Journal of Electrical and Computer Engineering Innovations
(JECEI)
Journal homepage: http://www.jecei.sru.ac.ir

Research paper

A Robust Control Centrality Applicable to Genetic Regulatory Networks with Structured Uncertainties

Z. Ghassemi Zahan [1], ***S. Ozgoli*** [1,*], ***S. Bolouki*** [2]

[1] *Department of Electrical and Computer Engineering, Tarbiat Modares University, Tehran, Iran.*

[2] *Department of Mechanical Engineering, Polytechnique Montréal, Quebec, Canada.*

Article Info

Article History:
Received 03 March 2024
Reviewed 17 April 2024
Revised 26 June 2024
Accepted 30 July 2024

Keywords:
Network analysis and control
Network centrality
Network controllability
Uncertain systems

*Corresponding Author's Email Address: *ozgoli@modares.ac.ir*

Abstract

Background and Objectives: In genetic network control, RC-Centrality is introduced as a new control centrality measure to address the control of linear time-invariant networks. The objective of this study is to propose an optimal control centrality metric that quantifies the centrality of individual nodes or groups of nodes within a network. Specifically, RC-Centrality identifies key nodes or node groups that can act as controllers, such as genes regulating the gene expression process. To assess the effectiveness of this method, RC-Centrality is compared with standard centralities in a real genetic network. Additionally, the research delves into the role of uncertainty structure in altering the priority order of RC-Centrality.

Methods: The RC-Centrality measure is introduced based on an optimal control problem to address weighted, directed, and signed networks. Robust controllers are designed to ensure Lyapunov stability under uncertainty. A cost function is introduced to measure the performance metric represented by input energy in the presence of uncertainty.

Results: The study presents RC-Centrality as an effective measure for identifying key nodes in genetic networks suitable for control. In-silico simulations are conducted to evaluate its performance in comparison to standard centralities. The research highlights the impact of uncertainty structure on the priority of RC-Centrality.

Conclusion: RC-Centrality offers a promising approach to identify essential nodes in genetic networks for control purposes. Its performance is demonstrated through simulations, and the study emphasizes the influence of uncertainty structure on the centrality measure's prioritization. This research has implications for understanding and controlling genetic networks, particularly in the presence of uncertainty.

Introduction

Graph theoretical representations are widely utilized to model biological networks and the relationships between various cellular components such as genes, proteins, mRNAs, and metabolites. The nodes of the graph, also referred to as agents, represent biological units, while links represent connections between them [1]. Identifying influential biological units plays an important role in designing and analyzing growth, death, division, and survival processes. Centrality analysis is proposed as a valuable guide to predict and identify key units in biological networks, such as genetic networks [2]-[6].

By combining centrality analysis with optimal control strategies, an effective approach has been developed to steer biological networks in the presence of uncertainty toward their desired states. This paper aims to contribute

to the subject by investigating novel control centrality that exploits the network's structure and performance metrics for optimal control in uncertain genetic networks.

A. Related Work

Centrality measures are employed to quantify the importance of components in biological, brain, social and urban traffic networks [7]-[9]. Here, several individual centrality measures for each agent have been listed for unweighted, undirected, and unsigned networks, used in our examples later on. Degree centrality $C_D(i)$ is defined as the number of agent i's neighbors. Closeness centrality $C_{cl}(i)$ is formulated as an inverse sum of the length of shortest paths between agent i and all other agents. The basic definition of Betweenness centrality measure $C_B(i)$ measures the extent to which an agent i lies on the shortest paths between other agents as an intermediate agent. The eigenvector centrality of agent i, $C_E(i)$, captures the agent's influence in the network based on the importance of its neighbors [7]. Although there are many methods for generalizing individual centralities, several papers are made on reformulations of individual centrality measures to extend them to group centrality [10], [11].

Energy optimization approach, which is also the approach taken in this work, is a branch of recent research used in Gramian-based centrality measures to control the given network in a desired direction [12], [13]. The control centralities $C_p(i)$ and $C_q(i)$ are formulated as the trace of the controllability and observability Gramian for node i, respectively [13]. The extension of this method to the discrete case introduces the proposed control centrality measures $C_W(i)$ and $C_M(i)$, formulated as the trace of the controllability and observability Gramian for node i, respectively [26]. Many recent papers on the subject of control energy requirements depend on the properties of controllability Gramian [14]-[16]. For uncertain networks, the influence of uncertainty on the energy is formulated in terms of the Lyapunov equation to minimize the required energy that guarantees stability [17]-[19]. The common characteristic of the efforts mentioned above in centrality measures' definition is that they are all proposed to quantify the importance of the focal node in the network. However, a great deal of research focuses on trying to quantify the power of a specific agent in controlling a network named control centrality [20], [21]. Several methods are used to quantify the influence of each agent or link in uncertain networks as their centrality measure [22], [23].

Despite research in the field of control centrality, some limitations are significant. First, the links' direction and weight in genetic regulatory networks (GRNs) model provide a more detailed and accurate description of gene expression process in biological systems' behavior. Second, interactions between genes are generally described by a signed graph, where the positive and negative weights represent the transcriptional activators and repressors attached to them, respectively. However, it should be noted that the specific studies discussed in [2], [6] do not address these key aspects. Furthermore, the dynamics of genetic networks are paramount for comprehending gene regulation processes and capturing the time-dependent behaviors of the genes and their interactions. However, references [3]-[5] do not specifically delve into the dynamics of their networks.

While in a genetic regulatory network, energy consumed by each gene from the external environment utilizes in gene expression process to control the network in a desired behavior to reach a given target. In practice, injecting the input energy into the cell for expressing genes in controlling biological processes is a costly and time-consuming process as they need to be done on living organisms [24]. On the other hand, the intrinsic nature of biological networks encompasses inherent uncertainty [25]. Thus, control centrality of genetic networks in presence of uncertainty according to optimal energy consumption is an important quantifier to identify the central genes to prevent off-target effects.

B. Contributions

While research on control centrality for weighted, directed, and signed networks with control inputs has been conducted (see [13] and [26]), these measures face limitations in dealing with network uncertainty, a common feature in biological networks. Furthermore, existing measures are solely based on network dynamics and do not adequately adapt to different control scenarios. Conversely, measures proposed in [22] and [23] consider network dynamics and performance metrics but are not suitable for directed, signed networks, or those with control inputs. To address these gaps, this paper proposes a comprehensive control centrality measure that incorporates dynamics, performance metrics, and control inputs, making it applicable across various weighted, directed, and signed network types and scenarios. In this paper, the RC-Centrality is proposed to characterize the centrality of feedback controllers in weighted, directed, and signed (WDS) networks without and in the presence of uncertainty. The proposed robust control centrality quantifies both individual and group centralities as a measure of control that each input set has on the rest of the WDS network in the presence of uncertainty (WDS+U). By introducing a Gramian-based control centrality, not only is the Lyapunov stability of closed-loop system achieved, but also the optimal value of required energy for each input set to place a target set states in their steady state from initial time to final time is minimized. An input set is a set of independent control agents (e.g., controlling genes) which receive input signals to steer target set, a set of agents that cannot be

controlled directly due to their biological characteristics, to desired states (e.g., gene concentrations).

Table 1 shows the comparison between our control centrality measure with established ones.

Table 1: Comparison of the proposed control centrality with existing centrality measures

Centrality measures	Considers dynamics of network	Applicable to weighted graph	Applicable to directed graph	Applicable to signed graph	Considers uncertainty in model	Considers effect of input signal(s)	Extendable to group centrality	Network & performance-driven measure
[13]	✓	✓	✓	✓	✖	✓	✓	✖
[26]	✓	✓	✓	✓	✖	✓	✖	✖
[20]	✓	✖	✓	✖	✖	✓	✖	✖
[22], [23]	✓	✓	✖	✖	✓	✖	✖	✓
[21]	✓	✖	✓	✖	✓	✓	✖	✖
[27], [28]	✖	✓	✓	✖	✖	✖	✖	✖
[29]	✖	✖	✓	✖	✖	✖	✓	✖
[30], [11], [31], [6]	✖	✓	✖	✖	✖	✖	✖	✖
[3]	✖	✖	✓	✖	✖	✖	✖	✖
[32], [4]	✖	✖	✖	✖	✖	✖	✓	✖
[33]	✓	✖	✖	✖	✖	✖	✓	✖
[2], [34], [35], [5]	✖	✖	✖	✖	✖	✖	✖	✖
Our measure	✓	✓	✓	✓	✓	✓	✓	✓

C. Paper Organization

The rest of this paper is organized as follows: In Section 2, the preliminaries of graph theory, network analysis, and a linear time-invariant (LTI) model of WDS genetic networks are represented. In Section 3, the RC-Centrality bounded by the eigenvalues of a proposed Gramian, is derived. Section 4 is about a control centrality algorithm based on the mathematical relation to stability conditions. Several numerical examples in matched and unmatched structures of uncertainties are simulated in Section 5 to illustrate the effectiveness of the proposed approach. The paper is summarized in Section 6, where future research directions are stated.

