PUMP: An Underspecification Analysis Tool

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Keywords: Underspecification, Deep Learning, Neural Network, Breast Cancer, Subtype Classification.

Abstract: In fields such as biomedicine, neural networks may encounter a problem known as underspecification, in which models learn a solution that performs poorly and inconsistently when deployed in more generalized real-world scenarios. A current barrier to studying this problem in biomedical research is a lack of tools engineered to uncover and measure the degree of underspecification. For this reason, we have developed *Predicting Underspecification Monitoring Pipeline* or PUMP. We demonstrate the utility of PUMP in predictive modeling of breast cancer subtypes. In addition to providing methods to measure, monitor, and predict underspecification, we explore methods to minimize the production of underspecified models by incorporating biological insight that aims to rank potential models.

1 INTRODUCTION

Computational power coupled with biomedical insight has resulted in a dynamic and robust new approach to the medical field. Deep learning networks in particular have bolstered various fields, including cancer subtype classification (Cascianelli et al., 2020), drug effects on biological pathways (Gupta et al., 2021), and protein analysis (Shi et al., 2019). Though the implementation of such networks have been successful, they are still liable to an issue known as underspecification, where a trained model fails to maintain expected accuracy on new datasets. This is especially a problem in biomedicine, where datasets frequently have more input features than data samples.

In the context of our work, we developed a tool named PUMP (Predicting Underspecification Monitoring Pipeline), an open-source Python package that aims to measure, monitor, predict, and visualize underspecification. Specifically for the use-case specified in this paper, PUMP will analyze the relationship between breast cancer subtyping and underspecification. To perform this task, we utilize a transcriptomic METABRIC dataset with 19,084 gene expressions and 2,133 patient samples, which is a perfect embodiment of the type of dataset that is prone to underspecification: having far more features than samples.

2 BACKGROUND

Underspecification is well-documented in the machine learning literature. However, the difference between predictors optimized for independent and identically distributed data (iid) and application-specific generalization is neglected (D'Amour et al., 2020). As a result, reducing the number of possible predictors and ensuring that these predictors can generalize due to data-set shifts is critical. Due to the high-stakes predictions involved in biomedical applications, it is important that algorithms and models produce consistent interpretations and behave in the "real world" as they do on test sets during development.

Underspecification is problematic with regard to machine learning models due to the complex nature of identifying when it is occurring. A model can be underspecified, yet still appear to be well-trained, resulting in the inability to transfer its knowledge to differ-

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Tang, J., Kressman, M., Lakshmankumar, H., Aduaka, B., Jakusovszky, A., Anderson, P. and Davidson, J.
PUMP: An Underspecification Analysis Tool.
DOI: 10.5220/0011697600003414
In *Proceedings of the 16th International Joint Conference on Biomedical Engineering Systems and Technologies (BIOSTEC 2023) - Volume 3: BIOINFORMATICS*, pages 101-108
ISBN: 978-989-758-631-6; ISSN: 2184-4305

ent datasets. As such, identifying underspecification early in development can help researchers diagnose issues with their machine learning model and avoid making any false conclusions in a medical setting.

Machine learning classifiers have become increasingly more involved in the medical diagnostic process. However, the issue of underspecification has been an ongoing struggle for bioinformaticians. In 2013, Fakoor et al. wrote about classifiers that could not be applied to new datasets because of performance concerns which limits these tools' utility (Fakoor et al., 2013). Producing inconsistent results from dataset to dataset is not practical for real-world use in settings like hospitals. In this paper, we will give a system overview, offer data analysis and discuss further how we minimize the issue of underspecification using our tool.

In our previous work, in which the three-gene model for breast cancer (Haibe-Kains et al., 2012) was incorporated into our models, we procured results with reduced underspecification (Anderson et al., 2021). The experiments conducted suggest that integrating biological knowledge can result in better specified models. As such, we hope to further reduce underspecification by exploring additional biological insights that can be used to train the models. It quickly became apparent that our ability to do so was being limited by a lack of easy to use tools.

