Generative Spatiotemporal Modeling Of Neutrophil Behavior

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https://github.com/quinngroup/Neutrophils

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ABSTRACT

Cell motion and appearance have a strong correlation with cell cycle and disease progression. Many contemporary efforts in machine learning utilize spatio - temporal models to predict a cell's physical state and, consequently, the advancement of disease. Alternatively, generative models learn the underlying distribution of the data, creating holistic representations that can be used in learning. In this work, we propose an aggregate model that combine Generative Adversarial Networks (GANs) and Autoregressive (AR) models to predict cell motion and appearance in human neutrophils imaged by differential interference contrast (DIC) microscopy. We bifurcate the task of learning cell statistics by leveraging GANs for the spatial component and AR models for the temporal component. The aggregate model learned results offer a promising computational environment for studying changes in organellar shape, quantity, and spatial distribution over large sequences.

INTRODUCTION and GOALS

Polymorphonuclear neutrophil granulocytes (neutrophils) are highly motile and the most abundant white blood cells in most mammals. Study of neutrophils and their underlying motion patterns provide insights into a host's response and behavior as a function of specific stimulus. Following are our goals:

- Simulate and synthesize the behavior of human neutrophils.
- Improve and test our understanding of cell behavior and cellular variation based on these simulations.

RESEARCH QUESTION

Using Generative Adversarial Networks' (GANs) features coupled with a weak motion model, can we realistically simulate a biological system?

PROPOSED APPROACH

We bifurcate the approach of synthesis into 2 tasks, capturing the statistics independently :

i) synthesizing appearance

ii) synthesizing motion

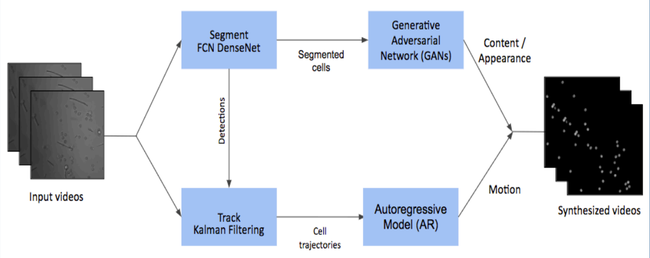

Fig. System Overview

i) Segment: Based on fully convolutional neural networks (CNN), this component reads the input images and generates the segmentation maps. We trained Fully Convolutional DenseNets to automatically segment neutrophils from images.

ii) Track: To develop a motion model and synthesize sequences, neutrophil trajectories are required. Trajectories were extracted by associating the segmented cells across consecutive video frames using Kalman filters based on a constant velocity model.

(these components extract data in relevant format enabling training of the generative models)

iii) Generative Adversarial Network (GANs): Synthetizes images of the cells.

iv) Autoregressive (AR) Models: Linear dynamical systems that synthesize motion of normal and inhibitor treated cells.

I. APPEARANCE

GENERATIVE ADVERSARIAL NETWORKS (GANs)

GANs are an adversarial framework for estimating generative models. They consists of 2 neural networks competing against each other: Generator **(G)** and Discriminator **(D)**.

- **G** generates images from random noise. While doing so, it tries to get as close as it can, to the distribution of real images.
- **D** classifies between the real images and fake images generated by **G**.

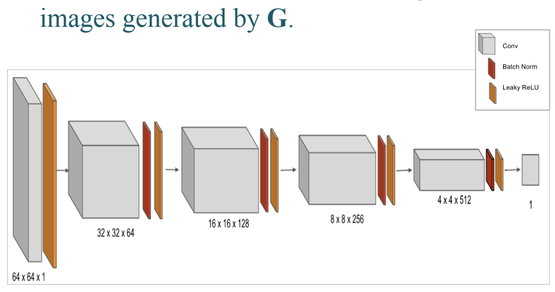

Fig. Architecture of discriminator **(D)**. width x height x no. of feature maps is denoted at the bottom of every block. D reads an image either from real training set or from **G** and after a series of convolutions, classifies it as real or fake.

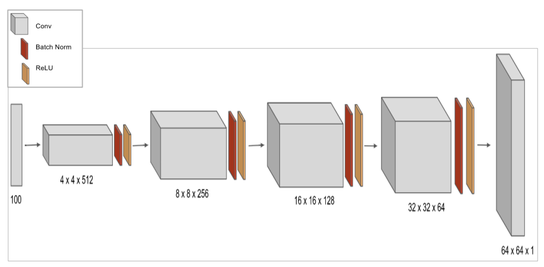

Fig. Architecture of Generator **(G)**. Z - a 100 dimensional uniform distribution is projected to a small spatial extent. 64 x 64 x 1 image is obtained after series of convolutions.

We trained models for 10000 epochs, based on DCGAN architecture with GAN, Wasserstein GAN (WGAN) and Improved WGAN loss functions.

