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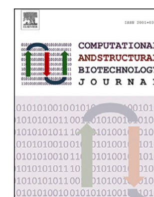

Software/Web server Article

AlloViz: A tool for the calculation and visualisation of protein allosteric communication networks

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A B S T R A C T

Allostery, the presence of functional interactions between distant parts of proteins, is a critical concept in the field of biochemistry and molecular biology, particularly in the context of protein function and regulation. Understanding the principles of allosteric regulation is essential for advancing our knowledge of biology and developing new therapeutic strategies. This paper presents AlloViz, an open-source Python package designed to quantitatively determine, analyse, and visually represent allosteric communication networks on the basis of molecular dynamics (MD) simulation data. The software integrates well-known techniques for understanding allosteric properties simplifying the process of accessing, rationalising, and representing protein allostery and communication routes. It overcomes the inefficiency of having multiple methods with heterogeneous implementations and showcases the advantages of using MD simulations and multiple replicas to obtain statistically sound information on protein dynamics; it also enables the calculation of “consensus-like” scores aggregating methods that consider multiple structural aspects of allosteric networks. We demonstrate the features of AlloViz on two proteins: β-arrestin 1, a key player for regulating G protein-coupled receptor (GPCR) signalling, and the protein tyrosine phosphatase 1B, an important pharmaceutical target for allosteric inhibitors. The software includes comprehensive documentation and examples, tutorials, and a user-friendly graphical interface.

1. Introduction

Proteins are highly dynamic macromolecules that carry out essential functions in organisms. They exist in an equilibrium of conformations that can shift due to mutations, post-translational modifications, media alterations or the interaction with other proteins or small molecules, such as drugs [1]. Conformational changes require a coordinated rearrangement of the polypeptide backbone and residue side-chains, creating communication networks along which the movement is transmitted throughout the structure. These networks are at the base of allostery, which is the intrinsic property of proteins that enables the transmission of signals across spatially distant parts of their structure [2]. These phenomena can be probed with *in vitro* techniques such as Nuclear Magnetic Resonance (NMR), mutational scanning or crystallography, which can reveal structural allosteric hotspots or describe potential allosteric communication pathways of residues. However, the highly dynamic nature of allostery, the short-lived allosterically relevant conformational states, and the limited resolution of the methods pose a challenge for their characterization at the amino acid and atomic resolution [3].

Numerous computational resources and tools have been devised to aid in the investigation of allosteric mechanisms and the development of allosteric drugs, such as computational methods to model proteins as interaction networks [4,5]. In protein interaction networks, residues are linked by edges that quantify inter-residue properties, providing a suitable graph representation to model the complex connectivity within the protein. Moreover, the integration of the extensive field of network theory allows for the quantitative analysis of the communication and long-range phenomena that are associated with allostery [6,7]. The protein networks are built with edge values that quantify inter-residue properties measured on the sequence (e.g., residue pair coevolution), the structure (e.g., contacts or distances), or the dynamics of the protein (e.g., atom motion cross-correlation) [8].

For instance, residues involved in allosteric regulation display a degree of sequence coevolution that maintains their functional coupling [9]. This has motivated the building of interaction networks using coevolution metrics as edge values, [10,11] such as the case of Statistical Coupling Analysis (SCA) built on the basis of multiple sequence alignments [12]. However, it has been observed that coevolution is biased

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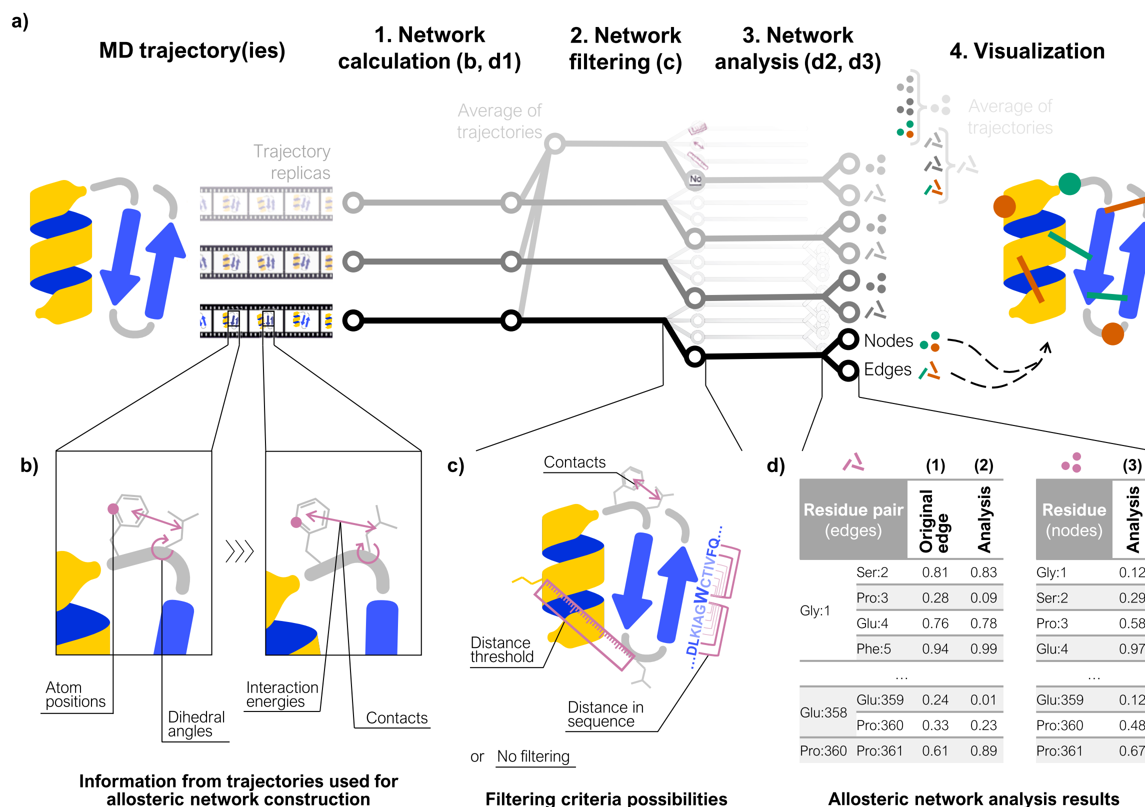

