Bayes Optimal Informer Sets for Early-Stage Drug Discovery

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Abstract

An important experimental design problem in early-stage drug discovery is how to prioritize available compounds for testing when very little is known about the target protein. Informer based ranking (IBR) methods address the prioritization problem when the compounds have provided bioactivity data on other potentially relevant targets. An IBR method selects an informer set of compounds, and then prioritizes the remaining compounds on the basis of new bioactivity experiments performed with the informer set on the target. We formalize the problem as a two-stage decision problem and introduce the Bayes Optimal Informer SEt (BOISE) method for its solution. BOISE leverages a flexible model of the initial bioactivity data, a relevant loss function, and effective computational schemes to resolve the two-step design problem. We evaluate BOISE and compare it to other IBR strategies in two retrospective studies, one on protein-kinase inhibition and the other on anti-cancer drug sensitivity. In both empirical settings BOISE exhibits better predictive performance than available methods. It also behaves well with missing data, where methods that use matrix completion show worse predictive performance. We provide an R implementation of BOISE at github.com/wiscstatman/esdd/BOISE.

Keywords: Bayes decision rule; Dirichlet process mixture model; experimental design; high-throughput screening; ranking; matrix completion.
1 Introduction

Chemical screening laboratories, such as core service facilities in academic medical centers, are often faced with the following experimental design problem. Having received some quantity of a purified protein target, they must plan and deploy experimental assays to identify which available compounds produce some desired effect (bioactivity) on the protein’s function. Naïve high-throughput screening (HTS), a “brute-force” approach in which massive, fixed collections of drug-like compounds are tested exhaustively, is often too expensive and risky for academic investigators. Less expensive alternatives to naïve HTS are needed for early-stage drug-discovery efforts, as in such cases where the risk merits limited resource commitment, e.g., a target protein’s therapeutic relevance has not been fully validated. Computational strategies that effectively prioritize compounds can reduce the amount of experimentation required to find active compounds. Compared to HTS, such strategies can also accommodate rapidly expanding accessible chemical space, where billions of virtual compounds are now readily synthesized and purchased on-demand. Thus, bioactivity experiments are frequently preceded by virtual screening calculations that utilize information in novel ways, such as through molecular docking computations when protein structures are available (e.g., Souza et al. 2020), or through machine learning computations that build predictive models based on compound testing data (e.g., Sliwoski et al. 2014; Liu et al. 2018; Bajorath et al. 2020). However, these established approaches depend on structural or bioactivity data that are typically limited for novel targets.

Within this large research domain, we focus on an extreme though not uncommon case involving a novel target from a well-characterized class of targets. Here very little information is available on the target protein, beyond the knowledge that the target is from a class of proteins for which bioactivity has been measured on some common set of molecules. We address the specific challenge problem described in Zhang et al. (2019) to deploy informer based ranking (IBR). IBR selects a small subset of drug-like compounds (informers) from the common set that, upon testing against a new target, provides sufficient information to enable bioactivity predictions for the remaining untested compounds. The predictions are used to rank-order the remaining compounds for testing (Figure 1)–rather than exhaustively testing the set. It is illuminating to recognize that an IBR strategy attempts to solve a two-stage finite statistical decision problem (e.g., Wald, 1950; Parmigiani and Inoue, 2009, page 230). There is first the question of how to constitute the small set of informer drugs and then the question of what to do with intermediate data measured on these drugs in order to prioritize the remaining compounds. In the present work we compare available IBR strategies to a novel strategy developed from the decision-theoretic perspective.

In Zhang et al. (2019), domain-specific baseline IBR’s were compared to alternatives guided by heuristics and machine learning. Baseline methods include informer-set selection by the frequent-hitters rule, which selects compounds showing activity against the most targets in the initial data set. Baseline chemometric strategies, by contrast, use available distances computed between compounds in chemical space to choose a chemically diverse informer set. The machine-learning strategies partition the bioactivity data, producing clusters of relatively similar targets; then informer compounds are selected as those predictive of cluster label. Since these effective IBR strategies leverage statistical patterns in the bioactivities, we reason that statistical modeling may provide a useful approach to deriving more effective strategies than are currently available.

To develop an IBR method using decision theory, consider a thought-experiment suggested by sequential analysis. If in addition to the initial bioactivity data we knew the identity of the informers as well as their bioactivity measurements against the new target, then we would be well positioned to rank the as-yet-untested compounds, say by their posterior expected activity in the context of a statistical model. But we know neither the informers nor the intermediate data they would provide. With a model we could consider the predictive distribution of intermediate data on any candidate informer set; indeed we could imagine simulating this predictive distribution given the initial bioactivities. In each simulated instance we would have sufficient information to rank the as-yet-untested compounds, and by some form of averaging we could assess the expected loss tied to this candidate set. By similarly scoring any candidate set we would obtain an objective function whose optimization provides the best possible informers in the context of the chosen
Figure 1: **Informer-based-ranking problem**: A matrix of binary bioactivity data is available (left; red active, blue inactive). The problem is to first identify a subset of the $n$ compounds as informer compounds that will be evaluated experimentally on new target, and then to prioritize all the compounds for further testing after intermediate data is obtained.

sampling model and loss function. Such Bayes Optimal Informer SEts (BOISE) are candidate compound sets that minimize an average loss computed on hypothetical intermediate data. To produce an effective and practical IBR scheme we need a flexible sampling model, a discriminating loss function, and a nimble algorithmic approach, which we propose in Section 2.

We evaluate BOISE retrospectively using the human protein kinase data set PKIS1, (Drewry et al. 2014), and the anti-cancer drug sensitivity data set GDSC1 (Yang et al. 2013). BOISE performs better than other IBR schemes in predicting compound activity from both complete and incomplete initial bioactivity data.

