ADAPTIVE EXPERIMENTAL DESIGN FOR DRUG COMBINATIONS

Mijung Park, Marcel Nassar, Brian L. Evans, Haris Vikalo

Department of Electrical and Computer Engineering
The University of Texas at Austin, Austin, Texas 78712 USA
Email: {mjpark@mail, mnassar@mail, bevans@ece, hvikalo@ece}.utexas.edu

ABSTRACT

Drug cocktails formed by mixing multiple drugs at various doses provide more effective cures than single-drug treatments. However, drugs interact in highly nonlinear ways making the determination of the optimal combination a difficult task. The response surface of the drug cocktail has to be estimated through expensive and time-consuming experimentation. Previous research focused on the use of space-exploratory heuristics such as genetic algorithms to guide the search for optimal combinations. While being more efficient than random sampling, these methods require a considerable amount of experiments to converge to good solutions. In this paper, we propose to use an information-theoretic active learning approach under the Bayesian framework of Gaussian processes to adaptively choose what experiments to perform based on current data points. We show that our approach is able to reduce the number of required data points significantly.

Index Terms— Drug Combinations, Active Learning, Experimental Design, Kernel Methods, Gaussian Process

1. INTRODUCTION

In the era of personalized medicine, finding effective drug combinations is of vital importance. Drug cocktails often provide more effective cures than single agents for complex diseases such as hypertension and cancer [1]. This is mainly because such diseases result from biological dysfunction in complex biological networks, which needs therapeutic interventions not on a single target but on multiple targets [2]. Traditionally, combination therapies rely on exhaustive empirical clinical experience which is expensive, time consuming, and suboptimal. As a result, an automated closed-loop directed search for drug combinations is highly desirable. However, this problem poses the following challenges: 1) the nonlinear response of drug combinations which is difficult to predict; and 2) the myriad number of possible drug combinations and their various doses result in an intractable solution space.

Prior work is based on stochastic search algorithms that guide the drug exploration in a closed-loop fashion such as the Gur Game proposed in [3] and a hill climbing-genetic hybrid proposed in [1]. This approach, however, considers combinatorial drug combinations and is inherently discrete and does not generalize well when considering continuous doses as design parameters. Another combinatorial approach, inspired by communications decoding algorithms, is presented in [2]. In this work, a directed combinatorial search is performed on the tree of possible drug combinations in the hope of arriving to a good drug candidate. However, this approach suffers from high computational complexity and the lack of any guarantees on the obtained solution. More importantly, both of the aforementioned approaches do not take into account the experimental error (i.e. measurement noise) that is involved in collecting biological measurements.

As a result, we propose a novel statistical continuous-dose solution to this problem based on the active learning paradigm. Active learning forms a closed loop by selecting experiments that optimize the exploration of the solution space, thereby reducing the number of experiments needed. This offers significant savings in time and cost, and has been widely applied in many fields such as robotics [4].

In this paper, we propose to use an information-theoretic active learning approach in the framework of Gaussian processes to optimize the drug combination design for the epidermal growth factor receptor (EGFR) signaling network [5]. Our method is able to find the optimal drug combination at a fraction of that required by random sampling and a genetic algorithm search.

2. PROBLEM STATEMENT

Consider a drug cocktail consisting of D drug candidates. Let $\mathbf{x} = [x_1 \cdots x_D]^T$ be a vector representing the normalized dose of each drug; i.e. x_i is the dose of drug i in the total drug combination. Further, let us denote the biological system response to a drug cocktail $\mathbf{x}$ by $f(\mathbf{x})$. This function is usually unknown which makes designing drug combinations that optimize it difficult. Without loss of generality, we assume that it is desired to minimize the response function. In a given experimental trial n of a drug cocktail $\mathbf{x}_n$, we observe y_n given by

$$y_n = f(\mathbf{x}_n) + \epsilon_n \tag{1}$$

where $\epsilon_n \sim \mathcal{N}\left(0, \beta^{-1}\right)$ is the experimental error assumed to be independent and identically distributed (*i.i.d.*). The experimental error can be reduced by averaging the result of multiple experiments at the same $\mathbf{x}_n$. We seek to find $\mathbf{x}^*$ such that

