DRUG REPURPOSING USING GRAPH NEURAL NETWORK

(Drug Discovery and Development)

A Project Report Submitted

in Partial Fulfillment of the Requirements

for the Degree of

BACHELOR OF TECHNOLOGY

in

COMPUTER SCIENCE AND ENGINEERING

by

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To

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APRIL 2023

DECLARATION

I, **KOMMIREDDY LAHARI** (**Roll No: CS20B1007**), hereby declare that, this report entitled **“Drug Repurposing Using Graph Neural Network'' submitted** to Indian Institute of Information Technology Raichur towards partial requirement of **Bachelor of Technology** in **Computer Science and Engineering Department** is an original work carried out by me under the supervision of **Prioyduti Pradhan** and has not formed the basis for the award of any degree or diploma, in this or any other institution or university. I have sincerely tried to uphold academic ethics and honesty. Whenever an external information or statement or result is used then, that has been duly acknowledged and cited.

Raichur-584135 KOMMIREDDY LAHARI

May 2023

CERTIFICATE

This is to certify that the work contained in this project report entitled **"Drug Repurposing Using Graph Neural Network"** submitted by **Kommireddy Lahari** (**Roll No: CS20B1007**) to the Indian Institute of Information Technology Raichur towards partial requirement of **Bachelor of Technology** in **Computer Science and Engineering** has been carried out by him under my supervision and that it has not been submitted elsewhere for the award of any degree.

Raichur-584135 (Dr. Priodyuti Pradhan)

May 2023 Project Supervisor

ABSTRACT

Repurposing pharmaceuticals is a crucial approach in pharmaceutical research that entails finding new medicinal applications for already-approved medications. Due to its ability to speed up medication research and address urgent healthcare requirements, this strategy has gained importance within the COVID-19 epidemic. In this quest, graph neural networks, or GNNs, have proven to be effective computational tools that help identify potential repurposing candidates and analyze drug-protein interactions. GNNs facilitate a thorough investigation of drug-target interactions by combining the data from several sources, including public databases, clinical trials, and genetic data. It also improves the evaluation of the safety profile of repurposed pharmaceuticals when side effect prediction models are included. An organized and effective framework for medication repurposing is provided by this multidisciplinary approach, which combines GNNs with adverse effect prediction, adding to the Treatments are developing quickly. This paper highlights the critical role that GNNs and side effect prediction play in expediting therapeutic discovery by offering insights into the tactics and approaches involved in drug repurposing.

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Chapter 1

Introduction

The process of employing an already-approved medication or medication candidate for a novel medical ailment or treatment for which it was not previously recommended is known as "drug repurposing". It was first created to address a distinct medical issue. It has been characterized as an unforeseen, serendipitous procedure. In this procedure, a drug's unwanted side effects may also serve as a cue to investigate if it might be useful for a completely unrelated medical issue . Typically, medications that have been proven safe for use in people as well as tested and developed for their usefulness in treating a different illness than the one for which they were intended . By bypassing the medication development process and going straight to preclinical and clinical trials, this method lowers risk.

Drug repurposing—also referred to as drug repositioning or drug reprofiling—has become a potent tactic in the field of contemporary drug discovery. The process of creating new medications typically takes a long time, a lot of money, and some risk. Drug repurposing, on the other hand, involves examining the effectiveness of already-approved medications for treating one medical condition in order to treat other illnesses or ailments.

This strategy makes use of the abundance of data on medications that have previously received approval, such as their pharmacokinetics, mechanisms of action, and safety profiles. Researchers can speed up the drug development

process and possibly avoid many of the difficulties involved in traditional drug discovery by utilizing this expertise.

Repurposing drugs has a number of benefits over developing new drugs from scratch. First off, because a large portion of the preclinical and early clinical testing for the repurposed drug has already been completed, it can drastically cut down on the time and expense needed to bring a medicine to market. Second, repurposed medications can have safety profiles that are already well-established, which would speed up the regulatory approval procedure. Ultimately, repurposing current medications may yield new therapeutic applications that increase patient treatment options.

Recent developments in computer modeling, high-throughput screening technology, and bioinformatics have significantly aided efforts in drug repurposing. With the use of these technologies, scientists may forecast the effectiveness of new drugs against a range of diseases, find promising therapeutic candidates, and conduct systematic analyses of vast datasets.

All things considered, drug repurposing exhibits considerable promise as a useful strategy in contemporary drug development, providing a quicker, more economical method of introducing novel medicines to patients while optimizing the effectiveness of currently available medications.

1.1 A deep dive into drug discovery

A complex process called "drug discovery" looks for and develops novel drugs. To make medications that are both safe and effective, it integrates scientific fields such as chemistry, biology, pharmacology, and computational modeling. Before receiving regulatory approval, this process usually starts with target identification and continues through hit discovery, lead optimisation, preclinical testing, and clinical trials. Every phase necessitates thorough investigation, cutting-edge technology, and cooperation amongst several disciplines to negotiate the difficulties involved in developing therapeutic solutions.

1.2 Steps in Drug Discovery and Development

A new medication must pass through a number of stages in the drug discovery and development process in order for it to be considered safe, effective, and suitable for use in treating a variety of ailments. The following are the main actions usually taken in this process:

Target Identification and Validation:

- This stage entails locating a biological target that is important to the course of a disease, such as a particular protein or gene and target validation is the process of confirming a putative target's relevance to the disease and usefulness as a target for pharmacological intervention after it has been identified.

Lead Discovery and Optimization:

- Lead discovery is the process by which scientists look for compounds that may interact with a target and change its activity. This is generally done through high-throughput screening or virtual screening techniques and lead Optimization is to improve potency, selectivity, and other pharmacological qualities while reducing possible adverse effects, the most promising lead molecules are further refined using medicinal chemistry procedures.

Preclinical Development:

- These are preliminary examinations carried out in lab environments with cells or tissues to evaluate the safety and effectiveness of the lead compounds.Research on animals is done to assess the lead compounds' pharmacokinetics—the way a medicine is absorbed, transported, metabolized, and eliminated—and toxicology—the possibility of negative side effects.

Clinical Trials:

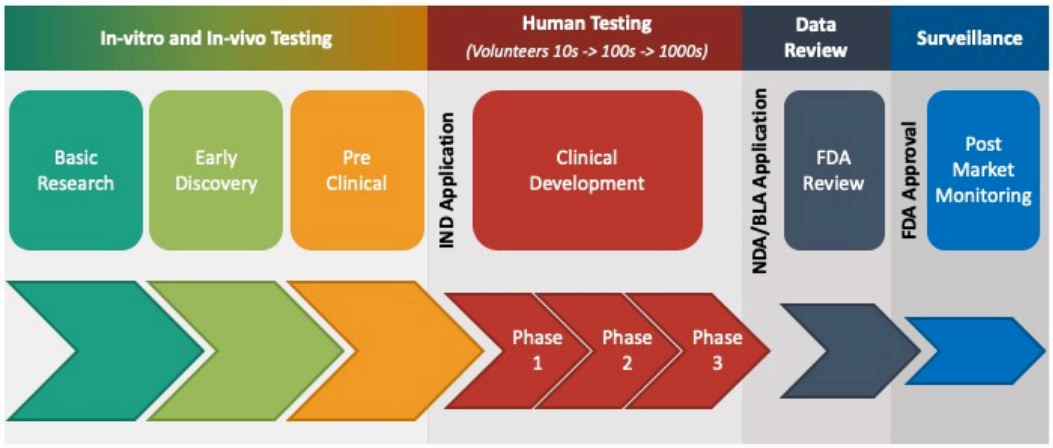
- Phase I: Safety, dose, and pharmacokinetics are the main topics of these studies, which have a modest number of healthy participants.
- Phase II: To test efficacy and further gauge safety, these trials enlist a larger cohort of patients with the intended illness.
- Phase III: Vast clinical trials are carried out to verify effectiveness, track adverse events, and contrast the novel medication with already available therapies or a placebo.
- Phase IV: After a medicine is licensed for use, post-marketing research keeps an eye on its efficacy and safety in actual use situations.