## 2 Methodology

### 2.1 Problem Setting

We are given an $m \times n$ matrix, denoted $x_0$, that contains bioactivity data measured on $m$ targets and $n$ compounds, and we denote the initial targets as $I = \{1, 2, \cdots, m\}$, and the set of available compounds as $J = \{1, 2, \cdots, n\}$. Our studies have considered data sets with $m$ and $n$ in the hundreds, though larger systems are quite relevant. Suppressing the ‘0’ subscript, we use $x_{i,j}$ to denote the $i/j$'th entry of matrix $x_0$. Thus $x_{i,j}$ is the outcome of a bioactivity experiment involving protein target $i$ and drug compound $j$. We treat the simplest case in the present paper, taking binary data: $x_{i,j} = 1$ indicates that compound $j$ is inferred to be active on target $i$ while $x_{i,j} = 0$ corresponds to inactivity. Much of the subsequent development is also relevant to quantitative bioactivity data.
Key to the problem is a new protein target, labeled \( i^* \notin I \), on which we have no bioactivity data at the outset of the experiment. We seek a relatively small set of compounds, \( A \subset J \), the choice of which will be guided by \( x_0 \). Experimentation will be performed to assess the bioactivity of compounds in this informer set \( A \) against target \( i^* \), resulting in intermediate data \( x_A = \{x_{i^*,j} : j \in A \} \). Taken together, \( x_0 \) and \( x_A \) are used to prioritize other compounds for further testing. One way to formalize this step is to suppose that we must select a final top set \( T = T^* = (x_0,A,x_A) \subset J \) on which we will perform further experimentation in order to identify as many compounds as possible with bioactivity against the target \( i^* \). We are thinking of scenarios where we cannot screen the entire set \( I \) (otherwise there’s no need for an informer set). Design parameters here include the cardinality of the informer set, say \( n_A \), and the cardinality of the top set, \( n_T \).

Our statistical analysis rests on an elementary sampling model, namely that bioactivity data \( \{x_{i,j}\} \) are realizations of mutually independent Bernoulli trials when conditioned on corresponding parameters \( \theta = \{\theta_{i,j}\} \). Further modeling will constrain these parameter values so that information may be readily shared among compounds and targets, but the Bernoulli observation component anchors the entire approach. We think of each \( \theta_{i,j} = P(x_{i,j} = 1|\theta_{i,j}) \) as a true bioactivity level balancing biological and technical variation of assays that measure the effect of compound \( j \) on protein \( i \). Roughly speaking, we seek compounds \( j \) for which \( \theta_{i^*,j} \) is large, and this goal is conveniently encoded by the proposed loss function:

\[
L(A,T,\theta) = \sum_{j \in T} (1 - \theta_{i^*,j}). \tag{1}
\]

Because inference requires both an informer set \( A \) and a top set \( T \), we express the loss in terms of these two actions as well as the full state of nature \( \theta \). The loss function would be trivial to minimize if parameters \( \theta \) were known, but barring this we elaborate the model and pursue actions to minimize an appropriate average loss.

### 2.2 Bayes optimal IBR

We are guided by Bayesian statistical decision theory (Berger, 1985; Robert, 2007; Parmigiani and Inoue, 2009). Relative to a to-be-specified prior distribution \( p(\theta) \), the Bayes risk of the two-stage rule \( \{A(T) = \{A(x_0),T(x_0,A,x_A)\}\} \) is the marginal expected loss, averaging (1) over the multi-Bernoulli sampling model \( p(x_0|\theta) \) and \( p(x_A|\theta) \) as well as over the prior \( p(\theta) \). Using integral notation for sums over respective sample or parameter spaces, and considering \( A \) and \( T \) as functions on their input, the (marginal) Bayes risk is

\[
r(A,T) = \int \int \int L(A(x_0),T(A,x_A,x_0),\theta) p(x_0|\theta)p(x_A|\theta)p(\theta) \, d\theta \, dx_A \, dx_0. \tag{2}
\]

An inference procedure that minimizes the Bayes risk is called a Bayes rule; in the context of the model, the prior and loss, its use is a rational way to design and carry out the experiment.

Our first finding concerns a simplification of the Bayes risk for the particular loss function (1). We place ourselves at the point at which we have named informer compounds \( A \) and have received intermediate bioactivity data \( x_A \); with modeling components at hand, we could compute the posterior mean \( \hat{\theta}_{i^*,j} = E(\theta_{i^*,j}|x_A,x_0) \) by averaging in the posterior distribution

\[
p(\theta|x_0,x_A) = p(x_0|\theta)p(x_A|\theta)p(\theta)/p(x_0,x_A). \tag{3}
\]

We define top set rule \( T^* \) to select \( n_T \) compounds having largest posterior means \( \hat{\theta}_{i^*,j} \), with ties broken arbitrarily if necessary. This set turns out to be the Bayes rule for the sub-problem to identify a top-set (e.g., Henderson, 2015, page 17), which we use to confirm:

**Theorem 1** For any rules \( A \) and \( T \), \( r(A,T) \geq r(A,T^*) \).
The lower bound above is the Bayes risk associated with the best possible top-set rule for any given informer-set $A$. Essentially, this shows how to score any informer-set rule by profiling out the top-set selection. The risk (2) is amenable to further simplification by formally integrating the parameters $\theta$:  

$$ r(A, T) \geq r(A, T^*) = \int_{x_0} \text{PEL}_1(x_0, A) \ p(x_0) \ dx_0. $$

PEL stands for posterior expected loss, and the subscript is meant to indicate that the distribution is posterior to the initial activity data $x_0$:

$$ \text{PEL}_1(x_0, A) = \int_{x_A} p(x_A | x_0) \left\{ \sum_{j \in T^*(x_0, A,x_A)} (1 - \hat{\theta}_{i^*j}) \right\} \ dx_A $$  \hspace{1cm} (4)

Using a standard result from decision theory, the rule $A$ that minimizes the marginal Bayes risk is obtained by finding the best informer set at each $x_0$ (e.g., Berger, 1985, page 159). Thus, the Bayes optimal informer set $A^*(x_0)$ is

$$ A^*(x_0) = \arg \min_{A \subset J, |A| = n_A} \ \text{PEL}_1(x_0, A). $$  \hspace{1cm} (5)

It is useful to name the quantity in braces in (4), for this too is a posterior expected loss, but conditional on both $x_0$ and $x_A$, and utilizing the top-set rule $T^*$. We denote it by $\text{PEL}_2(x_0, A, x_A)$ and note:

$$ \text{PEL}_1(x_0, A) = \mathbb{E} \{ \text{PEL}_2(x_0, A, x_A) | x_0 \}, \quad \text{PEL}_2(x_0, A, x_A) = \sum_{j \in T^*(x_0, A,x_A)} (1 - \hat{\theta}_{i^*j}). $$  \hspace{1cm} (6)

With these facts a general program is beginning to emerge (Algorithm 1). We may score any candidate informer set $A$ by $\text{PEL}_1$, which is computed as an average of $\text{PEL}_2$ scores, possibly obtained by sampling the predictive distribution of intermediate data $x_A$. In other words, we stochastically predict what intermediate data would emerge if we were to use informer set $A$, and we average the further expected loss associated with optimal top-set construction from those completed data. By varying $A$ we find the Bayes Optimal Informer Set (BOISE) associated with the least average loss. Our logic parallels dynamic programming for sequential decision analysis, from early developments in multi-stage finite decision problems (Wald, 1950) to more recent work in clinical trials (Berry, 2006).

