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Comparative Analysis of Drug Synergy Prediction Models

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Abstract

This article comprehensively reviews computational models for predicting drug interactions in cancer therapy, focusing on machine learning and deep learning. Synergism refers to the combination of two drugs having more than equal effects than their individual effects, providing significant benefits such as increased performance, reduced drug resistance, and reduced toxicity. However, traditional clinical trials to discover drug combinations are expensive and time-consuming, requiring computational alternatives. This article compares three modeling tools (DeepSynergy, TranSynergy, and MatchMaker) using different models and prediction targets. While DeepSynergy and TranSynergy predict synergistic scores, TranSynergy outperforms DeepSynergy in accuracy across multiple tissue types, primarily through the synergistic combination of self-monitoring and genes. MatchMaker, which predicts Loewe joint scores, outperformed both models in terms of accuracy, with lower mean square errors and higher Pearson and Spearman correlation values. We also explore tissue-specific performance, particularly issues arising from poor cell lines, and discuss the implications of general modeling—the importance of trialing to accelerate drug combination and inform oncology reality.

Keywords: Drug synergy; DeepSynergy; Transynergy; Matchmaker; Drug Represenation;

1. Introduction

In recent decades, drug synergy has become a major trend in cancer treatment, providing an effective strategy to combat malignant tumors characterized by uncontrolled growth of abnormal cells. Drug synergy refers to the phenomenon in which the combined effect of two drugs is greater than the sum of their individual effects. This approach has shown significant benefits in cancer treatment, including increased efficacy, decreased drug resistance, and decreased drug toxicity. In addition, drug synergy allows for the use of lower doses of each drug, minimizing the

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risk of side effects, a major concern in cancer treatment. This paper aims to provide a comprehensive review of recent developments in computational methods and deep learning approaches for predicting drug synergy, highlighting the progress, challenges, and opportunities in this rapidly evolving field.

However, the traditional clinical trial process to identify drug combinations with synergistic effects is time-consuming and expensive, making it difficult to rapidly develop effective cancer treatments. As the demand for more efficient methods for screening drug combinations increases, computational approaches are gaining attention. Incorporating artificial intelligence[2][3], particularly deep learning algorithms, into the drug discovery process has revolutionized the field, overcoming many of the limitations associated with traditional methods. Technological advances have led to the creation of massive databases containing complex genomic and chemical information, opening up new opportunities to model and predict drug synergy. Through this review, we summarize key advancements in machine learning and deep learning algorithms for drug synergy prediction, offering insights into how these methods have transformed the drug discovery process.

Machine learning models, especially those using high-throughput screening (HTS) data, have proven to be powerful tools for exploring the vast combinatorial space of potential drug synergies. These models can guide researchers in vitro and in vivo to generate accurate predictions[1]. These computational models not only improve our understanding of drug interactions by incorporating genomic information into their predictions, but also bring us closer to realizing precision medicine, where treatments can be tailored to an individual's genetic profile.

Predicting anticancer drug synergy has been accomplished using a variety of computational methods. These range from systems biology approaches and kinetic models to advanced machine learning methods, including Random Forest and Naive Bayes classifiers. However, recent advances in deep learning have significantly improved the predictive power of computational models. With the ability to learn complex patterns from large data sets, deep learning has outperformed traditional machine learning algorithms in a variety of biomedical applications, opening up new opportunities for drug discovery. The combination of computational models and experimental validation holds great promise for accelerating the discovery of effective drug combinations for cancer treatment, highlighting the importance of integrating these advanced technologies into the drug development process.

2. DeepLearning Models for Drug Synergy

In this comparative analysis, we examine the pioneering models—DeepSynergy, TransSynergy, and MatchMaker. Each model's focus and the kind of data it processes are reflected in the notable differences between their designs. This section examines these models' architectures, stressing their salient characteristics, methods of training, and approaches to handling their individual inputs.

2.1. DeepSynergy

The feed-forward neural network (FNN) architecture used by DeepSynergy[6] is tailored for regression issues. The primary objective is to estimate the synergy score of treatment combinations by learning chemical drug descriptors and genomic properties of cancer cell lines. A concatenated vector that combines the genomic characteristics of a cancer cell line with the chemical characteristics of two medications serves as the input for DeepSynergy. In order to investigate the intricate interaction between the drug and the biological effects on the cell line, the model considers a pair of medications as a whole and analyzes it in conjunction with cell line data. To aid in generalization, the model's hidden layer has a conical architecture.

