Dealing with sparse data in predicting outcomes of HIV combination therapies

Jasmina Bogojeska1,∗, Steffen Bickel2, André Altmann1 and Thomas Lengauer1
1Max Planck Institute for Informatics, Campus E1 4, 66123, Saarbrücken and 2Nokia Gate 5, Berlin, Germany

ABSTRACT

Motivation: As there exists no cure or vaccine for the infection with human immunodeficiency virus (HIV), the standard approach to treating HIV patients is to repeatedly administer different combinations of several antiretroviral drugs. Because of the large number of possible drug combinations, manually finding a successful regimen becomes practically impossible. This presents a major challenge for HIV treatment. The application of machine learning methods for predicting virological responses to potential therapies is a possible approach to solving this problem. However, due to evolving trends in treating HIV patients the available clinical datasets have a highly unbalanced representation, which might negatively affect the usefulness of derived statistical models.

Results: This article presents an approach that tackles the problem of predicting virological response to combination therapies by learning a separate logistic regression model for each therapy. The models are fitted by using not only the data from the target therapy but also the information from similar therapies. For this purpose, we introduce and evaluate two different measures of therapy similarity. The models are also able to incorporate phenotypic knowledge on the therapy outcomes through a Gaussian prior. With our approach we balance the uneven therapy representation in the datasets and produce higher quality models for therapies with very few training samples. According to the results from the computational experiments our therapy similarity model performs significantly better than training separate models for each therapy by using solely their examples. Furthermore, the model’s performance is as good as an approach that encodes therapy information in the input feature space with the advantage of delivering better results for therapies with very few training samples.

Availability: Code of the efficient logistic regression is available from http://www.mpi-inf.mpg.de/%7Etjasmina/fastLogistic.zip

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1 INTRODUCTION

The human immunodeficiency virus (HIV) targets the human immune system and leads to the acquired immunodeficiency syndrome (AIDS) that has a high mortality rate. Being a disease that claimed more than 25 million lives since its discovery in 1981, AIDS is highly ranked on the chart of most destructive world epidemics. Currently, there is no vaccine against HIV and there is no way of ridding HIV patients of the virus.

Therapy administration to patients is hampered by the high evolutionary dynamics of the virus which eventually escapes to resistance against any drug therapy. In order to prolong the time for which a therapy is effective, combinations of drugs are administered to patients. According to the WHO (UNAIDS/WHO, 2009) more than 30 million people were infected and approximately 4 million people were receiving antiretroviral therapy at the end of 2008. Since every therapy eventually fails, finding a successful regimen remains a major challenge for HIV treatment. Whenever a therapy regimen fails a physician decides on a new regimen based on the presence of a set of resistance-relevant mutations in the viral strands sampled from the patient’s blood serum. The large number of available drugs renders the number of potential therapy combinations too large for manual assessment. Thus, in recent years statistical models for therapy outcome prediction have been developed on the basis of clinical data. These data comprise samples of many different drug combination therapies taken from many patients over a couple of decades. Different therapies are represented in different abundance of samples: while for some therapies many samples exist, for others there are very few. Furthermore, due to the large number of possible combination therapies and the introduction of new antiretroviral agents, for many combinations no samples are available at all.

In a medical setting, we strive for every therapy to be effective. Thus, it is important to improve the quality of the prediction on these difficult to assess therapies that have very few training samples. The work we present in this article is inspired by the uneven therapy representation in the clinical datasets. We propose a method that tackles the problem of predicting the outcome of HIV drug combination therapies as follows. A separate model is trained for each distinct therapy combination by using not only the samples from the target therapy but also the available samples from similar therapies with appropriate sample weights. In order to quantify therapy similarity, we introduce two different similarity measures: the drugs kernel and the groups additivity kernel. Utilizing knowledge from similar therapies is particularly important for the therapy models that have very few or no examples in the available dataset. Since we learn separate models for each drug combination in order to provide efficient model fitting and model selection, we choose the trust region Newton method for training linear logistic regression (Lin et al., 2008) that takes advantage of the sparsity of the data. Furthermore, our method has the facility of integrating prior knowledge on therapy outcomes through a Gaussian prior.
In the article, we show how to integrate phenotypic models that give information on the in vitro effectiveness of each drug as prior knowledge.

