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SADIC v2: A modern implementation of the Simple Atom Depth Index Calculator

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ABSTRACT

Protein structure analysis plays a primary role in understanding their biological functions. Being able to determine the atom depth index within the protein is crucial to gain insights into molecular interactions and structural stability. To address this need, the original version of Simple Atom Depth Index Calculator (SADIC) software was developed in 2006. However, with the rapid advancement of computational methodologies and the evolution of programming libraries, the original SADIC software has become obsolete and incompatible with modern computational environments. This is why we present SADIC v2, a modernized version of the software that is fully compatible and integrated with modern Python libraries.

Code metadata

Current code version	v2.0.0
Permanent link to code/repository used for this code version	https://github.com/ElsevierSoftwareX/SOFTX-D-24-00195
Permanent link to Reproducible Capsule	
Legal Code License	MIT license
Code versioning system used	git
Software code languages, tools, and services used	Python3
Compilation requirements, operating environments & dependencies	NumPy, SciPy, BioPandas
If available Link to developer documentation/manual	https://github.com/nunziati/sadic/tree/sadic_SoftwareX
Support email for questions	giacomo.nunziati.0@gmail.com

Software metadata

Current software version	v2.0.0
Permanent link to executables of this version	For example: https://github.com/nunziati/sadic/tree/sadic_SoftwareX
Permanent link to Reproducible Capsule	
Legal Software License	MIT license
Computing platforms/Operating Systems	Linux, OS X, Microsoft Windows
Installation requirements & dependencies	NumPy, SciPy, BioPandas
If available, link to user manual - if formally published include a reference to the publication in the reference list	https://github.com/nunziati/sadic/tree/sadic_SoftwareX
Support email for questions	giacomo.nunziati.0@gmail.com

1. Motivation and significance

In recent times, the wealth of molecular structure data, particularly in the context of proteins, has seen an exponential increase. This surge can be attributed to both the advancements in three-dimensional structure extraction techniques [1–4] and the refinement of software tools [5] dedicated to this purpose. Notably, breakthroughs such as

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AlphaFold 2 [6] have significantly contributed to the accuracy and availability of protein structural information.

Atomic depth in proteins has proven to be a versatile structural indicator, showing correlations with a spectrum of molecular and atomic characteristics. More specifically, studies have revealed associations between atomic depth and crucial features such as the average size of protein domains, stability, free energy of protein complex formation, hydrophobicity of amino acids (also known as residues), residue conservation, and hydrogen/deuterium amide–proton exchange rate [7]. Furthermore, the concept of residue depth, derived from the aggregation of atom depths within the same residue, emerges as a particularly informative metric and shows a significant impact on the effects of mutations on protein stability and protein–protein interactions [8]. While protein surface features contribute to an understanding of the function, the core plays a key role in the correct folding and overall stability of the protein. Atomic depth acts as an extension of well-known descriptors such as solvent–accessible area and buried surface area, offering a unified view of the atoms and residues that lie deep within the protein's core. In particular, as the depth of the protein nucleus is reached, conventional parameters such as solvent accessibility and buried surface area show reduced sensitivity. Therefore, a sensitive measurement such as atomic depth becomes essential to capture the details of protein core structures. Given the significance of atomic depth in proteins, the escalating volume of molecular data further emphasizes the need for automated tools to quantify this metric.

In the literature, classical atomic depth measurements are based on various distance-based approaches. A common method involves determining the atom depth by calculating its distance to the nearest water molecule [8,9]. Another approach defines atomic depth as the distance between an atom and a molecular or solvent-accessible surface [10]. Molecular dynamics simulations offer a more precise but computationally intensive method, calculating the depth as the distance between each atom and the nearest surface point during the simulation of solvated protein dynamics [8]. However, the mentioned estimates of atom depth in proteins generally fail to consider the contribution of the local 3D shape of the molecule. This limitation is significantly relevant when examining atoms on the surface of the molecule. Indeed, despite the different levels of accessibility that surface atoms may have, distance-based definitions of atomic depth assign uniform values to them. Therefore, integrating 3D molecular shape information becomes crucial to capture this feature.

