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Modeling Dopaminergic Pathways in Schizophrenia with Directed Graphs and Linear Control Theory

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Abstract

Schizophrenia is considered not as a disorder isolated to a specific region of the brain, but rather as a disconnection syndrome in which interactions and communication between complex brain networks are disrupted. The dopamine hypothesis, which is among the most widely accepted neurobiological approaches for explaining the core mechanism of this disease, is based on a pathological imbalance between cortical and subcortical dopaminergic systems. According to the classical dopamine hypothesis, increased subcortical and striatal dopaminergic function is associated with positive symptoms, while decreased or dysregulated prefrontal dopaminergic function is linked to negative and cognitive symptoms. To fully comprehend these descriptive biochemical findings in neuroscience and to quantitatively model circuit-level disruptions, new mathematical frameworks are needed. In this study, the most extensively researched mesolimbic and mesocortical pathways in the pathophysiology of schizophrenia are examined; the nigrostriatal and other dopaminergic pathways are excluded from the scope of the study. The aim of the study is to transform the classic dopaminergic pathway hypotheses related to schizophrenia into a theoretical mathematical model within the frameworks of directed graphs, adjacency matrices, and linear control systems. As in network neuroscience approaches, specific anatomical regions of the brain affected by dopamine are considered as the "nodes" of the graph, while the directed communication and dopamine flow between these regions are regarded as the "edges" of the graph. While the adjacency matrix represents the presence and direction of anatomical connections, the magnitude and temporal changes of dopaminergic effects are modeled via a weighted state-transition matrix. In this way, the anatomical and dynamic properties of the dopamin-

ergic pathways associated with schizophrenia are expressed as a theoretical network model that can be analyzed with graph theory, matrix analysis, and controllability criteria. For the proposed five-node linear model, the controllability matrix is reduced to Vandermonde form, and it is shown that complete controllability of the system is equivalent to all weights from the VTA to the target regions being nonzero and the self-dynamic coefficients of the target regions being pairwise distinct.

Keywords

Schizophrenia, Dopaminergic Pathways, Directed Graph, State-Space Model, Network Controllability, Vandermonde Matrix

1. Introduction

The historical background of theoretical models regarding the disruption of neural networks and connectivity in schizophrenia extends back to 19th-century pioneers Theodor Meynert and Carl Wernicke. Wernicke and Meynert suggested that psychiatric disorders may arise from abnormal axonal connections between anatomically segregated cortical regions, that is, from a state of "miswiring" [1] [2]. This pioneering connectivity approach, based on classical morbid anatomy, has been reformulated today as the modern "disconnection" hypothesis by researchers such as Friston and Frith [1] [3]. Modern hypotheses define schizophrenia not merely as local tissue abnormalities in isolated brain regions, but as a systemic syndrome characterized by disrupted structural and functional integration between different cortical and subcortical areas of the brain, spanning from the level of cellular signaling to macro-scale networks [2].

The dominant theory explaining the pathophysiology of schizophrenia and the clinical manifestations of these connectivity disorders, the dopamine hypothesis, is based on a marked imbalance between cortical and subcortical dopaminergic systems. Subcortical mesolimbic projections extending from the ventral tegmental area to limbic structures such as the nucleus accumbens become hyperactive through excessive stimulation of receptors [3]. This mesolimbic hyperactivation within the fronto-striatal complex and the excessive release of dopamine in the synaptic cleft are the direct causes of positive symptoms in patients, such as hallucinations and delusions [3] [4]. In contrast, mesocortical projections extending to the prefrontal cortex (PFC) are hypoactive [4].

Graph theory provides a suitable framework for the mathematical analysis of complex brain networks by allowing brain regions to be represented as nodes and the anatomical or functional connections between these regions as edges [1] [5]. Scientists have long utilized discrete mathematics to model the complex structure of the nervous system and synaptic communication among billions of cells; the most established and effective mathematical tool used for this purpose is Graph Theory [6]. Originating from pure mathematics, this theory today forms the back-

bone of every field from computer science to the design of search algorithms and complex data structures [7]. Anatomical brain regions represent the nodes of the network, while the structural or functional interactions between them represent the edges that enable signal flow [8].