Regulatory Review and Approval:

- To ascertain if a medicine is safe and effective for its intended use, regulatory bodies examine data from clinical trials, preclinical research, and manufacturing methods.
- The medication can be promoted and made available to patients and healthcare professionals if it is approved.

Post-Marketing Surveillance:

- After licensure, pharmacovigilance programmes, real-world data analysis, and research are used to continue monitoring the drug's safety and efficacy.



1.3 Introduction to Drug Repurposing

In contemporary medicine, drug repurposing—also referred to as drug repositioning or drug reprofiling—has become a game-changing tactic. This creative method entails finding novel therapeutic applications for currently available medications that were first created for unrelated uses. The idea behind drug repurposing stems from the understanding that many drugs have unique pharmacological characteristics that extend beyond the ailments for which they are prescribed, providing potential to use them in novel ways to treat a range of illnesses. Numerous advantages are made possible by this introduction approach, such as time and cost savings, increased treatment alternatives, lower development risks, and quicker patient access to efficient therapies. To put it briefly, drug repurposing is a smart and effective way to innovate in healthcare by utilizing the potential of currently available

drugs to treat unmet medical needs and enhance patient outcomes for a variety of illnesses.

1.4 Stages in Drug Repurposing

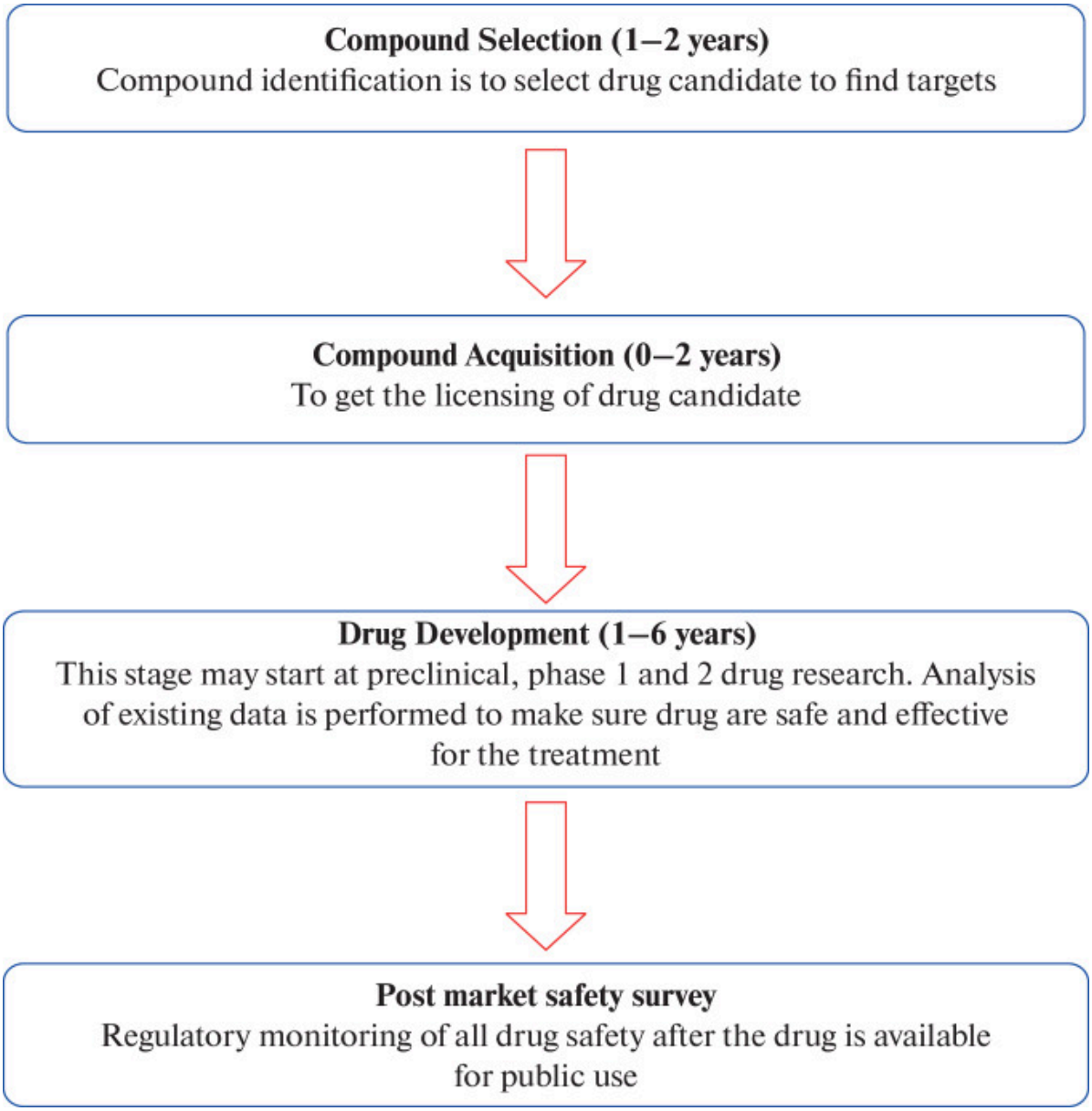
Compound Identification: Review of Literature: Researchers look through databases, extant literature, and scientific studies to find compounds that may be useful in the treatment of various illnesses. Examining medications that are now licensed for use in different contexts as well as experimental substances that have completed clinical trials but might not have met their intended goals are part of this process.To find possible candidate compounds, extensive information mining of several databases is carried out, such as databases on gene expression, chemical structures, and clinical trial information. In order to find compounds with possible therapeutic effects in the context of a novel disease or condition, this entails evaluating biological pathways, drug-protein interactions, and other pertinent information.Molecular docking, virtual screening, and machine learning algorithms are examples of computational techniques used in this context to forecast the possible effectiveness of already available medicines against novel targets or illnesses. chemicals that may have therapeutic effects in the setting of a particular disease are identified by simulating the interaction between chemicals and target proteins.

Acquisition of Compounds: Following the identification of possible candidate compounds, scientists get samples of these substances to be examined further. Getting samples from drug manufacturers, universities, or chemical suppliers may be necessary for this. Researchers occasionally create new compounds by using

the chemical structures of preexisting ones as a model.Preclinical testing is done on the obtained substances to assess their safety, pharmacokinetics, and effectiveness using animal models of the relevant disease or condition. This entails determining the toxicity, bioavailability, and mode of action of the substance to assess whether it is suitable for additional development.

Clinical Trials: In the event that preclinical research yields encouraging results for the molecule, human volunteers are used in clinical trials to assess the compound's safety and effectiveness. Phase I trials evaluate the compound's safety and pharmacokinetics in healthy volunteers; Phase II trials assess the compound's efficacy and safety in a small group of patients with the target disease; and Phase III trials confirm the compound's safety and efficacy in a larger patient group.

FDA Post-Market Safety Monitoring: Following an FDA approval for a new indication, a drug's safety and efficacy in real-world situations are monitored by post-market safety monitoring. This entails gathering and examining data from multiple sources,to find any possible safety issues that might surface when the medication is made available to the general population, such as adverse event reports, electronic health records, and clinical trials. If safety issues are found during post-market surveillance, the FDA may be obliged to intervene through regulatory measures, such as warnings or label revisions.


Compound Selection (1–2 years)
Compound identification is to select drug candidate to find targets
Compound Acquisition (0–2 years)
To get the licensing of drug candidate
Drug Development (1–6 years)
This stage may start at preclinical, phase 1 and 2 drug research. Analysis of existing data is performed to make sure drug are safe and effective for the treatment
Post market safety survey
Regulatory monitoring of all drug safety after the drug is available for public use

1.5 Importance of Drug Repurposing

- Because of its many benefits, drug repurposing is crucial to the pharmaceutical and medical industries. First of all, it provides a quick and affordable means of introducing novel treatments to patients. Repurposing existing pharmaceuticals for new purposes can be expedited, saving a great deal of time and money when compared to creating completely new therapies, because repurposed drugs have already completed extensive preclinical and clinical testing for their original indications.

- Additionally, repurposing drugs broadens the range of available treatments, filling in the gaps in healthcare where there are insufficient or no viable remedies. This holds special importance for uncommon illnesses, ailments with few therapeutic alternatives, or situations in which patients have grown resistant to prescribed drugs. Healthcare professionals can give creative solutions and enhance patient outcomes by repurposing current medications without having to start from scratch.

