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Applying Graph Neural Networks in Pharmacology

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Abstract

Objective: Techniques that are based on artificial intelligence, specifically machine learning, have played a major role in the enhancement of pharmacological methodologies and development of medical treatments, especially those that are individualized or those which fall in the province of precision medicine. In this article, we attempt to examine how graph neural networks have revolutionized certain important aspects of pharmacology.

Background: Pharmacological data is replete with unidirectional as well as bidirectional associations, with regards to, for example, drug interactions, patient-centered medicine, precision medicine, multi-omics data analysis, drug discovery, and optimization of experimental processes, and other fields. These associations can be more readily modeled using advanced computational methods and machine learning techniques like graph neural networks. The revolutionary advancements in the field of data mining have further fueled the need to create models that can resolve pharmacological correlations and dependencies into facilely interpretable outcomes.

Methods: We conducted a literature review to find those documents which provide relevant information about our objectives. With a comprehensive search plan in place, we sequestered applicable articles and studied them to identify pertinent points that assisted our understanding of graph neural networks as a tool to improvise, automate, and simplify the practical applications in pharmacology and pharmacotherapeutics.

Conclusion: The review of relevant research has confirmed our hypothesis that graph neural networks can be used to create an innovative, lasting, and radical departure in pharmaceutical therapeutics. Graph Neural Networks can automate and simplify many tasks based on large and complex datasets which are inherent in pharmacological science. Such techniques can help us achieve innovative methods in therapeutics using extant pharmaceuticals and in the development of new drugs, and therefore bode well for the future of healthcare.

Keywords: Graph Neural Networks, Pharmacology, Pharmacotherapeutics, Geometric priors, Indicators of Compromise, Pharmacomolecular, Drug-Drug Interactions, Multi-omics, Node embeddings, Topology, Graph-based attention mechanisms, Drug Discovery, Drug Target Mechanisms

1. Introduction

The multifariousness of pharmacological data impels it beyond the scope of traditional analytical methods, which have a diminished capacity to handle complex datasets. In order to grasp the interactions that underlie pharmacotherapeutical and pharmacomolecular mechanisms, it becomes imperative to analyze this data using improved computational methods, which involve the examination of associations within the data and data integration and over multiple dimensions.

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Graph neural networks are a rapidly developing approach in machine learning that provides a major bolster in this quest.

Pharmacological data and tools have been profusely harnessed in numerous provinces of biomedical sciences, such as diagnostic therapeutics, drug discovery, personalized medicine, preventive medicine, pharmacogenomics, synthetic biology, and in combating adverse drug effects arising from overdosage, biochemical intolerance, and drug-drug and drug-protein interactions. By coalescing various categories of pharmacological data into automated, interpretable, and actionable outcomes, machine learning approaches can expose fresh insights into the molecular effects of pharmacological interventions, detecting novel therapeutic agents, and making predictions for optimizing personalized treatments.

Pharmacological data faces a myriad of challenges which encompass the processes of data integration, exploration, analysis, and interpretation. Machine learning models designed to work on pharmacological data must be ready to handle the high dimensionality and heterogeneity of pharmacological data, which can impose substantial computational costs and statistical complexities. The interpretation and verification of the results of such analyses require skilled training in the subject of biomedical sciences, pharmacogenomics, and molecular biology, involving the scrutiny of disease processes and mechanisms at molecular and cellular levels in the body. Understanding the biological significance of pharmacological data and translating it into useful insights for drug development and clinical applications is a complex task that requires domain expertise. This review highlights the recent methods used in designing novel automated ways to interpret and integrate pharmacological data which can then be easily validated.

The obstacles that arrive with pharmacological data are multitudinous. Pharmacological data is complex, involving various parameters, molecular structures, and biological interactions. The sheer volume of pharmacological data generated from experiments, clinical trials, and studies is massive. Handling and processing such large datasets require advanced computational and analytical tools. Pharmacological data often comes with many missing values, particularly the details about less experimented drugs and those pertaining to patients, who often withhold their information or whose information could not be properly collected. Imputation is a statistical and computational technique which involves the replacement of missing data values with substituted values. Ensuring the quality and accuracy of pharmacological data is crucial. Inconsistencies in the data can lead to flawed analyses and conclusions.

Pharmacological data involves integration of diverse data sources, including multi-omic data, which itself includes, but is not limited to, microbiomic, genomic, proteomic, transcriptomic, metabolomic, ubiquitinomic, lipidomic, and epigenomic data. Pharmacological research involves data from diverse sources such as genomics, proteomics, and clinical trials. Integrating these disparate datasets to gain comprehensive insights poses a significant challenge. Further, the lack of uniform, standardized formats in which pharmacological data is available and accessible can not only make it unsuitable for specialized algorithms but also impede data integration. It can also cause interoperability and collaboration issues between different research groups and institutions.

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Reemphasizing the fact that pharmacological data is high-dimensional and heterogenous in nature, it is evident that performing complex analyses, simulations, and modeling on pharmacological data using inefficient or basic models may require substantial computational resources. Access to high-performance computing infrastructure can be a limitation.

Additionally, pharmacological data often includes sensitive information about patients and their health. Ensuring data privacy and handling ethical concerns related to the use of such data is a critical issue. Recognizing these challenges, which can be effectively tackled using modern artificial intelligence methodologies, machine learning methods, owing to their advanced predictive capabilities and the resultant enhancement in efficiency, are lucrative for the pharmaceutical industry. Modern computational systems also come with enhanced encryption which can safeguard sensitive data.

1.1. Machine Learning

Classical machine learning, or simply machine learning, is a process of decoding and elucidating complex data and drawing meaningful conclusions from it. It is a subset of artificial intelligence that focuses on developing algorithms and models capable of learning from data to make decisions without explicit programming. It involves the use of statistical techniques to enable systems to automatically improve their performance on a specific task over time.

Under machine learning, data is the mainstay. There are two types of classical machine learning, supervised learning and unsupervised learning. If the data that is fed to the model consists of input features and corresponding output labels the machine learning process is termed supervised learning. If the data must be analyzed without the presence of output labels, the process is termed unsupervised learning. Reinforcement learning takes a step further and involves training intelligent systems through a scheme of rewards and punishments, making them conditioned to perform those actions which glean rewards and shun those which glean penalties. It is akin to teaching a living creature how to thrive under the rule of law and how to function more and more competently over time.

With machine learning a computer builds a model that can learn and derive useful information from the available data by analyzing it, before making effective predictions that simplify intricate tasks for humans. Machine learning learns from data through a process called training, which allows it to generalize. Data collection is the first step in machine learning. Under this, relevant data is collected for the specific task the proposed machine learning model is intended to perform. Once the data is collected, it is preprocessed. Raw data is required to be cleaned and properly formatted for it to be entered into the model. During data preprocessing, missing values are handled through imputation or other methods, data is normalized and augmented, and categorical variables are encoded. After the data is preprocessed, features are extracted from it. Machine learning models can efficiently analyze patterns using distinctive features of the data. Feature extraction involves selecting and transforming relevant features that can contribute to the model's learning.

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Data mining is a process associated with the extraction of patterns and actionable knowledge from large datasets. In the context of the steps involved in machine learning, data mining comes into play during data collection, data preprocessing, and feature extraction. Data mining involves exploratory data analysis, which can be thought of as the exploration and extrication of valuable insights from large datasets before the formal training of a machine learning model begins. This is because summarizing and understanding the characteristics of the data is crucial for effective model development. Data mining identifies and handles noise and outliers present in the data. This is also termed as cleaning the data. Handling missing values and transforming variables are data mining tasks which enhance the quality of the dataset. Data also involves the identification of relevant variables which are significant contributors to the patterns present in the dataset. This is essential for optimizing the input parameters and weights employed in the machine learning model. Data mining is a precursor and an integral part of the broader machine learning process, helping to lay the foundation for effective model training and analysis.

Once features have been mined from the data, feature engineering is performed to make the data more comprehensible for the model, as well as for humans. Feature engineering involves creating new variables in the dataset based on existing variables. Then a suitable machine learning model is chosen relying on the nature of the task that is supposed to be performed on the dataset. Possible tasks may include classification, regression, clustering, prediction, anomaly detection, association rule learning, dimensionality reduction and the suchlike. The nature of the algorithm also depends on characteristics of the data. For example, if the features in the dataset have varying scales, such as age measured in years and income measured in dollars, algorithms like Support Vector Machines (SVM) or K-Nearest Neighbors (KNN) might perform poorly. If the dataset contains many categorical variables, algorithms like Decision Trees and Random Forests handle them naturally, while others like Linear Regression might struggle.

Once the model is created, it is fed with the training data, and the learning process begins. During training, the model adjusts its internal parameters, including weights and biases, iteratively to minimize the difference between its predictions and the actual outcomes. Optimization methodologies like the gradient descent algorithm are applied at this juncture to update the model's parameters in the direction that reduces the loss. A loss function measures the difference between the predicted output and the actual output. The model aims to minimize this loss by adjusting its parameters.

Once the parameters are concreted, the model is trained. The trained model is evaluated on a separate set of data not used during training to ensure it generalizes well to new data. This is called the process of validation. Through validation, the model’s parameters are verified to ensure that the model provides accurate results. Based on validation results, the model might undergo further adjustments, such as fine-tuning hyperparameters, to improve performance. The final model is tested on a completely independent dataset to assess its performance in real-world scenarios. Through this iterative process of adjusting parameters based on observed errors, the model learns to make accurate predictions or uncover patterns in new data. The ultimate goal of machine learning is to create models which can perform on all kinds of unseen data.

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A pivotal aspect of machine learning is its adaptability, enabling applications in various domains such as image and speech recognition, natural language processing, and recommendation systems. Neural networks, a fundamental concept in machine learning, draw inspiration from the human brain's structure. Neural networks form a part of deep learning, a subset of machine learning. Deep learning is sometimes considered a part of classical machine learning and sometimes considered distinct from it. Neural networks consist of interconnected nodes or neurons organized in layers, with each connection representing a weight. Neural networks excel in complex pattern recognition tasks, making them a cornerstone in deep learning, a subfield of machine learning focused on using deep neural networks (DNNs) for sophisticated tasks.

1.2. Neural Networks

Neural networks are computational models inspired by the structure and functioning of the human brain. They are the models which produce the most reliable and accurate outcomes and are widely used in the industry. Comprising interconnected artificial neurons, which are also called nodes or units, these networks can utilize data and learn more efficiently and make better decisions compared to other machine learning techniques. Neural networks consist of layers of nodes, organized into an input layer, one or more hidden layers, and an output layer. Each connection between nodes has an associated weight, and neurons apply activation functions to the weighted sum of their inputs.

The input layer receives data, the hidden layers process the data, and the output layer provides the result. The deeper the neural network, the higher the number of hidden layers. Connections between neurons have associated weights and biases, which are adjusted during training to enable the network to learn from data. Each neuron typically applies an activation function to the weighted sum of its inputs. Many activation functions introduce non-linearity to the neural network and enable it to capture complex relationships in the data.

Information flows forward through the network during the training or inference phase. The input data passes through the layers, and the final output is produced. This is termed feedforward propagation. Neural networks learn by adjusting weights and biases through a process called backpropagation. It involves minimizing the difference between predicted and actual outcomes, updating parameters to improve the model's performance.

Another concept related to neural networks, the learning rate, determines the size of adjustments made to weights during backpropagation. It influences the convergence speed and stability of the learning process. If the size of the adjustments (also known as steps, especially when gradient descent or stochastic gradient descent are used to optimize weights during backpropagation) is too low, the time taken to find the optimum parameters may become too large, causing the training to be slow. If the size of the adjustments is too large, the loss function, which quantifies the difference between predicted and actual values, may never attain minima because the model overshoots it every time.

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Neural networks may be typified into many kinds. Feedforward Neural Networks are the most basic type of neural networks. In feedforward networks, information travels in one direction, from input to output. Common feedforward architectures include Single-Layer Perceptrons (SLP) and Multi-Layer Perceptrons (MLP). Convolutional Neural Networks (CNN) are another type of neural networks which are specialized for image recognition and processing. CNNs use convolutional layers to automatically learn spatial hierarchies of features. Recurrent Neural Networks (RNN) are designed to process time sequence data. RNNs have connections that form cycles, allowing them to capture temporal dependencies. Long Short-Term Memory (LSTM) and Gated Recurrent Unit (GRU) are variants of RNN.

Generative Adversarial Networks (GAN) are another type of neural networks which consist of a generator and a discriminator trained simultaneously. GANs are used for generating new data instances, often in the form of images. Their origination has led to the fashioning of the field called Generative Artificial Intelligence. Autoencoders utilize unsupervised learning models designed for data compression and feature learning. They consist of an encoder and decoder, with the middle layer representing a compressed version of the input. Graph Neural Networks (GNN) are deep neural networks which extend neural networks to handle graph-structured data. Graphs consist of nodes and edges, and GNNs can capture relationships and dependencies in complex graph-structured data. They have applications in network analysis, molecular chemistry, recommendation systems, pharmacology, multi-omics and so on. GNNs leverage message passing and aggregation techniques to incorporate information from neighboring nodes, enabling them to model intricate relationships within graphs.

