DD-PRiSM: a deep learning framework for decomposition and prediction of synergistic drug combinations

Iljung Jin[1], Songyeon Lee[1], Martin Schmuhalek[2], Hojung Nam[1,2,3*]

[1]School of Electrical Engineering and Computer Science, Gwangju Institute of Science and Technology (GIST), Buk-gu, Gwangju, 61005, Republic of Korea

[2]AI Graduate School, Gwangju Institute of Science and Technology (GIST), Buk-gu, Gwangju, 61005, Republic of Korea

[3]Center for AI-Applied High Efficiency Drug Discovery (AHEDD), Gwangju Institute of Science and Technology (GIST), Buk-gu, Gwangju, 61005, Republic of Korea

Abstract

Combination therapies have emerged as a promising approach for treating complex diseases, particularly cancer. However, predicting the efficacy and safety profiles of these therapies remains a significant challenge, primarily because of the complex interactions among drugs and their wide-ranging effects. To address this issue, we introduce DD-PRiSM (Decomposition of Drug-Pair Response into Synergy and Monotherapy effect), a deep-learning pipeline that predicts the effects of combination therapy. DD-PRiSM consists of two predictive models. The first is the Monotherapy model, which predicts parameters of the drug response curve based on drug structure and cell line gene expression. This reconstructed curve is then used to predict cell viability at the given drug dosage. The second is the Combination therapy model, which predicts the efficacy of drug combinations by analyzing individual drug effects and their synergistic interactions with a specific dosage level of individual drugs. The efficacy of DD-PRiSM is demonstrated through its performance metrics, achieving a root mean square error of 0.0854, a Pearson correlation coefficient of 0.9063, and an R^2 of 0.8209 for unseen pairs. Furthermore, DD-PRiSM distinguishes itself by its capability to decompose combination therapy efficacy, successfully identifying synergistic drug pairs. We demonstrated synergistic responses vary across cancer types and identified hub drugs that trigger synergistic effects. Finally, we suggested a promising drug pair through our case study.