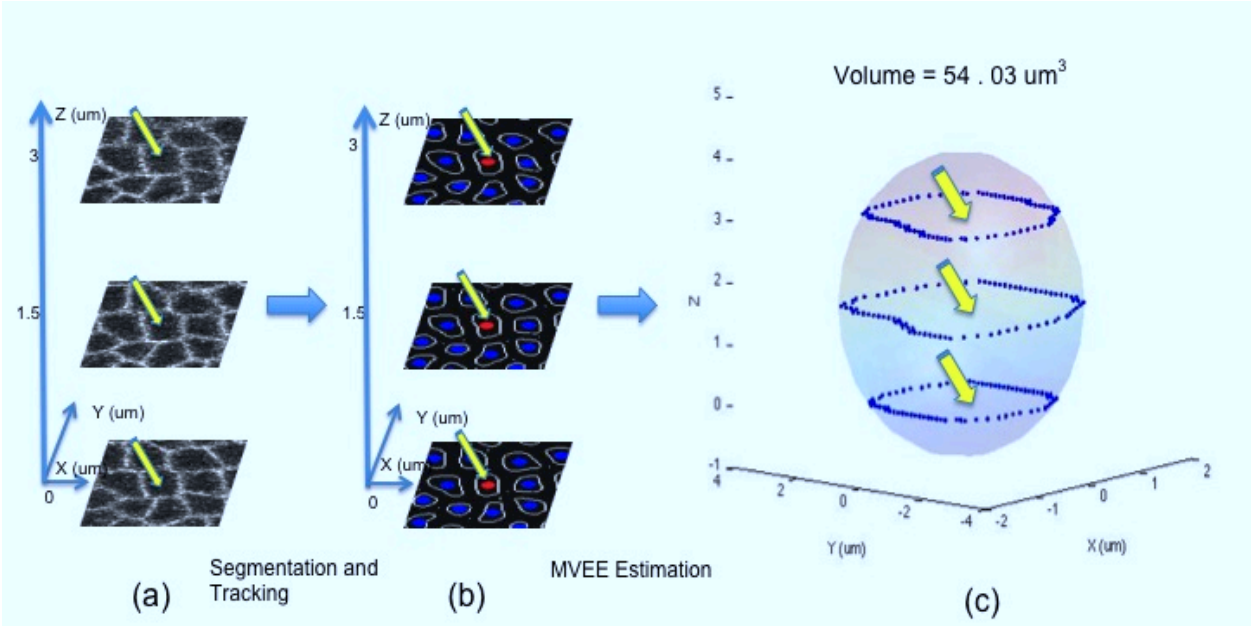

Figure 2: Case 1 - Cell volume estimation when all the cell slices are equally well segmented and the cell is close to ellipsoidal in shape. (a)Cell Slices from CLSM: Sections of three consecutive slices of SAM in Arabidopsis Thaliana and the arrows point to the cell of interest (b)Segmented and Tracked Cell Slices: The slices are segmented using level set segmentation and tracked using local graph matching technique, (c)Contours of one cell in 3 consecutive slices, Estimated MVEE and its volume: The estimated MVEE fits perfectly to the cell contours as the segmentation results for all three slices are equally good.

