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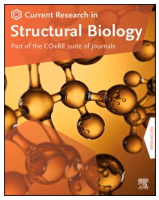

Research Article

GraSp-PSN: A web server for graph spectra based analysis of protein structure networks

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A R T I C L E I N F O

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A B S T R A C T

The function of a protein is most of the time achieved due to minute conformational changes in its structure due to ligand binding or environmental changes or other interactions. Hence the analysis of structure of proteins should go beyond the analysis of mere atom contacts and should include the emergent global structure as a whole. This can be achieved by graph spectra based analysis of protein structure networks. GraSp-PSN is a web server that can assist in (1) acquiring weighted protein structure network (PSN) and network parameters ranging from atomic level to global connectivity from the three dimensional coordinates of a protein, (2) generating scores for comparison of a pair of protein structures with detailed information of local to global connectivity, and (3) assigning perturbation scores to the residues and their interactions, that can prioritise them in terms of residue clusters. The methods implemented in the server are generic in nature and can be used for comparing networks in any discipline by uploading adjacency matrices in the server. The webserver can be accessed using the following link: https://pople.mbu.iisc.ac.in/.

1. Introduction

The three-dimensional structure of a protein is dictated by optimal non-covalent interactions between different amino acids in the chain. A Protein Structure Network (PSN) represents the structure of a protein at the backbone level by considering the c-alpha atoms or at the side chain level by considering the interactions of atoms in the side chains. To study gross characteristics such as domain identification and protein folding, backbone networks are handy. On the other hand, side chain networks are useful in tracking differences in interactions at local levels as well as their manifestation at the global level. Functional implications such as allosteric communication or the effect of ligand binding can be quantitatively inferred from the analysis of side chain networks. Protein structure networks are generally analysed by converting them into binary matrices, by selecting the interactions above a specified cut-off value to create the edges. However, incorporation of the variations in strength of interactions is essential to obtain realistic insights in a network analysis. In the last few years, we have developed graph spectral methods, which are known to capture maximal information with minimal loss, to investigate weighted networks (Gadiyaram et al., 2017). Further, we have demonstrated the utility of the methodology for protein structure comparison (Ghosh et al., 2017). Apart from standard parameters such as hubs, cliques, communities etc, the insight obtained by this approach is unique and has valuable information in terms of functions such as allostery (Gadiyaram et al., 2021). Recently, we have demonstrated the utility of the method in gaining insights to the structural variability in protein structures (Prabantu et al., 2022).

In this manuscript, we introduce GraSp-PSN, the first server to provide a means to construct, analyse and compare weighted protein structure networks of side chain interactions, using graph spectra-based methods. Currently, many protein structures are being solved by various experimental techniques (RCSB-PDB). Further, the capability of modelling protein structures has exponentially increased by the machine learning (ML) methods such as AlphaFold (Varadi et al., 2022) with newer versions. We expect that our program GraSp-PSN will become a valuable tool in comparing the structures at a high resolution, given that all atoms are taken into account in the evaluation in a rigorous manner. Also, our program has the potential application in integrated models using AI/ML approaches.

It is to be noted that the applicability of this program goes beyond

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protein structure networks, by accepting weighted adjacency matrices as inputs from any domain of biology or from any other discipline.

2. Materials and methods

2.1. Protein structure network (PSN)

Most of the common network parameters that are evaluated for side chain networks of protein structure are hubs, clusters, cliques, communities, clustering coefficient, centrality, and shortest paths. A detailed overview of analysis of various metrics from network methodology has been discussed in review articles (Bhattacharyya et al., 2015; Vishveshwara et al., 2009) and references therein; They are also available in Webservers like GraProStr (S. Vijayabaskar et al., 2011), Wordom (Seeber et al., 2011) and NAPS (Chakrabarty and Parekh, 2016). The weighted protein structure network is generated by transforming the uniquely folded geometry of the proteins at the side-chain level to a two-dimensional weighted matrix. The edge between two residues in a protein can be weighed in various ways, for example, interaction energy obtained by atomistic simulations, surface complementarity or knowledge-based potentials. In GraSp-PSN weighted PSNs are constructed based on interaction energy using geometric coordinates similar to the one suggested in, (Kannan and Vishveshwara, 1999) that is also the basis of edge strengths of several web servers (Graprostr, Wordom, NAPS). The edge weight is given by,