**Algorithm 1** Compute posterior expected loss of a candidate informer set

**Input:** Initial data $x_0$, candidate informer set $A$, size of top set $n_T$, model structure

**Output:** Monte Carlo approximation to posterior expected loss $\text{PEL}_1(x_0, A)$

1: while predictive sampling do
2: sample $\theta$ from $p(\theta | x_0)$
3: sample $x_A$ from $p(x_A | \theta)$
4: for all compounds $j$ compute future posterior summary $\hat{\theta}_{i^*j} = E(\theta_{i^*j} | x_0, x_A)$
5: form top set $T^*(x_0, A, x_A)$ holding $n_T$ compounds with largest $\hat{\theta}_{i^*j}$
6: compute $\text{PEL}_2(x_0, A, x_A) = \sum_{j \in T^*(x_0, A,x_A)} (1 - \hat{\theta}_{i^*j})$
7: end while
8: average $\text{PEL}_2$ scores to have approximate $\text{PEL}_1$

### 2.3 Modeling the parameter space

Specific BOISE schemes depend on the configuration of probability over parameters $\theta = \{ \theta_{ij} \}$. Allowing too much flexibility limits the utility of initial data $x_0$ to predict anything about the new target $i^*$. On the other hand, an overly restrictive model is liable to miss important bioactivity signatures. Also, a model supporting feasible computations is especially critical for contemporary applications. We pursue a theme proposed in Zhang et al. (2019) to cluster the
target space, and for our primary calculations we develop this theme using techniques from nonparametric Bayesian analysis (e.g., Hjort et al., 2010).

To retain flexibility while controlling the parameter-space complexity, we assume there is a partition \( C = \{ c_k \} \) of the \( m \) initial targets, wherein each cluster \( c_k \) contains identically distributed targets in the sense that \( \theta_{i,j} = \phi_{k,j} 1(i \in c_k) \) for a reduced set of cluster/compound parameters \( \phi = \{ \phi_{k,j} \} \). Furthermore, we propose three positive hyper-parameters \( m_0, \alpha_0, \) and \( \beta_0 \) to control the probability distribution over \( \phi \) and \( C \), which: (1) encodes independence between cluster structure and activity rates, (2) has all entries of \( \phi \) being mutually independent Beta\((\alpha_0, \beta_0)\), and (3) governs partition \( C \) by a Chinese-Restaurant distribution:

\[
p(C) = \frac{m_0^K \Gamma(m_0)}{\Gamma(m + m_0)} \prod_{k=1}^{K} \Gamma(m_k).
\] (7)

Here \( m_k \) counts the number of targets in \( c_k \) and \( C \) is composed of \( K \) clusters. We say the distribution encoded in (7) is CR\(_m\)(\(m_0\)). The proposed specification for the initial bioactivity data \( x_0 \) is thus:

\[
C \sim \text{CR}_m(m_0),
\]

\[
\phi_{k,j} \sim \text{Beta}(\alpha_0, \beta_0), \quad k = 1, \cdots, K, \quad j = 1, \cdots, n
\] (8)

\[
x_{i,j} \mid C, \phi \sim \text{Bernoulli}\left(\phi_{k,j} 1(i \in c_k)\right), \quad i = 1, \cdots, m, \quad j = 1, \cdots, n.
\]

An exchangeable connection to bioactivities \( x_{i^*, j} \) on the new target \( i^* \) is available immediately. CR\(_{m+1}(m_0)\) would assert that given \( C \), the new target \( i^* \) becomes part of cluster \( k \) with probability proportional to \( m_k \), in which case we write \( i^* \rightarrow c_k \). It populates a cluster by itself with probability proportional to \( m_0 \). If \( i^* \rightarrow c_k \), then \( x_{i^*, j} \) is Bernoulli\((\phi_{k,j})\) like the other targets in that cluster. If \( i^* \) populates a new cluster, say \( c_0 \), then there must be some other rates \( \phi_{0,j} \) governing these Bernoulli trials, and these rates themselves are distributed by the same Beta\((\alpha_0, \beta_0)\) distribution.

Model (8) is quite flexible, allowing that target \( i^* \) has a bioactivity pattern in common with some subset of initial proteins, and accounting for uncertainty in this cluster subset. There could be further benefit to clustering in the compound space or to adopting a more elaborate specification, though the direction taken is suggested by the inference task, which focuses on new targets for the fixed set of compounds. Also, computations appear to be considerably more difficult in elaborations of the present case. One advantage of (8) is that explicit integration eliminates all the \( \phi_{j,k} \) parameters, much like as happens for collapsed Gibbs sampler computations in a related context (Liu, 1994). Therefore, the predictive sampling in Algorithm 1 entails the sampling of clusterings \( C \) rather than fully elaborated parameter states \( \theta \). A second advantage of (8) comes from how it meshes with the loss function (1). PEL\(_2\) (and thus PEL\(_1\)) calculations generally require averaging with respect to the posterior distribution \( p(\theta|x_0, x_A) \) as in (3), which in more elaborate specifications may require posterior sampling under each simulated \( x_A \). For model (8) we find a scheme to obtain PEL\(_1\) via posterior sampling from \( p(C|x_0) \) and predictive sampling of \( p(x_A|x_0) \), but in which no sampling conditional upon \( x_A \) is required.