- Medication repurposing also lowers the risks related to medication development. With their well-established safety profiles, well-understood pharmacokinetics, and frequently an abundance of clinical data, repurposed medications reduce the risk of unanticipated toxicities or ineffectiveness. This feature not only expedites regulatory approvals but also gives patients and healthcare professionals confidence in the efficacy and safety of the repurposed drugs.

- The efficient use of resources for drug research is another crucial factor. Drug repurposing, which makes use of already-existing substances and expertise, enables researchers and pharmaceutical companies to simultaneously explore the potential of already-existing medications in new therapeutic areas and concentrate on novel targets and creative therapies. This tactical method maximizes resources, fosters scientific discoveries, and propels ongoing innovation in the medical industry.

- Drug repurposing also expedites patient access to therapies. Repurposed medications can be made rapidly available to patients, particularly those with life-threatening or incapacitating illnesses, provided they show speedy efficacy and safety in clinical studies. The quality of life and results for patients can be greatly enhanced by this quick access to efficient treatments.
- Essentially, drug repurposing is essential to the advancement of healthcare because it maximizes the benefits of currently available treatments, spurs innovation, lowers development risks, and ultimately enhances patient care for a wide range of illness

2. Chapter-2 Methods

2.1 Strategies for Drug Repurposing

1. **Phenotypic Screening:** Assessing a compound's effects at the cellular or organismal level without knowing the precise molecular target in advance is known as phenotypic screening. Using this approach, new therapeutic candidates may be found by identifying substances that exhibit desired phenotypes, such as the suppression of cell proliferation or the amelioration of illness symptoms.

2. **Target-Based Methods:** Compounds that interact with particular molecular targets that are known to be involved in disease processes are the focus of target-based techniques. These targets may include genes, proteins, or signaling pathways that are important to a disease's pathophysiology. Compound activity against the target of interest is measured via assays, which are commonly used in target-based methodologies.

3. **Knowledge-Based Methods:** Knowledge-based approaches use available data to help identify possible drug candidates, such as databases of chemical compounds, biological pathways, and illness connections. These techniques assist researchers pick drugs for additional experimental validation by analyzing and interpreting vast datasets using computer tools and algorithms.

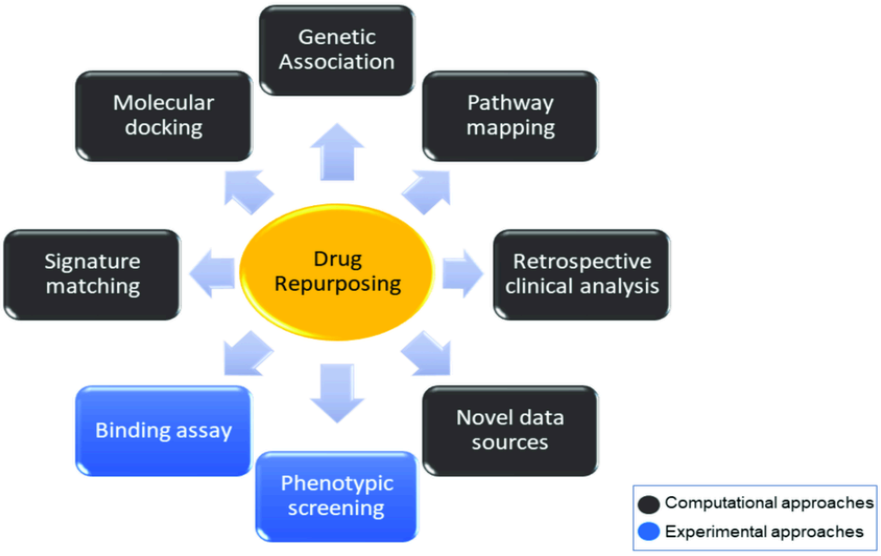
4. **Signature-Based Methods:** Molecular signatures connected to certain diseases or biological processes, such as patterns of gene expression or profiles of proteins, are analyzed in signature-based techniques. Researchers can find substances that elicit desired changes in gene expression or protein activity related to the target disease by comparing drug-induced signatures with disease signatures.

5. **Pathway- or Network-Based Methods:** The understanding of biological networks and pathways that are dysregulated in disease states is the main goal of pathway- or network-based approaches.

These techniques guide the selection of drug candidates with desired pharmacological effects by using computer models to predict how substances may influence these pathways or interact with specific components of the network.

6. **Targeted Mechanism-Based Methods:** Using computational modeling, experimental validation, and an understanding of particular disease mechanisms, targeted mechanism-based approaches find potential drugs that specifically target important biochemical pathways or processes that drive the course of the disease. These techniques frequently need a thorough comprehension of the molecular pathways and underlying biology connected to the target disease.

7. **Molecular Docking:** A computer technique called molecular docking is used to forecast the molecular interactions and binding affinities between tiny compounds (ligands) and target proteins (receptors). This technique aids in the discovery and development of drug candidates with desirable binding qualities and therapeutic effects by helping researchers understand how compounds attach to certain targets.



3. Chapter-3 Graph Neural Network Model

3.1 About Graph Neural Networks

Message forwarding is a technique used by GNNs to arrange graphs in a way that machine learning algorithms can comprehend. Each node in this process has information embedded in it regarding its location and the nodes nearby. Based on the embedded data, an artificial intelligence (AI) model can then identify trends and forecast outcomes.

Three fundamental major layers are used in the construction of GNNs: an input layer, a hidden layer, and an output layer. The graph data, which is usually a matrix or a collection of matrices, is fed into the input layer. The data is processed by the hidden layer, and the output layer generates the output response for the GNN.

Additionally, a rectified linear unit (ReLU), an activation function typically used in convolutional neural networks (CNNs) and deep learning models, is employed in the process. The ReLU function reads the value supplied as the input and adds a nonlinear property to the model.

Although GNN models are specifically designed for training with graph data, they are commonly trained using standard neural network training techniques like backpropagation or transfer learning.

3.2 Types of Graph Neural Networks

Graph convolutional networks (GCNs): GCNs examine neighboring nodes to gather feature information. They employ a nonlinear activation function and are composed of a linear layer and graph convolutions.

Recurrent graph neural networks (RGNNs): Diffusion patterns in multi relational graphs with several relations are learned by RGNNs.

Spatial graph convolutional networks: Convolutional layers designed for information passing and grouping activities are defined by spatial GCNs. In order to update a node's hidden embedding, they compile information from adjacent nodes and edges to that node.

Spectral graph convolutional networks: Graph signal filters are the foundation of spectral GCNs. They use the graph Fourier transform, a mathematical operation, to define the spectral domain of data.

Recurrent neural networks (RNNs): An artificial neural network type called an RNN makes use of time series or sequential data. An RNN's output depends on the elements of the previous sequence.

Graph autoencoder networks: These learn graph representations that use an encoder and decoder to rebuild the input graphs.

3.3 Knowledge Graph

An organized representation of information that shows the links and interconnections between objects in a domain is called a knowledge graph. Information is arranged using a graph structure, in which nodes stand for concepts, people, locations, or objects, and edges for the connections or relationships between these elements. Knowledge graphs offer a framework for storing, querying, and analyzing vast volumes of interrelated data and are used to describe complicated relationships.

Here are some key aspects and characteristics of knowledge graphs:

1. Graph Structure: Knowledge graphs are graphs with nodes (entities) and edges (relationships) as its building blocks. Nodes possess attributes that characterize their attributes, whereas edges specify the connections among nodes. The modeling of intricate semantic links and the representation of various knowledge types are made possible by this graph structure.

2. Linked Data: Knowledge graphs frequently make use of linked data concepts, which stress the use of standardized identifiers (URIs, for example) to connect data points from various sources. Users may traverse and study interconnected information because of this connection, which facilitates the seamless integration of disparate data sources.

3. Ontologies and Schemas: Typically, ontologies or schemas that specify the kinds of entities, relationships, and attributes inside the graph serve as the foundation for the construction of knowledge graphs. With the help of ontologies, domain knowledge can be formally represented, with concepts, classes, characteristics, and their relationships specified.