Being collected over two decades the clinical data cannot be representative for any given time point; the treatment trends change with the introduction of new drugs and the viral sequences evolve over time. We take this phenomenon into account by a time-oriented evaluation which uses the most recent data samples to assess the quality of the models and learns the models on the remaining samples.

The article is structured as follows. After reflecting on related work we give the details of the method, the similarity measures and the prior knowledge in Section 2. In Section 3, we describe the datasets, the experimental setting and present and discuss the results of the computational experiments. Section 4 concludes our article.

1.1 Related work

Machine learning methods, such as artificial neural networks, decision trees, random forests, support vector machines (SVMs) and logistic regression (Altmann et al., 2007, 2009b; Defoerche et al., 2008; Larder et al., 2007; Lathrop and Fazzani, 1999; Prosperi et al. 2005, 2009; Rosen-Zvi et al., 2008; Wang et al., 2003), have been used to tackle the problem of predicting virological response to therapies similar to the therapy of interest. In this way the separate computation of the similarities in a preprocessing heuristic but much more efficient and configurable alternative is obtained by solving the optimization problem given as follows.

\[ \min \frac{1}{|D|} \sum_{(x_i, y_i) \in D} k(z_i, t)^{-1} \frac{y_i - \mu(z_i, t)}{2\sigma^2} \]

\[ k(z_i, t) \text{ is a function that provides sample-specific weights that quantify the similarity of the therapy of interest } t \text{ with the therapy } z_i \text{ from the } i\text{-th sample, and } y_i \text{ is its smoothing parameter.} \]

\[ \mu(z_i, t) = \max \{0, \mu(z_i, t) + \gamma k(z_i, t)\} \]

\[ \gamma \text{ is the smoothing parameter.} \]

\[ \mu(z_i, t) \text{ is the mean on sample } z_i \text{ for therapy } t \text{ obtained by solving the optimization problem given in Section 2.2. We will refer to this model as therapy similarity model.} \]

\[ \text{The large number of distinct therapies and our approach of training a separate model for each of them demand an efficient method for solving Optimization Problem 1. To do this, we apply a trust region Newton method for training logistic regression (Lin et al., 2008) that takes advantage of the sparseness of our feature space. This enables fast model fitting which results in efficient model selection. In what follows, we give a detailed description of the therapy similarity kernels and the prior phenotypic knowledge on the therapy outcomes.} \]

2.1 Therapy similarity kernels

We quantify the pairwise similarity between the different drug combinations with two kernels: the drugs kernel and the groups additivity kernel. The method also allows for alternative definitions of pairwise therapy similarity that can include different types of additional information, e.g. expert knowledge or information obtained from phenotypic drug resistance tests.

The drugs kernel similarity is based on the number of common drugs that two combination therapies share. Let \( u_i \) and \( u_j \) be binary vectors indicating the distinct drugs comprising the therapies \( u_i \) and \( u_j \), respectively.

\[ k_d(z_i, z_j) = \frac{(u_i^T u_j)}{\max(|u_i|, |u_j|)} \]
Since the group similarities sim are very similar. We present them in Section 4 of the Supplementary Material.

Intuitively, the larger the number of common drugs making up a specific drug group of the two therapies of interest, the higher their group similarity. We derive the similarity \( k_z(z') \) between the therapies \( z \) and \( z' \) by averaging the similarities of their corresponding drug groups:

\[
\sum_{g} \text{ext}\left(\text{sim}(z, z')\right)
\]

Since the group similarities \( \text{sim}(z, z') \) are in the interval \([0, 1]\), \( k_z(z') \) also has values within \([0, 1]\).

Note that computing the kernel values for all therapies takes only several seconds. In the article, we only focus on the results obtained with the drugs kernels. The corresponding results obtained with the groups additivity kernel are very similar. We present them in Section 4 of the Supplementary Material.