1.2.1. Geometric Priors

A geometric prior is a mathematical assumption about the distribution of data in a geometric space. It represents prior knowledge regarding the spatial relationships, shapes, or structures within the data. It intuitively supposes and incorporates information about the geometry and the spatial arrangement of the data points before observing the actual data. This prior knowledge is useful in machine learning and statistics. In Bayesian statistics, prior distributions are combined with observed data to form a posterior distribution. In image processing, an assumption a geometric prior may make is that neighboring pixels in an image are likely to have similar intensities or colors. In natural language processing, a geometric prior may suppose that words with similar meanings are likely to be close together in a high-dimensional space.

Geometric priors can be particularly relevant in situations where there is limited data, and incorporating additional assumptions or prior knowledge helps regularize the learning process. They are used to guide the learning algorithm toward solutions that align with the expected geometric characteristics of the data. Geometric priors have been shown to be useful when the data suffers with high dimensionality or the curse of dimensionality. Assumptions like geometric priors are necessary when all the dimensions of the data cannot be comprehended. In a non-Euclidean space, the curse of dimensionality is common. Geometric priors, in case of high dimensional data, can help in reducing dimensions of the data alongside Principal Component Analysis (a statistical dimensionality reduction tool) and other dimensionality reduction techniques. If the data follows

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a non-Euclidean geometry and can be assumed to fit into a graph structure, Graph Neural Networks can be applied to it.

1.3. Graph Neural Networks

The use of graphs as a data structure has gained significant traction in the realm of machine learning due to the ability of graphs to effectively model relationships and dependencies among a set of objects. Graphs consist of nodes representing entities or objects, and edges representing relationships or connections between these entities. This non-Euclidean structure allows for a more nuanced representation of complex non-linear relationships compared to traditional tabular data, which involves linear relationship between entities and data points.

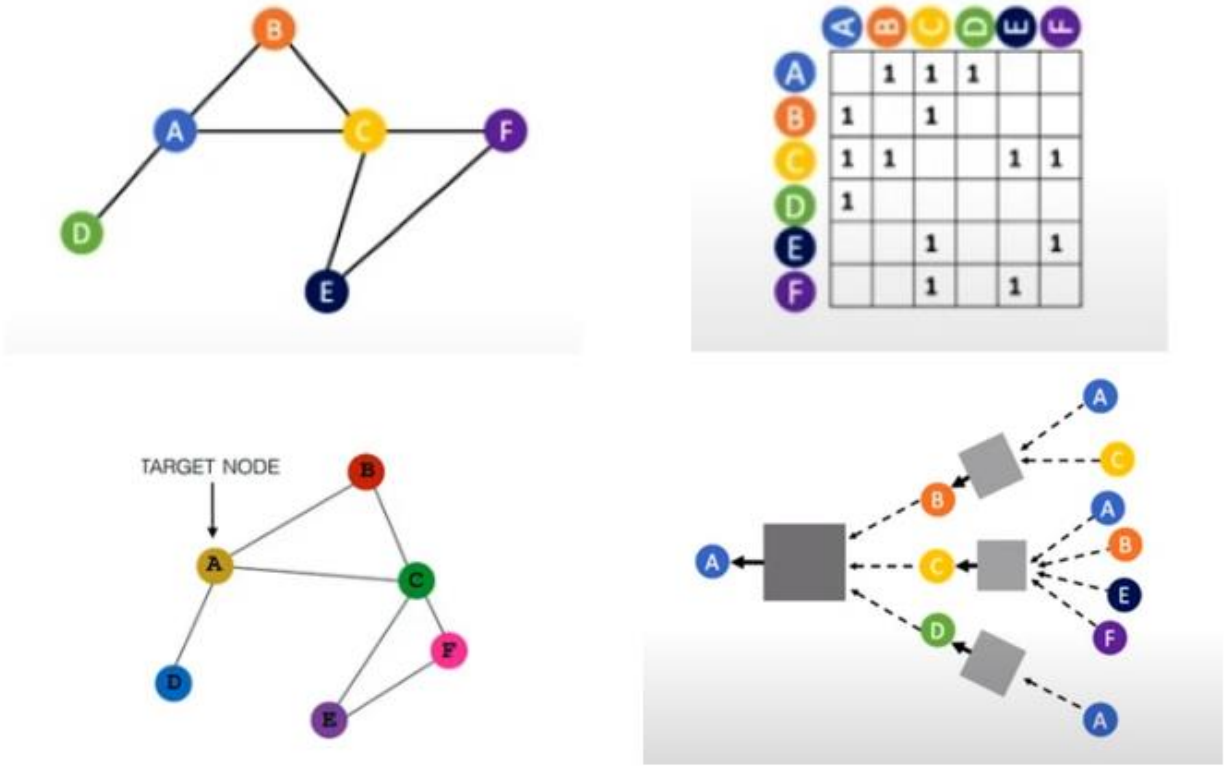

Figure 1 [1]: A pictorial representation of a graph (top left) and its adjacency matrix (top right). A graph chosen to be analyzed through a neural network architecture, with its target node highlighted (bottom left) and the Graph Neural Network (GNN) built using the said graph (bottom right). The figure is adapted from Yoon (2022). Yoon states that, given a graph and the features of its nodes (in the form of feature vectors or otherwise), a GNN can be constructed to find node embeddings. Yoon adds that a GNN can be used to predict labels for the target node by allowing the GNN to analyze the features of all the nodes, including those of the target node. Creating embeddings involves representing each node in the graph as a vector in a lower-dimensional space with a goal to summarize and leverage essential information about the node's role and relationships within the network. Nodes that are closer in the vector space are more similar than those which are farther to each other. A graph is also referred to as a network and the entirety of a graph can also be represented as a single vector which captures the overall structure and connections in the graph.

GNNs were proposed by Scarcelli *et al.* in 2009 [2]. Node and network embeddings are facilitated by GNNs. The vectors in which the graph structure is transformed isolate the topology of the network. Topology refers to the structure of the network, including the patterns of connections, the presence of clusters, and the overall organization of nodes and edges. Creating node and network embeddings involves learning representations that retain the essential structural characteristics of the graph, which includes preserving information about the dependencies between the nodes, the strength of connections, and the overall organization of the graph. Embeddings are formed based on similarity in the properties of the vertices, that is, vertices which are similar in characteristics have similar embeddings.

The basic structure of a GNN includes an encoder and a decoder. The encoder inputs a graph and generates and learns an embedding for each node of the graph. The decoder uses the learned embedding to make predictions. The properties of a node are judged through its vector or its embedding. The principle of encoding nodes with a similar vector based on the similarity of their neighborhoods in the graph is fundamental to capturing and leveraging structural information within the graph. A GNN uses iterative information aggregation mechanisms to capture and propagate information through the network, allowing nodes to learn features based on their local neighborhood. GNNs iteratively update the node representations based on information from neighboring nodes. The final learned embeddings encapsulate the structural and connectivity information of the graph. The embeddings are used in downstream tasks such as node classification, link prediction, or clustering, where preserving the inherent relationships and connectivity patterns is crucial for effective learning and prediction.

Certain classes of data are more explainable and understandable when represented in the form of graphs. These classes fall under various subject areas including multi-omics, image processing, pharmacotherapeutics, landscape analysis, software engineering, social networks, natural sciences including physical and chemical systems, education, and natural language processing, especially large language models. GNNs can make many kinds of predictions, such as predicting the property of the nodes, predicting the connections or similarities between two or more nodes or graphs, predicting the characteristics of an entire a graph, and the suchlike.

1.3.1. Practical Uses of GNNs

In recent years, there has been a surge in the development of GNNs. These neural networks leverage the connectivity information of nodes to enhance learning and prediction capabilities. GNNs have the power to capture complex dependencies within dynamic and evolving environments. The combination of graph theory and machine learning has opened new avenues for solving complex problems across diverse domains. For example, in network analysis, GNNs have been found to be increasingly useful. Other machine learning techniques were already deemed crucial for analyzing social networks, citation networks, biological networks, computer networks, trajectory analysis, and so on, when GNNs started making foray into network analysis. GNNs simplify multifold the identification of community structures, influential nodes, and patterns of influence in network analysis.

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In recommendation systems which provide trained suggestions relying on user analysis, graphs are employed to model user-item interactions. Recommender systems utilize graph-based algorithms to make personalized recommendations based on the preferences and behavior of similar users. In the domain of molecular chemistry, especially in subfields like drug discovery, molecules can be represented as graphs, where atoms are nodes and bonds are edges. GNNs have been found to be useful in predicting molecular properties and understanding chemical relationships, specifically protein-protein interactions, drug-protein interactions, and drug-drug interactions.

Figure 2: The Roadways of the World. A GNN model can be valuable in analyzing this data, finding various applications, such as traffic prediction, where the road network is represented as a graph where nodes are intersections or road segments, and edges represent connections between them. The model may learn and predict traffic patterns by considering historical data, weather conditions, and other events by capturing spatial dependencies and making them effective for predicting traffic flow at different locations. GNNs can also be used for route planning, urban development, infrastructure optimization, public transport augmentation, and emergency response scheduling.

In cybersecurity, graph-based machine learning techniques are now commonly used to analyze patterns in network traffic, identifying potential security threats and anomalies. Homophily, in a graph, refers to the propensity of nodes to form interconnections with nodes with similar features. In case this principle is found to be breached in a graph, anomalies can be found, leading to identification of potential threats. In anomaly detection, network traffic, user behaviors, or system activities can be represented as graphs, where nodes represent entities, for example individual users or standalone devices, and edges represent interactions between them. GNNs can be used for anomaly detection by learning normal patterns of interactions within the graph. Deviations from these learned patterns can indicate potential anomalous activities which can be security threats. In intrusion detection, network communications are modeled as graphs, where nodes represent IP addresses of individual devices, and edges represent interactions including data transfers. GNNs

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are used to identify patterns associated with known intrusion scenarios, and can adapt and learn from new attack patterns, making them effective for dynamic threat detection.

GNNs can also be applicable in user and entity behavior analysis, where the relationships between users and devices can be captured with edges as behaviors and reactions. User behavior graphs can be analyzed using GNNs to identify abnormal behaviors and thereby to detect compromised accounts and raising alerts. To analyze vulnerability, IT infrastructure can be represented as a graph with software components as nodes and interactions between them as edges. Applying GNNs would enable the assessment of chinks in the armor by scrutinizing the connections between system components, identifying critical nodes, and assessing potential points of exploitation. As to assessing threat intelligence, indicators of compromise (IoCs) can be modeled as graphs to encapsulate relationships between various threat entities.

Graph Neural Networks (GNNs) can be applied in Natural Language Processing (NLP) and Large Language Models (LLMs) to discern and leverage the intrinsic organization and relationships in language data. This can help computational systems to capture semantic nuances and improve performance on various language understanding and generation tasks. In syntax and dependency parsing, sentences are represented as graphs, where words are represented as nodes, and edges signify syntactic dependencies between words. GNNs have the capability to capture the hierarchical relationships between words in a more finespun way compared to traditional parsing techniques. In semantic role labeling, graphs are constructed such that their nodes represent words, and edges denote semantic relationships. GNNs are capable of labeling semantic roles by learning and predicting the functions of words within the context of a sentence while keeping the dependencies under consideration.

In entity recognition and linking tasks, for example in Named Entity Recognition (NER), graphs can be visualized where nodes represent entities, and edges indicate relationships between entities. The relationships can be in the form of their co-occurrence, of their semantic connections, and so on. GNNs can enhance entity recognition and linking by leveraging contextual information and relationships between entities within a corpus of documents. In document representation, entire documents are pictured as graphs. The nodes of these graphs correspond to paragraphs, or to sentences, or sometimes to words, and the edges encapsulate relationships, which may include document structure or co-occurrence. GNNs can learn rich document representations by considering the hierarchical structure and interconnections between different parts of the text.

In context of knowledge graph embeddings (KGEs), knowledge graphs that have been built are analyzed using low-dimensional embeddings. In knowledge graphs, nodes are entities and edges represent relationships between entities. GNNs can learn embeddings for entities and relationships in such graphs, facilitating improved reasoning and link prediction in semantic spaces. In language model training, text corpora are represented as graphs, with nodes representing phrases, words, or subword units and edges capturing sequential relationships. GNNs may contribute to language model training by capturing long-range dependencies and contextual information across sentences or documents, potentially improving the modeling of complex language structures. However,

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LSTM (Long Short-Term Memory) architectures are specifically built to denote long-range dependencies and can be more efficient at that task.

1.3.2. Types of GNN Tasks

GNNs are all-round models that can perform various tasks involving graph-structured data. A list of tasks where GNNs are effective are:

I. Node Classification: This is one of the foremost tasks that would come to mind of someone working with GNNs. Predicting class labels for each node in the graph based on the features of the node and the topology of the graph is a common task with GNNs. This can be used to identify the category of nodes in a social network, citation network, or a pharmacological network.

II. Link Prediction: This task is about predicting the likelihood of a connection (edge) between two nodes that currently do not have a direct link. It can, therefore, be used to predict the link between two nodes in a graph whose adjacency matrix is unfinished, that is, a graph where all existent links have not been calculated. Its applications lie in recommender systems, predicting potential interactions in a social network, or suggesting collaborations in a citation network based on common interests (displayed by the commonality of features of the nodes, where nodes represent the members of the citation network).