### 2.4 Computations

In the context of model (8), the general program (Algorithm 1) becomes more explicit. Sampling of intermediate bioactivity states \( x_A \) may be arranged by first sampling clusterings \( C \) from \( p(C|x_0) \) and then drawing data from \( p(x_A|x_0, C) \), recognizing the simplified form

\[
x_{i^*, j} \mid C, x_0 \sim_{\text{ind}} \text{Bernoulli}\left(\frac{a_{k,j}}{a_{k,j} + b_{k,j}}\right) \quad \text{when } i^* \rightarrow c_k,
\] (9)

where \( a_{k,j} = \alpha_0 + \sum_{i \in c_k} x_{i,j} \) and \( b_{k,j} = \beta_0 + \sum_{i \in c_k} (1 - x_{i,j}) \) counts actives and inactives, respectively. From CR\(_{m+1}(m_0)\), the probability that \( i^* \rightarrow c_k \) is \( m_k/(m + m_0) \), conditionally on \( C \) and \( x_0 \). There is also probability
where \( p \) does not cluster with the initial targets, in which case the bioactivities \( x_{i^* j} \) are i.i.d. Bernoulli \( \{ \alpha_0 / (\alpha_0 + \beta_0) \} \). It is convenient to represent the new singleton cluster as \( c_0 \), and set \( a_{0j} = \alpha_0 \) and \( b_{0j} = \beta_0 \).

A difficult aspect of this predictive sampling scheme is how to draw clusterings from \( p(C|x_0) \), which is analogous to calculations required in Dirichlet process mixture models (DPMMs). A great deal of progress has been made on this general problem, and we tap into these nonparametric Bayesian results to advance our calculations. Appendix B presents a Gibbs sampler adapted to the present context from MacEachern (1994) and Neal (2000).

The next computational challenge is the evaluation of the optimal top set \( T^*(x_0, A, x_A) \), which holds the \( n_T \) compounds having the highest values of \( \theta_{i^* j} = E(\theta_{i^* j} | x_0, x_A) \). Our approach is to re-use the sampled clusterings \( C \), noting by iterated expectations that \( \hat{\theta}_{i^* j} = E \left\{ \hat{\theta}_{i^* j} | x_0, x_A \right\} \), where \( \hat{\theta}_{i^* j} = E(\theta_{i^* j} | C, x_0, x_A) \). This inner expectation is an average over ways the new target \( i^* \) may (or may not) cluster with the existing targets, and we find:

\[
\hat{\theta}_{i^* j} = \sum_{k=0}^{K} p_k \left( \frac{a_{k,j} + x_{i^* j} \mathbb{I}(j \in A)}{a_{k,j} + b_{k,j} + \mathbb{I}(j \in A)} \right)
\]

(10)

where \( p_k \) is the conditional probability (given \( x_0, x_A, \) and \( C \)) that \( i^* \) links to cluster \( c_k \):

\[
p_k \propto m_k \prod_{j \in A} \left( \frac{a_{k,j}}{a_{k,j} + b_{k,j}} \right)^{x_{i^* j}} \left( \frac{b_{k,j}}{a_{k,j} + b_{k,j}} \right)^{1-x_{i^* j}}
\]

and where proportionality is resolved by \( \sum_{k=0}^{K} p_k = 1 \). The sought-after \( \hat{\theta}_{i^* j} \) is marginal to uncertainty in clusterings but conditional on intermediate data \( x_A \). The generic solution would be to re-apply MCMC sampling over clusterings for all the different posterior distributions, but we propose to recycle the sampled clusterings already available from \( p(C|x_0) \) through an importance-sampling argument. These modeling and computational elements allow for refinement of Algorithm 1, which we report as Algorithm 4 in Appendix C.

Our final job is to find the optimal informer set \( A^* \) in problem (5), which optimizes over discrete, size-\( n_A \) subsets of compounds \( J = \{1, 2, \cdots, n\} \). The complexity of \( \text{PEL}_1(x_0, A) \) in (4) makes this challenging, but there is an effective greedy method based upon adding one compound at a time to a sequentially growing solution (Algorithm 2). We provide an R implementation of the complete BOISE procedure at github.com/wiscstatman/esdd/BOISE.

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**Algorithm 2 Greedy Informer Selection**

**Input:** Initial data \( x_0 \), size of informer set \( n_A \), size of top set \( n_T \).

**Output:** Selected informer set of length \( n_A \)

1: **Initialization:** Evaluate \( \text{PEL}_1(x_0, A) \) for all \( |A| = 1 \). Let \( A^* = \arg \min_{|A|=1} \text{PEL}_1(x_0, A) \).
2: while \( |A^*| < n_A \) do
3: Evaluate \( \text{PEL}_1(x_0, A^* \cup \{j\}) \) for each \( j \in J \setminus A^* \).
4: Let \( A^* \leftarrow A^* \cup \{j^*\} \), where \( j^* = \arg \min_j \text{PEL}_1(x_0, A^* \cup \{j\}) \).
5: end while
6: Return \( A^* \) as selected informer set.

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**3 Empirical studies**

**3.1 Protein kinases**

Protein kinases comprise the second largest drug target class and are the primary target class for cancer therapeutics. Protein kinases attach phosphate groups to regulatory sites on the surfaces of other proteins, thereby modulating their functions. Discovering drugs that inhibit kinase activity is a problem of broad interest. To assess the operating characteristics of BOISE in this domain, we use a public kinase data set, PKIS1 (Drewry et al. 2014), downloaded
from CHEMBL. After preprocessing, PKIS1 contains the bioactivity scores for \( m = 224 \) kinase targets and \( n = 366 \) drug compounds. The data are continuous measures of kinase inhibition; we threshold to binary active/inactive records using the 2-standard-deviation rule as applied in Zhang et al. (2019); we also compare BOISE to baseline and machine-learning methods reported in that work.