Preliminaries

The set of $n \times m$ matrices with real entries is denoted by $R^{n\times m}$. Given a matrix A, the symbol A_{ij} denotes the (i,j)-th entry of A, while A^T and A^{-T} mean the transpose and the inverse of the transpose of A.

A generic WDS network is denoted by a graph $G = (V,E,A)$ where $V = \{v_1, \dots, v_n\}$ and $E \subset V \times V$ are the set of agents and the set of links, respectively, where a link is drawn from v_i to v_j, as $e_{ij} \in E$, if the agent v_j interacts with the agent v_i. In other words, if v_j influences v_i through its dynamics. In addition, $a(e_{ij}), : E \to R$ also denoted by a_{ij}, is the strength of the link e_{ij}, which captures the significance of the agent v_j to v_i.

Moreover, for simplicity, it is defined that $a_{ij} = 0$ if $e_{ij} \notin E$ and $a_{ii} = 0$, $\forall i = 1, \dots, n$. Then, the adjacency matrix $A \in R^{n\times n}$ comprised of coefficients a_{ij} is used to describe the network topology. For each agent v_i, a_i is defined as the total significance of other agents to v_i as [8]:

$$a_i = \sum_{j=1}^{n} a_{ij}\,.$$

The $n \times n$ Laplacian matrix of G, denoted by L, is defined as

$$L = \mathcal{D} - A$$

in which $\mathcal{D}$ is the degree matrix of graph G as [36]:

$$\mathcal{D}_{ij} = \begin{cases} a_i & \text{if } i = j \\ 0 & \text{otherwise} \end{cases}$$

The mathematical state of each agent $i \in V$ is described by a scalar state variable $x_i(t)$ at time $t \geq 0$. It is assumed that only an arbitrary, but fixed, subset $S \subset V$, which is the input set, receives control inputs. The control inputs can then be represented as:

$$u(t) = [u_1(t) \dots u_n(t)]^T$$

in which $u(t) \in R^n$ represents all possible control inputs, while $B \in R^{n\times n}$ restrict them to the subset S, where only a selected subset of control inputs is active. The input matrix B defines the agents in which the activated control inputs are injected. The structure of matrix B may vary depending on the location of the activated control inputs in the network.

RC-Centrality

Consider the following class of uncertain LTI systems with the state vector $x(t) \in R^n$ and the adjacency matrix $A \in R^{n\times n}$.

$$\dot{x}(t) = Ax(t) + Bu(t) + \Delta(p)v(t) \quad (1)$$

The control input is partitioned into two parts: 1) $u(t) \in R^n$ is the "certain" part, which affects the system via matrix $B \in R^{n\times n}$ that has no uncertainty, and 2) $v(t) \in R^n$ is the second part that enters the system via the bounded uncertainty $\Delta(p) \in R^{n\times n}$, where $p \in P$ is an uncertain parameter vector, and no uncertainty is imposed upon A and B matrices.

It is also assumed that the pair (A,B) is stabilizable and controllable.

A. Robust Control Energy level for a Network

In the biological context, control input could be a regulatory signal coming from outside of the considered process or an externally supplied agent applied to a cell. The process of applying control input into a cell by an experimenter can be very expensive and time consuming [24]. Thus, in this subsection, the cost function is proposed due to the importance of the control inputs in GRNs. An energy-based quantity is defined to consider the effect of uncertainty on the consumed energy of the WDS+U network $\mathcal{G}$.

Definition 1. The robust control energy level is defined as follows that tries to be a reflection of the consumed energy of uncertain LTI system (1) from the initial time $t_0 = 0$ to the final time $t_f \to \infty$:

$$J_R = \frac{1}{2}\int_0^\infty (u^T(t)Ru(t) + v^T(t)Qv(t))dt \quad (2)$$

where $R,Q \in R^{n\times n}$ are symmetric and positive definite weighting matrices.

RC-Centrality for an Input Set

Uncertainty is a significant factor influencing the consumed energy to steer a network from its initial states to desired final states. To capture this influence, the following control centrality measure is introduced for the activated input set S in the WDS+U network $\mathcal{G}$.

Definition 2. For a WDS+U network $\mathcal{G} = (\mathcal{V},\mathcal{E},A)$ described by (1), the *RC-Centrality* of input set S from the initial state $x(t_0)$ at $t_0 = 0$ to the given final state $x(t_f)$ at $t_f \to \infty$ is defined as

$$C_{RC}(S) = \frac{1}{J_R^*(B)} \quad (3)$$

where $J_R^*(B)$ is the optimal value of robust control energy level (2). The diagonal matrix B is designed in such a way that S is the activated input set. Only nonzero elements in matrix B are selected according to the set S to receive control inputs.

Energy-based Characterization of C_{RC}

In this subsection, we relate the optimal value of the robust control energy level (2) to the RC-Centrality by an auxiliary system. Consider the following LTI system:

$$\dot{x}(t) = Ax(t) + Bu(t) + \gamma(I - BB^\dagger)v(t) \quad (4)$$

where $B^\dagger \in R^{n\times n}$ is pseudo-inverse matrix of B defined as $B^\dagger = (B^T B)^{-1} B^T$ such that $B^T B$ is non-singular and γ is a design parameter which satisfies an inequality to guarantee the stability of the uncertain LTI system in (1) characterized later on in Section 4.2.

In the next theorem, it is proved that characterizing $C_{RC}(S)$ for the uncertain LTI system in (1) is equivalent to finding the inverse of the optimal value of input energy in (2), J_R^*, for the auxiliary system described as (4).

Theorem 1. Consider the uncertain LTI system described as (1). For any input set S, the robust control centrality $C_{RC}(S)$ can be expressed as:

$$C_{RC}(S) = \left(x(t_f) - e^{At_0}x(t_0)\right)^{-1}\left(\int_0^\infty e^{A\tau}\left[BR^{-1}B^T + \gamma^2(I - BB^\dagger)Q^{-1}(I - BB^\dagger)^T\right]e^{A^T\tau}d\tau\right)\left(x(t_f) - e^{At_0}x(t_0)\right)^{-T} \quad (5)$$

Proof. According to the Hamilton-Jacobi-Bellman (HJB) equation for optimality [19], the Hamiltonian form for the auxiliary system (4) based on the cost function (2) is represented as

$$H(t) = \frac{1}{2}(u^T Ru + v^T Qv) + \lambda^T(Ax + Bu + \gamma(I - BB^\dagger)v)$$

where $\lambda(t) \in R^n$ is a Lagrange multiplier. Using the stationary conditions, the optimal control laws are obtained as:

$$u^*(t) = R^{-1}B^T e^{A^T t}\left(\int_0^\infty e^{A\tau}\left[BR^{-1}B^T + \gamma^2(I - BB^\dagger)Q^{-1}(I - BB^\dagger)^T\right]e^{A^T\tau}d\tau\right)^{-1}\left[x(t_f) - e^{At_0}x(t_0)\right],$$

$$v^*(t) = \gamma Q^{-1}(I - BB^\dagger)^T e^{A^T t}\left(\int_0^\infty e^{A\tau}\left[BR^{-1}B^T + \gamma^2(I - BB^\dagger)Q^{-1}(I - BB^\dagger)^T\right]e^{A^T\tau}d\tau\right)^{-1}\left[x(t_f) - e^{At_0}x(t_0)\right] \quad (6)$$

The optimal value of robust control energy level affected by the optimal control laws in (6) is determined as

$$J_R^*(B) = \left[x(t_f) - e^{At_0}x(t_0)\right]^T \left(\int_0^\infty e^{A\tau} \left[BR^{-1}B^T + \gamma^2(I - BB^\dagger)Q^{-1}(I - BB^\dagger)^T\right] e^{A^T\tau} d\tau \right)^{-1} \left[x(t_f) - e^{At_0}x(t_0)\right] \quad (7)$$

which is the inverse of robust control centrality $C_{RC}(S)$, that completes the proof. ■

Remark 1. The proposed control centrality is consistent with physical interpretation in the sense that the higher the $C_{RC}(S)$ of input set S, the less input energy it consumes to steer the WDS+U network $\mathcal{G}$ to the given final states.

Remark 2. The proposed control centrality incorporates the dynamics of the network and the performance metric. Even with the fixed structure of the network, by changing the weighting matrix of the control inputs, the centrality of node or set of nodes will change accordingly.