III. Graph Classification: To classify entire networks into predefined clades is another task that GNNs can perform. Classifying chemical compounds based on molecular structures, identifying types of graphs in social networks, assigning labels to network security graphs based on their overall security status, or categorizing types of drugs fall under this task. Text classification is also included here.

IV. Graph Regression: Another GNN task can be to predict a continuous variable associated with each node in the graph. Calculating the popularity of products in a recommendation system, estimating properties of molecules in chemistry, collating sematic information in an LLM, and forecasting properties of nodes in a social network are examples of this task.

V. Community Detection: Identifying groups of nodes that are densely connected within the graph forms another task that can be performed by a GNN. Discovering subgroups of users with similar interests in a social network, identifying functional modules in pharmacological networks, identifying intersections, traffic hubs, neighborhoods, or individual vehicles which exhibit strong internal connections in a transportation network can be some examples of this task.

VI. Graph Embedding**:** Creating and analyzing low-dimensional representations for nodes or entire graphs. An example of this could be obtaining compact representations like vectors for nodes that capture their structural and contextual information in a graph which detects fraud by identifying variance and unusualness in the embeddings.

VII. Graph Generation: Generating new graphs that share similar structural properties with a given set of graphs is how this task can be outlined. Generating new graphs is data augmentation, which enriches the dataset with diverse examples. This augmentation helps in training more

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robust models for various machine learning problems. This approach is applicable to designing molecular structures in chemistry, generating realistic social network graphs, or creating realistic road networks. Generating new graphs may also aid in mitigating the cold-start problem in a recommender system that recommends books to potential readers, in case there is limited information about new books or readers. By learning structural patterns from existing graphs, the model can make informed recommendations even for items or users with sparse data.

Network effects refer to the impact of the user interactions on the performance of recommendation systems, particularly when dealing with new items or users. The cold start problem arises when a recommendation system encounters a lack of sufficient historical data for new items or users, making it challenging to provide accurate personalized recommendations. Network effects play a significant role in the cold start problem. As more users interact with an item, it becomes more popular. Positive network effects occur when the popularity of items increases with user interactions. For new items, this can be beneficial as the system can leverage the popularity of similar items to make initial recommendations.

VIII. Graph Anomaly Detection: Identifying nodes or subgraphs that exhibit unusual behavior compared to the rest of the graph is a anomaly detection task. One way of detecting anomalies is by generating graph embeddings and it has been discussed in the sixth point. Finding fraudulent activities in financial networks, identifying anomalies in communication networks, or spotting outliers in social networks are examples of anomaly detection tasks.

IX. Knowledge Graph Completion: Expanding a knowledge graph by predicting additional connections between entities or uncovering missing information becomes necessary to achieve completion. Finding missing relationships and generating weights for those edges whose information has not been provided is another task a GNN can perform.

X. Graph Alignment: Aligning nodes or subgraphs across multiple graphs to find instances of correspondence is also a GNN task. Integrating information from different sources or domains, aligning biological networks, or matching nodes across protein-drug interaction graphs and protein-protein interaction graphs are examples of this task.

1.3.3. Variants of Graph Neural Networks

GNNs come in various architectures and designs, each tailored to specific tasks and characteristics of the input graphs.

I. Graph Convolutional Networks (GCN): GCNs are one of the foundational architectures in GNNs. They use a localized convolutional operation to aggregate information from a node's immediate neighbors. They enable nodes to exchange information and learn representations based on the graph structure. They learn features by examining neighboring nodes. GNNs combine node embeddings to send output to the hidden layers. Some types of GCNs are Spatial Graph Convolutional Networks (SGCNs) (introduced by Danel *et al*., 2020 [3]) and Spectral Convolutional Networks (SCNs). SGCNs learn from graphs using their spatial features. SCNs perform Eigen decomposition on the Laplacian Matrix of the graph. Verma and Zhang, in 2018,

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presented the Graph Capsule Convolutional Neural Networks, introducing capsules to GCN [4]. They aimed to overcome the limitations of GCNs and those of capsule networks.

II. GraphSAGE (Graph Sample and Aggregated): Introduced by Hamilton *et al.,* (2018) [5], the GraphSAGE network generalizes the concept of aggregation by sampling and aggregating features from a node's neighbors. It allows for scalable and flexible learning on large graphs.

III. Graph Isomorphism Networks (GIN): GINs were introduced by Xu *et al*. in 2019 [6]. A GIN is designed to be invariant to the ordering of a node's neighbors. It uses a series of aggregation and readout functions to generate embeddings that are invariant under permutations. GINs have high representation power, that is, they have an enhanced capacity to classify nodes and assign them the correct labels. They are used for finding isomorphism in graphs. Isomorphism is a property of a graph where it retains its properties (adjacency matrix) with alteration in its structure.

IV. ChebNet (Chebyshev Graph Convolutional Network): ChebNet was introduced by Defferrard *et al*. in 2016 [7]. It uses Chebyshev polynomials to approximate spectral graph convolutions. It allows for a flexible aggregation of information from multiple hops in the graph.

V. Graph Attention Networks (GAT): GATs were introduced by Veličković in 2018 [8]. GAT establishes an attention mechanism that allows nodes to assign different attention weights to their neighbors. This enables nodes to focus more on informative neighbors during aggregation. Attention mechanisms enable a machine learning model to focus on specific parts of the input data while generating output such as predictions. Graph-based attention mechanisms can be applied to machine learning projects, including natural language processing tasks. Graph Recurrent Attention Network (GRAN) is a particular type of GAT which combines the concepts of graph attention networks (GAT) and recurrent networks to capture both spatial and temporal dependencies in dynamic graphs. They were introduced by Lia *et al.* in 2019 [9].

VI. Graph Variational Autoencoders: Introduced by Kipf *et al.* [10], Graph Variational Autoencoders are designed to efficiently learn low-dimensional representations of a graph by encoding and decoding the graph structure. They are unsupervised and can be used for graph generation and anomaly detection.

VII. Graph Neural Networks with LSTM (Graph-LSTM): Graph-LSTMs were proposed by Liang *et al.*, in 2016 [11]. The Graph-LSTM incorporates Long Short-Term Memory (LSTM) cells into the GNN architecture, allowing the model to capture temporal dependencies in dynamic graphs. LSTM systems are able to capture long-range dependencies and can be more efficient at that task. Therefore Graph-LSTM can capture both short-range and long-range dependencies. The application of Graph-LSTM lies in dynamic graph analysis.

VIII. Graph Recurrent Networks (GRN): GRN extends the idea of recurrent networks to graph-structured data. It captures sequential dependencies in node interactions over time. GRNs are defined as distinct cases of Recurrent Neural Networks (RNN) in which the signals at each point in time are supported on a graph [12]. Gating mechanisms in neural networks are used to handle exploding and vanishing gradient problems. These mechanisms allow a neural network

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to control the flow of the information (by forgetting certain features and inputting the rest) that enters and exits the layers of a neural network. Gated Graph Neural Networks are an enhancement to GRNs, and they work by introducing new nodes and edges, and time gates on long-term dependencies. Gated Recurrent Units (GRUs), where gating was combined with Recurrent Neural Networks, were introduced by Cho *et al.* in 2014 [13]. GRUs were combined with GNNs to produce Gated Graph Sequence Neural Networks (GGSNN) by li *et al.* in 2017 [14]. GGSNNs overcome the limitations of LSTMs and GRUs. Ruiz *et al.* in 2020 proposed another version of GGSNNs, the Gated Graph Recurrent Neural Networks [15].

IX. GraphSAINt (Graph Sample and Aggregated In-Sample Network): Introduced by Zeng *et al.* in 2020, GraphSAINt addresses scalability issues by using inductive sampling and aggregation methods. It efficiently scales up to large graphs while preserving expressive power. They improve GCNs as they construct minibatches by sampling the training graph. GraphSAINt builds a GCN at each iteration, ensuring a fixed number of well-connected nodes in all layers.

2. Methods

Our primary objective was to review various forms of GNN algorithms being applied to pharmacological problems in research. Unto this purpose, it was necessary that a systematic literature review or a meta-analysis be conducted to look for and study relevant articles including publications and preprints, where full text papers are available for a thorough scientific analysis. The PRISMA format was utilized to search and evaluate the literature about the role GNNs can play in helping us cognizably simplify pharmacological dependencies and extract utilizable and advantageous results from xenobiotic and related data.

For the initial searches, the keywords used in search queries were Graph Neural Networks (as a phrase), taken with pharmacology and pharmacologic, and pharmacological, all the three as alternatives to each other. The resulting search revealed a large number of articles not pertinent to our research question, that is, articles where pharmacological approaches or graph neural networks were not a part of the central theme. We then limited our search to those articles where these keywords were found only in the title, abstract, results, and in the keywords sections.

The search still provided a substantial number of articles that were not relevant to our needs, especially because keywords that were mentioned by the authors of the articles as well as those found through automated indexing of the articles were bereft of the needed quantity of accurateness. In this scenario, we further limited our search to include only those articles which contained the searched keywords only in the abstract, and this search resulted in the greatest proportion of articles which aligned with the research question (only 1 out of the 27 resulting publications was not relevant to our research question). Duplicates were removed to curb redundancy, and those publications where full text articles were not available, which could not be analyzed thoroughly, were also removed, leaving us with nineteen articles.

Articles published in or after the year 2022 were considered (with a single exception, which was published in the year 2021, but which had a very limited number of citations and which solved a unique therapeutic problem) because relevant articles published before that year were not only

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very few in number but the greater proportion of them had a considerable number of citations giving credence to the hypothesis that the preponderance of them might have already been reviewed. They also focused on such applications of pharmacology which had already been covered through later articles. Table 1 describes the articles that were finally selected for being reviewed:

S. No.	Title of the Publication	Year Published	Broad Area of Research
1.	DMFDDI: Deep Multimodal Fusion For Drug–Drug Interaction Prediction.	2023	Drug-Drug Interaction Detection
2.	Multi-view Feature Fusion Based on Self-attention Mechanism for Drug-drug Interaction Prediction	2023	Drug-Drug Interaction Detection
3.	An Explainable Framework for Predicting Drug-Side Effect Associations via Meta-Path-Based Feature Learning in Heterogeneous Information Network.	2023	Drug Safety and Drug Side Effect Detection
4.	PLA-GNN: Computational inference of protein subcellular location alterations under drug treatments with deep graph neural networks.	2023	Modeling Drug-induced Changes in Protein Subcellular Localization
5.	Predicting in vitro single-neuron firing rates upon pharmacological perturbation using Graph Neural Networks.	2023	Predicting Drug Induced Changes in Neuronal Firing Rates
6.	Exploring The Impact of Motif-Driven Causal Temporal Analysis Using Graph Neural Network in Improving Large Language Model Performance for Pharmacovigilance	2023	Drug Safety and Drug Side Effect Detection
7.	DrugAI: a multi-view deep learning model for predicting drug-target activating/inhibiting mechanisms	2023	Drug Discovery
8.	Cuproptosis gene-related, neural network-based prognosis prediction and drug-target prediction for KIRC.	2023	Drug Discovery
9.	Exploration of Chemical Space with Partial Labeled Noisy Student Self-Training and Self-Supervised Graph Embedding.	2022	Drug Discovery
10.	Graph Neural Network Models for Chemical Compound Activeness Prediction For COVID-19 Drugs Discovery using Lipinski's Descriptors	2022	Drug Discovery
11.	Machine learning and graph neural network for finding potential drugs related to multiple myeloma.	2022	Drug Discovery
12.	Graph Neural Networks as a Potential Tool in Improving Virtual Screening Programs	2022	Drug Discovery
13.	Learning Size-Adaptive Molecular Substructures for Explainable Drug–Drug Interaction Prediction by Substructure-Aware Graph Neural Network	2022	Drug-Drug Interaction Detection
14.	Multi-Type Feature Fusion Based on Graph Neural Network for Drug-Drug Interaction Prediction.	2022	Drug-Drug Interaction Detection
15.	A Novel Graph Neural Network Methodology to Investigate Dihydroorotate Dehydrogenase Inhibitors in Small Cell Lung Cancer.	2021	Drug Discovery

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Table 1: Literature Review Table

3. Discussion

In the modern landscape of technology and biomedicine, assessment of pharmacological data plays a pivotal role in elucidating the intricate interactions between drugs and biological systems. This process involves a meticulous examination of data derived from diverse sources, ranging from in vitro and in vivo experiments to real-world clinical observations. The comprehensive analysis of pharmacological data is instrumental in informing decisions at various stages of drug discovery, development, and post-marketing surveillance.

Pharmacological data encompasses a wide array of information, spanning molecular and cellular studies to clinical trials and real-world evidence. In vitro studies provide essential insights into drug mechanisms, including receptor binding, enzyme inhibition, and cellular responses. In vivo studies, often conducted in animal models, delve into the systemic effects and safety profiles of candidate compounds.