Varrazzo et al. [11] address the limitations of traditional atomic depth metrics and introduce an innovative solution referred to as Simple Atom Depth Index Calculator (SADIC). In contrast to traditional distance-based methods, SADIC takes into account the volume of the portion of the molecule surrounding each atom. The result is a depth index that more comprehensively accounts for the molecular environment around each atom. The first implementation of SADIC (SADIC v1) in [12] resulted in a significant contribution that led to the development of an improved version, SADIC v2. In particular, SADIC v1, relying on Python 2 and outdated packages, suffered from installation difficulties and lacked compatibility with modern computational frameworks. Its command-line interface (CLI) structure posed obstacles to smooth integration into larger projects, and a notable inefficiency resulted from its iterative approach to parameter determination. SADIC v2 addresses these issues by providing a Python 3 package with efficient modern dependencies and integration with contemporary molecular biology libraries, such as BioPython and BioPandas. It adopts a discrete geometry approach using a voxel grid for protein representation, facilitating the use of efficient and well-established algorithms. Furthermore, SADIC v2 innovates over SADIC v1 with respect to protein structure analysis. Specifically, SADIC v2 is based on the observation that atoms located on the surface of cavities inside proteins are not accessible to external molecules and therefore cannot be considered as surface atoms. For this reason, the algorithm assumes that the inaccessible cavities of proteins are considered internal parts and are included in the calculation of the internal volume of the protein.

2. Software description

2.1. Definitions

SADIC v2 was developed by exploiting the molecular model and depth index definition proposed in [11], which proved to be effective in overcoming the limitations encountered by traditional atom depth measurements [13]. Each protein is modeled as a solid object composed of spheres centered on individual atoms [14]. Structural details are extracted from the Protein Data Bank (PDB) [15], the most extensive publicly accessible and freely available repository of polypeptide chains.

In our model, each atom is systematically indexed based on information sourced from PDB files. We consider hydrogen (H), carbon (C), nitrogen (N), oxygen (O), sulfur (S), and phosphorus (P) atoms, together with their Van der Waals radii. These radii are increased by a constant k equal to the Van der Waals radius of a water molecule, ensuring that the surface cavities of the protein are properly filled if inaccessible. In this way, we consider the convex regions inaccessible to water or other small molecules as part of the protein's internal volume.

SADIC simulates the probing of the protein by identifying the largest sphere, centered on an atom and inscribed in its molecular structure, called reference sphere. Let r be the radius of such sphere and $V_{r_{max}}$ its volume. During the simulation, the reference sphere is iteratively centered on each atom i, and the exposed volume $V_{r,i}$ is computed. The exposed volume is the volume of the portion of the reference sphere centered on the i–th atom that does not intersect the solid representation of the protein. The concept of "exposed volume" is illustrated in Fig. 1, which highlights the regions that are considered in the calculation of the depth index.

The evaluation of the atom depth index $D_{i,r}$ for the i–th atom is determined by the formula:

$$D_{i,r} = \frac{2V_{r,i}}{V_{r_{max}}}.$$

This index emphasizes the different exposition of surface atoms and provides a relevant measure of the atom depth within the protein.

2.2. Software architecture

SADIC v2, implemented as a Python3 package, relies on NumPy and SciPy for numerical computation. The BioPandas package manages the protein data, while BioPython is employed for handling the integration with this widespread bioinformatic framework.

The software architecture of SADIC v2 is arranged into distinct subpackages: *pdb* for organizing the data of the input protein and managing the result of the execution of the algorithms, *solid* for modeling and manipulating the continuous-space and discrete-space solids representing the molecule, and *algorithm*, where the core algorithms are defined. The main *sadic* package exposes an API with a single function for executing the depth index computation pipeline.

To accommodate diverse user preferences, SADIC v2 offers a command-line interface (CLI) mirroring the API functionality.

Fig. 2 graphically shows the package architecture and the interconnections between the components.

2.3. Software functionalities

SADIC v2 offers a user-friendly API function, providing flexible input options and different output formats.

