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Heligeom: A web resource to generate, analyze, and visualize filament architectures based on pairwise association geometries of biological macromolecules

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Abstract

At the subcellular level, macromolecules self-assemble to form molecular machinery in which the assembly modes play critical roles: the structural integrity of cell walls that allows mechanical growth, the maintenance and repair of the genetic material, membrane flow control, protein chaperoning, and ATP production, to cite just a few examples. As molecular modeling expands its scope to such systems, structural biologists are faced with the difficulty of understanding the structure and dynamics of these supramolecular assemblies. We present Heligeom, a webserver that offers a simple and efficient means for analyzing and constructing oligomeric assemblies based on user-provided structures of two interacting units. The input 3D coordinates may result from structure determination, simulations, docking trials, or deep-learning tools such as AlphaFold. For a given interface, Heligeom outputs the mathematical helical parameters of the corresponding oligomeric form, including axis, pitch, handedness, number of monomers per turn, etc. The server also allows leveraging these parameters to construct oligomers of specified size, visualizing them interactively, and downloading them as PDB files. For subunits (protomers) having multiple interaction geometries, the different interfaces and their global assembly geometry can be visualized and compared. Heligeom thus allows explicitly linking protomer-protomer interfaces to the oligomeric architecture, illuminating possible sources of plasticity in protein filaments such as mutations or thermal, mechanical, or chemical perturbations. Heligeom thus constitutes an intuitive tool to accompany integrative modeling of oligomeric filamentous assemblies. Examples of its application at different structural levels are presented. Heligeom webserver can be accessed at <https://heligeom.galaxy.ibpc.fr>.

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1. Introduction

Most proteins perform their function in the cell as part of assemblies, which may be stable or transient. They frequently self-associate or participate in oligomeric associations such as filaments, rings, or capsids. Indeed, as noted nearly 25 years ago by Goodsell and Olson [1] and more recently by Levy and colleagues [2,3], macromolecular superstructures often present a symmetric organization comprising many copies of a single protein or hetero-oligomeric unit. For example, within the cell, networks of filaments form the cytoskeleton (actin, microtubules) which

strengthens, shapes and organizes the cell structure and its internal communications. Oligomeric/polymeric superstructures are found as components of extracellular architectures (pili, fibrils, virus capsid), and cyclic oligomers are common in the realm of membrane proteins or cyclic motor systems, many of which participate in DNA manipulation or maintenance (helicase, recombinase). Regular self-assembly of peptides can lead to the formation of toxic amyloid fibers associated with neurodegenerative disorders but may also result in biologically functional amyloid fibers [4]. Finally, controlling the formation of organized arrays of proteins or filaments is promising for synthetic biology applications: indeed, most globular proteins can self-associate as filaments provided that they are properly functionalized [5].

Self-assembled macromolecules found in the cell are generally not covalently linked, even in the large oligomeric molecular assemblies that form the cellular machinery or the cytoskeleton. This means that the architecture of these assemblies is the result of specific binding geometries at the level of each pair of macromolecule components. When the binding geometry is well defined and regularly repeated, the resulting architecture is a helical filament or a ring, following what is generically known as screw organization. Up to a few years ago, protein filament architectures were mainly characterized by global characteristics which could be measured from electron micrographs or atomic force microscopy experiments. Filaments only rarely form perfect crystals, therefore structures as familiar as actin filaments or microtubules were only recently experimentally resolved at atomic resolution [6-8], thanks to major progress in cryo-electron microscopy instrumentation and data treatment. Currently, the PDB contains many such oligomeric structures, most of which are cyclic assemblies or spiral filaments formed by a small number of symmetry units. Although these available structures still represent only a small portion of the filamentous assemblies that exist in the cell, they already show a large diversity in terms of architectures. Further, such oligomers may be polymorphic, presenting different binding organizations that are reflected in their overall shapes [9, 10]. In an example of this, the passage of the ClpB assembly from a closed hexameric ring to a spiral morphology has been captured in high-speed atomic force microscopy movies [11].

The key factor when rationalizing oligomer polymorphism is the binding interface. Self-assembling proteins can employ several different binding interfaces with affinities that depend on the environment: salt composition, concentration, pH, or the presence of different ligands such as ATP or ADP. Since the geometry of a symmetric helical filament is uniquely defined by the subunit-subunit binding geometry, an environmental change that changes the order of affinities of the possible interfaces leads to changes in the overall architecture. A single oligomeric assembly may also harbor different interfaces which coexist; one example is RecA in which an ATP hydrolysis event at a particular monomer induces large changes in the local helical geometry [12,13]. Ring motors use concerted interface shifts, resulting from a sequential change of the hydrolysis state of NTP molecules bound to those interfaces, thus transforming chemical energy into mechanical movements [14,15].