The foundational stage in the analysis of pharmacological data is exhaustive data collection. from different sources, where data is reliable, of sufficient quantity, and of high quality and disposability. Based on the research question and design, pharmacological data can be obtained from clinical trial repositories like European Clinical Trials Register, sources related to pharmaceutical companies like drug labels and package inserts, including FDA drug labels and European Medicines Agency product information, pharmacovigilance databases like WHO Global Individual Case Safety Reports database, Electronic Health Records like IBM Watson Health and Observational Health Data Sciences and Informatics, biomedical datasets and related literature from scientific journals, biochemical databases like PubChem, internal research databases of pharmaceutical research organizations, data on drug metabolism, pharmacokinetics, and pharmacodynamics, multi-omics data, and regulatory agency databases like EMA European Public Assessment Reports. Additionally, data obtained from cheminformatics, bioinformatics, pharmacoeconomic, pharmacogenomic, pharmacoepidemiology, biophysics, and toxicology studies can be useful for pharmacological research.

Beyond controlled environments, real-world data contributes to pragmatic insights. Observational studies provide a nuanced understanding of patient outcomes, treatment patterns, and the broader impact of drugs in routine clinical practice. The characteristics of the data obtained depend on the source and the experimental design. The second stage in pharmacological research is to integrate data from various sources. Data integration serves to amalgamate data in a meaningful way that enhances the significance of information content of all datasets. It is a challenging task, but advanced data analysis methods like GNNs are used to make this task easier, which can support processes like structure-based drug design.

In silico modeling of pharmacological data requires knowledge of techniques that fall within the domain of pharmacometrics. Principles of pharmacokinetic-pharmacodynamic (PKPD) analysis,

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systems biology, computational biology, computational biomedicine, systems pharmacology, pathophysiology, patient demographics, and pharmacological regulations and ethics are usually involved in pharmacological investigations. Dosing, microdosing, dose-response relationships, drug and biochemical concentration data, information concerning drug reactions in the body and their adverse effects are all examined within this domain. Such modeling can aid and inform various pharmacological and biomedical processes, including drug discovery. Building combinatorial libraries of synthetic chemicals is one of the many notable applications of in silico modeling of pharmacologic data.

In pharmacology, Graph Neural Networks (GNNs) are used to tackle various challenges in drug discovery, molecular property prediction, drug-target interaction prediction, and molecular representation learning. GNNs can encode molecular structures as graphs, enabling the capture of molecular properties and structure-activity relationships. They are used to predict various molecular properties such as solubility, bioactivity, toxicity, and binding affinity to biological targets. Additionally, GNNs aid in generating novel molecules with desired properties, optimizing molecular properties, predicting drug-target interactions, identifying multi-target drugs, performing molecular similarity searches, categorizing molecules into clusters, predicting adverse drug reactions and toxicity profiles, learning low-dimensional representations of molecules, and identifying existing drugs that could be repurposed for new indications or diseases. Furthermore, GNNs play a role in designing personalized therapies by considering individual patient data and molecular profiles.

GNNs have shown promise in pharmacology because of their ability to model and analyze graph-structured data, which the modern paradigm of pharmacology is replete with. In pharmacology, GNNs are applied towards the creation of useful compounds, simplify consequential information, and predict sophisticated results that can have profound implications in the modernization and evolution of medical therapeutics. GNNs have allowed us to uncover optimal drug combinations, to improve efficacy of drugs, and to evaluate drug use in diseases which are new, for which therapeutic drugs have not been discovered, or for which existing drugs have not been found effective. Some of the applications of GNNs in pharmacology are discussed in this article.

3.1. Drug-Drug Interactions

Drug-drug interactions (DDIs) represent complex pharmacodynamic phenomena in pharmacology where the effects of one drug are altered by the presence of another, influencing drug efficacy, safety, and overall pharmacokinetics [17]. These interactions can manifest at various levels, including alterations in drug metabolism through cytochrome P450 (CYP) enzymes, modulation of drug transporters, and competition for binding sites on receptors or plasma proteins [18–21]. It is the effects of DDIs through which they clinically manifest. DDIs can lead to synergistic effects, where the activity of one drug modifies favorably when it is taken in combination with one or more other drugs. However, DDIs are more feared because of their potential antagonistic effects, where the activity of one drug alters unfavorably when it is consumed in combination with one or more other drugs.

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The effects of DDIs impact therapeutic outcomes, potentially causing adverse reactions, and since adverse DDIs present severe and unpredicted risks for patients, it is critical to find and classify all potential DDIs [17, 22, 23]. Understanding the mechanisms and consequences of DDIs is crucial in clinical practice, influencing drug prescribing, dosage adjustments, and overall patient safety, particularly in scenarios where individuals are concurrently administered multiple medications. In this paper, we review Deep Multimodal Fusion for Drug-Drug Interaction Prediction (DMFDDI) as an effective DDI prediction approach [23].

DMFDDI is an approach designed for predicting DDIs using a deep multimodal feature fusion approach. Multimodal graphs are graphs with more than one type of edge, a phenomenon called versatility of edge types. DMFDDI consists of three main steps: learning multimodal drug features, fusing the learned feature embeddings, and predicting the DDIs based on the fused features. It includes feature extraction modules for drug molecular graph, drug interaction network, and biological similarity, as well as a multimodal feature fusion module and a predictor to determine the probability of any two drugs interacting with each other.

According to the authors [23], DMFDDI is a deep end-to-end multimodal feature fusion framework for DDI prediction. They assert that one of the reasons they built DMFDDI was that just one drug feature is insufficient to comprehensively represent drug information. DMFDDI leverages drug molecular graphs, DDI networks and the biochemical similarity features of drugs, integrating them to predict DDIs. They have used an attention-gated graph neural network (AGRUNN) which they have used to extract the molecular structure and to summarize the global features of the molecular graph and the local features of all the atoms. This helped them fully extract the drug molecular structure. They then used a sparse graph convolution network for learning the information regarding the topological structure of the DDI network. They have again used an attention mechanism to combine diverse features as part of their multimodal feature fusion module. The attention mechanism is calculated as follows:

$$(\alpha g, \alpha N, \alpha S) = att(FG, FN, FS)$$

where αg, αN and αS denote the attention coefficients of embeddings FG, FN, FS, respectively, FG, FN, and FS having been calculated previously. They have predicted DDIs as a binary classification problem, with binary cross entropy as their loss function. Validated against ten extant novel models, their study showed that their own model surpassed the performance of the ten benchmark models.

3.1.1. Multi-view Feature Fusion Based on Self-attention Mechanism

Han *et al.,* in their 2023 study, present a novel strategy, Multi-View Graph Attention Networks (MV-GAT), designed for effective feature fusion in the realm of molecular graph analysis [24]. Their approach aims to handle the problems with existing graph-based learning mechanisms to predict DDIs. The approach leverages graph representation learning techniques, specifically the bond-aware message passing neural network, to extract both local features of individual atoms within molecular graphs and global features of the entire molecular structure.

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The authors introduce an attention mechanism as part of a fusion strategy. The attention mechanism for fusion handles the integration of two crucial sources of information – drug features and topological information – under each view. Their goal is to facilitate a seamless fusion of features extracted from both molecular structures and interaction maps, providing a more comprehensive representation.

In order to address feature diversity and to tackle the challenge of oversmoothing during the transfer of information through GNN layers, the research incorporates an unsupervised contrastive learning component. This component is introduced in each GNN layer to ensure the diversity of node features, and by doing so, MV-GAT aims to prevent the loss of diverse information as it propagates through the network.

As a validation strategy, comprehensive experiments were conducted by the researchers using multiple real datasets to evaluate the performance of MV-GAT. The results have demonstrated their framework's robust generalization capabilities, indicating its effectiveness in handling feature fusion in the context of molecular graph analysis.

3.2. Polypharmacy and Drug Side Effect Prediction

Polypharmacy is described as an umbrella term which implies the concurrent usage of more than one medication by a patient for their conditions. In scientific circles, the term is usually defined as regularly taking five or more medicines. However, polypharmacy has a broader definition also, and the term has been used to explain a case when a person is prescribed more than one medicine coincidentally [25]. A related term, polypragmasy or polypragmasia, is defined as the simultaneous use of many medications on a patient with the aim to improve the effectiveness of therapy and to assist the patient in recovering from multiple conditions [26]. According to certain studies, about 46 percent of people over sixty-five years of age take five drugs or more. From some studies, it has also been found that 15 percent of US population is affected by unwanted effects of DDIs, and the annual costs to treat those side effects themselves exceeds USD 177 billion.

The simultaneous use of multiple drugs by a patient undergoing coexistent conditions and complex disorders (which is more common in geriatric patients than patients of other age groups) has alternately been referred to as using drug combinations, and one of the key effects of using drug combinations is a significantly enhanced risk of adverse side effects (also known as off-target effects) for the one who is taking them [27–30].

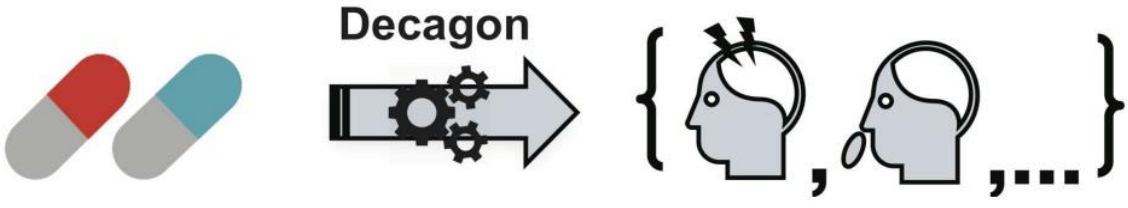

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Figure 3 [30]: A simple representation showing the basic function Decagon performs, that is, mining side effect information from data on pharmaceutical drugs (borrowed/adapted from Zitnik *et al,* 2018)

Polypharmacy side effects occur owing to drug–drug interactions, which have been discussed in the previous subsection. In this paper, we review Decagon, a multimodal framework which efficiently models polypharmacy side effects [30]. The framework involves the construction of a graph which includes information on protein–protein interactions, drug–protein target interactions, and also drug–drug interactions, which the authors term polypharmacy side effects. The term interactome describes the entire set of intracellular molecular interactions, referring particularly to protein-protein interactions; the interactome can be mined to predict the protein functions using protein–protein interactions [31].

Decagon involves generating a GCN for multi-relational link prediction in multimodal networks (heterogenous graphs). The authors of the article profess that their framework is better than those which are limited to predicting pure drug–drug interactions. Decagon, the authors say, can predict the precise adverse effects of a drug-drug interaction. An encoder-decoder model was built, and the loss function was minimized and parameters were tuned using categorical cross-entropy. The authors compared the performance of their model to multiple competing frameworks and discovered that because of the Decagon's multimodal network representation and the fact that it encompassed many side effects enabled it to beat other frameworks by significant margins. They used such metrics as area under ROC curve, area under precision-recall curve and average precision at 0.5 intersection over union threshold.

3.2.1. Enhanced Explainability in Predicting Drug Side Effects

Zhao *et al*., in 2023, have highlighted the problem of explainability in existing approaches to predict drug side effects. They emphasize the drawbacks of current methods, including underutilization of multiple drug-related databases, insufficient capturing of complex semantics among drugs and side effects, and a lack of explainability in predicted associations. They aim to reduce the monetary and temporal costs, and increase comprehensiveness of the drug side effect prediction tasks. Towards this objective, they have introduced a novel approach, termed Meta-Path-Based Graph Neural Network for Drug-Side Effect Associations Prediction (MPGNN-DSA) [32].

MPGNN-DSA involves a heterogeneous information network (HIN) and integrates various relevant datasets. The model incorporates a meta-path-based feature learning module to extract high-quality representations of drugs and side effects, leveraging the semantics within meta-paths as obtained from the HIN they built. The prediction module utilizes the learned features to forecast drug-side effect associations, and importantly, the proposed method provides enhanced explainability for the predicted associations. The authors claim that MPGNN-DSA has better capability compared to current approaches to learn the relationships between drugs and side effects. They have validated the effectiveness of MPGNN-DSA. Experimental results position the model as a promising solution for the task of predicting drug-side effect associations.

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3.3. Modeling Changes in Subcellular Localization of Proteins During Drug Treatments

Certain intracellular proteins have commonly been found to be present at specific locations within a cell. Subcellular localization of proteins is a phenomenon which aims to locate specific proteins inside a cell. Langlois *et al.*, in 2008, have defined subcellular localization as a multi-class classification problem in which a protein sequence is studied with regards to its assignment to one of the compartments (as depicted in Figure 4, compartments in a cell can be explained as distinct regions in a cell fractionated from the rest of the cell with the help of a semipermeable membrane; the compartments of a cell include cytosol, mitochondria, Golgi apparatus, lysosomes, nucleus, and so on) in a eukaryotic cell [33, 34]. While subcellular localization is typically used in context of the positioning of proteins in a cell, it is also sometimes used with regards to the locations of genes and other intracellular components and compounds.