Encapsulation

The robust reachability Gramian is defined as

$$G_R(B) = \int_0^\infty e^{A\tau} \left[BR^{-1}B^T + \gamma^2(I - BB^\dagger)Q^{-1}(I - BB^\dagger)^T\right] e^{A^T\tau} d\tau \quad (8)$$

This is in fact the reachability Gramian of [37] modified to uncertain system (1) from the initial time t_0 to the final time t_f. The final state difference vector $d_f = \left[d_{f_1} \dots d_{f_n}\right] \in R^n$ is defined as the difference between the final states and the zero-input solution as

$$d_f = x(t_f) - e^{At_0}x(t_0) \quad (9)$$

Based on Definition 2 and (5), the control centrality measure $C_{RC}(S)$ defined in (3) can be encapsulated as follows:

$$C_{RC}(S) = d_f^{-1}G_R(B)d_f^{-T} \quad (10)$$

Remark 3. Considering the challenges in applying control input, especially to genetic networks, such as the high cost of practical biological experiments, it is desirable to determine whether a selected input set S is central to control the WDS+U network $\mathcal{G}$. The concept of proposed control centrality concerns the optimal amount of required input energy in the controllable LTI system to steer the initial states to their final states.

Next, some lower and upper bounds for $C_{RC}(S)$ is established.

Bounds of RC-Centrality

The following theorem is provided to drive theoretical bounds of the RC-Centrality of (10). Lemma 1 is needed to later prove the theorem.

Lemma 1. [38] If $q(X) = X^TAX$ is a quadratic form in $X = [x_1, \dots, x_n]^T$ for a square matrix A, then there exists an invertible orthogonal matrix F such that

$$q(X) = \lambda_1\tilde{x}_1^2 + \cdots + \lambda_n\tilde{x}_n^2$$

where

$$\begin{bmatrix}\tilde{x}_1 \\ \vdots \\ \tilde{x}_n\end{bmatrix} = F^T \begin{bmatrix}x_1 \\ \vdots \\ x_n\end{bmatrix}$$

and $\{\lambda_1, \dots, \lambda_n\}$ is the set of A's eigenvalues. In the following theorem, the n eigenvalues of $G_R(B)$ are denoted, from the lowest to the highest, as

$$\lambda_{min}\left(G_R(B)\right) \le \cdots \le \lambda_{max}\left(G_R(B)\right).$$

Theorem 2. Consider the controllable LTI system in the presence of uncertainty in (1). The control centrality measure $C_{RC}(S)$ is bounded below and above as follows:

$$\sum_{i=1}^n \frac{\lambda_{min}\left(G_R(B)\right)}{\tilde{d}_{f_i}^2} \le C_{RC}(S) \le \sum_{i=1}^n \frac{\lambda_{max}\left(G_R(B)\right)}{\tilde{d}_{f_i}^2}$$

where

$$\begin{bmatrix}\tilde{d}_{f_1} \\ \vdots \\ \tilde{d}_{f_n}\end{bmatrix} = F^T \begin{bmatrix}d_{f_1} \\ \vdots \\ d_{f_n}\end{bmatrix}$$

for the existing orthogonal matrix F.

Proof. According to the Lemma 1 and the definition of $C_{RC}(S)$, we have:

$$\begin{aligned} C_{RC}(S) &= d_f^{-1}G_R(B)d_f^{-T} \\ &= \lambda_{min}\left(G_R(B)\right)\left(\tilde{d}_{f_1}^{-T}\right)^2 + \cdots \\ &+ \lambda_{max}\left(G_R(B)\right)\left(\tilde{d}_{f_n}^{-T}\right)^2 \end{aligned}$$

This can be expressed in matrix form as

$$C_{RC}(S) = \left[\lambda_{min}\left(G_R(B)\right) \quad \dots \quad \lambda_{max}\left(G_R(B)\right)\right] \left[\frac{1}{\tilde{d}_{f_1}^2} \quad \dots \quad \frac{1}{\tilde{d}_{f_n}^2}\right]^T$$

So, the bounds for $C_{RC}(S)$ can be found, which are functions of $\lambda_{min}(G_R(B))$ and $\lambda_{max}(G_R(B))$ as follows:

$$\lambda_{min}\left(G_R(B)\right)\sum_{i=1}^n \frac{1}{\tilde{d}_{f_i}^2} \le C_{RC}(S) \le \lambda_{max}\left(G_R(B)\right)\sum_{i=1}^n \frac{1}{\tilde{d}_{f_i}^2}$$

■

The bounds on $C_{RC}(S)$ for input set S could be helpful, especially in the case that characterizing the exact value of $C_{RC}(S)$ is computationally too complex. In the following corollary, the worst-case energy is considered that the WDS+U network $\mathcal{G}$ consumes the maximum amount of input energy to steer initial states to final states for matrix B.

Corollary 1. For any input set S, the upper bound on the control energy of $C_{RC}(S)$ is proportional to the inverse of the smallest eigenvalue of $G_R(B)$.

Proof. According to the definition of $C_{RC}(S)$, the bounds of input energy function are exactly the same as the method proposed in Theorem 2 as follows:

$$\frac{\sum_{i=1}^{n} \tilde{d}_{f_i}^2}{\lambda_{max}\big(G_R(B)\big)} \leq d_f^T G_R^{-1}(B) d_f \leq \frac{\sum_{i=1}^{n} \tilde{d}_{f_i}^2}{\lambda_{min}\big(G_R(B)\big)} < \infty$$

In the worst-case, the upper bound on the input energy would be obtained as

$$\max_S d_f^T G_R^{-1}(B) d_f \propto \lambda_{min}^{-1}\big(G_R(B)\big)$$ ■

The importance of the bounds is that for a controllable network in theory, the network may still not be controllable in practice. For instance, unreasonable values of the input energy are required to steer biological complex systems in some practical direction [39].

Special Case: In the Absence of Uncertainty

We compare the proposed control centrality with other known standard centrality measures (degree, closeness, betweenness, and eigenvector centrality) in Case Study 1. Therefore, the control centrality is defined based on the RC-Centrality's definition to quantify the impact of input set S in the WDS network $\mathcal{G}$ to compare other measures.

Definition 3. For a WDS network $\mathcal{G} = (\mathcal{V},\mathcal{E},A)$ described by the LTI controllable system in (11) as:

$$\dot{x}(t) = Ax(t) + Bu(t) \tag{11}$$

The, the control centrality of input set S is defined as

$$C_C(S) = C_{RC}(S) - d_f^{-1}\left(\int_0^{\infty} e^{At}\gamma^2(I - BB^{\dagger})Q^{-1}(I - BB^{\dagger})^T e^{A^T t} dt\right) d_f^{-T} \tag{12}$$

The value of $C_C(S)$ can be encapsulated in the following form:

$$C_C(S) = d_f^{-1} G(B) d_f^{-T} \tag{13}$$

where the reachability Gramian is represented as [37]

$$G(B) = \int_0^{\infty} e^{A\tau} BR^{-1}B^T e^{A^T\tau} d\tau \tag{14}$$

Remark 4. In the control centrality defined in (13), the importance of input set S is the inverse of the optimal value of input energy $J = \frac{1}{2}\int_0^{\infty} u^T(t)Ru(t)dt$ to steer the initial state $x(t_0)$ at $t_0 = 0$ to their desired state $x(t_f)$ at $t_f \to \infty$ through input set S.

Calculation of RC-Centrality

In the previous section, we introduced a novel control centrality measure designed for systems operating under uncertainty. The RC-Centrality emerged as the optimal solution for energy optimization in a scenario without uncertainty, a solution that we demonstrated to be applicable to systems in presence of uncertainty, as proven in the preceding section. In this section, we delve into the role of robust controllers in ensuring system stability. We establish that the control centrality of these robust controllers, acting as driver nodes, provides valuable insights into their placement while simultaneously guaranteeing the Lyapunov stability of the closed-loop system across individual or grouped inputs.

A. A Lyapunov-based Solution for $G_R(B)$

The first step in calculating $C_{RC}(S)$ in (10) is characterizing $G_R(B)$ formulated in the following theorem.

