Few-shot learning creates predictive models of drug response that translate from high-throughput screens to individual patients - A Comprehensive Review

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***Abstract*—This paper seeks to be a comprehensive review of the paper published in Nature Cancer: Few-shot learning creates predictive models of drug response that translate from high-throughput screens to individual patients[1]. It was written as a final exercise in the Biostatistics Course of the MVA program taught by Raphaël Porcher.**

Bibliography Note

I decided not to include a separate bibliography for this review as the paper is mostly about explaining the concept in the original paper. For references, please refer to the original paper.

I. Introduction

A. Contextualization

The disparity between the abundance of cell line data and the scarcity of clinical data presents a significant challenge in drug discovery. While thousands of potential treatments are identified, only a fraction make it through the rigorous journey from preclinical studies to a single approved drug. This process is hampered by the "valley of death," a phase characterized by high failure rates due to efficacy, safety, costs, regulatory hurdles, and the extensive time required for development. Two prevailing hypotheses suggest these failures arise either from fundamental differences in biological contexts between model systems and human conditions or from missed opportunities in identifying correct biomarkers and explanations. Such discrepancies highlight the complex transition from cell line and animal models to clinical applications.

This study introduces an innovative approach using few-shot machine learning to bridge this gap. The model, called **Translation of Cellular Response Prediction** (TCRP), leverages cell line data to inform clinical settings, even with limited clinical samples. TCRP facilitates a more fluid transition between preclinical and clinical research phases, enhancing the drug discovery process by identifying key molecular features and critical genes, such as those in the CDK and ATM pathways, vital for cancer treatment. Moreover, the model's design prioritizes explainability to meet regulatory standards and pave the way for personalized medicine. By enabling models trained on abundant cell line data to adapt to new, less-documented contexts, TCRP represents a promising step forward in making the most of existing data for drug discovery, emphasizing the importance of both predictive accuracy and regulatory compliance.

[1]Ma, J., Fong, S.H., Luo, Y. et al. Few-shot learning creates predictive models of drug response that translate from high-throughput screens to individual patients. Nat Cancer 2, 233–244 (2021). https://doi.org/10.1038/s43018-020-00169-2

B. Few-shot Learning versus Transfer Learning

Transfer Learning consists in reusing a model for a task as the starting point for a model on a similar task. First successful applications were in image recognition. In this project, we are dealing with few-shots learning that implies to adapt using a minimal amount of data. The model uses a meta-learning approach that seeks to learn widely applicable input features by optimizing their transferability rather than their overall prediction accuracy. Transfer learning needs a huge amount of data for the pre-training phase. Its objective is to apply what has been learned on one task to another while meta learning's objective is to learn the process of learning itself.

A 2-phases approach is applied on 3 context-transfer challenges: from one tissue to another, from tumor cell lines to patient-derived tumor cells (PDTC, in vitro) and from tumor cell lines to patient-derived tumor xenografts (PDX, in vivo). Features include gene expression and somatic mutation.

Figure 1 summarizes the study design followed in this paper. Phase I consists in trying to predict cellular response due to gene deletion (CRISPR) or drug response. Then, Phase II, using the same type of features, fine-tunes the model and see how it is able to predict response in new tissue, PDTC or PDX.

II. Results

The authors apply the few-shot learning paradigm to 3 context-transfer challenges in predictive medicine.