3 SYSTEM OVERVIEW

Since underspecification is not as well-known and well-defined as other common machine learning concepts, especially in biomedicine, our work aims to provide an easy way to analyze datasets for underspecification. To achieve this, we created PUMP (Predicting Underspecification Monitoring Pipeline) which functions as a generalized, reproducible, and user-friendly package for identifying underspecification. The structure of the package can be divided into five sections: data analysis, shifting datasets, evaluating model performances, viewing performance discrepancies, and generalized model selection (as seen in Figure 1). The tool is built iteratively with user interaction in mind, so a user is able to interact with results at each step and edit inputs to meet individual needs.

3.1 Data Analysis

To highlight significant features and significant data clusters, PUMP provides a method *analyze_dataset()* to visualize the data with PCA and clustering (e.g., *k*-means). Because PUMP divides the samples into clusters to focus in on areas most affected by underspecification, having a method to easily get feedback regarding features and potential clusters can lead to more valuable performance analysis later on.

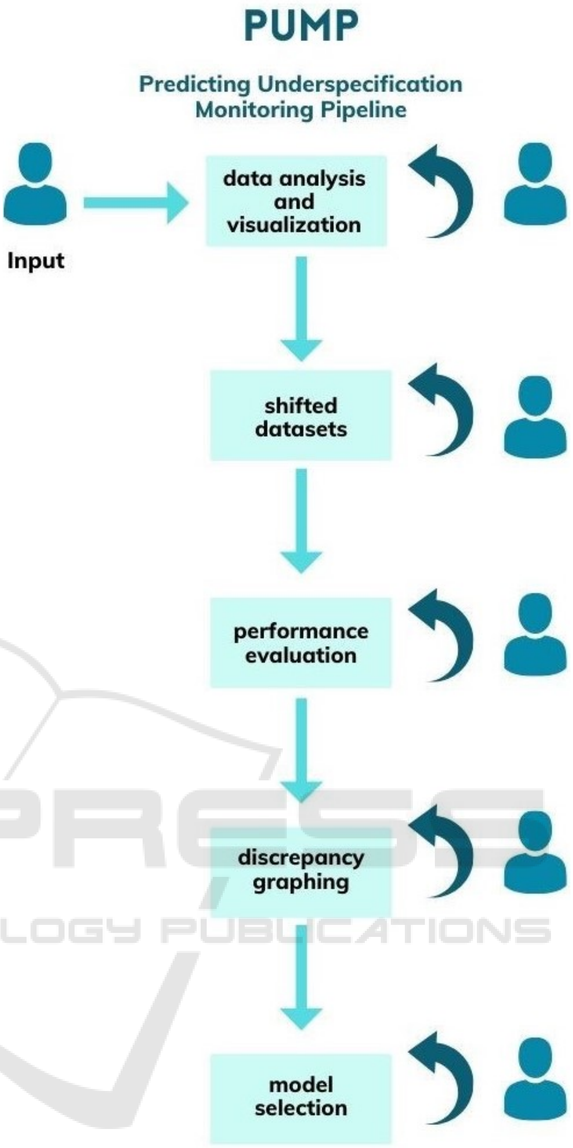


Figure 1: PUMP High-Level Design.

Since this method is meant to be exploratory, the user is allowed to modify number of clusters and perform cluster analysis on a filtered outcome class. After the method's execution, the user can evaluate the data through a PCA variance plot, a PCA scatter plot, a *k*-means inertia plot, a *k*-means cluster histogram, and a color-coded cluster scatter plot. These visuals can be found as PNGs and HTMLs in a user-specified directory.

3.2 Shifted Stress Testing

Similar to the methodology described by (D'Amour et al., 2020), PUMP aims to address underspecification by using shifted datasets as a stress test. To perform this stress test, the original dataset is repeatedly divided into three sets: training, unshifted test, and shifted test.