In the graph representation of brain networks, the nodes correspond to selected anatomical regions, while the edges represent anatomical, functional, or effective connections between these regions, depending on the research question. Mapping neural circuits onto a directed and weighted graph structure allows us to quantitatively measure how the brain's normal small-world network topology, clustering coefficients, and hierarchical organization are disrupted in schizophrenia [9]. Therefore, modeling the mechanisms of mesolimbic hyperactivation and mesocortical hypoactivation in schizophrenia using graph theory will prevent psychiatric circuit dysfunctions from remaining merely descriptive and enable their investigation as a topologically measurable and computable "network problem" [10] [2].

Accordingly, the present model deliberately focuses on five aggregated nodes—VTA, NAcc, amygdala, hippocampus, and PFC—because these regions represent the core mesolimbic and mesocortical dopaminergic projections considered in the proposed graph. Feedback circuits, striatal subdivisions, and non-dopaminergic pathways are excluded in order to keep the formal construction restricted to a minimal VTA-to-target dopaminergic architecture. This restriction does not imply that these excluded structures are biologically irrelevant; rather, it defines the boundary of the theoretical network analyzed in this study.

2. Anatomical Basis of the Dopaminergic Pathway

Dopaminergic neurotransmission within the brain plays a central role in the pathophysiology of many psychiatric and neurological conditions, including schizophrenia. According to the anatomical literature, there are four main dopaminergic pathways in the brain responsible for the integration of information, emotion, and movement: the nigrostriatal, mesolimbic, mesocortical, and tuberoinfundibular pathways. Most major dopaminergic projections originate from the substantia nigra pars compacta and the ventral tegmental area, where the cell bodies of dopaminergic neurons are concentrated [4] [11]. Examining the anatomical projections of these pathways is critically important for understanding the neurobiology of schizophrenia.

The mesolimbic pathway consists of projections originating from the Ventral Tegmental Area (VTA) in the midbrain and extending to key structures of the limbic system, namely the Nucleus Accumbens (NAc), Amygdala (AMYG), and Hippocampus (HIP). The mesolimbic pathway is a component of functional circuits associated with motivation, reward processing, goal-directed behavior, and the evaluation of emotional information. In the context of schizophrenia, excessive dopamine activity within this pathway leads to an intense accumulation of dopamine in the Nucleus Accumbens, forming the anatomical and neurochemical

basis of positive symptoms such as hallucinations and delusions experienced by patients [4] [11].

The mesocortical pathway, like the mesolimbic pathway, originates from the VTA; however, it is a dopaminergic pathway that this time extends to higher cognitive centers of the brain, predominantly to the medial prefrontal cortex (mPFC). Typically, together with the mesolimbic pathway, they are referred to anatomically and functionally as the "mesocorticolimbic system" [11]. This dopamine flow to the prefrontal cortex is critical for cognitive flexibility, working memory, and mood regulation. In patients with schizophrenia, insufficient dopamine transmission in this pathway has been directly associated with the emergence of negative and cognitive symptoms that signify impairments in the brain's executive functions [2].

The underlying pathophysiology of the disease is not merely isolated tissue damage; rather, it is a problem of cellular communication in which dopaminergic imbalances in the synaptic clefts (mesolimbic hyperactivation and mesocortical hypoactivation) are intertwined with glutamatergic transmission deficits. In the preliminary conference report of this study, several dopaminergic regions associated with schizophrenia were represented using a directed graph and adjacency matrix. The present study expands this static graph approach with linear state-space and controllability analysis. The brain's complex structure in this topological space can now be examined from a much broader perspective—not simply as communication between two points, but through high-order inter-network functional connections and the dynamics of information integration [12].

3. Mathematical Preliminaries

One of the most powerful tools currently used to mathematically model interactions and organization in complex systems is Graph Theory [6]. Many systems in the natural, social, or technological sciences are represented by topological structures called "graphs" in order to illustrate their elements and the relationships among those elements [7]. To formalize highly complex structures such as brain networks, some fundamental concepts of this mathematical framework need to be clearly defined.

Definition 3.1. (Graph): Mathematically, a graph is, in broad terms, $G=(V,E)$, a binary structure expressed by the formula. Where $V=(v_1,v_2,\cdots,v_n)$ denotes the finite and non-empty set consisting of the nodes of the graph, while $E=(e_1,e_2,\cdots,e_n)=((u_1,v_1),(u_2,v_2),\cdots,(u_n,v_n))$ represents the set of edges indicating the connections between these nodes. The number of edges is not required to be equal to the number of nodes [13].

Definition 3.2. (Directed and Undirected Graph): Nodes represent objects in the system, while edges indicate the relationship or interaction between these objects. If each edge has a specific start and end node, this structure is called a directed graph. In contrast, if the edges are not associated with any direction, it is defined as an undirected graph. In directed graphs, (u,v) and (v,u) represent

different connections, whereas in undirected graphs, these two representations denote the same connection [13].