The first hidden layer consists of 8192 neurons that capture complex interactions, while the second hidden layer focuses on improving these learned representations by narrowing the scope to 4096 neurons. This reduction in layer size helps minimize overfitting by allowing the model to prioritize the most important features. The hidden layers use the hyperbolic tangent (tanh) activation function, while the output layer uses a linear activation function that is suitable for the continuous nature of synergy score prediction.

DeepSynergy is trained using stochastic gradient descent with a learning rate of 10^{-5}, and employs dropout regularization to prevent overfitting (0.2 for the input layer and 0.5 for the hidden layers). Early stopping is implemented to halt training when the model's performance on a validation set ceases to improve. To ensure symmetry in drug pairs—where the combination A-B should produce the same result as B-A—DeepSynergy trains on both versions of

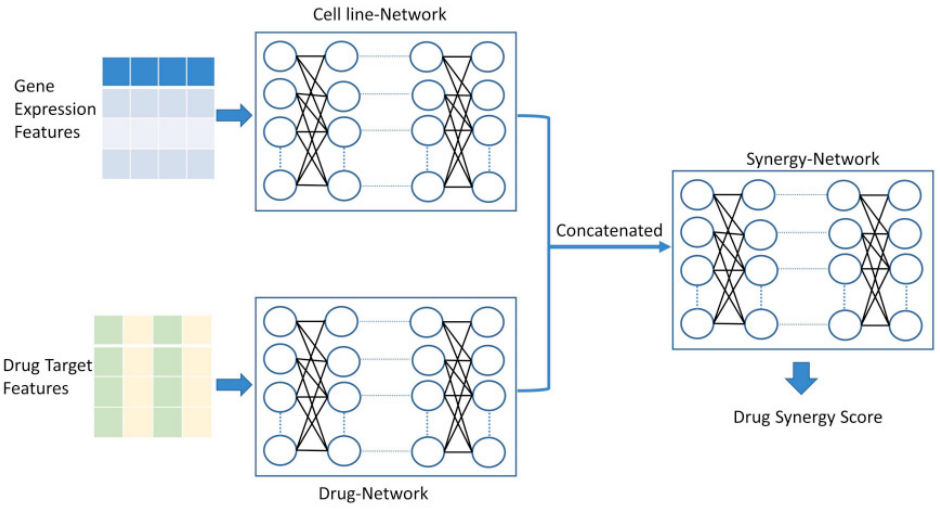

Fig. 1. Architecture of Deepsynergy Model

each pair. During prediction, both orders are processed, and the final prediction is the average, ensuring robustness and symmetry in the model's outputs.

2.2. *MatchMaker*

MatchMaker[8] uses a modular architecture that uses three main subnetworks to predict drug synergy. The design optimizes the model for large-scale synergy prediction, focusing on drug- and cell-line-specific interactions. There are two drug-specific networks (DSNs) to process drugs separately. These DSNs have three fully connected layers with dropout(to avoid overfitting) and ReLU non-linear activation. The final layer of DSN's creates latent drug representations to represent unique cell lines. These representations are used in later stage of the model to capture the impacts of each drug on the cell line. Synergy Prediction Network (SPN) is the third network in the model that combines the