### 2.2 Phenotypic prior knowledge on therapy outcome

Phenotypic resistance tests are laboratory experiments that produce continuous values, referred to as resistance factors, that measure the effectiveness of individual drugs against a given viral strain. Genotype-phenotype pairs (GPP) are sequences with the associated resistance factor measured in a phenotypic test using the virus defined by the sequence. The models trained on GPP data aim at predicting the resistance factors for each single drug for unknown genotypes. We will refer to these models as phenotypic models. One such model is described in Beerenwinkel et al. (2003a). Furthermore, this article reveals the bimodal nature of the distribution of the resistance factors common to all drugs. Such a distribution can be approximated with a two-component Gaussian mixture model. We derive drug-specific resistance cutoffs from the intersection of the two mixture components. The cutoffs can then be used to infer the effectiveness of each drug against a given genotype: a drug is effective when its resistance value is smaller than its resistance cutoff, otherwise it is ineffective.

Unlike other approaches that add predictions facilitated by phenotypic models as additional features in their input feature space (Altmann et al., 2007, 2009a), we incorporate the models themself via a logarithm of a Gaussian prior on the model parameters for each therapy combination. We will show that with the procedure described above one can better utilize the phenotypic knowledge compared with using the prediction of the phenotypic model as additional input feature in a single logistic regression model fit for all therapies.

### 3 RESULTS AND DISCUSSION

We developed a model that targets the problem of predicting the outcome of HIV combination therapies from the genotype of the most abundant virus strain in the patient’s blood serum. In the next sections we describe the datasets, the details of the computational study that assesses the quality of our model and its results.

#### 3.1 Datasets

We use the EuResist database (Rosen-Zvi et al., 2008) that incorporates information of 88 469 antiretroviral therapies administered to 18 255 HIV (subtype B) patients from several countries in the period from 1988 through 2008. This information includes the combination of drugs given to the patients, the sequence of the predominant viral variant and virus load measurements at different time points during a therapy.

The dataset we use to train our models is derived from the EuResist database as follows.

Each sample of the data corresponds to a therapy given to a patient and contains information describing the viral sequence obtained shortly before the respective therapy was administered. The virus genotype is represented by a binary vector indicating the occurrence or absence of a set of predefined resistance-relevant mutations based on the mutation list reported in Johnson et al. (2008). Each therapy is denoted by a binary vector indicating the presence or absence of the individual drugs comprising it. We label each therapy sample as success or failure based on the virus load (copies of viral RNA per ml blood plasma, cp/ml) measured in the course of the therapy. If the virus load drops below 400 cp/ml in the period from 21 days after the start of the therapy to the end of the therapy we label it with success (1); otherwise with a failure (−1). Figure 1 shows a schema of the labeling procedure. In this way we create a labeled dataset that includes 6336 therapy samples with 638 distinct therapy combinations.

![Fig. 1. Assigning a label and a viral sequence to therapy2, where therapy1 and therapy2 are two consecutive therapy administered to a patient.](https://academic.oup.com/bioinformatics/article-abstract/26/17/2085/199636)
After the filtering we end up with 200 samples. For representing the genotypic information describing the virus, we use the same binary interest based on the resistance factor of the most effective drug.

In this way our models learn from data seen in the more distant past and their performance is measured on unseen data from the more recent past. Such an evaluation scenario reflects the actual situation in HIV therapy outcome prediction: the outcomes of unseen future therapy samples are estimated by utilizing the information from past treatment records. We refer to this setting as time-oriented scenario. More details supporting such an evaluation scenario and plots depicting the changing therapy trends over time can be found in Section 1 of the Supplementary Material.

In the two following subsections, we report the results of computational experiments conducted with our method and several other reference methods used for comparison.

One reference method consists of training a separate logistic regression model for each combination therapy by using only the samples from the target therapy. If we had enough data for each therapy combination this would be the best choice as the separate model captures the characteristics specific to the corresponding therapy and therefore can also make the best predictions for it.

In our case we fit the separate models by using the data available for each individual therapy in the clinical database. The therapies with no samples available are either randomly classified as success or failure both with equal probability of 50%, or the phenotypic model (Section 2.2) is used to assign their labels. For therapies represented only with successful (failing) examples, we assign success probabilities of 1 (0). We will refer to this approach as partitioned evaluation scenario.

The second reference method, referred to as transfer evaluation scenario, implements the distribution matching approach by Bickel et al. (2008). In order to provide a fair comparison, we use a linear instead of a nonlinear logistic regression for the separate models learned for each therapy. The sample-specific weights for each therapy are obtained as described in Bickel et al. (2008) by using a nonlinear multi-class logistic regression.