To perform the described dataset shift based on data clusters, PUMP offers a method *created_clustering_shifted_datasets()* that creates those datasets with clustering as an optional method. Since the current functionality of the data analysis is built on data clustering, clustering is also reflected in the shifted dataset generation (clustering is not the only avenue for creating shifted datasets). Due to the nature of the method, *created_clustering_shifted_datasets()* offers the user a variety of parameters to tune: number of clusters, train-validation-test ratio, outcome class filter, and number of shifted datasets.

In practice, shifted datasets are not known prior to analysis; therefore, when selecting a machine learning model to utilize, the model that is best performing across multiple runs and with multiple seeds is often preferred and selected. The shifted datasets utilized for this analysis were created systematically to aid comparative analysis. This dataset creation system permitted us to rank the models based on the performance of unshifted and the shifted test sets.

Preliminary repetition model performance on unshifted datasets shows many repetition instances performing at an equal level, if not better, than top ranked models. This attests that test-set performance alone is not sufficient to determine the best model if underspecification is suspected. These datasets can be found separated by clusters in a user-specified directory.

3.3 Performance Evaluation

Following the creation of shifted datasets, PUMP allows for performance evaluation on said shifted datasets. The method *evaluate_shifted_sets()* trains three types of models for performance evaluation: Support Vector Machines (SVMs), Random Forest Classifiers, and Neural Networks (standard Multi-Layer Perceptron). Each model is trained on every configuration of the shifted dataset and its F1-score, recall, and precision are noted for each evaluation.

Due to the nature of the models, the Random Forest Classifiers and Neural Networks have a user-defined number of different trials on all of the shifted sets because randomness can be induced and controlled through a random seed. On the other hand, SVMs do not include the functionality nor the need for a random seed, so SVMs only have one trial for the entire shifted set.

Typically, deep learning networks are applied in the biomedical setting, but since they also tend to take the longest to train, training a significantly large of networks through PUMP would be both inefficient and time-consuming. With the addition of SVMs and Random Forests as possible models to train, underspecification can be analyzed in faster models before trying out controlled random seeds on deep learning networks. These results can be found as CSVs in a user-specified directory.

3.4 Discrepancy Graphing

Using the metrics obtained from the model performance evaluation, F1-score results are graphed based on shifted results vs unshifted results with *plot_shifted_results()*. By doing so, underspecification can be identified based on significant performance discrepancies between shifted and unshifted performance results.

Each seed (shifted set) is plotted on the same graph with performances from the same cluster and repetition (model random state). From there, a particular model's performances can be visually evaluated across all shifted datasets, displaying which shifted stress tests may potential induce underspecification. Moreover, in each graph the top *n* models (according to PUMP) are provided such that users can identify particular data and model configurations that are less likely to cause underspecification. These visuals can be found as HTMLs in a user-specified directory.

3.5 Generalized Model Selection

Though the analysis and diagrams thus far help the user in understanding underspecification in their dataset, it would benefit them more to be able to know which data configurations produced the most generalized models. To address this, the method *select_top_models()* allows the user to determine the top *n* models in their data configurations.

$$S_{knowledge} = F_{1,unshifted} - \frac{F_{1,unshifted} + F_{1,shifted}}{2} \quad (1)$$

To select the top *n* models, PUMP calculates model rankings with Equation 1, where model rank is based on the difference between the unshifted F1-score and the average score between shifted and unshifted F1-scores. Finally, PUMP returns the data file information for the top *n* models so the user can find all the desired metadata with the correct keys. These models will be returned directly to the user as a data frame containing necessary data configuration information and scores.

4 SYSTEM APPLICATION

For the findings presented in this paper, our works contain studies on a dataset from METABRIC. This dataset consists of 19,084 gene expression values from a set of 2,133 participants of the METABRIC group. Furthermore, this dataset includes additional clinical data for each patient, which is where patients are given subtype classifications including: basal-like, r-enriched, luminal A, and luminal B, normal, and claudin-low. For a more in-depth understanding of our work, please visit our Github repository at calpoly-bioinf/pump

4.1 Analyzing HER2 Patient Clusters

To begin data analysis on the breast cancer dataset, HER2 positive patients were isolated not only for a better understanding of underspecification, but also the HER2-enriched subtype has the highest level of variance present within this dataset according to (Haibe-Kains et al., 2012). This high level of variance has clinical significance as well, because variance in the HER2/EGFR protein complex and variance in the receptor for these proteins affect the efficacy of drug treatments.