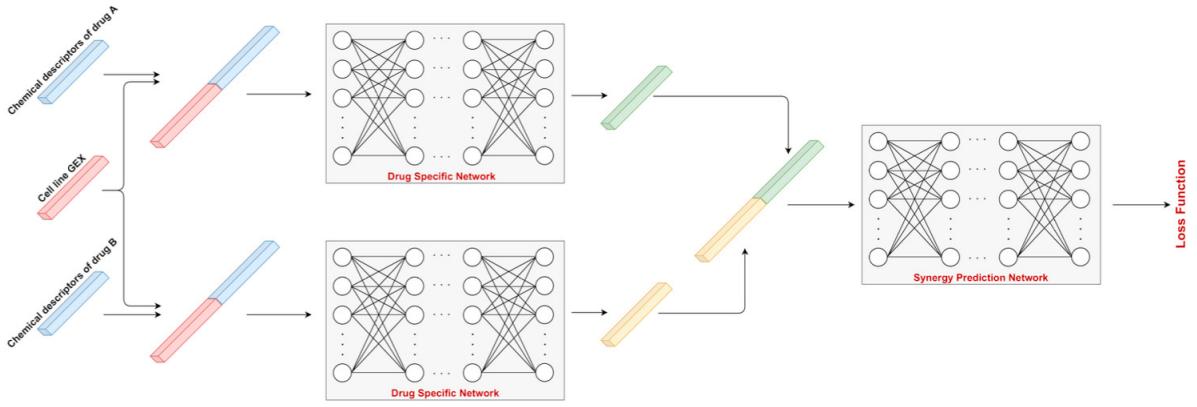

Fig. 2. Architecture of Matchmaker Model

latent representations of the two DSNs to forecast the synergy score. The SPN uses fully connected layer with ReLU

activation, same as DSN. Similar to DeepSynergy, MatchMaker also handles both A-B and B-A pairs and averages the predictions to provide consistency, guaranteeing the symmetry of the drug pair combinations.

MatchMaker's design is suitable for large-scale drug synergy predictions as it is efficient and similar in accuracy to Deepsynergy but process datasets without skipping on specific drug-cell line interactions.

2.3. TranSynergy

TranSynergy[5] is the most different model for comparison as it is a self-attention transformers optimized for capturing intricate relationships between genes and biological pathways. This design allows the model to understand complex interactions of drug combinations on cancer cell lines effectively, focusing on the most relevant gene interactions for accurate drug synergy prediction.[16][17]. TranSynergy[7]can learn gene-gene interactions and predict

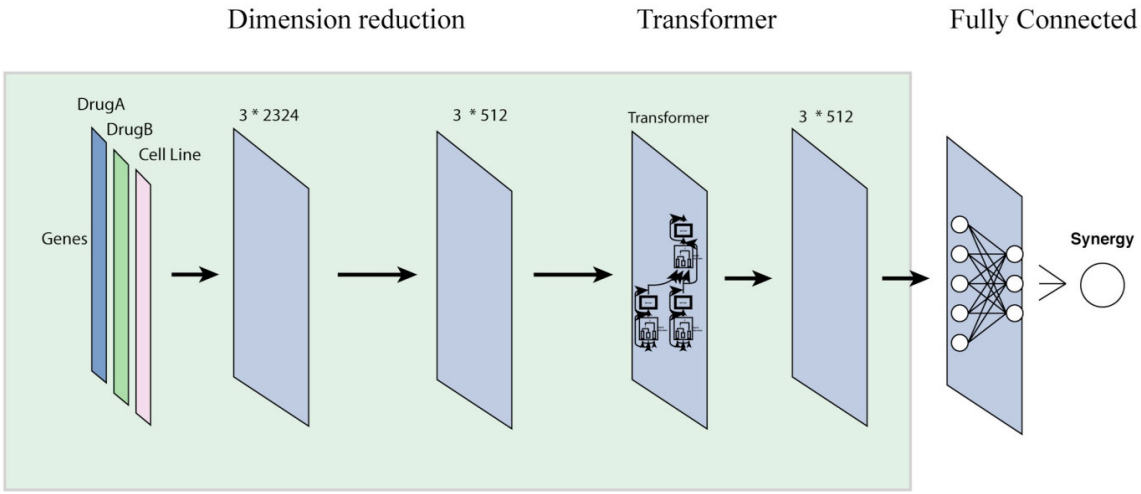

Fig. 3. Architecture of Transynergy Model

pathways that are most likely to contribute to drug synergy by assigning varying degrees of priority to genes. This is important as complex biological interactions result in the combined effect of drugs and the transformer architecture helps model to understand underlying effects.

By leveraging SHAP values, TranSynergy employs the Shapley Additive Gene Set Enrichment Analysis (SA-GSEA) method to determine each gene's contribution to the predicted synergy score. This approach clarifies which genes and pathways play key roles in observed synergy, ensuring the model's predictions are both accurate and biologically meaningful.

SA-GSEA further enhances the interpretability by deconstructing predictions to highlight the most influential genes within relevant pathways. This capability supports the discovery of new therapeutic targets or biomarkers, facilitating more personalized and precise medical treatments.