Here we present the Heligeom server, which facilitates linking knowledge about detailed protein-protein interface geometry to information about high-order filament or ring architecture resulting from oligomeric self-assembly. The Heligeom server is based on the PTools library [9,16], and exposes much of the functionality of those software tools without the need for programming. Given the 3D coordinates specifying the interaction geometry between two identical proteins, or protomers (which could also be domains or groups of proteins), Heligeom performs three main tasks: analyzing the binding geometry in terms of the helical parameters relating one protomer to the other, constructing symmetric oligomers of a provided number of protomers based on that geometry, and, when provided with two different binding geometries, comparing them in terms of their interface similarity (fraction of common contacts) and overall 3D-organization, as defined by their helical parameters. Heligeom currently addresses oligomeric assemblies defined as linear successions of protomer-protomer interfaces— a filamentous organization that is widely encountered

in the cell (e.g., actin, microtubules, recombinases). Organizations that involve multiple, adjacent binding interfaces, or more generally a combination of distinct symmetry transformations as found for example in isocahedric virus capsids, are not directly treated, but can be approached in successive steps employing different interfaces of the same starting monomer [17].

Among its possible uses, Heligeom can contribute to characterizing interface variability within x-ray or cryo-EM oligomeric structures or to comparing binding geometries. It can act as part of an integrative modeling processes or as a free-standing resource for exploring or prospecting possible assembly geometries in light of structural or non-structural experimental information. For example, the prediction of a ring-like structure for A β 42 oligomers by Tran and collaborators used Heligeom-related PTools functions in its modeling pipeline [18], which have now been incorporated into the Heligeom webserver. Solution structure resolution of protein filaments based on SAXS data can also benefit from Heligeom functionalities [19]. With the spectacular rise of deep learning methods that predict not only structures but also protein-protein binding geometries with high reliability, Heligeom becomes a partner for quickly selecting relevant interfaces that can produce an oligomeric architecture with desired characteristics. We provide examples of such uses in what follows.

Given the importance of symmetric oligomeric assemblies in the cell, several tools have already been developed that deal with different aspects of oligomer organization [16,20,21-24]. Prediction of 3D superstructure has often been the focus of such methodological developments, generally relying on the knowledge of the symmetry order [22-24]. These methods typically aim at generating a single, high quality prediction that fits the given symmetry criteria. However, many biological processes involve deviations from an ideal, static 3D-architecture or take advantage of ubiquitous binding modes. Because its conception is explicitly based on interfaces, the Heligeom webserver offers many ways to explore such deformations and investigate how variations in the binding geometry may influence the global architecture. We believe making such tools directly available to a wide audience via a webserver will foster the understanding of oligomer structure/function properties. The Heligeom webserver can be accessed at the address <https://heligeom.galaxy.ibpc.fr>.

2. Methods

2.1. Screw (*helical*) parameters

Heligeom is based on a representation of the spatial displacement of a rigid body in terms of a screw transformation. The concept of screw movement appeared with the early developments of the theory of rigid body kinematics in the nineteenth century, for example in the Chasles theorem [25, 26]. A screw motion is defined by the six degrees of freedom associated with the rotation in 3D around a specified axis and a translation along this axis (Figure 1C). The Heligeom webserver has been developed based on the PTools library [16], in which screw motions are calculated and stored in a compact implementation from the 4x4 rotation-translation matrix provided from a superposition procedure. The screw representation is particularly appropriate for managing helical structures such as filaments that result from the regular repetition of a given binding geometry of two protomers, which themselves could be proteins, protein domains, or more general macromolecular complexes. We note that helical geometry here is taken in its general sense, and thus includes both cyclic (no translation) and linear (no rotation) geometries.

The screw transformation in Heligeom is defined by the position P and direction Ω of a screw axis, a rotation θ (in degrees) around this axis and a translation $trans$ parallel to the axis (shown schematically in Figure 1). Global parameters describing the helix or ring shape, i.e. the pitch, the

number of monomers per turn (nb) and the direction of rotation (dir), are derived from the screw parameters as follows:

$$nb = 360^\circ/\theta$$

$$pitch = nb \times trans$$

$$dir = \begin{cases} R \text{ if } (\theta \times trans) > 0 \\ L \text{ if } (\theta \times trans) < 0 \end{cases}$$

To calculate screw parameters, Heligeom uses a method described by Angelidis [28]. In short, this method first calculates the axis unit vector as an invariant vector of the rotation-translation matrix. Then it calculates the translation as the scalar product of the axis unit vector and the translation vector encoded in the last column of the rotation-translation matrix. This enables computing the axis origin and the value of the rotation angle around the axis. Further details may be found in [28] and [9]. The Angelidis procedure is analytical, which confers high precision to these transformations.

