Bayesian Optimization for Dual Agent Dose-Finding Trials

Authors: **James Willard, McGill University and PharmaLex**
Shirin Golchi, McGill University
Erica E.M. Moodie, McGill University
Bruno Boulanger, PharmaLex
Bradley P. Carlin, PharmaLex

Abstract: Identification of optimal dose combinations in early phase, dual agent dose-finding trials is challenging due to the tradeoff between precisely estimating the large number of parameters required to flexibly model the dose-response surfaces, and the limited sample sizes which are characteristic of early phase trials. Historical methods have restricted the dose combination search to pre-defined dose matrices which may fail to identify regions of optimality in the dose combination space. These difficulties – many parameters, small sample sizes, limited dose combinations – are even more pertinent in the context of personalized dose-finding, where additional patient characteristics are used to identify tailored optimal dose combinations. To overcome these challenges, we propose the use of Bayesian Optimization (BayesOpt) to finding optimal dose combinations in standard ("one size fits all") and personalized dual agent dose-finding trials. BayesOpt is a method for globally optimizing expensive-to-evaluate black-box objective functions. It is a sequential design strategy which approximates the objective function using a Gaussian Process surrogate model and utilizes a so-called acquisition function to determine at which point in the domain to evaluate next. This work is motivated by an industry sponsored problem, where the focus is on finding an optimally efficacious dose combination in an oncology setting featuring low-grade toxicities. To illustrate the method's performance, a survey of findings from extensive simulations studies is presented. We close by discussing future extensions that can handle higher-grade toxicity settings via a clinical utility index.