The ability to localize a protein in a cell allows us to isolate its possible functional characteristics, which helps in modifying our experimental trajectories accordingly [36]. Protein sorting refers to the process by which newly synthesized proteins are directed to their correct locations within a cell. Protein sorting is an inalienable part of proteostasis, or protein homeostasis, which refers to the intracellular balance between synthesis of new protein molecules and time-bound disposal (protein turnover) of damaged and misfolded protein molecules that cannot be repaired or refolded as a rectificatory measure [37, 38]. Proteostasis helps maintain the health of the proteome. Aberrant protein sorting has been observed in various conditions, including diseases, drug treatments, and environmental stresses.

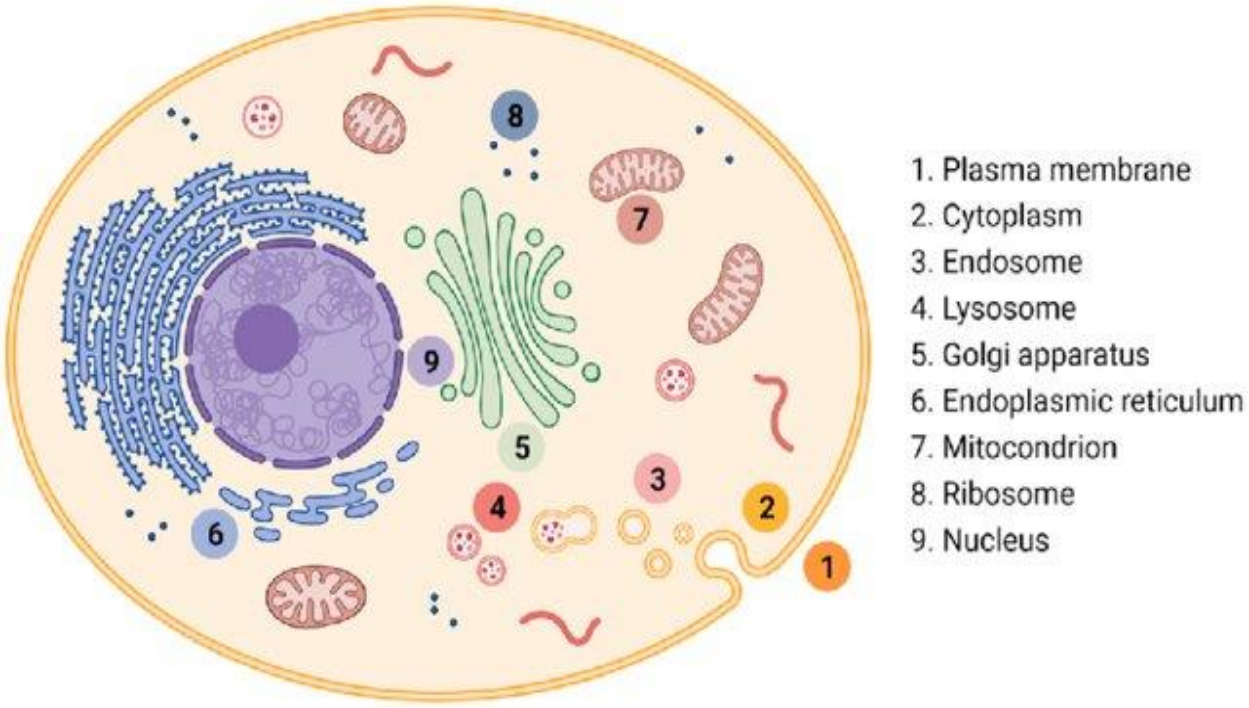

Figure 4 [39]: Some Important Subcellular Compartments (borrowed/adapted from Zhou *et al.*, 2022)

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Proteins are molecular functionaries within a cell that are synthesized through translation. Each protein has a set of specific roles to accomplish, and this set of roles is called its molecular function. Where the proteins are located inside the cell (subcellular localization) is crucial for them to perform their functions correctly, and, unto this, protein sorting must be an error-free procedure. If a protein is fallaciously situated in a compartment of cell not meant for it to be translocated in, it may negatively influence not only the usual function of the protein but also the normal function of the organelle in which it is aberrantly present, with an additional possibility of damaging the function of the organelle where it should be present but from where it is absent due to the aberration. This may lead to the muddling up of an entire biological process, causing cellular stress and even cell death. [38, 40, 41].

Network medicine is a field that studies the interaction between biochemical compounds, such as proteins, microRNAs, or metabolites, with the aim of understanding molecular pathways linked to disease pathogenesis [42]. PPIs come within the ambit of network medicine. In this regard, the local hypothesis becomes important. It states that proteins associated with a specific disease exhibit an increased likelihood of participating in common pathways and interacting with each other within cellular processes. A corollary of the local hypothesis suggests that if proteins involved in the same disease interact, genetic mutations affecting these interacting proteins could disrupt shared pathways and functions, leading to comparable disease phenotypes [43]. This makes the study of PPIs even more significant.

Wang *et al.*, (2023) have proposed a GNN-based computational method, named Protein Localization Alteration by Graph Neural Networks, or PLA-GNN [44]. They have designed it to identify modifications in protein subcellular locations in response to drug treatments. They suggest that traditional experimental methods for detecting mis-localized proteins are expensive and time-consuming.

PLA-GNN focuses on three drugs (TSA, bortezomib, and tacrolimus) and utilizes dynamic protein-protein interaction (PPI) networks. GNNs are applied to aggregate topological information under different conditions in order to allow for systematic reporting of potential protein mis-localization events. According to the authors, PLA-GNN represents the first attempt to computationally identify protein mis-localization events under drug treatment conditions. Their model, PLA-GNN, is validated against a series of existing computational models and literature findings, suggesting its potential in uncovering proteins associated with the pharmacological mechanisms of the drugs. The authors, in the form of future directions, suggest that the method can be extended to study other drugs and conditions.

To build their model, they first obtained PPI records. They used the edge clustering coefficient method to find the density of connections (the level of connectedness) between various vertices' neighbors (represented by proteins in PLA-GNN). The dynamic PPI network they created integrated gene expression profiles and PPIs, and consisted of a three-layered GraphSAGE encoder and a multilayer perceptron decoder. The decoder employed a multi-label loss function, which included a logit function. The authors harnessed GNN algorithms to aggregate high-order topology

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information. Ten-fold cross validation was employed to evaluate the performance of PLA-GNN. The authors claim that few existing studies took into account protein subcellular location alterations in separate cellular states, and that no existing study considered drug treatment states. This made their model unique.

3.4. Predicting Drug Induced Changes in Neuronal Firing Rates

Kim *et al.*, in their 2023 paper, have discussed the utilization of GNNs to study the activity patterns of biological neuronal networks [45]. They employed GNNs to rodent primary neuronal networks obtained through high-density microelectrode arrays (HD-MEAs). The researchers state that HD-MEAs allow for extended recording of extracellular spiking activity, providing insights at both single-neuron and population levels. Using established GNNs, the researchers combined features related to individual neurons and their connectivity from HD-MEA data. The authors initially aimed to predict changes in single-neuron firing rates induced by a pharmacological intervention, specifically Bicuculline, a GABAA receptor antagonist. The researchers had the goal to assess whether features from individual neurons and functional connectivity, extracted under baseline conditions, could predict changes in neuronal activity after perturbation.

To understand the impact of pharmacological perturbation on neuronal activity using advanced electrophysiological and connectivity analyses, the first thing that the authors did was to culture neurons from dissociated embryonic rat hippocampi in vitro, on high-density microelectrode arrays (HD-MEAs), until day 21. The researchers then performed whole-array activity scans to assess neuronal activity. The authors defined four dense electrode configurations per HD-MEA, and recorded electrical neuronal activity across a baseline period, followed by a perturbation with BIC (5μM) and monitoring of responses in activity. Their experiment included spike sorting of HD-MEA data, quality control, and the inference of single-neuron spike trains, extracellular waveform features, and functional connectivity.

The results of their research indicated that the joint representation of node features and functional connectivity, derived from baseline recordings, proved informative in predicting firing rate changes after perturbation [45]. Notably, the GNN model the researchers employed, GraphSAGE, beat other models relying solely on single-neuron features. The researchers validated their findings on two additional HD-MEA datasets, one pertaining to Bicuculline and another pertaining to cultures perturbed with another GABAA receptor antagonist Gabazine. They were able to demonstrate that the GraphSAGE model, that had one convolutional layer using max pooling, exhibited better prediction accuracy than their baseline model, which employed taking the average of the target variables of their training dataset to calculate the target variables of their testing dataset. The study underscores the significance of considering functional connectivity in understanding complex interactions between neurons, showcasing the potential of GNNs in unraveling the dynamics of neuronal networks.

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3.5. Drug Safety

Drug safety, the paramount aspect of pharmacovigilance, encompasses the systematic identification, assessment, understanding, and prevention of adverse effects of drugs or any other drug-related problems. It involves continuous monitoring and analysis of data from diverse sources, such as clinical trials, post-marketing surveillance, and real-world evidence, to ensure the ongoing safety of pharmaceutical products. Adverse Drug Reactions (ADRs), medication errors, and other safety concerns are meticulously evaluated to mitigate risks and enhance patient well-being. Advances in data analytics, artificial intelligence, and machine learning have bolstered drug safety efforts by enabling the efficient detection of potential safety signals, early identification of emerging risks, and the implementation of proactive risk management strategies. Rigorous regulatory frameworks, collaboration among stakeholders, and transparent communication further contribute to maintaining and improving drug safety standards, ensuring the optimal benefit-risk balance for patients worldwide.

Kalla *et al*. (2023) have proposed a novel approach for enhancing adverse drug reaction detection through causal temporal motif graphs [46]. Their framework for pharmacovigilance – the study of drug safety – utilizes a causal temporal motif-driven large language model. This method aims to improve adverse signal detection, which involves identifying potential negative side effects of drugs from various sources like medical reports and online platforms. The article also discusses the entity classification components of the model, including drug tagger, previous health condition tagger, adverse effect tagger, and causality relation tagger.

According to the authors, the challenges in adverse signal detection include the continual reliance on manual data extraction since processing vast amounts of text data to identify relevant information about drugs and their side effects is labor-intensive and prone to errors. The challenges are related to mass adverse effects, especially in the light of the fact that linking a drug to its side effects becomes tricky when numerous reports mention similar adverse events, potentially stemming from different causes, which leads to duplicate records and redundancy. Cold start issues, linked to traditional Named Entity Recognition (NER) approaches struggle with identifying new side effects, especially when they appear isolated without direct references to the drug. The challenges of causality inference in observational data are also acknowledged, as definitively proving causal relationships often requires controlled experiments.

The solution proposed in the research is a Causal Temporal Graph Neural Network (CT-GNN) model, which constructs a dynamic graph where nodes are multitype, representing entities like drugs and adverse effects, and edges represent temporal relationships between entities, potentially indicating causality. As to motif embedding, local linear embedding extracts patterns within the graph using centrality constraints, capturing causal motifs (subgraphs), which are recurring substructures. Motif-based similarity search identifies similar subgraphs, enabling causal relationship inference between drugs and adverse events. They technique of KGE embeds entities and relationships from an external knowledge graph into a low-dimensional space, aiding the CT-GNN in understanding the semantic context of drugs and side effects. The authors affirm that the

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significance of the models is diminished by the minimal loss value of 0.015. They used the causal relationship loss function to calculate loss.

The authors reported a number of benefits of their approach. According to them, causal motifs are able to capture subtle relationships, potentially leading to more accurate identification of true adverse signals. Further, the graph structure is able to handle mass adverse effects. It allows for differentiation between side effects linked to the same drug but arising from different causes. Their approach can also overcome cold start issues. Motif embedding helps uncover new side effects even when they lack explicit connections to the drug in individual reports.