2.4. Computational Cost and Efficiency

DeepSynergy, with its relatively simpler feed-forward neural network architecture, is computationally efficient and requires lower training time compared to more complex models. However, its efficiency comes at the cost of scalability when handling large datasets. MatchMaker improves scalability by introducing modular subnetworks for drug-specific interactions, making it more efficient for large-scale predictions while maintaining accuracy. This modularity allows the model to process extensive datasets with lower computational overhead compared to TranSynergy. TranSynergy, on the other hand, utilizes a transformer-based architecture with self-attention mechanisms, which significantly increases the computational cost. The complexity arises from modeling intricate gene-gene and pathway interactions, requiring greater GPU resources and training time. Despite the higher cost, TranSynergy's ability to

provide biologically interpretable results through SHAP-based SA-GSEA enhances its value for precision medicine applications.

Key Differences:

- MatchMaker uses a modular design with distinct subnetworks (DSNs) for every medication, whereas DeepSynergy uses feedforward neural networks. As a result, MatchMaker can concentrate on interactions unique to each drug and cell line before merging them.
- TranSynergy is more adapted to capturing biological relevance in medication synergy because it makes use of an advanced self-attention transformer design that can mimic intricate gene-pathway interactions.
- Through SA-GSEA, TranSynergy offers interpretability, revealing which genes and pathways influence medication synergy estimates. TranSynergy becomes more informative for drug development and precision medicine as a result.

3. Model Inputs

The inputs to the models vary significantly in the type and amount of information they use to predict drug synergy. The inputs ranges from the chemical properties of drugs to genomic features of cancer cell lines along with network representations of protein interactions in advanced models. We compare the types of input data used by these three models, highlighting how these variations affect their predictive capabilities.

3.1. DeepSynergy

DeepSynergy[6] has multimodal input data technique that uses genetic characteristics of cancer cell lines with intricate chemical compound descriptors. This method allows the model to have information about biological and molecular data to forecast synergy. In DeepSynergy drugs are represented by three primary categories of their chemical descriptors. Using the ChemoPy software, ECFP_6 (Extended Connectivity Fingerprints) first obtains 1309 characteristics for each drug by capturing chemical substructures based on a radius of 6. These fingerprints helps the model to identify the intricate chemical makeups. Second, physicochemical characteristics such as polarity, solubility, and molecular weight add characteristics to explain the structure of the drug which may influence how it behaves in the biological environment. Lastly, 2,276 toxicant descriptors encode known toxic chemical substructures to address possible negative impacts and safety issues.

DeepSynergy also uses genomic characteristics of cancer cell lines from the ArrayExpress database, 3984 characteristics per cell line that indicate gene expression profiles are obtained by preprocessing these genomic characteristics. Cancer cell line's molecular context can be understood by these profiles, demonstrating how various mutations or levels of gene expression can impact medication combination.

3.2. MatchMaker

MatchMaker[8] combine gene expression profiles and chemical descriptors.The ChemoPy Python package is used to calculate the 541 chemical descriptors that MatchMaker uses for chemical expressions. These descriptors cover essential molecular characteristics including hydrophobicity, molecular weight, and binding. Despite being less extensive than DeepSynergy, these descriptors offer valuable insights into drug chemistry by emphasizing scalability and efficiency. To represent cancer cell lines, MatchMaker uses 972-mer vectors to encode gene expression profiles. These profiles are taken from the dataset of Iorio et al. and reflect the expression levels of key genes known to play an important role in cellular processes. To ensure high data quality, the DrugComb dataset is also used but only drug combinations for which both chemical structures and gene expression data are available, are used. For multiple replicate combinations, conflicting experiments were removed and the synergy scores were averaged to obtain. In this way, they filtered out a dataset of 286,421 drug-cell line combinations.

3.3. TranSynergy

TranSynergy takes a more innovative approach, incorporating drug-target interaction profiles that leverage protein-protein interaction (PPI) networks to ensure biological relevance and interpretability. Unlike previous models that relied more heavily on chemical descriptors, TranSynergy uses a restarted random walk (RWR) algorithm to propagate drug-target interactions across the PPI network. This strategy has a number of benefits. By simulating how medications interact with their target proteins and how these interactions impact other proteins, it first adds biological relevance. The model can capture the indirect effects interactions and mimic a greater variety of biological effects. Second, PPI networks assist researchers by providing interpretability by connecting pharmacological effects to particular proteins and pathways.

