Workshop on Drug Response Measurement and Analysis

Beyond the use of small molecule inhibitors as tool compounds to study a variety of biological processes, assays of cellular response to drugs are a fundamental aspect of the development and characterization of therapeutic molecules and the investigation of drug mechanism of action. However, drug response measurements and their analysis are not as trivial as one thinks and large-scale efforts across panels of cell lines have been plagued by inconsistencies. In addition, the quantification of drug combinations has been a topic of controversy for decades, with multiple methodologies leading to conflicting conclusions. These issues have motivated recent efforts to advance the methodology and theory for drug-response assays. In this workshop, we will present improved experimental and computational methods to generate reproducible dose-response measurements across cell lines, as well as theoretical approaches to quantify the sensitivity of cells to single drugs and drug combinations.

References:

Workshop format and length
The workshop will last three hours and consist of three parts covering different aspects of drug response. Each part will comprise a 35-minute lecture including questions followed by 15 minutes of interactive examples and discussion. We plan on two 15-minute breaks between the parts to answer individual questions.

Main organizers
Marc Hafner, Caitlin Mills, Adam Palmer, and Kartik Subramanian

HMS LINCS Center
Laboratory of Systems Pharmacology
Harvard Program in Therapeutic Science
Harvard Medical School, Boston, MA 02115

Part 1. Reliable measurement of the sensitivity of cancer cells to drug treatments
In preclinical studies of cancer drugs, cells are exposed to multiple drug concentrations and cell viability is measured a few days later. In this section of the workshop, we will introduce the state-of-the-art experimental and analytical tools available for conducting reproducible studies of drug sensitivity and resistance in tumor cells and other cultured cell types. These tools significantly improve upon conventional methodologies for dose-response studies and mitigate artefacts due to manual data collection and handling. The topics covered will include: (1) best practices and automation technology for high-throughput dose-response experiments; (2) experimental design strategies to ensure reproducibility and avoid common pitfalls in cultured cell dose-response studies; and (3) automation of experimental design and analysis of drug-response data.

Exercise: Using software to automatically design and process drug-response experiments.

References:
Part 2. Robust parameterization of drug sensitivity in cell lines

In traditional approaches to quantify drug response, data comprising live cell counts in the presence of drug divided by counts for untreated controls are fitted to a sigmoidal curve to compute metrics such as IC_{50}, E_{max}, and area under the dose–response curve (AUC). In this section of the workshop, we will demonstrate the shortcoming of these metrics when they are used to quantify the sensitivity of dividing cells and will describe new sensitivity metrics, called normalized growth rate inhibition (GR) metrics. The GR method enables researchers to account for the confounding effect of differences in cellular growth rate and to differentiate the cytotoxic and cytostatic effects of drug treatments across dose and time. In addition, we will explain how to use python and R scripts to calculate GR values and metrics and will introduce an interactive website (www.grcalculator.org) for calculation, analysis, and visualization of dose-response data.

Exercise: Analyzing drug-response data using the Growth Rate (GR) metric.

References:
- Clark*, Hafner* et al., GRcalculator: an online tool for calculating and mining dose-response data. BMC Biology, in review.

Part 3. Quantification of drug synergy in combination therapies

Combinations of drugs are widely used in clinical settings, especially to treat infectious diseases and cancers, because combination therapy can synergistically enhance drug response and suppress the evolution of drug resistance. In the laboratory, the use of combination treatments can reveal functional interactions between biological processes. In this section of the workshop we will discuss the current theory and methods to understand and quantify drug interactions, including efficient experimental designs and analysis methods for high-order drug combinations. The basis for long-standing controversies in the field will be addressed by considering how the theoretical underpinnings of different methods define their appropriate experimental use and interpretation. Finally, we will discuss differences between drug combination responses in cell culture and in human patients, where concepts of ‘drug additivity’ and ‘drug synergy’ have different meanings and mechanistic causes.


References:
- Palmer & Sorger, Combination cancer therapy can confer substantial benefit via patient-to-patient variability without drug additivity or synergy. Cell, in review.

Additional Resources
A Harvard Medical School course on assay automation and quantitation:
http://lincs.hms.harvard.edu/cb399

Github resources for automated experimental design:
http://github.com/datarail

HMS – LINCS website supported by the NIH grant U54 HL127365:
https://lincs.hms.harvard.edu/