Fig. 1. Diagram of the allosteric network construction and analysis process followed by AlloViz. (a, b) Molecular Dynamics (MD) trajectories track atom positions throughout the simulation time; time series of dihedral angles, residue contacts and interaction energies can then be computed and used as raw data to calculate allosteric networks. (c) Networks can be filtered using different criteria and (d) analysed focusing on edges (1 and 2) or nodes (3). Results can be handled as tables or visualised on the protein structure.

by residues that are physically close and therefore undergo evolutionary selection [13]. Moreover, in contrast to the stronger preservation required for structural stability, allosteric networks of residues can exhibit considerable plasticity and robustness to mutations, as long as the allosteric information flow is maintained [14].

Protein networks based on *static* structures have been developed to use inter-residue distances, contacts or interaction energies as edge values [7]. However, allosteric changes are directly transmitted by global and local protein *dynamics*, and thus atomic-scale information is needed to model networks that capture a wider range of allosteric effects [15].

MD simulations allow us to model the motions and interactions of the residues in a quasi-physiological environment at the atomic resolution. Simulation trajectories provide vast amounts of data about their dynamics that are used to build protein interaction networks [16]. This popular method is successful in the identification of key network elements for allostery in different systems, which ultimately translate into a structural explanation for their importance [13,17–20]

Here we present AlloViz, an open-source Python package to compute, analyse and interactively visualise protein allosteric communication networks built using MD data. Our tool unifies several network construction methods proposed by earlier works (Table 1), in addition to a new network construction method we implemented. AlloViz facilitates the analysis of the resulting network(s) with common graph theory protocols as well as their visualisation on the protein structure (Fig. 1), through the use of both Python programming or a Graphical User Interface (GUI). Moreover, it eases the calculation and visualisation of delta-networks, which are obtained by subtracting the edge weights of the networks of any two comparable structures to facilitate their comparison. We showcase the package by describing the investigation of the allosteric communication in β-arrestin 1 (Section 3.2) and binding sites of protein tyrosine phosphatase 1B (Section 3.3). Code to reproduce

Table 1
Allosteric network construction options available in AlloViz. Bold text marks combinations first introduced in this package. MI with LNC: mutual information with local non-uniformity correction.

Structural data		Metric
Position of...	α carbons β carbons whole residues	Pearson correlation Mutual information Linear mutual inf.
Dihedral angle...	$\phi, \psi, \chi_1 \cdots \chi_4$ all backbone dih. all sidechain dih. all dihedrals	Pearson correlation Mutual information **MI with LNC**
Contacts		Frequency Strength
Interaction energy		

both case studies, as well as use cases notebook tutorials and extensive documentation are distributed with the software.

2. Materials and methods

The gist of computing an allosteric network from an MD trajectory is to condense the data into a single inter-residue value for each residue pair in the protein, representing their relationship, to generate a network. AlloViz provides a single point of entry for many allosteric network construction methods proposed by earlier works as well as our own (Table 1), and it also facilitates the filtering, analysis and visualisation of the networks, and the calculation of delta-networks of comparable structures.

Allosteric networks from MD trajectories can be constructed by measuring the correlation between the motion of atoms or between the dihedral angles of pairs of residues, as well as by quantifying the contacts or the interaction energies between them (Table 1). Besides implementing network construction methods from earlier works, we propose an additional novel method that measures the mutual information (MI) generalized correlation of individual dihedral angles or their combinations. This network construction method was not available previously in Python open software [17,20], and the MI coefficient is calculated with the application of the local non-uniformity correction (LNC) [21] to reduce its calculation inaccuracies (Supplementary Material S1.3). The main features of AlloViz are listed briefly below, and discussed in detail in Supplementary Section S1. The full list of methods currently provided is found in Table S1.

2.1. Network filtering

Filtering is useful to focus on specific interactions of interest and to reduce noise introduced by thermal motion. AlloViz provides the option to analyse the entire network as it is (using the `All` filter), or to apply specific filters beforehand, such as: (i) including only contact pairs identified by *GetContacts* (using the `GetContacts_edges` filter); (ii) excluding residue pairs that fall below a specified geometric distance threshold (using the `Spatially_distant` filter); and/or (iii) excluding residue pairs that fall below a certain sequence distance threshold (with the `No_Sequence_Neighbors` filter). Furthermore, if the protein in question is a GPCR and its residue generic numbering is available from the GPCRdb [22], one can apply the `GPCR_Interhelix` filter to only retain pairs of residues from different conserved GPCR structural elements.

