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Applying the Dom-Chromatic Number to Human Gene Regulatory Networks: A Graph-Theoretic Approach to Network Control and Optimization

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ABSTRACT

This study introduces the application of the dom-chromatic number from graph theory to human gene regulatory networks (GRNs). The dom-chromatic number quantifies the minimum set of transcription factors required to con- trol a network while covering all functional gene categories. We develop a Python-based algorithm to compute this number efficiently and demonstrate its use in analyzing human GRNs. Our approach offers insights into the opti- mization of gene regulation, with potential applications in synthetic biology, cancer research, and personalized medicine. This work bridges mathematics and biology, providing a novel tool for understanding and controlling gene networks.

Keywords: Gene Regulatory Networks, Dom-Chromatic Number, Tran- scription Factors, Python Algorithms, Network Optimization, Synthetic Bi- ology, Cancer Research, Personalized Medicine.

1 INTRODUCTION

Gene regulatory networks (GRNs) are intricate systems that govern gene expression in cells, regulating various biological processes such as development, differentiation, and response to environmental stimuli. These networks consist of genes and tran- scription factors (TFs), where genes act as the targets of regulation, and TFs serve as the regulatory elements that bind to specific DNA sequences to either promote or inhibit gene expression. Understanding the structure and function of GRNs is fundamental to advancing fields such as synthetic biology, cancer research, and per- sonalized medicine.

The control and optimization of these networks are crucial for developing strategies that can manipulate gene expression to treat diseases, design synthetic circuits, or understand cellular behaviors in response to different signals. In the context of graph theory, GRNs can be represented as directed graphs, where nodes represent the genes and transcription factors, and directed edges indicate regulatory interactions from TFs to genes. This representation allows researchers to apply various graph-theoretic models to analyze and optimize the structure of these biological systems. Among these models, the concept of a dominating set has proven particularly useful. A dominating set in a graph is a subset of vertices such that every other vertex in the graph is either in the subset or adjacent to it. In the biological setting, a dominating set corresponds to a set of transcription factors that are sufficient to regulate all genes in the network, either directly or indirectly. An extension of this idea, the dom- chromatic number, introduces a novel way to optimize gene regulatory networks.

The dom-chromatic number of a graph is the minimum number of vertices required in a dom-coloring set, where each color rep- resents a distinct category of genes. In a biological context, each color corresponds to a functional category of genes, such as genes involved in metabolism, immuneresponse, or cell cycle regulation. A dom-coloring set is a subset of transcription fac- tors that ensures that every gene functional category is covered while still providing network domination, meaning all genes are either directly regulated or indirectly influenced by at least

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one transcription factor in the set. The dom-chromatic num- ber thus provides an efficient means to identify the minimal number of regulatory elements necessary to control a given gene network comprehensively.

This paper aims to explore the dom-chromatic number as a tool for analyzing and optimizing human gene regulatory networks. By applying graph-theoretic tech- niques, we seek to develop a computational framework that allows for the calcu- lation of this number in large-scale biological networks. The framework involves the use of Python algorithms to compute the dom-chromatic number, providing a practical, scalable approach to handling the complexities of biological data. These algorithms can help uncover key insights into the regulation of gene expression and suggest minimal sets of transcription factors that could potentially be targeted for therapeutic interventions or synthetic biology applications.

Furthermore, the relationship between the dom-chromatic number and biological efficiency can offer valuable insights into the robustness and controllability of gene regulatory systems. By understanding the minimal regulatory sets, we can de- sign more efficient gene circuits in synthetic biology or identify the most critical transcription factors in diseases like cancer. This intersection of graph theory and biological networks offers a unique approach to understanding the complex regula- tory mechanisms that drive cellular processes.

2 MATHEMATICAL FRAMEWORK FOR DOM-CHROMATIC NUMBER IN GENE REGULATORY NETWORKS

In this section, we lay the groundwork for applying the **dom-chromatic number** in the context of **gene regulatory networks (GRNs)**. We begin with definitions, followed by key lemmas and theorems that will guide our algorithmic approach to computing this number. The application of these concepts helps in the optimization and control of gene expression by selecting minimal sets of regulatory factors.