Theorem 3. Consider a WDS+U network $\mathcal{G} = (\mathcal{V},\mathcal{E},A)$ described by (1). Suppose that there exists a design parameter γ such that satisfies (17). Then, the robust reachability Gramian, $G_R(B)$ is the unique solution that is positive definite of the following Lyapunov equation:

$$\begin{aligned} AG_R(B) + G_R(B)A^T \\ + (BR^{-1}B^T \\ + \gamma^2(I - BB^{\dagger})Q^{-1}(I - BB^{\dagger})^T) \\ = 0 \end{aligned} \tag{15}$$

Proof. The solution to the Lyapunov equation in (15) is obtained using the robust reachability Gramian in (8).

$$\begin{aligned} G_R(B) + G_R(B)A^T \\ = e^{At}[BR^{-1}B^T \\ + \gamma^2(I \\ - BB^{\dagger})Q^{-1}(I - BB^{\dagger})^T]e^{A^T t}\Big|_{t=0}^{\infty} \end{aligned}$$

It is clear that if A is Hurwitz, then $\lim_{t\to\infty} e^{At} = 0$. Therefore, $G_R(B)$ is the solution of the Lyapunov equation in (15). The proof of the uniqueness of $G_R(B)$ as the solution is straightforward and omitted. Consequently, $G_R(B)$ is the unique solution of the Lyapunov equation in (15), thereby completing the proof. ■

A necessary and sufficient condition for the analysis of Lyapunov stability of systems in the presence of uncertainty is the existence and uniqueness of solution to Lyapunov equation [19]. The result of the theorem is used in the next subsection to prove that the condition for the Lyapunov stability of the uncertain LTI system in (1) is satisfied.

The γ Condition on Robust Stability

A main step in measuring the RC-Centrality indices for input set S in (10) is finding design parameter γ. The result of Lemma 2 can be used to characterize γ, which is done next.

Lemma 2. Assume that $G_R(B)$ is the unique solution, which is positive definite, of the Lyapunov equation (15) for the LTI system with uncertainty in (1). Then, the optimal control laws are obtained as follows:

$$\begin{bmatrix} u(t) \\ v(t) \end{bmatrix} = \begin{bmatrix} R^{-1}B^T G_R(B) \\ \gamma Q^{-1}(I - BB^{\dagger})^T G_R(B) \end{bmatrix} x(t) = \begin{bmatrix} K \\ L \end{bmatrix} x(t) \quad (16)$$

Proof. The proof is very similar to that of Theorem 1 and is thus removed. ■

The coefficients of state feedback K and L are now utilized to find a suitable value for γ.

Theorem 4. Consider the controllable LTI system in (1) with bounded uncertainty $\Delta(p)$. The robust control centrality $C_{RC}(S)$ indicates the centrality of controllers $u(t) = Kx(t)$ activated by input set S which robustly stabilizes the closed-loop system (1) for all $p \in P$. The design parameter γ and feedback gains K and L can be found in such a way to satisfy the following inequality:

$$\text{inv}(\gamma) L^T Q \Delta(p) L > -\frac{1}{2}(K^T RK - L^T QL + 2K^T RB^{\dagger}\Delta(p)L) \quad (17)$$

Proof. Suppose that the robust control energy level defined in (2) is the Lyapunov function candidate for the uncertain system in (1) of the following form:

$$V(x) = \min_{u,v} \int_0^{\infty} (u^T(t)Ru(t) + v^T(t)Qv(t))\mathrm{d}t \quad (18)$$

the HJB equation is satisfied by the proposed $V(x)$, which reduces to

$$\min_{u,v} \left(u^T(t)Ru(t) + v^T(t)Qv(t) + V_x^T(Ax(t) + Bu(t) + \gamma(I - BB^{\dagger})v(t)) \right) \quad (19)$$

where $V_x \triangleq \frac{\partial V(x)}{\partial x}$. The optimal control laws $u(t) = Kx(t)$ and $v(t) = Lx(t)$ must make the derivative of $u^T(t)Ru(t) + v^T(t)Qv(t) + V_x^T(Ax(t) + Bu(t) + \gamma(I - BB^{\dagger})v(t))$ zero with respect to $u(t)$ and $v(t)$, respectively [18], [19]. Hence,

$$2x^T(t)K^T R + V_x^T B = 0 \quad (20)$$

$$2x^T(t)L^T Q + V_x^T \gamma(I - BB^{\dagger}) = 0 \quad (21)$$

It is clear that the integral type of Lyapunov function $V(x)$ proposed by (18) is a positive definite function for system in (1):

$$V(x) > 0 \quad x \neq 0$$
$$V(x) = 0 \quad x = 0$$

It will be shown that $\dot{V}(x) < 0$ for all $x \neq 0$ using (1). According to the HJB equation (19) and Lemma 2, we have:

$$\dot{V}(x(t)) = -x^T K^T RKx - x^T L^T QLx + V_x^T BB^{\dagger}\Delta(p)Lx + V_x^T(I - BB^{\dagger})\Delta(p)Lx - V_x^T \gamma(I - BB^{\dagger})Lx$$

which, combined with (20) and (21), implies that

$$\dot{V}(x) = -x^T K^T RKx + x^T L^T QLx - 2x^T K^T RB^{\dagger}\Delta(p)Lx - 2\gamma^{-1}x^T L^T Q\Delta(p)Lx \quad (22)$$

and consequently,

$$\dot{V}(x) = x^T(-K^T RK + L^T QL - 2K^T RB^{\dagger}\Delta(p)L - 2\gamma^{-1}L^T Q\Delta(p)L)x \quad (23)$$

Equation (23) has the form of $x^T H(p)x$, then by (17)

$$\dot{V}(x) < 0 \quad x \neq 0$$
$$\dot{V}(x) = 0 \quad x = 0$$

Then, it is clear that $V(x)$ is a Lyapunov function for system (1). Therefore, according to the Lyapunov stability theorem, the system in (1) using the optimal control laws $u(t) = Kx(t)$ and $v(t) = Lx(t)$ for all $p \in P$ would be asymptotically stable. ■

Corollary 2. For any input set $S \subseteq V$, the Lyapunov candidate function is the optimal value of robust control energy level to achieve the following property:

$$V(x) = J_R^*(B) = \frac{1}{C_{RC}(S)} \quad (24)$$

This shows the impact of robust controller $u(t)$ activated via matrix B, which holds the above property. In the next subsection, an algorithm is proposed for calculating the control centrality $C_{RC}(S)$ of input set S.

Algorithm to Calculate C_{RC}

The proposed control centrality measure is summarized as Algorithm 1. It should be noted that the first iteration starts with the nominal value of uncertainty. Moreover, during the calculation of RC-Centrality Algorithm, the optimal controllers $u(t)$ and $v(t)$ in (16) stabilize the LTI system (1) in the presence of uncertainty.

Algorithm 1: Robust Control Centrality

Input: Input set S, A, $B_{\Delta}(p)$, t_0, t_f, $x(t_0)$, $x(t_f)$
Output: $C_{RC}(S)$ or $C_C(S)$

1. Pick $s \in S$.
2. Compute d_f using (9).
3. If uncertainty exists % RC-Centrality
   3.1. Decompose $B_{\Delta}(p)$ into B and $\Delta(p)$ using s and (1).
   3.2. Find $G_R(B)$ and γ using (16) subject to (15) and (17).
   3.3. Calculate $C_{RC}(s)$ using (10).
   3.4. Repeat steps 3.1 to 3.3 for each individual or group set of S.
4. else % Control Centrality
   4.1. Find $G(B)$ using (14).
   4.2. Calculate $C_C(s)$ using (13).
   4.3. Repeat steps 4.1 to 4.2 for each individual or group set of S.
5. End

It is noted that step 3. 2 in Algorithm 1 could be done by convex optimization method in MATLAB. Also, in this step, metaheuristic methods such as particle swarms and genetic algorithms can be used. However, these approaches were not used in the case studies presented in this paper.

In the next section, the controllable and asymptotically stable system (1) in the presence of bounded uncertainty $\Delta(p)$ is considered. The RC-Centrality is used to identify input set's importance in the closed-loop system with robust control law $u(t)$. In this WDS+U genetic network $\mathcal{G}$, maximization of $C_{RC}(S)$ corresponds to minimizing input energy of input set S to reach the desired final state $x(t_f)$.

Numerical Examples

In this section, we present an example of a real genetic regulatory network to demonstrate the effectiveness of the proposed control centrality strategy using Algorithm 1. The GRN, consisting of five nodes, is relatively simple but serves to illustrate the method's effectiveness in various scenarios, including the absence and presence of uncertainty with different structures. Additionally, we evaluate the feasibility of numerical computation in MATLAB for the parameters γ and $G_R(B)$.

Let $\mathcal{A} = C = -\text{diag}(1)_{5\times5}$, $D = \text{diag}(0.8)_{5\times5}$, and the Hill function is $f(x) = \frac{x^2}{(1+x^2)}$. (Robust) control centrality is calculated to transfer the states of the linear GRN system in (11) from the initial concentrations of protein and mRNA, $M(0) = P(0) = [5]_{5\times1}$, to the final states at the origin. In this part, it is assumed that control input $u_i(t)$ is a repressor transcription factor of gene i to prevent the target genes from being upregulated [40].