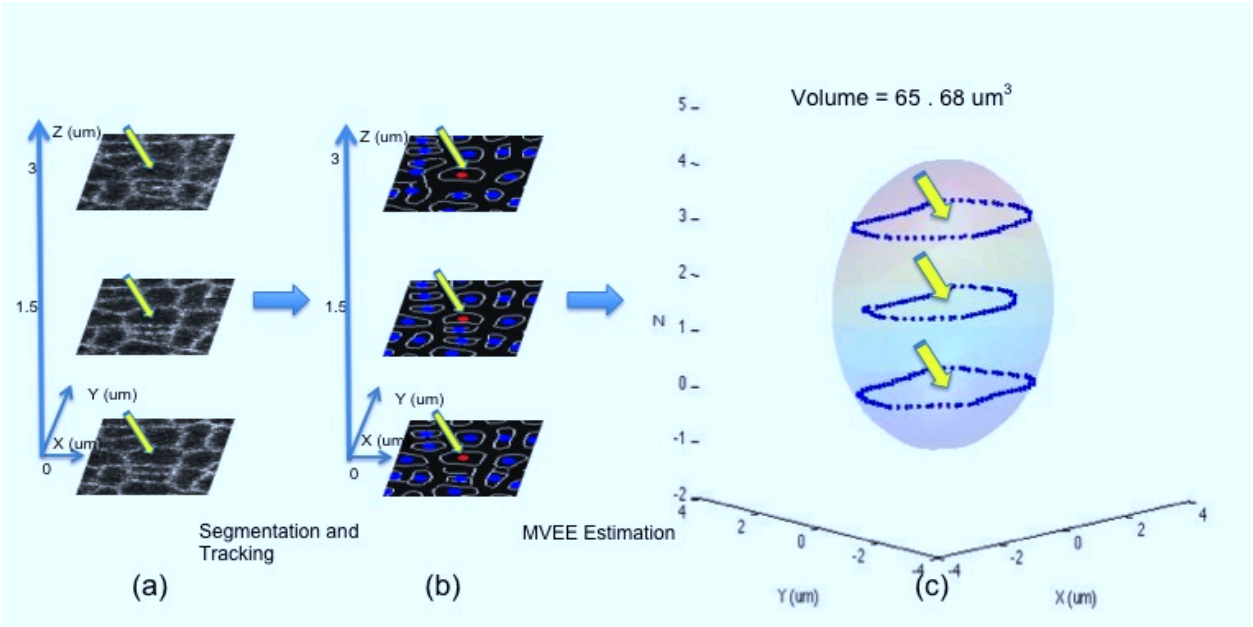

Figure 3: Case 2 - Cell volume estimation when one of the cell slices is not well segmented. (a)Cell Slices from CLSM: : The low SNR results in poor segmentation of the middle slice, (b)Segmented and Tracked Cell Slices, (c)Contours of one cell in 3 consecutive slices, Estimated MVEE and its volume: The shape and hence the volume of the estimated MVEE is governed by the two better segmented terminal slices, hence the error caused by the middle slice is mitigated to a large extent.