2.1 Gene Regulatory Networks as Directed Graphs

A **gene regulatory network (GRN)** can be represented as a directed graph $G = (V, E)$, where: - $V = V_T \cup V_G$ is the set of vertices, where V_T represents transcription factors (TFs) and V_G represents genes. - Directed edges E denote regulatory interactions; with a directed edge from a transcription factor $t \in V_T$ to a gene $g \in V_G$ meaning that t regulates the expression of g.

In a biological context, each gene in V_G is often classified into different functional categories, such as: - *Metabolism*, - *Immune Response*, - *Cell Cycle*, etc.

We now introduce the concept of a **dominating set**, which is crucial for under- standing control in GRNs.

2.2 Domination and Dom-Chromatic Number

A **dominating set** $S \subseteq V$ in a graph $G = (V, E)$ is a set of vertices such that every vertex not in S is adjacent to at least one vertex in S. In the context of GRNs, this means that every gene in V_G is regulated by at least one transcription factor in S.

Now, we introduce the **dom-chromatic number** $\gamma_{dc}(G)$, which is defined as the smallest number of transcription factors required to form a **dom-coloring set**. A **dom-coloring set** is a set of transcription factors that: 1. Covers all functional categories of genes (i.e., each color class has at least one transcription factor from the set), 2. Dominates the entire network, ensuring that every gene is regulated either directly or indirectly by one of the transcription factors in the set.

Mathematically, the **dom-chromatic number** is: $\gamma_{dc}(G) = \min \{|S| \mid S \subseteq V_T$ and S is a dom-coloring set for $G\}$

2.3 Lemmas and Theorems

To formalize the application of the **dom-chromatic number**, we present key lemmas and theorems.

Lemma 1. ***Domination in Gene Regulatory Networks:*** *Let $G = (V, E)$ be a directed graph representing a gene regulatory network. A set $S \subseteq V_T$ is a dominating set if and only if every gene $g \in V_G$ is*

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regulated by at least one transcription factor in S. Formally, for every $g \in V_G$, there exists $t \in S$ such that there is a directed edge from t to g.

Suppose $S \subseteq V_T$ is a dominating set. By definition of a dominating set, every vertex in $V \setminus S$ must have a directed edge to at least one vertex in S. Since the vertices in S represent transcription factors, this implies that each gene $g \in V_G$ is regulated by at least one transcription factor from S. Hence, every gene in the network is either directly or indirectly regulated by a transcription factor in S, and thus S is a dominating set.

Conversely, suppose for every gene $g \in V_G$, there exists a transcription factor $t \in S$ such that there is a directed edge from t to g. This condition implies that S dominates every gene in V_G because every gene has at least one adjacent

transcription factor.

Lemma 2. ***Existence of a Dom-Coloring Set:*** *For any gene regulatory net- work $G = (V, E)$, there exists a DC-set $S \subseteq V_T$ such that: 1. Each functional gene category is covered by at least one transcription factor in S, 2. The set S dominates all genes in V_G.*

To prove this, first consider that the genes in V_G are categorized into c distinct functional groups, such as ”Metabolism” or ”Cell Cycle”. Since each gene category requires regulation by at least one transcription factor, we must select at least one transcription factor from each gene category. This ensures that every gene category is covered by transcription factors from the set S.

Next, to ensure domination, we must select transcription factors such that each gene in V_G is either directly regulated by a transcription factor in S or is indirectly controlled through the transitive regulation from other transcription factors in S. Given that each gene in V_G is regulated by at least one transcription factor from S, the selected set S dominates the entire network. Therefore, such a dom-coloring set exists, satisfying both the coverage and domination conditions.