$$I_{ij} = n_{ij}/N_{ij}$$

Here n_{ij} is the number of atom contacts between residues i and j and N_{ij} is the maximum possible number of contacts between this pair of residues across a database of high-resolution protein structures. Weighted matrix representation captures the side-chain orientations with respect to each other. The normalization of the number of contacts with respect to the maximum possible contacts between two residues handles the huge variation in size and shape of the residues and weighs the interaction between them accordingly. The edge weights in this representation range between 0 and 1. A difference in edge weight between two residues can occur in the case of residues moving apart from each other either due to the difference in side chain orientation or due to a change of the secondary structural separation. While the differences at the backbone level are routinely detected by various programs, the global conformational changes due to differences at side chain level are difficult to capture. Indeed, the differences in the side chain interactions are involved in many biological functions such as allosteric communication due to ligand binding, transport of ions, molecules across membranes. By considering weighted side chain networks, perturbation induced conformational changes in the residues and their interactions can be studied more precisely from graph spectral methods. In addition, the deviations percolated to distal places in the protein structure can also be captured.

2.2. Graph spectral approach to PSN analysis

Graph spectral study involves the analysis of the eigen values and vectors of a given connectivity matrix. Historically it has been used in several disciplines, for instance to enumerate trees in electrical circuits (G Kirchhoff) or to find chemical isomers of a given formula (Graneau and Assis, 1994). Graph spectral applications to structural biology began in late 1990s on protein structure graphs with the amino acids in the polymer chain as nodes and their non-covalent interactions as edges. For example, the intrinsic dynamics of proteins (Bahar et al., 1997; Haliloglu et al., 1997) and characterization of their structural properties such as clusters, cluster centres, domains from backbone or side chain graphs (Vishveshwara et al., 2002) were extracted from the eigenvalues and vector components of connectivity matrices of non-covalent interaction. In the last two decades, a large number of studies has been done on PSN, characterising a number of metrics to address fundamental problems in biochemistry and structural biology. Currently data explosion has led to complex network studies with a phenomenal speed in several disciplines, including biological networks, such as those based on intra-protein interactions, protein-protein/drug interactions, disease related networks and so on. This has also stimulated the development of a number of mathematical and computational techniques. In this context, we have revisited the spectral properties of PSN in detail, in order to obtain more biological insights. Specifically, we have developed methods (Gadiyaram et al., 2017) to obtain and analyse the spectra of a) Weighted network; b) Network comparison and c) Perturbation analysis of Networks (Gadiyaram et al., 2019) which are described below.

2.3. Network comparison

The topological connections in networks are generally inferred through a number of measures. Specific metrics are evaluated depending on the real problem addressed. For instance, communication paths are calculated in transport systems or to investigate allosteric communication in protein structures, while hubs, cliques, communities are evaluated to identify rigid or flexible regions. However, a rigorous and analytical method of identifying node clustering is unique to graph spectral methods. Node clustering refers to grouping of nodes such that nodes in each group are related more among themselves compared with nodes in other groups. The clustering of nodes can be obtained from graph spectral decomposition of networks which involves obtaining eigenvalues and eigenvectors of adjacency or Laplacian matrix of the network (Sistla et al., 2005). Nodes of the same cluster have closer numerical values in the Fiedler vector (eigenvector corresponding to the second smallest eigenvalue) components. Therefore, sorted Fiedler vector components are used to obtain node clustering in the network. In many instances, functions of networks are due to specific patterns in node clustering or changes in those patterns. For example, the backbone topology and the residue-residue interactions differ only slightly between the active and inactive states of transmembrane regions of GPCR structures. However, the node clustering difference in the structures correlates with their functions (Gadiyaram et al., 2021). Further, network comparison becomes more formal by comparing the differences at the eigenvector level. Detailed methodology of network comparison (Gadiyaram et al., 2017) and an overview (Gadiyaram et al., 2019) are provided elsewhere. A brief description of network comparison scheme and its utility in evaluating the influence of perturbation is provided in the next two sections.

