AJMS
Asian Journal of Mathematical Sciences

RESEARCH ARTICLE

PAGERANK-INSPIRED APPROACH FOR MODELING LONG-TERM BEHAVIOR IN STOCHASTIC GENE REGULATORY NETWORKS

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Received: 28-06-2024; Revised: 26-07-2024; Accepted: 28-08-2024

ABSTRACT

Gene regulatory network (GRN) play a crucial role in understanding the complex interac-tions between genes and their regulatory elements. However, accurately modeling the long-term behavior of GRNs under stochasticity remains a challenging task. In this study, we propose a methodology that leverages the concept of PageRank, originally developed for ranking web pages, to analyze the long-term behavior of GRNs. This approach involves constructing a directed graph representation of the GRN, where genes are represented as nodes and regulatory interactions as directed edges. We then adapt the PageRank algorithm to the GRN context, considering the stochastic nature of gene expression and incorporating the inherent randomness in regulatory interactions. By iteratively computing the PageRank scores, we obtain a ranking of the transition states based on their long-term influence within the network. To evaluate the effectiveness of our approach, we apply it to synthetic GRN models. Our findings cap-tured essential aspects of the long-term behavior in stochastic GRNs. We observe that genes with higher PageRank scores tend to have a greater influence on the overall network dynamics and exhibit more stable and persistent expression patterns

Keywords: Gene regulatory network (GRN), Stochasticity, Long-term behavior, Network dynamics, Gene expres-sion, Directed graph, Page Rank scores.

INTRODUCTION

Understanding the intricate mechanisms of gene regulation is paramount in modern biology. Gene regulatory networks (GRNs) orchestrate complex cellular processes by controlling the production of proteins through a web of interactions between genes. Identifying key regulators within these networks is cru-cial for deciphering their function and potentially manipulating them for therapeutic interventions. Traditional methods for GRN analysis often assume deterministic behavior, meaning a specific gene state leads to a predictable outcome. However, inherent randomness, or stochasticity, plays a significant role in gene regulation. The timing of interactions, protein activation probabilities, and even cellular responses can exhibit variability [8, 23, 25]. This inherent noise necessitates the use of models that incorporate stochasticity for a more realistic representation of GRN dynamics. Stochastic Boolean Network Models (SBNMs) capture the qualitative dynamics of GRNs by representing genes as nodes that can be active or inactive and incorporating probabilities into the transitions between states [5, 18, 22]. Our approach

leverages the core principle behind the well-known PageRank algorithm, originally developed by Google to rank the importance of webpages [20].

Mathematical modeling offers a powerful tool for analyzing complex biological systems like GRNs. Boolean network models (BNMs) provide a simplified yet effective framework for capturing the qualitative dynamics of these networks [7, 11, 14]. However, BNMs typically assume deterministic behavior, limiting their ability to represent the inherent stochasticity within GRNs. To address this limitation, researchers have developed SBNMs. These models incorporate probabilities into the transitions between gene states, offering a more realistic representation of the inherent randomness within GRNs [2, 10, 18]. SBNMs have been successfully employed to analyze the dynamics of various GRNs, revealing insights into the role of noise in cellular processes [4, 17].

Identifying key regulators within GRNs is crucial for understanding their function and potential therapeutic applications. Various techniques have been employed for this purpose, including network centrality measures, control theory approaches, and analysis of network motifs [3, 12, 13, 16, 24]. Network centrality measures quantify the importance of a node within a network based on its connectivity or other topological features. Control theory approaches identify control strategies for manipulating specific genes to achieve desired network behavior, highlighting influential regulators [1, 13, 26]. Additionally, analyzing network motifs, recurring patterns of interactions within GRNs, can reveal how these substructures contribute to network dynamics and identify potentially crucial regulatory elements [12, 15]. The PageRank algorithm is a cornerstone of web search engines, assigning a score to each webpage based on the quality and number of links pointing to it [20]. Webpages with many high-quality links are considered more important or influential. The underlying principle of PageRank can be adapted to analyze various network structures beyond the web.