4. Semantic Enrichment: Semantic enrichment is integrated into knowledge graphs by the annotation of data with relevant metadata and semantic tags. Through this enrichment, the knowledge graph's sophisticated search and inference capabilities are supported, interoperability is facilitated, and the comprehension of data semantics is improved.

5. Inference and Reasoning: By using semantic links and logic-based rules to infer new information or draw logical conclusions, knowledge graphs facilitate inference and reasoning. Within the graph, this feature

facilitates knowledge discovery activities, semantic search, and sophisticated queries.

6. Scalability and Flexibility: The scalability and flexibility of modern knowledge graphs enable the integration of massive amounts of data from many sources. They are adaptable for expressing a variety of knowledge domains since they can handle organized, semi-structured, and unstructured data.

7. Applications: Semantic search engines, recommendation systems, data integration platforms, intelligent chatbots, knowledge management systems, and scientific research (biomedical knowledge graphs, for example) are just a few of the disciplines in which knowledge graphs find use. They support data-driven decision-making, semantic comprehension, and the organizing of knowledge.

In general, knowledge graphs are effective tools that facilitate semantic interoperability, intelligent data-driven applications across various fields, and the organization, navigation, and utilization of interconnected knowledge.

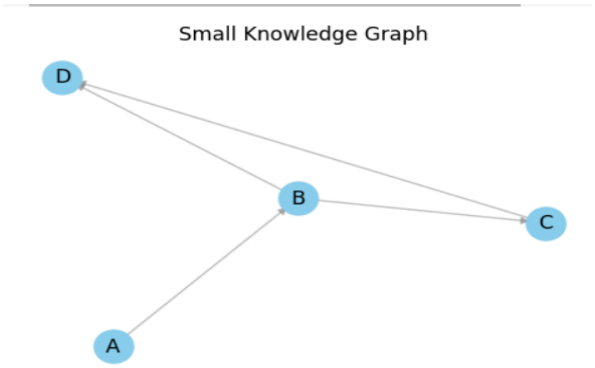
Code:

```
import networkx as nx #tool for creating, analyzing,and visualizing graphs in python

import matplotlib.pyplot as plt #used for plotting and visualizing data,including graphs.



# Step 1: Initialize a directed graph

kg = nx.DiGraph()  #Directed Graphs have edges that point in a specific direction,from source node to a target node.
```

```
# Step 2: Add nodes to the graph
nodes = ['A', 'B', 'C', 'D']
for node in nodes:
    kg.add_node(node)

# Step 3: Add edges to the graph
edges = [('A', 'B'), ('B', 'C'), ('B', 'D'), ('C', 'D')]
for edge in edges:
    kg.add_edge(edge[0], edge[1])

# Step 4: Visualize the knowledge graph
plt.figure(figsize=(6, 4))
pos = nx.spring_layout(kg)  # Positions for all nodes

# Draw nodes
nx.draw_networkx_nodes(kg, pos, node_color='skyblue', node_size=500)

# Draw edges
nx.draw_networkx_edges(kg, pos, width=1.0, alpha=0.5,
edge_color='gray')
```

```
# Draw labels

nx.draw_networkx_labels(kg, pos, font_size=12,
font_family='sans-serif')



plt.title("Small Knowledge Graph")

plt.axis('off')

plt.show()
```

Output:



3.4 About GCN

On graph-structured data, a Graph Convolutional Network, or GCN, is a semi-supervised learning method. It's based on a convolutional neural network variation that performs well and works directly on graphs. A localized first-order approximation of spectral graph convolutions serves as the motivation for the convolutional design selection. The model learns hidden layer representations that encode both local graph structure and node attributes, and it scales linearly in the number of graph edges.

We describe a scalable method based on an effective form of convolutional neural networks that function directly on graphs for semi-supervised learning on graph-structured data. Our convolutional architecture selection is based on a first-order approximation of spectral graphs that is localized.

Our approach learns hidden layer representations that encode both local network structure and node attributes, and it scales linearly in the number of graph edges. Our methodology performs significantly better than related methods in several experiments conducted on citation networks and a knowledge graph dataset.

3.5 Application of GCN

Graph Convolutional Networks (GCNs) are widely used in many different disciplines because of their powerful modeling and learning capabilities from graph-structured data. The following is a list of common applications for GCNs:

Social Network Analysis: In social networks, GCNs are utilized for recommendation systems, influence analysis, link prediction, and community detection. They are able to recognize significant nodes or communities by examining the connectivity patterns inside social graphs.

Biological and Chemical Sciences: GCNs are used in bioinformatics

and chemoinformatics for biological pathway analysis, drug discovery, molecular property prediction, protein function prediction, and protein-protein interaction prediction. They are able to simulate intricate chemical relationships and structures found in biological systems.

Semantic Web and Knowledge Graphs: In the semantic web area, GCNs are utilized for ontology alignment, semantic similarity calculation, knowledge graph completion, and entity linking. They can improve semantic understanding in knowledge graphs, clarify ambiguities, and infer missing relationships.

Recommendation Systems: Personalized recommendation algorithms, social influence modeling, and graph-based collaborative filtering are three ways that GCNs enhance recommendation systems. They can provide recommendations that are more pertinent and accurate by utilizing social connections and user-item interactions.

Fraud Detection and Anomaly Detection: GCNs are used in cybersecurity and finance for risk assessment, fraud detection, anomaly identification, and network intrusion detection. Based on graph-based features, they are able to recognize suspicious patterns, find outliers, and categorize anomalous activities.

Natural Language Processing (NLP): NLP operations like text categorization, sentiment analysis, named entity identification, and semantic parsing all make use of GCNs. By examining syntactic and semantic connections within textual data displayed as graphs, they can enhance the comprehension and manipulation of natural language.

Geospatial Analysis: By simulating spatial relationships, transportation networks, urban planning, and geographic data, GCNs make geospatial analysis possible. They are able to enable location-based services, anticipate traffic trends, optimize routing, and analyze geographic networks.

Healthcare and Medical Imaging: GCNs are used in healthcare for disease detection, patient stratification, medication repurposing, medical image analysis, and recommendation systems. They can help with clinical decision-making, process medical graphics, and gain knowledge from patient data.

Knowledge Graphs and Ontologies: By facilitating graph-based reasoning, semantic enrichment, concept embeddings, and knowledge inference, GCNs improve knowledge graphs and ontologies. They can help with semantic search, knowledge representation, and knowledge discovery task automation.

3.6 Implementation

Implementation Concept in Code:

Dynamic Graph Convolutional Network (GCN): Implemented a dynamic GCN model using PyTorch Geometric library. This model is designed to handle graph-structured data efficiently for drug data prediction.

Data Loading: Utilizing DataLoader from PyTorch Geometric, loaded molecular graph data in batches for efficient training.

Model Architecture: The model consists of multiple graph convolutional layers followed by global pooling and a dense output layer for binary classification.

Training Loop: The training loop iterates over epochs, batches, calculates loss, performs backpropagation, and updates model parameters using Adam optimizer. Additionally, you've incorporated learning rate scheduling and gradient clipping to stabilize training.

Evaluation: After training, you evaluate the model's performance using metrics like loss, F1 score, accuracy, and plot ROC curve and confusion matrix to assess classification performance.

3.7 Parameters and Definitions

Dynamic GCN: A graph neural network architecture capable of handling graph-structured data with varying sizes and structures. It consists of multiple graph convolutional layers followed by global pooling to aggregate node features.

Batch Size: The number of samples processed in each iteration during training. Larger batch sizes can improve computational efficiency but may lead to overfitting.

Learning Rate: The step size used by the optimizer to update model parameters during training. Learning rate scheduling techniques like ReduceLROnPlateau can dynamically adjust the learning rate based on the model's performance.

Gradient Clipping: A technique to prevent exploding gradients during training by capping the gradient values to a predefined threshold.

Loss Function: BCEWithLogitsLoss, a combination of sigmoid activation and binary cross-entropy loss, suitable for binary classification tasks.

F1 Score: A metric that balances precision and recall, commonly used for evaluating classification performance, especially in imbalanced datasets.