Definition 3.3. (Adjacency Matrix): One of the most widely used methods for algebraically representing the topological structure of a graph and converting it into a form that can be processed by computer-based algorithms is the adjacency matrix representation [7]. The adjacency matrix is a square matrix that systematically and mathematically expresses all the connections between the nodes of the graph. Through this representation, the graph structure is transformed from being merely a visual network into a numerical model that can be analyzed using linear algebra methods, matrix operations, and computational algorithms. Especially in the analysis of large-scale networks, adjacency matrices are used as one of the fundamental data structures both in theoretical analyses and in computer-assisted simulations.

For a graph consisting of n nodes, the adjacency matrix $A(G)$ is defined as an $n \times n$ square matrix. The rows and columns of the matrix represent the nodes of the graph, while each element indicates the existence or nature of the relationship between node i and node j. In its most basic form, the binary adjacency matrix is defined as follows [6] [13].

$$a_{ij} = \begin{cases} 1, & v_i \to v_j \text{ if there is a directional connection between them} \\ 0, & \text{in other cases} \end{cases}$$

Definition 3.4. (Vandermonde Matrix):

Vandermonde matrix is as follows.

$$V = \begin{bmatrix} 1 & a_1 & a_1^2 & \cdots & a_1^{n-1} \\ 1 & a_2 & a_2^2 & \cdots & a_2^{n-1} \\ \vdots & \vdots & \vdots & \ddots & \vdots \\ 1 & a_n & a_n^2 & \cdots & a_n^{n-1} \end{bmatrix}_{n \times n}$$

where $a_1, a_2, \cdots, a_n \in \mathbb{R}$. The determinant of this matrix is given as follows [14].

$$\det V = \prod_{1 \le i \le j \le n} \left(a_j - a_i \right)$$

In linear system theory, the evolution of a system over time is represented by state equations involving the system's current state and the inputs applied to the system. The state-space approach facilitates the analysis of a dynamic system's temporal behavior through matrix operations by expressing the system's internal states as a finite-dimensional vector. This approach constitutes a fundamental framework in the mathematical characterization of linear control systems [15] [16].

Definition 3.5 (Discrete-Time Linear and Time-Invariant System):

Let $n, m \in \mathbb{N}$, and let the matrices $M \in \mathbb{R}^{n \times n}$ and $B \in \mathbb{R}^{n \times m}$ be given. A discrete-time, linear, time-invariant control system $\Sigma = (M, B)$ is defined by the pair, given that the state equation of the system is

$$x(t+1) = Mx(t) + Bu(t)$$

where $t \in \mathbb{N}_0$. Here, $x(t) \in \mathbb{R}^n$ represents the state vector of the system at time t, $u(t) \in \mathbb{R}^m$ denotes the input vector applied to the system at time t, M is the state-transition matrix, and B is the input matrix. The M matrix characterizes how the system evolves under its internal dynamics in the absence of any external input, while the B matrix specifies in which directions the inputs influence the state variables [15]-[17].

Definition 3.6 (Complete Controllability):

Based on the discrete-time linear system, if it is possible to transition from any initial state $x_0 \in \mathbb{R}^n$ to any target state $x_f \in \mathbb{R}^n$ within a finite time T using an appropriate input sequence $u(0), \cdots, u(T-1)$, the system is referred to as completely controllable. In linear time-invariant systems, this property is determined using the Kalman controllability matrix [3] [18].

Definition 3.7 (Controllability Matrix and Kalman Rank Criterion):

The controllability matrix for the $\Sigma = (M, B)$ system with n state variables and m inputs is defined as follows.

$$\mathcal{C}(M, B) = \begin{bmatrix} B & MB & M^2B & \cdots & M^{n-1}B \end{bmatrix}$$

Since it is $B \in \mathbb{R}^{n \times m}$, it is $\mathcal{C}(M, B) \in \mathbb{R}^{n \times nm}$. In this matrix, B represents the direct effect of the input on the system; $M^k B$ shows the transformed effect of the input under the system dynamics over k time steps. According to the Kalman criterion, the $\Sigma = (M, B)$ system is fully controllable if and only if the $\operatorname{rank} \mathcal{C}(M, B) = n$ condition is satisfied [15] [16] [18]. In other words, the columns of the controllability matrix must span the $\mathbb{R}^n$ state space.