3.6. Drug Target Mechanisms and Drug Discovery

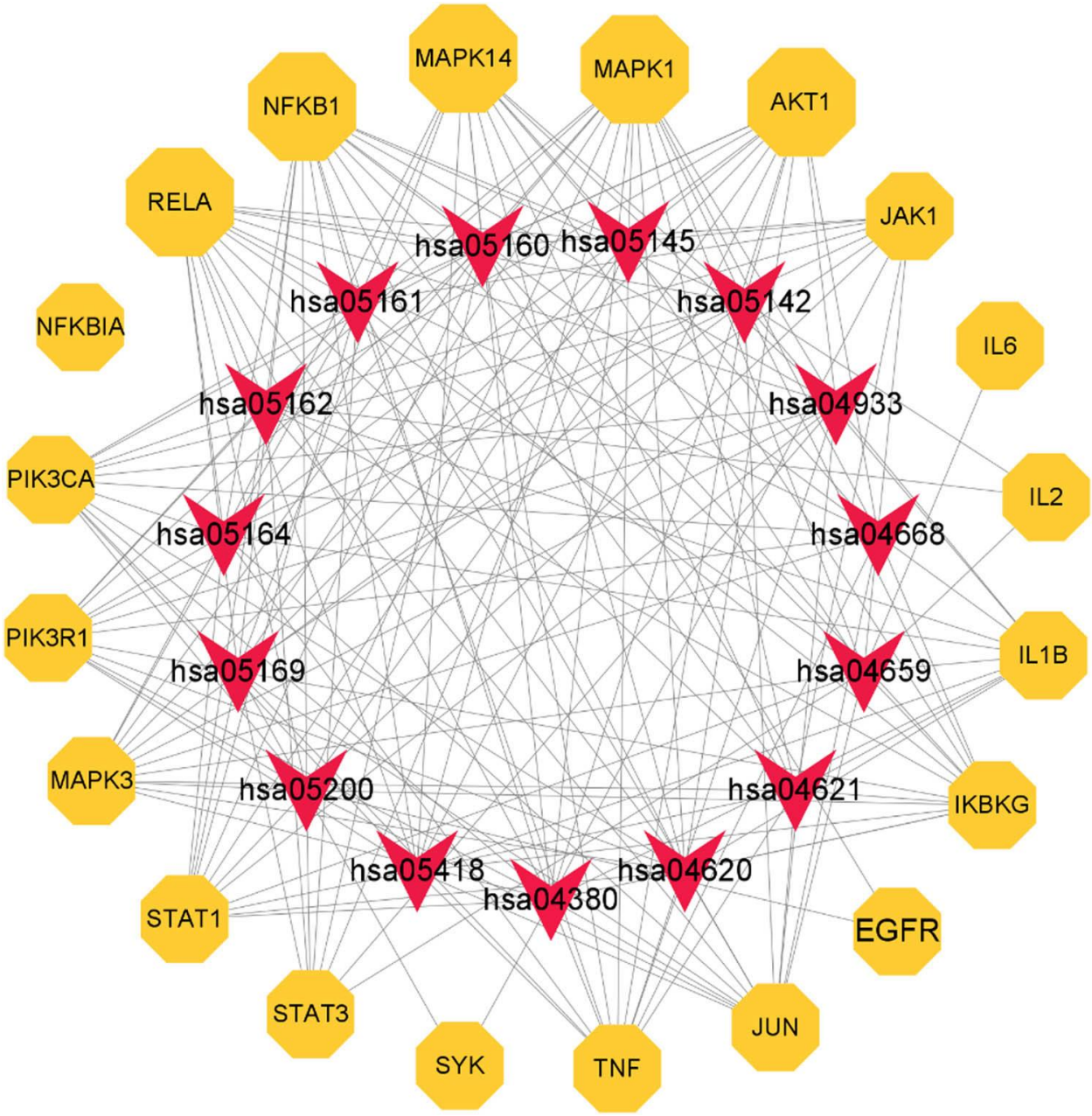

Figure 5 [47]: Integrating molecular docking and network pharmacological approaches to build a key target–pathway network. The yellow octagons are the key targets, and the red V shapes are the pathways. (borrowed/adapted from Peng *et al.*, 2022)

Drug target modeling involves the computational and experimental exploration of potential targets for drug molecules. It plays a crucial role in the early stages of drug discovery and development, aiming to identify and understand the interactions between drugs and their target biomolecules. Molecular docking integrates computational and structural biology approaches to accelerate the drug discovery process. Docking studies contribute to the elucidation of structure-activity relationships (SAR), providing insights into how changes in the chemical structure of a molecule may impact its interactions with a target protein. Docking aids in the discovery of new compounds that may have a therapeutic bearing by way of in silico detection of ligand-target interactions at a molecular level without the inferred knowledge of the molecular structure of the rest of the target modulators [48].

Network pharmacology (NP) is a key aspect of systems pharmacology, and in this manner systems biology, which involves the melding of computational and biological approaches to achieve a better grasp on biomedical issues faced by humans and their solutions. Network pharmacology represents a novel discipline that seeks to comprehensively understand the actions and interactions of drugs with multiple targets within biological systems. This field utilizes computational methodologies to systematically document and analyze the molecular interactions of a drug molecule within the complex environment of a living cell [49]. The fundamental goal of network pharmacology is to provide a holistic view of how drugs engage with diverse molecular components in biological networks, moving beyond the traditional focus on individual drug-target interactions. Therefore, it chooses holism over reductionism.

Network pharmacology has a multitarget perspective. Unlike traditional pharmacology, which often concentrates on the interaction between a drug and a single target, network pharmacology acknowledges the intricate web of interactions involving multiple targets. Drugs are recognized as having the potential to modulate various components within a biological network simultaneously. This strand of network pharmacology is termed polypharmacology [50].

Network pharmacology involves computational approaches, leveraging the power of virtual tools and algorithms to process vast amounts of biochemical data. This includes information about molecular interactions, signaling pathways, and the dynamic responses of biological systems to drug interventions. By considering the broader network context, network pharmacology aims to uncover the holistic effects of drugs, including potential off-target effects, side effects, and the modulation of complex biological pathways.

Drug discovery is a process which involves identification of compounds of therapeutic interest, especially in relation to specific pathologies. The complication of the process increases its costs, monetary as well as temporal. The advancement in multi-omic approaches has led to the knowledge that diseases involve complex genomic, transcriptomic, proteomic, and interactomic basis, along with potential network pharmacology-based therapeutic modalities [51].

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Zhang *et al.*, in 2023, have introduced DrugAI, a novel multi-view deep learning model for accurately predicting whether a drug activates or inhibits a specific target [52]. This model aids in molecular docking, providing valuable insights into network pharmacology information associated with diseases. Therefore, DrugAI contributes to streamlining and enhancing the drug discovery process. The fact that understanding drug-target (DT) mechanisms is crucial for drug development formed the foundation of their motivation. They were also motivated to develop an approach to accurately predict activating and inhibiting relationships between drugs and their targets, a task which, according to the authors, remains challenging due to its complex mechanisms and scarcity of available data.

DrugAI framework is trained on a curated benchmark dataset of DT activating/inhibiting mechanisms. The model combines four modules, a GNN module which extracts neural features from drug molecular graphs at micro-level, a CNN module which captures features from target amino acid sequences, also at micro-level, another GNN module with network embeddings to learn low-dimensional representations of drugs and targets in the drug-target network at macro-level, and a DNN which predicts activating/inhibiting relationships. In the prediction module of DrugAI, the researchers programmed a multi-layered neural network which inputted the concatenated features of drugs and targets from multi-view information, while producing, as output, the activating/inhibiting mechanisms as existing among drugs and their targets. Their prediction output was binary and therefore they utilized binary cross entropy as the loss function which was minimized to finetune the parameters.

According to the authors, multi-view learning leverages both micro (structure-based) and macro (network-based) information for comprehensive understanding, while network pharmacology utilizes network insights to enhance model accuracy and generalizability, fostering a deeper understanding of drug action. They showed that DrugAI outperformed a number of state-of-the-art methods and delivered superior accuracy in predicting DT mechanisms. DrugAI is also robust and generalizable, performing well on both balanced and unbalanced datasets. The authors add that the predictions of DrugAI are reliable, and are validated through bioassays, PubChem data and scientific literature. The authors suggest that a limited 3D target information remained a hurdle, and that further exploration of network pharmacology integration was needed for improving drug target mechanisms.

3.6.1. Drug Target Modeling in KIRC

Liu *et al.*, in 2023, published a paper about drug target modeling and predicting patient risk in Kidney Clear Cell Carcinoma (KIRC), or Renal Clear Cell Carcinoma, the most common form of renal cancer [53]. KIRC comprises 80 percent of all carcinomas of the kidney. It is known as the Internist's Tumor because its paraneoplastic indications imitate other malignant neoplasms, benign tumors, and other conditions [54]. The primary challenge addressed by Liu *et al.* was poor prognosis and limited specificity of existing prognostic markers in KIRC. They stated that KIRC prognosis is mainly reliant on imaging methods. Their study elaborated the concept of cuproptosis, a state-of-the-art cell death mechanism. Cuproptosis was found by them to be a potential biomarker for predicting disease outcomes in KIRC.

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Their primary objectives were threefold: they aimed to identify cuproptosis-related genes associated with KIRC prognosis; they intended to build a DNN model for predicting patient risk; and they aimed to develop a personalized nomogram model for predicting patient survival. As to the sources of their data, they relied on The Cancer Genome Atlas (TCGA), International Cancer Genome Consortium (ICGC), and DrugBank databases. They screened differentially expressed genes (DEGs) using TCGA data. They generated a DNN-based risk prediction model and validated it using ICGC data. They then classified patients into high- and low-risk groups relying on their prognostic model. KIRC-sensitive drugs were then screened, and, using the information obtained, a GNN was trained to predict the targets for the screened drugs. GraphSAGE was utilized by the researchers to be finetuned for their task. They programmed their algorithm using the TensorFlow framework, utilizing a Tanh activation function, a stochastic gradient descent optimizer, a hybrid L1 and L2 regularization method, and a dropout method for preempting overfitting.

The research identified 10 cuproptosis-related genes that constituted a prognostic model. TCGA dataset was used for training and ICGC dataset was used for validation. The model's predictive performance was evaluated Area Under the Curve (AUC), which was found to be 0.739 on the training set and 0.707 on the validation set. The main outcome was the identification of four drugs to which KIRC was found to be most sensitive. They found that GraphSAGE outperformed other methods, achieving an average accuracy of 0.817 ± 0.013. In this way, the study integrated molecular insights and cutting-edge computational techniques like GraphSAGE offered valuable insights for personalized treatment strategies in KIRC.

3.6.2. Drug Discovery with Self-Training and Self-Supervised Learning

Drug discovery is the panacea for safer and more effective drugs. However, a major hurdle in drug discovery lies in the scarcity of high-quality, balanced labeled data for training robust and generalizable supervised deep learning models. Liu *et al.*, in their 2022 article, have introduced a novel approach, PLANS-GINFP, that leverages both self-training and self-supervised learning to overcome this challenge and improve the predictive modeling in quantitative structure-activity relationship (QSAR) [55]. The upside of their model lies in its flexibility, that is, in the fact that it is agnostic. The approach is not tied to a specific deep learning architecture, making it readily applicable to diverse tasks and neural network models.

Their first framework, Graph-Isomorphism Network Fingerprint (GINFP) utilizes a GNN model called GIN (Graph Isomorphism Network) to capture the intricate substructures within molecular graphs, where nodes represent atoms and edges represent bonds. This is their self-supervised learning approach, capable of extracting valuable information from unlabeled data, thereby enriching the representations used for prediction. The researchers have used binary cross-entropy loss which was minimized to calculate the gradients. They ended the pretraining when the validation loss converged. They stated that the pre-trained GIN was used to generate embeddings (which they call the GIN Fingerprints or GINFPs) for the CYP450 dataset.

Their second framework Partially Labeled Noisy Student (PLANS) embodies the dynamic of a diligent student eager to learn from a teacher with limited knowledge. PLANS-GINFP combines

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two models, the “teacher” model (GINFP), and the “student” model (PLANS). The "teacher" model, trained on a small amount of labeled data, guides the "student" model through unlabeled data, gradually refining its understanding. This iterative process ultimately leads to a student model surpassing the teacher's performance. The “student” model was trained using the categorical cross entropy loss function. In the PLANS-GINFP workflow, unlabeled data feeds the GINFP module, enriching the chemical representations. These enhanced representations are then used by the PLANS framework for iterative self-training, culminating in an accurate prediction model.

Among the capabilities of PLANS-GIFP lies the prediction of Cytochrome P450 (CYP450) binding activity. CYP450 enzymes play a vital role in drug metabolism. Accurately predicting their interactions with potential drugs is crucial for optimizing drug development. PLANS-GINFP significantly outperforms other methods in this task. It is also capable of assessing chemical toxicity. Identifying potentially toxic drug candidates early in the development process can save lives and resources. PLANS-GINFP again shines, achieving impressive results on the Tox21 dataset containing diverse toxicity pathways.

3.6.3. SARS-CoV-2 Drug Discovery using GNNs

The COVID-19 pandemic, caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), had driven intensive research for effective drug discovery. Mswahili *et al.*, in 2022, conducted a study which explores the potential of graph neural networks (GNNs) in predicting the in vitro inhibitory bioactivity or pharmacological concentration of chemical compounds against SARS-CoV-2 [56].

The data acquisition was accomplished as 375 chemical compounds which were sourced from the public ChEMBL database. The data was extracted from SMILES (Simplified Molecular Input Line-Entry System) using RDKit software, including molecular weight (MW) data, octanol-water partition coefficient (LogP) data, details about the number of hydrogen bond donors (NumHDonors), details about the number of hydrogen bond acceptors (NumHAcceptors), and half-maximal inhibitory concentration (pIC50) information. To construct the graphs, they let the vertices represent the compounds, and edges were based on shared bioactivity against SARS-CoV-2. They used Lipinski’s descriptors as features of the compounds.

Two GNN Models were constructed, a Simple Graph Convolution (SGC) model and a GCN. The SGC model involved a k-step feature propagation process for aggregating information across neighboring nodes, while the GCN model learnt node embeddings while considering neighboring nodes and non-linearity introduced into it through specific activation functions. The researchers trained the models to classify compounds as active or inactive against SARS-CoV-2. Both their models were trained for binary classification using 20 training epochs. A test accuracy of 0.76 each was achieved for both the SGC and GCN models, and this demonstrated a promising predictive performance. The authors believe that the test accuracy can be further improved with more and better-quality data.

