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B.TECH ARTIFICIAL INTELLIGENCE IN DATA SCIENCE AND MEDICAL ENGINEERING

NETWORK VISUALISATON AND ANALYSIS OF GENE REGULATORY INTERACTIONS IN ACUTE MYELOID LEUKEMIA(AML)

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BONAFIDE CERTIFICATE

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NETWORK VISUALISATON AND ANALYSIS OF GENE REGULATORY INTERACTIONS IN ACUTE MYELOID LEUKEMIA(AML)

ABSTRACT:

This project aims to understand Acute Myeloid Leukemia (AML) by building a gene regulatory network using gene expression. We used network analysis to identify important genes and explored their roles in key cancer pathways such as Wnt, p53, Hedgehog, and NF-κB. Community detection and centrality measures helped highlight potential biomarkers and their related drug targets. This study supports better understanding of AML and offers insight into possible treatments, while also considering ethical use of data and model transparency.

CONTENTS

INTRODUCTION:

Acute Myeloid Leukemia (AML) is a genetically and clinically heterogeneous blood cancer characterized by the rapid growth of abnormal white blood cells in the bone marrow. Understanding the complex molecular mechanisms underlying AML is essential for improving diagnosis, prognosis, and treatment strategies. In recent years, gene regulatory networks (GRNs) have emerged as powerful tools to explore how genes interact and contribute to disease progression. This project focuses on constructing a GRN specifically for AML using high-throughput gene expression data .

By applying network analysis techniques such as centrality measures and community detection, we identified key regulatory genes and potential biomarkers involved in AML pathogenesis. Furthermore, we explored pathway crosstalks like those between the Wnt, p53, NF-κB, and Hedgehog pathways, which influence leukemia stem cell survival, differentiation block, and therapy resistance.our study highlights critical hubs and druggable targets that may enhance precision medicine approaches in AML.

LITERATURE REVIEW:

[1] Epigenetic-based Differentiation Therapy for Acute Myeloid Leukemia

This study investigates the potential of epigenetic-based differentiation therapies in AML treatment. Using agents such as DNA methyltransferase and HDAC inhibitors, it demonstrated the ability to induce differentiation in AML cells effectively. Enhanced efficacy was observed when combined with other therapeutic strategies and tailored to specific patient subtypes. The research highlights the role of epigenetic mechanisms in advancing AML treatments.Challenges include incomplete differentiation and a lack of comprehensive clinical trial data, which limits the translation of findings into clinical practice.

[2] Dynamic Modeling of AML Gene Regulatory Networks

This study explores dynamic modeling of AML gene regulatory networks using Boolean network models. It predicted regulatory changes and identified drug resistance mechanisms during therapy. The modeling approach provides insights into potential therapeutic strategies and deepens the understanding of AML gene interactions under treatment conditions.The models are limited by their simplistic approach and the absence of real-time patient data, restricting their clinical applicability.

[3] Multi-Omics Integration for AML Network Analysis

This research integrates multi-omics data (transcriptomics, epigenomics, and proteomics) using deep learning models to analyze AML regulatory networks. The approach offered a multi-layered perspective, identifying potential therapeutic targets and advancing AML network understanding.The study faced computational complexity and required high-quality multi-omics datasets, which are often unavailable. These limitations hinder broader applicability.

[4] Navigating Ethical Issues in Collaborative Genomic Research

This study examines ethical considerations in genomic data sharing, focusing on North-South research collaborations. It highlighted challenges like inequitable resource distribution, data ownership concerns, and the necessity of equitable policies and trust frameworks in collaborative research efforts. The findings are constrained by regional policy variations and cultural differences, making the development of universally applicable frameworks challenging.

METHODOLOGY:

Network Construction:

For this project, we used Google Colab with Python libraries—pandas for data handling, networkx for building the gene regulatory network, and matplotlib for visualization. I created a custom edge list representing biologically relevant gene interactions and uploaded it as a CSV file. We constructed a network where nodes are genes and edges represent interactions. This allowed us to visualize and analyze the connectivity and potential regulatory roles of selected biomarkers in AML.

TABLE 1: Edge List

Gene1	Gene2	Correlation
AIRE	ALX1	0.6043483252808242
AIRE	ALX3	0.6166829275002621
AIRE	ALX4	0.6085071924293471
AIRE	ARID3A	0.5690722764608099
AIRE	ARID5B	0.5349062848250213
AIRE	ARX	0.6125105523573788
AIRE	BARHL2	0.6224339493051371
AIRE	BARX1	0.6402341763969993
AIRE	BARX2	0.5915757077353222
AIRE	BATF	0.5211972013539474

Gene1: Represents the source gene in the interaction.
Gene2: Represents the target gene that interacts with Gene1.
Correlation: Indicates the strength of the interaction between Gene1 and Gene2. A higher value means a stronger relationship.