A prospective evaluation would use the PKIS1 data as initial data \( x_0 \) and identify an informer set \( A \) of compounds to evaluate on a new target. In place of this ideal study, we use cross validation in a retrospective design. We repeatedly drop out one kinase target, considering the retained proteins to provide data \( x_0 \), and the dropped-out target to play the role of \( i^* \), the novel target whose bioactivity data are initially hidden from the analyst. In each drop-out case, we apply BOISE to find informer compounds. We use the available \( x_A \) data on these informers as intermediate data that allows a prioritization of all compounds (taking advantage of documented experiments). Formally, BOISE imagines that our job is to report a top set \( T \) after processing intermediate data. In addressing this it produces a ranking of all compounds according to \( E(\theta_{t^*,j}|x_0,x_A) \), and this ranking can be evaluated, both by unveiling all the bioactivity data on \( i^* \) to reveal measured active compounds, and by comparing to rankings produced by other IBR schemes.

Computational chemists use a variety of metrics to compare drug ranking methods, and we report two commonly used metrics to evaluate BOISE and other IBR schemes: (1) the area under the receiver operating characteristic curve (ROCAUC), and (2) the normalized enrichment factor at 10% (NEF10). After the fact, we label the compounds \( x \) in order from the top of their IBR ranking; so in BOISE, \( E(\theta_{t^*,1}|x_0,x_A) \) is the largest posterior mean. As we move down the ranked list, say with index \( t = 1,2,\ldots,n \), and in light of complete experimental data on the target \( i^* \), we record the true positive rate \( TPR(t) = \sum_{j=1}^{n^*} x_{i^*,j}/\sum_{j=1}^{n^*} x_{i^*,j} \) and the false positive rate \( FPR(t) = \sum_{j=1}^{n^*} (1-x_{i^*,j})/\sum_{j=1}^{n^*} (1-x_{i^*,j}) \). The ROC curve plots \( TPR(t) \) vs \( FPR(t) \) as we vary the threshold \( t \), and ROCAUC is the area under this curve. Higher values, of course, correspond to prioritization schemes that put more of the truly active compounds near the top of the list. Alternatively, the normalized 10% enrichment factor NEF10 is a metric that emphasizes behavior in the top 10% of the ranking, and is a linear transformation of \( TPR([n/10]) \) (see Appendix D).

Figure 2 summarizes the predictive performance of BOISE and several published IBR methods using two informer set sizes \( n_A = 8, 16 \) and \( n_T = 36 \). Note the ROCAUC uses the entire ranking and NEF10 uses the top 10%; there is no particular connection to the value \( n_T \) used by BOISE. We find quite low sensitivity of BOISE to the value of \( n_T \) (data not shown). A formal statistical comparison affirms what seems evident from Figure 2, that BOISE has superior operating characteristics in this example. Specifically, we fit a linear model to each metric, including a factor for IBR method and a factor for protein target. Figure 3 shows 95% confidence intervals for contrasts between BOISE and other methods, adjusted for multiple pairwise comparison by Tukey’s method (e.g., Bretz et al. 2010).

### 3.2 Cancer cell lines

We apply retrospective IBR calculations using the Genomics of Drug Sensitivity in Cancer (GDSC) data set, downloaded from Cancerrxgene (Yang et al. 2013). It measures bioactivity of drugs against cell lines derived from cancer tumors. A cell line is obviously different than a purified protein, but the experimental design problem is the same, to identify an informer set of compounds that will be predictive of other compounds’ bioactivity against a new cancer. GDSC reports standardized growth response data (z-scores) from 304 anti-cancer drugs and 987 cancer cell lines. We assume bioactivity, \( x_{i,j} = 1 \), if the z-score is less than -2.

GDSC has a substantial amount of missing data (15.1% of the matrix), which provides an opportunity to compare IBR strategies in this context. We report two numerical experiments. In the first, we reduce GDSC to a complete sub-matrix, which has 281 cell lines and 207 drugs found by removing rows/columns with more than 100 missing entries. We then do the same cross-validation exercise as we did with PKIS1 (though we drop the coding selection method due to its heavy computational cost). Figure 4 shows that BOISE continues to have impressive metrics of predictive performance, and this is confirmed in the confidence intervals in Figure 5. For NEF10, for example, BOISE’s method effect exceeds the closest competitor by 0.031 units when \( n_A = 8 \) and 0.049 when \( n_A = 16 \).
Figure 2: **Predictive performance of IBR methods on PKIS1 targets.** Two metrics (rows) are computed for each IBR method and on each leave-one-out data set, and columns correspond to two choices of informer-set size ($n_A = 8, 16$). For both normalized enrichment (NEF10, top row) and ROCAUC (bottom row), a prioritization scheme that puts all active compounds ahead of all inactive ones gets a perfect score (1.0); random guessing gets 0.5. The median and interquartile ranges are displayed as a white circle and black bars, respectively, and violin plots show the empirical distribution of the metrics across the left-out targets. IBR methods, distinguished by colors, are as described in the text: BC$_w$ and BF$_w$ are baseline schemes based on chemometric or frequent-hitters information; CS, RS, and AS are coding selection, regression selection, and adaptive selection, and BOISE is the proposed Bayes optimal informer set method.

Missing data in the initial matrix $x_0$ can present a serious challenge to available IBR methods, which have to invoke some form of matrix completion as a pre-processing step. Missing data is not a fundamental problem for BOISE, considering that probabilities calibrate whatever information is available. Two aspects of BOISE are influenced by missing data: cluster label updates in DPMM clustering, and posterior expectation calculation in informer selection. Both procedures rely on $a_{k,j}$ and $b_{k,j}$ in (9) to determine the posterior Beta distribution of the $j$-th compound in the $k$-th cluster. Following Marlin (2008, Section 4.2), we introduce $z_{i,j}$ as a missing data indicator, assume missingness at random, and then recognize that the necessary counts record only data at non-missing entries:

$$a_{k,j} = a_0 + \sum_{i \in c_k} x_{i,j} I(z_{i,j} = 1), \quad b_{k,j} = b_0 + \sum_{i \in c_k} (1 - x_{i,j}) I(z_{i,j} = 1).$$

(11)

Computations in Algorithms 2, 3, and 4 proceed as usual with this adjustment.