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The authors showed that GNNs can effectively leverage the inherent relationships between chemical compounds based on their graph structure and bioactivity profiles. They have presented a proof-of-concept for GNN-based drug discovery against SARS-CoV-2, encouraging further research with larger datasets to boost model accuracy and generalizability, with advanced GNN architectures which would incorporate domain-specific knowledge for improved prediction, and with molecular symmetry analysis to integrate multiple graph structure analysis techniques to develop the capability to delve deeper into chemical properties and interactions, extracting more informed results.

3.6.4. Drug Discovery for Multiple Myeloma

MM is a challenging disease with high heterogeneity and treatment resistance, and finding effective therapeutic modalities for the disease requires an arduous and high-priced process. He *et al.*, in their 2022 article, have proposed a new virtual screening process to identify potential inhibitors of EZH2, which is an effective target for treating multiple myeloma (MM) [57]. Their article showcases a promising virtual screening approach that holds promise for developing personalized and targeted therapies for MM.

The researchers have adopted a three-step virtual screening approach combining network pharmacology, machine learning, and deep learning using GNNs. Through network pharmacology, they have identified related pathways and targets beyond EZH2. In the realm of machine learning, they have used the QSAR (Quantitative Structure-Activity Relationship) model to predict the activity of candidate small molecules based on their structural properties. Finally, their deep learning model was constructed with an aim to predict drug-target interactions while considering both molecule and protein structures.

They utilized the TCM (Traditional Chinese Medicine) Database to find potential drug candidates from traditional Chinese medicine. They further employed Lipinski's Rule to filter candidate drugs based on drug-likeness properties. They used docking simulations in order to assess candidate binding affinity to EZH2. Support Vector Machines (SVM) and Random Forests were utilized to build a QSAR model for activity prediction. They built the DeepDTA model, which is a CNN model and accepts SMILES sequence information of drugs and the amino acid sequence information of proteins as inputs to predict the binding affinity of protein target interactions. Finding that the CNN model (DeepDTA) could not model protein sequences correctly, the authors propose the WideDTA model which also inputs and processes protein sequences and SMILES strings. The authors used the GraphDTA (GNN) and DeepPurpose (DNN) models for comprehensive compound-protein analysis.

The authors were able to identify potential EZH2 inhibitors from Mulberry leaf and Ganoderma lucidum. They demonstrated a promising virtual screening approach for MM drug discovery. The potential benefits of their model include the fact that it shows promise to accelerate MM drug development and reduce costs more efficiently compared to traditional methods. Their approach also intends to provide a personalized approach to MM treatment targeting individual patient characteristics. Further validation of identified candidate drugs through in vitro and in vivo

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experiments is needed. What is also needed is the investigation of synergistic effects of combining multiple predicted drugs. Finally, the approach may benefit from refining the virtual screening models, leading to a broader applicability in drug discovery.

3.6.5. Virtual Drug Screening

Virtual screening is a computational technique used in drug discovery to identify potential drug candidates from large databases of chemical compounds. Instead of physically testing each compound in a laboratory, virtual screening relies on computer algorithms and simulations to predict which compounds are most likely to interact with a target biomolecule, such as a protein associated with a particular disease. Drug discovery is a broader and more complex process that encompasses various stages, including target identification, lead discovery, lead optimization, preclinical development, clinical trials, and ultimately regulatory approval. Virtual screening is a specific computational technique within the drug discovery process.

Alves *et al.*, in 2022, published a review in which they discuss the challenges in drug discovery, where only a small fraction of initially researched drugs successfully enter the commercial market [58]. The article highlights the historical use of mathematical modeling in pharmacology and chemistry, with a recent surge in computational power, GPU, and TPU advancements, along with the availability of cloud computing platforms for virtual screening. The chemoinformatic field's evolution, combining knowledge from various disciplines, is also acknowledged.

In this context, the authors contend that despite the utilization of virtual screening (VS) based on algorithms applying physical and chemical principles, the expected improvement in market-approved drugs has not been accomplished. They assert that the focus, therefore, must shift to the potential of GNNs, which they call a recent subtype of deep learning. They recommend that GNNs would enhance VS outcomes, particularly in the context of natural products. The authors have explored the advantages of GNN, including its learnable algorithm and potential to revolutionize drug discovery. Their article emphasizes the need to address obstacles related to spatial coordinates, datasets, and some other factors.

4. Additional Articles Reviewed

In addition to those articles which have already been delineated, we analyzed three other articles which are outlined in the following paragraphs.

Yang *et al.*, in 2022, introduced in their study a substructure-aware graph neural network, termed SA-DDI, for predicting DDIs [59]. SA-DDI incorporates a substructure attention mechanism, designed to capture irregular size- and shape-adaptive substructures in molecules. Additionally, a substructure–substructure interaction module (SSIM) is introduced to model substructure interactions by highlighting crucial substructures and de-emphasizing minor ones.

He *et al.*, attempted to address the challenge of predicting DDIs in drug research and, in 2022, proposed a Multi-Type Feature Fusion Graph Neural Network (MFFGNN) model for enhanced DDI prediction [60]. MFFGNN effectively integrates topological information from molecular graphs, drug interaction information, and local chemical context in SMILES sequences. The model employs a feature extraction module to capture both global and local features of the molecular

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graph, addressing the over-smoothing problem with a gating mechanism in the multi-type feature fusion module.

Zhi *et al.,* in their 2021 study, have focused on Small Cell Lung Cancer (SCLC) while identifying dihydroorotate dehydrogenase (DHODH) as a therapeutic target for this aggressive tumor subtype [61]. Network pharmacology analysis and virtual screening were employed to identify related proteins and potential candidates with high docking capacity to multiple targets. The research introduces a novel concept of multi-Graph Neural Networks (multi-GNNs) and develops three models (GIAN, GIAT, and SGCA) that exhibit satisfactory results on a dataset of 532 molecules, with R^2 values exceeding 0.92 on the training set and over 0.8 on the test set. Comparative analysis with machine learning algorithms, including random forest (RF) and support vector regression (SVR), indicates that multi-GNNs outperform in terms of modeling drug effect and precision.

5. Conclusion

Big data refers to extremely large and complex datasets that cannot be easily managed, processed, or analyzed with traditional data processing tools or methods. Big data analytics facilitate the mining of extensive datasets, which the discipline of pharmacology is often found to be replete with. Pharmacology and big data intersect at various critical points within the drug development and healthcare landscape. In drug discovery, big data analytics help in identifying potential drug targets and optimizing lead compounds using machine learning models. Clinical trials benefit from big data by expediting patient recruitment and leveraging real-world evidence to assess drug effectiveness and safety.

Pharmacovigilance efforts are enhanced through the monitoring and analysis of adverse events using sophisticated algorithms, while personalized medicine benefits from genomics data for tailoring treatment plans. Big data also plays a crucial role in population health management, predictive analytics, supply chain optimization, drug repurposing, and regulatory compliance. The large, intricate pharmacology datasets that are typically characterized by their unusual volume, velocity, variety, and, increasingly, veracity, often require to be visualized as networks to be more easily understood. In this light, graph neural networks, which are patterned on graph-structured data, have found patent usage in modeling pharmacological data. Graph neural networks, therefore, have a large variety of potential applications in pharmacology.

However, our research proves that, so far, in pharmacology, graph neural networks have been found to be mostly utilized for understanding and modeling drug-drug interactions, drug side effects, and drug targets and drug discovery. The bulk (thirteen) of the publications (a total of fifteen) that we reviewed are concentrated in these realms. We embarked on the task of completing this review with the hypothesis that graph neural networks have a pervasive presence wherever computational approaches have been applied to pharmacological data. The vast majority of applications of graph neural networks in pharmacology was encountered during and after the year 2022. While graph neural networks have been in existence since the year 2009, they have gained

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popularity only in the last six or seven years. Our research shows that in pharmacology, their usage became popular even more recently.

There is a lot of scope of graph neural networks in pharmacology. We hope that in the near future, many of the complexities of pharmacological data will be simplified by graph neural networks and many of the problems in pharmacology and pharmacotherapeutics will also be resolved by them. Drug discovery is the one area that shows the highest amount of promise with graph neural networks in action. Combined with advances in multi-omic research for identifying drug targets [62], this provides us hope that many of the diseases that have no cure or limited scope of treatment as of now, including progressive diseases, autoimmune disorders, and malignant neoplasms, will have effective pharmacotherapeutic options in the coming years thanks to graph neural networks, paving way for a healthier humanity.

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Declaration of Conflict of Interest

The author(s) declare(s) no conflict of interest.

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References

1. Yoon, M., (2022). [CMU 10-707 Introduction to Deep Learning] Lecture 12. Introduction to Graph Neural Network [Video]. YouTube. https://www.youtube.com/watch?v=3WXhnQr4ADQ
2. Scarselli, F., Gori, M., Tsoi, A. C., Hagenbuchner, M., & Monfardini, G. (2009). The Graph Neural Network Model. IEEE Transactions on Neural Networks, 20(1), 61–80. https://doi.org/10.1109/tnn.2008.2005605
3. Danel, T., Spurek, P., Tabor, J., Śmieja, M., Struski, Ł., Słowik, A., & Maziarka, Ł. (2020). Spatial Graph Convolutional Networks. ArXiv:1909.05310 [Cs, Stat]. Retrieved from https://arxiv.org/abs/1909.05310
4. Verma, S., & Zhang, Z.-L. (2018). Graph Capsule Convolutional Neural Networks. ArXiv:1805.08090 [Cs, Stat]. Retrieved from https://arxiv.org/abs/1805.08090
5. Hamilton, W. L., Ying, R., & Leskovec, J. (2018). Inductive Representation Learning on Large Graphs. ArXiv:1706.02216 [Cs, Stat]. Retrieved from https://arxiv.org/abs/1706.02216
6. Xu, K., Hu, W., Leskovec, J., & Jegelka, S. (2019). How Powerful are Graph Neural Networks? ArXiv:1810.00826 [Cs, Stat]. Retrieved from https://arxiv.org/abs/1810.00826

Posted to TechRxiv on 27 Feb 2024 | CC-BY-NC-SA 4 | https://doi.org/10.36227/techrxiv.170906927.71541956/v1

7. Defferrard, M., Bresson, X., & Vandergheynst, P. (2017). Convolutional Neural Networks on Graphs with Fast Localized Spectral Filtering. ArXiv:1606.09375 [Cs, Stat]. Retrieved from https://arxiv.org/abs/1606.09375
8. Veličković, P., Cucurull, G., Casanova, A., Romero, A., Liò, P., & Bengio, Y. (2018). Graph Attention Networks. ArXiv:1710.10903 [Cs, Stat]. Retrieved from https://arxiv.org/abs/1710.10903
9. Liao, R., Li, Y., Song, Y., Wang, S., Nash, C., Hamilton, W. L., Duvenaud, D., Urtasun, R., & Zemel, R. S. (2019, October 2). Efficient Graph Generation with Graph Recurrent Attention Networks. ArXiv.org. https://arxiv.org/abs/1910.00760
10. Kipf, T. N., & Welling, M. (2016). Variational Graph Auto-Encoders. ArXiv:1611.07308 [Cs, Stat]. Retrieved from https://arxiv.org/abs/1611.07308
11. Liang, X., Shen, X., Feng, J., Lin, L., & Yan, S. (2016, March 23). Semantic Object Parsing with Graph LSTM. Retrieved from arXiv.org website: https://arxiv.org/abs/1603.07063
12. Liu, Z., & Zhou, J. (2020). Graph Recurrent Networks. Springer EBooks, 33–37. https://doi.org/10.1007/978-3-031-01587-8_6
13. Cho, K., van Merrienboer, B., Bahdanau, D., & Bengio, Y. (2014). On the Properties of Neural Machine Translation: Encoder-Decoder Approaches. ArXiv:1409.1259 [Cs, Stat]. Retrieved from https://arxiv.org/abs/1409.1259
14. Li, Y., Tarlow, D., Brockschmidt, M., & Zemel, R. (2017). Gated Graph Sequence Neural Networks. ArXiv:1511.05493 [Cs, Stat]. Retrieved from https://arxiv.org/abs/1511.05493 Ruiz, L., Gama, F., & Ribeiro, A. (2020, February 3).
15. Gated Graph Recurrent Neural Networks. Retrieved in 2024, from arXiv.org website: https://arxiv.org/abs/2002.01038
16. Zeng, H., Zhou, H., Srivastava, A., Kannan, R., & Prasanna, V. (2020). GraphSAINT: Graph Sampling Based Inductive Learning Method. ArXiv:1907.04931 [Cs, Stat]. Retrieved from https://arxiv.org/abs/1907.04931
17. Niu, J., Straubinger, R. M., & Mager, D. E. (2019). Pharmacodynamic Drug–Drug Interactions. Clinical Pharmacology & Therapeutics, 105(6), 1395–1406. https://doi.org/10.1002/cpt.1434
18. Nigam, S. K. (2014). What do drug transporters really do? Nature Reviews Drug Discovery, 14(1), 29–44. https://doi.org/10.1038/nrd4461
19. Zhao, Q., Chen, Y., Huang, W., Zhou, H., & Zhang, W. (2023). Drug-microbiota interactions: an emerging priority for precision medicine. Signal Transduction and Targeted Therapy, 8(1), 1–27. https://doi.org/10.1038/s41392-023-01619-w
20. Palleria, C., Di Paolo, A., Giofrè, C., Caglioti, C., Leuzzi, G., Siniscalchi, A., De Sarro, G., & Gallelli, L. (2013). Pharmacokinetic drug-drug interaction and their implication in clinical management. Journal of Research in Medical Sciences: The Official Journal of Isfahan University of Medical Sciences, 18(7), 601–610. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3897029/
21. Zhao, M., Ma, J., Li, M., Zhang, Y., Jiang, B., Zhao, X., Huai, C., Shen, L., Zhang, N., He, L., & Qin, S. (2021). Cytochrome P450 Enzymes and Drug Metabolism in Humans. International Journal of Molecular Sciences, 22(23), 12808. https://doi.org/10.3390/ijms222312808