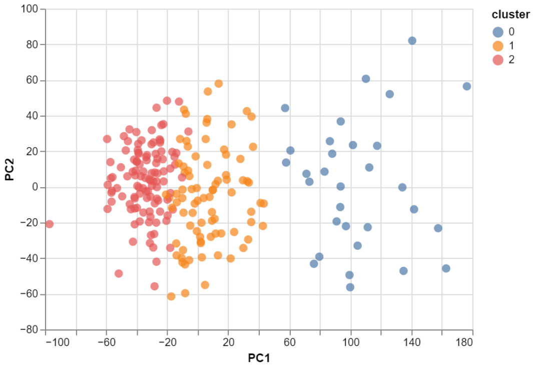


Figure 2: Three Clusters in PC1 vs PC2 Dimensions.

According to the data analysis done by PUMP, seen in Figure 2, having three clusters in the dimensions of PC1 and PC2 separated the data points quite well.

To further support these parameters, the generated *k*-means inertia graph as illustrated in Figure 3 indicate that it is after three clusters that the value of inertia does not have significant change.

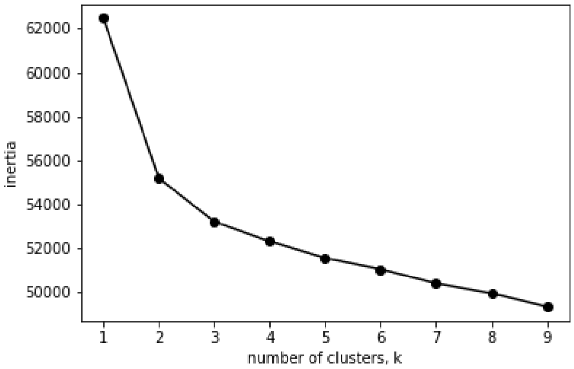


Figure 3: Cluster Inertia Graph.

4.2 Shifting Datasets on HER2

As a result, the aforementioned parameters were specified in the creation of the shifted datasets along with an 80-20 train-test split. Because not all models would face underspecification, the introduction of a degree of randomness was implemented to be able to identify models that were underspecified. 50 variations in seeds (50 shifted datasets) were set for each data set, to be able to compare the performance of each seed to one another. Further randomization of each data set was done by setting five repetitions of model random states from which to sample.

Moreover, due to the clinical significant and high variance of the HER2 subtype class, PUMP was given HER2 as a parameter. By doing so, PUMP would ensure that though random, the shifted datasets would factor in an imbalance with HER2 positive patients.

4.3 Performance Metrics

Firstly, SVMs were run on each of the generated shifted datasets. For these runs, SVMs were given the following parameters: linear kernel, one-vs-one decision function, and 0.001 regularization. As seen in Figure 5, there were interesting differences in results between each clusters. Generally, cluster 0 was able to produce relatively good and consistent SVM models, whereas cluster 2 had a large amount of models have consistently bad performance. However, most interesting is cluster 1, where there is a significantly large amount of models having decent unshifted F1-scores but having poor shifted F1-scores.

To get a better feel for the differences between the random states, Random Forests were run on each of the shifted datasets with random states from 0-5. Additionally, the classifier was given a maximum depth

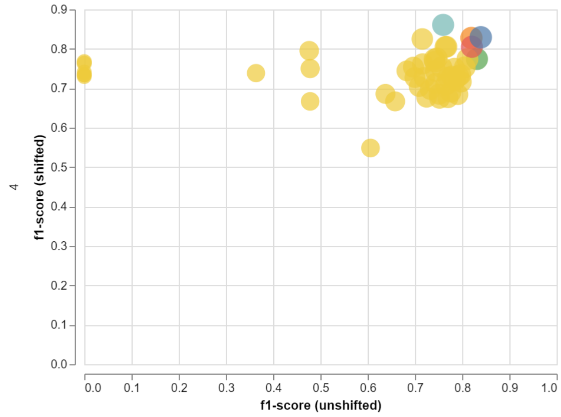


Figure 4: Subtyping Random Forest Performance (Example).

of 3. Surprisingly, results from the Random Forest were not affected much by underspecification; in fact, all performances across different clusters and random states were relatively consistent. An example performance cluster 0 and random state 4 is shown in Figure 4.