2.2. Interface analysis

Typical Heligeom analysis of the geometry of the assembly requires one pair of interacting monomers or protomers, provided from either a PDB flat-format file that can be uploaded from the user's file system or obtained by providing the server with the appropriate `pbid`. Each monomer can be referenced either by its chain id alone or by specifying the chain and a range of residue ids. Heligeom handles cases of incomplete coordinates within the provided residue ranges in the PDB data by using only the common residues in the two monomers for analysis. The resulting list of contacts between the interacting monomers can be downloaded by the user.

If two interfaces are provided, then in addition to returning both sets of helical parameters the server calls other PTools functionalities to compare them. For example, the `fnat` function provides f_{NAT} , the proportion of contacts in interface 1 that are present in interface 2, a measure of similarity commonly used to evaluate protein-protein docking predictions [29].

If the protein under consideration presents one or more flexible regions whose conformation varies from monomer to monomer, the analyses should be restricted to a "core" region that is structurally similar in the two monomers, ideally with a RMSD value no greater than 2Å. The core region can be defined by the user as a set of residue id ranges. An example will be given below.

2.3. Construction

Based on the user-provided binding geometry, the Heligeom webserver can construct regular structures of desired length (up to 100 protomers), in which the protomer that is replicated is the first monomer specified ("Monomer 1"). Note that if a core region has been specified (as discussed above and in the 4ESV example below), then the core selection defines the helical geometry of association, but, again, it is the monomer specification that defines the protomer to be replicated in the construction. In this way it is possible to break free from structural deviations that are often encountered in loops, linkers or mobile domains, while retaining them in the construction to visualize potential clashes or interactions. This functionality may also be used to decorate the constructed filament with ligands, so long as they have the same chain id as monomer 1.

The resulting assembly may be downloaded in the traditional PDB format or as a mmCIF file— the latter format allows unique chain ids in assemblies with more than 62 protomers. For convenience,

the Heligeom server can be requested to align the helix axis of the generated complex with the Z-axis.

2.4. Targeted Adjustment

In our experience a common situation in supramolecular modelling consists of adjusting an experimental or a predicted helical assembly having a small pitch and a number of monomers per turn close to an integer N to attain to a ring structure, with zero pitch and precisely N monomers per turn. Heligeom assists in performing this task using the method described in [9]. In short, after calculating the screw parameters corresponding to two interacting subunits, the helix-to-ring adjustment process consists in slightly re-positioning and re-orienting the first subunit with respect to the screw axis, which is kept fixed, in such a way that the interaction energy between the subunit 1 and its image subunit in the plane perpendicular to the axis, obtained via rotation of $2\pi/N$ around the axis, is acceptable. Initial radial positioning, with respect to the axis, of the first subunit center of mass is evaluated using simple geometrical considerations. Subsequently, concerted moves consisting of radial translations and rotations around their centers of mass of the two interacting subunits, considered as rigid bodies, are accepted or rejected based on a Metropolis Monte Carlo criterion (the move is attempted only if the f_{NAT} value is greater than 0.3). The process uses a reduced representation of the proteins [30], which enables decreasing the sensitivity to side-chain conformational variability at the interface.

The code of Heligeom webserver, together with documentation and installation, can be found at https://github.com/ptools/heligeom_webserver, licensed under the GNU General Public License.

3. Application examples

The primary use of Heligeom is to easily and precisely display the helical parameters that correspond to a given binding geometry. Of particular interest are the axis direction and position, which are often difficult to extract from the structure of oligomeric helical assemblies with a non integer number of turns.

3.1. Analyzing oligomeric assemblies

The example provided on the website features two monomers of the glutamine synthetase, PDB code 2GLS, chains A and B, which are loaded from the Protein Data Bank. Clicking on the “Analyze” button readily shows that the structure is a hexameric ring structure, with pitch of 0 Å and exactly 6 monomers per turn. Additionally, values for the screw parameters and the inner and outer radius of the assembly are displayed on the screen (see Figure 1A for an example of analysis). The user can also download a detailed list of atomic contact pairs across the interface.

