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GRAPHS OF NEUROPEPTIDES INVOLVED IN LEARNING AND MEMORY PROCESSES

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Abstract

Graph theoretical analysis is an important area of research in biological networks. In this work we defined a new graph called Neuropeptide $\mathcal{C}^{**}-$ graph obtained from $\mathcal{C}^{**}-$ set of each protein/peptide graphs of fifteen neuropeptides which involved in the brain function – learning and memory processes. From the graph theoretical analysis we got some observations about the relation among the fifteen neuropeptides. The highest centrality measures of the neuropeptides Beta-endorphin, Galanin, Neuropeptide Y, Oxytocin and Substance P revealed the critical vertices of the graph and they also gave the prominent neuropeptides involved in the learning and memory processes. The neuropeptide $\mathcal{C}^{**}-$ graph showed that all the neuropeptides were connected because every pairs of neuropeptides were inter related by atleast one amino acid which recieved atleast one highest centrality measure and revealed the strength of the relation between neuropeptides with in the brain function – learning and memory processes. This work may help in the study of the mechanisms involved in learning, memory processes and other brain functions and would aid in developing better solutions to treat diseases like Alzheimer's. Its application may also help in the study of the evolution of neuropeptides involved in learning and memory processes and other brain functions in different species of animals.

Keywords:

Amino acid,
neuroeptide,
Pt-graph,
Neuropeptide graph,
Centrality measure.

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1. Introduction

Proteins are polymers of amino acids, with each amino acid residue joined to its neighbour by a specific type of covalent bond [3]. Twenty different types of natural amino acids are commonly found in peptide/protein. The sequence of amino acids in a protein is characteristic of that protein and is called its primary structure [3]. Peptides/proteins are the compounds of amino acids in which a carboxyl group of one is united with an amino group of another. Neuropeptides are peptides formed and released by neurons. They are involved in a wide range of brain functions. The role of neuropeptides in cognitive functions including learning and memory processes has been studied earlier [6]. Moreover, neuropeptides may be of importance in neurogenerative and neuropsychiatric disorders associated with cognitive impairments. Cognition is the mental activities associated with thought, decision making, language and other higher mental processes like learning,

memory, etc. [5]. Learning is any relatively permanent change in behavior (or behavior potential) resulting from experience and memory is the cognitive system(s) for storing and retrieving information.

In [7], we can see so many graph theoretical applications in various fields. Amino acid network within protein was studied by S. Kundu [4]. By using some physico-chemical properties (Hydrophobicity, Hydrophilicity, Polarity, Non-polarity, Aliphaticity, Aromaticity and Charge (Positive and Negative)) of amino acids, the amino acid network was studied by Adil Akthar and Nisha Gohan graph theoretically [1]. The centralities in amino acid networks were used by Adil Akhtar and Tazid Ali [2]. Sven Ove Ogren, Eugenia Kuteeva, Elin Elvander-Tottie and Tomas Hokfelt were studied about the neuropeptides involved in learning and memory processes [6]. By using the concept of amino acid network we defined and analysed the peptide/protein graph (Pt-graph) and species-wise peptide/protein graph (Species-wise Pt-graph) of galanin presented in fourteen species of animals graph theoretically [8] and the bipartite Pt-graphs and physico-chemical subgraphs (physico-chemical property-wise) of human galanin and its three receptors on the basis of the physico-chemical properties of amino acids [9]. In this work we define and then analyse neuropeptide $\mathcal{C}^{**}-$ graph obtained from the $\mathcal{C}^{**}-$ sets of each Pt-graph of fifteen neuropeptides Angiotensin-1, Beta-endorphin, Bombesin, Corticotropin-releasing factor, Dynorphin A, Endomorphin, Galanin, Neuropeptide Y, Neurotensin, Nociceptin, Oxytocin, Rimorphin (Dynorphin B), Somatostatin 28, Substance P, Vasoactive intestinal polypeptide involved in the brain function – learning and memory processes through graph theoretical modeling using the sequences of neuropeptides [10]. The neuropeptides are involved in a wide range of brain functions and linked to a number of diseases including Alzheimer's disease, epilepsy, depression, eating disorders, cancer, etc.

2. Basic Concepts

Definition 2.1: A graph $\mathcal{G}$ is a pair $\mathcal{G} = (\mathcal{V}, \mathcal{E})$ consists of a finite set $\mathcal{V}$ and a set $\mathcal{E}$ of 2-elements subset of V. The element of $\mathcal{V}$ are called vertices and elements of $\mathcal{E}$ are called edges. The set $\mathcal{V}$ is called the vertex set of $\mathcal{G}$ and $\mathcal{E}$, the edge set of $\mathcal{G}$. If $\{u, v\}$ is a member of $\mathcal{E}$, then we say u and v are adjacent and the corresponding edge is denoted/written as uv. Two edges are said to be adjacent if they have a common vertex. If the edge set is empty, then it is called a null/empty/void graph. A graph $\mathcal{G}$ with n vertices and m edges is called a (n, m) graph, where n is called the order of the graph and m is the size of the graph.