Because there were no significant differences between each random state, random state 0 was chosen when evaluating the neural networks. Due to the nature of neural networks being time and resource intensive, the neural networks were given a maximum of 200 iterations to train on the data. Though the neural networks ended up exhibiting the same patterns as the SVMs, the networks also ended up generally having higher F1-scores, as seen in Figure 6.

Performance varied between the shifted and unshifted datasets across three repeated experiments. The discoveries from the three models seem to indicate a couple of ideas.

Firstly, Random Forests generally did not seem affected by underspecification, at least with this dataset. Perhaps the way that the bagging method is designed helps with minimizing underspecification by randomly splitting up the data into small subsets that may have an easier focus on more biologically correct pathways.

Secondly, the performances from SVMs and Neural Networks suggest that models trained on clusters 0 tend to have more consistently good training, while on the other hand, models trained on cluster 2 may have a good chance of producing generally bad models (in terms of classifying HER2). But more importantly, cluster 1 has a large number of models having performance discrepancies between shifted and unshifted datasets, whereas the other two clusters do not. From the performance visualizations, it appears that cluster 1 is most affected by underspecification since a large portion of SVMs and Neural Networks. On the other hand, cluster 2 is slightly affected and cluster 0 is hardly affected.

4.4 Model Selection

Given our understanding of the current state of the performances of models on a variety of shifted data configurations, we can finally fetch the PUMP's top ranked models. Since we were focused on addressing the HER2 subtype, we will take the top 10 trained classifiers in the HER2 category. The top models can be seen in Figure 7.

5 EXTENDED APPLICATION

Though PUMP simply provides visualizations on underspecification and thus does not possess the tools to fix it, we aim to show how discoveries with PUMP can be used to address issues with underspecification. In the case of breast cancer subtyping, we utilize the work a three-gene model (Haibe-Kains et al., 2012) for predicting breast cancer subtypes. Although the three-gene model was developed to classify five breast cancer subtypes, we believe it is still applicable to our slightly extended list of breast cancer subtypes, which has an addition of the claudin-low subtype.

5.1 Biological Knowledge Processing

To incorporate biological knowledge into machine learning systems, we opted to utilize the three-gene model as a sample-sample graph. Our method analyzes the correlation between a sample-sample graph and potential models. PUMP can then rank these models using this correlation with the objective of limiting underspecification through knowledge-driven model selection.

In the scope of the three-gene model, an adjacency matrix was formed using the three specified gene features (ESR1, ERBB2, AURKA) (Haibe-Kains et al., 2012). This was accomplished by scaling the gene expression values with a min-max scaler and using the ball-tree algorithm to generate a k-nearest neighbors matrix, where $k = 10$. To calculate the adjacency matrix, Euclidean distance was utilized to take advantage of the scaled floating point values used to describe gene expressions.

For the purposes of our work, we elected to work with a weighted k-nearest neighbors as opposed to an unweighted binary graph so that we could emphasize the distance between patients. This meant that two patients would share an edge if those two patients were k-nearest neighbors.

