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Development of an Automatic Computational Machine Learning Pipeline to Process Confocal Fluorescence Images for Virtual Cell Generation

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Abstract : Background: Microscopy plays a central role in cell and developmental biology. In particular, fluorescence microscopy can be used to visualize specific cellular components and subsequently quantify their morphology through development of virtual-cell models for study of effects of mechanical forces on cells. However, there are challenges with these imaging experiments, which can make it difficult to quantify cell morphology: inconsistent results, time-consuming and potentially costly protocols, and limitation on number of labels due to spectral overlap. To address these challenges, the objective of this project is to develop an automatic computational machine learning pipeline to predict cellular components morphology for virtual-cell generation based on fluorescence cell membrane confocal z-stacks. Methods: Registered confocal z-stacks of nuclei and cell membrane of endothelial cells, consisting of 20 images each, were obtained from fluorescence confocal microscopy and normalized through software pipeline for each image to have a mean pixel intensity value of 0.5. An open source machine learning algorithm, originally developed to predict fluorescence labels on unlabeled transmitted light microscopy cell images, was trained using this set of normalized z-stacks on a single CPU machine. Through transfer learning, the algorithm used knowledge acquired from its previous training sessions to learn the new task. Once trained, the algorithm was used to predict morphology of nuclei using normalized cell membrane fluorescence images as input. Predictions were compared to the ground truth fluorescence nuclei images. Results: After one week of training, using one cell membrane z-stack (20 images) and corresponding nuclei label, results showed qualitatively good predictions on training set. The algorithm was able to accurately predict nuclei locations as well as shape when fed only fluorescence membrane images. Similar training sessions with improved membrane image quality, including clear lining and shape of the membrane, clearly showing the boundaries of each cell, proportionally improved nuclei predictions, reducing errors relative to ground truth. Discussion: These results show the potential of pre-trained machine learning algorithms to predict cell morphology using relatively small amounts of data and training time, eliminating the need of using multiple labels in immunofluorescence experiments. With further training, the algorithm is expected to predict different labels (e.g., focal-adhesion sites, cytoskeleton), which can be added to the automatic machine learning pipeline for direct input into Principal Component Analysis (PCA) for generation of virtual-cell mechanical models.

Keywords : cell morphology prediction, computational machine learning, fluorescence microscopy, virtual-cell models
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