A. Transferring a predictive model learned in one tissue type to other tissue contexts.

The first challenge (1a) assessed the TCRP model's ability to predict tumor cell lines growth rates with limited data. Data from 335 human cell lines across 19 tissues, obtained via CRISPR (clustered, regularly interspaced, short palindromic repeats) of a genome-wide panel of gene disruptions, was used. For each cell line, the survey summarized the binary genotype status of genes (0 = unmutated or synonymous

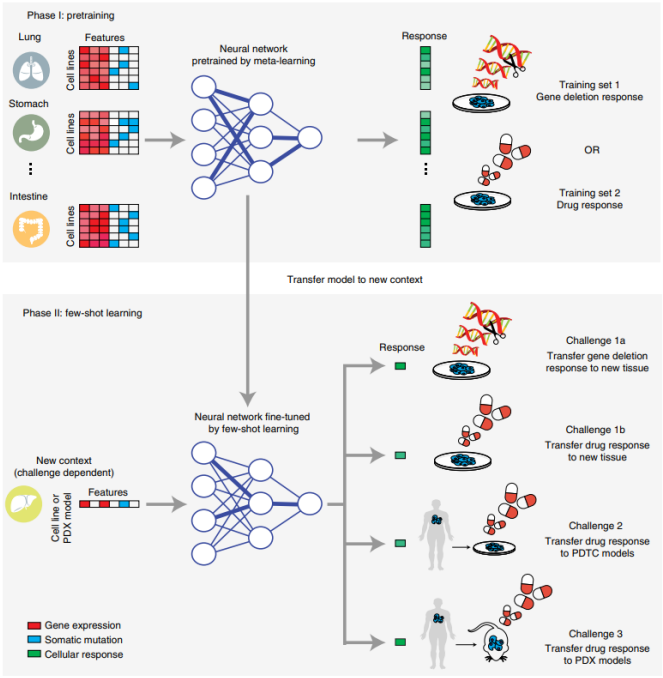

Fig. 1. Study design. Three distinct translation challenges are considered. Each challenge involves a pretraining phase (top) based on cell-line response data across tissues, followed by a few-shot learning phase (bottom) in which data in the new context are presented for additional learning, one sample at a time.

mutation; 1 = nonsynonymous mutation) and their mRNA levels during nominal growth. The authors focused on 469 genes with demonstrated tumor growth dependencies from the literature. The TCRP model, along with conventional learning models, was trained to predict growth responses of all cell lines for each CRISPR gene disruption. One of the 19 tissues was chosen as the target tissue, and the training set was built based on cell lines from the other 18 tissues (use for pretraining) and only a few from the target tissue (use for the few-shot phase) while the remaining target tissue formed the test set. Conventional models were trained using a standard one-phase training procedure.

In a related challenge (challenge 1b), cell growth response data were drawn from a high-throughput pharmacogenomic screen of 255 anti-cancer drugs administered to each of 990 cancer cell lines encompassing 30 tissues. Similar to challenge 1a, TCRP was trained alongside conventional learning models to predict the growth sensitivity of cell lines using their molecular markers.

In both of the experiments, during pre training, models displayed a range of prediction accuracies, with conventional random forests performing best. However, when testing on the target tissue, no model performed better than random, demonstrating the difficulty posed by new contexts. Thanks to the few-shot learning phase, TCRP improved rapidly, and quickly outperformed all conventional models, showing that TCRP learned rapidly when switching context to the target tissue while conventional models improved very slowly. Those results are shown in Figure 2 for both challenges.

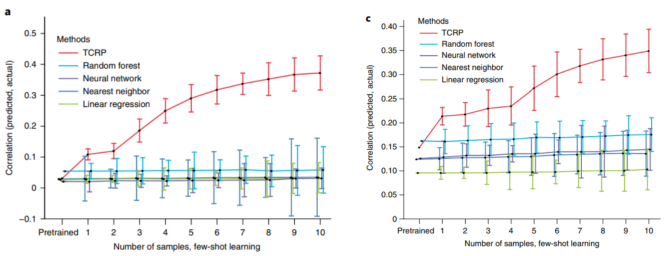

Fig. 2. The plot shows the average model accuracy across CRISPR knockouts for every gene considered and every target tissue. Model accuracy is measured by Pearson's correlation between predicted and actual drug responses. 95th percentile is shown with the vertical bars. a = challenge 1a; c = challenge 1b