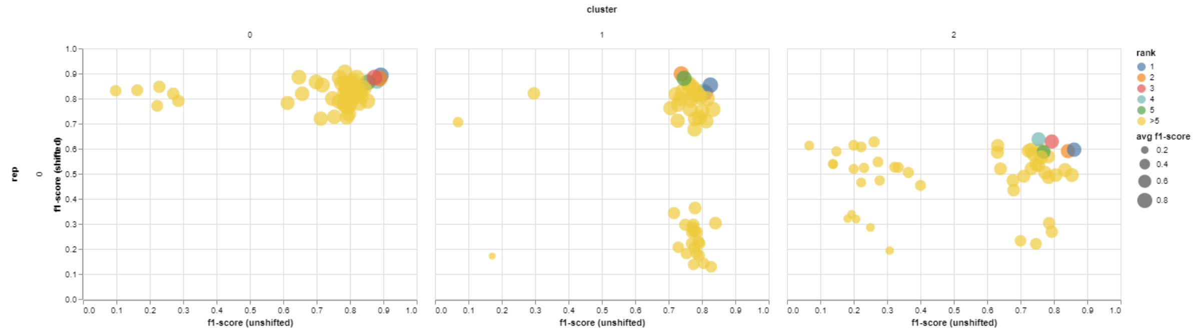


Figure 5: Subtyping SVM Performance.

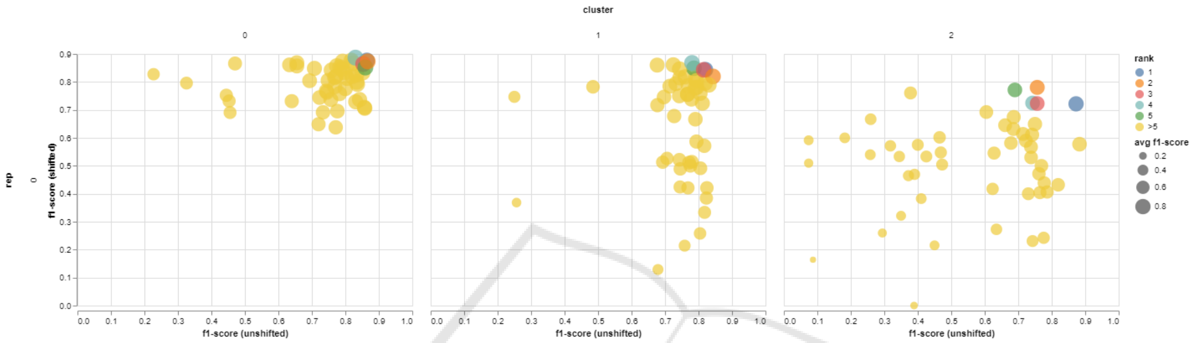
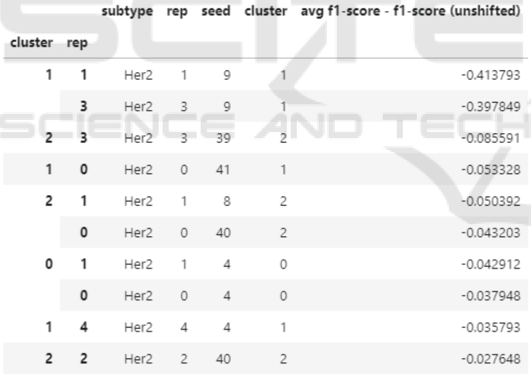


Figure 6: Subtyping Neural Network Performance (Rep 0).



		subtype	rep	seed	cluster	avg f1-score - f1-score (unshifted)
cluster	rep					
1	1	Her2	1	9	1	-0.413793
	3	Her2	3	9	1	-0.397849
2	3	Her2	3	39	2	-0.085591
1	0	Her2	0	41	1	-0.053328
2	1	Her2	1	8	2	-0.050392
	0	Her2	0	40	2	-0.043203
0	1	Her2	1	4	0	-0.042912
	0	Her2	0	4	0	-0.037948
1	4	Her2	4	4	1	-0.035793
2	2	Her2	2	40	2	-0.027648

Figure 7: Top 10 Models on HER2.

5.2 Knowledge Correlation

Following the creation of the weighted k-nearest neighbors sample-sample graph, we wanted to find a way to incorporate that knowledge into a re-ranking of the models from the ranking by PUMP. To gain a broader understanding of the effect of knowledge on the re-ranking of models and also to not waste computation on evaluating all of the models, we selected the top 18 models to study.