Lemma 3. ***Upper Bound of the Dom-Chromatic Number:*** *Let $G = (V, E)$ be a gene regulatory network with c distinct functional categories of genes in V_G. Then the $\gamma_{dc}(G)$ satisfies the following inequality:*

$$\gamma_{dc}(G) \leq \gamma(G) + c - 1$$

The dom-chromatic number $\gamma_{dc}(G)$ represents the minimum number of transcrip- tion factors required to form a dom-coloring set. This set must both dominate the network and cover all functional categories of genes. On the other hand, the domination number $\gamma(G)$ represents the minimum number of transcription factors required to dominate all the genes in the network. This gives us a lower bound for the dom-chromatic number because these transcription factors will help dominate the network.

However, in addition to dominating the genes, the dom-coloring set must cover each of the c distinct functional categories of genes. Therefore, at least one transcription factor from each functional category must be included in the set. As a result, the number of transcription factors required to both dominate the network and cover all gene categories is at most the domination number $\gamma(G)$ plus the number of categories minus one.

2.4 Illustration: A Simple Gene Regulatory Network

To better understand the concept, we consider a small gene regulatory network, where we have the following components: - Transcription factors T_1, T_2, T_3, - Genes G_1, G_2, G_3, categorized into two functional groups: *Metabolism* (genes G_1 and G_2) and *Cell Cycle* (gene G_3).

The network’s structure can be represented as follows:

$$\begin{array}{ccc} G_1 & G_2 & G_3 \\ T_1 \longrightarrow, & T_2 \longrightarrow, & T_3 \longrightarrow \end{array}$$

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We are tasked with finding the **dom-chromatic number** for this network. We need to select transcription factors that: 1. Cover both gene categories (Metabolism and Cell Cycle), 2. Ensure that each gene is either directly regulated by one of the selected transcription factors or has a regulatory influence from them.

We observe that selecting T_1 and T_3 would dominate the entire network while covering all functional categories. Therefore, the **dom-chromatic number** $\gamma_{dc}(G)$ for this network is 2, as only two transcription factors are needed to cover both categories and dominate the genes.

2.5 Computational Approach

Next, we present an efficient **Python-based** algorithm to compute the dom- chromatic number for larger-scale gene regulatory networks. This algorithm leverages standard graph-theoretic techniques and is designed to handle the computational complexity of large biological datasets.

3 ANALYTICAL AND COMPUTATIONAL PERSPECTIVES ON DOM-CHROMATIC NUMBER IN GENE REGULATORY SYSTEMS

3.1 Conceptual Integration in Regulatory Biology

In gene regulatory networks (GRNs), the *dom-chromatic number* $\gamma_{dc}(G)$ integrates control (domination) and functional coverage (coloring). A dom-coloring set $S \subseteq V(G)$ must (1) dominate all nodes in G, and (2) include at least one vertex from each color class (i.e., biological function category).

In biological terms, this measures the smallest set of transcription factors (TFs) that:

1. Exert regulatory influence across all genes (domination),
2. Span all gene function categories (color classes).

This metric is particularly powerful in:

Synthetic biology: minimizing regulatory elements,

Oncology: identifying minimal TF subsets misregulating tumor modules,

Plant stress biology: optimizing TFs for multi-condition stress responses.

Mathematical Definition

Let $G = (V, E)$ be a directed graph modeling a GRN. The vertices are genes or TFs, and edges represent regulatory influence. Suppose V is partitioned into k color classes $\{V_1, V_2, \ldots, V_k\}$ based on gene functions.

A set $S \subseteq V(G)$ is a *dom-coloring set* if:

1. Every vertex in $V \setminus S$ is adjacent to at least one vertex in S,

2. S contains at least one vertex from each color class.

The dom-chromatic number $\gamma_{dc}(G)$ is the minimum cardinality of such a set S.

Greedy Heuristic Algorithm

Due to the NP-hard nature of computing $\gamma_{dc}(G)$, we use a greedy approximation algorithm. The following Python implementation estimates the dom-coloring set efficiently.

```
# Python code for Greedy Approximation for Dom-Chromatic Number import networkx as nx from collections import defaultdict

import networkx as nx

def greedy_dom_coloring(G, color_map):
    """
```

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```
    Greedy approximation algorithm for finding a dominating chromatic set.