B. Transferring a predictive model learned in tumor cell lines to patient-derived tumor cell (PDTC) cultures in vitro.

The second challenge investigated whether models of drug response trained on cell lines could be transferred to preclinical contexts, specifically to PDTCs. For this challenge, data on breast cancer PDTCs were obtained from Project Biobank. In this previous study, 83 tumors were biopsied, subjected to whole-exome and mRNA sequencing to generate molecular profiles, and implanted in immunodeficient mice. PDTCs were then isolated from the host mice and tested for drug responses in vitro. The authors selected 50 drugs with well-characterized protein targets, administered to 15-19 PDTCs each. For each drug, the TCRP model was pre trained using the cell-line drug-response data from challenge 1b before switching context to PDTCs.

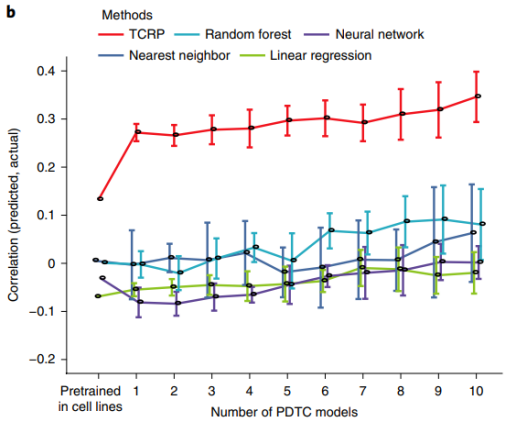

Fig. 3. The plot shows the average model accuracy responses of breast cancer cell lines to targeted perturbations with a particular drug. Model accuracy is measured by Pearson's correlation between predicted and actual drug responses. 95th percentile is shown with the vertical bars. Results averaged across 48 drugs on n=83 PDTC models

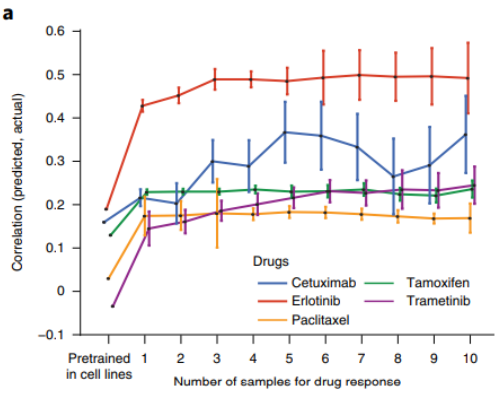

Fig. 4. The plot shows the average model accuracy responses of breast cancer cell lines to targeted perturbations with a particular drug. Model accuracy is measured by Pearson's correlation between predicted and actual drug responses. 95th percentile is shown with the vertical bars. Results averaged across 48 drugs on n=83 PDTC models

As observed in earlier challenges, all models performed poorly when switching contexts, achieving accuracies near or below zero. However, TCRP improved substantially (Figure 3) after exposure to each new patient sample, with an average performance of r=0.30 at 5 samples and r=0.35 at 10 samples, compared to r¡0.10 for the runner-up. Nearly all drug predictions were improved by the few-shot learning paradigm.

C. Transferring a predictive model learned in tumor cell lines to patient-derived tumor xenografts (PDXs) in mice in vivo.

The final challenge evaluated the transfer of drug response models from PDTCs tested against drugs in vitro to PDXs tested against drugs in live mice. For this purpose, data for 228 PDX mouse models were obtained from the PDX Encyclopedia, where each model was exposed to one of the 5 drugs on which TCRP had been trained in cell lines (cetuximab, erlotinib, paclitaxel, tamoxifen, and trametinib). Genotype and mRNA transcriptomes of each PDX were also provided to obtain the molecular features used by TCRP to make drug-response predictions.

As seen in the previous experiments, the TCRP models pretrained on cell-line data initially performed poorly in predicting PDX responses, but significant improvements (Figure 4) were observed during training on the first few PDX samples. Such improvements were seen for all five drugs and led to a range of final prediction accuracies from r=0.50 for erlotinib to r=0.18 for paclitaxel.