The last reference method, referred to as one-for-all evaluation scenario, fits a single logistic regression model to the viral genotypes of all therapies. The information about the drugs comprising the corresponding therapies is added to the input feature space. This is the most common approach in the field.

### 3.3 Experiments and discussion

In this subsection, we present and discuss the results of the validation experiments. The therapy similarity models and each of the different reference models, as explained in the previous subsection, are trained on the EuResist clinical dataset by using the time-oriented scenario. The goal of each model is to predict the outcomes of the combination therapies for the most recent therapy samples in the dataset. We are primarily interested in the accuracy as a measure of the quality of the different models. However, sometimes one is not only interested in the absolute results, but also in the quality of the ranking of the therapies based on their success probability. This is especially important when choosing a future therapy for a patient. Therefore, we also carry out model selection based on AUC (area under the receiver operating characteristic (ROC) curve) performance and report AUC results. Table 1 summarizes the classification accuracies (ACCs) and the AUCs for the different methods:

- **drugs kernel** denotes our therapy similarity models with the drugs kernel
- **drug similarity model** denotes the reference models
- **phenotypic model** denotes our therapy similarity models with the drugs kernel
- **partitioned evaluation scenario** denotes the reference models, as explained in the previous subsection, are trained on the EuResist clinical dataset by using the time-oriented scenario.
- **transfer evaluation scenario** implements the distribution matching approach by Bickel et al. (2008)
- **one-for-all evaluation scenario** fits a single logistic regression model to the viral genotypes of all therapies.
using only the samples belonging to the target therapy; the label with prior (no prior) can refer to any of the previously described models with (without) additional phenotypic knowledge encoded as a Gaussian prior; one-for-all refers to the reference method that fits a single logistic regression model to the samples from all combination therapies where the therapy information is encoded in the input feature space; the label with prior for the one-for-all approach refers to encoding the prediction of the phenotypic model described in Section 2.2 as an additional feature; transfer refers to the linear version of the transfer model by Bickel et al. (2008). As we mentioned before, efficient model fitting is important for the approaches that fit a separate model for each combination therapy. By using the trust region Newton method for training logistic regression (Lin et al., 2008), we fit a single model in a split of a second. For example, fitting 154 separate models for the different therapies in the test set takes only 13 s on a normal desktop computer. In what follows, we will first discuss the performance of the different models with respect to the accuracy and then continue with a similar discussion for the AUC. Resampling techniques (e.g. bootstrap) to estimate the standard errors (SEs) of these measurements are not readily applicable in the time-oriented scenario in which the data samples are ordered by the starting times of their corresponding therapies. Therefore, we resort to calculating SEs of the accuracies based on the paired t-test detailed in Section 2 of the Supplementary Material and SEs of the AUCs are computed as described in DeLong et al. (1988).

As shown in Table 1, our approach (drugs kernel) of utilizing information of similar therapies, the transfer model and the model from the one-for-all scenario perform significantly better than training separate models by solely using the samples from the target therapies (partitioned scenario). We assess the significance of the accuracy with a paired t-test where we observe p-values ≤ 0.01 for all pairwise comparisons between the models from the partitioned scenario and the other models. The performance of the partitioned models is worse because for many therapies there are only few samples in the dataset (Fig. 2). The therapy similarity kernels in our approach and the sample-specific weights in the transfer scenario compensate for this lack of data by using the samples from the similar therapies for making the predictions.

In order to further investigate the performance of the models, we take the uneven representation of the different therapies into account. We do this by grouping the therapies in the test set based on the number of samples they have in the training set and then computing the accuracies of all the groups. The details on both the test used for pairwise method comparisons and the computations of the SE bars are given in Section 2 of the Supplementary Material. The results are depicted in Figure 3. All models, including the derived in the

Table 1. Classification accuracies (ACCs) and AUCs with their corresponding SEs for our therapy similarity model (drugs kernel) and the three reference models (one-for-all, partitioned and transfer) that predict the outcomes of drug combination therapies.