2.2. Network analysis

Centrality plays a pivotal role in network analysis [23]. The classical *betweenness* centrality metric, for example, measures the number of shortest paths that cross a given node or utilise a given edge in the studied network, which accounts for the importance of edges or nodes for information propagation across the network. However, a limitation of betweenness centrality is its exclusive focus on the shortest paths, neglecting nodes and edges that are nearly but not directly on these paths, despite their potential relevance in information transmission. Botello-Smith and Luo discuss the shortcomings of the metric for the analysis of allosteric communication networks from MD simulations, and propose the current-flow betweenness centrality as a robust alternative [24]. Current-flow betweenness centrality, also known as random-walk betweenness centrality, uses an electrical current model for information spreading in contrast to betweenness centrality which uses shortest paths. The latter metric, drawing parallels with the information centrality metric used in analyzing information propagation networks, offers a more comprehensive view by considering a broader array of pathways for communication. Both betweenness and current-flow betweenness-based analysis are available in AlloViz (Section S1.4).

2.3. Delta networks

Delta-networks, calculated from the difference of two allosteric networks, allow the comparison of differences in information flow between structures, such as different activation states of a receptor, or a protein bound to two ligands with differing signalling profiles. They are obtained by subtracting the edge weights of two networks that have “comparable” nodes (e.g., two networks of simulations of the same protein in different activation states). The global structure and communication of the two systems compared are expected to be alike (except for just a few changes due to the perturbation), and thus most residue pair interactions will have similar weights. Differential analysis, i.e. the calculation of a delta-network, reduces this noise, potentially exposing more subtle differences between the two networks [25].

3. Results

3.1. Software

AlloViz is a Python 3 package and it can be installed from the source code available in GitHub using the instructions therein. It is designed to be used either as a library, interactively e.g. through Python notebooks such as *Jupyter* [26], or with a graphical user interface (GUI) (Fig. 2) which extends Visual Molecular Dynamics (VMD) [27]. Specifics about the software implementation are reported in the Supplementary Material (Section S2). Detailed installation instructions, full documentation, and notebooks with use cases tutorials (which can also be run online with MyBinder [28]) and to reproduce the case studies in this work are provided in the code repository and online (https://alloviz.readthedocs.io/) and described in Section S2.2.

The GUI (Fig. 2, left-hand window) displays an interface for allosteric calculations that integrates with VMD to display protein structures and trajectories along with the computed allosteric networks. The window contains all the options available for the calculation and analysis of a network, namely the atom selection to be taken into account (for example, only the protein atoms if a whole trajectory in solvent has been loaded), the network to compute, filters to apply and the network analysis to perform. Selecting *Compute and Visualise* runs the calculations in the background, after which the result is shown in the structure visualisation window. All the calculations performed are logged in the right-hand panel of the AlloViz GUI window, from where they can be recalled for visualisation and comparison, or saved as text-based tables for further use.

3.2. Application to β-arrestin 1

G protein-coupled receptors (GPCRs) and their intracellular coupling partners are excellent examples of proteins for which allostery is fundamental [29]. For instance, β-arrestins are a protein family that couple to activated and phosphorylated GPCRs. For their own activation, they undergo an important conformational change that involves a rotation of their C-domain respective to their N-domain [30]. What’s more, β-arrestin 1 has been found to reach different levels of activation depending on the phosphorylation pattern of the activation partner [31], demonstrating the crucial and precise operation of allostery.

To illustrate the robust allosteric network construction methods of AlloViz, we carried out a systematic analysis incorporating all potential combinations of network construction methods, network filters, including `All`, `Spatially_distant`, `GetContacts_edges`, and a combination of `GetContacts_edges` with `No_Sequence_Neighbors`, along with node analysis methods such as betweenness centrality and current-flow betweenness centrality. These computations were applied to β-arrestin 1, exploring both its inactive (apo) and active (V2RppWT-bound) conformations, as well as the resulting delta-network. MD simulations used here were reported in a previous study [31], and have been taken from the corresponding deposited entries of the GPCRmd database [32]. Simulations of β-arrestin 1 in the inactive conformation (PDB code: 1G4M) (3×500 ns) and the active conformation bound to the wild-type phosphopeptide of the Vasopressin receptor subtype 2 receptor (V2RppWT, PDB code: 4JQI) (5×2 μs) were used.

We sought to analyse how all the networks computed using AlloViz as a homogenising interface pinpoint the residues vital for system function. We compiled a list of residues which have proven to be critical for β-arrestin 1 function *in vitro*, including those responsible for the crucial inter-domain allostery in arrestin (i.e., polar core) or phosphorylation sites (Supplementary Table S2). We also include an additional analysis of the combinations of network construction methods, filters and centrality analyses that could most effectively pinpoint these residues vital for system function in Supplementary Material S3.3. An interactive application to explore the complete results of both analyses is available online at gandalf.upf.edu/shiny/ArrestinExperimental.

