A073 · PerturbRx: Treatment-Conditioned Latent Transitions for Patient Drug Response Prediction

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Patient-level cancer treatment-response prediction remains challenging because clinical response data are limited and matched pre- and post-treatment molecular profiles are rarely available. We introduce PerturbRx, a treatment-conditioned representation learning framework that leverages large-scale single-cell perturbation data to learn latent transitions for patient drug-response prediction. PerturbRx first learns a drug- and dose-conditioned transition predictor in a shared pretrained latent space using context-matched but unpaired control and perturbed populations from the Tahoe-100M single-cell perturbation atlas. The pretrained predictor is then frozen and applied to pretreatment patient transcriptomic profiles to generate patient- and drug-conditioned latent transitions without requiring matched post-treatment measurements. On Tahoe-100M, PerturbRx outperformed identity, global-transition, linear, MLP, and conditional autoencoder baselines in predicting treatment-induced latent transitions, achieving a maximum mean discrepancy (MMD) of 0.0682 and a transition cosine similarity of 0.6715. For patient response prediction on a TCGA benchmark comprising 508 treatment episodes from 462 patients, PerturbRx achieved the highest overall performance among the four evaluated drug-response methods, with an AUROC of 0.692 ± 0.055 and an AUPRC of 0.787 ± 0.055. These results suggest that perturbation-pretrained latent transitions provide useful representations for patient-level drug-response prediction and offer a practical strategy for transferring single-cell perturbation information to settings where only pretreatment patient profiles are available.

PerturbRx: Treatment-Conditioned Latent Transitions for Patient Drug Response Prediction

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Patient-level cancer treatment-response prediction remains challenging because clinical response data are limited and matched pre- and post-treatment molecular profiles are rarely available. Large-scale single-cell perturbation atlases provide an opportunity to learn such drug-induced state changes across diverse drugs, doses, and cellular contexts.

We introduce PerturbRx, a treatment-conditioned representation learning framework that leverages large-scale single-cell data to learn latent transitions for patient drug-response prediction. To do so, PerturbRx first learns a drug- and dose-conditioned transition predictor in a shared pretrained latent space that accounts for both biological and chemical features using frozen scFoundation embeddings and ChemBERTa drug representations. This is done using context-matched but unpaired control and perturbed populations in the Tahoe-100M single-cell perturbation atlas. Next, the pretrained transition predictor is frozen and applied to pretreatment patient transcriptomics to generate patient- and drug-conditioned latent transitions, which are then fed into a multi-layer perceptron (MLP) for binary response prediction.

PerturbRx outperformed linear, MLP, and conditional autoencoder baselines in calculating the distance between predicted transition and ground truth perturbed state transition for Tahoe-100M; it achieved a maximum mean discrepancy (MMD) of 0.0682 and transition cosine similarity of 0.6715. For patient response prediction on a TCGA benchmark comprising 508 treatment episodes from 462 patients, PerturbRx achieved the highest overall performance for binary response labels among four drug-response methods evaluated (AUROC of 0.692 ± 0.055 and AUPRC of 0.787 ± 0.055). Adding the pretrained transition to patient embeddings and drug features improved AUROC from 0.681 to 0.692, whereas shuffled and random transition controls did not reproduce the gain. In an independent patient-derived xenograft benchmark comprising 791 treatment episodes from 177 models across 10 drugs, PerturbRx achieved the highest aggregate performance, with AUROC = 0.669 ± 0.025 and AUPRC = 0.608 ± 0.037. These patient datasets include chemically and mechanistically diverse drugs, such as erlotinib (kinase inhibitor) and cisplatin (DNA cross-linker). Despite this heterogeneity, PerturbRx achieves the highest aggregate AUROC and shows promising transfer to drugs without exact support in Tahoe-100M. These results suggest that perturbation-pretrained latent transitions provide useful representations for patient-level drug-response prediction and offer a practical strategy for transferring single-cell perturbation information to settings where only pretreatment patient profiles are available.

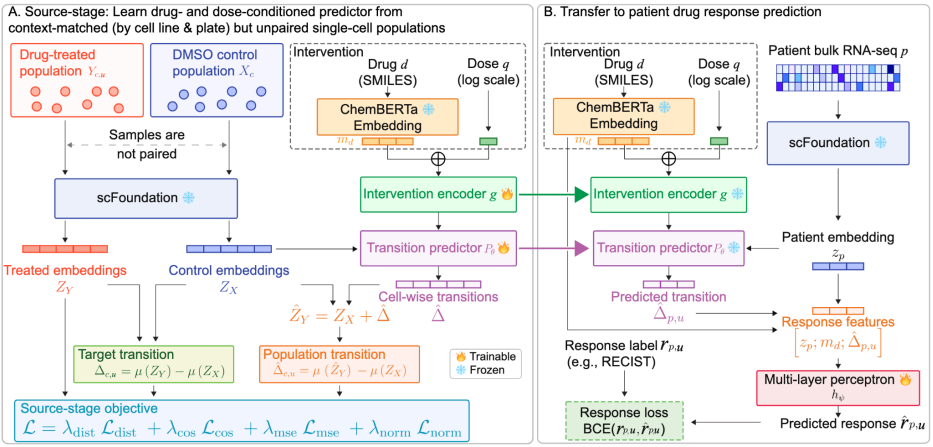

Figure 1. Overview of PerturbRx. (A) A drug- and dose-conditioned latent transition predictor is trained on context-matched but unpaired control and perturbed single-cell populations. **(B)** The pretrained encoder ("Intervention encoder") and predictor ("Transition predictor") are frozen and transferred to pretreatment patient profiles to generate treatment-conditioned transition features for drug-response prediction.