Definition 2.2: Centrality measures in Graphs [2] are the vertex representation which gives the relative importance within the graph. A centrality is a real-valued function f which assigns every vertex $v \in \mathcal{V}$ of a given graph $\mathcal{G}$ a value $f(v) \in \mathbb{R}$.

Definition 2.3: A Pt-graph is defined as a graph $\mathcal{G} = (\mathcal{V}, \mathcal{E})$ of a peptide/protein in which the vertex set, $\mathcal{V}$ is the collection of all different amino acids presented in the peptide/protein and weight of a vertex in $\mathcal{G}$ is the number of times it appears in the sequence of the peptide/protein. Two vertices are said to be adjacent in $\mathcal{G}$ if they are consecutive elements in the sequence and also have at least one common physico-chemical property.

Remark 2.4: Weight of a vertex implies the frequency of occurrence of a specific amino acid in a sequence. Obviously greater the weight of a vertex of a Pt-graph implies greater the characteristics of those particular amino acid can be attributed to the peptide/protein.

Remark 2.5: Centrality Measures of a Pt-graph help us to identify the quantity of related amino acids by direct or indirect with neighbour amino acids in the sequence of corresponding peptide/protein which shares at least one common physico-chemical property. The degree of a vertex of a Pt-graph gives the immediate importance of the vertex and the number of adjacent amino acids in the sequence which shares at least one common physico-chemical property. The closeness centrality of a Pt-graph gives the idea about the closeness of the relations of the amino acid to other amino acids within the peptide/protein. If a vertex in a Pt-graph is close to others then the vertex will be adjacent to them by peptide bond as well as their physico-chemical properties. The betweenness centrality of a vertex in a Pt-graph implies the number of shortest paths going through the vertex and the highest value gives the importance of the amino acid in the peptide/protein. Eigen vector centrality of a Pt-graph gives the direct as well as indirect importance of amino acids in a peptide/protein.

Remark 2.6: The connectedness of a Pt-graph shows the strength of the relation between amino acids within the peptide/protein by peptide bond as well as their physico-chemical properties. Obviously the strength of the relation between amino acids in a disconnected Pt-graph will be feeble and the number of connected components of the Pt-graph is inversely proportional to the strength of the relation between amino acids.

For all terminologies and notations not mentioned in this work, we follow [7] (related to graph theory) and [3], [5] (related to biology).

3. Neuropeptide $\mathcal{C}^{**}-$ graph of neuropeptides

Here we define and then analyse neuropeptide $\mathcal{C}^{**}-$ graph obtained from the $\mathcal{C}^{**}-$ sets of each Pt-graphs of fifteen neuropeptides involved in the brain function – learning and memory processes.

Definition 3.1: A $\mathcal{C}^{**}$- set of a Pt-graph of a peptide/protein is defined as a subset of the vertex set whose elements are the amino acids which recieve the highest centrality measures for each physico-chemical properties of amino acids.

Definition 3.2: Neuropeptide $\mathcal{C}^{**}-$ graph is a graph obtained from each Pt-graph of neuropeptides and their $\mathcal{C}^{**}-$ sets. It is defined as a graph $\mathcal{G}=(\mathcal{V},\mathcal{E})$ of neuropeptides in which the vertex set, $\mathcal{V}$ is the collection of neuropeptides. Two vertices $\mathcal{N}_1$ and $\mathcal{N}_2$ in Neuropeptide $\mathcal{C}^{**}-$ graph are said to be adjacent if the $\mathcal{C}^{**}-$ sets of Pt-graphs have at least one common amino acids.

Next we construct the neuropeptide $\mathcal{C}^{**}-$ graph from the Pt-graphs of fifteen neuropeptides. The vertex set will be the fifteen neuropeptides Angiotensin-1, Beta-endorphin, Bombesin, Corticotropin-releasing factor, Dynorphin A, Endomorphin, Galanin, Neuropeptide Y, Neurotensin, Nociceptin, Oxytocin, Rimorphin (Dynorphin B), Somatostatin 28, Substance P and Vasoactive intestinal polypeptide involved in the brain function – learning and memory processes. For, first we construct all the $\mathcal{C}^{**}-$ sets from the Pt-graphs. For galanin neuropeptide, G_5 (Hydrophoic and Non-polar), S_4 and N_3 (Hydrophilic and polar), L_4 (Aliphatic), Y_1 and W_1 (Aromatic), H_2, K_1 and R_1 (Positive), D_1 (Negative) are the amino acids which receive the highest centralities for each physico-chemical properties. Then we get the $\mathcal{C}^{**}-$set for the galanin as $\{G_5,S_4,N_3,L_4,Y_1,W_1,H_2,K_1,R_1,D_1\}$. Similarly we obtain all the $\mathcal{C}^{**}-$ sets for each neuropeptides as follows:

