[BIOINFO 2023]

Deconvolution of transcriptomic changes caused by drug multi-target perturbation using matrix factorization

Jieun Sung[1], Wankyu Kim[1,*]

[1]*Department of Life Sciences, Ewha Womans University*

In the process of drug discovery and development, understanding drug mode-of-action (MoA) is an essential but challenging task. Analyzing gene expression changes resulting from drug perturbations offers a systematic and comprehensive means to understand a drug's impact on cellular processes. However, due to the mixed effects by multiple targets (i.e. on-targets and off-targets), it is difficult to clearly decompose the transcriptomic effects by each target of a drug. Here, we propose a matrix factorization model to uncover the relationship between the changes of gene expression and their causal targets. We deconvolute transcriptomic changes caused by drug multi-target perturbation down to a single target. Our model takes a vector of target profile as input and generates normalized transcriptomic changes as output, resulting in a weight matrix of hidden relationship between targets and the resulting expression changes. As a result, the model predicted known drug target interaction with median AUROC=0.85. Moreover, we confirmed that the predicted perturbation profiles of drug targets exhibit reasonably high similarity to the differentially expressed genes induced by the corresponding drugs. Remarkably, the consideration of multi-target effects yielded the highest degree of similarity in comparison to the assessment of individual targets. By clustering targets based on their weight values, each cluster revealed distinct pathway signatures. Furthermore, we employed our model to predict potential therapeutic targets for triple-negative breast cancer, offering the prospect of identifying novel targets for this challenging disease.