4. Dopaminergic Network Model Based on Schizophrenia

In this study, the VTA, NAcc, amygdala, hippocampus, and PFC are defined as anatomical nodes. Mesolimbic projections extending from the VTA to the NAcc, amygdala, and hippocampus, as well as mesocortical projections extending from the VTA to the medial prefrontal cortex, are modeled as directed edges. The model includes only dopaminergic efferent projections from the VTA to target structures; indirect feedback circuits, the nigrostriatal pathway, and non-dopaminergic connections are excluded [11]. Since there are no edges in the reverse direction in the defined edge set, the adjacency matrix is not symmetric.

The adjacency matrix represents only the presence and direction of connections. An increase or decrease in dopaminergic activity relative to the healthy reference level can be incorporated into the model only by defining a weighted matrix or a state-transition matrix. Therefore, clinical symptom dimensions cannot be directly derived from the adjacency matrix; the weights must be estimated from empirical data and separately correlated with clinical outcomes.

The cell bodies of dopaminergic neurons are located in the ventral tegmental area (VTA), and their axons extend toward target brain regions. Therefore, the mesolimbic and mesocortical dopamine pathways possess a directed network structure. Accordingly, in this study, a directed graph approach will be used for

the mathematical modeling of dopaminergic pathways. In this way, the anatomical projections of the dopamine signal from the VTA to the nucleus accumbens, amygdala, hippocampus, and prefrontal cortex can be represented using graph theory.

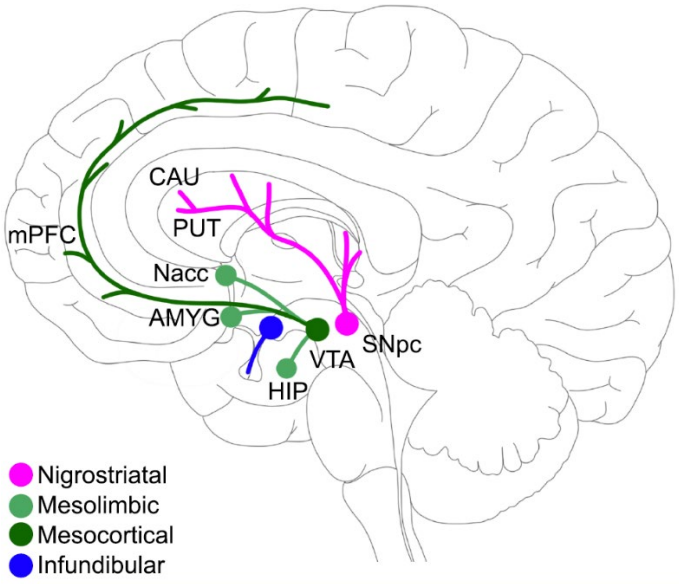

Figure 1. Dopaminergic pathways [11], adapted under the CC BY 4.0 license.

Based on the anatomical projections summarized in **Figure 1**, a directed graph model of the dopaminergic pathway was constructed. The anatomical regions included in the model were defined as the ventral tegmental area (VTA), nucleus accumbens (NAcc), amygdala, hippocampus, and prefrontal cortex (PFC). In this study, the PFC node was used as an aggregated high-level node representing the medial prefrontal cortex, which is one of the principal cortical targets of the mesocortical pathway. Accordingly, the set of nodes and edges can be denoted as follows.

$$V = \{\text{VTA}, \text{NAcc}, \text{Amygdala}, \text{Hippocampus}, \text{PFC}\}$$

$$E = \{(\text{VTA}, \text{NAcc}), (\text{VTA}, \text{Amygdala}), (\text{VTA}, \text{Hippocampus}), (\text{VTA}, \text{PFC})\}$$

The edge set can be partitioned into mesolimbic and mesocortical subsets as follows.

$$E_{ML} = \{(\text{VTA}, \text{NAcc}), (\text{VTA}, \text{Amygdala}), (\text{VTA}, \text{Hippocampus})\}$$

$$E_{MC} = \{(\text{VTA}, \text{PFC})\}$$

With the E set, it can be expressed as follows.

$$E = E_{ML} \cup E_{MC}$$

Thus, from here, we can represent the graph structure of the dopaminergic pathway as shown in **Figure 2** below.