TranSynergy provide a more comprehensive understanding of drugs interactions and biological outcomes by capturing how drug effects spread throughout the network. Both gene expression profiles and gene dependency data are included in Transynergy from the standpoint of cell line expression[10]. Gene dependency profiles collected through large-scale RNAi or CRISPR screens provide information about cancer cell lines. With this data, TranSynergy predicts the inhibition of genes which will affect drug synergy. Additionally, gene expression data from CCLE and GDSC provides information about the molecular status of each cancer cell line, allowing the model to adjust predictions based on gene expression levels. By integrating gene expression profiles and gene dependencies, TranSynergy can make context-specific predictions refelcting unique molecular characteristics of each cancer cell line.

3.4. Overall Comparison

Each of these models' strengths is shaped by a variety of inputs. DeepSynergy provides a thorough examination of genomic information and chemical structures, enabling it to forecast outcomes based on toxicity and molecular compatibility. With its simplified inputs, MatchMaker prioritizes scalability, processing massive amounts of data effectively while maintaining uniformity across drug-cell line combinations. With its systems-level methodology, TranSynergy distinguishes itself by using gene dependence information and drug-target interaction networks to produce predictions that are interpretable and biologically significant. As a result, the input design of each model represents its own method of forecasting drug synergy.

Chemical Descriptors:

- DeepSynergy is very good at predicting the molecular characteristics and possible toxicity of pharmaceuticals because it uses a comprehensive set of chemical descriptors, such as ECFP_6 fingerprints, physicochemical qualities, and toxicophore traits.
- With 541 chemical descriptors and a reduced input format, MatchMaker strikes a balance between scalability and efficacy when working with huge datasets.
- TranSynergy employs a mechanism-driven approach with drug-target interaction profiles, capturing how pharmaceuticals alter biological networks, rather than depending just on chemical fingerprints.itemize

Genomic Features:

- Gene expression profiles are used by both DeepSynergy and MatchMaker to represent cancer cell lines; however, DeepSynergy incorporates more features per cell line (3984 vs. 972 in MatchMaster).
- By including gene dependency profiles, TranSynergy goes beyond gene expression data to capture critical genes and how medication combinations take advantage of genetic weaknesses in particular cell lines.

4. Dataset

A critical aspect of evaluating machine learning models for drug combination synergy prediction is analyzing the datasets[19][20] they utilize. Researchers interested in drug synergy should be aware of the relevant datasets, as research in this field is driven by the quality and quantity of available data. Publicly accessible datasets of chemical and genomic information play a vital role in drug development research as shown in Table 1 and Table 2. Historically,

much of drug development has been conducted through clinical experience or chance. However, in recent years, high-quality experimental drug combination datasets have become essential for the success of deep learning models.

4.1. Merck & Co.

A large cancer screening dataset from Merck & Co., which contains 23,062 individual samples. Each sample records the interaction between two drug combinations and a specific cancer cell line, and the dataset contains 583 unique drug pair combinations tested on 39 human cancer cell lines derived from seven tissue types. The pharmaceutical compounds included 14 investigational drugs and 24 approved drugs, providing a comprehensive spectrum for synergy analysis. The experimental protocol systematically studied various dose interactions using a 4x4 concentration matrix. After a 48-hour drug exposure period, the researchers quantified the synergy using the Loewe additivity model, a widely used framework to classify drug interactions as synergistic, additive, or antagonistic. The underlying principle of this model is that compounds that share similar mechanisms of action will exhibit synergistic effects when combined. The dataset is further enriched with additional information, including chemical properties of the compounds, genomic profiles of cancer cell lines, and baseline cell growth measurements. However, a notable limitation of the DeepSynergy dataset is the lack of experimental replication for individual drug combinations, which limits the assessment of inter-assay variability in synergy measurements. Additionally, the dataset's focus on specific cancer cell lines and a limited number of drug combinations may introduce a selection bias, potentially restricting the model's applicability to other cancer types or underrepresented tissues.

4.2. DrugComb

The DrugComb[9] database, a curated repository of high-throughput combinatorial drug screening data. This dataset aggregates synergy scores from several notable sources, such as the O'Neil dataset, the Forcina dataset, the NCI Almanac, and the Cloud dataset, ensuring a diverse collection of drug combination experiments across various cell lines. After extensive filtering, the MatchMaker dataset encompasses 335,692 drug pair-cell line combinations, involving 3,040 drugs and 81 cell lines. It incorporates gene expression profiles and drug structure information to predict synergy, with a particular emphasis on the Loewe synergy score. A significant strength of the MatchMaker dataset is its attention to experimental variability; it excludes inconsistent replicates where one experiment shows synergy and another indicates antagonism, thereby enhancing the consistency and reliability of predictions, especially in large-scale combinatorial data. However, despite the dataset's strengths, its reliance on curated and filtered data may introduce biases by excluding inconsistent replicates, which could affect the model's ability to handle real-world variability.