Recent research has explored adapting PageRank for applications in networks. For instance, stud-ies have employed PageRank-inspired approaches to analyze interaction networks, aiming to identify influential nodes within these systems [6, 9, 19]. However, applying PageRank directly to SBNMs for identifying key regulators is challenging due to the inherent differences between static web networks and dynamic, probabilistic GRNs. This work addresses this gap by extensively modelling an approach that adapts the core concept of PageRank to the context of SBNMs. By considering the network structure and the probabilistic interactions between genes, this method aims to identify key regulators that play a crucial role in shaping the long-term dynamics of gene regulatory networks.

Stochastic Boolean Network Model (Sbnm)

Stochastic Boolean Network Model (SBNM) is analogous to the well-known Probabilistic Boolean Network (PBN) [13] framework, but will not be discussed in detail here. Both SBNM and PBN provide suitable setups for modeling the impact of noise on network behavior. An SBNM, representing the dynamics of elements $\{y_1, \ldots, y_m\}$, is defined as a collection of m triples:

$$G = \{g_j, q_j^{\uparrow}, q_j^{\downarrow}\}_{j=1}^{m} \quad (1)$$

where for $j = 1, \ldots, m$:

- $g_j : \{0, 1\}^m \rightarrow \{0, 1\}$ is the update function for element y_j,
- $q^{\uparrow}_j \in [0, 1]$ is the activation propensity, and
- $q^{\downarrow}_j \in [0, 1]$ is the degradation propensity

The stochasticity arises from the propensity parameters $q^{\uparrow}_j$ and $q^{\downarrow}_j$. These parameters are interpreted as follows: if element y_j is inactive at time t ($y_j(t) = 0$) and its update function indicates activation ($g_j(y_1(t), ..., y_m(t)) = 1$), then y_j will become active at the next time step ($y_j(t + 1) = 1$) with probability $q^{\uparrow}_j$. The degradation probability $q^{\downarrow}_j$ is defined similarly for the transition from active to inactive states.

An SBNM can be represented as a Markov chain by defining its transition matrix. The dynamics of the SBNM, $G = \{g_j, q^{\uparrow}_j, q^{\downarrow}_j\}_{j=1}^{m}$, is characterized by the transition probabilities between the states of the system. For an SBNM with m elements, there are 2^m possible vector states, forming the state space $T = \{0, 1\}^m$. For any two states $w = (w_1, ..., w_m) \in T$ and $z = (z_1, \ldots, z_m) \in T$, the transition probability

from state w to state z is given by:

$$b_{w,z} = \prod_{i=1}^{m} \text{Prob}(w_i \to z_i) \tag{2}$$

where $\text{Prob}(w_i \to g_i(w))$ represents the probability of element w_i changing its value, defined as:

$$\text{Prob}(w_i \to g_i(w)) = \begin{cases} q_i^{\uparrow}, & \text{if } w_i < g_i(w), \\ q_i^{\downarrow}, & \text{if } w_i > g_i(w), \\ 1, & \text{if } w_i = g_i(w). \end{cases} \tag{3}$$

The probability of element i maintaining its current value is given by:

$$\text{Prob}(w_i \to w_i) = \begin{cases} 1 - q_i^{\uparrow}, & \text{if } w_i < g_i(w), \\ 1 - q_i^{\downarrow}, & \text{if } w_i > g_i(w), \\ 1, & \text{if } w_i = g_i(w), \end{cases} \tag{4}$$

for all $i = 1, ..., m$. Note that $\text{Prob}(w_i \to w_i) = 0$ for all $z \neq w$, $z_i \in \{w_i, g_i(w)\}$. The transition matrix is defined as:

$$B = (b_{w,z})_{w,z \in T}. \tag{5}$$

In Markov chain representation, the transition probability $b_{w,z} = \text{Prob}(W_t = w | W_{t-1} = z)$ represents the probability of being in state w at time t given that the system was in state z at time $t-1$.

2.2 Relationship to Deterministic Systems

For the type of stochastic system $G = \{g_j, q^{\uparrow}_j, q^{\downarrow}_j\}_{j=1}^{m}$ described here, we can consider an underlying

deterministic system given by G = (g1, ..., gm). The dynamics of this deterministic system is obtained by synchronous updates, that is, z = G(w) for w, z ∈ T . It is straightforward to observe that the stochastic and deterministic systems share the same fixed points. However, for more complex attractors, such as periodic limit cycles or strongly connected components in the state space of SBNM, this equivalence does not hold in general.