A. Case Study 1: A Non-WDS Network

A case study is here given to show the differences and similarities between the control centrality and standard centrality measures such as degree, closeness, betweenness and eigenvector centrality for unweighted and undirected networks. Consider a GRN without loops, shown in Fig. 1.

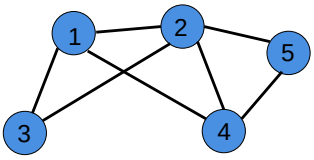

Fig. 1: The GRN model of Case Study 1.

The coupling matrix is $G_1 = \begin{bmatrix} 0 & 1 & 1 & 1 & 0 \\ 1 & 0 & 1 & 1 & 1 \\ 1 & 1 & 0 & 0 & 0 \\ 1 & 1 & 0 & 0 & 1 \\ 0 & 1 & 0 & 1 & 0 \end{bmatrix}$.

The control centrality in (13) is compared with the well-known aforementioned centrality measures in Tables 2 and 3.

According to Tables 2 and 3, the proposed control centrality agrees with the previous individual centrality measures for simple (non WDS) networks. Node 2 is more central, and nodes 1 and 4 have the same centrality based on degree, closeness, betweenness, eigenvector, and the proposed control centrality measures. Table 2 presents the order of individual and group centralities to illustrate the similarity and difference between the control centrality and other established measures.

Table 3: Priorities based on various centrality measures

Order of Centralities
$C_D(\{1,2,4\}) = C_D(\{2,4\}) = C_D(\{1,2\}) = C_D(\{1,4\}) = C_D(\{2\}) > C_D(\{1\}) = C_D(\{4\})$
$C_{cl}(\{1,2,4\}) > C_{cl}(\{2,4\}) = C_{cl}(\{1,2\}) = C_{cl}(\{1,4\}) > C_{cl}(\{2\}) > C_{cl}(\{1\}) = C_{cl}(\{4\})$
$C_B(\{1,2,4\}) > C_B(\{2,4\}) = C_B(\{1,2\}) > C_B(\{2\}) > C_B(\{1,4\}) > C_B(\{1\}) = C_B(\{4\})$
$C_E(\{2\}) > C_E(\{1\}) = C_E(\{4\})$
$C_C(\{1,2,4\}) > C_C(\{2,4\}) = C_C(\{1,2\}) > C_C(\{1,4\}) > C_C(\{2\}) > C_C(\{1\}) = C_C(\{4\})$

Table 2: Scores based on various individual and group centrality methods

	Input set S	$C_D(S)$	$C_{cl}(S)$	$C_B(S)$	$C_E(S)$	$C_C(S)$
Individual Centrality	{1}	0.75	0.2	0.14	3.1	4.5
	{2}	1	0.25	0.37	3.7	4.7
	{4}	0.75	0.2	0.14	3.1	4.5
Group Centrality	{1,2}	1	0.33	0.66	N.A.	5.5
	{1,4}	1	0.33	0.25	N.A.	5.3
	{2,4}	1	0.33	0.66	N.A.	5.5
	{1,2,4}	1	0.5	1	N.A.	6

N.A.: Not applicable

It is clear from Table 3 that based on control centrality, $C_C(\{1,2,4\})$ also gets the highest score as other methods to prevent upregulation of target set $\{3,5\}$. The degree centrality scores of input sets $\{1,2\}$,$\{1,4\}$,$\{2,4\}$,$\{1,2,4\}$ are all equal to 1 and the scores of the input sets $\{1,2\}$,$\{1,4\}$,$\{2,4\}$ are equal per the group closeness centrality. However, the groups which contain individual with high centrality score, $\{1,2\}$,$\{2,4\}$, inherit some of these scores in group betweenness and input centrality than the other group centrality $\{1,4\}$.

Case Study 2: A Real Genetic Network

In this subsection, we consider the application of control centrality to a real genetic regulatory network (GRN), which has been both theoretically predicted and experimentally validated in *Escherichia coli* [41]. We specifically focus on the dynamics of the repressilator, a well-studied system. The repressilator is composed of three repressor genes ($lacl$, $tetR$, and cl) along with their corresponding promoters.

Consider the WDS genetic network with five genes drawn in Fig. 2 [41], in which each agent describes a gene. The $\downarrow$ sign denotes an activation link, and the $\perp$ sign denotes a repression link. The coupling matrix is

$$G_2 = 0.5 \times \begin{bmatrix} 0 & -0.5 & 0.75 & 0 & 0 \\ -0.5 & 0 & 0 & 0.5 & 1 \\ 0 & 0.75 & 0 & 0 & 0 \\ 1 & -0.5 & 0 & 0 & 0 \\ 0 & 0 & 0 & 1 & 0 \end{bmatrix}.$$

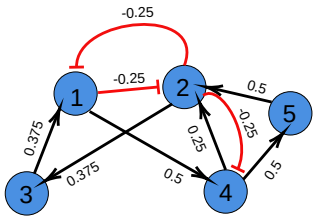

Fig. 2: Genetic regulatory network model [41].

This network has the same nodes and connections, as the one in previous case study, but weights and directions and signs are also added.

The individual and group control centralities for this network are calculated using (13) and are depicted in descending order in Fig. 3.

The target set $\{3,5\}$ in this genetic network will be paid attention to again. Based on control centrality investigation in Case Study 1, input nodes $\{1\}$ and $\{4\}$ gain the same centrality measures, and it can't be determined which one is more important. However, in this example, input node $\{1\}$ has a higher rank than $\{4\}$ since, according to the coupling matrix G_2, tf_1 has a more repression influence over all other genes in this network topology rather than tf_4, which explains why input node $\{1\}$ requires less input energy to steer the system towards the desired final state.

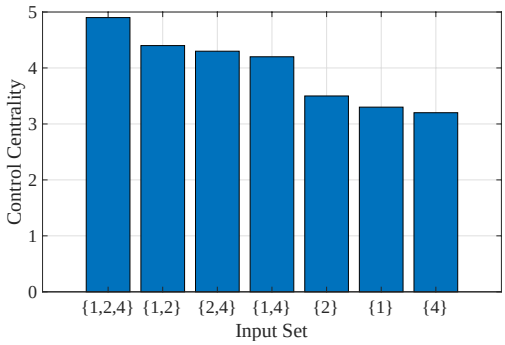

Fig. 3: Control Centrality Without Uncertainty.

In comparison between the control centrality measures for weighted, directed, and signed networks considering the effect of control inputs proposed in [13] and [26] and our measure, we use Table 4 to demonstrate the similarities between them.

In the following subsection, the control centrality for GRN would be calculated in the presence of uncertainty.

Table 4: Priorities of control centrality measures for the WDS network

Order of Centralities
$C_C(\{1,2,4\}) > C_C(\{12\}) > C_C(\{24\}) > C_C(\{1,4\}) > C_C(\{2\}) > C_C(\{1\}) > C_C(\{4\})$
$C_p(\{1,2,4\}) > C_p(\{12\}) > C_p(\{24\}) > C_p(\{1,4\}) > C_p(\{2\}) > C_p(\{1\}) > C_p(\{4\})$
$C_q(\{1,2,4\}) > C_q(\{12\}) > C_q(\{24\}) > C_q(\{1,4\}) > C_q(\{2\}) > C_q(\{1\}) > C_q(\{4\})$
$C_W(\{2\}) > C_W(\{1\}) > C_W(\{4\})$
$C_M(\{2\}) > C_M(\{1\}) > C_M(\{4\})$

RC-Centrality in the Genetic Network

Genetic regulatory networks often contain a significant amount of uncertainty. This uncertainty is categorized into two broad classes. Matched uncertainty stems from the lack of knowledge or inherent biological phenomena in the intrinsic dynamics of the system under examination without input. In GRNs, for example, noise in gene expression can induce uncertainty in the products. The second type of uncertainty results from the applied input to the system. The unmatched uncertainty is profoundly present due to practical limitation and measurement errors or noises of the inputs in various experimental experiences, such as a moderate change of the input in a transition region [25].

In this part, the uncertainty should be decomposed into matched and unmatched parts defined mathematically next. It is proven that the unmatched uncertainty needs more input energy to satisfy the condition (17) in order to guarantee robust stability. This condition depends on the design parameter γ that can be found by computer programming, e.g., the MATLAB toolbox and Yalmip.

Case Study 3: Matched Uncertainty

If the uncertainty $\Delta(p)$ can be written in the form of $B\varphi(p)$ for some $\varphi(p)$, it can be considered as the matched uncertainty. In this subsection, matched uncertainty is applied to the model using degree structure for the uncertainty $\Delta(p)$.