Network Visualization:

To visualize the gene regulatory network, I used a force-directed layout which simulates physical forces—like springs and repulsion—between nodes. In this layout:

Connected genes are pulled closer, like they're linked by springs.

Unconnected genes repel each other to avoid overlap.

This creates an intuitive and biologically realistic structure, where highly connected genes (hubs) often cluster in the center, and less connected genes remain on the periphery.

The force-directed layout helps highlight central vs. peripheral genes, mimicking real biological regulatory hierarchies and identifying potential master regulators in diseases like AML

```
import matplotlib.pyplot as plt

# Apply force-directed layout
pos = nx.spring_layout(G, seed=42, k=0.8)  # k controls node spacing

# Draw network
plt.figure(figsize=(12, 12))
nx.draw(G, pos, with_labels=True, node_color="lightblue", edge_color="gray", alpha=0.7, font_size=8)
plt.title("Force-Directed Gene Regulatory Network")
plt.show()
```

Community Detection with Louvain Algorithm:

The Louvain algorithm has successfully grouped the genes into multiple color-coded clusters. These clusters likely represent functionally related genes — potentially co-regulated or involved in similar biological processes.The central region of the network has a dense group of interconnected nodes from multiple communities. This suggests that some genes serve as bridging nodes or hubs, possibly playing key roles in cross-talk between pathways or multi-pathway regulation in AML.

Example : The IRF Cluster Genes: IRF4, IRF8, IRF9, GBX1

Interpretation:

These are Interferon Regulatory Factors, involved in immune signaling and inflammation.Their clustering suggests a shared role in immune response regulation, which is relevant in AML's inflammatory microenvironment.

```
# Create an undirected graph
G = nx.Graph()
for _, row in df.iterrows():
    G.add_edge(row[gene1_col], row[gene2_col])

# Apply Louvain algorithm for community detection
partition = community_louvain.best_partition(G)

# Assign colors to communities
unique_communities = list(set(partition.values()))
colors = {node: unique_communities.index(community) for node, community in partition.items()}

# Define biomarkers to highlight
biomarkers = {"ZFHX3", "POU4F1", "POU3F3", "MSX1", "MSX2", "HMG20B"}

# Draw the network
plt.figure(figsize=(15, 10))
pos = nx.spring_layout(G, seed=42)  # Improved layout for clarity
nx.draw(G, pos, node_color=[colors[node] for node in G.nodes()], cmap=plt.cm.jet, with_labels=False, node_size=300)

# Draw labels separately for better readability
for node, (x, y) in pos.items():
    fontweight = 'bold' if node in biomarkers else 'normal'
    fontsize = 12 if node in biomarkers else 9
    color = 'red' if node in biomarkers else 'black'
    plt.text(x, y, node, fontsize=fontsize, ha='right', va='bottom',
             bbox=dict(facecolor='white', alpha=0.7, edgecolor='none'), fontweight=fontweight, color=color)

plt.title("Louvain Community Detection on Gene Network")
plt.show()
```

Biomarker Identification:

The following six biomarkers were selected based on their high degree centrality in the gene regulatory network, indicating their role as key regulators, and their biological relevance to AML. Additionally, their membership in distinct Louvain clusters suggests potential functional associations within regulatory modules.

Selected Biomarkers:

MSX1,MSX2 ,POU4F1, POU3F3,HMG20B, ZFHX3

Pearson Correlation Analysis:

Pearson correlation analysis was used to identify co-expression relationships between genes based on their expression profiles. Gene expression data was first structured into a matrix format, where each gene's expression levels across samples were compared pairwise

The Pearson correlation heatmap shows the pairwise correlation between the six selected AML biomarkers *MSX1, MSX2, POU3F3, POU4F1, HMG20B, and ZFHX3. T*hese values range from -1 to +1, where values close to +1 indicate strong positive correlation (co-expression), and values near 0 or negative indicate weak or inverse relationships.

