Characterizing Spatiotemporal Changes in Mitochondrial Morphology using Evolving Networks

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Abstract

The use of fluorescence microscopy has led to the development of new technologies and quantitative modeling approaches as biomedical imaging data has become amenable to analysis through computer vision and machine learning methods. Extracting and modeling quantitative knowledge of biological systems has become more common, and many molecular and cellular phenotypes can now be automatically characterized. However, much of this work is still nascent; in particular, there are a number of approaches to modeling spatial patterns of solid morphologies, such as cell membranes or nuclei, but considerably fewer approaches to modeling diffuse organellar patterns such as mitochondria or actin. Furthermore, little work has focused on the development of spatiotemporal models that capture the relationships between spatial quantities--size, shape, and distribution--as functions of time. Such models are extremely useful for characterizing conditional events, such as the addition of a toxin or invasion by a pathogen.

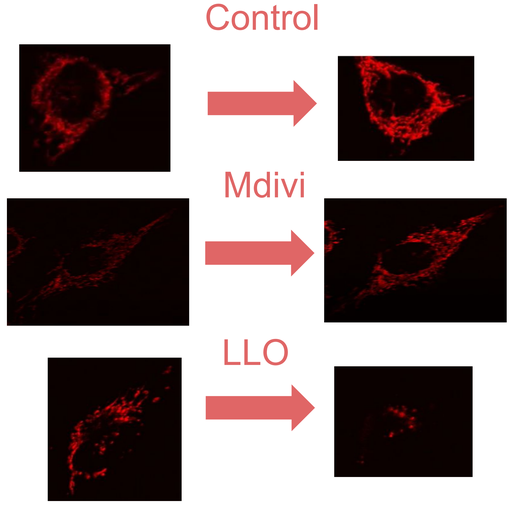
Here, we discuss initial work into building spatiotemporal models of diffuse subcellular morphologies, specifically the mitochondrial protein patterns of alveolar cells. We leverage principles of graph theory and consider the mitochondrial patterns an instance of a *social network*: a collection of vertices interconnected by edges, indicating spatial relationships. By studying the changing topology of the social networks over time, we gain a statistical understanding of the types of stresses imposed on the mitochondria by external stimuli, and can relate these effects in terms of graph theoretic quantities such as centrality, connectivity, and flow. We demonstrate how the gradients of the graph Laplacian underlying the social network, and the changes in its principal components, can yield biologically-meaningful interpretations of the evolving morphology. Our primary goal is the development of a bioimaging toolbox, built from existing open source packages in the scientific Python ecosystem (SciPy, NumPy, scikit-image, OpenCV), which builds dynamic social network models from time series fluorescence images of diffuse subcellular protein patterns, enabling a direct quantitative comparison of network structure over time and between cells exposed to different conditions.

Goal

To build a pipeline for analysis of diffuse subcellular structures using social network analogues

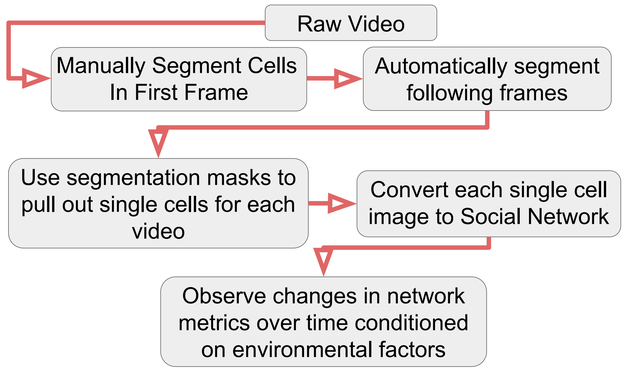
Data

Timelapse footage of mitochondria protein patterns in alveolar cells in three ctegories based on introduced environmental factors