The degree uncertainty is a matched uncertainty form that can be considered in RC-Centrality. In this case, the dynamics of the state space model are given by

$$\dot{x}(t) = Ax(t) + Bu(t) + \mathcal{D}(p)v(t), p \in [-1,1] \qquad (25)$$

where p is an uncertain parameter vector, and $D(p) = p.\text{diag}([d_1 \dots d_5])$ is the degree matrix of the underlying coupling graph of the GRN. In this case study, the matrix $D(p)$ is $D(p) = p.\text{diag}([0.125,0.5,0.375,0.25,0.5])$ and a design parameter γ for the input set S, that satisfies condition (17), can be obtained using Yalmip.

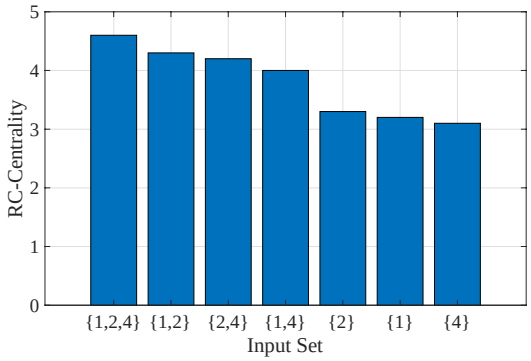

Fig. 4: RC-Centrality for the Degree Uncertainty.

According to the RC-Centrality depicted in Fig. 4, parameter γ is not sufficiently large to change the priority of $C_{RC}(S)$ compared to $C_C(S)$ in Fig 3. These plotted figures reflect that the value of $C_C(S)$ of each input set is larger than $C_{RC}(S)$ obtained for the uncertain model, that is since a cost applies to deal with uncertainty.

As a consequence of the above case study, the matched uncertainty cannot change the order of priority for the robust control centrality. The case of unmatched uncertainty will be examined next.

Unmatched Uncertainty

In this section, two types of unmatched uncertainty $\Delta(p)$ are considered, which cannot be written in the form of $B\varphi(p)$, and the RC-Centrality would be calculated for each case.

Case Study 4: Laplacian Uncertainty

The second type is Laplacian uncertainty. The updated equation of the state space model can now be described as follows:

$$\dot{x}(t) = Ax(t) + Bu(t) + L(p)v(t), p \in [-1,1] \qquad (26)$$

where $L(p) = p.L$ is the Laplacian uncertainty matrix. The value of the RC-Centrality can be computed and drawn in Fig. 5.

According to Fig. 5, while agents 2 and 1 are the most individual central agents responding to the matched uncertainty, respectively, they are the least central agents in the presence of Laplacian uncertainty. This observation can be explained as the following: since the non-zero entries of unmatched uncertainty of each input set are larger, the input set needs more energy to deal with the uncertainty by activated input set, which is compatible with our simulation results to characterize design parameter γ and feedback gains K and L in Theorem 4.

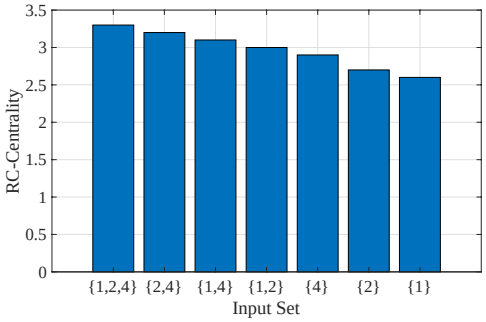

Fig. 5: RC-Centrality for the Laplacian Uncertainty.

Case Study 5: Adjacency Uncertainty

The third type of uncertainty can be considered due to the communication with its regulatory neighbors of the input set. The following relation is taken into account:

$$G(p) = G_{rep}(p) + G_{act}(p)$$

where, $G_{act}(p)$ and $G_{rep}(p)$ are the repression and activation uncertainties, respectively, defined as:

$$G_{act}(p) = \begin{cases} p\alpha_{ij} & \text{if } e_{ij} > 0 \\ 0 & \text{otherwise} \end{cases},$$

$$G_{rep}(p) = \begin{cases} -p\alpha_{ij} & \text{if } e_{ij} < 0 \\ 0 & \text{otherwise} \end{cases}$$

This uncertainty model applies to the adjacency matrix of the underlying coupling of the GRN.

$$\dot{x}(t) = Ax(t) + Bu(t) + G(p)v(t), p \in [-1,1] \qquad (27)$$

with regard to the adjacency uncertainty $G(p)$, the RC-Centrality for all input sets is depicted in Fig. 6.

It is worth noting that while Fig. 3-5 imply that input set $\{1,2,4\}$ is the most central set, it can be seen from Fig. 6 that based on the RC-Centrality, input node $\{2\}$ is the most central set with respect to the proposed type of unmatched uncertainty. That is due to its position with other genes in the network, i.e., input node $\{2\}$ has many repression links with both the target set and other agents to steer states to the origin and consumes less energy based on Theorem 4 to deal with the adjacency unmatched uncertainty matrix entries. However, it is observable that the input set $\{1,2,4\}$ needs much more input energy to reach the desired states, which can be deduced from the adjacency unmatched uncertainty matrix.

According to Fig. 6, it is also concluded that the group RC-Centrality may improve or diminish compared to the individual indices depending on the structure of unmatched uncertainty, which confirms the utility of the proposed centrality measure in the presence of unmatched uncertainty.

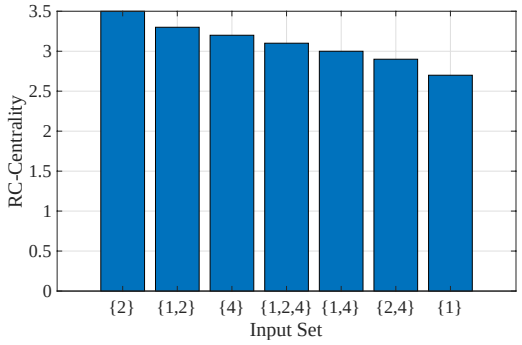

Fig. 6: RC-Centrality for the Adjacency Uncertainty.

We note that the term expressed in the last part of (12) is a function of the parameter γ and weighting matrix Q, which are designed to properly with uncertainty. In the presence of unmatched uncertainty, γ requires a larger amount of input energy to satisfy the condition (17). So, it is expected to see more energy for the unmatched uncertainty highly related to the non-zero entries of $\Delta(p)$.

Conclusion

A Robust Control Centrality measure is introduced in this paper based on an optimal value of input energy level needed for steering the states of an LTI network from the initial values at t_0 to their desired states at the final time t_f in presence of uncertainty.

In biological context, the proposed measure can be used to characterize the amount of control inputs used in controlling biological process. The proposed control centrality measure is related to the reachability Gramian of the weighted, directed, signed genetic networks that can be associated with the individual agents and agent groups. In genetic networks, the presence of inherent uncertainty poses a significant challenge in characterizing a robust control centrality. However, this challenge is addressed by adopting an optimal control approach in terms of the centrality of the robust controllers to stabilize the uncertain controllable GRN. Finally, the effectiveness of the proposed centrality measure is verified via simulation of a real GRN network under different scenarios of matched and unmatched uncertainties and comparison with established measures. The input resource allocation framework discussed in this paper is general, therefore, studying strategies for fixed budget constraints or variation in the cost of different control inputs in the network forms an interesting future research direction.

Results and Discussion

In future work, we shall introduce centrality measures as energy calculation for unstable systems with regard to the optimal energy to reach a desired steady state. Moreover, questions surrounding the terminal time and final steady states as two essential elements, which may affect the structure of the optimal energy, will be investigated.

Appendix A. An LTI model for GRNs

GRNs describe relationships between genes in a cell. They can be modeled as a WDS network [42]. The network's agents are genes, and the agent's state is the concentration of mRNA and protein of the gene expression. Each weighted and directed link in the WDS network represents power and direction of regulatory relationships, respectively. The activator or repressor transcription factor associates, respectively, with the positive or negative sign of the link in GRN's model.