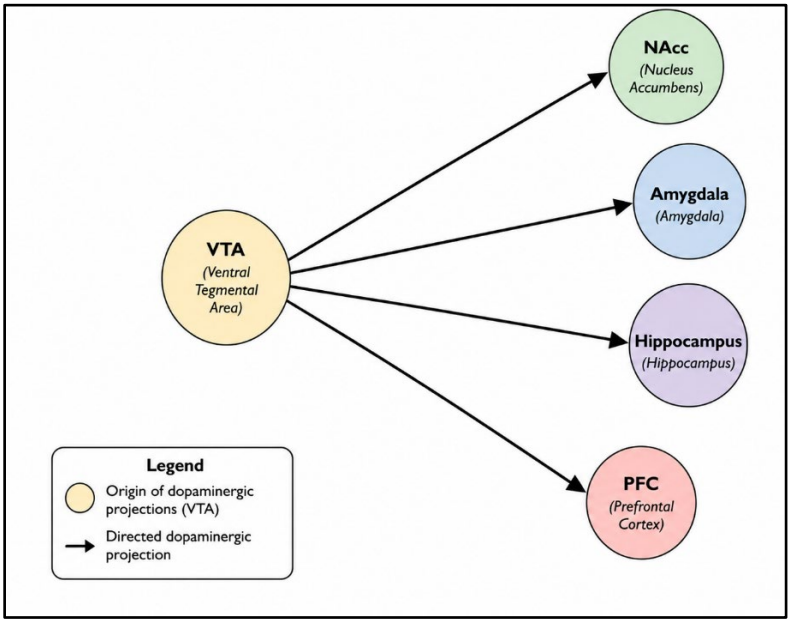

Figure 2. Dopaminergic pathways graph (directed).

In order to algebraically represent the directed graph depicting dopaminergic pathways, the graph structure can be converted into an adjacency matrix, as shown below.

$$A(G)=\begin{bmatrix}0 & 1 & 1 & 1 & 1\\ 0 & 0 & 0 & 0 & 0\\ 0 & 0 & 0 & 0 & 0\\ 0 & 0 & 0 & 0 & 0\\ 0 & 0 & 0 & 0 & 0\end{bmatrix}$$

The four 1 values in the first row of the matrix represent the direct projections from the VTA to the NAcc, amygdala, hippocampus, and PFC. The fact that all the other rows are zero stems from the lack of any defined directed edge originating from these target regions in the current simplified model. The zeros in the diagonal elements indicate that there are no self-loops in which a node projects onto itself in the model. Since there is only a single nonzero row in the adjacency matrix, the rank is 1. This rank value does not mean that the VTA solely controls all target regions in the biological system; it simply shows that the defined simplified graph has only a single independent output pattern. The $a_{ij}=1$ value does not indicate how strong the relevant connection is, or whether dopaminergic activity increases or decreases compared to the reference level. Therefore, the current adjacency matrix represents only the topological skeleton of the dopaminergic network; it does not explain its functional state. The directed graph model defined in earlier stages of the study is also based on this binary anatomical representation.

Definition 4.1 (Structurally Compatible Weighted Matrices):

Let $A(G)$ be the adjacency matrix of the proposed dopaminergic graph. The

set of structurally compatible weighted matrices with $A(G)$ is defined as

$$\mathcal{W}(A)=\left\{W\in\mathbb{R}^{5\times5}: w_{ij}=0\Leftrightarrow a_{ij}=0\right\}.$$

From here, the transformation to the adjacency matrix is provided by the

$$\mathcal{B}(W)_{ij}=\begin{cases}1, & w_{ij}\neq 0\\ 0, & w_{ij}=0\end{cases}$$

operator. That is, it is $\mathcal{B}(W)=A(G)$.

Lemma 4.1: Different weighted dopaminergic states with the same anatomical connectivity pattern can be transformed into the same binary adjacency matrix. Therefore, the adjacency matrix alone cannot determine the signs and magnitudes of the connections.

Proof: Let $W^{(1)}$ and $W^{(2)}$ be two different weighted matrices compatible with the $A(G)$ adjacency matrix, as follows.

$$W^{(1)}=\begin{bmatrix}0&1&1&1&1\\0&0&0&0&0\\0&0&0&0&0\\0&0&0&0&0\\0&0&0&0&0\end{bmatrix},W^{(2)}=\begin{bmatrix}0&2&-1&0.5&-3\\0&0&0&0&0\\0&0&0&0&0\\0&0&0&0&0\\0&0&0&0&0\end{bmatrix}$$

It is clear that these two matrices are different from each other. If a transformation operation is applied to both matrices,

$$\mathcal{B}\left(W^{(1)}\right)=\mathcal{B}\left(W^{(2)}\right)=A(G)$$

is obtained. Two distinct dopaminergic systems with different weights can be represented by the same adjacency matrix. Therefore, the transformation is not one-to-one, and the original weighted matrix cannot be recovered from the adjacency matrix. The lemma has been proven.