Angiotensin-1	-	$\{Y_1,D_1,R_1,H_2,F_1,V_1,I_1,L_1\}$
Beta-endorphin	-	$\{Y_2,T_3,K_5,G_3,S_2,L_2,F_2,E_2,Q_1,P_2,V_1\}$
Bombesin	-	$\{Q_2,G_2,L_2,N_1,W_1,V_1,E_1,R_1\}$
Corticotropin-releasing factor	-	$\{E_6,L_7,S_3,R_3,H_2,M_2\}$
DynorphinA	-	$\{G_2,F_1,P_1,D_1,N_1,L_2,R_3,K_2\}$
Endomorphin	-	$\{P_1,W_1\}$
Neuropeptide Y	-	$\{P_4,A_4,Y_5,K_1,D_3,M_1,R_4,H_1,L_2,I_2\}$
Neurotensin	-	$\{Y_2,L_2,E_1,N_1,I_1\}$
Nociceptin	-	$\{A_3,F_2,T_1,R_2,K_2,S_1,N_1,L_1\}$
Oxytocin	-	$\{C_2,Y_1,I_1,P_1,L_1\}$
Rimorphin	-	$\{F_2,L_1,R_2,V_2,T_1\}$
Somatostatin 28	-	$\{K_3,A_4,N_3,P_2,W_1,E_1\}$
Substance P	-	$\{P_2,L_1,R_1,K_1,Q_1,F_2\}$
Vasoactive intestinal polypeptide	-	$\{S_2,D_2,T_2,N_2,L_3,Y_2,K_3,F_1\}$

Here two vertices will be adjacent in the neuropeptide $\mathcal{C}^{**}$- graph if $\mathcal{C}^{**}$- sets of each Pt-graph have at least one common amino acid. When we consider the neuropeptides Galanin and Angiotensin-1, we have Aspartic Acid (D), Histidine (H), Leucine (L), Tyrosine (Y) and Arginine (R) are the common amino acids between them and therefore the neuropeptides will be adjacent in the Neuropeptide $\mathcal{C}^{**}$- graph as in figure 1. Since the $\mathcal{C}^{**}-$ sets of Angiotensin-1 and Somatostatin 28 have no common amino acids, they are non adjacent vertices in the Neuropeptide $\mathcal{C}^{**}-$ graph. Proceeding like this, we obtain all the adjacencies of the vertices of Neuropeptide $\mathcal{C}^{**}-$ graph as in Figure 1.

Further we analyse the Neuropeptide $\mathcal{C}^{**}-$ graph and we obtain the values of four centrality measures for each neuropeptides as in Table 1.

By analyzing the neuropeptide $\mathcal{C}^{**}-$ graph we get some simple observations among neuropeptides, amino acids and physico-chemical properties of amino acids.

Observation 3.1: The amino acid which receives the highest value of degree centrality and eigen vector centrality for the neuropeptides, Neuropeptide Y, Endomorphin and Substance P is Proline (P).

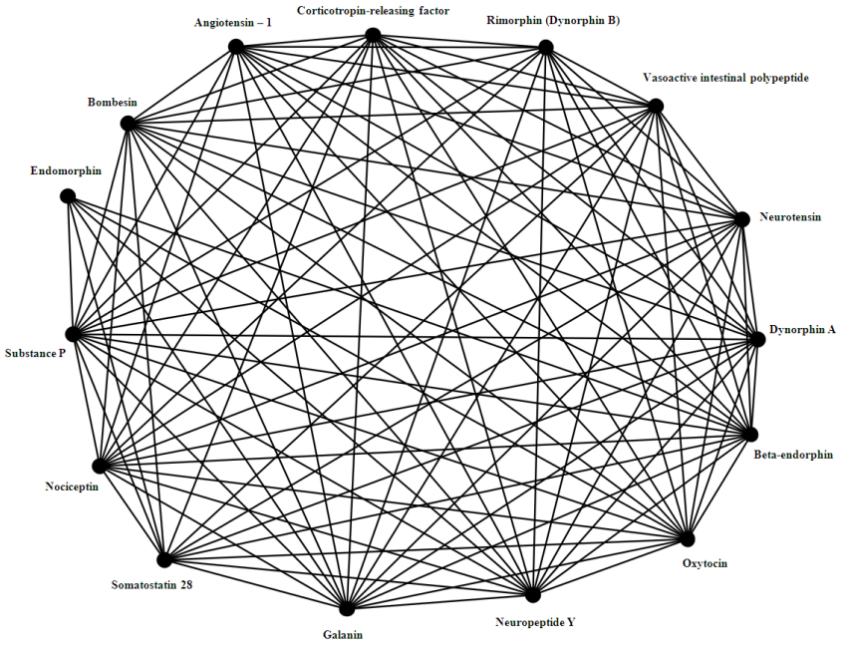

Figure 1. Neuropeptide C^{**}- graph of neuropeptides

Table 1. Centrality measures for each neuropeptides.

