A UNIFIED APPROACH TO EXPECTATION-MAXIMIZATION AND LEVEL SET SEGMENTATION APPLIED TO STEM CELL AND BRAIN MRI IMAGES

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ABSTRACT

We present a unified approach to Expectation-Maximization (EM) and Level Set image segmentation that combines the advantages of the two algorithms via a geometric prior that encourages local classification similarity. Compared to level sets, our method increases the information returned by providing probabilistic soft decisions, is easily extensible to multiple regions, and does not require solving PDEs. Relative to the basic mixture model EM, the unified algorithm improves robustness to noise while smoothing class transitions. We illustrate the versatility and advantages of the algorithm on two real-life problems: segmentation of induced pluripotent stem cell (iPSC) colonies in phase contrast microscopic images and information recovery from brain magnetic resonance images (MRI).

Index Terms: brain, Expectation-Maximization (EM), induced pluripotent, iPSC, level set, MRI, segmentation, stem cell.

1. INTRODUCTION

Background and motivation. Image segmentation and region identification is a necessary first step in many real life biomedical imaging problems and other applications. Two challenging applications include the segmentation of unstained iPSC colonies in phase contrast images and information extraction from brain MRI scans.

Induced pluripotent stem cells offer many therapeutic and research opportunities, but require constant monitoring to assess quality and pluripotency. The present approaches are: (1) chemical staining, which is rapid and consistent but destructive, rendering a portion of the colony unfit for further experimental or therapeutic use, and (2) visual inspection by a trained microscopist, which is non-invasive but time-consuming and subjective. As an alternative, we have accurately identified stem cells [6], [7], [8] using multiresolution texture analysis as a non-invasive, non-destructive pluripotency biomarker.

Contributions. We exploit the similarity of Expectation-Maximization (EM) and Level Set algorithms to present a unified segmentation routine combining their advantages. A soft classifier, our algorithm yields more information than Level Sets and eases implementation by requiring no solution to PDEs or maintenance of a Level Set function. Furthermore, this approach easily extends to multi-region segmentation without tracking multiple level set functions. In comparison to the EM, our algorithm greatly enhances noise robustness by using a prior based on the geometry of the soft decision, thereby encouraging local classification similarity in a manner that benefits from the insight in [12]. We apply this approach to the disparate tasks of iPSC colony and brain MRI image segmentation.

2. UNIFIED EM / LEVEL SET SEGMENTATION

We first review the EM and level set algorithms before developing the unified approach. The hidden data is the true classification \( Z(x) \), which assigns a class to each pixel \( x \) in image domain \( \Omega \) from set \( C \). Observations \( Y \) are generated stochastically from \( Z \) according to parameters \( \Theta \).
2.1. EM Segmentation

The EM algorithm [4] is an iterative method for estimating $Z$ from $Y$ that is commonly used to segment biomedical images such as brain MRI [11]. At each iteration $k$, the algorithm performs an $E$-Step that updates the soft classification for $c \in C$ according to Bayes’ Rule:

$$p_{k+1}(Z = c \mid Y; \Theta_k) = \frac{p_k(Y \mid Z = c; \Theta_k) p_k(Z = c)}{\sum_{l \in C} p_k(Y \mid Z = l; \Theta_k) p_k(Z = l)} \quad (1)$$
We suppress indexing by \( x \) for legibility. In the \( M\)-Step, parameter estimates \( \Theta \) (including prior \( p_k(Z) \)) are updated via maximum likelihood.

\[
\Theta = \arg \max_{\Theta} p(Y \mid \Theta; Z) \tag{2}
\]

If \( p_k(Z) \) is estimated from the mixture ratio:

\[
 p_{k+1}(Z = c) = \frac{1}{|\Omega|} \sum_{x \in \Omega} p_k(Z(x) = c \mid Y(x); \Theta_k) \tag{3}
\]

the result is the finite mixture model EM (FMM-EM).

### 2.2. Level Set Image Segmentation

Level set algorithms have enjoyed extensive use in image segmentation for over a decade, e.g. [1], [2]. The region competition formulation [13] segments an image into two classes \( c_0 \) and \( c_1 \) by minimizing a functional of an auxiliary surface \( \phi \):

\[
E(\phi, \Theta; Y) = -\int_{\Omega} H(\phi(x)) \cdot \log p(Y(x) \mid c_0; \Theta) \, dx - \nu \int_{\Omega} H(-\phi(x)) \cdot \log p(Y(x) \mid c_1; \Theta) \, dx
\]

\[
- \int_{\Omega} H(\phi(x)) \, dx + \lambda \int_{\Omega} \|
abla H(\phi(x))\| \, dx
\]

As the regularized Heaviside step function \( H(\cdot) \) demarcates the two regions \( \{ x \mid \phi(x) > 0 \} \), the zero level set of \( \phi \) thus partitions the image. Constants \( \nu \) and \( \lambda \) respectively penalize the area of \( c_0 \) and the length of the segmenting contour. This functional is minimized via gradient descent:

\[
\frac{\partial \phi}{\partial t} = H'(\phi(t)) \cdot \left( \log \frac{p(Y \mid c_0; \Theta(t))}{p(Y \mid c_1; \Theta(t))} + \nu + \lambda \kappa(\phi(t)) \right) \tag{5}
\]

where \( \kappa(\phi) \) is the curvature of the iso-contours of \( \phi \).

