CHEMICAL AND PHYSICAL BIOLOGY

Modeling drug perturbations at multiple resolutions: Mechanism extraction from multi-omic, multiple timepoint data to single cell mechanistic simulations.

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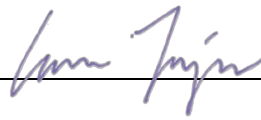
Predicting how cells respond to drugs is a core concept in systems biology modeling. Current available methods for these signaling analyses can be broadly be classified into two categories: local "bottoms-up" and global "top-downs" approach. Bottom-up mechanistic approach builds a simplified but physical representation models based on known consequences of the drug. In contrast, the top-down approach provides an unbiased, global description of the response – albeit at a low resolution. Both methods have limitations. The local approach is time consuming and models limited in scope due to the difficulty in calibrating, simulating, and validating large models. The global approach yields large and complex datasets that impede mechanism of action discovery due to challenges in data management, analysis, visualization, and interpretation. In this work, we develop methods that address limitations on both fronts. First, we introduce methods to extract mechanism from complex time-course multi-omics datasets needed for predictive analysis. We combine data management, enrichment, and network analysis and visualization within an interactive, Jupyter notebook-based environment to enable human-in-the-loop inquiry of complex datasets. Next, we introduce computational methods to expediate the simulation, training, and characterization of mechanistic models. These advances allow the identification of components needed for the construction of large models of drug response as well as enable efficient tools required for their training and characterization.

Approved  Date July 1, 2020