ROC Curve: Receiver Operating Characteristic curve illustrates the trade-off between true positive rate and false positive rate across different threshold values, providing insights into the model's classification performance.

Confusion Matrix: A table that visualizes the performance of a classification model by comparing actual and predicted class labels, useful for identifying true positives, true negatives, false positives, and false negatives.

SMILES: **S**implified **M**olecular **I**nput **L**ine **E**ntry **S**ystem (SMILES)

- String based notation to represent chemical structures in a human-readable and computer-interpretable way
- SMILES strings consist of alphanumeric characters that represent

atoms, bonds, and connectivity in a molecule

A simple set of rules:

- Atoms are represented by their atomic symbols (e.g., C for carbon, O for oxygen)
- Bonds are symbols or characters that denote the connectivity between atoms (e.g., single bonds are usually represented by '-', double bonds by '=', etc.)

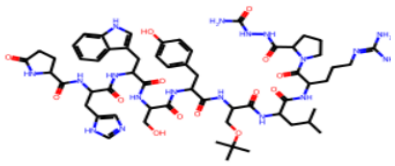
code:

```
from rdkit import Chem
from rdkit.Chem import Draw

# Take SMILES input from the user
smiles = input("Enter the SMILES representation of the molecule: ")

# Convert the SMILES string to a molecule object
mol = Chem.MolFromSmiles(smiles)

if mol is not None:
    # Count the number of atoms (nodes) and bonds (edges)
    num_atoms = mol.GetNumAtoms()
    num_bonds = mol.GetNumBonds()

    # Draw the molecule and display it
    img = Draw.MolToImage(mol)
    display(img)

    # Print the number of nodes (atoms) and edges (bonds)
    print("Number of nodes (atoms):", num_atoms)
    print("Number of edges (bonds):", num_bonds)
else:
```

```
print("Invalid SMILES representation. Please check and try again.")
```

Input:CC(C)CC(C(=O)NC(CCCN=C(N)N)C(=O)N1CCCC1C(=O)NNC(=O)N)NC(=O)C(COC(C)(C)C)NC(=O)C(CC2=CC=C(C=C2)O)NC(=O)C(CO)NC(=O)C(CC3=CNC4=CC=CC=C43)NC(=O)C(CC5=CN=CN5)NC(=O)C6CCC(=O)N6

output:



Number of nodes (atoms): 91
Number of edges (bonds): 96

4. Chapter-4 Databases

4.1 Pathway Omics Data

A strong framework for modeling and studying complex biological pathways and their interactions with omics data is offered by pathway omics data displayed in a graph format. Each node in this graph structure represents a unique biological entity, such as genes, proteins, metabolites, and routes themselves. A more sophisticated comprehension of the complex network of biological processes is made possible by the edges in the graph, which represent interactions between different entities such as gene-protein links or pathway linkages. Additionally, nodes and edges can be enhanced with quantitative information that enhances the biological context inside the graph, such as protein abundances, gene expression levels, or regulatory annotations.

This graph-based form makes a number of analyses and revelations easier. Graph algorithms can be used for a variety of purposes, such as biologically significant motif detection, central node or pathway identification, and network clustering. Furthermore, multi-omics analysis is made possible by the pathway graph's integration of multiple omics datasets. This enables researchers to correlate changes in various biological information layers, such as protein-protein interactions, gene expression patterns, and metabolite concentrations, with pathway activity and cellular functions.

For researchers studying disease understanding, tailored medicine, and systems biology, graph-based visualization of pathway omics data is crucial. It makes it possible to identify important pathways, biomarkers, and regulatory processes, which helps to clarify disease causes and identify potential treatment targets. In the end, pathway omics data graphs are effective instruments for deciphering biological systems' intricacies and converting omics data into useful knowledge for therapeutic purposes.

4.2 Target Omics Data

A methodical strategy to comprehend the molecular subtleties connected to a particular biological target, such as a gene, protein, or pathway, is required to generate target omics data. The procedure starts with a well-planned experimental design in which scientists choose the target with great care, considering factors such as biological significance, applicability to a particular disease or condition, or possibility for therapeutic intervention. The target's activity or expression is then manipulated through the establishment of experimental settings, which may entail genetic modifications, medication administration, exposure to environmental stimuli, or comparisons between samples of healthy and diseased individuals.

The next stage after designing an experiment is gathering data at several omics levels. By using methods like DNA sequencing, genomic data is produced that makes it possible to identify genetic variants, mutations, or regulatory elements connected to the target gene. RNA sequencing, or RNA-seq, yields transcriptome data that sheds light on target regulatory networks, alternative splicing processes, and patterns of gene expression. Proteomic methods, like mass spectrometry, examine the target protein's post-translational changes, protein-protein interactions, and expression levels of the protein. Insights into cellular metabolism and biochemical processes can be gained from metabolomic data, which records metabolite profiles and metabolic pathways impacted by the target.

The integration process starts as soon as omics data are obtained, with the goal of producing a cohesive and all-encompassing picture of the target's molecular landscape. Data integration includes mapping metabolite changes to metabolic networks, connecting protein abundance with functional pathways, and comparing genetic variants with changes in gene expression. Systems-level analysis is made possible by this comprehensive method, which helps researchers to discover important participants in signaling cascades, uncover regulatory mechanisms, and clarify cross-omic connections pertaining to the target of interest.

Retrieving valuable insights and biological relevance from target omics data requires careful analysis and interpretation. Differential expression analysis, pathway enrichment analysis, network analysis, and machine learning

algorithms are used in conjunction with bioinformatics tools and statistical techniques to find meaningful relationships with the target. In order to help researchers view omics data in graphical formats and make it easier to grasp intricate linkages, pathway dynamics, and regulatory networks connected to the target, visualization tools are essential.

In the end, target omics data provide insightful biological information about drug responses, cellular processes, disease causes, and target-related pathways. This information bridges the gap between fundamental research findings and clinical applications for better patient outcomes and customized therapies. It also aids in the identification of biomarkers, therapeutic targets, drug development techniques, and personalized medicine approaches.

4.3 Clinical Trials and Adverse Effect Data

Clinical trials are vital to the drug development process because they offer vital information about the efficacy, safety, and tolerance of experimental medications or therapies in human participants. Phased clinical trials are carried out according to a well-defined methodology with the aim of gradually evaluating the safety and efficacy of the medication. Data on side effects are vital for assessing the drug's overall risk-benefit profile during the clinical trial phases. The following is the relationship between adverse impact data and clinical trials:

1. Clinical Trial Phases: Phase I of clinical trials usually focuses on safety and dosage; Phase II assesses efficacy and side effects; Phase III validates efficacy and tracks adverse reactions; and Phase IV takes place after marketing to collect extra safety and efficacy data. At every stage, adverse event data is methodically gathered and examined to evaluate the safety profile of the medication.

2. Adverse Effect Monitoring: Adverse effects are closely observed and meticulously documented during clinical trials. Gastrointestinal symptoms, allergic responses, unexpected lab results, changes in vital

signs, and unfavorable drug interactions are examples of common side effects. The frequency and severity of adverse effects are rigorously evaluated throughout the trial, and they can range in intensity from mild to severe.

3. Reporting and Analysis: It is the duty of clinical trial investigators to promptly and accurately notify sponsors, regulatory bodies, and ethics committees of any adverse consequences. The analysis of adverse event data aims to ascertain the frequency, intensity, length, and cause-and-effect relationship between the investigational drug and control or placebo groups.

4. In order to determine dose-dependent effects, evaluate the association between drug exposure and side effects, and find any unexpected or severe adverse reactions that might require additional research or regulatory action, statistical studies are carried out.

5. Risk-Benefit Assessment: Information about adverse effects is essential to evaluating the risk-benefit of the experimental medication. The effectiveness of the medication in curing the intended ailment is evaluated against the safety profile, which includes the kinds and frequency of side events. Regulations pertaining to medication approval, labeling, dose recommendations, and risk-reduction tactics are guided by this assessment.

6. Post-Marketing Surveillance: Following commercialization and regulatory approval, post-marketing surveillance keeps an eye out for negative effects in actual clinical settings. Pharmacovigilance programs gather and examine reports of adverse events from patients, healthcare professionals, and other sources in order to identify uncommon or chronic side effects, evaluate medication safety patterns, and update safety data as necessary.