#### 2.3. A Unified Approach

For two classes, we unify these methods by specifying that the level set function \( \phi \) is equal to the log-likelihood ratio of classification at steady-state:

\[
\phi = \log \frac{p(Z = c_0 \mid Y; \Theta)}{1 - p(Z = c_0 \mid Y; \Theta)} \tag{6}
\]

where \( p(Z = c_1 \mid Y; \Theta) = 1 - p(Z = c_0 \mid Y; \Theta) \). Equivalently, \( \phi \) relates to the soft decision according to the logistic function \( p(Z = c_0 \mid Y; \Theta) = (1 + e^{-\phi})^{-1} \).

The log-likelihood ratio of equation (1) at steady-state is:

\[
\log \frac{p_k(Z = c_0 \mid Y; \Theta)}{1 - p_k(Z = c_0 \mid Y; \Theta)} = \log \frac{p_k(Y \mid Z = c_0; \Theta_k)}{p_k(Y \mid Z = c_1; \Theta_k)} + \log \frac{p_k(Z = c_0)}{1 - p_k(Z = c_0)} \tag{7}
\]

If we assume that parameter estimates \( \Theta \), and hence posterior \( p_k(Y \mid Z; \Theta) \), are equal for both the EM and level set, we may use relation (6) to solve for the prior \( p_k(Z = c_0) \) that causes the right hand side of (5) to be zero:

\[
p_{k+1}(Z = c_0) = \sum_{l \in c} p_{k+1}^m(Z = l) p_k^m(Z = l) \tag{8}
\]

This prior is a function of terms \( p_k^m(Z) \) and \( p_k^i(Z) \) which we define below and whose significance we shall discuss shortly.

\[
p_{k+1}(Z = c_0) = (1 + e^{-\nu})^{-1} \tag{9}
\]

\[
p_{k+1}^i(Z = c_0) = (1 + e^{-\nu})^{-1} \tag{10}
\]

\[
L = \log \frac{p_k(Z = c_0 \mid Y; \Theta_k)}{1 - p_k(Z = c_0 \mid Y; \Theta_k)} + \lambda \kappa(p_k(Z = c_0 \mid Y; \Theta_k)) \tag{11}
\]

Naturally, \( p_i(Z = c_1) = 1 - p_i(Z = c_0) \) for \( i \in \{ g, m, s \} \). Given this prior, steady-state solutions to equations (1) and (5) coincide under the log-likelihood relation (6).

The factorization process in equation (8) represents two distinct aspects of the algorithm. The term \( p_m(Z) \) is a function which is constant with respect to both iteration \( k \) and coordinate \( x \); similar to (3), this mixture prior acts as a constant weight on classification. The quantity \( L \) is the previous log-likelihood of classification smoothed via flow-by-curvature and varies with respect to both \( k \) and \( x \). Therefore, the term \( p^i(Z) \) biases coordinates towards the classification of their neighbors. The smoothing prior thus creates stochastic dependence in a spatially localized neighborhood in order to encourage local classification similarity. As both terms are derived from the geometry of the previous soft classification \( p_k(Z \mid Y; \Theta) \), we refer to the combined (8) as the geometric prior.

Our unified approach is implemented as an EM with priors as specified in (8)-(11) or the above replacements.

#### 3. APPLICATION TO IPSC COLONIES

Here, we automate the segmentation of a set of iPSC colony images by combining our unified EM / level set algorithm with a wavelet energy-based texture feature.
3.1. Data Collection

Induced pluripotent stem cells (iPSCs), line ESIMR90-3 (a gift from J. Thomson, U. Wisconsin) were cultured in feeder-free mTeSR media (Stem Cell Technologies) on Matrigel coated plates (BD Sciences). Colonies were imaged 1-3 days after passing with collagenase (Invitrogen) via phase-contrast microscopy using a 4x Nikon 0.13 NA objective on a TMS cell culture microscope with a 10M Pixel Nikon D40x SLR camera. Light levels and exposure were set to minimize noise while avoiding detector saturation. Images were reduced to grayscale from the green channel as phase contrast optics are optimized for green light and the camera’s Bayer color filter produces slight color registration errors.

3.2. Texture Features

We segment using texture features based on wavelet energy, which we have also used to classify hESC colony images [7]. We compute conditional probabilities:

$$
\log p_k(Y(x) \mid Z = c; \Theta_k) \propto -\sum_{b \in \{h,v,d\}} \left( r^b(x) - \mu^b_k(c) \right)^2
$$

from the second horizontal (h), vertical (v), and diagonal (d) subbands of the stationary wavelet transform [10]. The scaled and squared coefficient at pixel $x$ in subband $b$ is $r^b(x)$, and $\mu^b_k(c)$ is mean energy at $b$ for class $c$ at iteration $k$.