As a second example, we successively analyzed pairs of adjacent monomers from a short nucleoprotein filament (5 monomers) consisting of the RecA protein assembled on DNA (PDB code 3CMW)[31]. Here, because the proteins were engineered and covalently linked in order to obtain a crystal, the structure consists of a unique chain (labelled A) and the residues are numbered from 37 to 333 for monomer 1, 1001 to 1333 for monomer 2, up to 4001 to 4328 for monomer 5. Table 1 displays the helical parameters that were obtained when successively analyzing pairs of adjacent monomers. Small variations found in the local (pitch, nb) values reflect small variations in the binding geometries. As could be expected, the variations are higher at the helix extremities.

Monomers	Pitch	Nb	Handedness	Residue Range
1-2	98.95	6.26	R	(1–333) - (1001–1333)
2-3	95.54	6.09	R	(1001–1333) - (2001–2333)
3-4	96.03	6.13	R	(2001–2333) - (3001–3333)
4-5	90.02	6.17	R	(3001–3333) - (4001–4333)

Table 1: Heligeom analysis of a small RecA filament, PDB code 3CMW. The first column shows the numbers of the two bound monomers. The last column displays the residue ranges that was used for referencing each monomer for analysis; note that missing residues in the PDB file for monomer 1 (residues 1-36) and monomer 5 (residues 4329-4333) are handled automatically by the Heligeom server.

3.2. Constructing oligomers with flexible regions

In the following example, we illustrate construction of oligomers of the DnaB protein, which contains two domains separated by a linker. In the spiral 6-protein assembly structure with PDB code 4ESV [32], the two domains are assembled as two stacked helices; however the assembly organization for the C-terminal domain differs from that for the small N-terminal domain— a type of modular organization that is common in ring motors. Notably, while the larger C-terminal domain assembles in a regular head-to-tail fashion spiraling around the helix axis, the N-terminal domains alternatively interact head-to-head or tail-to-tail. Heligeom analysis of the entire protein therefore produces completely different results depending on the set of protein-protein interfaces submitted for analysis: using whole chains B and C leads to a 14-mer helix with a 70 Å pitch, whereas construction based on chains C and D produces a tetrameric assembly with a pitch of only 13 Å (Figure 1D). The reason for this discrepancy can be understood by considering the nearly 16 Å RMSD value highlighted in red on the Heligeom output screen (not shown): when successive monomers are taken as a whole, the superposition of monomer 1 onto monomer 2, needed to derive the helical parameters, is unreliable due to the large structural deviations within the monomers.

This situation illustrates the need for defining a “core” region in the case of flexible monomers. If one defines the core region as the C-terminal domains (residues 184 to 365), then analysis and construction using either chains B and C or chains C and D leads to the same spiral arrangement (Figure 1E, left), suggesting that these interfaces are likely to be the pertinent ones for defining the morphology seen in the crystal structure.

3.3. Interface comparison

Another useful functionality of the Heligeom webserver is to compare interfaces. This analysis could be carried out for similar interfaces, such as those seen in 3CMW above. But oligomers do not always assemble according to a single binding geometry. Filamentous assemblies or rings, with their sequential interface organization, can host different binding geometries (assembly modes), as was discussed when considering ATP or ADP-forms of a given monomer. Also, there are many examples where oligomers built from the same components self-assemble in different regular forms, for example rings and spirals, under different conditions.

Comparing the interface similarity permits evaluating whether different binding geometries are easily interconvertible, or if the transition from one to another may require disassembling and reassembling the oligomer. In the Heligeom webserver, interfaces can be readily visualized in the graphical representation of the constructed oligomer, and their composition in terms of contacting