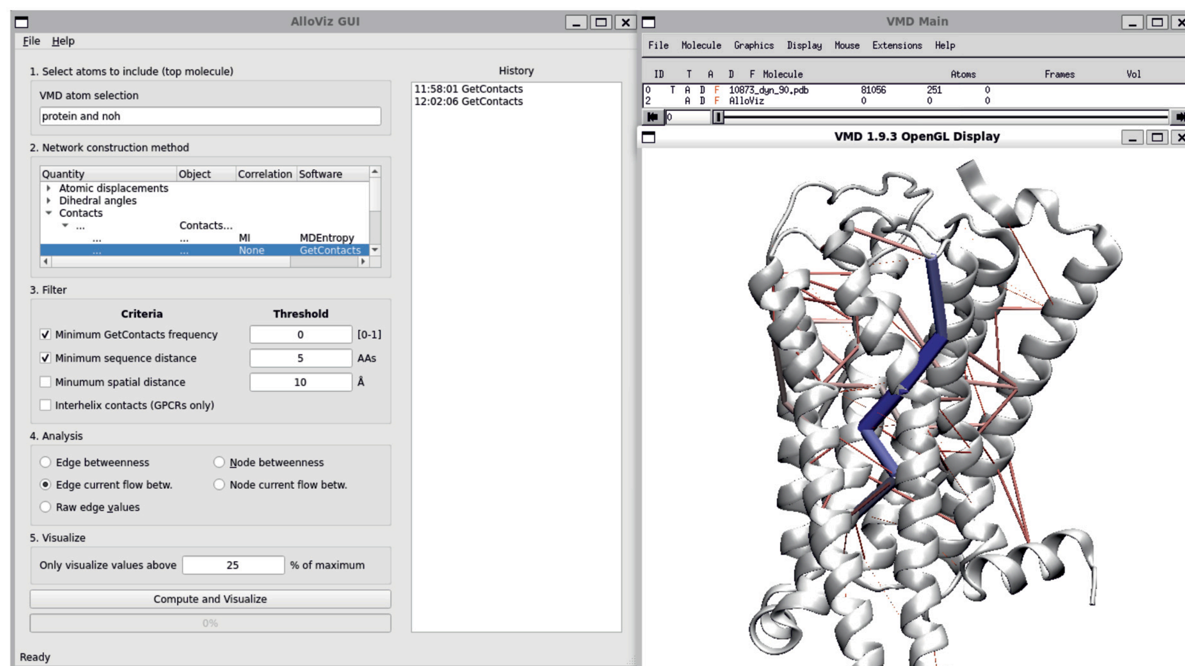

Fig. 2. The AlloViz GUI enables interactive analysis and visualisation. Here, it is shown the GPCR 5-hydroxytryptamine receptor 1B in complex with agonist ergotamine (GPCRmd ID 90) together with a network measuring physico-chemical contacts, filtered to retain only residue pairs that are at least 5 residues apart in the sequence. The current-flow betweenness of the network edges is computed, and edges whose betweenness value is greater than 25% of the maximum will be superimposed to the 3D structure.

Taking a look at the consensus of the results obtained with all the different analysis methods, it emerges how the delta-networks between the inactive and active β-arrestin 1 capture the functionally important residues of the protein, together with others in their close vicinity. Fig. 3 shows the average of all the network combinations together with the results of a Statistical Coupling Analysis (SCA) that measures coevolution between residue pairs, a sequence-based approach to model allosteric networks (Section S3.1). The highly modulated residues qualitatively form clusters, likely allosteric hubs, of residues with high centrality in the respective allosteric networks of the active or inactive structures.

For example, one of the clusters includes residues Gly211 and Pro213, which undergo significant changes with respect to the wild-type in the phosphorylation site mutant T275D (Supplementary Table S2). This allosteric hub is picked up by the delta-networks computed with AlloViz even when the mutant is not part of the systems used for the delta-network calculation, and the area is spatially distant to the phosphopeptide binding site of the active structure and it does not show any major rearrangement in the initial static structures (Fig. 3, structural inset (3)). This finding highlights the ability of *in silico* allosteric networks to identify functional hubs on proteins, as confirmed by experimental data.

In addition, residues Arg62 and Arg76 are not discussed in literature for their functional implication, to our knowledge, but nonetheless exhibit a high positive value in the average of the delta-networks (Fig. 3, “Networks average” annotation on top of the central heatmap). Such positive value indicates that they have a high “consensus” centrality in multiple allosteric networks of the apo structure, and that the consensus centrality in the V2Rpp-bound structure networks is not as significant. Indeed, these two residues interact directly with the phosphopeptide in the active structure, interrupting the allosteric information flow with respect to the apo. This result further points to the usefulness of allosteric networks analysed with centrality metrics to capture the acute change in the allosteric communication within proteins due to perturbations. Consensus scoring improves the confidence in constructing a global view of allostery that considers several structural and statistical descriptors.

3.3. Application to protein tyrosine phosphatase 1B

We further tested AlloViz on the human tyrosine-protein phosphatase non-receptor type 1 (PTP1B), an intracellular tyrosine phosphatase, for which the discovery of allosteric binding sites is an important pharmacological goal. Protein tyrosine phosphatases (PTPs), together with protein tyrosine kinases (PTKs), are responsible for the reversible phosphorylation of tyrosine residues in proteins, being thus key regulators of signalling pathways; unsurprisingly, aberrations in their function or regulation may lead to diverse human diseases. PTP1B specifically is a negative regulator of the insulin and leptin pathways, being thus involved in the development of type 2 diabetes and obesity, and it has also proven to have a role in cancer, either as tumour suppressor or promoter, depending on the cellular context [33]. PTP1B inhibitors are highly sought-after for the treatment of diabetes, but finding pharmaceutically viable candidates has proven challenging due to the conservation of its orthosteric active site [34]. The identification of allosteric inhibitors and pockets is therefore of high interest to reach the desired specificity and avoiding off-target effects. In 2004, allosteric inhibition was shown by Wiesman et al. for a set of lead compounds in development at Sunesis [35]. More recently, Greisman et al. identified two fragments, DES-4799 and DES-4884, able to allosterically bind PTP1B by performing very long-timescale MD simulations and later validating the results using X-ray crystallography. They eventually were able to identify a new allosteric pocket to which DES-4799 binds; they also observed a rearrangement of aromatic side chains residues upon binding of DES-4884, unseen in PTP1B X-ray structures, in the allosteric pocket identified by Sunesis [36].