2.3 Long term dynamics

This subsection delves into methods for analyzing the long-term behavior of systems modeled within the SBNM framework. We begin by introducing the concept of stationary distributions. For each possible state of the system, the stationary distribution provides the probability of finding the system in that state after a sufficiently long time, as if taking a random snapshot of the system's evolution.

Recall that the transition probability $b_{w,z} = \text{Prob}(W_t = w|W_{t-1} = z)$ represents the probability of transitioning from state z to state w in a single time step. Let $\rho_t = \text{Prob}(W_t = w)$ denote the probability of being in state w at time t. We represent these probabilities as a row vector ρ, where each entry corresponds to the probability of being in a specific state at time t. If ρ_0 represents the initial distribution at time t = 0, then at time t = 1, we have:

$$\rho_1 = \sum_{w \in T} \rho_0(w) b_{w,z}. \quad (6)$$

Iterating this equation, we arrive at a point where:

$$\rho = \sum_{w \in T} \rho(w) b_{w,z}. \quad (7)$$

This indicates that the Markov chain has reached its stationary distribution ρ. The entries of ρ can be interpreted as the long-term occupation times for each state, providing the probability of finding the system in a particular state after a long period. The following lemma guarantees the existence of a unique stationary distribution ρ under the condition that the transition matrix B is regular. A regular transition matrix is one where some power B^k contains only strictly positive entries.

Lemma 1. (Perron-Frobenius). Let B be the transition matrix of a finite-state Markov chain. If B is regular (i.e., there exists a positive integer k such that all entries of B^k are strictly positive), then there exists a unique stationary distribution ρ satisfying:

- $\rho B = \rho$
- $\rho(w) > 0$ for all states w in the state space T.

2.4 Pagerank Algorithm

To introduce randomness into our system to ensure a stable long-term behavior. We'll focus on a system represented by a set of update rules and probabilities, denoted as $\hat{H} = \{h_j, q_j\}_{j=1}^{m}$. To inject randomness, we use a special matrix called the "Google Matrix," represented by R. This matrix is constructed by combining the original system's transition matrix, B, with a uniform distribution matrix, S. The formula for R is:

$$R = rB + (1 - r)S, \quad (8)$$

where r is a propensity constant between 0 and 1, and S is a square matrix (m ×m) where every element is equal to $_m{}^1$ and m is the number of all possible transitions. The Google Matrix, R, is guaranteed to have a stable long-term behavior, meaning it has a stationary distribution. This distribution, denoted as σ, tells us the probabilities of the system being in each of its possible states after a long time. We can represent this distribution as a vector:

$$\sigma = \sigma R = (\sigma_1, \ldots, \sigma_{2m}). \quad (9)$$

This stationary distribution, σ, provides a good approximation of the long-term dynamics of our original system. The larger the value of σ_y for a particular state y, the more important that state is considered. This is similar to how Google's PageRank algorithm assigns importance to web pages. We'll refer to σ_y as the "PageRank Score" of state y.

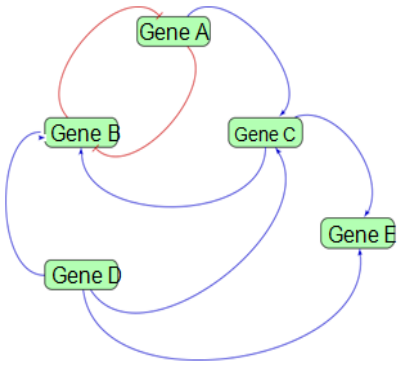

Figure 1: The 5-node gene regulation network, where blue arrows highlight activating connections and red hammerheads signify inhibitory relationships, revealing how the network functions.