<table>
<thead>
<tr>
<th>Method</th>
<th>Drugs kernel</th>
<th>One-for-all</th>
<th>Partitioned</th>
<th>Transfer</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No prior</td>
<td>With prior</td>
<td>No prior</td>
<td>With prior</td>
</tr>
<tr>
<td>ACC ± SE</td>
<td>0.850 ± 0.010</td>
<td>0.848 ± 0.010</td>
<td>0.850 ± 0.010</td>
<td>0.856 ± 0.010</td>
</tr>
<tr>
<td>AUC ± SE</td>
<td>0.703 ± 0.022</td>
<td>0.695 ± 0.023</td>
<td>0.700 ± 0.023</td>
<td>0.703 ± 0.022</td>
</tr>
</tbody>
</table>

![Sample counts of therapies in training data](image)
improvement of the accuracy ($p$-value $= 0.006$). However, including this prior knowledge makes the results worse for the therapies with 14–40 training samples. It also does not improve the accuracy results for the therapy similarity or the one-for-all models. The reason for this may be that with respect to accuracy the samples from the similar therapies in the clinical data probably carry at least as much relevant information as the prior itself. It is encouraging to see that the added phenotypic information does not deteriorate the similarity models, either.

Section 3 of the Supplementary Material depicts and discusses the accuracy results of several different groupings of the group of test therapies with few training samples. We give this additional detail as this is the group of therapies that is most in the focus of our investigation. The results in the Supplementary Material confirm the advantage of our therapy similarity model regarding the accuracy performance for the therapies with very few training samples.

Inspecting the overall AUC performance in Table 1 we can observe that all models except for the transfer model and the partitioned models have comparable performance. The reason for the poor performance of the partitioned models is that they very often assign probabilities of 1 or 0 for therapies with very few training samples because they will be very often either all successful or all failing. That is why we do not look at the AUC performance of the partitioned models into more detail.

We take the uneven therapy representation into account by splitting the data into two groups: one with 0–20 training samples and another with more than 20 samples. The AUC results for the different methods are shown in Table 2. In this case our therapy similarity model with phenotypic prior knowledge significantly improves the AUC results compared with those of the transfer model ($p$-value $= 0.002$) for the therapies with 0–20 available training samples. This group of therapies comprises about 25% of the test data. Integrating the prediction of the phenotypic model as additional input feature in the one-for-all model does not boost its AUC performance for the therapies with fewer training samples. Our therapy similarity model that incorporates the model parameters of the phenotypic model via a Gaussian prior outperforms the one-for-all model with prior knowledge for the therapies with 0–20 available training samples ($p$-value $= 0.04$). This demonstrates the ability of our approach to better integrate the additional information provided with the phenotypic model. The differences between the AUCs of the one-for-all model (with and without prior) and the therapy similarity model (with and without prior) for the therapies with >20 available training samples were not significant (all $p$-values $> 0.149$). We compute the significance of the difference of the AUCs and its SE as described in DeLong et al. (1988).

To summarize, with respect to measured accuracies our approach that trains separate models for each therapy by utilizing the data from similar therapies has its prime advantage for therapies with few (<4) training samples. The transfer model also achieves (slightly less) significant results for this group of therapies. However, it has lower accuracy for the group of therapies with 4–14 available training samples and has a significantly worse AUC performance. Another disadvantage of this method is the compute-intensive calculation of the sample-specific weights: fitting a single multi-class logistic regression model for a large number of classes (in our case several hundreds) and training samples takes several days; in order to update such model with new data one has to fit many multi-class logistic regression models since they also have a tuning parameter.

The phenotypic prior knowledge added to the therapy similarity model significantly improves the AUC performance for therapies with 0–20 available training samples. Here, the added phenotypic information is essential in bringing the performance of the model to a level, which is also achieved for the abundant therapies.

Our method also allows for alternative definitions of therapy similarity. For example, one can derive a similarity measure that includes phenotypic knowledge. Another advantage of our approach is that one can analyze the profile of similar therapies chosen by the model of a given target therapy that harbors relevant information. An interesting example is illustrated in Figure 4. This figure shows a heatmap that depicts the magnitude of similarity of each of six randomly chosen test therapies from the group of therapies with no available training samples with all therapies from the training set with similarity values greater than 0.5 according to the drugs kernel. In this way we can easily see how much each of the drug combinations contributed to predicting the outcome for the test treatments with no training samples available. As an example, let us consider the model for the combination therapy ZDV 3TC ABC TDF RTV ATV. From the heatmap, we can easily see that the model assigns the highest weights to the examples from the therapies: ZDV 3TC TDF RTV LPV, 3TC ABC TDF RTV ATV, ZDV 3TC ABC TDF SQV RTV ATV and ZDV 3TC ABC RTV ATV.