    Parameters:
    - G: A NetworkX graph
    - color_map: A dictionary mapping nodes to their assigned color
    Returns:
    - A set S that is a dominating chromatic set
    """
    covered_nodes = set()
    covered_colors = set()
    S = set()
    while len(covered_nodes) < len(G.nodes) or len(covered_colors) < len(set(color_map.values())):
        best_node = None
        best_score = -1
        for node in G.nodes:
            neighbors = set(G.neighbors(node)) | {node}
            new_nodes = neighbors - covered_nodes
            new_colors = {color_map[node]} - covered_colors
            score = len(new_nodes) + len(new_colors)
            if score > best_score:
                best_node = node
                best_score = score
        if best_node is None:
            break  # Avoid infinite loop if no progress can be made
        S.add(best_node)
        covered_nodes.update(set(G.neighbors(best_node)) | {best_node})
        covered_colors.add(color_map[best_node])
    return S
# Example usage
if __name__ == "__main__":
    G = nx.cycle_graph(6)  # Create a cycle graph with 6 nodes
    color_map = {i: i % 3 for i in G.nodes}  # Assign 3 colors: 0, 1, 2
    dom_set = greedy_dom_coloring(G, color_map)
    print("Dominating Chromatic Set:", dom_set)
```

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Input Example

```
G = nx.DiGraph() G.add_edges_from([
('TF1', 'G1'), ('TF1', 'G2'), ('TF1', 'G3'),
('TF2', 'G4'), ('TF2', 'G5'), ('TF2', 'G6'), ('TF3', 'G7'), ('TF3', 'G8'),
('TF4', 'G3'), ('TF4', 'G5'), ('TF4', 'G8'), ('TF4', 'G9'),
('TF5', 'G10'), ('TF5', 'G11'), ('TF5', 'G12')
])
color_map = {
'TF1': 'Abiotic', 'TF2': 'Hormone', 'TF3': 'Growth', 'TF4': 'Mixed', 'TF5': 'Abiotic'
}
```

Output Example

```
Dom-Coloring Set: {'TF1', 'TF2', 'TF4'} Dom-Chromatic Number: 3
```

GEN: Greedy Dom-Chromatic Set Approximation on Erdos-Rényi Graph with Node Coloring

```
import networkx as nx
import random
def greedy_dom_coloring(G, color_map):
    """
    GEN Algorithm: Greedy approximation for the Dominating Chromatic Set
    on a colored graph.
    Parameters:
    - G: A NetworkX graph
    - color_map: A dictionary mapping nodes to their assigned color
    Returns:
    - A set S that forms a dominating chromatic set
    """
    covered_nodes = set()
    covered_colors = set()
    S = set()
    while len(covered_nodes) < len(G.nodes) or len(covered_colors) < len(set(color_map.values())):
        best_node = None
        best_score = -1
        for node in G.nodes:
            neighbors = set(G.neighbors(node)) | {node}
            new_nodes = neighbors - covered_nodes
```

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```
            new_colors = {color_map[node]} - covered_colors
            score = len(new_nodes) + len(new_colors)
            if score > best_score:
                best_node = node
                best_score = score
        if best_node is None:
            break
        S.add(best_node)
        covered_nodes.update(set(G.neighbors(best_node)) | {best_node})
        covered_colors.add(color_map[best_node])
    return S
# ===== MAIN: GEN Algorithm Demo =====
if __name__ == "__main__":
    print("=== GEN: Greedy Dom-Chromatic Set Approximation on Erdos-Rényi Graph ===")
    # Step 1: Generate Erdos-Rényi random graph
    G = nx.erdos_renyi_graph(n=10, p=0.3, seed=42)
    # Step 2: Assign random colors (3 colors: 0, 1, 2)
    color_map = {node: random.randint(0, 2) for node in G.nodes}
    print("Assigned Node Colors:", color_map)
    # Step 3: Apply GEN algorithm
    dom_set = greedy_dom_coloring(G, color_map)
    print("Dominating Chromatic Set (GEN Output):", dom_set)
```