4.3. DrugBank

This dataset is built from publicly available resources such as DrugBank[11] and ChEMBL[12], focusing on 36 drugs selected for their known protein targets. The dataset is structured as a binary matrix that links each drug to its target proteins. Gene expression profiles of cancer cell lines were sourced from the CCLE and GDSC databases, and gene dependency profiles were drawn from Project Achilles and Sanger CRISPR screens. To fill in the missing values, multivariate imputation is used resulting in a robust representation of cell line characteristics. Synergy scores are determined by Loewe Additivity, Bliss Independence, and Highest Single Agent (HSA). These attributes help the model to capture a variety of pharmacological interactions and their effects on cancer cells.

While these datasets have greatly contributed to drug synergy prediction, it is important to acknowledge potential biases. Many datasets, such as Merck Co. and DrugComb, focus on specific cancer cell lines, tissues, or drug combinations, which may limit the generalizability of the models. Furthermore, biases can arise from experimental variability, as seen in the lack of replicates in some datasets (e.g., DeepSynergy), or from the exclusion of inconsistent results, as in DrugComb. These factors may influence model performance when applied to broader or underrepresented datasets. Addressing these biases through diverse data collection and careful model evaluation is critical to improving robustness and generalization.

5. Results and Discussion

5.1. Dataset Comparison

Table 1. Comparison of Datasets information type

Model	Data Source	Sample Size	Information Type
Deepsynergy	Merck & Co. oncology screening	23,062 samples (583 combinations)	Chemical descriptors, genomic features, cell growth rates
Matchmaker	DrugComb (O'Neil, Forcina, NCI Almanac)	335,692 drug-cell line combinations	Gene expression, chemical structures
Transynergy	DrugBank, ChEMBL, CCLE, GDSC, Achilles, Sanger CRISPR	18,553 samples (523 combinations)	Gene expression, gene dependencies, drug-target profiles

Table 2. Comparison of Synergy Datasets

Model	Synergy Measurement	Replicates	Strength
Deepsynergy	Loewe Additivity (48 hours)	No	Multimodal data, comprehensive features
Matchmaker	Loewe	Yes	Large-scale, conflict-resolved replicates
Transynergy	Loewe, Bliss, HSA	Yes	Network-based drug-target data, replicates for robust predictions

5.2. General Comparison

DeepSynergy, MatchMaker, and TranSynergy are compared using a variety of accuracy metrics, including regression and classification metrics, and each model outperforms the others in a variety of aspects. In this section, we review the accuracy metrics used in these models, highlight their strengths and weaknesses, and analyze their performance on a variety of datasets.

Both DeepSynergy and TranSynergy predict an overall synergy score that reflects the overall effect of a drug combination that produces synergy in cancer cell lines. The formulation of the synergy score may differ slightly between the two models, but they are designed to predict drug synergy in a variety of settings and contexts, regardless of the specific synergy calculation model (e.g., Loewe, Bliss, or ZIP). DeepSynergy predicts an overall synergy score using a combination of chemical descriptors and genomic features. Building on this approach, TranSynergy uses an internal attention transformer and models genetic interactions to identify more complex biological interactions and predict overall synergy scores of similar types.

In contrast, MatchMaker focuses on predicting the Loewe Synergy Score, a specific mathematical model that measures the interaction between two drugs based on the assumption that drugs with the same mechanism of action produce additive effects. Antagonism or synergy is indicated by deviations from this additivity. As a result, MatchMaker is made especially for the Loewe model and offers a great starting point for calculating medication interactions for the total synergy score that DeepSynergy and TranSynergy predict. To differentiate between synergistic and non-synergistic drug pairs, DeepSynergy creates a continuous synergy score for drug combinations. This score is assessed using regression metrics like the mean squared error (MSE) and Pearson correlation coefficient, as well as classification metrics like the ROC AUC. With an MSE benchmark of 255, the model outperforms other machine learning models with MSE ranges of 275–478. These models include support vector machines, random forests, and gradient boosting machines. The effectiveness of DeepSynergy in reducing the error between the anticipated and observed synergy estimations is demonstrated by these low MSEs. Furthermore, a strong linear relationship between the expected and actual synergy scores is demonstrated by the model's 0.73 Pearson correlation coefficient. This strong association shows that DeepSynergy can recognize patterns of medication synergy. Additionally, DeepSynergy's PR AUC score of 0.56 suggests modest effectiveness in striking a balance between precision and recall when categorizing drug com-

binations as synergistic, while its ROC AUC score of 0.90 shows that it can reliably rank drug pairs by their likelihood of synergy.