2.3.1. Network similarity score (NSS)

Recent developments in protein structure analysis involve comparison of weighted protein structure networks and capturing changes in residue clustering using graph spectral methods. Network similarity scoring scheme (NSS) is based on the spectra of normalized Laplacian matrices, which normalises the entire network with respect to the degree and volume of the nodes and therefore makes the comparison effortless across different networks (even for weighted networks). The scheme can not only compare networks which are very much similar to each other but can also serve as a clustering technique to group them in a large pool of networks. This technique has been introduced to validate and study protein structures (Ghosh et al., 2017). The sensitivity of NSS allows an in-depth analysis of small structural changes occurring at various levels of protein structure organisation. It considers both local and global changes of a chosen protein with respect to a reference protein. The global changes are efficiently captured by comparing node clusters, a technique which is unique to graph spectra-based schemes like NSS and is elusive to standard structure validation techniques.

NSS comprises of three components which capture differences at various levels - (1) Correspondence Score (CRS) capturing global level changes, (2) Eigenvalue Weighted Cosine Score (EWCS), quantifies the differences in local node clustering, (3) Edge Difference Score (EDS),

quantifies edge weight differences between the networks. An explanation of the formulae and their significance are detailed in (Gadiyaram et al., 2017). However, a brief explanation of the mathematical formulation of the components of NSS between two networks, say A and B is given below.

Let A and B be the adjacency matrices of network A and network B of size n (number of nodes is n), let M be the difference of the two adjacency matrices A and B, and $||M||_F$ be the Frobenius Norm of the difference matrix M, then Edge Difference Score (EDS) is given by

$$EDS = \frac{\|M\|_F}{\sqrt{(\sum edge\ weight_A \times \sum edge\ weight_B)}} \quad (1)$$

The eigenvectors of the normalized Laplacian matrices of networks A and B are aligned by considering the maximum of cosine values between all eigenvectors of A and all eigenvectors of B. The cosine between the vectors is given by

$$cosine\ (\theta_{ij}) = \frac{\left(Evec_i^A . Evec_j^B\right)}{\left\|Evec_i^A\right\|\left\|Evec_j^B\right\|}\ i,j\ \epsilon\ N, 1 \le i,j \le n \quad (2)$$

The difference at local clustering level (with in node groups) is calculated by EWCS, which is the weighted sum of deviations of cosine values from 1 (which is optimal in the case of perfect match of the vectors), the weights considered by dominance of the associated eigenvalues.

$$EWCS = \frac{\sum \left(1 - cosine(\theta_{ij})\right)^2 |1 - Eval_A||1 - Eval_B|}{\sum |1 - Eval_A||1 - Eval_B|} \quad (3)$$

Where $EVec_i^A$ is the ith eigenvector of network A and $EVec_j^B$ is the ith eigenvector of network B, which is aligned with $EVec_i^A$. $Eval_i^A$ and $Eval_i^B$ are the eigenvalues of $EVec_i^A$ and $EVec_i^B$.

The global difference which is the change in the node clusters is captured by the shift in the alignment of the eigenvectors. This is captured by CRS, which is Spearman's correlation between the indices of aligned eigenvectors.

$$CRS = 1 - \frac{6\sum (Index\ Evec_A - Index\ Evec_B)^2}{n(n^2 - 1)} \quad (4)$$

Where, n is the size of these networks and $IndexEvec_A$ and $IndexEvec_B$ are the indices of n pairs of aligned eigenvectors of networks A and B with maximum cosine values.

The final form of NSS is as shown below (Gadiyaram et al., 2017):

$$NSS = \sqrt{EDS^2 + EWCS^2 + (1 - CRS)^2} \quad (5)$$

It should be noted that lower NSS reflects higher similarity between two networks. NSS between two networks (specifically protein structure networks) can be calculated using GraSp-PSN, details of which are discussed in Section 3.

2.3.2. Network perturbation score

The product of all the interactions between the components of a network leads to complex behaviour of the network. Identifying crucial components that are responsible for maintaining the integrity of networks is essential, to understand the emergent properties of networks or to control them. This is achieved by systematically perturbing (eliminating) nodes/edges and comparing the perturbed network with the original network. Recently developed method ranks the participation of nodes and edges in a network using perturbation analysis and identifies crucial players contributing to the integrity of the network (details provided in (Gadiyaram et al., 2019). Unlike earlier methods that evaluate perturbation in a network based on the variation in centralities or paths, this method uses the graph spectral based Network Similarity Score (NSS, Section 2.3.1) to quantify the change occurred in a network due to perturbation in it. Perturbation scores can be calculated at node level (Node perturbation score, NPS) or at edge level (Edge perturbation score, EPS).