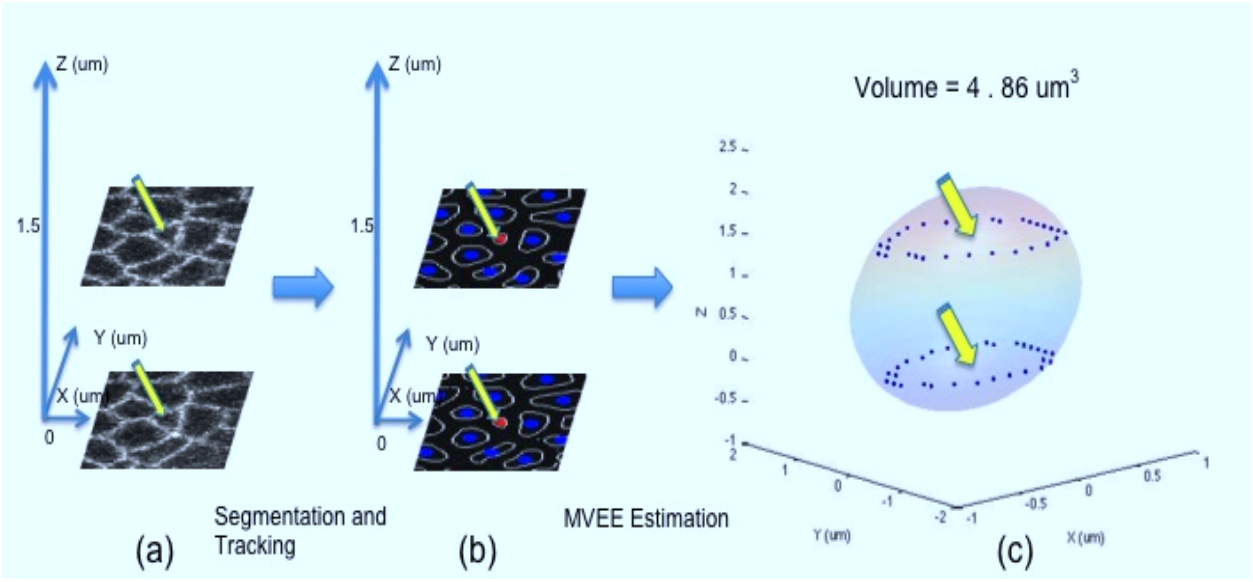

Figure 4: Case 3 - Cell volume estimation when we only have 2 slices per cell. (a)Cell Slices from CLSM, (b)Segmented and Tracked Cell Slices, (c)Contours of one cell in 2 consecutive slices, Estimated MVEE and its volume.

scanning microscopy based live imaging set up to acquire a series of time-lapse images which construct a 4-D stack. The 4-D stack is composed of 24 3-D stacks imaged at a time interval of 3 hours between consecutive observations and these 3-D stacks contain optical slices separated by approximately 1.5 μm. Each of these stacks is registered using the alignment method of maximization of mutual information [14, 9]. Each 2-D slice is then segmented using the existing level-set based segmentation method.

Now, to detect a cell across multiple slices in a 3-D stack we need an automated cell tracking mechanism. For this purpose, we have used the robust tracking algorithm proposed in [8]. This algorithm starts by finding out a *seed cell pair* between two SAM slice images using 'local graph matching' and progressively moves outward from the seed-pair to obtain correspondences between neighboring cells until all the cells are tracked. This method is robust because it fuses tracking results over the entire 4-D image stack and thereby minimizes the chances of losing a cell in any of the slices caused by poor segmentation of noisy data. Another advantage comes from the batch processing capability of this method which enables us to estimate volumes of a large number of SAM cells at a time. Once we can detect a cell in consecutive slices of any 3-D stack, we estimate the minimum volume ellipsoid which encloses all the cell contours of that cell and the cell volume is obtained by computing volume of the estimated ellipsoid.

In the first part of results section we shall show the different steps in the proposed method and how they are applied to various possible situations for computation of cell volumes. We consider three different cases. The first case shows the estimation result on three slices of a cell that are well segmented. The second result is for the case when one of the three cell slices is poorly segmented. And in the third case, we describe a situation when we can not find more than two slices of a cell as the cell is too small to appear in three or more slices.

4.2 Case 1

Figure 2 presents the main steps involved in computing the volume of a cell from its cross sectional slices. Figure 2(a) shows three consecutive optical slices of a SAM cell placed 1.5 μm apart. As we can see from the figure, these cell slices are well segmented and the correspondence between the cell slices in different layers is found by the help of a tracker. A sample of segmented and tracked result is shown in Figure 2(b). The arrows mark the cross sections of a particular cell found in three slices. Finally, Figure 2(c) shows the three contours of the cell we are interested in and also the Minimum Volume Ellipsoid enclosing all the points on the cell contours computed using the method described in the previous section. The volume of this ellipsoid is computed using Equation(13) which is nothing but the approximated volume of the cell.

4.3 Case 2

In Figure 3(a), we can see that the middle slice of the cell is poorly segmented. But the slices above and below are better segmented and that, in effect, makes the resulting MVEE to mitigate the error caused by the middle slice. The advantage of using MVEE over mean or best-fit ellipsoid can be best understood through this case. If we use best fit ellipsoids for this type of data with equal weighting for all the three slices, the estimated cell volume is invariably going to be less than the actual. But the MVEE (Figure 3(c)) takes care of this situation by enclosing all the slices including the better segmented ones thereby compensating for the loss in area of the poorly segmented middle slice.