The main conclusion of this lemma is that the adjacency matrix is inadequate for characterizing the functional state of the dopaminergic system. For example, whether the connection between the VTA and NAcc exhibits higher or lower dopaminergic activity compared to the healthy reference level, as long as the connection anatomically persists, it will be represented in the same way in the binary matrix as $a_{\mathrm{VTA,NAcc}}=1$

The positive and negative signs used in the weighted matrix should not be confused with positive and negative symptoms in the clinical sense. In this study, $w_{ij}>0$ represents deviation in the positive direction according to the selected normative reference, while $w_{ij}<0$ represents deviation in the negative direction. These signs do not indicate the directly excitatory or inhibitory nature of the connection.

In addition to all this, even if the weighted matrices resulting from dopaminergic activity at different time points are in the form $W^{(1)},W^{(2)},\cdots,W^{(t)}$, as long as the anatomical connections are preserved, the $\mathcal{B}\left(W^{(t)}\right)=A(G)$ equality holds at all time points. This result indicates that the binary adjacency matrix can be

used for topological analysis, but it is not sufficient by itself to distinguish functional magnitudes and temporal variations.

Definition 4.2 (Dopaminergic State-Space Model):

The proposed dopaminergic system is defined as a discrete-time linear time-invariant state-space model consisting of five state variables corresponding to the VTA, NAcc, amygdala, hippocampus, and PFC. According to this ordering, the state vector is

$$x(t)=\begin{bmatrix} x_V(t) \\ x_N(t) \\ x_A(t) \\ x_H(t) \\ x_P(t) \end{bmatrix} \in \mathbb{R}^{5\times 1}.$$

The state-transition matrix is defined as follows.

$$M=\begin{bmatrix} d_V & 0 & 0 & 0 & 0 \\ w_N & d_N & 0 & 0 & 0 \\ w_A & 0 & d_A & 0 & 0 \\ w_H & 0 & 0 & d_H & 0 \\ w_P & 0 & 0 & 0 & d_P \end{bmatrix}.$$

Here, $x_V(t)$ represents the modeled state of the VTA at time t; $x_N(t)$ of the NAcc; $x_A(t)$ of the amygdala; $x_H(t)$ of the hippocampus; and $x_P(t)$ of the PFC. The state variables are modeled as abstract normalized node states rather than direct measurements of absolute extracellular dopamine concentration. Each $x_i(t)$ represents the effective dopaminergic activity of node i at time t with respect to a chosen reference condition. Thus, $x_i(t)$ should be interpreted as a model-level deviation from a reference state, not as a directly observed biochemical dopamine level. The d parameters indicate the nodes' intrinsic dynamic coefficients. A d_i coefficient represents the contribution of the given node's state at time t to its own state at time $t+1$. For example, d_N indicates the persistence or attenuation effect of the current state of the NAcc on its own state at the next time point.

The coefficients w_N, w_A, w_H, w_P are model-level dynamic coupling weights from the VTA to the corresponding target nodes. They do not represent purely anatomical connection strength. Rather, they parameterize the signed magnitude of the modeled dopaminergic influence transmitted along the selected anatomical projections relative to the chosen reference state.

Since the external input is assumed to act directly only on the VTA state, the input matrix is defined as follows.

$$B=\begin{bmatrix} 1 \\ 0 \\ 0 \\ 0 \\ 0 \end{bmatrix} \in \mathbb{R}^{5\times 1}.$$

This single-input choice is motivated by the fact that the selected mesolimbic and mesocortical projections share the VTA as their dopaminergic origin. Therefore, the external input is modeled as acting directly on the VTA state, whereas the target regions are affected indirectly through the VTA-to-target weights in the state-transition matrix M [4] [11].

