Deep Learning for Interpretable Imaging Mass Cytometry

Introduction: Cancer pathology is an incredibly complex field with studies ranging from macroscopic lifestyle choices to the microscopic single cell. With numerous breakthrough advances in single-cell technology, datasets collected toward understanding cancer pathologies are in increasingly higher dimensions. Such is the case with imaging mass cytometry and spectrometry (IMC/IMS) where grids of single cells express over 10 to 40 or more different types of proteins [4]. As such, one can imagine the data space to be an image with possibly over 40 different color channels, one for each type of protein. IMC data is becoming increasingly available, especially within the field of cancer research where snapshot images of tumors are being collected from hundreds of patients [4]. While cell types can be discerned from such datasets, their relationship with patient outcomes is not always immediately obvious. Understanding the composition, spatial features, and cellular dynamics embedded within these datasets are key to furthering our understanding of cancer pathologies.

Intellectual Merit: Conventional methods such as mechanistic modeling may not be suitable for uncovering cell-to-cell dynamics within such a high-dimensional space due to its high computational costs, making large-scale studies infeasible. Furthermore, mechanistic modeling requires a deep prior understanding of the studied system at hand, which is challenging given the complexity of IMC data. Deep learning methods, especially transformer models commonly used in the natural language processing field [3], provide a useful alternative in tackling these sparse high dimensional problems. However, deep neural networks are prone to noise and extreme variations within datasets, both of which are common within single-cell datasets. I intend to (1) extend my prior research experience in analyzing single-cell data in noisy conditions towards deep learning architectures in conjunction with (2) pre-training existing transformer models for tumor classification from IMC data, and (3) use developed model interpretability methods such as Grad-Cam [6] to highlight regions of interest for future study as well as for validating predictions with the accepted literature.

Research Plan: First, to account for single-cell variation and noise, in past research, in collaboration with the Das lab, I have leveraged the commonly-used econometrics method, generalized method of moments (GMM), to perform parameter estimation for mechanistic models on noisy simulated and experimental CyToF data [5]. In recent years, a reformulation of the GMM cost function was developed for deep convolutional neural network architectures with promising results [1]. As it has been shown that transformer models can successfully perform image classification [3], should it be shown that default transformer models fail on IMC data due to intrinsic and extrinsic noise, I will adapt DeepGMM towards transformer models for use in high dimensional imaging mass cytometry data.

As training time for transformer models is often computationally expensive, pre-training, a form of transfer learning, has become mainstream for training these architectures efficiently and effectively [7]. In recent years, transformer models have expanded into the spatial transcriptomics field where a mixture of convolutional neural networks and transformer models were trained to predict RNA sequences from cell histology images [8]. Using their architecture's weights as a baseline, I intend to fine-tune, modify, and scale up from their model to account for the higher dimensional IMC data and perform cell phenotype and tumor type classification tasks for such datasets. Should transfer learning prove unsuitable, I will perform full supervised training using lighter transformer models.

Once trained and if performance metrics are reasonable, I will run interpretability experiments such as Grad Cam and newer transformer interpretability methods using the Deep Taylor Decomposition Principle on the dataset at hand [6] [2]. Such interpretability methods highlight regions in the data that directly affect the model prediction. To validate any interpretability results of the model, a deep dive into the literature is required. If results are consistent with pre-existing literature on cell function and past cancer pathology studies, the interpretability of transformer models may prove useful in uncovering previously unexplored subsets of data.

Broader Impacts: As transformer models are highly flexible with the ability to plug and swap different neural network architectures for any modality of data, their flexibility and ability to identify regions of interest within complex biological datasets provide a useful framework for future experiments. Since domain-specific transfer learning training is becoming widespread for language and vision tasks, the computational costs of training tasks on single-cell data can be reduced, saving time for scientists and researchers. Such contributions would accelerate the processing required for furthering our understanding of cancer. Furthermore, testing transformer models on these highly complex datasets provide a useful testing ground for validating the hypothesis of foundational models and their validity in extreme domains. From another cost perspective, we may be able to abstract the intermediary steps of phenotyping and clustering through the transformer's embedded representations, streamlining the pre-existing IMC data analysis pipeline as shown in Figure 1. Such an area, however, would still need to be explored and tested through interpretability analyses. Due to the project's interdisciplinary nature, I intend to open-source all code for anyone to freely use and modify. In an even broader sense, I deeply agree with Chris Olah's idea of research debt. As models become increasingly complex, the prerequisite knowledge required for research is ever-increasing. I will run workshops, as well as make educational videos and blogs breaking down the underlying mechanics of deep learning architectures through interpretability methods for both undergraduate and high school students. When attempting to break down complex concepts, interpretability and explainability is key.

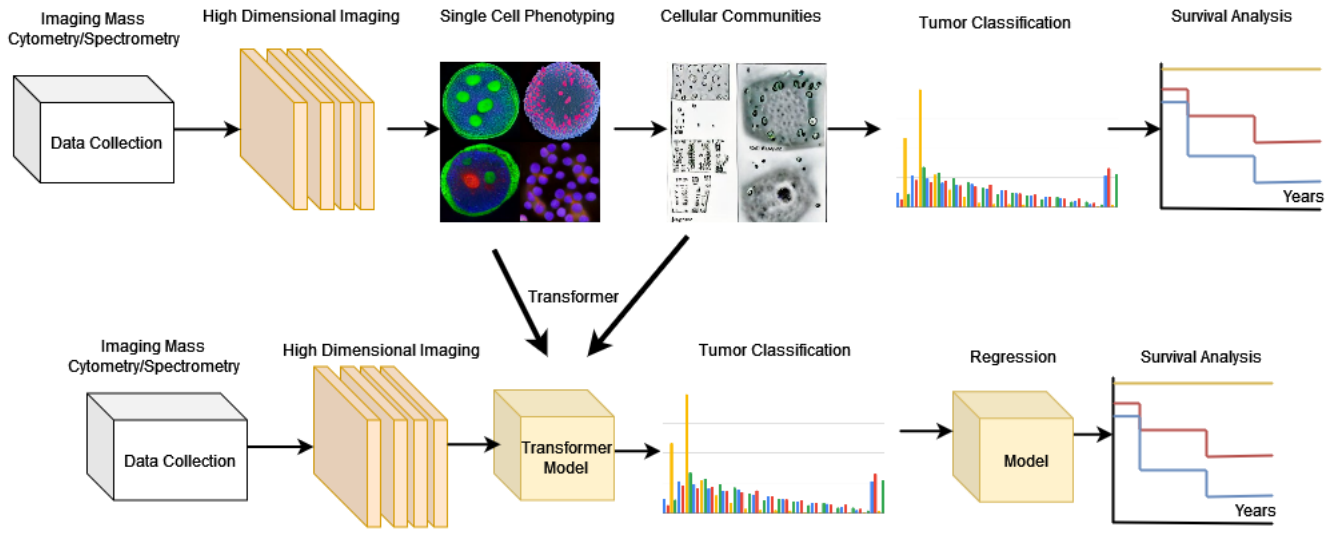

Figure 1: Proposed IMC Workflow: Streamline single-cell phenotyping and cellular community clustering from usual IMC workflow into a single transformer step for tumor classification.