Leveraging multi-way interactions for the prediction of anticancer effects of drug combinations

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Combination therapies have emerged as a powerful treatment modality to overcome drug resistance, improve treatment efficacy, and reduce risk of adverse reactions. However, experimental drug combination discovery is complicated by the immense number of possible combinations which increases very rapidly with the number of individual drugs in consideration. Computational approaches can aid this process by offering cost-effective means for large-scale, fast, and systematic pre-screening and prioritization of potential drug combinations for further pre-clinical and clinical evaluation.

In this talk, I will introduce our recent machine learning framework for learning complex functions describing responses of combinatorial therapies in various doses and cancer cell-contexts. We leverage the fact that dose-response matrices of drug combinations can be represented by a higher-order tensor indexed by drugs, their concentrations, and cancer cell lines. The method captures multi-way interactions between the different modes of the tensor using powerful factorization machines that estimate highly nonlinear target functions using symmetric polynomials and factorized parametrization. We demonstrated that our approach produces highly accurate results in several practical prediction scenarios, including the inference of full dose-response matrices for previously untested drug combinations. As an example, experimental validation of the predictions confirmed a novel synergy between anaplastic lymphoma kinase (ALK) inhibitor crizotinib and proteasome inhibitor bortezomib in lymphoma cells.