We performed a graph-to-graph comparison with the created knowledge graph and a graph derived from the output layer of our trained neural networks. Based on the values found the output layer of the neural networks, the same type of graph (weighted, 10 nearest neighbors) was created between the trained networks. With the two comparable graphs, cosine similarity scoring was applied on both adjacency matrices— this score $S_{knowledge}$ could then be factored into the calculation for ranking models. To calculate the new metric S_C for the re-ranking of models, we used Equation 2, where $\alpha = 0.5$.

$$S_C = \alpha S_{F1} + (1 - \alpha) S_{knowledge} \qquad (2)$$

Next, Pearson correlation r was used to calculate correlation for model ranking and S_C (new metric for ranking), along with model ranking and S_{F1} (PUMP metric for ranking). To understand the change in this sample's ranking correlation, we took the absolute increase in correlation from the old ranking metric to the new ranking metric.

As seen in Figure 8, a majority of models experience an increase in correlation when knowledge is introduced to ranking. Furthermore, the top 3 ranked models experience a significantly large growth in correlation with the new knowledge. Over these 18 samples, there is an average 6.83% increase in Pearson correlation r. This insight suggests that knowledge may be influential in the selection of more generalized models. Moreover, this insight seems to suggest that if knowledge were introduced to the re-training of

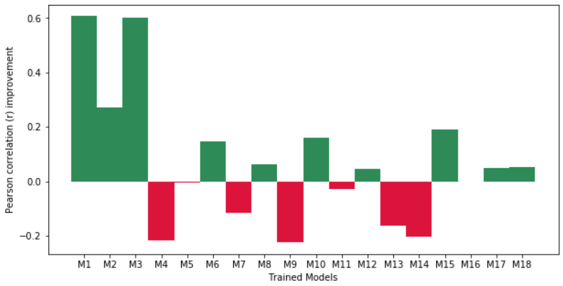


Figure 8: Correlation Improvement.

models on shifted datasets, the quality of the training would be positively affected.

6 FUTURE WORK

Though PUMP provides an easy-access method to analyze underspecification, it currently does not possess all desired functionalities. On top of that, there are many avenues in which attempts can be made to minimize underspecification and better generalize models.

6.1 System Improvements

As currently constructed, PUMP has a heavy focus on clustering algorithms to perform analysis and to generate shifted datasets. While relatively effective, clustering algorithms are not the only way to do either of the aforementioned tasks. In the future, we hope to introduce a greater variety of algorithms to perform these tasks so that underspecification analysis can be more generalized to other datasets.

Aside from an increase in algorithm options, other areas of improvement include an increase in model options. Though SVMs, Random Forests, and Neural Networks (MLP) generally cover many use cases, there exist many more types of prediction modeling. In the future, we hope to include a more extensive list of models to select as options for performance evaluation.

6.2 Minimizing Underspecification

Outside of the scope of PUMP, underspecification still exists and is yet to be addressed. In our extended application of PUMP, we illustrate how particular knowledge can be applied to breast cancer subtyping and how there is a good correlation between that knowledge and more well-specified models.

In the application of sample-sample graphs, biological insight can perhaps be leveraged in machine learning models by incorporating knowledge directly into its training via the loss function. Examples of such models exist, such as neural graph machines (Bui et al., 2017) and graph convolution networks (Kipf and Welling, 2017). Of course, models similar to these have already been used in biomedical applications; however, the introduction of PUMP allows for an simple way to ensure underspecification in a dataset for a particular model is not a prevalent issue.

ACKNOWLEDGEMENTS

This study was made possible thanks to William and Linda Frost Fund and the College of Science and Math at California Polytechnic State University, San Luis Obispo. Additionally, we would like to thank the College of Engineering for their support of this work. We would also like to acknowledge and thank the European Genome-Phenome Archive for access to the METABRIC transcriptomics and metadata dataset as well as the authors of the DeepType study for the initial classifier algorithm. We are grateful to the Cal Poly Bioinformatics Research Group for their assistance in this research project and review of this article.

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