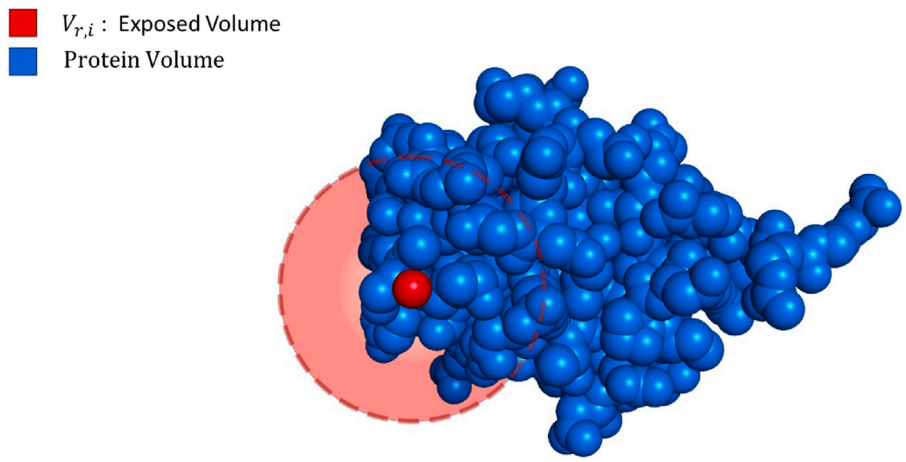


Fig. 1. Volumes involved in the computation of the depth index. The ith atom is represented in red, while the other atoms constitute the remaining part of the protein volume and are represented as blue balls. The dashed circle represents the sphere of radius r centered on the ith atom. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

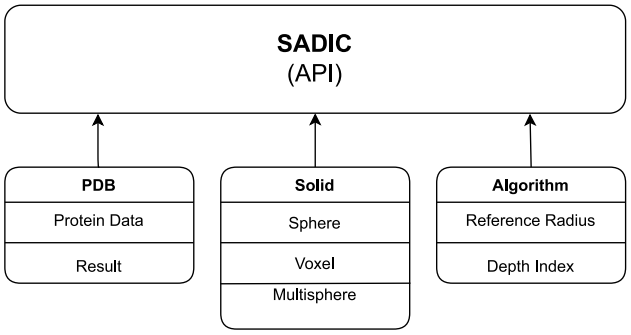


Fig. 2. Package architecture.

2.3.1. Input

The algorithm for the computation of the depth index can accept different types of inputs:

- a string containing the PDB code of the protein: the corresponding .pdb file will be automatically downloaded from the RCSB database;
- uncompressed .pdb or compressed .tar.gz PDB files, which allow users to directly load locally stored protein structure data;
- PandasPdb entity or BioPython structure representing proteins, ensuring integration with the two popular bioinformatic libraries.

The function also accepts a set of optional parameters:

- protein models – users can specify protein models for which the algorithm computes the depth index; indeed, PDB proteins from the RCSB database may have multiple models originating from different experiments or Nuclear Magnetic Resonance (NMR) 3D structure extractions;
- atom filter – a filter parameter enables the computation of the depth index for specific atoms, selected based on diverse criteria defined by the users;
- reference sphere radius – users can define the radius of the reference sphere used in the algorithm, whether fixed or computed from a specific model of the PDB protein data;
- Van der Waals radii – allows customization of Van der Waals radii used for constructing the continuous–space model of the protein;
- grid resolution – users can set the resolution of the grid used for the discretization of the protein solid.

2.3.2. Output

SADIC v2 returns the output through a structured result object. It encapsulates all execution outcomes, particularly the results of the SADIC algorithm on each model of the PDB entity. Users can obtain depth indexes in various forms, including Python lists and NumPy arrays. Depth indexes can be saved in different formats such as .txt or NumPy array on disk. Additionally, users can save results as PDB files (raw or compressed in .tar.gz format) corresponding to the original PDB file, with one column modified to report the computed depth indexes. Before obtaining depth indexes or saving results, users have the flexibility to apply additional post–processing steps. This includes the ability to filter desired atoms again or aggregate different models and/or groups of atoms based on user-defined similarity criteria.