4.4 Case 3

Figure 4 is used to show the performance of our method in one of the extreme cases where the cell is not large enough to span more than two slices. This is often observed in the peripheral region when the cell is in very early stage of its development. Figure 4(c) shows the estimated ellipsoid from

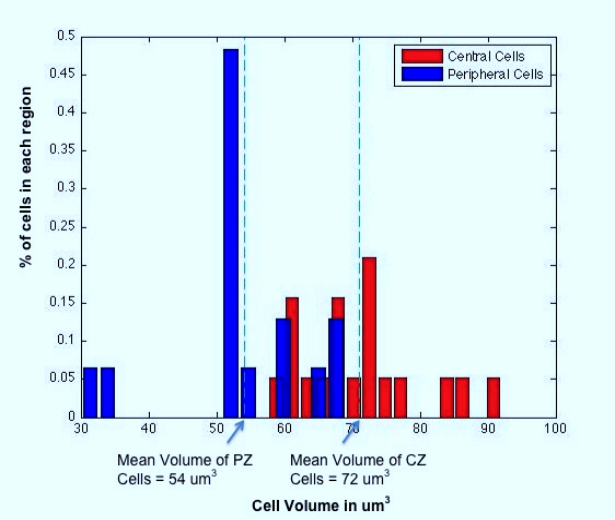

Figure 5: Cell volume distribution in Central Zone(CZ) and Peripheral Zone(PZ) of SAM - Volumes of the CZ cells are shown by red bars and blue bars represent the PZ cells' volumes. It can be clearly noticed from the volume distribution that the central cells are larger than those of periphery.

the two cell slices. The estimation result depends on both the segmentation of the cell slices as well as the number of slices for each cell. The more slices we have per cell, the better the estimation result would be.

4.5 Validation of The Proposed Approach

The SAM cells are organized in three distinct radial domains - the Central Zone, Peripheral Zone and Rib Zone. A small group of large, highly vacuolated cells lie at the tip of the SAM. This cluster of cells, which is the pluripotent stem cell niche, is termed as the Central Zone (CZ). These cells divide at a much slower rate relative to the other cells in the SAM. Beneath the central zone, into the deeper layers of SAM, there is a cluster of large vacuolated cells. This region is known as the Rib Zone (RZ) and it constitutes the bulk of the meristem. The cells in the central zone are surrounded by a group of small, densely staining cells that divide at a much faster rate than the central zone cells. These cells are collectively known as the Peripheral Zone (PZ) cells. A number of papers such as [4] have mentioned about this noticeable difference in cell sizes between the central and the peripheral zones in SAM while comparing them and we have utilized this prior knowledge to perform an experiment for validating our approach.

From the CLSM image stacks, we collected a set of fifty cells (2-4 slices per cell) from both the L1 and L2 layers of the central and peripheral regions. Next, we computed the volume of each of these cells at a time point which is the last observational time point before that cell divided. This is essentially the maximum volume a cell attains on its growth curve. The distribution of these cell volumes for both the CZ and PZ cells is plotted in a single histogram (see Figure 5). The histogram shows a clear difference between the range of cell volumes for these two regions as well as a notable shift between the average volume of the cells. The overlap between the histograms represents the transition region from the central zone to the peripheral zone. It can be noticed that the central zone cells are, in general, larger than the peripheral cells, as expected from the prior biological knowledge. Thus, the outcome of this experiment satisfies a well observed natural phenomenon and indeed validates our approach of volume estimation.

5. CONCLUSIONS

In this paper, we have presented a simple and automated method for estimating the volume of a cell from a very limited number of parallel cross sectional slices obtained through CLSM imaging technique. We have shown that the Minimum Volume Enclosing Ellipsoid (MVEE) can be a reasonably good model for cell volume estimation and it mitigates the error from segmentation of noisy images to a good extent. We tested this method on SAM cells of *Arabidopsis Thaliana* and compared the mean volumes of the central and the peripheral region SAM cells. The results are reasonably good and valid from biological perspectives, too. We are presently trying to improve this method by minimizing the effect of segmentation error on the estimated volume through a neighborhood structure analysis.

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