From the heatmap, we observe that *MSX2 a*nd *POU3F3 ex*hibit a very strong positive correlation (0.94), suggesting they may be co-regulated or functionally related in AML. Similarly, *POU3F3* and *ZFHX3* also show a strong positive correlation (0.96), reinforcing their potential involvement in a shared regulatory mechanism. *MSX1* and *HMG20B* display a strong positive correlation (0.91), which may indicate a functional linkage, possibly in epigenetic regulation or tumor suppression. Additionally, *POU4F1* correlates moderately with *MSX1* (0.55) and *ZFHX3* (0.77), further supporting the idea that these biomarkers may interact within related molecular pathways.

```
import seaborn as sns
import matplotlib.pyplot as plt

# Compute Pearson correlation
corr_matrix = data.corr(method='pearson')

# Plot heatmap
plt.figure(figsize=(8, 6))
sns.heatmap(corr_matrix, annot=True, cmap='coolwarm', fmt='.2f')
plt.title('Pearson Correlation between AML Biomarkers')
plt.show()
```

PATHWAY DETECTION:

Following the identification of key biomarkers using network centrality and clustering analysis, a comprehensive literature review was conducted to determine their biological relevance in Acute Myeloid Leukemia (AML). Each biomarker was mapped to a specific pathway based on previous experimental and clinical findings. *MSX1* has been linked to the p53 pathway, which plays a critical role in apoptosis and tumor suppression, indicating MSX1's potential involvement in regulating AML cell survival. *MSX2* was associated with the Wnt/β-catenin signaling pathway, known for its role in hematopoietic stem cell proliferation and differentiation, suggesting a role in leukemogenesis when dysregulated. The transcription factors *POU4F1* and *POU3F3* were connected to the Hedgehog signaling pathway, which is implicated in maintaining leukemic stem cells and promoting chemoresistance in AML. *HMG20B* is known to influence *LSD1*-mediated epigenetic repression, a mechanism frequently hijacked in AML to silence tumor suppressor genes and maintain an undifferentiated state. Lastly, *ZFHX3* was found to be involved in the *NF-κB* signaling pathway, which has been reported to contribute to inflammation-driven oncogenesis and resistance to chemotherapy in AML patients. This pathway mapping reinforces the biological significance of these biomarkers and highlights their potential as therapeutic targets or diagnostic indicators in AML.

```
!pip install networkx matplotlib
import networkx as nx
import matplotlib.pyplot as plt

# Create a directed graph
G = nx.DiGraph()

# Define pathway interactions
pathway_edges = [
    ("MSX1", "p53 Pathway"), ("p53 Pathway", "Apoptosis Suppression (AML)"),
    ("MSX2", "Wnt Pathway"), ("Wnt Pathway", "Leukemic Stem Cell Survival"),
    ("POU3F3", "Hedgehog Pathway"), ("Hedgehog Pathway", "Differentiation Block"),
    ("POU4F1", "Hedgehog Pathway"),
    ("HMG20B", "LSD1 Epigenetic Repression"), ("LSD1 Epigenetic Repression", "AML Progression"),
    ("ZFHX3", "NF-κB Pathway"), ("NF-κB Pathway", "Chemoresistance in AML")
]

# Add edges and nodes to the graph
G.add_edges_from(pathway_edges)

# Draw the graph
plt.figure(figsize=(10, 6))
pos = nx.spring_layout(G, seed=42)
nx.draw(G, pos, with_labels=True, node_color="lightblue", edge_color="gray", node_size=2500, font_size=10, font_weight="bold")
plt.title("AML Biomarkers and Pathway Interactions")
plt.show()
```

PATHWAY INTERACTIONS:

Wnt Pathway → p53 Pathway
The Wnt/β-catenin signaling, activated by *MSX*2, not only supports leukemic stem cell survival but may also intersect with the p53 pathway. Wnt signaling can suppress p53 activity, reducing apoptosis and allowing malignant cells to proliferate.

NF-κB Pathway → p53 Pathway
ZFHX3 links to the NF-κB pathway, which can negatively regulate p53 signaling. This suppression contributes to apoptosis evasion and enhances chemoresistance, making treatment less effective.

LSD1 Epigenetic Repression → p53 Pathway
HMG20B, through LSD1 repression, may silence tumor suppressor genes like p53, indirectly reducing apoptosis and promoting AML progression.

Hedgehog Pathway → Wnt Pathway
Both *POU3F3* and *POU4F1* influence the Hedgehog pathway, which is known to synergize with Wnt signaling. This crosstalk contributes to stemness and differentiation block, supporting leukemogenesis.

This layered interaction suggests that targeting one pathway (e.g., Wnt or NF-κB) may influence others (like p53), offering potential combinational therapeutic strategies. The network reveals not only individual biomarker-pathway links but also how pathways collectively drive AML hallmarks such as stem cell survival, epigenetic silencing, differentiation block, and chemoresistance.

