Active Learning for Primary Drug Screening

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Abstract

We study the task of approximating the $k$ best instances with regard to a function using a limited number of evaluations. We also apply an active learning algorithm based on Gaussian processes to the problem, and evaluate it on a challenging set of structure-activity relationship prediction tasks.

1. Introduction

High Throughput Screening (HTS) is a step in the drug discovery process, in which chemical compounds are screened against a biological assay. The goal of this step is to find a few lead compounds within the entire compound library that exhibit a very high activity in the assay. In this type of application, only partial information can be obtained by testing specific instances for their performance. Such tests correspond to experiments and can be quite expensive. The challenge then is to identify the best performing instances using as few experiments as possible.

2. Problem statement

Our work is especially motivated by the structure-activity relationship domain, where HTS approaches often assume the availability of a large but fixed library of chemical compounds. Hence, we assume the learner must select the next example from a finite pool. We formally specify the problem as follows:

Given:
- a pool $\mathcal{P}$ of instances,
- an unknown function $f$ that maps instances $x \in \mathcal{P}$ on their target values $f(x)$,
- an oracle that can be queried for the target value of any example $x \in \mathcal{P}$,
- the maximal number $N_{\text{max}}$ of queries,
- the number $k$ of best examples searched for.

Find:
- the top $k$ instances in $\mathcal{P}$, that is, the $k$ instances in $\mathcal{P}$ that have the highest values for $f$.

From a machine learning perspective, the key challenge is to determine the policy for determining the next query to be asked on the basis of the already known examples. This policy will have to keep the right balance between exploring the whole pool of examples and exploiting those regions in the pool that look most promising.

3. Model and selection strategies

We will use a Gaussian process (GP) model for learning (Gibbs, 1997). Detailed explanations can be found in several textbooks, e.g. (Bishop, 2006). The GP model allows us to calculate the probability distribution of the target value $t_*$ of a new example $x_*$ given the tested examples $X_N$ and their measured target values $T_N$:

$$t_*|X_N, T_N, x_* \sim \mathcal{N}(t_*, \text{var}(t_*))$$ (1)

Different active learning strategies exist. In line with the customary goal of inducing a model with maximal accuracy on future examples, most approaches involve a strategy aiming to greedily improve the quality of the model in regions of the example space where its quality is lowest. One can select new examples for which the predictions of the model are least certain or most ambiguous. Depending on the learning algorithm, this translates to near decision boundary selection, ensemble entropy reduction, version space shrinking, and others. In our model, it translates to maximum variance on the predicted value or arg max(var($t_*$)).

(Warmuth et al., 2003) found that in a highly skewed distribution, recall increases quickly when one selects examples for testing that are most likely to belong to the minority class. For our optimization problem we
will test the equivalent method of selecting the example that the current model predicts to have the best target value, or \( \arg\max(t_x) \). We will refer to this as the **maximum predicted** strategy.

Another strategy is to always choose the example for which the optimistic guess is maximal. The idea is not to test the example in the database where the predicted value \( t_x \) is maximal, but the example where \( \hat{t}_x + k_{\text{optimism}} \cdot \text{var}(t_x) \) is maximal.

An alternative strategy is to select the example \( x_{N+1} \) that has the highest probability of improving the current solution, as described by (Lizotte et al., 2007). Let the current step be \( N \), the aggregate value of the set of \( k \) best examples be \( \|T_{N}\|_{\text{best-}k} \) and the target value of the \( k \)-th best example be \( t_{\#(k,N)} \). We can evaluate this probability computing the cumulative Gaussian

\[
P(t_x > t_{\#(k,N)}) = \int_{t=t_{\#(k,N)}}^{\infty} (t - t_x)P(t_x = t)dt. \tag{2}
\]

We call this the **maximum gain probability** strategy.

### 4. Experimental evaluation

We evaluated the algorithm on the US National Cancer Institute (NCI) 60 anticancer drug screen (NCI60) dataset (Shoemaker, 2006). A pool of 2,000 compounds was randomly selected from each assay.

We used a linear kernel using for each compound 1024 Open Babel FP2 fingerprints as features. The algorithm was bootstrapped with measurements of ten random compounds. Each experiment was repeated 20 times for every assay and the results were averaged.

<table>
<thead>
<tr>
<th>Budget</th>
<th>10%</th>
<th>15%</th>
<th>20%</th>
<th>25%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Max predicted (0(\sigma))</td>
<td>0.251</td>
<td>0.684</td>
<td>0.040</td>
<td>0.021</td>
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<td>Optimistic (0.5(\sigma))</td>
<td>0.521</td>
<td>Best</td>
<td>0.251</td>
<td>0.111</td>
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<td>Optimistic (1(\sigma))</td>
<td>0.182</td>
<td>0.469</td>
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<td>Best</td>
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<tr>
<td>Optimistic (2(\sigma))</td>
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<td>0.958</td>
<td>0.179</td>
<td>0.298</td>
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<tr>
<td>Max variance ((\infty\sigma))</td>
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<td>(\epsilon)</td>
<td>(\epsilon)</td>
<td>(\epsilon)</td>
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<tr>
<td>Max gain prob</td>
<td>Best</td>
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<td>0.189</td>
<td>0.052</td>
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<tr>
<td>Random selection</td>
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<td>(\epsilon)</td>
<td>(\epsilon)</td>
<td>(\epsilon)</td>
</tr>
</tbody>
</table>

Table 1. Best strategy (attaining highest \( \|T_{N_{\text{max}}}\|_{\text{best-10}} \)) and Wilcoxon signed-rank test p-value for the null hypothesis that the difference between the top-10 values of this strategy and those of the best strategy is on average zero. \( \epsilon \) indicates that \( p < 10^{-10} \). Budget shown as % of pool size.

From the results presented in Figure 1 and Table 1 one can see that all strategies, except maximum-variance, clearly perform much better than random example selection. The 1\(\sigma\) optimistic strategy performs best over the widest range of budgets.

### 5. Conclusions

To summarize: we introduced the best-k optimization problem in a machine learning context, we proposed an approach based on Gaussian processes to tackle it, and we applied it successfully to a challenging structure activity relationship prediction task.

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### References