The GDSC data set is well structured to assess the effect of missingness on IBR methods. From the original 987 cell lines, 23 have complete data on all 304 drugs. Data on the remaining 964 cell lines constitute our training data set $x_0$, 

---

**Figure 2:**

- **NEF10 for $n_A = 8$:**
  - BC$_w$, BF$_w$, CS, RS, AS, BOISE.
- **NEF10 for $n_A = 16$:**
  - BC$_w$, BF$_w$, CS, RS, AS, BOISE.
- **ROCAUC for $n_A = 8$:**
  - BC$_w$, BF$_w$, CS, RS, AS, BOISE.
- **ROCAUC for $n_A = 16$:**
  - BC$_w$, BF$_w$, CS, RS, AS, BOISE.
which is sprinkled with missing data. Each of the 23 remaining lines serves as a novel target \( i^* \) that each IBR method may operate on to prioritize bioactive compounds. In revealing the complete data on any \( i^* \), we have a test set from which NEF10 and ROCAUC metrics are derived; conveniently, the absence of missing data from the test set makes these metrics easier to compute.

Figure 6 summarizes the predictive performance of BOISE, with \( n_A = 8 \), as well machine-learning IBRs adaptive selection (AS) and regression selection (RS), and one of the baseline frequent-hitter rules. The non-BOISE methods operate on completed data; we experimented with several matrix-completion tools and report results from Python package fancyimpute (https://pypi.org/project/fancyimpute/). Among the imputation methods provided by fancyimpute, KNN imputation, with \( K = 3 \), leads to the best retrospective results. In spite of that selection for non-BOISE IBRs, BOISE is empirically stronger on both metrics. The advantages are not statistically significant by the method used earlier, though the test-set size is relatively small. For NEF10, for example, BOISE’s closest competitor has CI of \([-0.18, 0.036]\); for ROCAUC, the closest competitor has CI of \([-0.13, 0.016]\). More directly, on the 23 test-set targets, BOISE has better NEF10 than the best competitor (AS) on 7 of the targets, has worse numbers on 2, and gives the same top 10% predictions as AS on the other 14. With ROCAUC, BOISE is better on 16 targets and worse on 7.
4 Discussion

Virtual screening trades biochemical experimentation for computer time. It advances drug discovery efforts if the deployed algorithms effectively encode information on protein targets and drug compounds. Computational chemists are sometimes faced with the setting studied in this manuscript, wherein the target of interest is known only to be a member of a class for which limited bioactivity data are available across a panel of drug compounds. Effective though somewhat ad hoc machine-learning approaches have been developed for this experimental design problem. For example, regression selection (RS) clusters initial targets via \( K \)-means clustering with \( K \) obtained through cross validation. Then it fits a regularized multinomial logistic regression to identify which compounds (the informers) best predict the cluster labels. The fact that RS and other machine-learning IBR methods perform better than domain-specific baseline methods suggests there is critical information in the bioactivity data available at the outset of the experiment. We reason that statistical approaches may offer further insights, especially as we recognize the two-stage problem structure and the opportunity for explicit risk minimization.

The proposed BOISE IBR scheme shows strong predictive performance in two retrospective empirical studies. The source for the improvements is not entirely clear. The statistical model may be accurate, and then risk minimization does produce the most effective procedure. It may be that model inaccuracies are less important than some key aspects of the computation, such as the fact that BOISE averages over uncertainties in how targets should be clustered. In any
case the calculations reveal how Bayesian decision theory may operate in the realm of virtual drug screening and what levels of prediction accuracy are possible.

Like for many Bayesian methods, a limitation of BOISE is its computational complexity. Our prototype R code used approximately 20 CPU hours on an Intel Core i5 processor to select an informer set with size \( n_A = 8 \) for one PKIS1 target, while \( n_A = 16 \) required about 300 CPU hours. For PEL1 computation, the number of possible intermediate data values \( x_A \) increases as \( 2^{n_A} \). The sampling strategy in Algorithm 4 avoids complete enumeration, but there is a trade-off between sample size and running time. For the PKIS1 retrospective analysis, we used parallel computing available at the UW-Madison Center for High Throughput Computing, completing calculations on 224 compute nodes in 2 weeks of wall time.

Having developed a complete BOISE formulation, we can pursue approximations that capture the essential structure with less computational effort. The key step to compute PEL1, for example, is to evaluate \( E(\theta_{t^*j} | C, x_0, x_A) \) in (10), which consists of the posterior probability \( p_k = P(i^* \in c_k | C, x_0, x_A) \), and also the posterior expectation \( E(\theta_{t^*j} | x_0, x_A, C, i^* \in c_k) \). Inspection shows that the informer set \( A \) may have little impact on the second term, since for \( j \notin A \), intermediate data \( x_A \) are not involved, while for \( j \in A \) we already know the interaction of \( j \) on \( i^* \) through \( x_A \). Hence the quantities \( E(\theta_{t^*j} | x_0, x_A, C, i^* \in c_k) \) have a limited role in selecting top set \( T^*(A, x_A, x_0) \), and aspects of the distribution \( p = (p_0, p_1, \cdots, p_K) \) alone may effectively score informer sets. These probabilities constitute the conditional distribution of the cluster label for target \( i^* \) given \( C, x_A \) and \( x_0 \), and they are relatively easy to compute.

Figure 5: Statistical comparison of performance metrics, GDSC. Intervals are 95% multiplicity adjusted confidence intervals of differences between other IBR methods and BOISE, based on a linear model fit to the performance metrics in Figure 4.
Figure 6: **Predictive performance of IBR methods in the presence of missing data.** Metrics and methods are as in Figures 2 and 4, but a single training set of 963 cell lines and 304 drugs from GDSC has 15.5% missing entries. For non-BOISE methods (which require complete data), we performed matrix completion on the original data set each method; BOISE, by contrast, operated on the available, incomplete matrix.

From Algorithm 4 we see that $p_k$ can be calculated directly from $x_A$ and $x_0$ for each given $C$, while $E(\theta_{i^*j} \mid x_0, x_A)$ needs two rounds of averaging over all samples of $x_A$ and $C$. Guided by the ID3 decision-tree method (Quinlan, 1986), we take the entropy $H(p) = -\sum_{k=0}^{K} p_k \log_2(p_k)$ and propose $H(A) = E\{H(p) \mid x_0\}$, which averages over $x_A$ and $C$, as an objective function to minimize in a simplified BOISE scheme. The predictive performance of this entropy-based procedure is comparable to BOISE in the PKIS1 and GDSC retrospective studies, but substantially better than other IBR methods (e.g., ROCAUC and NEF10 medians in PKIS1 with $n_A = 16$ were 0.951 and 0.877, respectively, compared to values in Figure 2). However, the running time for the entropy-based method is dramatically reduced: one PKIS1 target takes 25 CPU hours compared to BOISE’s 300 CPU hours.

