A154 · A Bayesian approach to dose-response modeling in sparse data regimes

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Dose-response curves are usually generated from assays to understand key biological mechanistic relationships. Typically, measurements and replicates are collected at a dense series of doses to derive biological parameters of interest. However, when designing large-scale experiments over multi-protein, multi-ligand assay panels, it becomes prohibitively expensive to gather data at many different doses. As a motivating example, we examine the readouts from a large-scale experiment testing all combinations of 192 chemically diverse kinase inhibitors against 468 kinases, which measures response only at a limited set of doses (between 2 and 4 for each inhibitor-kinase pair).

The sparsity and spread of concentrations pose strong challenges for standard dose-response fitting algorithms which assume dense coverage of the relevant dose range. To overcome this, we propose a Bayesian framework over a 2-parameter Hill-curve model, representing broad and physically realistic parameter priors and heteroscedastic noise coupled to a chosen numerical sampler or maximum a posteriori probability estimator to reconstruct model parameters.

We compared the proposed framework against 13 existing dose-response log-logistic and sigmoidal style models (from R packages dr4pl, drc, drda, and nplr) spanning 2 to 5 parameters. Results show the Bayesian model remains robust under degenerate and noisy measurements where other methods often fail to converge in these settings. Further, when validating Kd's inferred from dose-response curves against experimental assay data from the ChEMBL database, the Bayesian model outperforms existing approaches both in number of inhibitor-kinase combinations for which it predicts a Kd and mean squared error of predicted Kd's against the experimental reference.