To calculate node perturbation scores for nodes in a network A of size n, each node (i) in A is perturbed and the resultant network (A_i) is compared with the original network (A) using NSS, resulting $NSS_{(i)}$. Perturbation of a node is done by deleting, all edges connected to that node. Hence, the node still remains in the network as an isolated node. We will still be comparing a network of size n with another network of size n. Normalization of the resultant NSS values of all nodes between 0 and 100 results in node perturbation scores.

Node perturbation score (NPS) for a node i is calculated as (Gadiyaram et al., 2019):

$$NPS_{(i)} = \frac{NSS_{(i)} - NSS_{min}}{NSS_{max} - NSS_{min}} \quad (6)$$

where NSS_{min} and NSS_{max} denote the minimum and maximum of $NSS_{(i)}$ of all nodes (1 to n) in the network. Edge perturbation scores of edges in a network are obtained in a similar way by deleting each edge (e) in the network, obtaining $NSS_{(e)}$. Edge perturbation score (EPS) for a given edge e is given by:

$$EPS_{(e)} = \frac{NSS_{(e)} - NSS_{min}}{NSS_{max} - NSS_{min}} \quad (7)$$

where NSS_{min} and NSS_{max} denote the minimum and maximum NSS values respectively considering all edges in the network. The nodes or edges with higher perturbation scores (approaching 100) are the ones whose perturbation will cause more change in the network and hence are crucial. NPS and EPS of nodes and edges in a network (or protein structure network) can be calculated using GraSp-PSN. Details regarding the input and results are discussed in Section 3.

3. Outline of the server

The webserver GraSp-PSN can be accessed using the following link: https://pople.mbu.iisc.ac.in/. GraSp-PSN accepts protein structure in RCSB PDB format as input and provides backbone network and weighted side chain network, corresponding edgelists, node - residue mapping file, Fiedler vector and Pymol session files containing residue clustering using Fiedler vector. The layout of the server is depicted in Fig. 1 and the usage of the server is explained in detail in the tutorial file available on the website. Apart from PDB format files, GraSp-PSN also accepts adjacency matrices as input. This enables users to input protein structure networks obtained from various other definitions or networks from any discipline and perform graph spectra-based analysis.

Fig. 2 shows the usage of the network analysis tool. Users can download the networks and also visualise the graphs using the cytoscape plugin. Parameters such as hubs, cliques and clusters can also be selected and their neighbourhood can be analysed. NSS between a pair of structures with a detailed list of NSS components (Fig. 3) and perturbation scores of a structure with respect to nodes (NPS) and edges (EPS) can also be obtained (Fig. 4). The user interface was developed in PHP and CSS and the backend implemented using perl, cgi and shell scripts. Scripts for NSS and NPS run using the open source mathematical package 'Octave'.

4. Applications

Accurate structure validation of proteins is of extreme importance in studies like structure prediction and analysis of molecular dynamic simulation trajectories. NSS has been demonstrated to better quantify differences in connectivity between residues in models compared to that of reference structure. One such example from CASP submitted models to target TR821 is shown in Fig. 5. In model TS216_1, the two domains of the protein come closer and atom contacts are formed between