We set out to test whether AlloViz was capable of detecting allosteric residues on this system on the basis of simulated PTP1B trajectories. We used the first 10 μs of the 100 μs MD trajectories of PTP1B simulated with its fragment ligand DES-4799 (PDB code: 8G65), described in [36] and kindly provided by D. E. Shaw Research. For our analysis, for instance, we used the `pytraj_CA` network construction method together with the `Spatially_distant` filter, performing network analysis with the betweenness centrality and current-flow be-

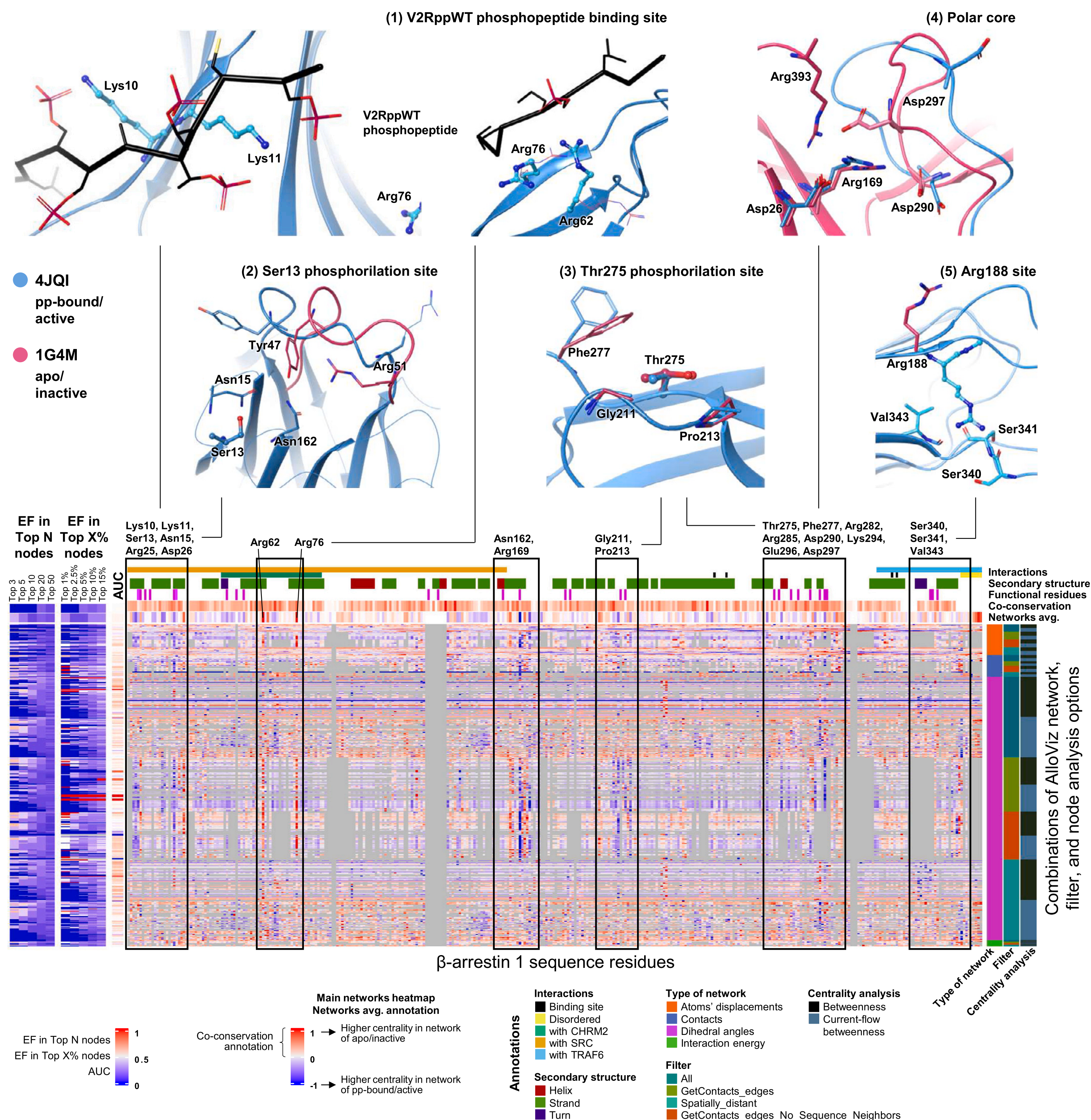

Fig. 3. AlloViz network analysis combinations of the β-arrestin 1 delta-network. Rows of the central heatmap represent each of the analysis combinations (sorted by the EF in the top 20 nodes, and grouped by *Type of network, Filter*, and *Centrality analysis type*); residues are in columns. Annotations on top show the interacting and secondary structure regions of β-arrestin 1, the functionally important residues identified experimentally (see Supplementary Table S2), the average values of the coevolution entropy for each residue derived from statistical coupling analysis (SCA), and the average of the allosteric network values computed by the various methods (consensus). Heatmaps on the left show Enrichment Factors (EFs) of the top N nodes, EFs of the top X% nodes and Area Under the Receiver Operating Characteristic (ROC) Curve (AUC) (Section S3.2). Right-hand annotations show the type of network, filter and centrality metric used on each row, i.e. analysis combination. Residue clusters are highlighted with black boxes and a selection of them is represented in structural snapshots above the heatmap.