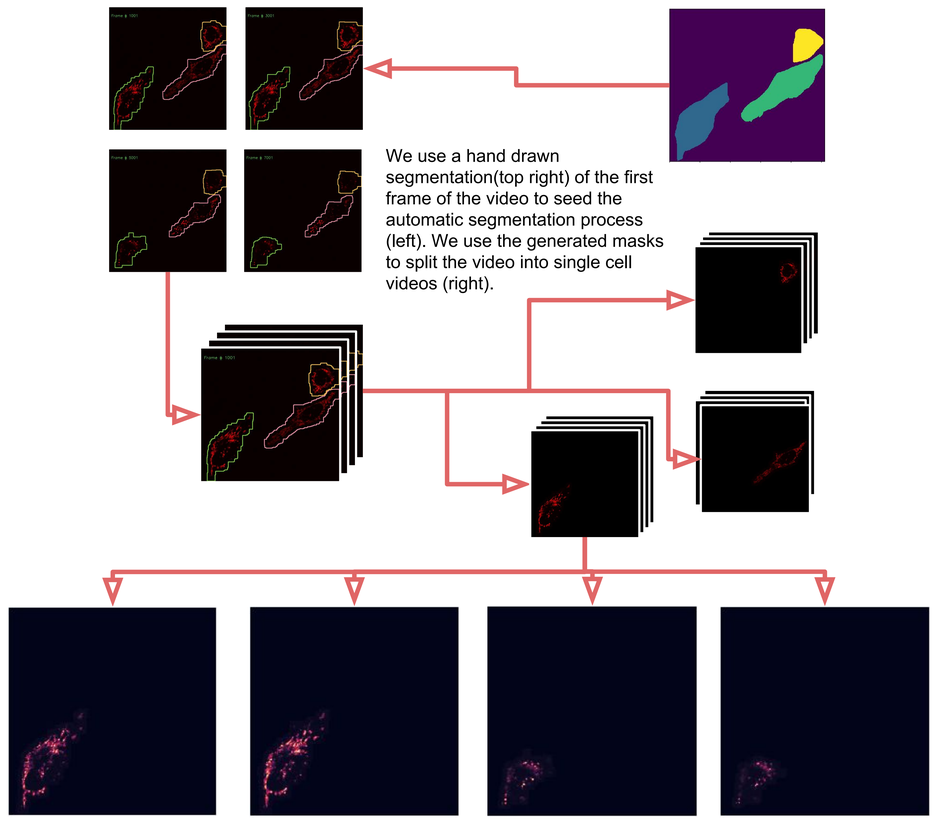


The three classes of data we have are Control, in which the mitochondrial patterns behave normally. Mdivi, which is a mitochondrial division inhibitor, which brings the protein together. And LLO, which causes the protein to divide and fragment

Pipeline



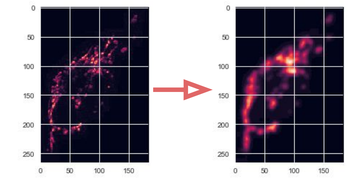
Segmentation Process



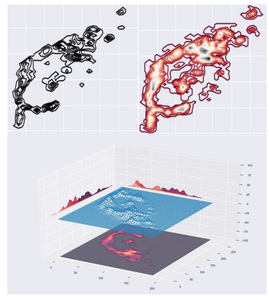
We use a hand drawn segmentation(top right) of the first frame of the video to seed the automatic segmentation process (left). We use the generated masks to split the video into single cell videos (right).

Social Network Construction

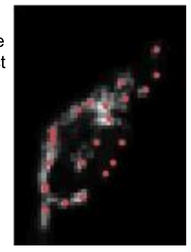
- View each Cell as a 2 dimensional surface
- Find the Number of peaks in the first frame
- Apply a Gaussian Mixture Model
- Create network where each Gaussian is a node and their neighbors are based on the variance



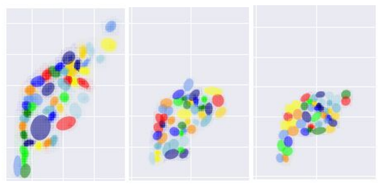
Once the video is split, we apply a filter to remove artifacts from video capture and smooth our later surface.



We look at the contour of the single cell (top) and project it as a surface in 3 dimensional space (bottom). Then we identify and count local maxima in the cell(right), this becomes the number of gaussians in our GMM

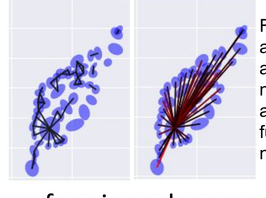


The Gaussian Mixture Model applied to the first (left), five thousandth (mid), and last(right) frames of footage featuring a cell reacting to LLO



Conclusions and Future Work

After applying the Gaussian Mixture Model, we've begun trying various affinity functions to create network out of the data. Once we determine our final affinity functions, we will begin construction networks of each cell and compute their eigenvectors for eigen decomposition.



First attempts at affinity functions, a binary affinity network (left), and a weighted fully connected network (right).

References

"Large-scale Analysis of Spatiotemporal Organellar Network Evolution." _Quantitative Bioimaging Conference_, 2017.

Work supported by NSF-1459766