No.	Neuropeptides	Centrality Measures			
		Degree	Closeness	Betweenness	Eigenvector
1	Angiotensin-1	12	0.88	0.00	0.90
2	Beta-endorphin	14	1.00	1.58	1.00
3	Bombesin	13	0.93	0.18	0.97
4	Corticotropin-releasing factor	13	0.93	0.18	0.97
5	Dynorphin A	13	0.93	0.18	0.97
6	Endomorphin	6	0.64	0.00	0.45
7	Galanin	14	1.00	1.58	1.00
8	Neuropeptide Y	14	1.00	1.58	1.00
9	Neurotensin	13	0.93	0.18	0.97
10	Nociceptin	13	0.93	0.18	0.97
11	Oxytocin	14	1.00	1.58	1.00
12	Rimorphin	12	0.88	0.00	0.90
13	Somatostatin 28	12	0.88	1.00	0.87
14	Substance P	14	1.00	1.58	1.00
15	Vasoactive intestinal polypeptide	13	0.93	0.18	0.97

Observation 3.2: Tyrosine (Y) is the only common amino acid which receives the highest value of all centrality measures for the neuropeptides, Angiotensin-1 and Neurotensin.

Observation 3.3: Phenylalanine (F) is the only common amino acid which receives the highest value for all centrality measures for the neuropeptides, Dynorphin A and Rimorphin (Dynorphin B).

Observation 3.4: The hydrophobic and non-polar amino acids - Proline (P) and Tryptophan (W), Phenylalanine (F), Tyrosine (Y), Alanine (A), and the hydrophilic and polar amino acid - Cystein (C) are the most central amino acids among all the fifteen neuropeptides involved in the brain function – learning and memory processes.

Observation 3.5: The Pt-graphs of Beta-endorphin, Endomorphin, Galanin, Neuropeptide Y, Neurotensin, Nociceptin, Oxytocin, Somatostatin 28 and Vasoactive intestinal polypeptide are connected graphs and the Pt-

graphs of Angiotensin-1, Bombesin, Corticotropin-releasing factor, Dynorphin A, Rimorphin (Dynorphin B) and Substance P are disconnected graphs.

Observation 3.6: The common neuropeptides which receive the highest values of all centrality measures are Beta-endorphin, Galanin, Neuropeptide Y, Oxytocin and Substance P.

Observation 3.7: Beta-endorphin, Bombesin, Corticotropin-releasing factor, Dynorphin A, Galanin, Neuropeptide Y, Neurotensin, Nociceptin, Oxytocin, Substance P and Vasoactive intestinal polypeptide are the neuropeptides which receive the values above the average degree centrality.

Observation 3.8: The neuropeptide $\mathcal{C}^{**}-$ graph is a connceted graph. Hence every pairs of neuropeptides are inter related by atleast one amino acid which recieves atleast one highest centrality measure.

4. Conclusion

Here we analysed Neuropeptide $\mathcal{C}^{**}-$ graph obtained from $\mathcal{C}^{**}-$ set of each protein/peptide graphs of fifteen neuropeptides which are involved in the brain function – learning and memory processes. The highest centrality measures of the neuropeptides Beta-endorphin, Galanin, Neuropeptide Y, Oxytocin and Substance P reveal the critical vertices of the graph and they also give the prominent neuropeptides involved in learning and memory processes. They show their strength of the direct and indirect relations to other neuropeptides. The neuropeptide $\mathcal{C}^{**}-$ graph shows that all the neuropeptides are connected because every pairs of neuropeptides are inter related by atleast one amino acid which recieves atleast one highest centrality measure and it reveals strength of the relation between neuropeptides with in the brain function – learning and memory processes. The knowledge of key amino acids and neuropeptides is very much essential because the physico-chemical properties of proteins depend on the summation of the physico-chemical properties of the constituent ligands. This work may help in the study of the mechanisms involved in learning, memory processes and other brain functions and would aid in developing better solutions to treat diseases like Alzheimer's. Its application may also help in the study of the evolution of neuropeptides involved in learning and memory processes and other brain functions in different species of animals.

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