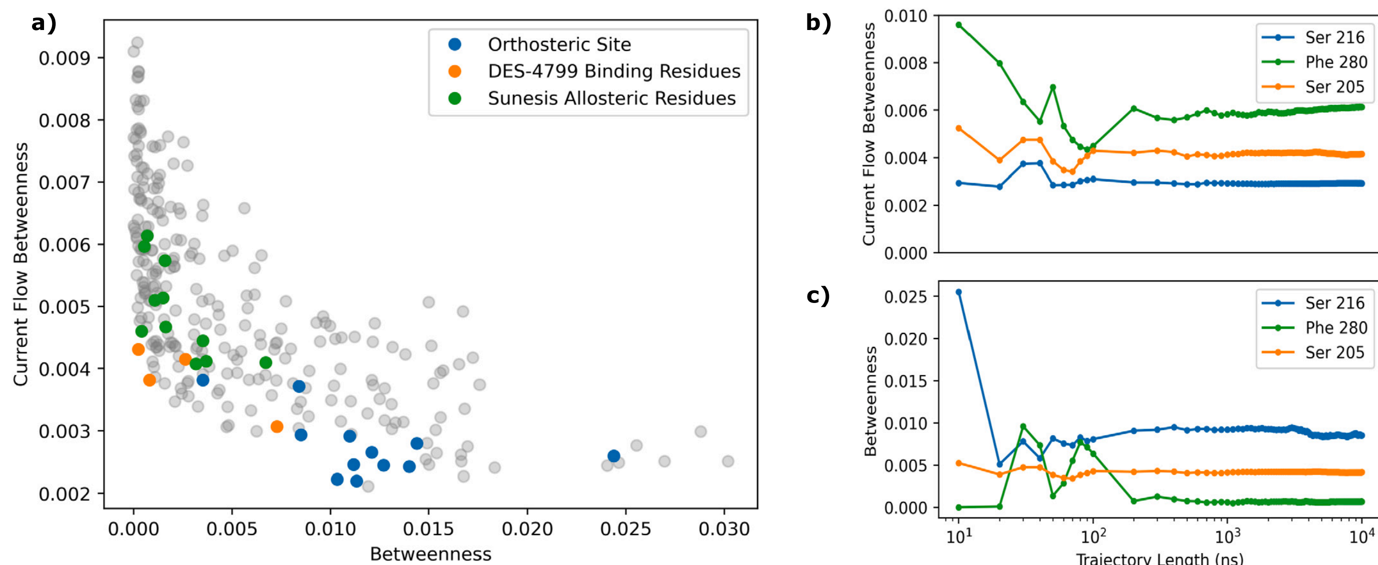

Fig. 4. (a) Current flow betweenness and betweenness centrality metrics of PTP1B residues, calculated after the construction of allosteric networks over 10 μs of the MD simulation; (b) current flow betweenness and (c) betweenness behaviour over the 10 μs simulation time. Residues of interest (see Supplementary Table S3) are coloured accordingly to their belonging to the allosteric or orthosteric sets.

tweenness centrality metrics. We cross-referenced the results with the known-allosteric and known-orthosteric residue sets of PTP1B (Supplementary Table S3).

Fig. 4 (a) shows the betweenness centrality and current flow betweenness centrality for all of the protein's residues, computed throughout the first 10 μs of the PTP1B:DES-4799 trajectory. Residues involved in the orthosteric and allosteric sites are separated along both axes in two distinct groups. Furthermore, residues identified by Wiesman et al. (green, Sunesis) and Greisman et al. (orange, DES-4799), both allosteric, belong to two distinct sites. They cluster together, suggesting that the metrics are related to allostery rather than specific residue positions. The analysis on the full 100 μs trajectory provides essentially the same results.

3.4. Sensitivity to simulation length

We then further set to study the convergence of the two centrality metrics with respect to increasing trajectory lengths: we repeated the analysis on portions of the original trajectory truncated at lengths increasing from 10 ns to 10 μs. Figs. 4 (b, c) show the convergence of current-flow betweenness and betweenness for three representative residues of the allosteric (Phe280), DES-4799 binding (Ser205) and orthosteric (Ser216) sets, respectively; convergence is achieved approximately at 200 ns. This is consistent with previous works that use simulation lengths of a few hundreds of nanoseconds to build allosteric networks [37,38,16,39]. In addition, Singh and Bowman [40] report that at least a microsecond of accumulated simulation time is necessary to obtain robust, converged and experiment-matching allosteric networks between trajectory replicas. This timescale is the one used in other recent publications [41,42], and it is reached by the total simulation times used for the two case studies here as well, which are 1.5 μs and 10 μs for the inactive and active β-arrestin 1, respectively, and 10 μs for the part of the simulation of PTP1B used.

4. Conclusion

AlloViz offers a platform designed for studying how proteins communicate internally through their allosteric networks, using data from molecular dynamics (MD) simulations. This platform combines various analytical methods and their respective tools, uniforming pre- and post-processing steps, into one accessible package, made accessible through both a Python interface and a graphical user interface (GUI). It enables users to apply several analysis techniques under uniform conditions, such as combining them into a single "consensus" scoring function. We show on a complex system of biological relevance, β-arrestin 1, that the consensus approach recovers many functionally important (experimentally validated) residues, and on the protein tyrosine phosphatase 1B, it successfully discriminates allosteric vs orthosteric sites. As a result, AlloViz can be incorporated into automated MD analysis workflows (a direction for further development), providing valuable insights into the behaviour of proteins and the mechanisms of allostery.