III. Model

The model used in this project is a shallow neural network using 1 or 2 layers and maximum 20 neurons, taking for each case the best combination. The loss function is the mean square error. They use a model agnostic meta-learning algorithm (MAML) for the learning procedure.

A. Model Agnostic Meta-Learning Algorithm

This algorithm seeks to identify universal knowledge across multiple conditions and then transfer this knowledge to make robust predictions in new conditions. It is a flexible approach as it can be applied to any gradient-based learning algorithm.

Here is the general objective for learning:

$$E_{s,e\sim E_s}\left[E_{\langle T,V\rangle\sim e_s}\left[L\left(V,\theta-\alpha\frac{\partial L(T,\theta)}{\partial\theta}\right)\right]\right]$$

For each training iteration, they first sample a subset S_i of 12 tissue types from the pool S of all types available. S_i is then randomly partitioned into two non overlapping sets of six cell lines T (target) and six cell lines V (validation). L is a mean square error function with respect to V. It represents the expectation of the gradient of the loss (mean-square error) with respect to the parameters averaged over all tasks sampled. It shows the 2 level optimization in MAML. The inner loop updates the parameters for each specific task and the outer loop updates the initial parameters to improve the performance across all tasks. To put it differently, during pre-training, the starting point is not too specific but good enough for all tasks. Then with new data, you make small adjustments to have tuned parameters for your task.

Classical approach focuses on finding the best parameters for a single task whereas MAML focuses on finding the best starting parameters to adapt quickly (not the end point, the starting point).

B. Few-shots learning phase

The authors use only one iteration of gradient descent to achieve new values of parameters. They observe a task Q with only a few training samples.

$$\theta_{\text{few-shot}}=\theta_{\text{pretraining}}-\alpha\left.\frac{\partial L(Q,\theta)}{\partial\theta}\right|_{\theta=\theta_{\text{pretraining}}}$$

We could perform multiple iterations until convergence but one of the main problems (yet unsolved) of meta learning is that it can easily overfit on a new task. With very few examples, each data point can have a large influence on the direction of the gradient. Multiple steps could lead the model to fit noise in the data rather than the underlying pattern. Incorporating a regularization method during the few-shot learning process could enhance the update's effectiveness. This might include meta-regularization that functions at the meta-level. Additionally, increasing task diversity could also contribute to improvements.

IV. Model Explainability

A frequent criticism of neural network systems is their opacity, often likened to "black boxes" due to the challenge in understanding how decisions are made. However, the Local Interpretable Model-Agnostic Explanations (LIME) technique offers a breakthrough by enabling us to identify which features influence the decision-making process for each individual sample.

A. LIME : Local Interpretable Model-Agnostic Explanations

LIME operates by randomly altering the values of a sample's feature vector, generating numerous similar, yet slightly varied, samples around the original. Within this "perturbed" vicinity, a straightforward and interpretable model, such as linear regression, is trained to pinpoint the features critical to the decision outcome for the sample in question. Unlike traditional feature selection methods that apply broadly across all samples, LIME's approach is localized, focusing on individual samples. In a more detailed process, for each molecular feature vector F, LIME generates 10,000 perturbed samples by incorporating Gaussian noise into the original features. Predictions for each of these samples are then made using linear regression, Elastic Net, and Lasso regression, each with varying hyperparameters. The proximity of each new sample to the original dictates its assigned weight; the closer a sample, the greater its weight. The ultimate feature ranking is derived by averaging the rankings from all tested models. Figure 5 illustrates this approach.

LIME was selected over alternative methods, such as SHAP or Layerwise Relevance Propagation, due to its unique ability to provide explanations that are specific to individual samples, offering a more nuanced understanding of model decision-making.