2.4. Main pipeline

The execution of the SADIC v2 algorithm is articulated in multiple stages, detailed in the following (see Fig. 3).

- Loading of protein data;
- Creation of the structured PDB entity;
- For each model found in the PDB file:
  - creation of the continuous–space model of the protein under analysis;
  - voxelization and definition of the discrete-space model approximating the protein solid;
  - filling of the internal cavities of the protein;
  - computation of the reference radius, that will be used for the depth index calculation;
  - computation of the depth indexes for the atoms selected by the user.

2.4.1. CLI interface

SADIC v2 command-line interface offers equivalent functionalities to the Python API. It uses a configuration file where the user can specify the optional input arguments, output formats, filters, and aggregation options.

2.5. Analysis

In this section, we present three analyses conducted to evaluate the performance and validity of SADIC v2 in quantifying atom depth within protein structures. The execution time evaluation for the characterization of superficial atoms are performed for three representative

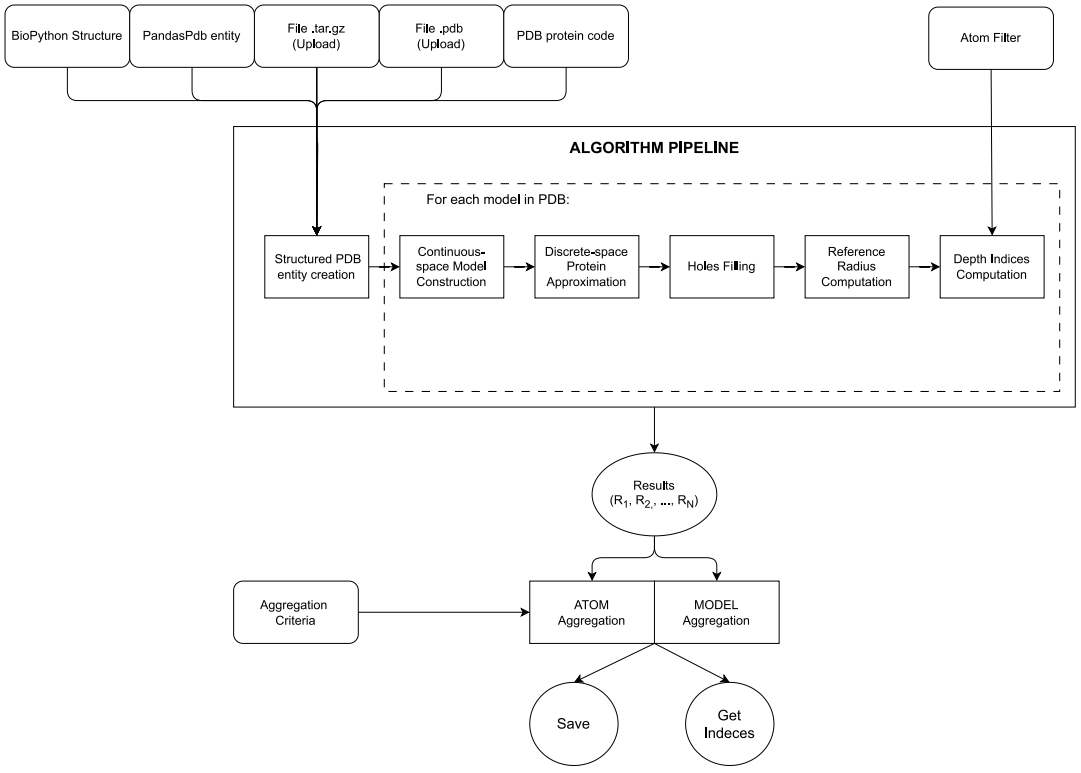


Fig. 3. SADIC v2 pipeline.