A modified state space model for GRNs, based on the models provided in [41], [43] is proposed in this paper as follows:

$$\begin{aligned} \dot{m}_i(t) &= -\sigma_i m_i(t) + \sum_{j=1}^{n} b_{ij}(p_j(t)) + \mathcal{B}_i u_i(t) \\ \dot{p}_i(t) &= -c_i p_i(t) + d_i m_i(t) \qquad i = 1,2,\dots,n \end{aligned} \qquad (28)$$

where the concentration of mRNA and protein of gene i are denoted by $m_i(t)$, $p_i(t) \in R$. σ_i and c_i's are the degradation rates of mRNA and protein, respectively, and d_i is a bounded constant. Control input u_i is applied to gene i if it is activated via B_i; otherwise, it is zero. $b_{ij}(.)$ is expressed by the Hill form as:

$$b_{ij}\left(p_j(t)\right)=\begin{cases}\alpha_{ij}\frac{(p_j(t)/\beta)^H}{1+(p_j(t)/\beta)^H} & \text{if } a_{ij}>0\\ \alpha_{ij}\frac{1}{1+(p_j(t)/\beta)^H} & \text{if } a_{ij}<0\\ 0 & \text{otherwise}\end{cases} \quad (29)$$

where β is a positive constant, H is the Hill coefficient, and transcription rate α_{ij} is a bounded constant that determines the power of gene j to gene i in the regulation mechanism. The coupling matrix between genes is defined as

$$G_{ij}=\begin{cases}\alpha_{ij} & \text{if } a_{ij}>0\\ -\alpha_{ij} & \text{if } a_{ij}<0\\ 0 & \text{otherwise}\end{cases}$$

We know that:

$$\alpha_{ij}\frac{\left(p_j(t)/\beta\right)^H}{1+\left(p_j(t)/\beta\right)^H}=\alpha_{ij}-\alpha_{ij}\frac{1}{1+\left(p_j(t)/\beta\right)^H}$$

Then, (28) can be rewritten as

$$\begin{aligned}\dot{m}_i(t)&=-\sigma_i m_i(t)+\sum_{j=1}^{n}G_{ij}g\left(p_j(t)\right)+\mathcal{B}_i u_i(t)\\&\quad+l_i\\ \dot{p}_i(t)&=-c_i p_i(t)+d_i m_i(t),\qquad i=1,2,\dots,n\end{aligned} \quad (30)$$

where $l_i=\sum_{j\in V_{i1}}\alpha_{ij}$ is the basal rate, V_{i1} is the set of repressors of gene i, i.e., $a_{ij}<0$, and $g(p)=\frac{(p/\beta)^H}{1+(p/\beta)^H}$. In compact matrix form, (30) can be rewritten as

$$\begin{aligned}\dot{m}(t)&=\mathcal{A}m(t)+Gg\big(p(t)\big)+\mathcal{B}u(t)+l\\ \dot{p}(t)&=Cp(t)+Dm(t)\end{aligned} \quad (31)$$

where $G=G_{ij}\in R^{n\times n}$, $m(t)=[m_1(t),\dots,m_n(t)]^T$, $p(t)=[p_1(t),\dots,p_n(t)]^T$, $\mathcal{A}=\mathrm{diag}(-\sigma_1,\dots,-o_n)$, $\mathcal{B}=\mathrm{diag}(\mathcal{B}_1,\dots,\mathcal{B}_n)$, $C=\mathrm{diag}(-c_1,\dots,-c_n)$, $D=\mathrm{diag}(d_1,\dots,d_n)$, $l=[l_1,\dots,l_n]^T$, $g\big(p(t)\big)=\left[g\big(p_1(t)\big),\dots,g\big(p_n(t)\big)\right]^T$.

Consider an equilibrium point (m^*,p^*,u^*) of the nonlinear system (31), meaning that $\mathcal{A}m^*+Gf(p^*)+\mathcal{B}u^*+l=0$, and $Cp^*+Dm^*=0$. It will be shifted to the origin by letting $M(t)=m(t)-m^*$, $P(t)=p(t)-p^*$ [44]. Thus, we have

$$\begin{aligned}\dot{M}(t)&=\mathcal{A}M(t)+Gf\big(P(t)\big)+\mathcal{B}u(t),\\ \dot{P}(t)&=CP(t)+DM(t).\end{aligned} \quad (32)$$

where $M(t)$, $P(t)\in R^n$ and $f\big(P(t)\big)=g(P(t)+p^*)-g(p^*)$.The linearized control system at (m^*,p^*,u^*) is:

$$\begin{bmatrix}\dot{M}(t)\\ \dot{P}(t)\end{bmatrix}=\begin{bmatrix}\mathrm{A}_{11} & \mathrm{A}_{12}\\ \mathrm{A}_{21} & \mathrm{A}_{22}\end{bmatrix}\begin{bmatrix}M(t)\\ P(t)\end{bmatrix}+\begin{bmatrix}\mathcal{B}\\ 0\end{bmatrix}u(t)$$

where $A_{11}=\mathcal{A}$, $A_{12}=G\frac{\partial f}{\partial P}(m^*,p^*,u^*)$, $A_{21}=D$, $A_{22}=C$. So, an LTI model of GRNs with state variables $x(t)=\begin{bmatrix}M(t)\\ P(t)\end{bmatrix}$ is as follows:

$$\dot{x}(t)=Ax(t)+Bu(t) \quad (33)$$

where

$$A=\begin{bmatrix}\mathrm{A}_{11} & \mathrm{A}_{12}\\ \mathrm{A}_{21} & \mathrm{A}_{22}\end{bmatrix},\ B=\begin{bmatrix}\mathcal{B}\\ 0\end{bmatrix}.$$

The LTI system (33) is formed by applying control input to capture the dynamics of gene networks in an efficient way [45].

Author Contributions

S. Ozgoli and S. Bolouki served as the supervisor and advisor of the current research paper, respectively. They outlined the research framework and the roadmap and analyzed the results. Z. Ghassemi wrote the manuscript, proved the theoretical results, simulated the numerical case studies, and interpreted the results under the supervision and guidance of S. Ozgoli and S. Bolouki.

Acknowledgment

This work is entirely self-supported, and no financial support from any agency was involved.

Conflict of Interest

The authors declare no potential conflict of interest regarding the publication of this work. Furthermore, ethical issues including plagiarism, informed consent, misconduct, data fabrication and/or falsification, double publication and/or submission, and redundancy have been fully addressed by the authors.

Abbreviations

GRNs	Genetic Regulatory Networks
HJB	Hamilton-Jacobi-Bellman
LTI	Linear Time Invariant
WDS	Weighted Directed Signed

References

[1] P. H. Guzzi, S. Roy, Biological network analysis: trends, approaches, graphical theory and algorithms. Amsterdam: Elsevier, 2020.

[2] X. Chen, M. Xu, Y. An, "Identifying the essential nodes in network pharmacology based on multilayer network combined with random walk algorithm," J. Biomed. Inform., 114: 103666, 2021.

[3] J. Lü, P. Wang, "Identifying important nodes in bio-molecular networks," in Modeling and Analysis of Bio-molecular Networks, J. Lü and P. Wang, Eds., Singapore: Springer Singapore: 315-396, 2020.

[4] M. Ashtiani et al., "A systematic survey of centrality measures for protein-protein interaction networks," BMC Syst. Biol., 12(1), 2018.

[5] J. Wang, R. Peng, Z. Zhang, Y. Zhang, Y. Dai, Y. Sun, "Identification and validation of key genes in hepatocellular carcinoma by bioinformatics analysis," BioMed Res. Int., 6662114, 2021.

[6] H. B. Chakrapani, S. Chourasia, S. Gupta, T. Kumar D, G. P. Doss C, R. Haldar, "Effective utilisation of influence maximization technique for the identification of significant nodes in breast cancer gene networks," Comput. Biol. Med., 133, 2021.

[7] M. Newman, Networks: An Introduction. OUP Oxford, 2010.

[8] V. Latora, V. Nicosia, G. Russo, Complex networks: principles, methods and applications. Cambridge, United Kingdom; New York, NY: Cambridge University Press, 2017.

[9] S. Gómez, "Centrality in networks: Finding the most important nodes," in Business and Consumer Analytics: New Ideas, P. Moscato and N. J. de Vries, Eds., Cham: Springer International Publishing, 401-433, 2019.

[10] M. G. Everett, S. P. Borgatti, "The centrality of groups and classes," J. Math. Sociol., 23(3): 181-201, 1999.

[11] J. Tang et al., "Identification of top-k influential nodes based on enhanced discrete particle swarm optimization for influence maximization," Phys. Stat. Mech. Its Appl., 513: 477-496, 2019.

[12] G. Baggio, F. Pasqualetti, S. Zampieri, "Energy-Aware controllability of complex networks," Annu. Rev. Control Robot. Auton. Syst., 5(1): 465-489, 2022.

[13] G. Lindmark, C. Altafini, "Centrality measures and the role of non-normality for network control energy reduction," IEEE Control Syst. Lett., 5(3): 1013-1018, 2021.

