

# Gene Regulatory Network Models

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This model represents a Gene Regulatory Network (GRN) — a map of how genes regulate each other through activation or suppression. In the context of autophagy-deficient tumors, this is crucial for:

1. Understanding Alternative Pathways:
  - When autophagy is defective, tumors often compensate via alternative gene circuits.
  - Our model can identify which genes are regulatory bottlenecks or amplifiers.
2. Coherent Feed-Forward Loops (C1-FFLs):
  - The motifs we injected and detected ( $X \rightarrow Y \rightarrow Z$  and  $X \rightarrow Z$ ) are robust signaling units.
  - These motifs filter noise, delay signals, or amplify effects, making them key to system resilience.

Finding them in a GRN can point to stabilizing mechanisms a tumor may exploit.

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[1]: import networkx as nx
import numpy as np
import pandas as pd
import matplotlib.pyplot as plt

# Step 1: Create mock expression data
np.random.seed(42)
genes = [f'Gene_{i}' for i in range(1, 21)]
expression_data = pd.DataFrame({
    'Gene': genes,
    'Expression_Level': np.random.rand(20) * 100
})
expression_dict = dict(zip(expression_data['Gene'],
    ↪expression_data['Expression_Level']))

# Step 2: Define initial GRN edges
edges = [
    ('Gene_1', 'Gene_2'), ('Gene_2', 'Gene_3'), ('Gene_3', 'Gene_4'),
    ('Gene_5', 'Gene_3'), ('Gene_6', 'Gene_7'), ('Gene_8', 'Gene_9'),
    ('Gene_10', 'Gene_11'), ('Gene_11', 'Gene_12'), ('Gene_12', 'Gene_13'),
    ('Gene_14', 'Gene_15'), ('Gene_15', 'Gene_16'), ('Gene_17', 'Gene_18'),
    ('Gene_18', 'Gene_19'), ('Gene_19', 'Gene_20'), ('Gene_6', 'Gene_1'),
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    ('Gene_13', 'Gene_14'), ('Gene_7', 'Gene_10')
]

# Step 3: Create GRN and add initial nodes/edges
grn = nx.DiGraph()
grn.add_edges_from(edges)
nx.set_node_attributes(grn, expression_dict, name='expression')

# Step 4: Inject known C1-FFLs
c1_ffl_injections = [
    ('Gene_A', 'Gene_B'), ('Gene_B', 'Gene_C'), ('Gene_A', 'Gene_C'),
    ('Gene_D', 'Gene_E'), ('Gene_E', 'Gene_F'), ('Gene_D', 'Gene_F'),
    ('Gene_G', 'Gene_H'), ('Gene_H', 'Gene_I'), ('Gene_G', 'Gene_I')
]

for u, v in c1_ffl_injections:
    if u not in grn:
        grn.add_node(u, expression=np.random.rand() * 100)
    if v not in grn:
        grn.add_node(v, expression=np.random.rand() * 100)
grn.add_edges_from(c1_ffl_injections)

# Step 5: Detect C1-FFLs
def find_c1_ffls(graph):
    motifs = []
    for x in graph.nodes():
        for y in graph.successors(x):
            for z in graph.successors(y):
                if graph.has_edge(x, z) and x != y and y != z and x != z:
                    motifs.append((x, y, z))
    return motifs

c1_ffls = find_c1_ffls(grn)
c1_ffl_nodes = set()
c1_ffl_edges = set()
for x, y, z in c1_ffls:
    c1_ffl_nodes.update([x, y, z])
    c1_ffl_edges.update([(x, y), (y, z), (x, z)])

# Step 6: Visualize the network with highlights
pos = nx.spring_layout(grn, seed=42)
node_colors = ['orange' if node in c1_ffl_nodes else 'skyblue' for node in grn.
    ↪ nodes()]
node_sizes = [grn.nodes[n].get('expression', 30) * 10 for n in grn.nodes()]
edge_colors = ['red' if (u, v) in c1_ffl_edges else 'gray' for u, v in grn.
    ↪ edges()]

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plt.figure(figsize=(14, 10))
nx.draw_networkx_nodes(grn, pos, node_color=node_colors, node_size=node_sizes)
nx.draw_networkx_edges(grn, pos, edge_color=edge_colors, arrows=True)
nx.draw_networkx_labels(grn, pos, font_size=9)
plt.title("Gene Regulatory Network with Highlighted C1-FFLs")
plt.axis('off')
plt.tight_layout()
plt.show()