Posted to TechRxiv on 27 Feb 2024 | CC-BY-NC-SA 4 | https://doi.org/10.36227/techrxiv.170906927.71541956/v1

22. Roberts, A. G., & Gibbs, M. E. (2018). Mechanisms and the clinical relevance of complex drug–drug interactions. Clinical Pharmacology: Advances and Applications, 10, 123–134. https://doi.org/10.2147/CPAA.S146115
23. Gan, Y., Liu, W., Xu, G., Yan, C., & Zou, G. (2023). DMFDDI: Deep Multimodal Fusion for Drug–Drug Interaction Prediction. Briefings in Bioinformatics, 24(6). https://doi.org/10.1093/bib/bbad397
24. Han, H., Zhang, W., Sun, X., & Lu, W. (2023, June). Multi-view Feature Fusion Based on Self-attention Mechanism for Drug-drug Interaction Prediction | IEEE Conference Publication | IEEE Xplore. Retrieved January 27, 2024, from ieeexplore.ieee.org website: https://ieeexplore.ieee.org/document/10191890
25. Masnoon, N., Shakib, S., Kalisch-Ellett, L., & Caughey, G. E. (2017). What is polypharmacy? A systematic review of definitions. BMC Geriatrics, 17(1), 230. https://doi.org/10.1186/s12877-017-0621-2
26. Sychev, D. A., Otdelenov, V. A., Krasnova, N. M., & Ilyina, E. S. (2016). Polypragmasy: A clinical pharmacologist's view. Terapevticheskii Arkhiv, 88(12), 94–102. https://doi.org/10.17116/terarkh2016881294-102
27. Shah, B. M., & Hajjar, E. R. (2012). Polypharmacy, Adverse Drug Reactions, and Geriatric Syndromes. Clinics in Geriatric Medicine, 28(2), 173–186. https://doi.org/10.1016/j.cger.2012.01.002
28. Queneau, P. (2006). [Pitfalls of polypharmacy, particularly in the elderly]. Bulletin et Memoires de l'Academie Royale de Medecine de Belgique, 161(6), 408–421; discussion 422-424. Retrieved from https://pubmed.ncbi.nlm.nih.gov/17288274/
29. Tulner, L. R., Kuper, I. M. J. A., Frankfort, S. V., van Campen, J. P. C. M., Koks, C. H. W., Brandjes, D. P. M., & Beijnen, J. H. (2009). Discrepancies in reported drug use in geriatric outpatients: Relevance to adverse events and drug-drug interactions. The American Journal of Geriatric Pharmacotherapy, 7(2), 93–104. https://doi.org/10.1016/j.amjopharm.2009.04.006
30. Zitnik, M., Agrawal, M., & Leskovec, J. (2018). Modeling polypharmacy side effects with graph convolutional networks. Bioinformatics, 34(13), i457–i466. https://doi.org/10.1093/bioinformatics/bty294
31. Plewczyński, D., & Ginalski, K. (2009). The interactome: Predicting the protein-protein interactions in cells. Cellular and Molecular Biology Letters, 14(1), 1–22. https://doi.org/10.2478/s11658-008-0024-7
32. Zhao, W., Yao, W., Jiang, X., He, T., Shi, C., & Hu, X. (2023). An Explainable Framework for Predicting Drug-Side Effect Associations via Meta-Path-Based Feature Learning in Heterogeneous Information Network. IEEE/ACM Transactions on Computational Biology and Bioinformatics, 20(6), 3635–3647. https://doi.org/10.1109/TCBB.2023.3308094
33. Alberts, B., Johnson, A., Lewis, J., Raff, M., Roberts, K., & Walter, P. (2010). The Compartmentalization of Cells. Retrieved from Nih.gov website: https://www.ncbi.nlm.nih.gov/books/NBK26907/
34. Langlois, R. E., & Lu, H. (2008, January 1). Chapter 3 - Machine Learning for Protein Structure and Function Prediction (R. A. Wheeler & D. C. Spellmeyer, Eds.). Retrieved January 27, 2024, from ScienceDirect website: https://www.sciencedirect.com/science/article/pii/S1574140008000030

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35. Eisenhaber, F., & Bork, P. (1998). Wanted: subcellular localization of proteins based on sequence. Trends in Cell Biology, 8(4), 169–170. https://doi.org/10.1016/S0962-8924(98)01226-4
36. Di Domenico, F., & Lanzillotta, C. (2022, January 1). Chapter Two - The disturbance of protein synthesis/degradation homeostasis is a common trait of age-related neurodegenerative disorders (R. Donev, Ed.). Retrieved from ScienceDirect website: https://www.sciencedirect.com/science/article/abs/pii/S1876162322000505
37. Yousefi, R., Jevdokimenko, K., Kluever, V., Pacheu-Grau, D., & Fornasiero, E. F. (2021). Influence of Subcellular Localization and Functional State on Protein Turnover. Cells, 10(7), 1747–1747. https://doi.org/10.3390/cells10071747
38. Mellman, I., & Nelson, W. J. (2008). Coordinated protein sorting, targeting and distribution in polarized cells. Nature Reviews Molecular Cell Biology, 9(11), 833–845. https://doi.org/10.1038/nrm2525
39. Zhou, Z., Maxeiner, K., David, Y. W. N., & Weil, T. (2022). Polymer Chemistry in Living Cells. Accounts of Chemical Research, 55(20), 2998–3009. https://doi.org/10.1021/acs.accounts.2c00420
40. Schmidt, V., & Willnow, T. E. (2016). Protein sorting gone wrong – VPS10P domain receptors in cardiovascular and metabolic diseases. Atherosclerosis, 245, 194–199. https://doi.org/10.1016/j.atherosclerosis.2015.11.027
41. Guo, Y., Sirkis, D. W., & Schekman, R. (2014). Protein Sorting at the trans-Golgi Network. Annual Review of Cell and Developmental Biology, 30(1), 169–206. https://doi.org/10.1146/annurev-cellbio-100913-013012
42. Maron, B. A., Altucci, L., Balligand, J.-L., Baumbach, J., Ferdinandy, P., Filetti, S., Parini, P., Petrillo, E., Silverman, E. K., Barabási, A.-L., & Loscalzo, J. (2020). A global network for network medicine. Npj Systems Biology and Applications, 6(1), 1–3. https://doi.org/10.1038/s41540-020-00143-9
43. Barabási, A.-L., Gulbahce, N., & Loscalzo, J. (2011). Network medicine: a network-based approach to human disease. Nature Reviews. Genetics, 12(1), 56–68. https://doi.org/10.1038/nrg2918
44. Wang, R.-H., Luo, T., Zhang, H.-L., & Du, P.-F. (2023). PLA-GNN: Computational Inference of Protein Subcellular Location Alterations Under Drug Treatments With Deep Graph Neural Networks. Computers in Biology and Medicine, 157, 106775. https://doi.org/10.1016/j.compbiomed.2023.106775
45. Kim, T.-H., Chen, D., Hornauer, P., Emmenegger, V., Bartram, J., Ronchi, S., Hierlemann, A., Schröter, M., & Roqueiro, D. (2023). Predicting in vitro single-neuron firing rates upon pharmacological perturbation using Graph Neural Networks. Frontiers in Neuroinformatics, 16. https://doi.org/10.3389/fninf.2022.1032538
46. Kalla, A., Mukhopadhyay, S., Ralte, Z., & Kar, I. (2023). Exploring The Impact of Motif-Driven Causal Temporal Analysis Using Graph Neural Network in Improving Large Language Model Performance for Pharmacovigilance. IEEE Conference Proceedings, 2023(ICACCS), 1769–1776. doi: 10.1109/ICACCS57279.2023.10112876.
47. Peng, J., Zhang, K., Wang, L., Peng, F., Zhang, C., Long, K., Chen, J., Zhou, X., Gao, P. & Fan, G. (2022). Integrating network pharmacology and molecular docking to explore the

Posted to TechRxiv on 27 Feb 2024 | CC-BY-NC-SA 4 | https://doi.org/10.36227/techrxiv.170906927.71541956/v1

potential mechanism of Xinguan No. 3 in the treatment of COVID-19. Open Chemistry, 20(1), 570-582. https://doi.org/10.1515/chem-2022-0178
48. Pinzi, L., & Rastelli, G. (2019). Molecular Docking: Shifting Paradigms in Drug Discovery. International Journal of Molecular Sciences, 20(18), 4331. https://doi.org/10.3390/ijms20184331
49. Chandran, U., Mehendale, N., Patil, S., Chaguturu, R., & Patwardhan, B. (2017). Network Pharmacology. Innovative Approaches in Drug Discovery, 127–164. https://doi.org/10.1016/B978-0-12-801814-9.00005-2
50. Kabir, A., & Muth, A. (2022). Polypharmacology: The science of multi-targeting molecules. Pharmacological Research, 176, 106055. https://doi.org/10.1016/j.phrs.2021.106055
51. Boran, A. D. W., & Iyengar, R. (2010). Systems approaches to polypharmacology and drug discovery. Current Opinion in Drug Discovery & Development, 13(3), 297–309. Retrieved from https://pubmed.ncbi.nlm.nih.gov/20443163/
52. Zhang, S., Yang, K., Liu, Z., Lai, X., Yang, Z., Zeng, J., & Li, S. (2023). DrugAI: a multi-view deep learning model for predicting drug-target activating/inhibiting mechanisms. Briefings in Bioinformatics, 24(1), bbac526. https://doi.org/10.1093/bib/bbac526
53. Liu, Y., Shao, Y., Hao, Z., Lei, X., Liang, P., Chang, Q., & Wang, X. (2023). Cuproptosis gene-related, neural network-based prognosis prediction and drug-target prediction for KIRC. Cancer Medicine. https://doi.org/10.1002/cam4.6763
54. Arora, R. D., & Limaiem, F. (2022). Renal Clear Cell Cancer. Retrieved from PubMed website: https://www.ncbi.nlm.nih.gov/books/NBK563230/
55. Liu, Y., Lim, H., & Xie, L. (2022). Exploration of Chemical Space with Partial Labeled Noisy Student Self-Training and Self-Supervised Graph Embedding. BMC Bioinformatics, 23(S3). https://doi.org/10.1186/s12859-022-04681-3
56. Mswahili, M. E., Hwang, J., Jeong, Y.-S., & Kim, Y. (2022). Graph Neural Network Models for Chemical Compound Activeness Prediction For COVID-19 Drugs Discovery using Lipinski's Descriptors | IEEE Conference Publication | IEEE Xplore. Ieeexplore.ieee.org. https://ieeexplore.ieee.org/stamp/stamp.jsp?tp=&arnumber=10123676
57. He, H., Chen, G., & Chen, C. Y.-C. (2022). Machine Learning and Graph Neural Network for Finding Potential Drugs Related to Multiple Myeloma. New Journal of Chemistry, 46(11), 5188–5200. https://doi.org/10.1039/D1NJ04935F
58. Alves, L. A., Ferreira, N. C. da S., Maricato, V., Alberto, A. V. P., Dias, E. A., & Aguiar, J. (2022). Graph Neural Networks as a Potential Tool in Improving Virtual Screening Programs. Frontiers in Chemistry, 9. https://doi.org/10.3389/fchem.2021.787194
59. Yang, Z., Zhong, W., Lv, Q., & Chen, C. Y.-C. (2022). Learning Size-Adaptive Molecular Substructures for Explainable Drug–Drug Interaction Prediction by Substructure-Aware Graph Neural Network. Chemical Science, 13(29), 8693–8703. https://doi.org/10.1039/d2sc02023h
60. He, C., Liu, Y., Li, H., Zhang, H., Mao, Y., Qin, X., Liu, L., & Zhang, X. (2022). Multi-Type Feature Fusion Based on Graph Neural Network for Drug-Drug Interaction Prediction. BMC Bioinformatics, 23(1). https://doi.org/10.1186/s12859-022-04763-2
61. Zhi, H.-Y., Zhao, L., Lee, C.-C., & Chen, C. Y.-C. (2021). A Novel Graph Neural Network Methodology to Investigate Dihydroorotate Dehydrogenase Inhibitors in Small Cell Lung Cancer. Biomolecules, 11(3), 477. https://doi.org/10.3390/biom11030477

62. Ivanisevic, T., & Sewduth, R. N. (2023). Multi-Omics Integration for the Design of Novel Therapies and the Identification of Novel Biomarkers. Proteomes, 11(4), 34. https://doi.org/10.3390/proteomes11040034

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