Figure 1, represents the gene regulation network where gene A is regulated by the negation of gene B, gene B is regulated by the negation of gene A and the logical AND of genes C or D, gene C is regulated by the logical OR of genes A or D, gene D is regulated by the logical OR of genes A, B, or E, and gene E is regulated by the logical OR of genes C or D, all this translates to

$$\begin{aligned} &\text{Gene A} = \neg\ \text{Gene B} \\ &\text{Gene B} = \neg\ \text{Gene A} \wedge (\text{Gene C} \vee \text{Gene D}) \\ &\text{Gene C} = \text{Gene A} \vee \text{Gene D} \\ &\text{Gene D} = \text{Gene A} \vee \text{Gene B} \vee \text{Gene E} \\ &\text{Gene E} = \text{Gene C} \vee \text{Gene D} \end{aligned} \quad (10)$$

Furthermore, we present a proposed Boolean network model for the system, to simplify our analysis. The components of the model are represented by nodes;

$$\begin{aligned} x_1 &= \text{Gene A}, \\ x_2 &= \text{Gene B}, \quad x_3 = \text{Gene C} \\ x_4 &= \text{Gene D}, \\ x_5 &= \text{Gene E} \end{aligned} \quad (11)$$

Then

$$
\begin{aligned}
x_1 &= \neg x_2 \\
x_2 &= \neg x_1 \wedge (x_3 \vee x_4) \\
x_3 &= x_1 \vee x_4 \qquad (12) \\
x_4 &= x_1 \vee x_2 \vee x_5 \\
x_5 &= \\
x_3 &\quad \vee x_4
\end{aligned}
$$

The 5-node network model is represented as a signed graph in 1, where arrows indicate positive or negative influences between components. This network exhibits three stable states: ”11111 (fixed point in the third attractor) and 10111”, lets assume they represent the healthy state where Gene A is active (focusing on Gene A as a key regulator), ”01111 and 00111”, represent the disease state with inactive Gene A.

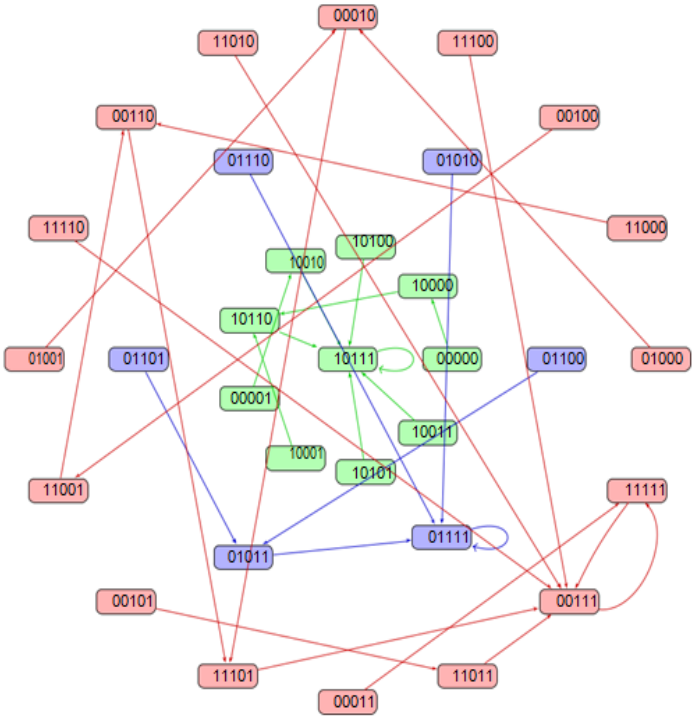

Figure 2: The state space graph of the 5-node network, with all transition probabilities (propensity) set to

Green nodes represent the basin of attraction for the attractor state (10111), blue node for state 01111, while red nodes represent the basin of attraction for the complex state (11111 ⇔ 00111). Edge colors indicate the target state of each transition.

For simplicity, we’ll always use a shorthand notation for these states, omitting spaces, commas, and parentheses. Also note that the attractor 11111 ⇔ 00111, is a complex attractor, because it forms a cycle, while the other two are simple attractors. Figure 2 depicts the deterministic state space of the network, where transitions are governed by the regulatory functions defined in Equation (12). This state space graph reveals three distinct areas, each representing a basin of attraction for one of the stable states.

Notably, one basin of attraction is significantly larger than the others.