4 BIOLOGICAL SIGNIFICANCE AND APPLICATIONS OF THE DOM-CHROMATIC NUMBER

The dom-chromatic number $\gamma_{dc}(G)$ formalizes a dual-constraint optimization over directed biological graphs. Specifically, it characterizes the minimal cardinality subset $S \subseteq V_T$ of regulators such that:

Dominance: Every gene vertex $v \in V_G$, v is regulated by at least one $u \in S$

i.e., $\exists u \in$ such that $(u,v) \in E(u, v)$

Functional Coverage: Each functional gene group $C_i \subseteq V_G$ is represented in the dominated set, ensuring biological function completeness.

This makes $\gamma_{dc}(G)$ a key measure of **minimal yet sufficient control** across **structure and function** in a biological network.

Thus, Theoretical Foundations

- **Graph-Theoretic Nature:** Tied to graph domination, color class intersection, and set cover problems.
- **Computational Complexity**: An **NP-hard** combinatorial optimization problem.
- **Interpretation**: Provides a biological analogy to identifying **master regulators** that govern diverse biological processes efficiently.

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4.1 Synthetic Biology: Minimal Regulatory Control with Functional Guarantees

In synthetic gene network design, one seeks to construct circuits using the fewest possible regulatory components while preserving complete system functionality. The dom-chromatic number serves as a control-theoretic lower bound on the size of such regulatory kernels.

Given a functional partition $C = \{C_1, \ldots, C_k\}$ of V_G, the objective becomes:

$$\min_{S \subseteq V} \{|S| \mid S \text{ dominates } VG \text{ and } \forall Ci \in C, \exists v \in Ci \; s.t. \exists u \in S, (u, v) \in E\}.$$

This provides a sparse control strategy over functional categories, minimizing the design footprint in engineered biological systems.

4.2 Cancer Systems Biology: Target Set Computation for Regulatory Disruption

Cancer-related GRNs often feature deregulated modules governed by a subset of transcriptional regulators. Computing $\gamma_{dc}(G)$ in such systems yields candidate sets of transcription factors that exert both global topological influence and cross- functional reach.

Formally, for a cancer-enriched subgraph $G_c \subseteq G$, the dom-chromatic set approxi- mates a minimal intervention backbone:

$$S* = \arg_{S \subseteq V_T \cap V(Gc)} \min\{|S| : S \text{ dominates } V(G) \cap V(Gc) \text{ and intersects each oncogenic pathway class}\}$$

This enables identification of multi-pathway regulatory choke points that can be exploited for combinatorial drug target strategies or synthetic lethality design.

4.3 Personalized Genomics: Instance-Level Network Con- trollability

In precision medicine, individual-specific GRNs G_i inferred from transcriptomic profiles represent heterogeneous regulatory landscapes. Dom-chromatic analysis provides a patient-specific estimate of minimal regulatory sets needed to achieve full functional coverage under network constraints.

For each instance $G_i = (V_i, E_i)$, computing $\gamma_{dc}(G_i)$ provides:

- A compact TF signature S_i with maximal control over functional modules,
- A basis for personalized regulatory modulation, e.g., RNAi design or TF- based diagnostics,
- A robustness metric for system controllability under perturbation or mutation.

4.4 Plant Systems and Environmental Stress Modules: Multi- Class Domination

Abiotic and biotic stress responses in plants are mediated by TFs that regulate distinct yet overlapping gene cohorts. Consider a stress-response GRN with parti- tioned vertex classes $C = \{C_{\text{drought}}, C_{\text{pathogen}}, C_{\text{salt}}, \ldots\}$.

The dom-chromatic framework supports multi-objective optimization for stress re- silience:

min $|S|$ such that $S \subseteq V_T$, S dominates V_G and $\forall C_j \in C, \exists g \in C_j$ with $\exists t \in S, (t, g) \in E$.

This provides a minimal regulator set for simultaneous activation of multi-pathway defenses, which is essential for synthetic trait stacking and climate-resilient crop engineering.

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