In accordance with Definition 3.5, the proposed dopaminergic system is denoted by

$$\Sigma_D = (M, B),$$

where the subscript D refers to the dopaminergic model. Accordingly, the system dynamics are governed by

$$x(t+1) = Mx(t) + Bu(t), u(t) \in \mathbb{R}$$

Applying Definition 3.7 to the model defined in Definition 4.2, the controllability matrix of the proposed dopaminergic system is obtained as

$$\mathcal{C}(M, B) = \begin{bmatrix} B & MB & M^2B & M^3B & M^4B \end{bmatrix}$$

where $n = 5$. According to the Kalman criterion, the dopaminergic system is considered fully controllable through the VTA if and only if the $\operatorname{rank}\mathcal{C}(M, B) = 5$ condition is met. Here, full controllability refers to the ability to steer any of the five state variables in the model to a desired target state in finite time with an appropriate mathematical input sequence applied to the VTA. This concept does not directly imply clinical treatability; it only demonstrates a mathematical property of the defined linear dynamic system.

Lemma 4.2 (Reduction of the Controllability Matrix to Vandermonde Form):

Let

$$\mathcal{C} = \begin{bmatrix} c_0 & c_1 & c_2 & c_3 & c_4 \end{bmatrix}, c_k = M^k B, k = 0,1,2,3,4 .$$

Let C be the controllability matrix of the model defined in Definition 4.2. This matrix can be reduced to the following form.

$$\tilde{\mathcal{C}} = \begin{bmatrix} 1 & 0 & 0 & 0 & 0 \\ 0 & w_N & w_N d_N & w_N d_N^2 & w_N d_N^3 \\ 0 & w_A & w_A d_A & w_A d_A^2 & w_A d_A^3 \\ 0 & w_H & w_H d_H & w_H d_H^2 & w_H d_H^3 \\ 0 & w_P & w_P d_P & w_P d_P^2 & w_P d_P^3 \end{bmatrix}$$

Proof:

For $k = 0$, $c_0 = B$. By Definition 4.2,

$$c_0 = B = \begin{bmatrix} 1 \\ 0 \\ 0 \\ 0 \\ 0 \end{bmatrix} = e_1.$$

For $k \geq 1$, the first component of the $c_k = M^k B$ vector corresponding to the VTA is

$$(c_k)_V = d_V^k$$

in this form. For the target component $i \in \{N, A, H, P\}$,

$$(c_k)_i = w_i \sum_{r=0}^{k-1} d_i^{k-1-r} d_V^r$$

is obtained. Let us apply the $c_k \leftarrow c_k - d_V c_{k-1}$ column operation to the controllability matrix, following the $k = 4,3,2,1$ sequence. Applying the operations in decreasing order of k ensures that at each step the previously unchanged column is used. Adding or subtracting a constant multiple of another column to a column does not change the determinant or the rank [14]. If we denote the transformed columns by $q_k = c_k - d_V c_{k-1}$, the first component is obtained as follows.

$$(q_k)_V = d_V^k - d_V d_V^{k-1} = 0.$$

For the target node i, the more general form is as follows.

$$(q_k)_i = w_i \sum_{r=0}^{k-1} d_i^{k-1-r} d_V^r - d_V w_i \sum_{r=0}^{k-2} d_i^{k-2-r} d_V^r.$$

From here, $(q_k)_i = w_i d_i^{k-1}$ is obtained. Thus, the components of the transformed columns corresponding to the target nodes are

$$w_i \quad w_i d_i \quad w_i d_i^2 \quad w_i d_i^3$$

respectively. In this way, the controllability matrix is reduced to the form $\tilde{\mathcal{C}}$. Since this matrix is obtained by elementary column operations, its determinant does not change.

Theorem 4.1 (Full Controllability Condition for the Proposed Dopaminergic State-Space Model):

Let M and $B = e_1$ be as defined in Definition 4.2. The proposed five-dimensional dopaminergic state-space model is fully controllable under a single input applied via the VTA if and only if

$$w_N w_A w_H w_P \neq 0$$

and

$$d_i \neq d_j \quad \text{for every distinct} \quad i, j \in \{N, A, H, P\}.$$

Proof:

It is reduced from the $\mathcal{C}$ matrix to the $\tilde{\mathcal{C}}$ matrix by column operations according to Lemma 4.2. Therefore, the equality $\det(\mathcal{C}) = \det(\tilde{\mathcal{C}})$ holds.