To create a stochastic model of the network using the SDDS framework, we need to assign probabil-ities to each node's potential transitions. We begin by assigning a probability of 0.8 to each transition, meaning there's a 80% chance of applying the regulatory function and a 20% chance of maintaining the current state. The transition matrix for this model, denoted as A, is a 32 ×32 matrix where each row and column represents a unique binary state, ordered lexicographically. To calculate the entries of A, we use Equation (12).

For example, to calculate the probability of transitioning from the state 1, (000000), to itself, we need to consider the potential updates. Without stochasticity, the system would transition to state (10000) (see Figure 2) based on the regulatory functions. However, under the SDDS framework, there's a chance the system remains in state 1. For this to happen, the first coordinate of state 1 must not change. Since the probability of each coordinate changing is 0.8, the probability of it not changing is 0.2. As the remaining coordinates remain unchanged, their probability is 1. Multiplying these probabilities gives the overall transition probability from state 1 to itself.

$$b_{1,1} = \prod_{i=1}^{5} \text{Prob}(w_i \to w_i) = 0.2 \times 1 \times 1 \times 1 \times 1 = 0.2 \tag{13}$$

Here $\text{Prob}(w_i \to z_i) = 1 - 0.8 = 0.2$ for $i = 1$ and $\text{Prob}(w_i \to z_i) = 1$ for $i = 2, 3, 4, 5$. Now, to find the probability of transitioning from state 000000 to 10000 (assuming it is represented by entry (1, 2) in the transition matrix), we need the first coordinate to change. Since each change has a probability of 0.8, the overall transition probability is

$$b_{1,2} = \prod_{i=1}^{5} \text{Prob}(w_i \to z_i) = 0.8 \times 1 \times 1 \times 1 \times 1 = 0.8, \tag{14}$$

Similarly, to find the probability of transitioning from 00000 to 00111 (assuming it is the entry (1, 9)), only the last three coordinates need to change. This gives us a probability of

$$b_{1,9} = \prod_{i=1}^{5} \text{Prob}(w_i \to z_i) = 1 \times 1 \times 0.8 \times 0.8 \times 0.8 = 0.512 \tag{15}$$

The most likely transition from state 1 is to state 9, with a 51.2% chance. However, this probability can vary depending on the specific values assigned to the transition probabilities (propensity parameters). The state space of the 5-node network under the SBNM framework, with all propensity parameters set to 0.8, is depicted in Figure 3. Comparing this stochastic state space to the deterministic state spaces presented in Figure 2, we observe both similarities and differences. In the deterministic state space (Figure 2), each state has a single, predetermined next state, with a 100% probability of transition. In contrast, the stochastic state space (Figure 3) allows for transitions to multiple states from each node, with probabilities defined by the transition matrix. Despite these differences, both systems share same fixed

points. While the most likely transitions in the stochastic system correspond to synchronous transitions in Figure 3, this is not a general rule. Ultimately, both the deterministic and stochastic systems exhibit the same long-term behavior: all states eventually converge to all available fixed points.