Making BOISE maximally applicable for broad biological targets may require addressing additional computational challenges. In both retrospective analyses, the targets (protein kinases or cancer cell lines) were known in advance to be reasonably biologically similar. However, in general a new target could be biologically distant from the targets with initial chemical screening data, for instance, a protein from a different family or an assay of a different cellular phenotype. We can explore a wider variety of targets through retrospective analyses of bioassay data from PubChem (Kim et al 2019). PubChem can also support testing BOISE’s scalability to much larger datasets, as we can construct an initial bioactivity matrix containing partially-complete screening data for hundreds of targets and hundreds of thousands of compounds. The PubChem-scale application may require algorithmic development to further improve the compute time and methodology development in order to degrade gracefully when the new target clusters poorly with initial targets.
Some advantages may come from further consideration of loss functions and stochastic models. For example, the current implementation allows overlap between T and A, which might be handled differently for experiment prioritization. Also, the approach does not penalize molecules that have broad, non-specific activity. It was not an issue in the examples presented here but a more elaborate parameter-space model may be helpful in larger cases. Numerous factors warrant further study, and we hope the present framework is relevant in this effort.

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A Proof of Theorem 1

Considering the risk (2), it is sufficient to show that for any fixed \(x_A, x_0\), we have

\[
\int_{\Theta} L(A, T) p(\theta|x_A, x_0) d\theta \geq \int_{\Theta} L(A, T^*) p(\theta|x_A, x_0) d\theta. \tag{12}
\]

To confirm this, expand the loss function \(L(A, T)\) and evaluate:

\[
\int_{\Theta} L(A, T) p(\theta|x_A, x_0) d\theta = \int_{\Theta} \left( n_T - \sum_{j \in T} \theta_{i,j} \right) p(\theta|x_A, x_0) d\theta \\
= n_T - \sum_{j \in T} \hat{\theta}_{i,j} \\
\geq n_T - \sum_{j \in T^*} \hat{\theta}_{i,j} \\
= \int_{\Theta} L(A, T^*) p(\theta|x_A, x_0) d\theta.
\]

B Sampling clusterings given initial data

A Dirichlet process mixture model (DPMM) has data \(x_i\) distributed \(F(\cdot, \theta_i)\), parameters \(\{\theta_i\}\) i.i.d. from \(G\), and uncertainty in \(G\) following a Dirichlet process with base measure \(m_0G_0\). In BOISE, each \(x_i\) is a multivariate random
vector, and each component $x_{i,j}$ is an independent Bernoulli trial with success rate $\theta_{i,j}$. Therefore, $F(x_i, \theta_i) = \prod_{j=1}^n \theta_{i,j}^{x_{i,j}} (1 - \theta_{i,j})^{1-x_{i,j}}$ and $G_0$ is a homogeneous Beta$(\alpha_0, \beta_0)$ on each component $\theta_{i,j}$.

Let $c(i)$ be the cluster label of target $i$, $i = 1, 2, \cdots, m$, and $\phi_k$ be the shared parameter in cluster $k$. Our goal is to sample $C = (c(1), \cdots, c(m))$ given $x_0$. Following the collapsing method from MacEachern (1994) and Neal (2000), Algorithm 3, a Gibbs sampler uses:

$$P(c(i) = k | c(-i), x_0) \propto \left\{ \begin{array}{ll}
\prod_{j=1}^n \left( \frac{m-1+k}{m+1+m_0} \right) \int F(x_i, \phi_k) dH_{-i,k}(\phi_k), & \text{if } \exists \ c(j) = k, j \neq i \\
\prod_{j=1}^n \left( \frac{m_0}{m+1+m_0} \right) \int F(x_i, \phi) dG_0(\phi), & \text{if } \nexists \ c(j) = k, j \neq i.
\end{array} \right.$$

Here $m_{-i,k} = \sum_{j \neq i} 1(c(j) = k)$ is defined to be the number of targets other than $i$ that are currently in cluster $k$, and $H_{-i,k}(\phi) = P(\phi_k | G_0, \{x_j : j \neq i, c(j) = k\})$ is the posterior distribution of $\phi_k$ given $G_0$ and all other observations $x_j$ in cluster $k$ except $x_i$. We set $F(x_i, \phi)$ as above and $H_{-i,k}(\phi_k)$ as the product of independent Beta densities:

$$H_{-i,k}(\phi_k) = \prod_{j=1}^n \frac{1}{B(a_{-i,k,j}, b_{-i,k,j})} \phi_k^{a_{-i,k,j} - 1} (1 - \phi_k)^{b_{-i,k,j} - 1}$$

where $a_{-i,k,j}$ and $b_{-i,k,j}$ are similarly defined as in (9). Notice that we use $k > 0$ to denote an existing cluster and $k = 0$ to denote a new cluster. The updating formula and corresponding algorithm for Gibbs sampler are:

$$P(c(i) = k|c(-i), x_0) \propto \left\{ \begin{array}{ll}
\prod_{j=1}^n \left( \frac{m-1+k}{m+1+m_0} \right) \left( \frac{a_{-i,k,j}}{a_{-i,k,j} + b_{-i,k,j}} \right)^{x_{i,j}} \left( \frac{b_{-i,k,j}}{a_{-i,k,j} + b_{-i,k,j}} \right)^{1-x_{i,j}}, & \text{if } k > 0 \\
\prod_{j=1}^n \left( \frac{m_0}{m+1+m_0} \right) \left( \frac{\alpha_0}{\alpha_0 + \beta_0} \right)^{x_{i,j}} \left( \frac{\beta_0}{\alpha_0 + \beta_0} \right)^{1-x_{i,j}}, & \text{if } k = 0.
\end{array} \right.$$

