DynaMorph: self-supervised learning of morphodynamic states of live cells

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1. Background

Cellular morphology and dynamics is widely used to analyze healthy and disease states of cells in clinical pathology and to discover fundamental biological mechanisms. However, due to difficulties in labelling functional states (with either molecular markers or manual annotations), analyzing morphodynamic state of human cells still remains a challenging task. In this work, we seek to develop a high-throughput method based on self-supervised learning that could perform automated quantitative analysis on morphodynamic behavior of human cells.

Previous work on cell morphological analysis has focused on imaging of cells labeled with fluorescent markers or genetic markers, or phase contrast imaging of live cells. Morphological state analysis has relied on low dimensional representations from geometric or biophysical models. Recent introduction of supervised and self-supervised learning enabled more complex and diverse morphological labeling and representations.

Key technological limitations hindered the application of high-throughput analysis on human cells with temporal dynamics: a) Difficulties in labelling live human cells with no/minimum perturbation; b) Huge amount of annotations required for large cell imaging dataset; c) Complexity in morphological description of cell states due to the high dimensionality. Therefore, in this work we explore use of quantitative label-free measurements of cellular morphodynamics and deep learning to overcome these limitations.

We acquired reproducible measurements of cellular architecture and dynamics of human microglia under immunogenic perturbations (Figure 1A) using quantitative label-free imaging with phase and polarization (QLIPP, Figure 1B) (Guo et al., 2020). To discover and identify morphodynamic states, we developed DynaMorph, a self-supervised learning based framework. DynaMorph utilizes a autoencoder based model to learn quantitative and generalizable latent representations of morphology (Figure 1D), resulting descriptors are used for identification of morphological states as well as state transitions (Figure 1E).

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2. Results Highlights

2.1. Label-free imaging of cultured human microglia under diverse perturbations

We performed two sets of label-free imaging experiments on primary human microglia, composed of one control experiment used as training set and one perturbation experiment for validation and cell state discovery. In both experiment phase contrast and retardance channels were reconstructed and used in the following analysis. In the perturbation experiment, multiple treatments relevant to infection or cancer were applied to mimic different inflammatory brain states.

2.2. Learning interpretable description of morphology with unsupervised encoding that generalizes across perturbations

Collected imaging data were first processed by in-house developed segmentation (U-Net (Ronneberger et al., 2015) based) and tracking modules (Jaqaman et al., 2008) to generate patches and movies of individual cells. Then a vector quantized variational autoencoder (VQ-VAE) (van den Oord & Vinyals, 2017) is applied to extract latent representations, which are used as morphological descriptors in downstream analysis. The autoencoder, trained on a combination of reconstruction task and self-supervision task enforced by a temporal matching loss, demonstrates strong robustness and generalizability when applied to unseen test data.

Furthermore, we conducted quantitative analysis on the latent space and observed correlations between top morphological modes and major geometric properties of cells including cell size, peak phase intensity, cell orientation, etc.

Concatenation of latent representations from static frames

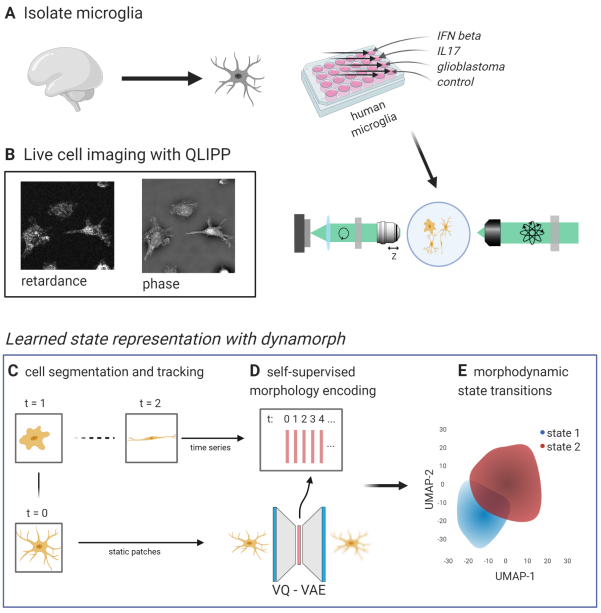

Figure 1. **DynaMorph enables automated discovery of morphodynamic transitions in human microglia: (A)** Human microglia are isolated from brain tissue and plated in 24-well plates and perturbed with cytokines of relevance to infection (IFN beta, IL17) or cancer (glioblastoma supernatant), (B) Morphodynamics of perturbed microglia, along with control cells, are imaged using quantitative label-free imaging with phase and polarization imaging (QLIPP), which measures isotropic and anisotropic optical path lengths of cells. **(C)** Cells were segmented and tracked by in-house developed tools. **(D)** A generalizable and quantitative representation of morphological states was learned from the thousands of tracked cells using a self-supervised model that reconstructs cell morphology. **(E)** Morphological states and transitions among states under each perturbation were revealed via dimensionality reduction (PCA and UMAP) algorithms and clustering of most significant features.

along trajectories allows for study of cell morphodynamics. In our observation, most trajectories that have stable morphology also have localized latent representations, while rare events of cells undergoing morphological transition displayed "leaps" in latent space that could be easily spotted and isolated for further analysis.

2.3. Discovery of cell states from multimodal inputs: morphology and motion

We evaluated the morphodynamic differences between microglia treated with pro- and anti-inflammatory perturbations. Results show that microglia displayed a broad range of morphology and motility upon perturbations. Among the test conditions applied, two major groups: IL17 and IFN beta versus GBM and control could be separated based on top morphological modes and cell movement speed indicator, suggesting existence of multiple cell morphodynamic states.

The hypothesis is further evaluated through an unsupervised clustering of cell morphodynamic descriptors, which are composed of morphological representations (from VQ-VAE) and cell movement speed indicator. We applied Gaussian Mixture Model (GMM) and detected 2 major components representing different morphodynamic states, both having distinct appearance and motion patterns. The separation of two components paralleled well with scRNA sequencing measurement of microglia, which hints a potential correlation between morphodynamic/behavioral change and transcriptomic change in response to perturbation.

3. Paper and Code Availability

Full manuscript of this work is available at https://www.biorxiv.org/content/10.1101/2020.07.20.213074v1

Open source python software for reconstruction of label-free optical properties is available at https://github.com/mehta-lab/reconstruct-order and for analyzing cell states (DynaMorph) is available at https://github.com/czbiohub/dynamorph.

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