Speaker: Trey Ideker

Title:
Predicting drug response and synergy using deep learning models of human cancer

Abstract:
Most drugs entering clinical trials fail, often related to an incomplete understanding of the mechanisms governing drug response. Machine learning techniques hold immense promise for better drug response predictions, but most have not reached clinical practice due to their lack of interpretability and their focus on monotherapies. To address these challenges I will describe development of DrugCell, an interpretable deep learning model of human cancer cells trained on the responses of thousands of tumor cell lines to thousands of approved or exploratory therapeutic agents. The structure of the model is built from a knowledgebase of molecular pathways important for cancer, which can be drawn from literature or formulated directly from integration of data from genomics, proteomics and imaging. Based on this structure, alterations to the tumor genome induce states on specific pathways, which combine with drug structure to yield a predicted response to therapy. The key pathways in capturing a drug response lead directly to design of synergistic drug combinations, which we validate systematically by combinatorial CRISPR, drug-drug screening in vitro, and patient-derived xenografts. We also explore a recently developed technique, few-shot machine learning, for training versatile neural network models in cell lines that can be tuned to new contexts using few additional samples. The models quickly adapt when switching among different tissue types and in moving to clinical contexts, including patient-derived xenografts and clinical samples. These results begin to outline a blueprint for constructing interpretable AI systems for predictive medicine.