B. A biological example of the LIME explainability power

In the context of PDTC response to Palbociclib drug, two important features arise when investigating using the LIME method. These 2 features : gene encoding RB-like factor and somatic mutation of SMAD4 are very accurate from a biological perspective.

CDK proteins, when paired with Cyclin D, form essential complexes that are instrumental in advancing a cell from the G1 phase to the S phase—the G1 phase being a period of cell growth prior to DNA replication, and the S phase being the

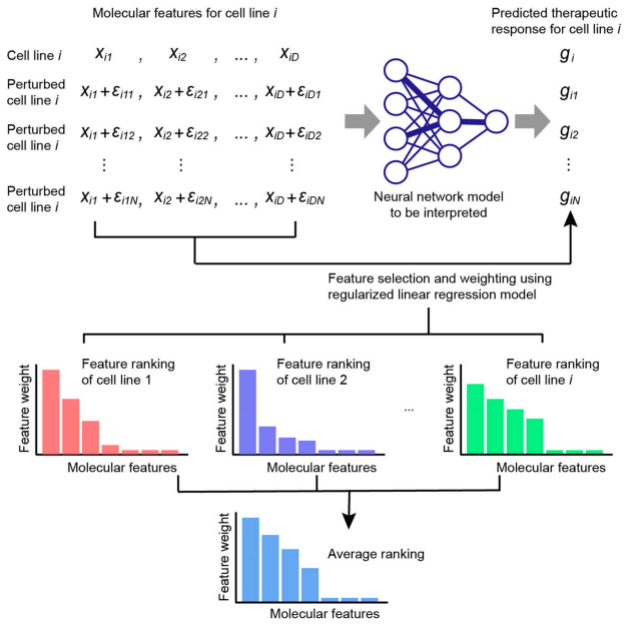

Fig. 5. Interpreting the TCRP model with the framework of LIME.

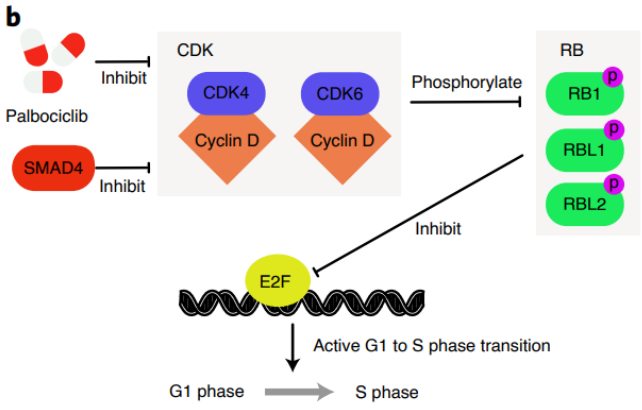

Fig. 6. Interpreting the TCRP model with the framework of LIME.

stage at which DNA replication occurs. These complexes have the capability to phosphorylate RB proteins, thereby rendering them inactive. Palbociclib, a drug explored in the second task of the paper, can inhibit CDK proteins, preventing them from phosphorylating RB proteins. Consequently, E2F remains bound and inactive, preventing the cell from progressing to the S phase. This mechanism underpins Palbociclib's potential to impede the growth of cancer cells. SMAD4 is another protein that can suppress the transcription of CDK4, helping to regulate CDK4 levels when active. However, if SMAD4 is deactivated due to a somatic mutation, it loses the ability to control CDK4, potentially leading to an increase in CDK4 levels. This increase can counteract Palbociclib's effects, enabling the cell cycle to advance despite the presence of the drug, thereby contributing to drug resistance. In this scenario, despite Palbociclib's efforts to inhibit CDK4, its action appears inefficient. If RB is present at high levels, it can inhibit E2F,

initiating the cell cycle. Figure 6 is an illustration of the described pathway.

Both genes responsible for RB proteins and SMAD4 are among the top 5 features identified using the LIME methodology, highlighting their significance in this context.