CRediT authorship contribution statement

Francho Nerín-Fonz: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Software, Validation, Visualization, Writing – original draft, Writing – review & editing. **Camilla Caprai:** Formal analysis, Investigation, Writing – review & editing. **Adrián Morales-Pastor:** Formal analysis, Investigation, Software. **Marta Lopez-Balastegui:** Formal analysis, Investigation. **David Aranda-García:** Formal analysis, Investigation. **Toni Giorgino:** Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. **Jana Selent:** Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing.

Declaration of competing interest

We have no conflicts of interest to disclose.

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Appendix A. Supplementary material

Supplementary material related to this article can be found online at https://doi.org/10.1016/j.csbj.2024.04.047.

References

[1] Hilger Daniel, Masureel Matthieu, Kobilka Brian K. Structure and dynamics of GPCR signaling complexes. Nat Struct Mol Biol January 2018;25(1):4–12.
[2] Vaidehi Nagarajan, Bhattacharya Supriyo. Allosteric communication pipelines in G-protein-coupled receptors. Curr Opin Pharmacol October 2016;30:76–83.
[3] Wodak Shoshana J, Paci Emanuele, Dokholyan Nikolay V, Berezovsky Igor N, Horovitz Amnon, Li Jing, et al. Allostery in its many disguises: from theory to applications. Structure April 2019;27(4):566–78.
[4] Haliloglu Turkan, Hacisuleyman Aysima, Erman Burak. Prediction of allosteric communication pathways in proteins. Bioinformatics July 2022;38(14):3590–9.
[5] Bowerman S, Wereszczynski J. Detecting allosteric networks using molecular dynamics simulation. In: Voth Gregory A, editor. Computational approaches for studying enzyme mechanism part B. Methods in enzymology, vol. 578. Academic Press; 2016. p. 429–47.
[6] Böde Csaba, Kovács István A, Szalay Máté S, Palotai Robin. Network analysis of protein dynamics. FEBS Lett 2007;581(15):2776–82.
[7] Greene Lesley H. Protein structure networks. Brief Funct Genomics November 2012;11(6):469–78.
[8] Schueler-Furman Ora, Wodak Shoshana J. Computational approaches to investigating allostery. Curr Opin Struct Biol December 2016;41:159–71.
[9] de Juan David, Pazos Florencio, Valencia Alfonso. Emerging methods in protein co-evolution. Nat Rev Genet April 2013;14(4):249–61.
[10] Novinec Marko, Korenč Matevž, Caflisch Amedeo, Ranganathan Rama, Lenarčič Brigita, Baici Antonio. A novel allosteric mechanism in the cysteine peptidase cathepsin K discovered by computational methods. Nat Commun February 2014;5(1):3287.
[11] Baldessari Filippo, Capelli Riccardo, Carloni Paolo, Giorgetti Alejandro. Coevolutionary data-based interaction networks approach highlighting key residues across protein families: the case of the G-protein coupled receptors. Comput Struct Biotechnol J 2020;18:1153–9.
[12] Rivoire Olivier, Reynolds Kimberly A, Ranganathan Rama. Evolution-based functional decomposition of proteins. PLoS Comput Biol June 2016;12(6):e1004817.
[13] Ni Duan, Chai Zongtao, Wang Ying, Li Mingyu, Yu Zhengtian, Liu Yaqin, et al. Along the allostery stream: recent advances in computational methods for allosteric drug discovery. WIREs Comput Mol Sci 2022;12(4):e1585.
[14] Leander Megan, Yuan Yuchen, Meger Anthony, Cui Qiang, Raman Srivatsan. Functional plasticity and evolutionary adaptation of allosteric regulation. Proc Natl Acad Sci October 2020;117(41):25445–54.
[15] Feher Victoria A, Durrant Jacob D, Van Wart Adam T, Amaro Rommie E. Computational approaches to mapping allosteric pathways. Curr Opin Struct Biol April 2014;25:98–103.
[16] Melo Marcelo CR, Bernardi Rafael C, de la Fuente-Nunez Cesar, Luthey-Schulten Zaida. Generalized correlation-based dynamical network analysis: a new high-performance approach for identifying allosteric communications in molecular dynamics trajectories. J Chem Phys October 2020;153(13):134104.
[17] Bhattacharya Supriyo, Vaidehi Nagarajan. Differences in allosteric communication pipelines in the inactive and active states of a GPCR. Biophys J July 2014;107(2):422–34.
[18] Guo Jingjing, Pang Xiaodong, Zhou Huan-Xiang. Two pathways mediate interdomain allosteric regulation in Pin1. Structure January 2015;23(1):237–47.
[19] Verkhivker Gennady M, Agajanian Steve, Hu Guang, Tao Peng. Allosteric regulation at the crossroads of new technologies: multiscale modeling, networks, and machine learning. Front Mol Biosci 2020;7.
[20] Jefferson Robert E, Oggier Aurélien, Füglistaler Andreas, Camviel Nicolas, Hijazi Mahdi, Villarreal Ana Rico, et al. Computational design of dynamic receptor—peptide signaling complexes applied to chemotaxis. Nat Commun May 2023;14(1).