$$\mathbf{x}^* = \arg\min_{\mathbf{x}} f(\mathbf{x}). \tag{2}$$

However, given that $f(\cdot)$ is unknown, we need to learn it by experimental exploration in addition to optimizing its response. In practice, we seek to find $\hat{\mathbf{x}}$ such that its response satisfies

$$|f(\hat{\mathbf{x}}) - f(\mathbf{x}^*)| < \epsilon \tag{3}$$

where ϵ is a specified tolerance.

3. GAUSSIAN PROCESSES FOR REGRESSION

A Gaussian process (GP) is a probability distribution over functions $f(\mathbf{x})$, where the set of $f(\mathbf{x})$ values evaluated at an arbitrary set of points $\mathbf{x}_1, \cdots, \mathbf{x}_N$ has a joint Gaussian distribution, which is specified completely by the mean and the covariance [6]. Here, we put a GP prior on the unknown function $f(\mathbf{x})$ that we aim to model. In general, with no prior information about $f(\mathbf{x})$, the mean is assumed to be zero. The covariance of $f(\mathbf{x})$ evaluated at any two data points $\mathbf{x}_m$ and $\mathbf{x}_n$ is defined by a kernel function $k(\mathbf{x}_m, \mathbf{x}_n)$ that can be specified by some hyperparameters θ. Thus, the GP prior over the function is given by

$$P(\mathbf{f}|\mathbf{X}, \theta) \;=\; \mathcal{N}(\mathbf{f}|0, \mathbf{K}), \tag{4}$$

where $\mathbf{K}$ is a covariance matrix whose element is $k(\mathbf{x}_m, \mathbf{x}_n)$. Given a data set $\mathcal{D} = \{\mathbf{X}, \mathbf{y}\}$ where $\mathbf{X} = \{\mathbf{x}_n^T\}_{n=1}^N$ and the corresponding targets $\mathbf{y} = \{y_n\}_{n=1}^N$, the joint distribution of the observations from eq. 1 is

$$P(\mathbf{y}|\mathbf{X}, \mathbf{f}) \;=\; \mathcal{N}\left(\mathbf{y}|\mathbf{f}, \beta^{-1}\mathbf{I}\right), \tag{5}$$

where $\mathbf{f} = f(\mathbf{X})$ and $\mathbf{I}$ is a $N \times N$ identity matrix. By Bayes rule, the posterior distribution is given by

$$P(\mathbf{f}|\mathcal{D}) = N(\mathbf{f}_{map}, \Lambda), \tag{6}$$

where $\mathbf{f}_{map} = \beta\Lambda\mathbf{X}^T\mathbf{y}$ and $\Lambda^{-1} = (\beta\mathbf{X}^T\mathbf{X} + \mathbf{K}^{-1})$.
We choose to use the following kernel function, since biological systems are in general assumed to be smooth:

$$k(\mathbf{x}_m, \mathbf{x}_n) = \theta_0 \exp\left[-\frac{\theta_1}{2}||\mathbf{x}_m - \mathbf{x}_n||^2\right] + \theta_2 + \theta_3\mathbf{x}_n^T\mathbf{x}_m, \tag{7}$$

where a point estimate of the the hyperparameters $\theta = (\theta_0, \theta_1, \theta_2, \theta_3)$ can be set by maximizing the likelihood of hyperparameters (the so-called *evidence*) given by

$$\hat{\theta} \;=\; \arg\max_{\theta} P(\mathbf{y}|\mathbf{X}, \theta), \tag{8}$$

$$\;=\; \arg\max_{\theta} \int P(\mathbf{y}|\mathbf{X}, \mathbf{f}) P(\mathbf{f}|\mathbf{X}, \theta) d\mathbf{f}. \tag{9}$$