[14] G. Lindmark, C. Altafini, "Combining centrality measures for control energy reduction in network controllability problems," in Proc. 2019 18th European Control Conference (ECC): 1518-1523, 2019.

[15] N. Bof, G. Baggio, S. Zampieri, "On the role of network centrality in the controllability of complex networks," IEEE Trans. Control Netw. Syst., 4(3): 643-653, 2017.

[16] G. Lindmark, C. Altafini, "Minimum energy control for complex networks," Sci. Rep., 8(1), 2018.

[17] L. Geris, D. Gomez-Cabrero, Uncertainty in Biology: A Computational Modeling Approach. in Studies in Mechanobiology, Tissue Engineering and Biomaterials. Springer International Publishing, 2015.

[18] F. Lin, Robust control design: an optimal control approach, John Wiley & Sons, 2007.

[19] Y. Lin, C. Lin, "Optimal control approach for robust control design of neutral systems," Optim. Control Appl. Methods, 30(1): 87-102, 2009.

[20] Y. Y. Liu, J. J. Slotine, A. L. Barabási, "Control centrality and hierarchical structure in complex networks," PLoS ONE, 7(9): e44459, 2012.

[21] U. Usman, A. Mahmood, L. Wang, "Robust control centrality," in Proc. 2019 Chinese Control Conference (CCC): 5486-5491, 2019.

[22] M. Siami, S. Bolouki, B. Bamieh, N. Motee, "Centrality measures in linear consensus networks with structured network uncertainties," IEEE Trans. Control Netw. Syst., 5(3): 924-934, 2018.

[23] Y. Ghaedsharaf, M. Siami, C. Somarakis, N. Motee, "Centrality in time-delay consensus networks with structured uncertainties," Automatica, 125: 109378, 2021.

[24] M. Amodio et al., "Generating hard-to-obtain information from easy-to-obtain information: Applications in drug discovery and clinical inference," Patterns, 2(7): 100288, 2021.

[25] G. Batt, B. Yordanov, R. Weiss, C. Belta, "Robustness analysis and tuning of synthetic gene networks," Bioinformatics, 23(18): 2415-2422, 2007.

[26] P. V. Chanekar, E. Nozari, J. Cortes, "Energy-Transfer edge centrality and its role in enhancing network controllability," IEEE Trans. Netw. Sci. Eng., 8(1): 331-346, 2021.

[27] L. Zhai, X. Yan, G. Zhang, "Bi-directional h-index: A new measure of node centrality in weighted and directed networks," J. Informetr., 12(1): 299-314, 2018.

[28] H. Ando, M. Bell, F. Kurauchi, K. I. Wong, K. F. Cheung, "Connectivity evaluation of large road network by capacity-weighted eigenvector centrality analysis," Transp. Transp. Sci., 17(4): 648-674, 2021.

[29] E. C. Baek, R. Hyon, K. López, E. S. Finn, M. A. Porter, C. Parkinson, "In-degree centrality in a social network is linked to coordinated neural activity," Nat. Commun., 13(1), 2022.

[30] X. Qi, E. Fuller, Q. Wu, Y. Wu, C. Q. Zhang, "Laplacian centrality: A new centrality measure for weighted networks," Inf. Sci., 194: 240-253, 2012.

[31] J. Laeuchli, Y. Ramírez-Cruz, R. Trujillo-Rasua, "Analysis of centrality measures under differential privacy models," Appl. Math. Comput., 412: 126546, 2022.

[32] Y. Li, Y. Sheng, X. Ye, "Group centrality algorithms based on the h-index for identifying influential nodes in large-scale networks," Int. J. Innovative Comput. Inf. Control, 16(4): 1183-1201, 2020.

[33] M. R. F. Mendonca, A. M. S. Barreto, A. Ziviani, "Approximating network centrality measures using node embedding and machine learning," IEEE Trans. Netw. Sci. Eng., 8,(1): 220-230, 2021.

[34] X. Li, Y. Liu, Y. Jiang, X. Liu, "Identifying social influence in complex networks: A novel conductance eigenvector centrality model," Neurocomput., 210: 141-154, 2016.

[35] Y. Yang, X. Wang, Y. Chen, M. Hu, C. Ruan, "A novel centrality of influential nodes identification in complex networks," IEEE Access, 8: 58742-58751, 2020.

[36] J. J. Molitierno, Applications of combinatorial matrix theory to Laplacian matrices of graphs. CRC Press, 2016.

[37] F. L. Lewis, D. L. Vrabie, V. L. Syrmos, Optimal control, 3rd ed. Hoboken: Wiley, 2012.

[38] V. V. Prasolov, S. Ivanov, Problems and theorems in linear algebra. in Translations of mathematical monographs, no. v. 134. Providence, R.I: American Mathematical Society, 1994.

[39] C. Tu, R. P. Rocha, M. Corbetta, S. Zampieri, M. Zorzi, S. Suweis, "Warnings and caveats in brain controllability," NeuroImage, 176: 83-91, 2018.

[40] M. Imani, U. Braga-Neto, "Optimal control of gene regulatory networks with unknown cost function," in Proc. 2018 Annual American Control Conference (ACC): 3939-3944, 2018.

[41] C. Li, L. Chen, K. Aihara, "Stability of genetic networks with SUM regulatory logic: Lur'e system and LMI approach," IEEE Trans. Circuits Syst. Regul. Pap., 53(11): 2451-2458, 2006.

[42] X. Zhang, Y. Wang, L. Wu, Analysis and Design of Delayed Genetic Regulatory Networks, vol. 207. in Studies in Systems, Decision and Control, vol. 207. Cham: Springer International Publishing, 2019.

[43] Y. Mori, Y. Kuroe, B. Ingalls, "A method for design of expression tracking controllers for gene regulatory networks," IFAC-PapersOnLine, 52(26): 135-142, 2019.

[44] Y. Y. Liu, A. L. Barabási, "Control principles of complex systems," Rev. Mod. Phys., 88, 2016.

[45] Y. J. Shin, L. Bleris, "Linear control theory for gene network modeling," PLOS ONE, 5(9), 2010.

Biographies

Zeinab Ghassemi Zahan received her B.Sc. degree in Computer Engineering from Ferdowsi University of Mashhad, Mashhad, Iran, and her M.Sc. degree in Electrical Engineering. She is currently a Ph.D. student in Electrical Engineering at Tarbiat Modares University, Tehran, Iran. Her experience includes being an international visiting graduate student in the Applied Mathematics department at the University of Waterloo, Canada. Her research interests include the area of control theory, complex networks, and systems biology.

- Email: zeinab.ghasemi@modares.ac.ir
- ORCID: 0000-0001-6995-8418
- Web of Science Researcher ID: NA
- Scopus Author ID: NA
- Homepage: NA

Sadjaad Ozgoli received the B.S. and M.S. degrees in Electrical Engineering from Sharif University of Technology, Tehran, Iran Engineering Department. His current research interests include robust and nonlinear control, applied in systems biology and Mechatronic systems., in 1997 and 1999 respectively. His Ph.D. studies were in Electrical Engineering from K.N. Toosi University, Tehran, Iran, received in 2005. Since September 2006, he has been with the School of Electrical and Computer Engineering, Tarbiat Modares University in Tehran where he is currently an Associate Professor at the Control.

- Email: ozgoli@modares.ac.ir
- ORCID: 0000-0001-8567-1679
- Web of Science Researcher ID: NA
- Scopus Author ID: NA
- Homepage: NA

Sadegh Bolouki received the B.S. and Ph.D. degrees in Electrical Engineering from Sharif University of Technology, Tehran, Iran and Polytechnique Montréal, Montreal, QC, Canada in 2008 and 2014, respectively. Since September 2018, he has been an Assistant Professor of Electrical and Computer Engineering in Tarbiat Modares University, Tehran, Iran. He is also a Research Associate with the Department of Mechanical Engineering in Polytechnique Montréal, Montreal, Canada. His past experience includes postdoctoral tenures at the Department of Mechanical Engineering and Mechanics, Lehigh University, PA, USA and Coordinated Science Laboratory, University of Illinois at Urbana-Champaign, IL, USA. His research interests broadly include the areas of machine learning, network science, and game theory.

- Email: bolouki@modares.ac.ir
- ORCID: 0000-0002-4175-5894
- Web of Science Researcher ID: NA
- Scopus Author ID: NA
- Homepage: NA

How to cite this paper:
Z. Ghassemi Zahan, S. Ozgoli, S. Bolouki, "A robust control centrality applicable to genetic regulatory networks with structured uncertainties," J. Electr. Comput. Eng. Innovations, 12(2): 511-524, 2024.

DOI: 10.22061/jecei.2024.10506.714

URL: https://jecei.sru.ac.ir/article_2150.html