However, DeepSynergy shows limitations when applied to new drugs or cell lines that are not included in the training set. For new drugs, the MSE increases to 414, and for new cell lines, the accuracy decreases significantly to 387. This performance degradation suggests that DeepSynergy has difficulty generalizing to completely new data, which becomes a problem when applied to new drug combinations or cell lines that are outside the training data.

On the other hand, TranSynergy demonstrates excellent ability to accurately predict synergy scores, achieving an MSE of 231, which is lower than DeepSynergy's 255. This improvement reflects TranSynergy's advantage in capturing more complex biological interactions through its architecture. TranSynergy also achieved a Pearson correlation of 0.746, which is slightly better than DeepSynergy's 0.73, indicating a stronger linear relationship between predicted and actual synergy estimates. Additionally, TranSynergy showed a high Spearman correlation of 0.730, demonstrating its ability to maintain rank consistency in predicted synergy scores, which is especially important when predicting across multiple datasets. In particular, TranSynergy outperformed DeepSynergy with a 5.6% improvement in PR AUC on the classification task, highlighting its better performance in distinguishing between synergistic and non-synergistic drug pairs, especially on imbalanced datasets.

The Shapley Additive Gene Set Enrichment Analysis (SA-GSEA) method improves TranSynergy's model interpretability, one of its main advantages. By pinpointing the key genes and pathways causing the anticipated synergy, this feature enables the model to provide an explanation for its predictions. Because of its interpretability, TranSynergy offers practical insights into the molecular mechanisms driving therapeutic synergy, which makes it useful in precision medicine and biomedical research.

Drug-Specific Networks (DSNs) and Synergy Prediction Networks (SPNs) are two components of MatchMaker's modular architecture that enable it to excel at both regression and classification tasks. With an MSE of 79.49, the model was the most accurate in predicting Loewe's synergy scores, outperforming both DeepSynergy (MSE: 112.6) and TreeCombo (MSE: 132.7). This demonstrates how well MatchMaker's modular architecture processes data particular to drugs and cell lines. With a Pearson correlation of 0.79, MatchMaker outperformed DeepSynergy (0.73) and TranSynergy (0.746) in terms of accuracy. Additionally, MatchMaker revealed a Spearman correlation of 0.74, indicating that it can reliably rank medicine combinations according to their synergy scores.

With a ROC AUC of 0.97 as opposed to DeepSynergy's 0.90, MatchMaker performs better in the classification task than both DeepSynergy and TranSynergy. MatchMaker is highly good at differentiating between antagonistic and synergistic drug combinations, as evidenced by this higher ROC AUC. Additionally, MatchMaker's PR AUC of 0.85 is significantly higher than DeepSynergy's 0.56, indicating that it can sustain balanced recall and high precision—two critical attributes in imbalanced datasets.

5.3. Common-ground for comparison

Given that MatchMaker estimates Loewe's integration score while DeepSynergy and TranSynergy estimate integration scores, their results are not directly comparable to the case. The Loewe score is based on specific mathematical concepts that model drug interactions differently than the joint score. Therefore, each model has different parameters and values, so using MSE (Mean Square Error) to compare these models would not make sense. This is because MSE is sensitive to the output size, and each model is optimized for different predictions as shown in Table 3.

Table 3. Pearson Correlation of Models for Predicting Drug Integration Scores

Model	**Integration Score Type**	**Pearson Correlation**
MatchMaker	Loewe Score	0.79
TranSynergy	Joint Score	0.746
DeepSynergy	Joint Score	0.73