In conclusion, assessing drug safety, guiding risk-benefit analyses, and guaranteeing patient safety during and after the drug development lifecycle depend on the systematic collection, reporting, and analysis of adverse event

data in clinical trials. These data-driven procedures support regulatory supervision, evidence-based decision-making, and ongoing enhancement of medication safety standards.

4.4 Drug Omics Data

1. Drug Omics Data: Defining thorough molecular profile of pharmaceuticals, including their molecular structures, pharmacokinetics, pharmacodynamics, and mechanisms of action, is known as drug omics data.

2. Chemical structures: details regarding the molecular weight, molecular formula, and 2D and 3D molecular structures of pharmaceuticals. Data on the body's drug distribution, metabolism, excretion, and absorption (ADME) include bioavailability, half-life, and clearance rates. This is known as pharmacokinetics.

   Knowledge regarding the molecular targets of medications, their affinities for binding, and the subsequent impacts on biological processes and cellular pathways is known as pharmacodynamics. The mechanisms of action of medications provide information on how they interact with certain molecular targets, alter signaling pathways, and have therapeutic effects.

3. Uses: Drug omics data is employed in drug development and discovery to find novel drug candidates, enhance the qualities of existing drugs, and comprehend the processes underlying the toxicity and efficacy of drugs.

   Drug omics data can assist in customizing treatment plans for individual patients based on their genetic composition, disease features, and medication reactions. This is known as personalized medicine.

4.5 Toxicity Data

Toxicity data is information concerning possible negative effects on biological systems, such as cells, tissues, organs, and organisms, that medications, chemicals, or other substances may have.

Information on a substance's immediate harmful effects after exposure; usually determined by in vitro tests or animal research.

Information regarding a substance's long-term harmful effects, such as carcinogenicity, reproductive toxicity, and organ damage, can be found under its section on chronic toxicity.

Toxicological thresholds and dose-response curves are examples of data pertaining to the link between a substance's concentration or dose and its harmful effects.

1. The toxicological mechanisms: perspectives on the molecular processes that underlie toxicity brought on by drugs, including oxidative stress, mitochondrial malfunction, and genotoxicity.
2. Application:
    2.1. Safety assessment: To assess a substance's safety profile, find possible health hazards, and guide regulatory decisions, toxicity data is used.

To evaluate the risk of exposure to medications, environmental toxins, and consumer products, toxicity data is useful in determining the possibility and intensity of negative consequences.

4.6 Genomics Data

Genetic Variations (e.g., single nucleotide polymorphisms) and DNA sequences are examples of genetic variations. Genomics data is defined as information about an individual's genetic makeup.Information about the nucleotide base order in a person's DNA can be obtained through whole-genome, exome, and targeted sequencing of particular genomic regions.

1. Gene Expression: Details regarding the amounts of gene expression in various tissues or cell types, usually ascertained using RNA sequencing (RNA-seq) or microarray methods.

   Information about genetic differences, such as single nucleotide polymorphisms (SNPs), copy number variations (CNVs), and structural variants, both within and between populations.

   The study of epigenetics provides insights into how chemical changes to DNA or histone proteins, such as DNA methylation and histone acetylation.

2. Applications:

   2.1. Disease research: Targeted medicines and diagnostic tests are developed using genomic data, which is utilized to investigate the genetic foundation of diseases, uncover genes and pathways linked to disease development.

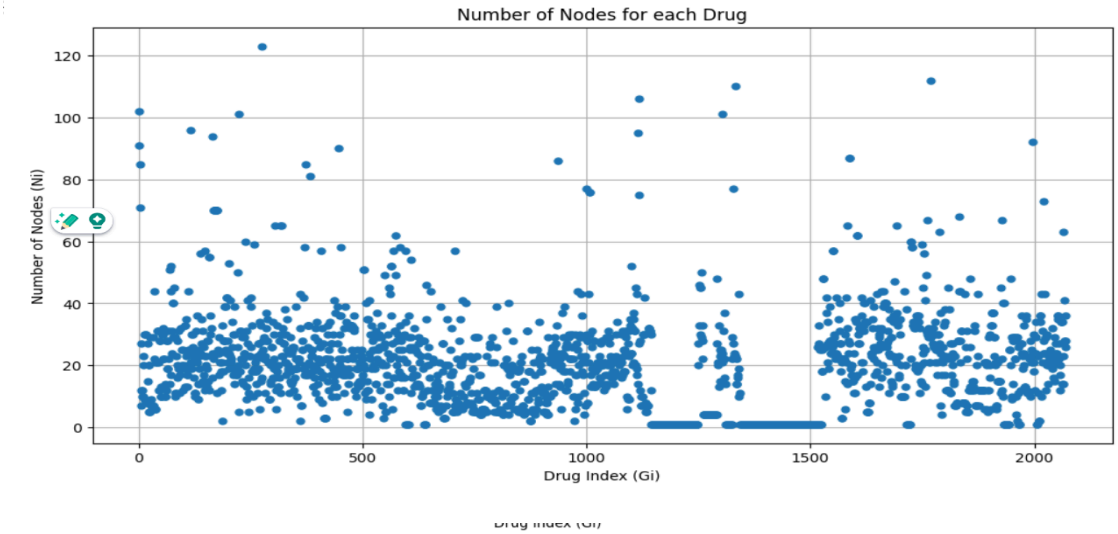
3. Pharmacogenomics: Because each person's genetic profile is unique, genomics data can be used to predict how each person will respond to medications, optimize dosage schedules, and reduce the likelihood of negative side effects.

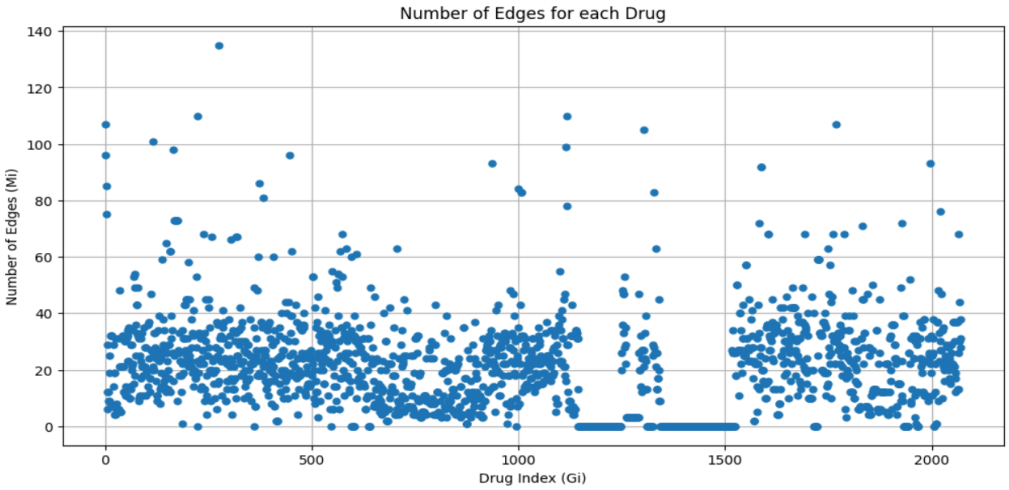
4.7 Analysis of Molecular Complexity in Drug Molecules Using Graph Metrics

We conducted an analysis of molecular complexity in a dataset of drug molecules sourced from DrugBank, a comprehensive database of drug information. Utilizing the RDKit library in Python, we extracted molecular structures from the dataset and calculated the number of nodes (atoms) and edges (bonds) for each drug molecule. Our findings reveal significant variability in the molecular complexity across the drug molecules, as demonstrated by the distribution of nodes and edges. The plot depicting the number of nodes (Ni) for each drug index (Gi) illustrates the diversity in molecular size and composition, with some drugs exhibiting higher node counts indicative of larger and more complex molecular structures. Similarly, the plot representing the number of edges (Mi) highlights variations in bond connectivity and complexity among the drug molecules. This analysis

provides valuable insights into the structural diversity of drug molecules, which can inform further studies on drug design, optimization, and therapeutic efficacy.