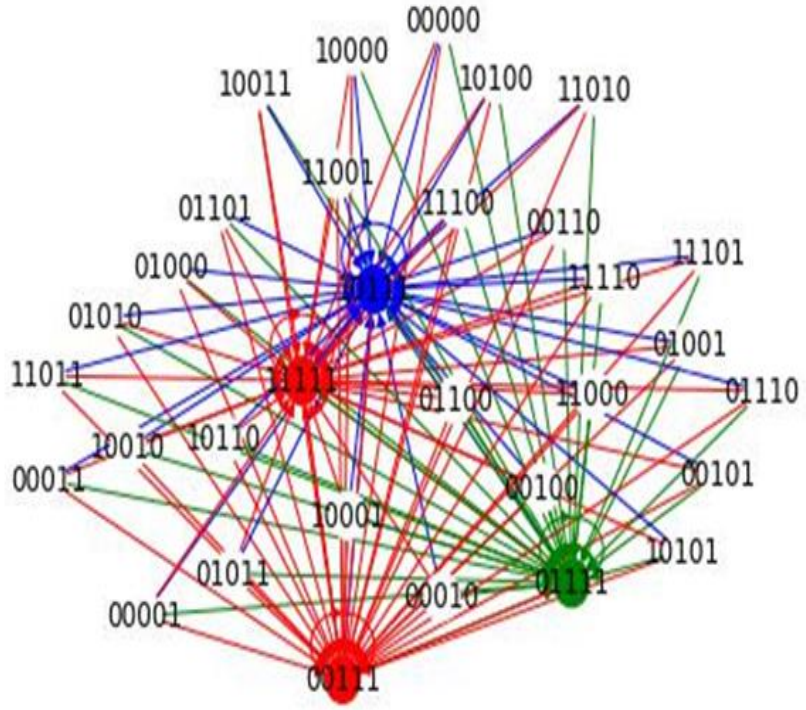

Figure 3: the state space of the stochastic 5-node network, where all transition rates (propensities) are set to 0.8. The nodes are color-coded to represent their eventual fate: green nodes will ultimately reach the fixed point 01111, red nodes will converge to the complex attractor (11111, 00111), and blue nodes can transition to the fixed point 10111.

From here on, we will set all transition rates (propensities) for analysing the 5-node network depicted in Figure 3 to 0.8. To estimate the long-term behavior (stationary distribution) of this system, we employ the PageRank approach. The transition matrix, denoted by A, represents the probabilities of transitioning between states. With a damping factor g of 0.8, we construct the Google matrix G as follows:

$$G = 0.8A + (1 - 0.8)K \quad (16)$$

Here, K is a 32 ×32 matrix where each entry is 1/32, representing a uniform probability of transitioning to any state. The Perron-Frobenius theorem allows us to calculate the stationary distribution π by finding the eigenvector of G associated with the eigenvalue 1. This eigenvector represents the long-term probabilities of being in each state. While there are software packages specifically designed for eigenvector calculations, a practical approximation involves repeatedly multiplying the matrix G by itself (raising it to a high power). As the power increases, the columns of the resulting matrix will converge to the desired eigenvector, providing an approximation of the stationary distribution.

Table 1: Top 10 PageRank Scores for the Stationary Distribution with a 0.8 activation propensity

Rank	State ID	State	Score
1	2	11111	0.20
2	49	110000	0.18
3	34	100001	0.16
4	4	000011	0.15
5	16	001111	0.075
6	42	101001	0.055
7	19	010010	0.066
8	10	001001	0.059
9	57	111000	0.0043
10	31	011110	0.0034

To understand the long-term behavior of the 5-node network, we calculated the stationary distribu-tion, which represents the probabilities of the system being in each state after a very long time. We then ranked the states based on these probabilities, with the highest probability states appearing first. Table 1 presents the top 10 states with the highest probabilities. As expected, the fixed points, occupied the top most positions. This confirms that the system is likely to spend most of its time in these stable states. Interestingly, the fixed point 11111, which has the larger basin of attraction, accounts for a significant 20% of the stationary distribution. This means that the system will reside in this state for roughly 20% of the time in the long run. The another fixed point, 01111, accounts for 15% of the stationary distribution, indicating a much lower probability of being in this state. These findings highlight the dominance of the complex attractor (11111,00111) in the long-term dynamics of the network with all propensities set to 0.8. The system's tendency to converge to this state suggests that it might be more stable or more easily accessible compared to the other fixed point. Further analysis could explore the factors contributing to this dominance and the implications for the overall behavior of the network.

CONCLUSION

In this work, we introduced a approach for modeling long-term behavior in stochastic gene regulatory networks based on the PageRank algorithm. We demonstrated the effectiveness of our approach by applying it to synthetic GRN models. Our findings highlight the ability of the PageRank approach to capture important characteristics of gene regulatory networks and provide insights into the long-term dynamics of gene expression. By considering the stochastic nature of gene expression and incorporating the randomness in regulatory interactions, our approach allows for a more realistic representation of the complex dynamics within GRNs. The iterative computation of PageRank scores enables the identifica-tion of genes that play a crucial role in shaping the overall behavior of the network. We observed that genes with higher PageRank scores exhibit greater influence and exhibit more stable expression patterns.

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