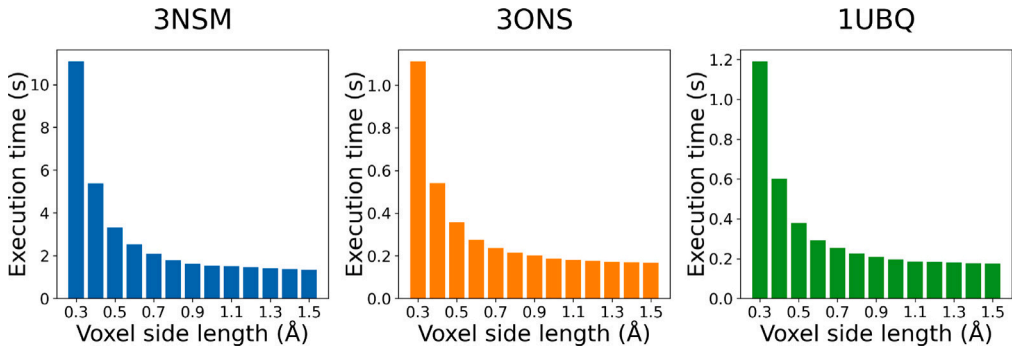


Fig. 4. Execution time depending on resolution.

proteins, with PDB codes *3NSM* (4615 atoms, 572 residues), *3ONS* (574 atoms, 72 residues), and *1UBQ* (601 atoms, 76 residues). Only the protein with PDB code 3NSM was considered for the residue type analysis, as it is the only one with a significant number of residues.

Execution time. We measured SADIC v2 execution time across different grid resolutions (0.3 to 1.5 Å) to assess its computational efficiency. Fig. 4 shows that lower resolutions lead to faster executions. This intuitive result highlights the relevance of assessing a good trade-off between accuracy and efficiency.

Superficial atom characterization. To evaluate SADIC v2 effectiveness, we compared it with ResidueDepth, a conventional distance-based method for computing atom depth in protein structures [16]. Specifically, we computed both ResidueDepth and SADIC v2 atom depth indexes for the 10% most superficial atoms according to ResidueDepth. For a fair comparison, each atom depth obtained with ResidueDepth is normalized to the same range of the SADIC v2 depth indexes. The results reported in Fig. 5 show that the depth of atoms measured by ResidueDepth exhibits small variations, while the depth index computed by SADIC v2 shows a greater variability. This suggests that SADIC v2 more accurately captures the accessibility of surface atoms. To show this difference visually, in Fig. 6 we have colored the atoms of the protein with code 1UBQ according to the atom depth resulting from ResidueDepth (Fig. 6(a)) and to the SADIC depth index (Fig. 6(b)).

Core and surface residue characterization. In this study, we aimed to use the SADIC v2 depth index to highlight the differences among distinct classes of amino acids within the protein 3NSM. Amino acids are categorized based on their physico–chemical properties, with nonpolar amino acids predominantly constituting the core of the protein, serving as structural elements. These include Alanine, Valine, Isoleucine, Leucine, Methionine, Phenylalanine, Tyrosine, and Tryptophan. Conversely, charged and polar amino acids are more likely to be located on the surface of the protein. Our analysis encompassed Serine, Threonine, Asparagine, Glutamine, Arginine, Histidine, Lysine, Aspartic Acid, and Glutamic Acid. Notably, we excluded three other amino acids, Cysteine, Proline, and Glycine, due to their versatile roles in protein structure and function, which can vary depending on the specific protein context. We computed residue depth indexes as the average of the atom depth