Finally, the predictive distribution $P(\mathbf{f}^*|\mathcal{D}, \mathbf{X}^*)$ at any test points $\mathbf{X}^*$ is given by (see [6] for the derivation)

$$P(\mathbf{f}^*|\mathcal{D}, \mathbf{X}^*) \sim N(\mu, \Sigma), \tag{10}$$

$$\text{where} \quad \mu = K(\mathbf{X}, \mathbf{X}^*)^T\mathbf{C}_N^{-1}\mathbf{y}, \tag{11}$$

$$\Sigma = K(\mathbf{X}^*, \mathbf{X}^*) - K(\mathbf{X}, \mathbf{X}^*)^T\mathbf{C}_N^{-1}K(\mathbf{X}, \mathbf{X}^*). \tag{12}$$

where $\mathbf{C}_N$ is the $N \times N$ covariance matrix whose elements are $C(\mathbf{x}_m, \mathbf{x}_n) = k(\mathbf{x}_m, \mathbf{x}_n) + \beta^{-1}\delta_{mn}$ for $n, m = 1, ..., N$. $K(\mathbf{X}, \mathbf{X}^*)$ and $K(\mathbf{X}^*, \mathbf{X}^*)$ are matrices evaluated at all pairs of training and test data points, and at all pairs of test points respectively.

4. INFORMATION-THEORETIC ACTIVE LEARNING

To characterize $\mathbf{f}$ rapidly from limited data, one can actively query data using an optimal criterion. Here, we use an information-theoretic approach that selects the next input in order to maximize the expected information gain about $\mathbf{f}$, equivalently, the expected change in entropy of $\mathbf{f}$ [7]. Let $\{\mathbf{x}, y\}$ denote a candidate input chosen from a grid of (evenly-spaced) points defined in the input space, and the corresponding future output. The criterion is give by:

$$\mathbf{x}^* \;=\; \arg\max_{\mathbf{x}} \mathbb{E}_{p(y|\mathbf{x},\mathcal{D}_t)}[H(\mathbf{f}|\mathcal{D}_t) - H(\mathbf{f}|\mathcal{D}_t, \mathbf{x}, y)],$$

$$\;=\; \arg\max_{\mathbf{x}} \tfrac{1}{2}\log|\Sigma_t| - \tfrac{1}{2}\log|\Sigma_{t+1}|, \tag{13}$$

$$\;=\; \arg\max_{\mathbf{x}} \tfrac{1}{2}\log(1 + \beta u^T\Sigma_t u). \tag{14}$$

We obtain eq.13 since the predictive distribution (eq.10) is Gaussian distributed. Eq.14 is based on the fact that the posterior at $t+1$ is proportional to the product of the posterior at t and the likelihood at $t+1$, i.e., $\Sigma_{t+1}^{-1} = \Sigma_t^{-1} + \beta uu^T$, where u is a column vector, whose entries are all zeros except that an entry is 1, where the new input is located. Further, we obtain $\log|\Sigma_{t+1}| = -\log(1 + \beta u^T\Sigma_t u) + \log|\Sigma_t|$, using the matrix determinant lemma.
Under the GP-Gaussian model, this approach is tantamount to the *D-optimality* criterion and *uncertainty sampling* [8], where the learner queries the instance which currently has the highest variance (assuming the same noise β on all measurements). After measuring the output given the selected point, we compute the posterior mean in order to find the best drug combination where the function is minimized. The algorithm is summarized in Algorithm 1.

5. PRIOR WORK: GENETIC ALGORITHM

For comparison purposes, we implemented the genetic algorithm first proposed by Holland (1975). Genetic algorithms randomly vary combinations of drugs in the first generation. In the consecutive generations, based on the knowledge from

Algorithm 1 Adaptive sampling using maximum information gain under a GP-Gaussian model

Repeat

1. Given $\mathcal{D}_t$, estimate θ by maximizing evidence (eq.9) and update the posterior (eq.10).
2. Given θ, search a new combination $\mathbf{x}_{t+1}$ that has the largest predictive variance (eq.14), and measure the corresponding output y_{t+1}.

