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Image-derived generative modeling of complex cellular organization in both space and time

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Understanding cellular organization is a major goal of systems biology. Cellular organization affects the behavior of cells and many diseases and disorders impact the spatial organization of cells and their morphologies in turn. There are many current means of studying these systems and their effects. High-content imaging is one high-resolution way in which to study the location of proteins within cells. Advances in imaging technologies have allowed for high quality data to be acquired from live cells in three dimensions over time. Historically, imaging data have been analyzed using image-feature based approaches to create models predicting cell state using classification or regression based machine learning. Generative modeling tools such as CellOrganizer offer an alternative approach to modeling cells and their subcellular structures. The added benefit of this class of approaches is that they describe the statistical distributions of cells and can be sampled from to create realistic *in silico* instances of cells and their subcellular organization. Despite our ability to model static subcellular organization, modeling the dynamic restructuring of cells and their components remains a major challenge in systems biology. These subcellular dynamics are strongly correlated with cell cycle and disease progression and understanding them will aid in the development of treatments. Towards this goal we trained generative models describing cellular morphology dynamics by using both time series and static-time cell image datasets. At a more granular level, cell function is dependent on the proteins within it and their interactions. Not only is the organization of cells correlated with cell response, but it may also be a driving force. To study the impact of cell shape and organization on these biochemical interactions we developed a computational pipeline to perform high-throughput spatially resolved simulations using realistic cellular geometries generated with CellOrganizer. In addition to exhibiting complex responses over time, some cells such as neurons are highly morphologically complex. As such, traditional generative modeling methods are ineffective or fail completely. We addressed this issue by expanding the capabilities of CellOrganizer to include models for neuronal shape. Together these works allow for the study of cellular and subcellular structure for realistic and complex cellular morphologies and their dynamic responses over time in high-throughput.

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