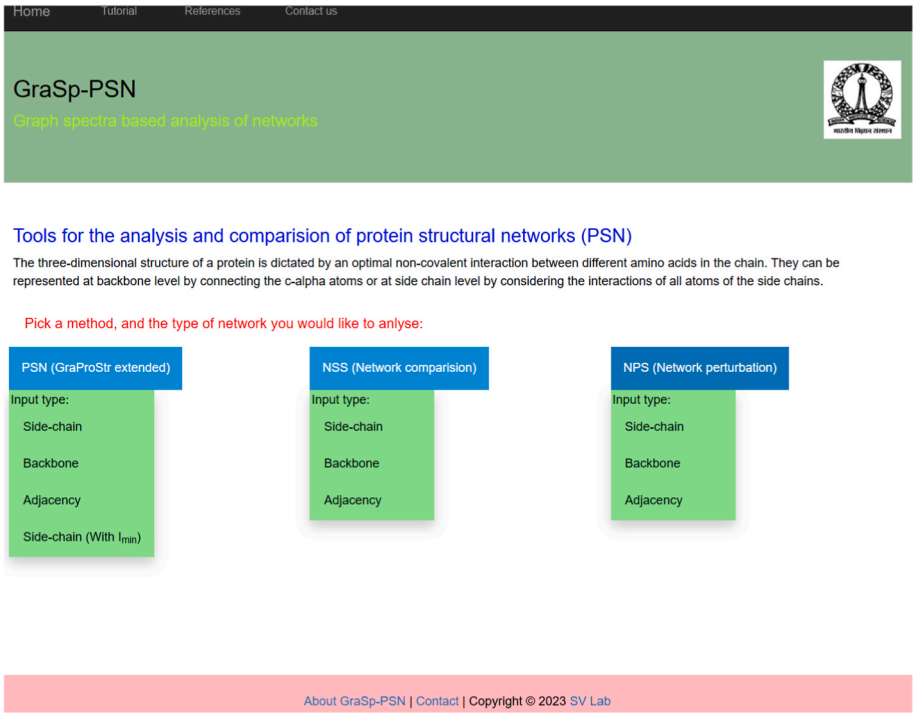

Fig. 1. Layout of the server. There are three modules in this server, namely, Protein structure network analysis (PSN), Network similarity score (NSS) and Network perturbation score (NPS). All the modules can use a sidechain-based network, backbone structure network or an adjacency matrix of the graph as input. An interaction cut-off can also be used in the PSN module.

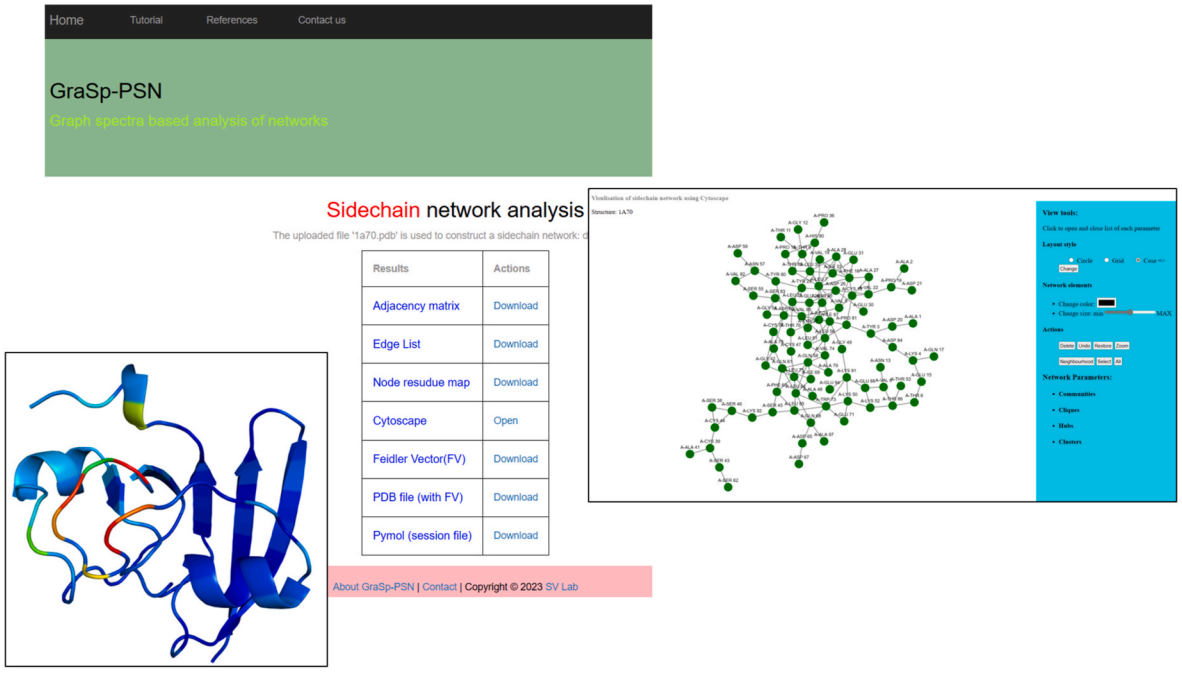

Fig. 2. The protein structure network analysis (PSN) module is for the network analysis of protein structures that is submitted as input. One can generate the constructed adjacency matrix, edge list between nodes of protein structure and even fielder vectors. The network can also be visualised using the built-in cystoscope plugin using customisable features.