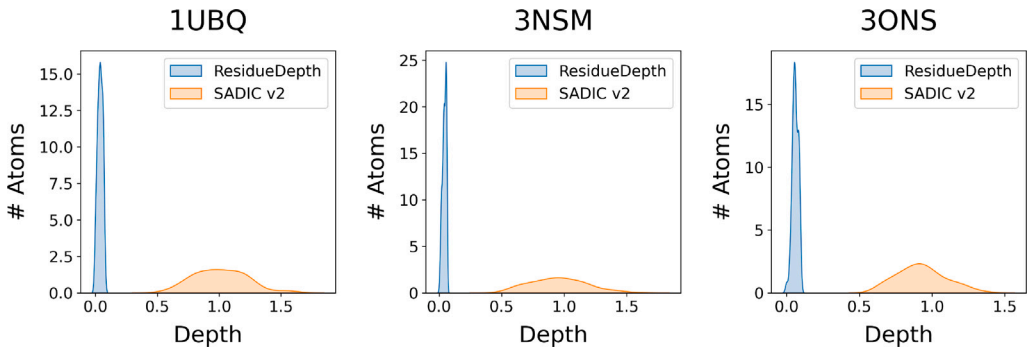
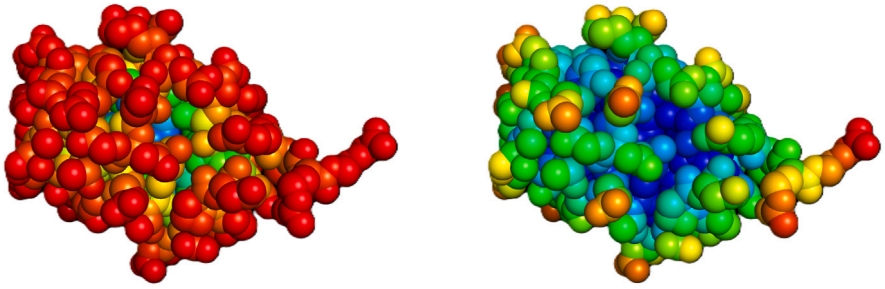


Fig. 5. Distribution of atom depth computed with ResidueDepth and SADIC v2.



(a) ResidueDepth atom depth (b) SADIC depth index

Fig. 6. Sphere representation of the protein with PDB code 1UBQ, color-coded according to the atom depth resulting from (a) ResidueDepth and (b) SADIC depth index.

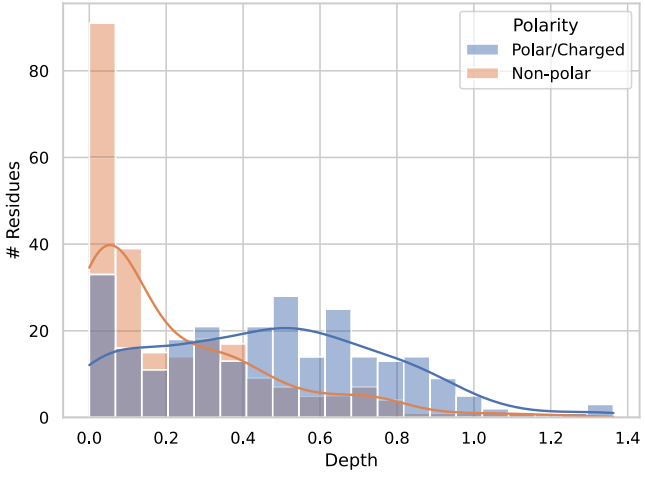


Fig. 7. Distribution of residue depth index values, grouped by residue type (Polar/Charged vs Non-polar), for the protein with PDB code 3NSM.

indexes of the same residue. The distribution of the residue depth index values for the two considered amino acid groups is shown in Fig. 7.

3. Illustrative example

An example of a software use case is presented below.

Consider a scenario in which the significance of the conservation of a specific amino acid in a protein needs to be analyzed. This situation can occur because a mutation in an amino acid located in the active site of a protein can lead to the loss of its function. Thus, understanding the depth of the residue becomes crucial in assessing its degree of exposure and participation in molecular binding that should occur in the active site. Assume the following required setup:

- `1GWD` is the protein code in the RCSB database;
- the PDB entity has a single protein model;
- it is known that its active site is located in a specific region in space, surrounded by a sphere with center `C` and radius `R`;
- the optimal radius for the reference sphere should be automatically computed;
- the default values for the Van der Waals radii are accepted;
- the user is more interested in a high throughput algorithm, rather than an accurate result;
- the user is interested in evaluating the depth of the residues rather than the depth of the atoms (with the depth index of a residue defined as the average of the depth indexes of the atoms that compose it);
- the user wants to obtain a Python list as the output of the computation.