V. Discussion

The two-phase procedure enhances the traditional process of converting observations from in vitro studies to predictive markers in tumors. This approach demonstrates promising results across multiple datasets and translation scenarios where standard learning methods fall short. In three distinct challenges, this transfer task has led to performance improvements. TCRP could play a vital role in advancing precision medicine, where the goal is to align a patient's unique molecular profile with the most effective therapy. Molecular tumor boards have emerged, where clinical experts often need to make treatment decisions based on a limited number of cases that share histopathology and molecular profiles.

Another application could prove valuable in the pharmaceutical industry, particularly in identifying patients most likely to benefit from targeted therapies. Traditional predictive models have faced obstacles due to the scarcity of clinical samples that are both well-characterized and linked to detailed treatment outcome data.

A. To what extent the model TCRP is ready?

Regarding the readiness of an approach like TCRP, its predictive accuracy has shown variability, with notable successes such as in the PDX analysis of Paclitaxel. This analysis accurately predicted drug nonresponse in 23 tumors, with an 87% agreement with actual tumor growth observations in mice. Similarly, tamoxifen nonresponse in PDX tumors was accurately predicted in 96% of cases, where nonresponse was defined as a tumor change greater than 30%. With additional data and focused clinical studies, it is possible to further refine these predictions to enhance performance. Raising the decision threshold to over 60% yielded 100% accuracy. Future research with larger groups will provide deeper insights into the optimal clinical applications of few-shot learning.

In both PDTC and PDX models, the efficacy of few-shot learning improves rapidly before reaching a plateau, which is linked to the balance of training versus test samples. As the training phase expands, the number of samples available for testing diminishes, thus reducing the statistical power and increasing the variance in prediction performance evaluation.

The predictability of drug responses also varied across different tissues, potentially due to molecular diversity within certain cancers. For instance, lung tumor cell lines have been categorized into nine subtypes based on transcriptomic profiles, while pancreatic tumor cell lines show more homogeneity. These findings are consistent with our observations, where lung cancer predictions were less accurate than those for pancreatic cancer.

B. Limitations and possible Extensions

In the discussion of our model, we highlighted overfitting as a significant challenge for these methods. To mitigate this, introducing regularization or meta-regularization strategies could be beneficial.

The presented results were achieved using gene mutation and mRNA expression data. However, the TCRP framework is versatile enough to incorporate additional features, such as copy-number variants, histopathological image attributes, or data from disease models in other species.

Moreover, each CRISPR or drug perturbation was treated as an independent machine learning task. A promising avenue for future research is to investigate how information can be shared across perturbations. This approach could pave the way for a unified model capable of making predictions across a broad range of drugs.

Another future research direction involves examining the correlation between a drug's predictability and its pharmacological characteristics. The current challenge with TCRP is its preference for incorporating more features from drugs with numerous known targets, influenced by the selection of features based on the pathway of each known target. However, our understanding of drug-target interactions and pathways is incomplete, and the protein network used for feature selection is not specific to cancer. Future models that standardize the number of biomarkers across drugs could provide deeper insights into the intricate dynamics between drug response and polypharmacology, including recognized targets and off-target effects.

VI. Conclusion

This study demonstrates the potential of a two-phase few-shot learning approach, named Translation of Cellular Response Prediction (TCRP), to significantly improve the translation of preclinical findings to clinical settings, addressing the critical gap between cell line data and the scarcity of clinical samples in drug discovery. TCRP shows promising results in predicting tumor growth and drug response across different contexts, including tissue types and patient-derived models, with notable improvements over conventional models. This approach not only enhances the precision medicine framework by aligning patients' molecular profiles with effective treatments but also offers a novel strategy for the pharmaceutical industry to identify patients most likely to benefit from targeted therapies. Moreover, the study highlights the importance of continuing to refine predictive models with additional data and clinical studies, suggesting future research directions to further improve the accuracy and applicability of few-shot learning in medicine.