sidechains from the two domains, leading to green-yellow cluster and a highly connected orange cluster, which are not present in the native. Fiedler vector components sorted according to native values shows more deviations for this model (TS216_1). The table at the bottom of the figure shows that NSS, with its higher score for this model is able to capture this deviation, while RMSD is unable to distinguish them.

NPS and EPS have been evaluated on protein structures of muscarinic acetylcholine receptors (a member of G-Protein Coupled Receptors), bringing out several aspects of perturbation effect, which has been elusive from conventional methods of analysis. Fig. 6 shows an agonist bound receptor (PDB ID: 4MQS) with residues showing top NPS values (left) and interactions between residues showing top EPS values (right).

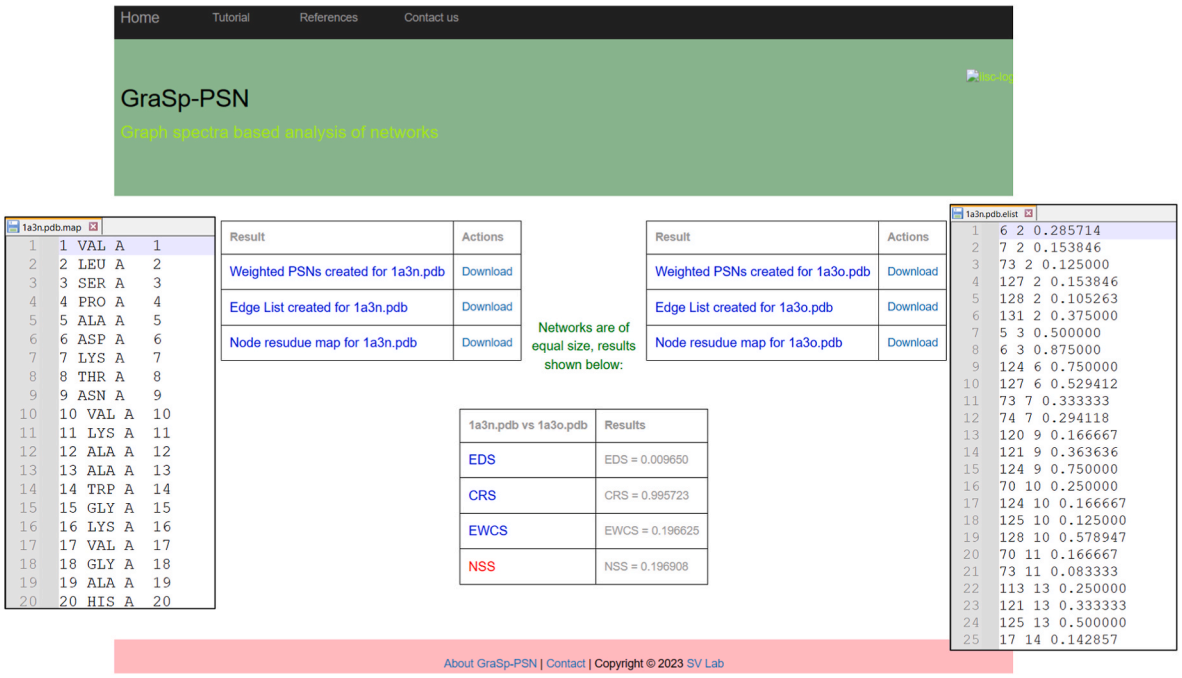

Fig. 3. The Network similarity score (NSS) module compares any pair of protein structures and computes the network similarity score and its components. The weighted PSNs that are constructed for the comparison of proteins of equivalent length are downloadable from here.