Algorithm 3 DPMM clustering

1: Set the prior mass $m_0$ and hyperparameters $\alpha_0$ and $\beta_0$
2: Initialize $c(1), \cdots, c(m)$
3: Set sample size of clustering assignments $M$, and gaps between successive draws $N$
4: while Sample size $< M$ do
5: \hspace{0.5cm} for $i = 1, \cdots, m$ do
6: \hspace{1cm} Update $i$th cluster label from $P(c(i) | c(-i), x_0)$ in (13)
7: \hspace{0.5cm} end for
8: Record clustering assignment after every $N$ cycles.
9: end while

We follow the empirical Bayes principle to choose hyperparameters. We select $\alpha_0 = \text{mean}(x_0)$ and $\beta_0 = 1 - \alpha_0$ and select prior mass $m_0$ to make prior cluster numbers as close to posterior cluster numbers as possible. For PKIS1 data, we select $m_0 = 15$ and $\alpha_0 = 0.066$; For GDSC complete data, we select $m_0 = 3$ and $\alpha_0 = 0.067$. The sample size $M$ is 100 and the thinning step $N$ is 50 for both data sets, which shows adequate mixing in MCMC output analysis.

C Recycling algorithm

To compute the optimal top set $T^*$ associated with hypothetical intermediate data $x_A$, we need to compute posterior means $\hat{\theta}_{i,*}$ for all compounds $j$. By tilting the expectation as in importance sampling, we have, summing over all
partitions $C$ of initial proteins $I$,

\[
\dot{\theta}_{i^*, j} = E (\theta_{i^*, j} | x_0, x_A)
\]

\[
= \sum_{C} \left( \dot{\theta}_{i^*, j} \right) p(C | x_0, x_A)
\]

\[
= \sum_{C} \left( \dot{\theta}_{i^*, j} \right) \frac{p(C | x_0, x_A)}{p(C | x_0)} p(C | x_0)
\]

\[
= \sum_{C} \left( \dot{\theta}_{i^*, j} \right) \frac{p(x_A | x_0, C)}{p(x_A | x_0)} p(C | x_0)
\]

where, because of (9),

\[
p(x_A | x_0, C) = \sum_{k=0}^{K} \frac{m_k}{m + m_k} \prod_{j \in A} \left( \frac{a_{k,j}}{a_{k,j} + b_{k,j}} \right)^{x_{i^*, j}} \left( \frac{b_{k,j}}{a_{k,j} + b_{k,j}} \right)^{1-x_{i^*, j}}.
\]

Thus, quantities $\dot{\theta}_{i^*, j}$ are also all expectations of modified objects with respect to the original posterior $p(C | x_0)$, and so we may re-use the Monte Carlo samples to approximate for each predictive sample $x_A$. The only trick is to get $p(x_A | x_0)$, which we can get directly by averaging the values $p(x_A | x_0, C)$ over these sampled clusterings. If $C$ is a collection of $N$ clusterings $C$’s sampled from $p(C | x_0)$, then we approximate $\dot{\theta}_{i^*, j}$ by

\[
\frac{1}{N} \sum_{C \in \mathbb{C}} \left\{ \sum_{k=0}^{K} m_k \left( \frac{a_{k,j}}{a_{k,j} + b_{k,j}} \right)^{x_{i^*, j}} \left( \frac{b_{k,j}}{a_{k,j} + b_{k,j}} \right)^{1-x_{i^*, j}} \right\} = \frac{1}{N} \sum_{C' \in \mathbb{C}} p(x_A | x_0, C')
\]

Our use of recycled samples is similar to their use other contexts (e.g., Newton and Geyer 1994; Trotter and Tukey, 1954). Pseudocode is in Algorithm 4.

---

**Algorithm 4** PEL Computation

| Input: | Initial data $x_0$, informer set $A$, size of top set $n_T$, samples $\mathbb{C}$ from $p(C | x_0)$. |
|-------|--------------------------------------------------------------------------------------------------|
| Output: | PEL$_1(x_0, A)$ as score of informer set $A$. |
| 1: | for each $C$ in $\mathbb{C}$ do |
| 2: | Sample $\mathcal{X}_{A,C}$ from $p(x_A | C, x_0)$ as (9) |
| 3: | end for |
| 4: | Set $\mathcal{X}_A = \bigcup \mathcal{X}_{A,C}$ |
| 5: | for each distinct $x_A$ in $\mathcal{X}_A$ do |
| 6: | for each $C$ in $\mathbb{C}$ do |
| 7: | Calculate $\dot{\theta}_{i^*, j} = E(\theta_{i^*, j} | C, x_0, x_A)$ using (10); |
| 8: | Calculate $p(x_A | x_0, C)$ using (14). |
| 9: | end for |
| 10: | Calculate $\dot{\theta}_{i^*, j} = E(\theta_{i^*, j} | x_A, x_0)$ for each $j$ using (15) |
| 11: | Calculate PEL$_2(x_0, A, x_A)$ loss as in (6) |
| 12: | end for |
| 13: | Calculate PEL$_1(x_0, A)$ by averaging PEL$_2(x_0, A, x_A)$ over all $x_A \in \mathcal{X}_A$. |

---

**D Normalized enrichment factor (NEF10)**

Enrichment factor (EF) is a commonly used metric in context of virtual screening. It reflects how much increase in active compounds compared to random selection. EF is actually a scaled form of TPR: After IBR ranking, we can relabel compounds $j = 1, 2, \cdots, n$ by highest to lowest priority for further testing on target $i^*$. The 10% enrichment
factor is

\[
EF_{10i^*} = \frac{\sum_{j=1}^{[n/10]} x_{i^*,j}}{\frac{n}{10}} / \frac{\sum_{j=1}^{n} x_{i^*,j}}{n}
\]  

(16)

In (16), we can see that \(EF\) is influenced by the number of active compounds of the target. Therefore a normalized \(EF\) (NEF) is introduced in Zhang et al. (2019) to make better comparison across targets with different active ratios:

\[
NEF_{10i^*} = \left(1 + \frac{EF_{10i^*} - EF_{\text{base}}}{EF_{10\text{max}} - EF_{\text{base}}}\right) / 2
\]  

(17)

where \(EF_{\text{base}} = 1\) corresponds to random guessing, and \(EF_{10\text{max}}\) is the maximum theoretical value of \(EF_{10}\). The \(NEF_{10}\) value is between 0 and 1 with random guessing at 0.5.