Until a stopping criterion is satisfied.

the previous generation, the algorithm generates new sample points in a search space in a way of achieving the maximum fitness [9]. Thus, this method is commonly used to efficiently search enormous solution spaces. However, the process sometimes gets stuck in a local maximum of the fitness function and also it performs poorly under the presence of noise.

6. SIMULATION RESULTS

6.1. The EGFR signaling network

We tested our algorithm on the epidermal growth factor receptor (EGFR) network. The EGFR is a type of tyrosine kinase receptor and plays a key role in regulation of cellular proliferation, differentiation, and survival [5]. The EGFR is often over-expressed in various tumor cells and the activation of EGFR hinders chemotherapy and radiation treatment in tumor cells. Thus, inhibiting the EGFR is desired to improve the activity of anticancer drugs.

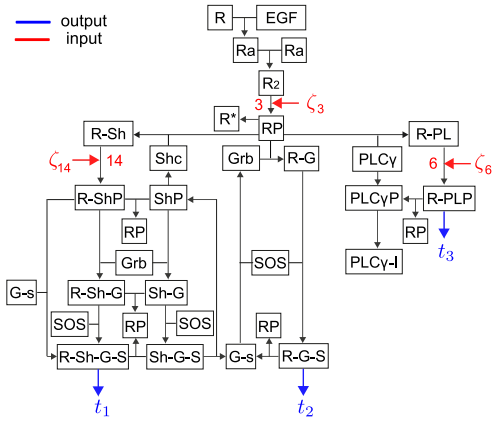

Fig. 1. Kinetic scheme for EGFR signaling network (adapted from [10] and [11]): There are three cycles: Shc cycle, Grb cycle, and R-PL cycle. These are interconnected via cross-talk and feedback leading to a highly non-linear interaction.

Figure 1 shows the EGFR signaling network studied in [10] and [11], which comprises 23 variables (names in each box) that changes 25 kinetic reactions (nodes) and 50 associated rate constants (forward and reverse rate constants in each node are given in appendix A of [11]). The temporal evolution of this set of variables can be explained by 23 coupled ordinary differential equations [11]. The three nodes (3), (6), and (14) are where the tyrosine kinase inhibitors are applied directly. The inverse inhibition rate is defined as a pre-multiplier ζ_i at each node ($i = 3, 6, 14$) respectively. Note that $\zeta_i = 1$ means no inhibition and $\zeta_i = 0.1$ means 90% inhibition. The effect of the inhibitors is a reduction in the forward rate constants in the nodes. In this network, the key variables are the most downstream variables in each of the pathways, i.e. R-Sh-G-S, R-G-S, R-PLP. For example, the downstream target of R-Sh-G-S and R-G-S is the membrane-bound Ras protein which may activate other signaling proteins to relay the signal downstream to other cytoplasmic and nuclear targets [11].

6.2. Objectives

Here, we wish to attenuate the downstream signals (R-Sh-G-S, R-G-S, R-PLP) in the EGFR network. In addition to that, we take the toxicity of doses that may increase therapeutic benefit into account. Thus, two objectives in this paper are: 1) lower the key output variables, R-Sh-G-S: t_1, R-G-S: t_2, and R-PLP: t_3, and 2) lower the toxicity of drug combinations: t_4, by varying the combinations of three inhibitors applied to nodes (3, 6, 14).

6.3. Key Assumptions

Here are the key simulations assumptions:
1. The variable for the dose of each drug is continuous and the allowed inhibition is between 1% and 90%(equivalently $0.1 \leq \zeta_i \leq 0.99$).
2. The target variables t_1, t_2, t_3 are equally important and thus, without loss of generality, we assume they have been normalized.
3. The toxicity of each drug is defined as $1 - \zeta_i$. Thus, the total toxicity of a combination of three drugs is defined as $t_4 = 3 - \sum \zeta_i$. We predetermined the toxicity threshold as 2 (this number was randomly chosen, and in practice the user can choose any number for this constraint). Therefore, any drug combination whose toxicity is larger than 2 are ignored.
4. The target is a single variable that depends on the input variables in a highly non-linear fashion. The target variable is defined as following:

$$f = \sum_{i=1}^{3} \exp(t_i). \tag{15}$$

First, we used 50 data points (i.e. 50 experiments) and examined the performance of genetic algorithms, random sampling, and the adaptive sampling using the maximum information gain. In Figure 2, the estimated three target variables,