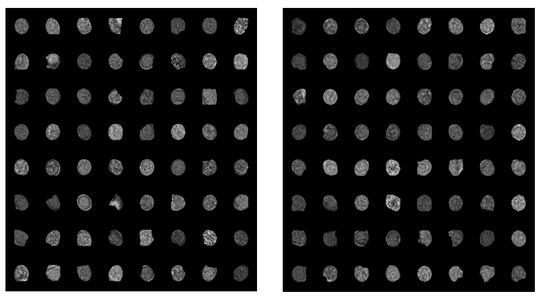

Fig. Real (left) and synthesized (right) images of neutrophil. The synthetic images were created using above GAN architecture combined with Improved WGAN loss function.

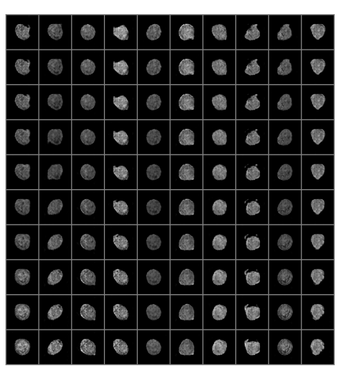

Fig. Interpolating between points in the latent space and understanding the landscape can help to identify if there are any sharp transitions and whether the network has memorized.

II. MOTION

AUTOREGRESSIVE (AR) MODELS

AR is a parametric modeling technique, which models every point in sequence as a linear combination of previous points.

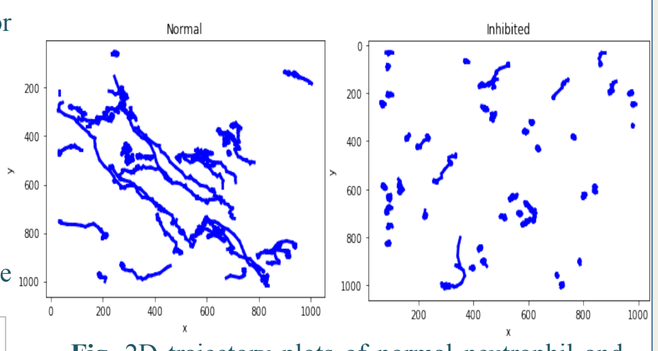

Fig. 2D trajectory plots of normal neutrophil and inhibitor-treated (MRS) neutrophil. The inhibitor-treated (MRS) neutrophil tend to exhibit less movements in comparison to the normal ones.

Different motion patterns are observed based on the cell conditions. We build a global motion model for normal and inhibited cells respectively. Based on the existing motion characteristics, new sequences can be synthesized for the corresponding cells using the learned AR models.

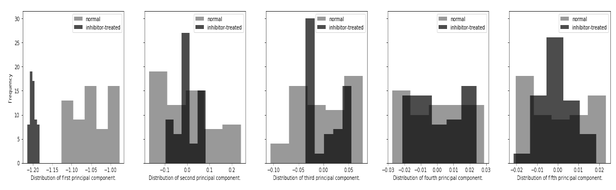

Fig. Histograms show the distributions of values taken by normal (gray) and inhibitor - treated (black) neutrophil for top 5 principal components.

- Trajectories belonging to normal and inhibited cells are pooled separately.
- These high dimensional sequences are then projected into a low-dimensional space using Principal Component Analysis (PCA).
- The original trajectories can be viewed as digital signatures through the low-dimensional space.
- New sequences can then be synthesized by moving through the low-dimensional space and creating similar signatures.

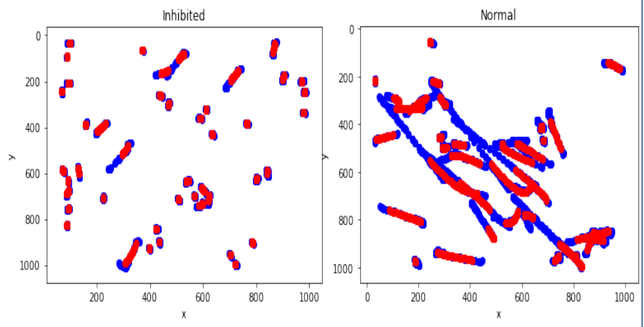

Fig. Synthesized sequences of normal and inhibited neutrophils. To synthesize a sequence we randomly selected a starting point and predicted their motion for 25 frames ahead in the sequence for all the neutrophils. Superimposing synthesized sequences (red) over the original sequences (blue) helps to understand that the synthesized sequences do indeed follow the original distribution.