The accuracy of actual and predicted synergy scores is shown by Pearson's correlation coefficient (CCP). It is used to further explore the variability in the prediction model. CCP is defined as:

$$\mathrm{CCP} = \frac{\sum_{x=1}^{s}(f_x^{\mathrm{ob}} - \bar{f}^{\mathrm{ob}})(f_x^{\mathrm{pd}} - \bar{f}^{\mathrm{pd}})}{\sqrt{\sum_{x=1}^{s}(f_x^{\mathrm{ob}} - \bar{f}^{\mathrm{ob}})^2} \cdot \sqrt{\sum_{x=1}^{s}(f_x^{\mathrm{pd}} - \bar{f}^{\mathrm{pd}})^2}} \tag{1}$$

where $\bar{f}^{\mathrm{ob}}$ and $\bar{f}^{\mathrm{pd}}$ indicate the mean values of observed synergy scores and predicted synergy scores, respectively. The value of CCP can lie in the range of -1 to 1. The absolute value of CCP indicates the degree to which the observed and predicted values are related. The Pearson correlation coefficient r measures the closeness of data points to a best-fit line. A Pearson value between 0.5 and 1 indicates the accuracy of the predicted model's synergy score.

Attempting to directly compare MSEs can lead to misleading results, as the objective prediction models are not consistent. Correlation is about how well each model captures the relationship between the predicted outcome and the actual outcome, or how well the drug combinations are related. Unlike MSE, the correlation metric is not sensitive to the size or variance of the output data, making it suitable for comparison in this context. The score is 0.73, indicating a good relationship between the predictor and the joint outcome. TranSynergy performs slightly better than DeepSynergy with a Pearson correlation of 0.746, indicating that it accurately captures the relationship between the predicted and actual costs. MatchMaker, optimized to predict Loewe's integrated score, achieved a Pearson correlation of 0.79 and outperformed DeepSynergy and TranSynergy on certain tasks.

6. Conclusion and Future Work

In summary, this review highlights significant advances in computational models for drug combination prediction, focusing on the growing role of machine learning and deep learning in cancer therapy. The complexity and costs associated with clinical trials have always emphasized the need for computational methods to accelerate drug combination discovery. Deep learning models leveraging large-scale genomic and chemical datasets have demonstrated superior capabilities, enabling experimental research and advances in precision medicine. Clearly, each model has its own advantages and limitations.

TranSynergy, which models gene interactions by listening to each other, generally outperforms DeepSynergy in predicting synergistic scores across multiple tissues, except for prostate cancer, where the cell line causes specific problems. The comparison of models such as TranSynergy, DeepSynergy, and MatchMaker demonstrates clear performance differences, with TranSynergy excelling across multiple tissue types and MatchMaker achieving high accuracy for Loewe's joint scores. These results highlight the strengths of targeted modeling approaches in specific contexts. MatchMaker, which predicts Loewe's joint score, demonstrates the value of specific models in joint models by achieving full accuracy. It highlights the differences between different tissues and cell types, chemicals, and cell lines. Future efforts should focus on improving model robustness, collecting more diverse data, and further improving interpretation to facilitate the translation of predictions into treatment. The integration of Graph Neural Networks presents a promising direction for the advancement of drug synergy prediction. Due to their ability to capture the intricate connections within graph-based data, GNNs are well-suited to modeling the structural and relational properties of drugs. Incorporating attention mechanisms into this framework can enhance the model's ability to compute synergy scores for drug combinations. The integration of Graph Neural Networks (GNNs) is particularly viable for addressing current limitations in drug synergy prediction. GNNs excel at modeling relational data, such as drug-drug interactions and complex biological pathways, which are inherently graph-structured. By explicitly representing drugs, proteins, and pathways as nodes and their interactions as edges, GNNs can learn intricate relationships that traditional models often miss. This capability is crucial for improving predictions in scenarios where structural and pathway-based information significantly influences synergy outcomes.

Attention mechanisms further enhance this framework by prioritizing the most relevant nodes and edges in the graph, allowing the model to focus on critical relationships within high-dimensional datasets. This selective focus addresses the challenge of noise and redundant information, which often hinders the performance of existing models. By combining GNNs with attention mechanisms, the resulting models can achieve better interpretability and prediction accuracy, particularly for complex drug combinations and underrepresented tissue types where current models strug-

gle. This hybrid approach has the potential to overcome key limitations in scalability, generalizability, and biological relevance, paving the way for more robust and clinically meaningful predictions.

In this review, we have analyzed how recent advances, including the integration of genomic data and model-specific improvements, contribute to the accurate prediction of drug synergy scores. The discussed results illustrate how machine learning models, such as TranSynergy and MatchMaker, provide reliable predictions across diverse datasets, paving the way for their practical application in precision medicine.

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