[21] Gao Shuyang, Ver Steeg Greg, Galstyan Aram. Efficient estimation of mutual information for strongly dependent variables. arXiv:1411.2003 [physics, stat], March 2015.
[22] Isberg Vignir, de Graaf Chris, Bortolato Andrea, Cherezov Vadim, Katritch Vsevolod, Marshall Fiona H, et al. Generic GPCR residue numbers – aligning topology maps while minding the gaps. Trends Pharmacol Sci January 2015;36(1):22–31.
[23] Latora Vito, Nicosia Vincenzo, Russo Giovanni. Centrality measures. Cambridge University Press; 2017. p. 31–68.
[24] Botello-Smith Wesley M, Luo Yun. Investigating protein–protein allosteric network using current-flow scheme. J Comput Chem March 2020;41(6):552–60.
[25] Botello-Smith Wesley M, Luo Yun. Robust determination of protein allosteric signaling pathways. J Chem Theory Comput April 2019;15(4):2116–26.
[26] Kluyver Thomas, Ragan-Kelley Benjamin, Pérez Fernando, Granger Brian, Bussonnier Matthias, Frederic Jonathan, et al. Jupyter notebooks – a publishing format for reproducible computational workflows. In: Loizides F, Schmidt B, editors. Positioning and power in academic publishing: players, agents and agendas. IOS Press; 2016. p. 87–90.
[27] Humphrey William, Dalke Andrew, Schulten Klaus. VMD – visual molecular dynamics. J Mol Graph 1996;14:33–8.
[28] Jupyter Project, Bussonnier Matthias, Forde Jessica, Freeman Jeremy, Granger Brian, Head Tim, et al. Binder 2.0 - reproducible, interactive, sharable environments for science at scale. In: Akici Fatih, Lippa David, Niederhut Dillon, Pacer M, editors. Proceedings of the 17th Python in science conference; 2018. p. 113–20.
[29] Morales-Pastor Adrian, Nerín-Fonz Francho, Aranda-García David, Dieguez-Eceolaza Miguel, Medel-Lacruz Brian, Torrens-Fontanals Mariona, et al. In silico study of allosteric communication networks in GPCR signaling bias. Int J Mol Sci 2022;23(14).
[30] Shukla Arun K, Manglik Aashish, Kruse Andrew C, Xiao Kunhong, Reis Rosana I, Tseng Wei-Chou, et al. Structure of active β-arrestin-1 bound to a G-protein-coupled receptor phosphopeptide. Nature May 2013;497(7447):137–41.
[31] Baidya Mithu, Chaturvedi Madhu, Dwivedi-Agnihotri Hemlata, Ranjan Ashutosh, Devost Dominic, Namkung Yoon, et al. Allosteric modulation of GPCR-induced β-arrestin trafficking and signaling by a synthetic intrabody. Nat Commun August 2022;13:4634. Publisher: Nature Publishing Group.
[32] Rodríguez-Espigares Ismael, Torrens-Fontanals Mariona, Tiemann Johanna KS, Aranda-García David, Ramírez-Anguita Juan Manuel, Stepniewski Tomasz Maciej, et al. GPCRmd uncovers the dynamics of the 3D-GPCRome. Nat Methods August 2020;17(8):777–87.
[33] Villamar-Cruz Olga, Loza-Mejía Marco A, Arias-Romero Luis E, Camacho-Arroyo Ignacio. Recent advances in ptp1b signaling in metabolism and cancer. Biosci Rep November 2021;41(11):BSR20211994.
[34] Liu Rongxing, Mathieu Cécile, Berthelet Jérémy, Zhang Wenchao, Dupret Jean-Marie, Rodrigues Lima Fernando. Human protein tyrosine phosphatase 1b (ptp1b): from structure to clinical inhibitor perspectives. Int J Mol Sci 2022;23(13).
[35] Wiesmann Christian, Barr Kenneth J, Kung Jenny, Zhu Jiang, Erlanson Daniel A, Shen Wang, et al. Allosteric inhibition of protein tyrosine phosphatase 1b. Nat Struct Mol Biol August 2004;11(8):730–7.
[36] Greisman Jack B, Willmore Lindsay, Yeh Christine Y, Giordanetto Fabrizio, Shahamadtar Sahar, Nisonoff Hunter, et al. Discovery and validation of the binding poses of allosteric fragment hits to protein tyrosine phosphatase 1b: from molecular dynamics simulations to x-ray crystallography. J Chem Inf Model May 2023;63(9):2644–50.
[37] Brown David K, Penkler David L, Sheik Amamuddy Olivier, Ross Caroline, Atilgan Ali Rana. MD-TASK: a software suite for analyzing molecular dynamics trajectories. Bioinformatics September 2017;33(17):2768–71.
[38] Lange Oliver F, Grubmüller Helmut. Generalized correlation for biomolecular dynamics. Proteins, Struct Funct Bioinform 2006;62(4):1053–61.
[39] Tiberti Matteo, Invernizzi Gaetano, Lambrughi Matteo, Inbar Yuval, Schreiber Gideon, Papaleo Elena. PyInteraph: a framework for the analysis of interaction networks in structural ensembles of proteins. J Chem Inf Model May 2014;54(5):1537–51.
[40] Singh Sukrit, Bowman Gregory R. Quantifying allosteric communication via both concerted structural changes and conformational disorder with CARDS. J Chem Theory Comput April 2017;13(4):1509–17.
[41] Sora Valentina, Tiberti Matteo, Beltrame Ludovica, Dogan Deniz, Robbani Shahriyar Mahdi, Rubin Joshua, et al. Pyinteraph2 and pyinknife2 to analyze networks in protein structural ensembles. J Chem Inf Model 2023;63(14):4237–45.
[42] Maschietto Federica, Allen Brandon, Kyro Gregory W, Batista Victor S. MDiGest: a Python package for describing allostery from molecular dynamics simulations. J Chem Phys 2023;158(21):215103.