Furthermore, we can assess how different mutations in the viral genome contribute to predicting the outcome of a given target therapy. Since we have a separate model for the target therapy, we can simply do this by quantifying the importance of the model features. One way to do this is to calculate $z$-scores for each of the model coefficients, which corresponds to a test of the null hypothesis that the coefficient of interest is zero, while all the others are not. The coefficients with the highest $z$-scores are the most significant ones. The table of the $z$-scores for the coefficients of the model for the combination therapy ZDV 3TC ABC TDF RTV ATV are given in Section 6 of the Supplementary Material. According to them, for this therapy the three most important positions in the protease sequence are 54, 90 and 10; and in the reverse transcriptase sequence the most relevant positions are 215, 210 and 41.

### Table 2. AUCs pertaining to the therapy similarity models (drugs kernel) with their corresponding SEs for two groups of test therapies: with 0–20 and >20 available training samples

<table>
<thead>
<tr>
<th>Method</th>
<th>Drugs kernel</th>
<th>One-for-all</th>
<th>Transfer</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No prior</td>
<td>With prior</td>
<td>No prior</td>
</tr>
<tr>
<td>0–20 (SE)</td>
<td>0.659 (0.041)</td>
<td>0.690 (0.059)</td>
<td>0.641 (0.041)</td>
</tr>
<tr>
<td>&gt;20 (SE)</td>
<td>0.694 (0.028)</td>
<td>0.681 (0.028)</td>
<td>0.697 (0.029)</td>
</tr>
</tbody>
</table>
Therapy similarity model

Fig. 4. Heatmap of the similarity profile of six test therapies with no training samples available. The profile considers only the training therapies with similarity value >0.5. The test therapies are depicted on the horizontal axis and the training therapies are depicted on the vertical axis. The similarity values are derived according to the drugs kernel.

4 CONCLUSIONS

This article presents an approach that tackles the problem of predicting virological response to combination therapies by learning a separate logistic regression model for each different combination therapy. Each model is fitted by using not only the data from the target therapy but also the information from therapies similar to it. For this purpose, we introduce and evaluate two different measures of pairwise therapy similarity which are used as weights in the logistic regression models. The model is also able to incorporate phenotypic knowledge on the therapy outcomes through a Gaussian prior. With such an approach we balance the uneven therapy representation in the datasets and produce higher quality models for the therapies with very few training samples. Our model is not only advantageous for therapies with few training samples, but also for all other therapies. Having a separate model for each therapy increases the interpretability of the fitted models in that users have access to the argumentative basis of the prediction. On the one hand, the scores of the mutations contributing to therapy effectiveness, which result from the linear predictions are derived in a therapy-specific manner and can, therefore, be considered more informative than for a general model. On the other hand, the therapy similarity kernel affords information on which similar therapies were most informative for the prediction. It has to be stressed that interpretability of the prediction is a prime requirement for use of a prediction method in a medical setting. Finally, the use of an efficient optimization method that takes advantage of the sparseness of our input data ensures very fast model fitting and model selection, although we train a separate model for each combination therapy.

In terms of accuracy, our therapy similarity model performs significantly better (at the 1% level) than training separate models for each therapy by using solely its samples. Furthermore, the therapy similarity model significantly outperforms (at the 4% level for the drugs kernel and the 8% level for the groups additivity kernel), the one-for-all scenario for the group of therapies with few (fewer than four) training samples. Although this group comprises only about 8% of the test data, it contains around 40% of the different drug combinations in the test set. For therapies with a sizeable number of samples (above four) both the similarity and the one-for-all models have comparable performance. Our model achieves similar accuracy and significantly better AUC performance than the transfer model, which uses a compute-intensive distribution matching approach to quantify the therapy similarities. This demonstrates the quality of our therapy similarity measures.

The phenotypic prior knowledge included via a Gaussian prior does not improve the accuracies of the similarity models, but it significantly improves (at the 4% level) the AUC of the test therapies that have 0–20 available training samples. This group comprises about 25% of the test data and contains around 77% of the different drug combinations in the test set.

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