Centrality measures:

Degree Centrality:

The number of direct connections (edges) a node has.In networks: A node with high degree centrality is highly "connected.In a gene network, a gene (node) with high degree centrality interacts with many other genes it's like a "hub gene."*MSX2* has high degree centrality and functionaly related to AML so it is a hub gene.

```
G = nx.Graph()
G.add_edges_from(zip(df['Gene1'], df['Gene2']))

# Compute degree centrality for all genes
degree_centrality = nx.degree_centrality(G)

# Sort genes by degree centrality in descending order
sorted_centrality = sorted(degree_centrality.items(), key=lambda x: x[1], reverse=True)

# Display the top 10 genes with the highest degree
print("Top genes based on degree centrality:")
for gene, centrality in sorted_centrality[:20]:
    print(gene, centrality)
```

Betweenness Centrality:

A node with high betweenness acts like a bridge between different parts of the network.: A gene or pathway with high betweenness might control or mediate communication between clusters often a key regulator.Hedgehog pathway is found to be the pathway with hiigh betweenness centrality.

```
# Add edges to the graph with weights
for u, v, w in edges_with_scores:
    G.add_edge(u, v, weight=w)

# Compute centrality (betweenness) to identify key regulators
centrality = nx.betweenness_centrality(G, weight='weight')

# Apply force-directed layout
pos = nx.spring_layout(G, seed=42)

# Draw the graph
plt.figure(figsize=(12, 7))
edges, weights = zip(*nx.get_edge_attributes(G, 'weight').items())
nx.draw(G, pos, with_labels=True, node_color="lightblue", edge_color=weights,
        width=[w * 3 for w in weights], node_size=3000, font_size=10, font_weight="bold", cmap=plt.cm.Blues)
nx.draw_networkx_edge_labels(G, pos, edge_labels={(u, v): f'{w:.2f}' for u, v, w in edges_with_scores})

plt.title("NetworkX Analysis of AML Pathways")
plt.show()

# Print key regulators based on centrality
sorted_centrality = sorted(centrality.items(), key=lambda x: x[1], reverse=True)
print("Key Regulators (Betweenness Centrality):")
for node, score in sorted_centrality[:5]:
    print(f"{node}: {score:.4f}")
```

Therapeutic Drug Target Identification:

Based on the pathway analysis of selected biomarkers, We identified potential drug targets by querying pharmacological databases such as PubChem. Each identified drug has a direct link to the associated biomarker pathway.

The table below summarizes the gene targets, their related AML pathways, drug names, and PubChem links where the mechanism and structure can be explored further.

Biomarker	Associated Pathway	Drug Name	Drug Function	PubChem Link
MSX2	Wnt/β-catenin Pathway	XAV939	Wnt pathway inhibitor	XAV939
MSX1	p53 Pathway	Nutlin-3	MDM2 antagonist, activates p53	Nutlin-3
POU4F1	Hedgehog Signaling	Vismodegib	Smoothened (SMO) inhibitor	Vismodegib
POU3F3	Hedgehog	GANT61	GLI1/2 transcription	GANT61

Biomarker	Associated Pathway	Drug Name	Drug Function	PubChem Link
	Signaling		inhibitor	
HMG20B	LSD1Mediated Repression	ORY-1001 (Iadademstat)	LSD1 inhibitor	ORY-1001
ZFHX3	NF-κB Pathway	BAY 11-7082	NF-κB inhibitor via IκBα phosphorylation	BAY 11-7082

ETHICAL CASE-STUDIES:

PATENT 1: Biomarkers for Acute Myeloid Leukemia (US Patent 10,501,802)

1. **Biomarker Identification**:

The patent details a set of specific **genes, proteins, or metabolites** whose expression levels or mutational status are significantly associated with AML.

Biomarkers are identified through advanced techniques such as:

High-throughput genomic or proteomic analyses.

RNA sequencing or protein mass spectrometry.

Statistical correlation with clinical outcomes.

2. **Diagnosis**:

Biomarkers are used to distinguish AML from other hematological disorders.

They provide higher accuracy and sensitivity than traditional diagnosic methods like blood smears or bone marrow analysis.

This approach can detect AML at earlier stages, improving treatment outcomes.

3. **Prognosis**:

Certain biomarkers are linked to disease progression, treatment response, and patent survival rates.

By evaluating these markers, clinicians can stratify patents into:

High-risk (likely to relapse or progress rapidly).

Low-risk (favorable prognosis with standard treatment).

4. **Therapeutic Guidance**:

Biomarkers can identify patents who are likely to respond to specific therapies.

For example:

Targeted treatments (e.g., inhibitors for mutated FLT3 or IDH genes).

Predicting resistance to chemotherapy or relapse.