III. APPEARANCE + MOTION

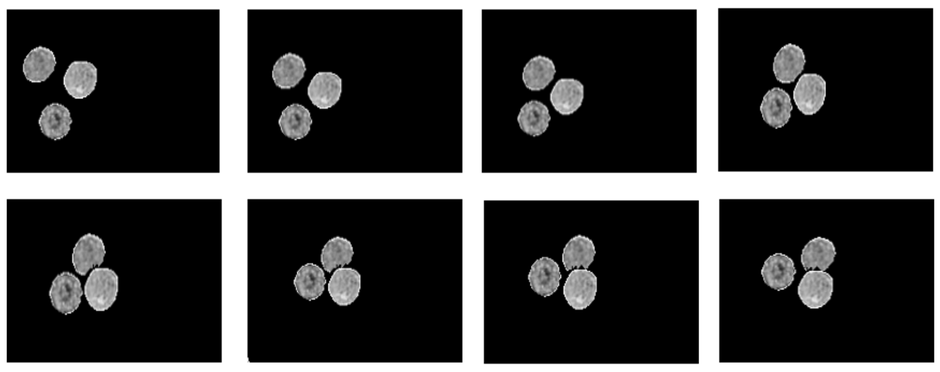

Fig. Sample results of appearance and motion synthesis

DATASET

- Videos imaging the two dimensional motion of human neutrophils were recorded using DIC microscopy.
- Dataset consists: 11 videos, 3 normal neutrophil videos, 8 videos of neutrophils treated with an inhibitor.
- Average length of videos: 3.0secs.
- Using ffmpeg individual grayscale frames of size 1024 x 1024 were extracted at the rate of 20fps.

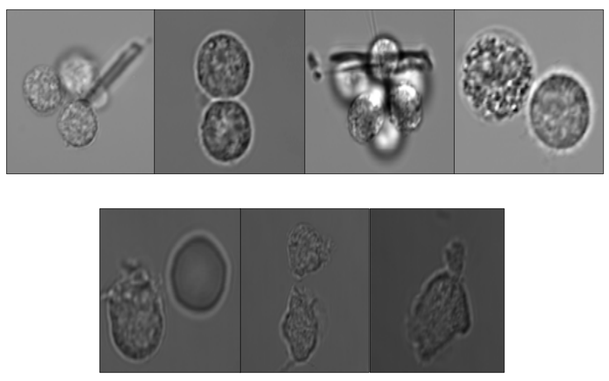

Fig. Sample neutrophil images. Top row represents lobed neutrophils with texture. Bottom row represents cells that are not neutrophils.

CONCLUSION

Owing to the very limited data at our disposal, we utilized:

- GANs to learn the spatial statistics and
- AR models to learn the temporal statistics.

Bifurcation of appearance and motion allows a controlled video generation process. This work can enable us to quantify changes in organellar appearance, spatial distribution and help in understanding how subsets of the organellar ensembles evolve, improving our understanding of cellular mechanisms as they respond to their environments.

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REFERENCES

1. AW. Sehgal, "How Neutrophils Kill Microbes," *Annual Review of Immunology*, vol. 23, 2005.
2. Ian I. Goodfellow, Jean Pouget-Abadie, Mehdi Mirza, Bing Xu, David Warde-Farley, Sherjil Ozair, Aaron Courville, and Yoshua Bengio, "Generative adversarial nets," in *Advances in Neural Information Processing Systems 27*, Z. Ghahramani, M. Welling, C. Cortes, N. D. Lawrence, and K. Q. Weinberger, Eds., pp. 2672– 2680. Curran Associates, Inc., 2014.
3. Alec Radford, Luke Metz, and Soumith Chintala, "Unsupervised representation learning with deep convolutional generative adversarial networks," *CoRR*, vol. abs/1511.06434, 2015.
4. Ziwei Liu, Ping Luo, Xiaogang Wang, and Xiaoou Tang, "Deep learning face attributes in the wild," in *Proceed- ings of International Conference on Computer Vision (ICCV)*.
5. RE. Carazo Salas A. Osokin, A. Chessel and Federico Vaggi, "GANs for biological image synthesis," in *Proceedings of the International Conference on Computer Vision (ICCV)*, 2017.
6. Ruben Villegas, Jimei Yang, Seunghoon Hong, Xunyu Lin, and Honglak Lee, "Decomposing motion and con- tent for natural video sequence prediction," *CoRR*, vol. abs/1706.08033, 2017.
7. Ting Zhao and Robert F Murphy, "Automated learning of generative models for subcellular location: building blocks for systems biology," *Cytometry Part A*, vol. 71, no. 12, pp. 978–990, 2007.
8. Simon Je´gou, Michal Drozdzal, David Va´zquez, Adri- ana Romero, and Yoshua Bengio, "The one hundred lay- ers tiramisu: Fully convolutional densenets for semantic segmentation," *CoRR*, vol. abs/1611.09326, 2016.
9. M. Arjovsky, S. Chintala, and L. Bottou, "Wasserstein GAN," *arXiv preprint arXiv:1701.07875*, 2017.
10. Ishaan Gulrajani, Faruk Ahmed, Mart´ın Arjovsky, Vincent Dumoulin, and Aaron C. Courville, "Im- proved training of wasserstein gans," *CoRR*, vol. abs/1704.00028, 2017.
11. SP. Quinn, MJ. Zahid, Durkin JR, Francis RJ., Lo CW, and Chennubhotla SC, "Automated identification of abnormal respiratory ciliary motion in nasal biopsies," *"Science Translational Medicine"*, vol. 7, pp. 299ra124, 2015.