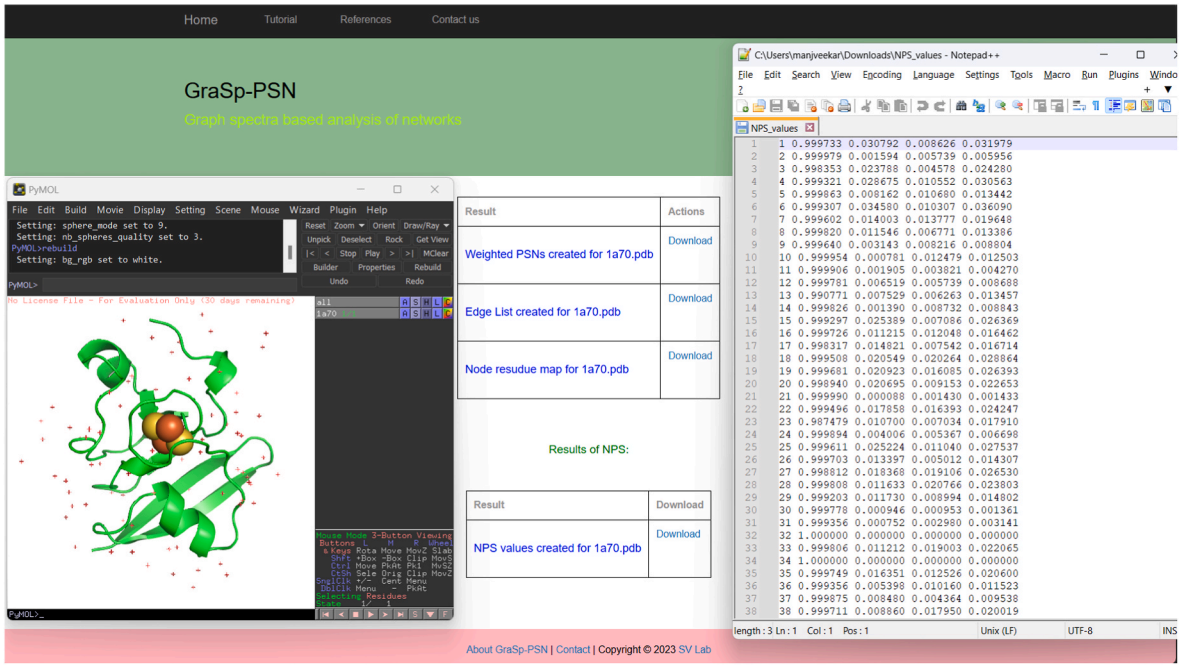

Fig. 4. The Network perturbation score (NPS) module computes the node perturbation score and edge perturbation scores for all nodes and edges. The final output table can be downloaded to analyse the importance of each node or edge in the network.

The functional importance of these residues and interactions has been correlated with experimental data, giving an indication of the potential of perturbation scores as a predictive tool to identify players that are responsible for an action in a global context.

5. Conclusion

GraSp-PSN facilitates unique graph spectra-based analysis and comparison of protein structures. These methods have wide range applications in protein model validation, studies of long-range communications in allostery, functional analysis of proteins etc. Apart from protein structure analysis, its utility is under progress in analysing protein-protein interactions and homologous families. Networks from other disciplines can also be analysed using the server by uploading adjacency matrices in the server. In view of the scenario where a huge number of structures are generated using AI/ML methods and integrative modelling, GraSp-PSN plays an important role in the coming days for analysis, validation and selection of protein structure models.