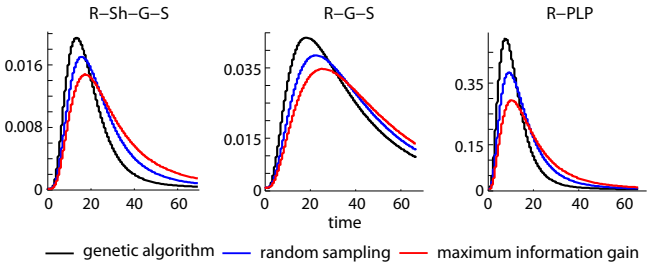

Fig. 2. The most downstream variables (R-Sh-G-S, R-G-S, R-PLP) in the pathways of EGFR signaling network in Fig. 1. The proposed method (red line) achieved the smallest peak values of three target variables in Fig. 2, which coincides with the minimum target value in table 1.

Table 1. Input variables and target values in Fig. 2

Method	ζ_3	ζ_6	ζ_{14}	Target
Genetic	0.3324	0.4294	0.4354	6.8852
Random	0.1502	0.5032	0.6196	6.2074
Max Info	0.1000	0.4333	0.6251	4.7006

'R-Sh-G-S' (t_1), 'R-G-S' (t_2), and 'R-PLP' (t_3) are shown. In GP, 90% of the data (i.e. 45 data points) were used to set the hyperparameters in the kernel function by the simple gradient method [1] and 5 experiments were done to find the best combination. Table 1 shows the solutions of the drug doses by each method and the normalized-combined target values (eq.15) at the each solution.

Next, we varied the number of samples (experiments) and checked how the target values change in each method. Figure 3 shows the simulation results that are the mean of 100 trials at each data point. In each trial, we drew new samples rather than adding the samples, which is why the graphs are not monotonically decreasing. Notice that the maximum information gain criterion outperformed other methods, even when the limited number of data points are observed. For initialization of hyperparameters, we drew a coarse grid over four-dimensional space of hyperparameters, computed evidence at those points, and finally fixed the point maximizing the evidence to the initial values of hyperparameters. Genetic algorithm performed even worse than random sampling under the existence of noise.

7. CONCLUSION

In this paper, we proposed to use an information-theoretic active learning paradigm to find the best drug combination while using the least number of experiments as possible. We tested our algorithm on an EGFR network and showed that our approach requires significantly less data than other methods.

[1] The derivative expression of the log marginal likelihood is given by [12]

$$\frac{\partial}{\partial \theta_i} \ln P(\mathbf{y}|\mathbf{X},\theta) = -\frac{1}{2} Tr\left(\mathbf{C}_N^{-1}\frac{\partial \mathbf{C}_N^{-1}}{\partial \theta_i}\right) + \frac{1}{2}\mathbf{y}^T\mathbf{C}_N^{-1}\frac{\partial \mathbf{C}_N^{-1}}{\partial \theta_i}\mathbf{C}_N^{-1}\mathbf{y}.$$

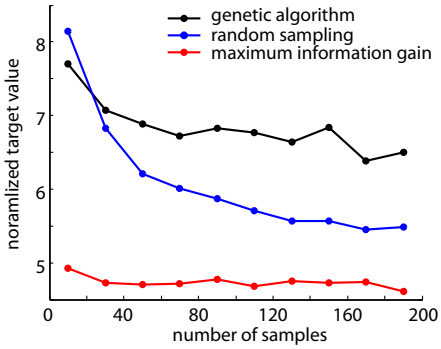

Fig. 3. Target value change with the increasing samples. Note that the proposed method even with a very small amount of data (e.g., 10 data points) outperformed the other two methods.

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