This ensures a personalized medicine approach, improving treatment effectiveness and reducing unnecessary toxicity.

5. **Biomarker Panels**:

The patent describes the use of a panel of biomarkers, which collectively provide a more comprehensive understanding of the disease.

Panels are validated for clinical use to improve diagnostic precision and prognostic accuracy

PATENT 2: Classification, Diagnosis, and Prognosis of Acute Myeloid Leukemia by Gene Expression Profiling (EP Patent 1,723,257)

1. **Gene Expression Profiling**:

The method involves examining the expression levels of a large set of genes within AML samples.

High-throughput technologies like micro arrays or RNA sequencing are used to collect this data.

2. **Classification**:

AML is a highly heterogeneous disease with many sub types, each with distinct genetic and molecular features.

The patent proposes identifying subgroups of AML based on specific gene expression signatures.

By clustering patents into sub types, treatment strategies can be better tailored to individual needs.

3. **Diagnosis**:

Using gene expression data, the method allows for the identification of AML by comparing patent data to known disease signatures.
This approach provides higher sensitivity and specificity than traditional diagnostic methods like cytogenetics or morphology.
4. **Prognosis**:
The gene expression profiles can predict the clinical outcome of the disease, such as:
Likelihood of survival.
Risk of relapse.
Response to specific therapies.
This allows clinicians to categorize patents into risk groups (e.g., high risk vs. low risk).
5. **Data Analysis and Algorithms**:
The system relies on advanced computational tools to analyze complex gene expression datasets.
Algorithms identify patterns and correlations between gene expression levels and clinical outcomes.
Machine learning models are likely employed to refine predictions.

PATENT 3: Molecular Analysis of Acute Myeloid Leukemia (WO Patent 2012/156515)
1. **Molecular Profiling**:
The patent outlines the use of high-throughput molecular techniques to analyze:
Genetic mutations: Identifying mutations in genes such as FLT3, NPM1, IDH1/2, TP53, and others that are common in AML.
Chromosomal rearrangements: Detecting abnormalities like translocations (e.g., t(8;21), inv(16)) or deletions.
Gene expression: Examining patterns of gene activity specific to AML.
2. **Comprehensive Data Collection**:
The analysis integrates data from multiple sources, including:
Whole-genome or targeted sequencing.
Copy number variation (CNV) analyses.
Epigenetic modifications such as DNA methylation or histone acetylation.
3. **AML Subclassification**:
The patent emphasizes using molecular data to classify AML into distinct sub types.This is critical as different AML sub types respond differently to treatments, and the molecular profile helps identify these subgroups.
4. **Prognostic Insights**:
The molecular analysis reveals markers associated with:
Disease progression.
Likelihood of relapse.
Overall survival rates.
Patents are stratified into risk groups based on these findings.
5. **Therapeutic Implications**:
Molecular analysis aids in identifying:
Patents who may benefit from specific targeted therapies (e.g., FLT3 inhibitors for FLT3 mutations).
Resistance mechanisms to standard chemotherapy or emerging therapies.
This allows clinicians to adopt a personalized treatment approach.
6. **Biomarker Discovery**:
The molecular data enables the discovery of new biomarkers for AML, which can serve as therapeutic targets or diagnostic tools.
PATENT 4: Methods for Assessing Patents with Acute Myeloid Leukemia (CA Patent 2,589,055)
1. **Patent Evaluation**:
The method uses a comprehensive assessment that combines:
Molecular and genetic markers (e.g., mutations in FLT3, NPM1, CEBPA).
Chromosomal abnormalities (e.g., translocations like t(15;17), deletions, or inversions).
Clinical data, such as patent age, white blood cell count, and bone marrow characteristics.
2. **Diagnostic Tools**:
The approach includes techniques such as:

Gene sequencing: Detecting mutations associated with AML.
Cytogenetcs: Identifying chromosomal rearrangements and abnormalines.
Flow cytometry: Assessing cell surface markers characteristic of AML blasts.
3. **Prognostic Models**:
Prognostic algorithms are described to predict:
Disease progression.
Survival rates.
Likelihood of achieving complete remission treatment.
Risk groups (e.g., low-risk, intermediate-risk, high-risk) are assigned based on molecular and clinical factors.
4. **Therapeutic Guidance**:
The methods provide insights into selecting the most effective treatment options for individual patents:
Chemotherapy regimens.
Targeted therapies (e.g., FLT3 inhibitors or IDH1/2 inhibitors).
Stem cell transplantation for high-risk patents.
Resistance markers are identified to predict and avoid ineffective treatments.
5. **Monitoring Disease Progression**:
The patent includes methods to track AML progression or relapse by measuring:
Minimal residual disease (MRD) using molecular markers.
Changes in genetic or cytogenetic profiles over Ѳmega.
6. **Biomarker Integration**:
Biomarkers are highlighted as key indicators for AML assessment:
Predictive biomarkers for treatment response.
Prognostic biomarkers for disease outcome.
Diagnostic biomarkers to confirm AML presence.

