A184 · CellVELA: Functional Alignment of Cell Foundation Models for Cancer Vulnerability Discovery

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CellVELA: Functional Alignment of Cell Foundation Models for Cancer Vulnerability Discovery

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Abstract

Genome-scale CRISPR screens have mapped genetic dependencies across hundreds of cancer models, but their bulk readouts obscure the cellular states associated with target sensitivity. Cell foundation models offer a way to represent those states from single-cell transcriptomes, although it is not yet clear whether their embeddings retain the cancer-specific variation needed to predict vulnerability. We developed CellVELA (Cellular Vulnerability Estimation through Latent Alignment) to align single-cell representations with independently measured CRISPR fitness profiles from matched cancer models. We evaluated the framework in cell lines shared between the Kinker pan-cancer single-cell atlas and DepMap. Its sparse component, FaST (Functional Alignment through Sparse Transcoding), maps pretrained cell embeddings through a compact bottleneck trained against CRISPR dependencies. In held-out cell lines, functional alignment improved dependency prediction in every evaluation fold. The sparse bottleneck retained nearly all of the performance of a dense model, produced more reproducible features, and recovered a program with target-specific attribution on held-out data. Applying the same alignment to expression-derived representations yielded comparable gains, indicating that functional supervision is informative while current pretrained embeddings have not yet surpassed strong expression baselines. We are now applying the framework to osteosarcoma models, where ranked vulnerabilities will be integrated with independent functional evidence and tested experimentally. In the longer term, coupling prediction with experimental validation could enable a lab-in-the-loop AI scientist that learns from experimental outcomes and helps guide cancer vulnerability discovery.