Results:





Chapter-5

5.1 Applications of Drug Repurposing

1. **Repurposing medications for COVID-19:** SARS-CoV-2 therapeutics may be possible through the repurposing of currently available medications, according to research conducted in response to the COVID-19 pandemic.

   Medications that are already licensed for other uses must be identified and their effectiveness against COVID-19 must be evaluated before being repurposed.

   Repurposed and examined in clinical trials for the treatment of COVID-19 are a few medications, including dexamethasone, hydroxychloroquine, and remade it.

   A thorough list of medications that have been repurposed is given in Table 2, which includes those that have been tested especially for treating COVID-19.

2. **As an Anticancer Medication:** Metformin Preclinical and clinical research on metformin, a drug originally created to treat diabetes, have revealed anticancer properties.

   Metformin can prevent the growth and migration of cancer cells as well as lower the occurrence of a number of malignancies, according to studies.

   Metformin inhibits the epithelial-mesenchymal transition (EMT), activates apoptosis (programmed cell death), and suppresses metastasis as some of its many anticancer actions.

   The possibility of using current medications for novel therapeutic uses is demonstrated by the repurposing of metformin for the treatment of cancer.

3. **Repurposing Drugs to Combat Antibiotic Resistance:** Repurposing drugs presents a viable approach to tackle the

issue of antibiotic resistance, namely in the context of treating tuberculosis (TB).

Globally, tuberculosis strains that are resistant to common antibiotic combinations have surfaced, presenting a serious risk to public health.

A 1950s discovery, pyridomycin is an antibiotic that is not commonly used but has been repurposed as a possible treatment for drug-resistant tuberculosis.

In place of isoniazid, a drug used frequently to treat tuberculosis, pyridomycin may help prevent antibiotic resistance by offering a new therapeutic option.

4. **Detailed List of Repurposed pharmaceuticals**: offers a thorough list of pharmaceuticals that have been repurposed, along with their original indications and new applications.

   The table highlights the potential of these medications to meet unmet medical needs and enhance patient outcomes by providing useful information on medications that have been successfully repurposed for new therapeutic purposes.

   Adoption of repurposed medications in clinical practice, clinical trials, and additional research are all facilitated by thorough documentation of repurposed drugs.

Examples of repurposed drugs

S. No.	Drug	Discovered	Repurposed
1	Amiloride	Acid-sensing ion channel antagonist	Secondary progressive multiple sclerosis (SPMS)
2	Anastrazole	Ovulation induction	Breast cancer
3	Angiotensin-converting enzyme 2 (ACE2) inhibitor, angiotensin receptor blocker (ARB) and statins	Antihypertensives	Effective against SARS-CoV-2 (COVID-19) [Few controversies are seen apart from promising results]
4	Aripiprazole	Antipsychotic/Antidepressant	Active against fungal biofilms
5	Artesunate	Anti-infective	Active against fungal biofilms
6	Aspirin and ibuprofen	Inflammation	Antibacterial and antifungal
7	Atorvastatin (generic Lipitor)	Hyper-cholesterolaemia	Cavernous angioma
8	Auranofin	Rheumatoid arthritis	Antibacterial and antifungal
9	Avermectin B1a	Anti-infective	Active against fungal biofilms
10	Azathioprine	Crohn's disease	Antibacterial and antifungal

5.2 Challenges

Benefits of Drug Repurposing: Drug repurposing makes use of already-approved medications for novel therapeutic indications after their early phases of clinical development are finished.

It speeds up the process of introducing new therapies to the market by avoiding the pricey and drawn-out early phases of medication development.

Compared to conventional drug discovery techniques, drug repurposing has a number of benefits. Researchers can save time and money by repurposing

medications that are already on the market rather than starting from scratch and creating new ones. The pharmacokinetic characteristics and safety profiles of repurposed medications are already known, thus clinical trials for the new therapeutic indication can begin right away. This shortens the time and money needed to introduce a new medicine to the market by streamlining the medication development process.

1. **Difficulties in Discovering Novel Therapeutic Indications:** Determining appropriate therapeutic domains for repurposed medications is a difficult task that necessitates meticulous evaluation of the drug's mode of action and any therapeutic advantages.

   If the available data for repurposed medications are inadequate or do not comply with regulatory standards, it can be essential to restart clinical or preclinical investigations.

   Determining the most promising therapeutic indications for already available medications is one of the primary problems in drug repurposing. Assessing the drug's pharmacological characteristics, mode of action, and possible therapeutic advantages in various illness scenarios are all part of this process. Determining whether the preclinical or clinical data currently available are adequate for the new indication or whether additional research is required is also critical. Restarting research can make the repurposing process more time- and money-consuming, but it can be required to ensure the safety and efficacy of the repurposed drug.

2. **Problems with intellectual property rights (IPR):**

   Investment in drug repurposing initiatives may be discouraged by limited patent protection for repurposed medications.

   Investment uncertainty is further increased by regulatory restrictions and the possibility that subpar outcomes would result in project abandonment.

Since patents can grant businesses the sole right to sell a repurposed drug, intellectual property rights (IPR) are important in the context of drug repurposing. But compared to novel chemicals, repurposed medications have less patent protection, which could discourage funding for repurposing initiatives. Regulatory limitations and the possibility of project termination owing to subpar outcomes can also deter investment in medication repurposing. Uncertainty around intellectual property rights and legal requirements may make it more difficult to manufacture and market medications with modified uses.

3. **Market Demand as a Motivator:**

Researchers and investors may be encouraged to pursue drug repurposing projects if there is a growing need for medicines in particular therapeutic areas.

Investment in repurposing initiatives may be motivated by market prospects, especially in regions with a high rate of unmet medical needs.

Market demand for medicines in specific therapeutic areas can act as a strong motivator for researchers and investors, notwithstanding the difficulties and uncertainties involved in drug repurposing. High unmet medical requirements could present chances for repurposing medications to address important healthcare issues, such as in the case of drug-resistant infections or new infectious diseases. Investment and innovation in drug repurposing initiatives might be stimulated by the possibility of market success as well as the chance to significantly improve patient care.

Chapter-6

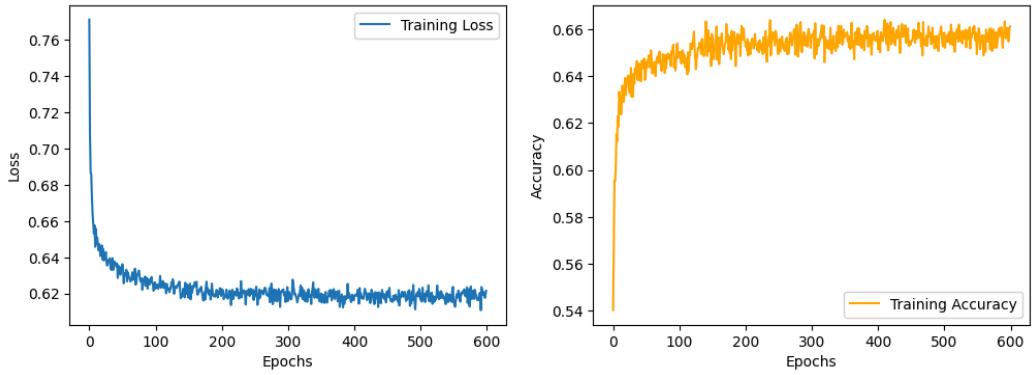
6.1 Results:

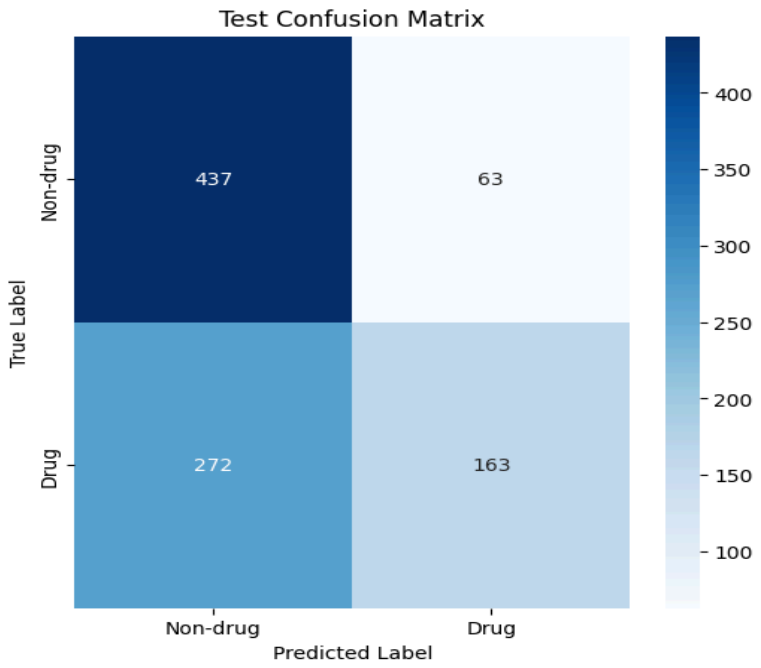
F1 Score: The F1 score is a measure of a model's accuracy, considering both precision and recall. It is the harmonic mean of precision and recall, providing a single metric to evaluate the model's performance. It ranges from 0 to 1, where 1 indicates perfect precision and recall, and 0 indicates the worst performance.