RESULTS AND DISCUSSION:

In this project, a gene regulatory network (GRN) specific to Acute Myeloid Leukemia (AML) was constructed using gene expression correlation data. After preprocessing, including duplicate removal and correlation thresholding, a refined network was generated and analyzed using network science techniques. Community detection via the Louvain algorithm revealed clusters of genes that may represent co-regulated pathways. Centrality analysis identified key genes such as *MSX1, MSX2, ZFHX3, POU3F3, POU4F1,* and *HMG20B*, which were strongly connected and/or acted as bridges between pathways. These genes were mapped to critical AML-related pathways including Wnt, p53, NF-κB, Hedgehog, and LSD1 inhibition. Observed crosstalk among these pathways suggested synergistic effects in blocking differentiation and promoting leukemic stem cell survival, underlining their importance in AML progression.Overall, the findings contribute to identifying potential therapeutic targets and understanding the molecular complexity of AML.The following are the outputs of our project

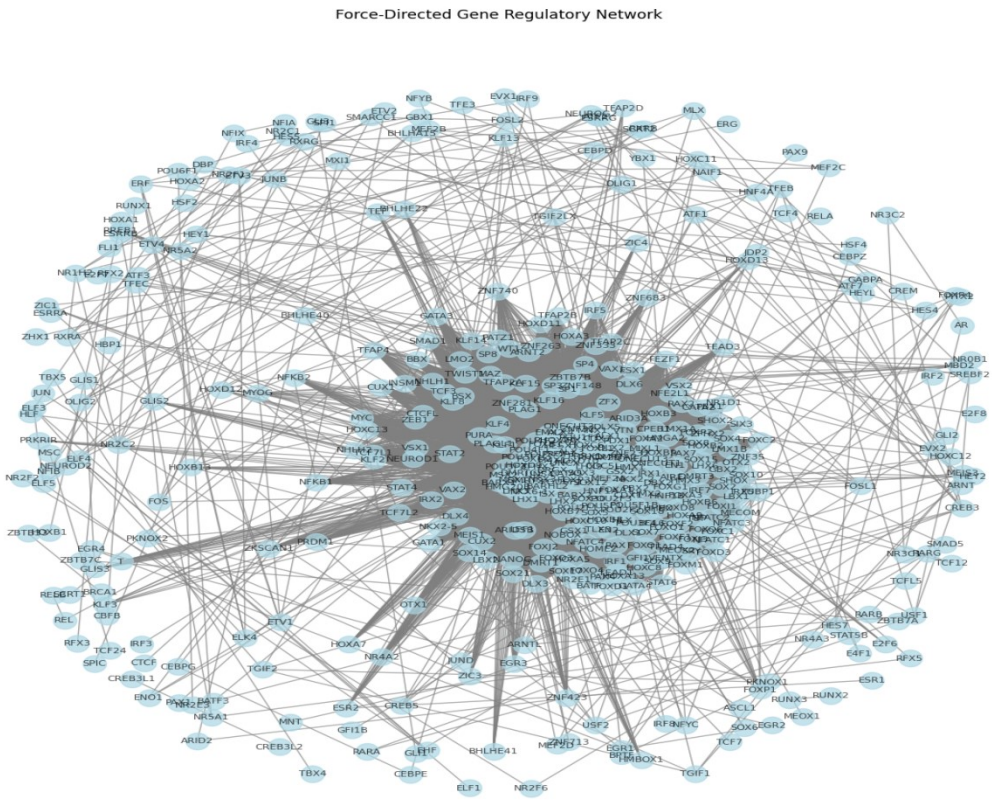

Fig 1. Force directed layout

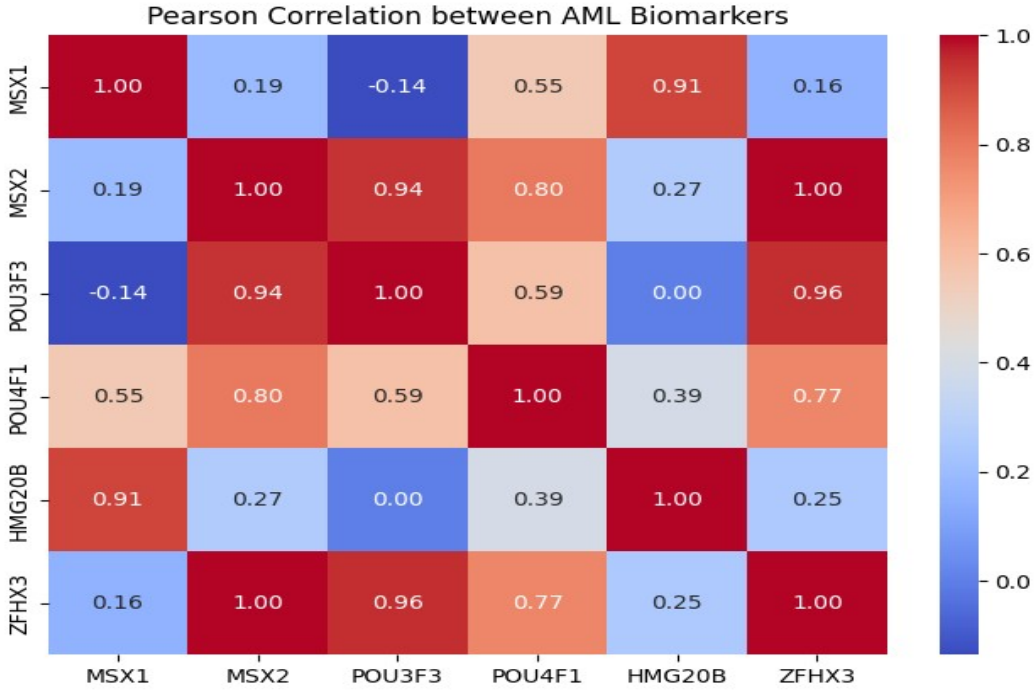

Fig 2: Pearson Correlation analysis

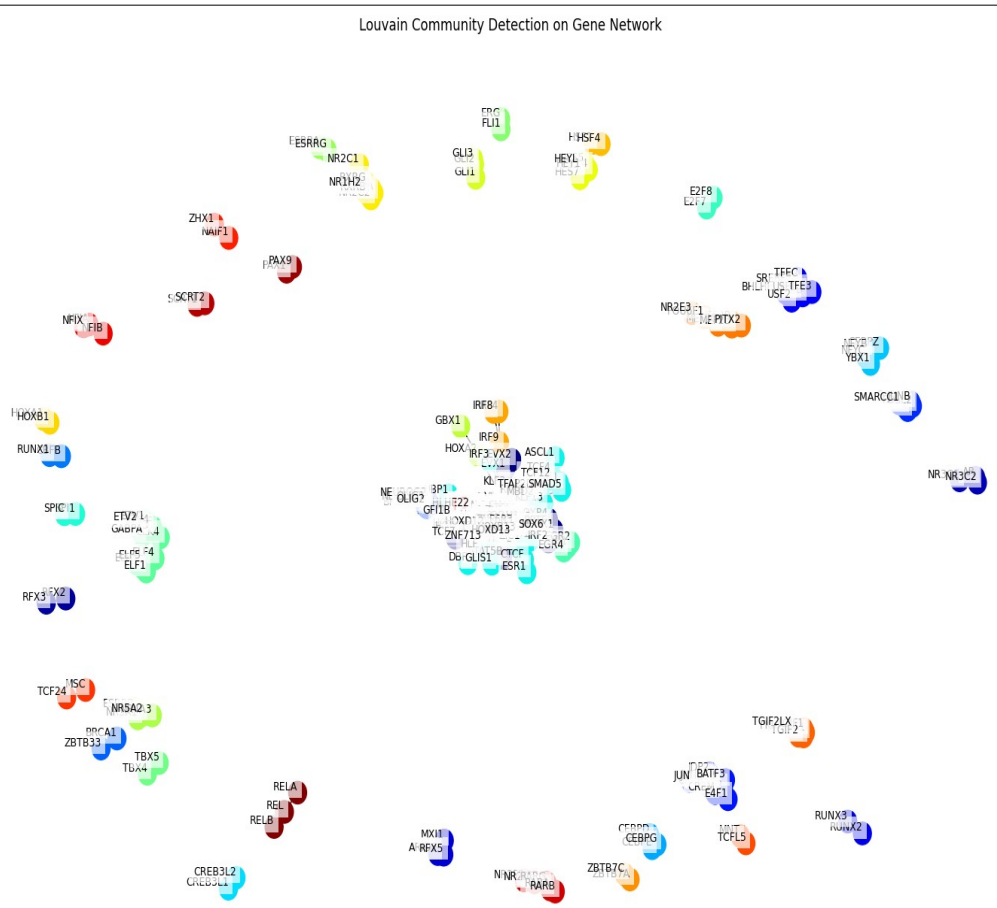

Fig 3.Louvain Community Detection

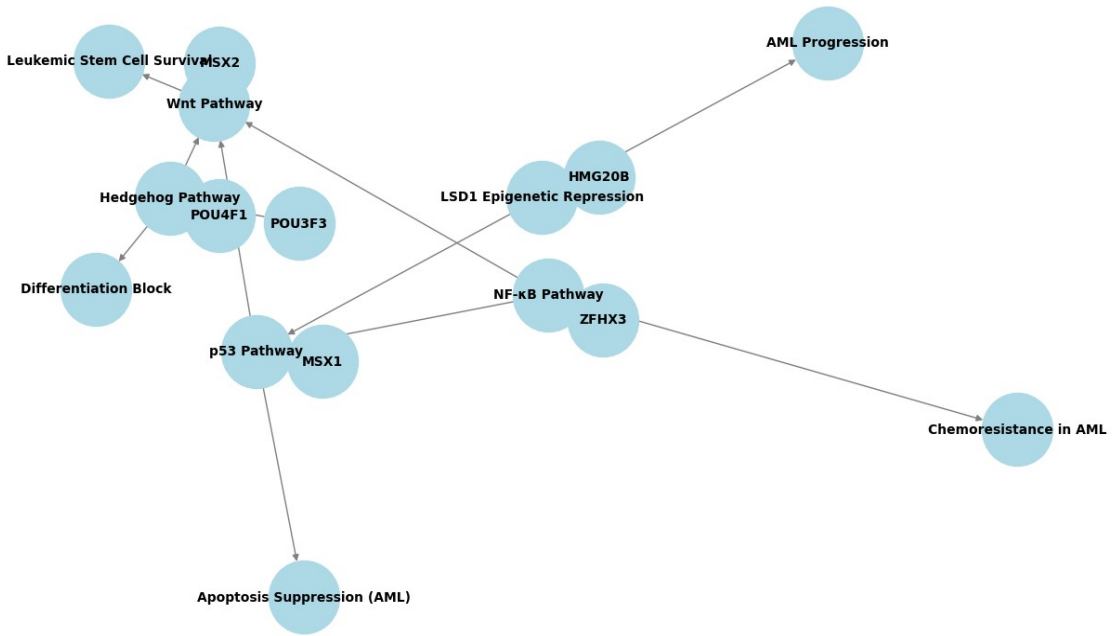

Fig 4: Pathway detection and interactions

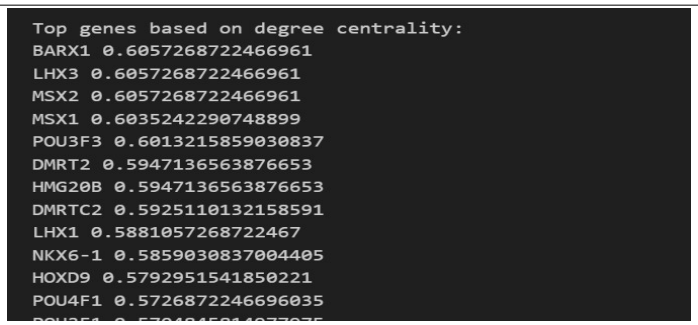

Fig 5. Degree Centrality

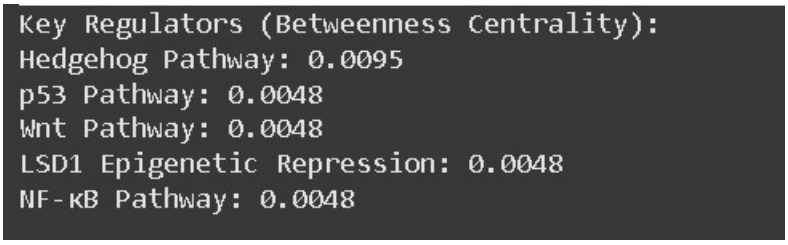

Fig 6. Betweness Centrality

Conclusion:

This project successfully demonstrates how gene regulatory network analysis can uncover critical molecular mechanisms underlying Acute Myeloid Leukemia (AML). By applying network science techniques—such as community detection and centrality analysis—we identified key transcription factors and biomarkers involved in AML progression. These genes were linked to important signaling pathways, including Wnt, p53, NF-κB, Hedgehog, and LSD1 inhibition, revealing their potential roles in maintaining leukemic stem cells and promoting resistance to therapy.This approach can guide future studies in personalized medicine and targeted drug development for AML.

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