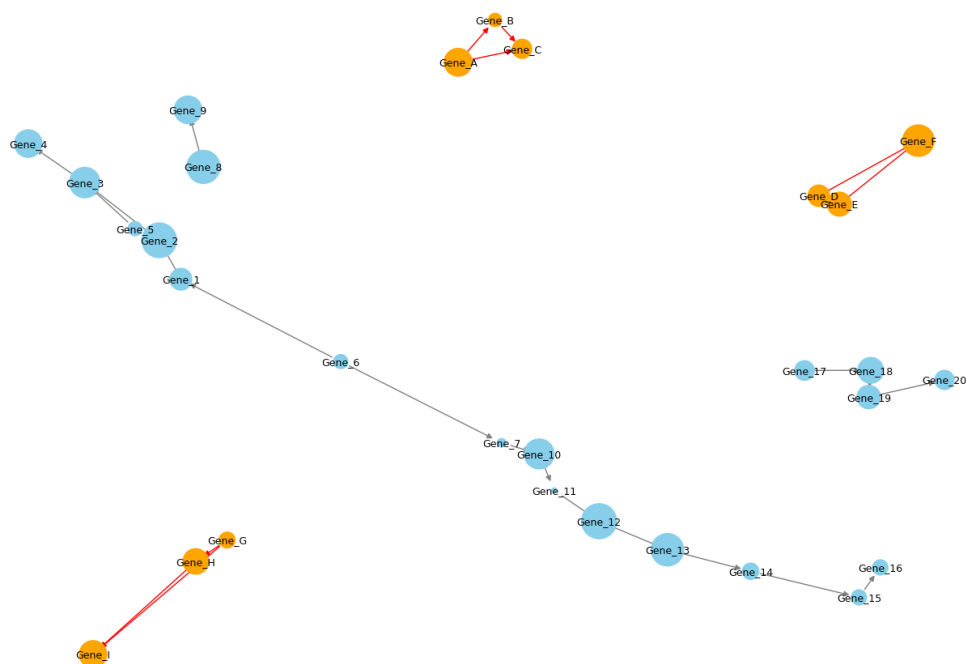
# Step 7: Export nodes and edges to CSV
nodes_data = [{
    'Gene': node,
    'Expression_Level': grn.nodes[node].get('expression', None),
    'In_C1FFL': node in c1_ffl_nodes
} for node in grn.nodes()]
edges_data = [{
    'Source': u,
    'Target': v,
    'Is_C1FFL_Edge': (u, v) in c1_ffl_edges
} for u, v in grn.edges()]

nodes_df = pd.DataFrame(nodes_data)
edges_df = pd.DataFrame(edges_data)

nodes_df.to_csv("grn_nodes_with_ffl.csv", index=False)
edges_df.to_csv("grn_edges_with_ffl.csv", index=False)

```

Gene Regulatory Network with Highlighted C1-FFLs



Interpreting the GRN: This network represents a Gene Regulatory Network (GRN) annotated with:

Orange nodes: Genes involved in Coherent Feed-Forward Loops (C1-FFLs).

Red edges: Regulatory interactions forming part of those FFLs.

Sky blue nodes: Genes outside of FFL motifs.

Node size: Proportional to the expression level of the gene.

### 0.0.1 Biological Insights:

Three Distinct C1-FFLs Identified:

- $\text{Gene\_A} \rightarrow \text{Gene\_B} \rightarrow \text{Gene\_C}$  with direct  $\text{Gene\_A} \rightarrow \text{Gene\_C}$ .
- $\text{Gene\_D} \rightarrow \text{Gene\_E} \rightarrow \text{Gene\_F}$  with  $\text{Gene\_D} \rightarrow \text{Gene\_F}$ .
- $\text{Gene\_G} \rightarrow \text{Gene\_H} \rightarrow \text{Gene\_I}$  with  $\text{Gene\_G} \rightarrow \text{Gene\_I}$ .

These motifs suggest redundant regulation or signal buffering—hallmarks of robust control systems in biology.

Implications in Autophagy-Deficient Tumors:

Such motifs may represent compensatory mechanisms activated when canonical autophagy fails.

Nodes like Gene\_A, Gene\_D, or Gene\_G are primary regulators capable of both direct and indirect control.

Gene\_C, Gene\_F, Gene\_I are targets under layered regulation, ideal candidates for intervention or tracking expression changes under stress.

### **0.0.2 Therapeutic Insight:**

Targeting just one edge may be insufficient; you'd have to disrupt both the direct and indirect paths to affect output.

This suggests potential resistance mechanisms in therapy if FFLs are intact.

The code executes a systems biology pipeline that mirrors real research workflows:

1. Network Construction:

Built with NetworkX, it allows us to treat biological regulation as a graph problem.

2. Motif Detection:

Identifying C1-FFLs is a form of network motif mining, akin to detecting reusable logic in a circuit.

3. Quantitative Prioritization:

By attaching expression levels and computing centrality, we can prioritize genes for:

Experimental validation

Therapeutic targeting

4. Visualization & Export:

The network is graphically visualized and export-ready for Cytoscape or machine learning workflows.