Results

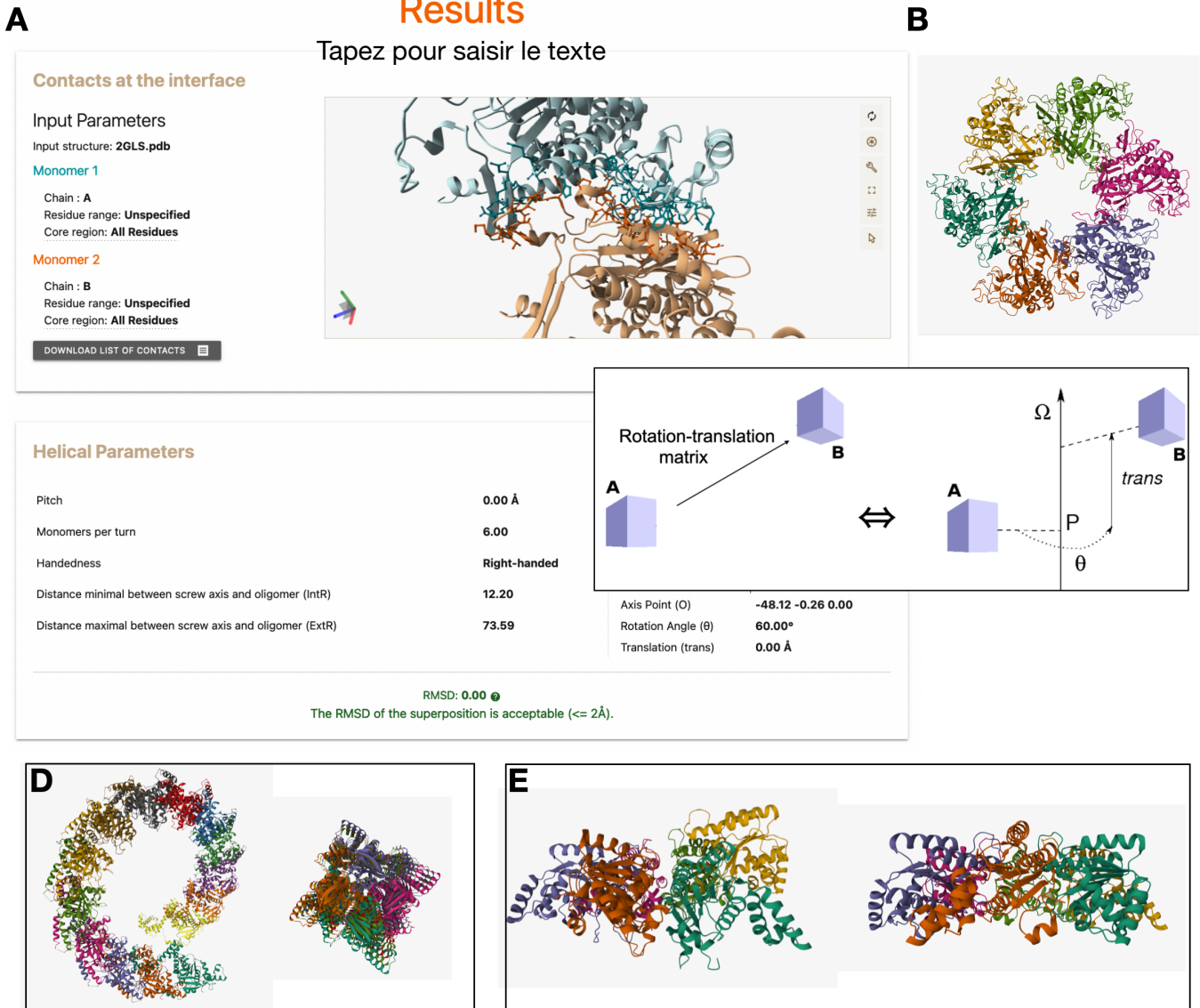


Figure 1: Heligeom analysis and construction output. (A) Screenshot of Heligeom output analysis for chains A and B of the structure with pdbid 2GLS; (B) Graphical output of the construction functionality for 2GLS, 6 monomers; (C) definition of the screw transformation of angle θ and translation *trans* around the (P, Ω) axis from rigid body A to rigid body B; (D) heligeom output for DnaB, pdbid 4ESV, when using either chains B and C (left, $pitch=70.4\text{\AA}$, $nb=13.9$) or chains C and D (right, $pitch=13.0\text{\AA}$, $nb=4$); (E) Heligeom output for DnaB, pdbid 4ESV, when restricting the analysis to the C-terminal domain residues 184-365: the structure represents an hexamer obtained from chains B and C, before (left, $pitch=38\text{\AA}$) and after (right, $pitch=0.$) helix to ring adjustment. Graphical molecular representations are integrated into Heligeom using Mol* [27].

residues can be issued as an output file for exhaustive comparison. In addition, a good indicator for similarity is the fraction f_{NAT} of pairs of interacting residues (one from each monomer) in one interface that are also present in the other interface. If the f_{NAT} value is higher than 0.5, only half of the interface interactions will need to be broken and reformed to go from one interface to the other. A value of 0.5 is commonly accepted as a threshold for distinguishing similar from dissimilar interfaces [29,33].

Here we consider an irregular hexameric ring structure of the Rho transcription termination factor, which represents an intermediate state during the ATP hydrolysis cycle that takes place within this ring (PDB code 3ICE). If we simultaneously upload two sets of successive subunits in the ring to the Heligeom webserver, the corresponding f_{NAT} value is provided as output, together with the

individual Heligeom analysis of each interface. