A Deep Bayesian Bandits Approach for Anticancer Therapy: Exploration via Functional Prior

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Abstract

Learning personalized cancer treatment with machine learning holds great promise to improve cancer patients’ chance of survival. Despite recent advances in machine learning and precision oncology, this approach remains challenging as collecting data in preclinical/clinical studies for modeling multiple treatment efficacies is often an expensive, time-consuming process. Moreover, the randomization in treatment allocation proves to be suboptimal since some participants/samples are not receiving the most appropriate treatments during the trial. To address this challenge, we formulate drug screening study as a ‘contextual bandit’ problem, in which an algorithm selects anticancer therapeutics based on contextual information about cancer cell lines while adapting its treatment strategy to maximize treatment response in an “online” fashion. We propose using a novel deep Bayesian bandits framework that uses functional prior to approximate posterior for drug response prediction based on multi-modal information consisting of genomic features and drug structure. We empirically evaluate our method on three large-scale in vitro pharmacogenomic datasets and show that our approach outperforms several benchmarks in identifying optimal treatment for a given cell line.

1. Introduction

Compared to conventional clinical guidelines, treating cancers as homogeneous entities, precision oncology approaches seek molecular targets for each individual. By using individuals’ genomic signatures and identifying druggable targets, the landscape of precision oncology has progressed rapidly. The development of molecular and genetic models has been made possible through several recent large-scale efforts to profile panels of human cancer cell lines and drugs. (Yang et al., 2012; Jordi et al., 2012; Iorio et al., 2016). Recently, with the advance in machine learning, predicting drug sensitivity has been studied extensively. (Preuer et al., 2017; Zagidullin et al., 2019). Major efforts have been made in an offline setting where a model is first trained to predict drug sensitivity based on gene expression in a static training dataset, then it is used to predict the rank of drugs for an unseen test set. (Suphavilai et al., 2018)

In this paper, we argue that offline learning is not ideal in treatment recommendation for precision oncology for three reasons: 1) Therapies recommended by an offline approach are limited by treatment options that were included in the training dataset, in other words,
those that have been explored; whereas, in reality, new therapeutics with better efficacy could be introduced at any time. 2) Moreover, if the training dataset is collected by a biased strategy (e.g., not containing the cancer types or subtypes considered in the testing phase), it may easily be trapped in local optima, recommending sub-optimal treatment. (Beel et al., 2013; Zhou et al., 2019) 3) Alternatively, to obtain knowledge on new treatments, it is necessary to conduct randomized control trials (RCTs) through in-vitro/in-vivo experiments. However, given all the combinations of available treatments, conducting an RCT can be extremely expensive and at the cost of sacrificing trial patients’ survival outcomes at the clinical level or undermining cell lines utilities by selecting a sub-optimal combination at the pre-clinical level. (Berry and Erick, 1995; Berry, 2011) This paper proposes an online learning approach to simultaneously attempt to acquire new knowledge (called ‘exploration’) and optimize treatment decisions based on existing knowledge (called ‘exploitation’). Our algorithm not only learns to maximize treatment efficacy given the data that have been seen (exploitation) but also identifies the best treatment that has not been seen so far (exploration). We demonstrate its utility in adaptive treatment allocation in a trial by using real-world pharmacogenomic datasets.

To solve in-vitro anticancer therapeutics allocation in an online environment, a natural attempt is to cast it as a contextual bandit problem which is a well-known tool for personalization (Li et al., 2010). It learns dynamically in an online environment and seeks to balance the exploration-exploitation trade-off by sequentially selecting actions to maximize treatment efficacy. Specifically, we consider the problem described as follows. Individuals are coming sequentially with particular genomics information (context). At each round, after observing individual genomics information, the agent would prescribe a treatment (action) and then observe drug sensitivity response (reward). Notice that the agent’s decision is made based on past observation of individuals’ genomics information, treatments, and corresponding feedback.

One of the fundamental challenges for such online decision-making algorithms is the exploration-exploitation dilemma – whether to explore or exploit. (Lattimore, 2020 - 2020; Cesa-Bianchi and Lugosi, 2006). For example, given a set of mono-therapies associated with unknown probabilistic rewards, an agent has to decide whether to exploit treatments that have been tested or to explore novel combinations to maximize treatment efficacy. Quantifying the uncertainty associated with the value of each action-context pair is one of the key components of algorithms for addressing the exploration-exploitation dilemma. In particular, alternative methods driven by uncertainty have been proposed with theoretical guarantees of regret bounds, including Linear Upper Confidence Bound (LinUCB) (Li et al., 2010) based on the principle of Optimism in the Face of Uncertainty (OFU) and Thompson Sampling (TS) (Agrawal and Goyal, 2013), a Bayesian-control-rule based algorithm.

Despite the success in both theory and practice for linear contextual bandits and its extensions (Li et al., 2010; Abbasi-yadkori et al., 2011; Agrawal and Devanur, 2016; Vernade et al., 2020), non-linear and non-convex bandits suffer from restrictive assumptions on the reward function. Naively applying conventional bandit algorithms to our problem is not feasible. First of all, as the performance relies on accurate assumptions about the reward environment, which can be highly complex and non-linear. Finding a proper set of candidate models to map genomic features to drug sensitivity may be difficult. Moreover, due to inherent heterogeneity across and within different cancer types and drug metabolism...
(Dagogo-Jack and Shaw., 2018), modeling uncertainty plays an important role in determining the right decision. Second, the exploration-exploitation dilemma adds another layer of complexity, meaning that more action-context pairs would be required to obtain a better approximation of different policies. Insufficient sample size or model of less expressive power would lead to a wrong decision. (Zhou et al., 2019) Finally, most conventional contextual bandit algorithms treat each action as an unrelated discrete point and fail to leverage the similarity and inherent structure between each action. For example, in cancer trial, OTX015, a BET inhibitor (BETi) that exhibits antitumor activity in non-small cell and small cell lung cancer, shares a similar structure with JQ1 (Riveiro et al., 2016). Under a conventional bandit setting, without knowing the inherent relationship between two similar drugs, unnecessary exploration would be conducted.

- To deal with the first challenge, we choose Bayesian neural networks which have been proven successful in tackling complex environments by learning mappings from high-dimensional observations to value estimates. A number of existing works leverage the representation power of deep learning in contextual bandits including Zhou et al. (2020); Zhang et al. (2020a) and Ban et al. (2021). More importantly, Bayesian neural network provides a natural solution to uncertainty estimation with high-dimensional data.

- To deal with the second challenge, we cast our problem to a deep Bayesian bandit setting. Significant efforts have been dedicated to applying deep Bayesian methods for contextual bandits. (Riquelme et al., 2018; Osband and Roy, 2015) Further, in Bayesian neural network, since weight distribution is intractable, the key is to find an approach to approximate posterior distribution of our drug response prediction function. Therefore, we leverage the power of ‘functional prior’ (Hafner et al., 2019; Sun et al., 2019; Tran et al., 2020) and, following Sun et al. (2019), update functional posterior with variational inference through Stein gradient estimator (SSGE) proposed by Liu and Wang (2019).

- To avoid unnecessary exploration and improve the predictive power of functional Bayesian neural network in a bandit setting, we integrate structural information of drugs and genomics features as contexts. For functional posterior update, to select proper measurement data points, we use bootstrapped procedure to sample from both perturbed genomics contexts and drug compound features. For technical details, we refer readers to Section 3.2 for more details.

Contributions and Generalizable Insights

In this work, our contributions are as follows. First, unlike the majority of existing works in predicting drug response/activity in an offline setting, we investigate a Bayesian bandits approach in an online environment. Second, in a deep Bayesian bandit, we show how one can utilize personalized gene signatures and therapeutics context with functional prior to obtain a better posterior approximation for pharmacogenomics data, balancing exploration and exploitation. Third, we empirically evaluate our method and compared it with other treatment allocation strategies among three large-scale drug sensitivity screens. Our method delivers the best performance against several benchmarks algorithms. Despite the success
in theory analysis of bandits algorithm and applications in domains such as robotic control (Mahler et al., 2016), article recommendation (Li et al., 2010), and search engine advertising (Graepel et al., 2010), there are only a handful of applied works in biology or healthcare. We hope that our work will serve as a stepstone towards improving the efficacy and quality of treatment allocation strategy in both pre-clinical therapeutic discovery and clinical study.

2. Background and Related Work

2.1. Contextual Multi-Arm Bandits

The multi-armed bandit models an agent that simultaneously attempts to acquire new knowledge (through exploration) and optimize their decisions based on existing knowledge (through exploitation). The agent attempts to balance these two tasks to maximize their total rewards over a period of time. (Lattimore and Szepesvari, 2020)

Contextual bandits (Li et al., 2010) is a generalization of the multi-armed bandit in which the policy for choosing future actions is dependent on context information $x_t \in \mathcal{X}$ at each step $t$. For example, in clinical trial, the context could be patients’ symptoms or laboratory observations for treatment decision. It is characterized by a sequence of a context-loss pairs $\{(x_t, r_t)\}_{t=1,2,...,T}$, where $x_t \in \mathcal{X}$ is the context at time $t$ for some arbitrary context space $\mathcal{X}$, $r_t \in \mathbb{R}^{|A|}$ is the reward vector at each time corresponding to each arm $a \in \mathcal{A}$, and $\mathcal{A}$ is an arbitrary arm space (e.g., a set of treatment choices). The contextual bandits problem aims to learn a policy $\pi : \mathcal{X} \rightarrow \mathcal{A}$, or a mapping from context to actions that maximizes cumulative rewards, or equivalently to minimize the total regret compared to the best policy in hindsight, as defined by:

$$\arg \max_{\pi \in \Pi} \sum_{t=1}^{T} r_t(\pi(x_t)),$$

where $\Pi$ is the policy space.

There is a variety of assumptions on the generation of $\{(x_t, r_t)\}_{t=1,2,...,T}$ sequence. Here we specifically tackling the stationary stochastic contextual bandits where each $(x_t, r_t)$ is drawn independently from an unknown underlying distribution.

There are many algorithms that can solve the contextual bandits problem such as Upper Confidence Bound (UCB) (Li et al., 2010) and Thompson Sampling (TS) (Thompson, 1933). These approaches have been well studied and with a good theoretical guarantee. In particular, Thompson Sampling is a Bayesian approach (Agrawal and Goyal, 2011) that one can sample from the posterior distribution, $P(\theta)$, over plausible problem instances such as rewards or model parameters. At each round $t$, it observes the context, $x_t$, and each arm $a$ is chosen according to the probability that it maximizes the expected reward. The posterior distribution is then updated after the result of an action is observed.

2.2. Deep Bayesian Bandits

Through the lens of Thompson Sampling, deep Bayesian bandits refer to tackling contextual bandits by parameterizing the action-value function and a prior distribution over $P_0(\theta)$ placed over the parameters. Although the weight posterior for neural networks is analytically intractable, it can be approximated by methods such as Dropout (Kingma et al.,
Algorithm 1 Thompson Sampling

**Input:** $f(\cdot | \hat{\theta}_0)$; prior distribution over models, $P_0(\theta) : \hat{\theta}_0 \in \Theta \rightarrow [0,1]$

for $t = 1, 2, \ldots, T$

- Observe context $x_t \in R^d$.
- Sample model parameter $\hat{\theta}_t \sim P_t(\theta)$.
- $a_t = \arg \max_a f(x_t, a | \hat{\theta}_t)$.
- Select action $a_t$ and observe reward $r_t(a_t)$.
- Update the history $D_t \leftarrow D_{t-1} \cup (x_t, a_t, r_t(a_t))$.
- Update the posterior distribution $P_{t+1}(\theta) = \text{PosteriorUpdate}(D_t, P_t)$.

In the healthcare domain, with offline methods or control-based approaches, researchers attempt to build an accurate model for the complex physiological system and its response to administered treatments. On the other hand, online algorithms can find optimal policies using only previous experiences, without requiring any prior knowledge. This makes online algorithms more appealing as it is usually difficult or impossible to build such a model. In recent years, researchers have explored framing medical decision making as an online optimization problem such as reinforcement learning (RL) (Komorowski et al., 2018; Yu et al., 2019) or contextual bandits (also sometimes known as a special case of RL with only one step instead of a long trajectory in each observation). Note that RL relies on the assumption of Markov Decision Process (Sutton and Barto, 2018); whereas, there’s no temporal dependency in contextual bandits. Compared to RL which requires more frequent observations within a short period of time, contextual bandits is more suitable for chronic diseases such as cancer treatment in which physicians continuously update their knowledge as a patient receives treatment over a long period of time.

An instantiation of the contextual bandits framework in treatment recommendations is described in Algorithm 2. It enables effective personalized intervention by taking appropriate actions based on individual characteristics rather than using an identical policy for a variety of patients. Recently, contextual bandits methods, especially Thompson Sampling, are being tailored to healthcare applications in different domains, including mobile health (Tomkins et al., 2020), risk stratification for multiple myeloma (Zhou et al., 2019), dose-finding for ischemic stroke (Varatharajah et al., 2018), maximum tolerated dose identi-
tification (Aziz et al., 2019), and precision oncology (Rindtorff et al., 2019). Our approach, to our knowledge, is the first to use multi-modal data including treatment information, and apply it to multiple pharmacogenomic datasets.

Algorithm 2 Contextual Bandits in Healthcare

Input: Available treatment options \( a \in A \), and the treatment period length \( T \).

for \( t = 1, 2, \ldots, T \) do

   Agent receives the context information \( x_t \) for the current patient.

   A treatment decision \( a_t \) is determined based on the history and the context information.

   Record the post-treatment health outcome \( r_t \) for the patient.

end

3. Methods

Our algorithm consists of three components. First, in addition to genomics contexts, we leverage the features of the drug compound to model the reward function. Second, we utilize the concept of functional Bayesian neural network to efficiently yield a posterior estimation. Finally, we use Bootstrapped sampling with perturbed samples to explore more efficiently in functional space.

3.1. Problem Setup

We formulate treatment allocation in anticancer therapeutics as a Bayesian contextual bandit problem, that is context set \( \mathcal{X} \subset \mathbb{R}^{d_1} \), defined as the individual genomics information with \( d_1 \)-dimension; a discrete action set \( \mathcal{A} \subset \mathbb{R}^{d_2} \), defined as a set of given drugs whose compounds can be expressed as a \( d_2 \)-dimension feature vector; and a reward set \( R \subset \mathbb{R}^{|\mathcal{A}|} \), where each reward vector is a possible collection of corresponding drug responses (pIC-50/Activity Area) for all drugs. Finally, we are given a policy set \( \Pi : \mathcal{X} \rightarrow \mathcal{A} \). The protocol is as follows:

- At time \( t \), we are given a uniformly sampled context, \( x_t \in \mathcal{X} \), and a non-observable reward vector \( r_t \in R \), that are jointly drawn from some unknown i.i.d distribution \( \mathcal{D} \). In our case, this scenario can be regarded as randomly sampled cancer cell line at time \( t \) whose actual responses to various drugs are unknown.

- Then we play \( a_t \in \mathcal{A} \) based on previous history and observe only the corresponding \( r_t(a_t) \), for example, the drug response in our case, not in the whole \( r_t \) vector.

By repeating this process for a total of \( T \) times (or \( T \) incoming samples), we can obtain the total cumulative reward \( \sum_{t=1}^{T} r_t(a_t) \). In general, we want our strategy to be as good as a universal best policy \( \pi^* \in \Pi \), defined as:

\[
\pi^* = \arg \max_{\pi \in \Pi} \sum_{t=1}^{T} r_t(\pi(x_t)).
\]
In particular, we measure the difference between our algorithm performance and the benchmark performance by a term called cumulative regret $R(T)$, defined as

$$R(T) = \sum_{t=1}^{T} r_t(\pi^*(x_t)) - \sum_{t=1}^{T} r_t(a_t).$$  \hspace{1cm} (3)

### 3.2. Drug Response Prediction with Genomics and Drug Contexts

In precision oncology, treatment efficacy depends not only on patients’ genomics features but also on therapeutics information which have shown to improve the predictive performance. (Kuenzi et al., 2020; Preuer et al., 2017) Here, our solution is to treat both genomics features and therapeutics context as a combined input into our neural network and show that the trained neural net can automatically capture inherent relationships between the two, genomics information (RNA expression) and drug features (MorganFingePrint); therefore, explore more efficiently. Specifically, on each round $t$ for each action $a$, we denote such concatenated feature vector as $x_t = (x_g, x_d) \in \mathbb{R}^{d_1+d_2}$, where $d_1$ and $d_2$ are the dimension of genomics and drug features, respectively. When the agent selects action $a$ based on $x_g$, drug information $x_d$ will be provided to estimate reward on for all $a$.

### 3.3. Functional Prior and Posterior Approximation for multi-modal Data

Even though drug features can provide additional information in reward prediction, multimodal data of different data types complicates determining the prior distribution. As Hafner et al. (2019) and Tran et al. (2020) mentioned, the weight distribution would be highly variable and difficult to express with some commonly used prior distributions, such as the Gaussian distribution. Therefore, in this work, we are not aiming to learn a distribution of weights in weight space but a distribution of functional prior (Hafner et al., 2019; Sun et al., 2019; Tran et al., 2020) which is a function space that maps pharmacogenomics data to drug response. Sun et al. (2019) introduce function space variance, analogous to weight space variational inference.

$$f(x) = g_\phi(x, \xi)$$  \hspace{1cm} (4)

Here $f(x)$ is a sampled function for some function $g_\phi$, and $\xi$ is a random noise vector, corresponding to randomness in functional space. For any given dataset $D$, the functional variance inference maximizes functional ELBO (fELBO) defined as:

$$\mathcal{L}(q) = \mathbb{E}_q[\log(p(D|f))] - \sup_{n \in \mathcal{N}, x \in \mathcal{X}} KL[q(f^X)||p(f^X)].$$  \hspace{1cm} (5)

As there is no analytical form for the functional KL divergence, following Sun et al. (2019), we also utilize the spectral Stein gradient estimator (SSGE) to approximate log density derivatives. SSGE is proposed by Liu and Wang (2019) is an estimator that only requires measurement samples from the targeted implicit distribution.

### 3.4. Sampling Measurement Sets for Cancer Treatment Exploration

To estimate KL divergence properly with SSGE, we need unbiased samples from the implicit distribution of genomic contexts and drug features. Typically, one can sample from the
training set where noise is injected into the data (Hafner et al., 2019). In applications where we know the input region of the test data, one can include it. (Sun et al., 2019) Here we use a combination of two approaches (Tran et al., 2020): to encourage exploration, we use sample not only from history \(D_t\) but also from random drug feature \(x_{a'}\) in the action space that we are interested in exploring. To address this problem, we use a simple bootstrapped method (Osband and Roy, 2015) to sample measurement sets. Accordingly, we sample a new history set \(H\) from both training history \(D_t\) and \(\tilde{D}_t\) with perturbed action-context-concatenated features \(\tilde{x}_t\).

\[
\tilde{D}_t = (\tilde{x}_1, \ldots, \tilde{x}_t); \tilde{x}_t = (x_g, x_d)
\]

\[
H_t \sim D_t \cup \tilde{D}_t.
\]

Therefore, with \(H\) as our measurement set, \(f\)ELBO can be re-written as

\[
L_H(q) = \mathbb{E}_q[\log(p(D|f))] - \sup_{n \in N, x \in \mathcal{X}^n} KL[q(f^H)||p(f^H)].
\]

With SSGE and proper measurement samples, we can approximate the entropy of both \(q\) and \(p\), which are both from implicit distribution; then, we can sample from the implicit posterior of drug response prediction for different compounds in bandits settings.

### Algorithm 3 Functional Posterior Update

1. **Universal parameters**: KL weight \(\lambda\)
2. **Input**: \(D_t\), functional variational posterior \(g(\cdot|\phi)\)
3. \(\tilde{D}_t \sim D_t\); \(\triangleright\) Sample \(\tilde{D}_t\) from \(D\) with perturbed action contexts.
4. \(f = g([\tilde{D}_t, D_t], \mathcal{E}|\phi)\) \(\triangleright\) Sample a new function \(f(\cdot)\) with noise vector \(\mathcal{E}\).
5. \(\Delta_1 = \frac{1}{|\tilde{D}_t|} \nabla_{\phi} \log p(y|f_t)\) \(\triangleright\) Compute reconstruction loss.
6. \(\Delta_2 = \text{SSGE}(\tilde{D}_t, D_t)\) \(\triangleright\) Estimate KL divergence from implicit posterior.
7. \(\phi \leftarrow \text{optimize}(\phi, \Delta_1 - \lambda \Delta_2)\)
8. **Return** functional variational posterior \(g(\cdot|\phi)\)

### 4. Experimental Design and Data

#### 4.1. Cohort Selection and Data Curation

In this work, we simulate anticancer treatment trials and evaluate our algorithms in three large-scale cancer cell line screenings, including Genomics in Drug Sensitivity in Cancer (GDSC-1 and GDSC-2) (Yang et al., 2012; Iorio et al., 2016) and the Cancer Cell Line Encyclopedia (CCLE) (Jordi et al., 2012). GDSC is the resource for therapeutic biomarker discovery in cancer cells. The GDSC1 dataset was generated between 2009 and 2015 using a matched set of cancer cell lines; contains 987 cell lines and 367 compounds. GDSC2 was generated in 2015 following improvements to screen design and assay (Iorio et al., 2016); contains 198 Compounds and 809 cell lines. The Cancer Cell Line Encyclopedia (CCLE) project, started in 2008, contains pharmacological profiles for 24 anticancer drugs across 479 cell lines.
For all datasets, we first filtered out cancer cell lines with missingness in drug-dose response greater than 70%. We then filtered out drug compounds with missing sensitivity in at least one of the curated cell lines. The result datasets were GDSC-1, which consists of 472 cancer cell lines with 17,737 genes and 133 drug compounds; GDSC-2, which consists of 602 different cancer cell lines with 17,737 genes and 116 drug compounds; CCLE, which consists of 411 cancer cell lines with 19,177 genes and 21 drugs.

4.2. Gene Expression and Drug Compound Preprocessing

For cancer cell lines, we used RNA expressions and performed principal component analysis (PCA) to reduce the RNA expression dimension to 500. For drug context, we converted the drug SMILE string to Morgan fingerprint with 256 bits. (Capecchi et al., 2020) For drug-dose response, in GDSC, we adapted negative log of half-maximal inhibitory concentration, pIC50. In CCLE, since some IC50 measurements are missing, we used activity area (AA) instead. All cancer cell lines and drug responses were scaled into the range of [0,1].

4.3. Evaluation Metrics and Benchmark Algorithms

As described in Equation 3, we reported cumulative regrets, the reward difference between competing algorithm and an oracle that would have access to the (unknown) treatment effect functions:

$$\text{Regret}(T) = \sum_{t=1}^{T} R^*(x_t) - \sum_{t=1}^{T} R(\pi(x_t), x_t),$$

where $x_t$ is random selected context, $R^*$ is the optimal reward based on the oracle policy (described in section 4.4) at each step $t$, and $R(\pi(x_t), x_t)$ is the reward based on policy $\pi$. We test our algorithm against competing algorithms with baselines and different posterior approximations that demonstrated promising results in balancing between exploration and exploitation in a bandit setting. (Riquelme et al., 2018) These algorithms include:

**Uniform** a baseline for which an agent takes each action at random with equal probability.

**NeuralGreedy** is a algorithm trained with a neural network and acts greedily (take action that predicted with the highest drug response.) where a random action is selected with probability $\epsilon$.

**BayesByBackprop (BBB)** is proposed by Blundell et al. (2015) and is one of the commonly used variational approaches that approximate posterior by minimizing KL divergence. It is a Bayesian neural network with sampled weights from the variational posterior, $w \sim q(w|\theta)$. Variational parameters $\theta$ are updated with KL divergence between a mixture of two Gaussian densities prior and model weights distribution. BBB is a commonly used baseline in deep Bayesian bandits.

**Dropout** is a training technique where the output of each neuron is independently zeroed out with probability $p$ at each forward pass (Srivastava et al., 2014; Kingma et al., 2015). Following the best action with respect to the random dropout prediction can be interpreted as an implicit form of Thompson sampling.
BootstrappedNN is an empirical approach to approximate the posterior sampling distribution (Osband and Roy, 2015). The idea is to train $q$ models with different dataset $D_i$ where $D_i$ is typically created by sampling with replacement from an original dataset, $D$. In our case, we train $q$ models with the same structure as NeuralGreedy and $D$ is the history context that the agent has seen. In action selection, we sample a model uniformly at random (with probability $1/q$) and take action predicted reward to be the best by the sampled model.

DirectNoiseInjection is a recently proposed method by Plappert et al. (2018). Parameter-noise injection is an exploration technique proved successful in RL. Through noise injection in parameter space: $\tilde{\theta} = \theta + \mathcal{N}(0, \sigma^2)$, we can perform state-dependent exploration(). When selecting action, model weights are perturbed with isotropic Gaussian noise so that we get $a_t = \pi_{\tilde{\theta}}(s_t)$. The magnitude of noise is adaptively adjusted based on distance measure between perturbed and non-perturbed policy in action space. (Plappert et al., 2018)

4.4. Network Structure and Hyper-Parameter Tuning

For our oracle policy, we trained a 2-layer fully connected feedforward network with full access to genomics features, drug structure and corresponding drug response in the dataset. For each experiment, we ran 20 trials with 5,000 steps in each trials. All algorithms were updated every 30 steps. The size of each batch is 32. For all neural network structures, we adopted the same number of layers and hidden dimensions as our oracle policy. We performed a grid search over parameters within a plausible range and reported the best results for each algorithm. We did a grid search over $\{1e^{-1}, 1e^{-2}, 1e^{-3}, 1e^{-4}, 1e^{-5}\}$ for learning rate. For NeuralGreedy, we performed grid search for $\epsilon$ over $\{0.05, 0.1, 0.2, 0.3, 0.4, 0.5, 0.6\}$. For DirectNoiseInjection, we searched noise range over $\{1e^{-1}, 1e^{-2}, 1e^{-3}, 1e^{-4}, 1e^{-5}\}$. For Dropout, we searched over probability $\{0.2, 0.4, 0.6, 0.8\}$. For BayesByBackprop, we searched prior noise over $\{1, 1e^{-1}, 1e^{-2}\}$ and prior mean over $\{1, 1e^{-1}, 1e^{-2}\}$. For BootstrappedNN, we searched the number of models over $\{2, 3, 5, 10\}$.

5. Results

5.1. Efficient Exploration with Drug Context

To test our hypothesis that action context can help balance extrapolation and exploitation, we compared cumulative regrets between a functional Bayesian neural network with and without drug compound features as input contexts. In Figure 5.1, the one without drug compound feature demonstrates both higher variance and regrets than the one with drug compound features. To verify that action perturbation improves uncertainty estimation, we compared the performance between the one with perturbation only in sampled genome contexts and the one with perturbation in both sampled genome and action contexts during network updates. As shown in Figure 5.1, the one with perturbed drug compound features demonstrates lower cumulative regrets.
5.2. Molecular Therapeutics Recommendation in Cancer Treatment

Now we empirically evaluate our functional Bayesian neural bandit with benchmark algorithms in deep bayesian bandits. As noted in Section 4.3, we compared our method with Neural Greedy, BayesByBackprop (BBB), DirectNoiseInjection, Dropout, BootstrappedNN in selecting drug compounds that would maximize drug response, pIC-50 or Activity Area. As shown in Figure 5.2, in all three pharmacogenomics datasets - GDSC1, GDSC2, and CCLE - our method consistently outperforms all other algorithms, achieving the lowest cumulative regrets. The next best algorithm is DirectNoiseInjection; despite the low mean regret, its performance is relatively unstable with high variance. Compared to DirectNoiseInjection, BootstrappedNN demonstrates comparable but more stable performance. Neural-Greedy, provides a reasonable baseline for a greedy policy in a non-linear bandit setting. In GDSC1 and CCLE Dropout, outperforms NeuralGreedy but in GDSC2, its performance is somewhat poor. Ranking at the bottom, BayesByBackprop performs poorly compared to all other algorithms, which is consistent with findings in Riquelme et al. (2018) and Sun et al. (2019).

6. Conclusion and Discussion

Precision medicine in oncology requires an algorithm that suggests effective anti-cancer drugs based on complex molecular profiles of the tumor and noisy pharmacogenomic assays and provides reasonable recommendations. In this work, we introduce a new deep Bayesian
Figure 2: Comparison of cumulative regrets at each step in maximizing cancer treatment effect for 5,000 rounds over 20 trials in the Genomics of Drug Sensitivity Cancer (GDSC-1 & GDSC-2) and, Cancer Cell Line Encyclopedia (CCLE) datasets. (From top left to bottom.)

Table 1: Cumulative regret distribution at the final step in 3 different databases. We report the mean and standard error of the mean over 20 trials.

| Algorithm                   | GDSC-1       | GDSC-2       | CCLE        |
|-----------------------------|--------------|--------------|-------------|
| Uniform                     | 2011 ± 10.2  | 995 ± 6.7    | 2509 ± 12.3 |
| NeuralGreedy                | 531.4 ± 194.3| 262.2 ± 152  | 1361.4 ± 361.7|
| BayesByBackprop(BBB)        | 1500.2 ±396.4| 497.3 ± 187.3| 1682.3 ± 390.0|
| DropOut                     | 508.3± 33.4  | 378.2 ± 84.0 | 1176.2 ± 342.1|
| BootstrappedNN              | 429.7 ± 162.2| 179.1 ± 70.5 | 705.5 ± 409.8|
| ParameterNoise              | 467.5 ± 287.5| 170.6 ± 65.4 | 785.51 ± 585.5|
| **FunctionalPosterior**     | **202.4 ± 70.0**| **98.46 ± 30.3**| **252.8 ± 35.5**|

bandit approach for *in-vitro* anticancer therapeutics selection. To enable efficient exploration in a contextual bandit setting with drug compound features and gene expression, we use functional variational approach to approximate this pharmacogenomics posterior. Empirically, we demonstrate that our approach explores efficiently and outperforms baselines and several commonly used posterior approximation approaches in deep Bayesian bandits. The result is consistent across three publicly available pharmacogenomics datasets in cancer treatment recommendations.

**Limitations** Our approach is the first few attempts at this problem and thus has some limitations. Despite recent efforts in pharmacogenomics research (Iorio et al., 2016; Jordi et al., 2012), the amount of data on predictive genomic biomarkers of drug response is still limited and fragmented. With both GDSC and CCLE in which each sample consists of only one cell population, the model can only be tested in a simplified scenario of cancer cell lines. However, in reality, tumor tissue from a single cancer patient usually consists of multiple subpopulations, each exhibiting a distinct molecular profile.
On the other hand, we believe, this also strengthens the rationale of applying Bayesian style algorithms which could map heterogeneity across cancer cells more naturally.

Another important assumption for bandit algorithms is that an appropriate reward is always upfront. However, in reality, designing a proper reward function to quantify biological responses is a challenging task. In our experiment, we only consider the pIC-50/Activity area as the reward; whereas, in practice, treatment outcome does not solely depend on drug sensitivity. The toxicity of a given drug is usually an important factor to be considered before prescribing any treatment. For example, Fluorouracil (5FU) is well-known for its efficacy for various cancers but its side effect can sometimes be intolerable. On top of it, cancer treatment usually involved combination therapies where estimation of synergy effect should also be counted, further complicating the reward function. Moreover, bandit algorithms do not take into account the delayed impacts of the agent’s action. In practice, cancer treatment is a sequential process with multiple actions/drugs of different biological half-life.

Finally, from the ethical perspective, there’s still a very long road ahead for broader applications of online decision-making algorithms in healthcare. Most of these algorithms, including ours, rely on naive online learning settings which may jeopardize patients’ safety and sacrifice their survival outcomes by naively uncertainty-minimization exploration. To address this, one common strategy to ensure safety is incorporating prior knowledge from existing offline data at the initial point, therefore, without a cold-start, the learner no longer needs to explore “risky” strategies. Another approach is to impose hard constraints, such as maximum dose level, during the online learning process. We believe those refinements can also be applied in our algorithm and left the detailed validation as future works.
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Appendix A.

A.1. Summary of GDSC and CCLE

| Dataset | number of cell lines | number of drugs | Drug Response |
|---------|----------------------|-----------------|---------------|
| GDSC1   | 472                  | 133             | IC-50         |
| GDSC2   | 602                  | 116             | IC-50         |
| CCLE    | 411                  | 21              | Activity Area |

Table 2: Summary Statistics of drug response dataset used in the work
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### Table 3: List of Drugs

| Dataset  | Drugs (Actions) |  
|----------|-----------------|
| GDSC-1   | (5Z)-7-Oxozaenol, 5-Fluorouracil’, 'AICA Ribonucleotide’, 'AR-42’, AS605240’, 'AT-7519’, AZD6482’, 'AZD7762’, AZD8055’, 'Afatinib’, 'Alectinib’
|          | 'Amuvatinib’, 'Avagacestat’, 'Axitinib’ 'BMS-345541’, 'BX-912’, 'BX795’, 'Bicalutamide’, 'Bleomycin (50 uM)’, 'Bosutinib’, 'CAY10603’, 'CCT007093’, 'CHIR-99021’, 'CI-1040’, 'CP466722’, 'CP724714’, 'CUDC-101’, 'CX-5461’, 'Cabozaatinib’, 'Cisplatin’, 'Cytarabine’, 'Dactolisib’, 'Daporinad’, 'Docetaxel’, 'Doramapimod’, 'EHT-1864’, 'Elesclomol’, 'Enzastaurin’, 'Etoposide’, 'FR-180204’, 'FTI-277’, 'Fedratinib’, 'Foretinib’, 'GSK269962A’, 'GSK429286A’, 'GSK690693’, 'GW-2580’, 'GW441756’ 'Gefitinib’, 'I-BET-762’, 'IOX2’, 'Idelalisib’, 'Ispinesib Mesylate’, 'JNK Inhibitor VIII’, 'JNK-9L’, 'JQ1’, 'KIN001-244’, 'KIN001-266’, 'KIN001-270’, 'KU-55933’, 'Lenalidomide’, 'Lestaurtinib’, 'Linifanib’, 'MK-2206’, 'NG-25’, 'NSC-207895’, 'MPS-1-IN-1’, 'Masitinib’, 'Methotrexate’, 'Motesanib’
|          | 'NVP-BHG712’, 'Navitoclax’, 'Nilotinib’, 'Nutlin-3a (-)', 'OSI-930’, 'Olaparib’, 'Omisalisib’, 'PD0325901’, 'PD173074’, 'PF-4708671’, 'PFI-1’, 'PHA-793887’ 'PI-103’, 'PIK-93’, 'PLX-4720’, 'Palbociclib’, 'Peltinib’, 'Phenformin’, 'Pictilisib’, 'Piperlongumine’, 'Quizartinib’, 'Refometinib’, 'Rucaparib’, 'Ruxolitinib’, 'SB505124’, 'SB52334’, 'SGC0946’, 'SL0101’, 'SN-38’, 'SNX-2112’, 'STF-62247’, 'Selisistat’, 'Selumetinib’, 'Seremetan’, 'T9001317’, 'TAK-715’, 'TPCA-1’, 'TW 37’, 'Tamoxifen’, 'Tanespimycin’, 'Temozolomide’, 'Temsurolimus’
|          | 'Tivozanib’, 'Trametinib’, 'Tretinoin’
|          | 'UNC0638’, 'UNC1215’, 'VNLG/124’, 'VX-11e’, 'VX-702’, 'Velparib’, 'Vinblastine’, 'Vinorelbine’, 'Vismodegib’, 'Vorinostat’, 'WHI-P97’, 'Y-39983’
|          | 'YM201636’, 'ZM447439’, 'ZSTK474’, 'Zibotentan’

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Actions (Drugs) in GDSC-2

| '5-Fluorouracil', 'ABT737', 'AGI-5198', 'AGI-6780', 'AMG-319', 'AZD3759', 'AZD4547', 'AZD6738', 'AZD7762', 'AZD8186', 'Afatinib', 'Afuresertib', 'Alisertib', 'Alpelisib', 'BIBR-1532', 'BMS-345541', 'Bortezomib', 'CZC24832', 'Camptothecin', 'Cediranib', 'Cisplatin', 'Crizotinib', 'Cyclophosphamide', 'Cytarabine', 'Dabrafenib', 'Dactolisib', 'Dasatinib', 'Dinaciclib', 'Docetaxel', 'EPZ004777', 'EPZ5676', 'Entinostat', 'Entospletinib', 'Epirubicin', 'Erlotinib', 'Foretinib', 'Fulvestrant', 'GDC0810', 'GNE-317', 'GSK1904529A', 'GSK2578215A', 'GSK343', 'GSK591', 'Gefitinib', 'Gemcitabine', 'I-BET-762', 'I-BRD9', 'IWP-2', 'Ipatasertib', 'Irinotecan', 'KRAS (G12C) Inhibitor-12', 'LCL161', 'LGK974', 'LJI308', 'LY2109761', 'Lapatinib', 'Leflunomide', 'Linsitinib', 'MG-132', 'MIRA-1', 'MK-1775', 'MK-2206', 'MK-8776', 'ML323', 'MN-64', 'NVP-ADW742', 'Navitoclax', 'Nilotinib', 'Niraparib', 'Nutlin-3a (-)', 'OF-1', 'OTX015', 'Obatoclax Mesylate', 'Olaparib', 'Osimertinib', 'Oxaliplatin', 'P22077', 'PCI-34051', 'PD0325901', 'PD173074', 'PFI3', 'PLX-4720', 'PRIMA-1MET', 'PRT062607', 'Paclitaxel', 'Palbociclib', 'Pevonedistat', 'Picolinici-acid', 'Pictilisib', 'Pyridostatin', 'Ruxolitinib', 'SCH772984', 'Sapitinib', 'Savolitinib', 'Sepantronium bromide', 'Sorafenib', 'Tamoxifen', 'Taselisib', 'Telomerase Inhibitor IX', 'Temozolomide', 'Tametinib', 'UMI-77', 'Uprosertib', 'VE-822', 'VE821', 'VX-11e', 'Venetoclax', 'Vinblastine', 'Vinorelbine', 'Vorinostat', 'WEHI-539', 'WIKI4', 'WZ4003', 'Wee1 Inhibitor', 'Wnt-C59', 'YK-4-279' |

Table 4: Caption

| Dataset | Actions (Drugs) |
|---------|-----------------|
| CCLE    | '17-AAG', 'AEW541', 'AZD0530', 'AZD6244', 'Erlotinib', 'L-685458', 'LBW242', 'Lapatinib', 'Nutlin-3', 'PD-0325901', 'PF2341066', 'PHA-665752', 'PLX4720', 'Paclitaxel', 'Panobinostat', 'RAF265', 'Sorafenib', 'TAE684', 'TKI258', 'Topotecan', 'ZD-6474' |