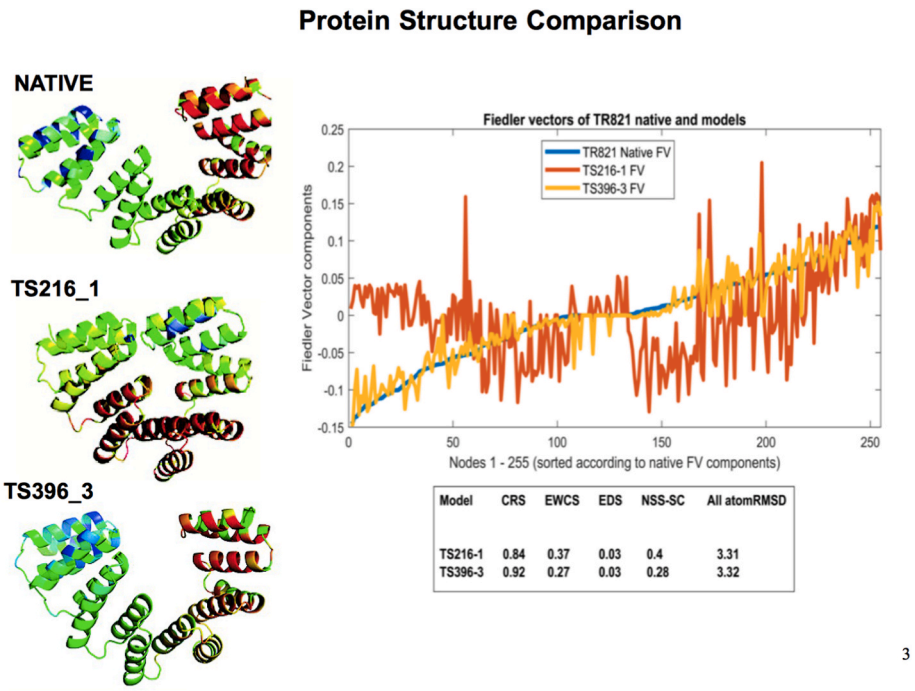

Fig. 5. On the left panel, side chain clustering of CASP11 Target TR821 native (top), TS216_1 (middle) and TS396_3 (bottom). On the right panel, (top) sorted Fiedler vectors of the native and the two models plotted (Bottom) RMSD and NSS scores of the models, compared with the native.
Gadiyaram et al. (2019).

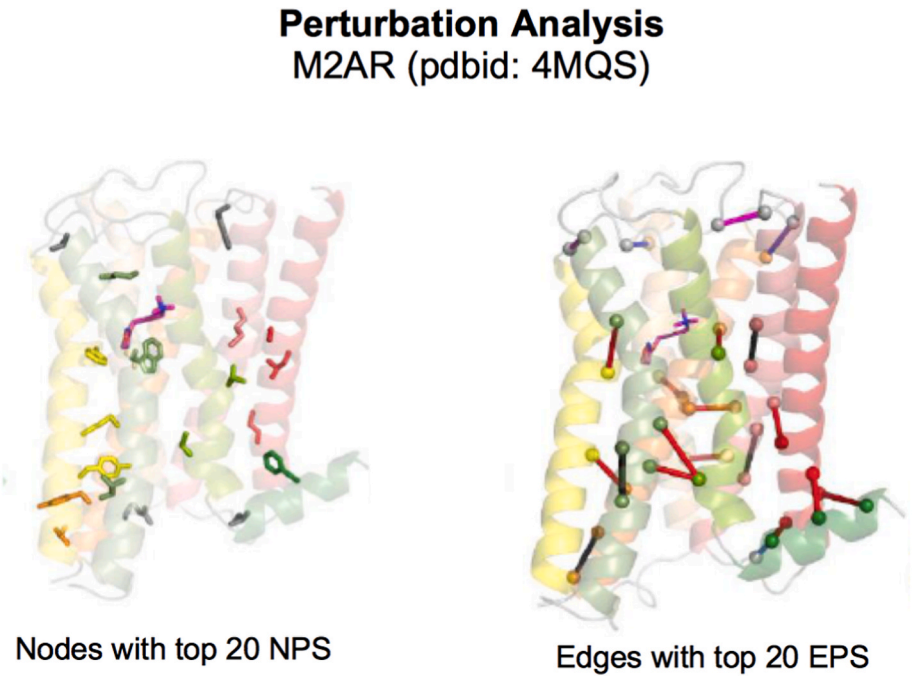

Fig. 6. An agonist bound muscarinic acetylcholine receptors (a member of G-Protein Coupled Receptors) (PDB ID 4MQS) with residues showing top NPS values (left) and interactions between residues showing top EPS values (right).
Ghosh et al. (2017).

CRediT authorship contribution statement

Vasundhara Gadiyaram: Conceptualization, algorithm development, and integration of modules in webserver. **Vasam Manjveekar Prabantu:** Web-development, integration of the separate modules, and user interface. **Arinnia Anto Manjaly:** User interface and server acess. **Ananth Muthiah:** Server Access and network troubleshooting. **Saraswathi Vishveshwara:** Concept and algorithm development.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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