3.3. Analysis

Figure 1 shows the application of our unified algorithm to an iPSC colony. Figure 1a shows the colony with ground truth established under direction of a microscopist outlined in red. Initial conditions are in Figure 1b; the area within the blue contour is set to $p_0(Z = c_0 \mid Y) = 1$, between blue and red $p_0(Z = c_0 \mid Y) = 1/2$, and external to red $p_0(Z = c_0 \mid Y) = 0$. Results for the curvature (equation (10)) and Gaussian (equation (12), $\sigma = 4$) priors are shown in Figure 1c and e, respectively. In both cases, $\nu = 1/2$. In Figure 1d, f, we recover a hard decision by thresholding at $p(Z = c_0 \mid Y) = 1/2$ in order to assess agreement with the ground truth via the Dice coefficient:

$$
d = 2 |A \cap B| / (|A| + |B|)
$$

where $A$ and $B$ are sets identifying the image foreground. In Figure 1, this corresponds to the area in which $p(Z \mid Y; \Theta) \geq 1/2$.

Both solutions exhibit significant agreement with the ground truth; $d = 0.89, 90$ for the curvature and Gaussian priors respectively. Error is largely due to oversmoothing at borders relative to manual segmentation. Since flow-by-curvature and diffusion converge as $p(Z \mid Y; \Theta) \to 0, 1$ [5], the two solutions are nearly identical, and the dice coefficient between these two solutions is $d = 0.99$. As the Gaussian prior is simpler to compute, we prefer it for automation.

In Figure 1g-h, we compare these results to FMM-EM (prior as in (3), $d = 0.41$) and level set ($d = 0.90$) implementations. Due to the high variability of this feature set, adequate performance requires some method of enforcing local similarity, and the FMM-EM fails, finding only the feature peaks.

We then use our algorithm to automate the segmentation of a series of nine iPSC images. To automatically generate initial $p_0(Z)$, we independently thresholded each feature layer [9] and set $p_0(Z = c_0) = 1$ if any one layer exceeded its threshold. This is illustrated in Figure 1i, and Figure 1j plots Dice coefficients $d$ for the nine colonies (mean $d = 0.90$ with standard deviation of 0.05).

4. APPLICATION TO BRAIN MRI

We demonstrate extensibility to multi-region segmentation and robustness to noise by applying our algorithm to brain MRI segmentation, a popular application of the FMM-EM. We use the Montreal Neurological Institute (MNI) brain phantom [3] (Figure 2a), corrupted by noise with 25% power.

Figure 2 compares our unified approach to an FMM-EM when used to segment the phantom into white matter, gray matter, and cerebrospinal fluid (CSF). Both algorithms assume $p(Y \mid Z; \Theta)$ to be Gaussian. The FMM-EM uses the mixture prior (equation (3)), while the unified algorithm uses a Gaussian prior ((12), $\sigma = 3$). Initial $\Theta$ were determined from manually delineated patches (Figure 2b; white matter is blue, gray matter red, and CSF green). No bias or gain correction was performed.

Figures 2c-e show results from the unified approach on gray matter, CSF, and white matter, respectively. In Figure 2f, FMM-EM results are given for white matter. A comparison is made between the two algorithms in Figure 2g, which plots Figure 2e minus Figure 2f. Lighter voxels thus indicate coordinates which the EM / level set classifies as more likely to be white matter and indicate its superior robustness to noise. Based on visual inspection of Figures 2e-g, the unified approach suppresses speckling, causing it to be more confident both in locating white matter in the correct region and rejecting it elsewhere.

5. CONCLUSION

A unified approach to EM and level set segmentation combines the advantages of both algorithms. This methodology retains the topological flexibility of level sets, but is simpler in implementation and more naturally extensible to multiple regions. Relative to the FMM-EM, this approach enhances noise rejection and smoothes class transitions. The results demonstrated indicate that this approach is thus a significant
Fig. 2. MRI Phantom Segmentation: (a) MRI Phantom corrupted by 25% power noise (SNR $20\log_{10}0.8 = -4.5$dB); (b) manual reference patches: white matter (blue), gray matter (red), cerebrospinal fluid (CSF, green); (c) gray matter soft decision from unified approach; (d) CSF from unified approach; (e) white matter from unified approach; (f) white matter from FMM-EM; (g) white matter comparison, results in (e) minus results in (f), positive (light) results indicate the unified approach is more likely to classify voxel as white matter; note the improved noise rejection of the unified approach, (e) is clearly superior to (f) in suppressing speckling due to noise.

step towards the automated, texture-based detection and analysis of iPSC colonies and promotes analysis and classification of highly degraded brain MRI images.

6. REFERENCES