If we separate the first row and column of matrix $\tilde{\mathcal{C}}$

$$S = \begin{bmatrix} w_N & w_N d_N & w_N d_N^2 & w_N d_N^3 \\ w_A & w_A d_A & w_A d_A^2 & w_A d_A^3 \\ w_H & w_H d_H & w_H d_H^2 & w_H d_H^3 \\ w_P & w_P d_P & w_P d_P^2 & w_P d_P^3 \end{bmatrix}$$

the submatrix remains. We can write this matrix in a way that can be separated as

$$S = \operatorname{diag}\left(w_N, w_A, w_H, w_P\right)\begin{bmatrix} 1 & d_N & d_N^2 & 3 \\ 1 & d_A & d_A^2 & d_A^3 \\ 1 & d_H & d_H^2 & d_H^3 \\ 1 & d_P & d_P^2 & d_P^3 \end{bmatrix}.$$

The second matrix on the right is a Vandermonde matrix. If we take the determinant, the determinant of the Vandermonde matrix is

$$\det\left(S\right) = w_N w_A w_H w_P \prod_{1 \le i \le j \le 4} \left(d_j - d_i\right).$$

So, from this, the determinant of the controllability matrix is as follows.

$$\det\left(\mathcal{C}\right) = w_N w_A w_H w_P \prod_{1 \le i \le j \le 4} \left(d_j - d_i\right)$$

If all connection weights are nonzero and the self-dynamic coefficients of the target nodes are pairwise distinct, all factors constituting the determinant are nonzero. That is, $w_N w_A w_H w_P \neq 0$ and for every $i \neq j$, $d_i \neq d_j$. In this case, $\det\left(\mathcal{C}\right) \neq 0$ is obtained. Therefore, $\operatorname{rank}\left(\mathcal{C}\right) = 5$, and according to the Kalman criterion, the dopaminergic system is fully controllable.

Conversely, if at least one of the weights is zero, for example, let it be $w_N = 0$. No dynamic transfer occurs from the VTA to the NAcc state, and the row of the controllability matrix corresponding to the NAcc becomes zero. Therefore, it results in $\operatorname{rank}\left(\mathcal{C}\right) < 5$. Similarly, if the self-dynamic coefficients of two target nodes are equal, for example, let them be $d_N = d_A$. Here, when $d_N - d_A = 0$, the factor in the Vandermonde determinant becomes zero, so it becomes $\det\left(\mathcal{C}\left(M, B\right)\right) = 0$, which causes the system to lose full controllability. This completes the proof.

5. Results and Recommendations

In this study, dopaminergic mesolimbic and mesocortical pathways in schizophrenia are modeled using a directed graph, with the VTA as the source and the NAcc, amygdala, hippocampus, and PFC as the target nodes. It is demonstrated, with a developed unidentifiability lemma, that the constructed binary adjacency matrix only indicates the existence of anatomical connections and cannot distinguish connection weights or temporal variations. Therefore, the static graph is extended into a discrete-time linear state-space model in the form $x\left(t+1\right) = Mx\left(t\right) + Bu\left(t\right)$.

In controllability analysis, it has been shown that full controllability of the proposed five-node linear model via the VTA depends on all connection weights being nonzero and the self-dynamic coefficients of the target nodes being pairwise distinct. The resulting Vandermonde determinant revealed that merely having anatomical connectivity is not sufficient; the temporal dynamics of the target regions must also differ from one another. However, this result does not indicate that the

real brain is clinically controllable, but rather expresses a mathematical property of the proposed five-node linear model.

In this theoretical network, full controllability means that the five modeled state variables can be mathematically steered from any initial state vector to any target state vector in finite time by a suitable input sequence applied to the VTA. It does not mean that clinical symptoms can be controlled through direct VTA intervention, nor does it imply that pharmacological or neuromodulatory treatments can arbitrarily set dopaminergic activity in the biological brain.

The proposed model is a linear and time-invariant approach representing mesolimbic and mesocortical dopaminergic projections with five aggregated anatomical nodes and a single VTA input. Striatal subregions, indirect feedback circuits, non-dopaminergic connections, stochastic effects, and nonlinear receptor dynamics are not included in the model. In addition, the star-shaped topology of the proposed graph cannot represent reciprocal modulation among the NAcc, amygdala, hippocampus, and PFC. Therefore, the model should be interpreted as a minimal VTA-centered dopaminergic projection model rather than as a complete representation of the broader schizophrenia-related brain network. Furthermore, the w_i and d_i parameters were not estimated from experimental data. Therefore, the obtained controllability condition indicates a structural property of the defined mathematical system rather than clinical treatability.

In future studies, the model can be extended in terms of stability, controllability Gramian, minimum control energy, observability, parameter identifiability, and condition number. In addition, a more comprehensive mathematical framework can be developed by adding multilayer network models incorporating stochastic effects, nonlinear dynamics, feedback connections, and dopamine-glutamate-GABA interactions.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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