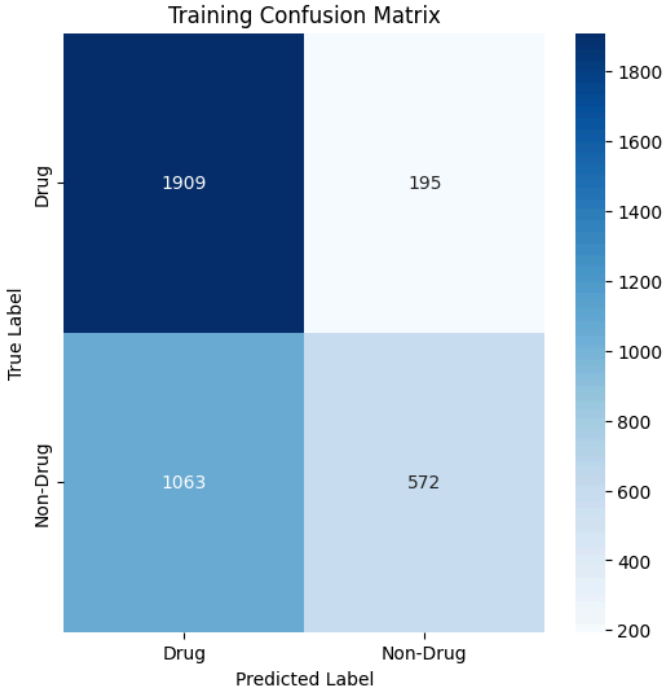
Training Loss: Training loss refers to the error or discrepancy between the actual and predicted values during the training phase of a machine learning model. It is computed as a measure of how well the model is learning from the training data. The goal is to minimize the training loss, indicating that the model is effectively capturing patterns in the data.

Confusion Matrix: A confusion matrix is a table used to evaluate the performance of a classification model. It compares the predicted labels of the model with the actual labels across different classes. The matrix consists of four components: true positives (TP), false positives (FP), true negatives (TN), and false negatives (FN). It provides insights into the model's ability to correctly classify instances and identify any misclassifications or errors.

Here are the plotting of results:





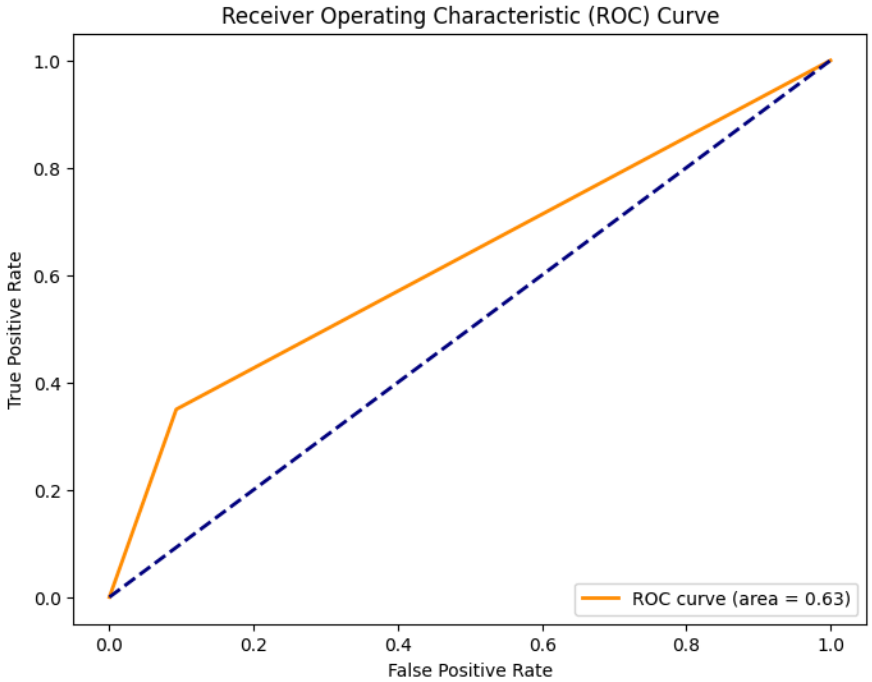


Epoch 600/600, Loss: 0.6214870581431176, F1 Score: 0.485586682907024, Training Accuracy: 0.6611393420700722

Test Accuracy: 0.6417112299465241

ROC Curve Graph:

The ROC (Receiver Operating Characteristic) curve is a graphical representation used to evaluate the performance of a binary classification model. It plots the true positive rate (sensitivity) against the false positive rate (1 - specificity) at various threshold settings. The curve illustrates the trade-off between sensitivity and specificity, showing how the model's performance changes as the classification threshold is varied. A perfect classifier would have a curve that reaches the top-left corner of the plot, indicating high sensitivity and low false positive rate across all thresholds. The area under the ROC curve (AUC-ROC) quantifies the overall performance of the classifier, with values closer to 1 indicating better discrimination between classes.



6.2 Conclusion

In many diseases when there are no suitable medicines, there are therapeutic gaps that can be filled. One potential solution is the idea of repurposing drugs. Through repurposing of currently licensed medications, scientists can uncover the latent value of compounds that have previously received approval for alternative uses, resulting in a more effective and economical use of medicinal medicines. This method increases the number of medicines available for a wide range of medical diseases while also speeding up the drug development process.

Developing a better knowledge of the molecular mechanisms behind the target disease and the pharmacological activities of current medications is crucial to improving the success rates of drug repurposing initiatives. In order to do this, a multidisciplinary strategy combining experimental and computational methodologies is needed. Computational methods that can assist in identifying possible drug candidates with therapeutic relevance to the target disease include network pharmacology, molecular docking, and virtual screening. Concurrently, the effectiveness and safety of repurposed medications must be confirmed through experimental validation using in vitro and in vivo investigations.

Furthermore, the effective application of medication repurposing strategies depends on cooperation between academic institutions, pharmaceutical corporations, government agencies, and healthcare providers. In the end, patients will gain faster access to innovative therapies as a result of sharing data, resources, and experience to help identify and validate repurposed pharmaceuticals.

To conclude, the repurposing of drugs exhibits significant potential in meeting unfulfilled medical needs and increasing the range of therapeutic alternatives for diverse illnesses. Researchers can increase the success rates of drug repositioning initiatives, resulting in better patient outcomes and improved healthcare delivery, by utilizing already-approved medications and using an integrated approach combining computational and experimental methodologies.

6.3 Future work

I want to work on the side effects as it is a drawback in the drug repurposing

- Some drugs that have gone through several stages of clinical development and have been unsuccessful for this reason.
- In this process,the undesired side effects of Drug molecules can be a pointer to exploring the possibility of effectiveness.

Example: Thalidomide indicated for vomiting, was used to treat nausea in pregnant women and resulted in several disabilities. This tragic side effect on fetal development, its use was banned or restricted in several countries.

In conclusion,my future work in drug repurposing should emphasize thorough investigations into potential side effects, aiming to optimize safety profiles and enhance patient outcomes. This proactive approach is essential for maximizing the benefits of repurposed drugs while minimizing associated risks.

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