Based on the requirements, some input parameters can be set and the main pipeline can be launched:

```
# Input protein
pdb_code = "1GWD"

# Filter on the atoms
center = C
radius = R
sphere = (center, radius)

# Coarse-grained grid, for efficiency
resolution = 0.8 # (1 Angstrom = 10^-10 meters)

# Run the pipeline
result = sadic.sadic(
  pdb_code,
  filter_by = sphere,
  resolution = resolution
)
```

After the computation, the result can be aggregated and manipulated to obtain the desired output.

```
# Define the aggregation options
group_by = "residue_number"
aggregation_function = "mean"
aggregation = (group_by, aggregation_function)

# Return the output depth indexes as a list
output = result.get_depth_index(
  get_index = True,
  atom_aggregation = aggregation
)

# Visualize the depth indexes
for id, depth_index in zip(*output):
  print(f"id = {id}, depth_index = {depth_index}")
```

The output variable is a tuple containing two lists with as many elements as the number of residues in the protein. The first list contains the unique ID associated with the residues and the second one contains the associated depth index.

4. Impact

SADIC v2 allows 3D atomic depth quantification in complex biomolecules, as could previously be achieved by SADIC [12], which is now obsolete and no longer usable. The latter has been a precious tool for understanding the surface accessibility of small uncharged paramagnetic molecules towards proteins [17] and nucleic acids [18]. Furthermore, the 3D atom depth analysis has permitted a detailed investigation of amino acid distribution in protein structural layers [19]. Models for the 3D atom depth calculation have also been used to characterize protein core compositions as a basis for understanding the molecular folding process [20].

The versatility of the software is exemplified through its application in various studies:

- SADIC has facilitated a detailed analysis of the COVID-19 spike glycoprotein, focusing on identifying concave moieties at protomer–protomer interfaces [21];
- SADIC has played a crucial role in studying human thymidylate synthase, providing insights into the structural features of the 72 kDa homodimeric enzyme [22];
- The integration of SADIC with 2D NMR spectroscopy for the analysis of individual stability curves of Yfh1 protein core hydrophobic residues has gained recognition in publications focused on protein dynamics and folding [23].

All the above-described applications of 3D atomic depth quantification retain great relevance in the field of biochemistry and biotechnology for understanding biological processes at the molecular level. Our software will continue to facilitate the analysis of all these fundamental aspects of structural biology investigation, now enhanced by the wide availability of biomolecular structures that new technologies offer researchers.

5. Conclusions

In this paper, we present SADIC v2, a software for calculating the depth index of atoms within complex molecules, particularly proteins. As a modern and improved version of SADIC v1, SADIC v2 is designed to address the dynamic needs of researchers, prioritizing ease of use to ensure accessibility to a wide range of users. Compatibility with other software platforms enhances its integration into existing workflows, fostering a collaborative and interdisciplinary approach to molecular analysis. We also report different validation tests and present a particular use case, as well as a set of past applications of the SADIC method. The development of this tool is driven by its utility for biologists, atom depth being a key factor that strongly influences protein properties. By providing an easy–to–use and efficient solution, SADIC v2 responds to the evolving needs of researchers, contributing significantly to the analysis and understanding of molecular structures.

CRediT authorship contribution statement

Sara Marziali: Writing – original draft, Visualization, Validation, Methodology, Investigation, Conceptualization. **Giacomo Nunziati:** Writing – review & editing, Writing – original draft, Visualization, Validation, Software, Methodology, Investigation, Conceptualization. **Alessia Lucia Prete:** Writing – original draft, Visualization, Validation, Methodology, Investigation, Conceptualization. **Neri Niccolai:** Writing – review & editing, Supervision, Conceptualization. **Monica Bianchini:** Writing – review & editing, Supervision.

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

The data used in this work is available in a public repository and its access details have been detailed.

Declaration of Generative AI and AI-assisted technologies in the writing process

During the preparation of this work, the author(s) used ChatGPT in order to improve the clarity of the contents and the correctness of the English language. After using this tool/service, the author(s) reviewed and edited the content as needed and take(s) full responsibility for the content of the publication.

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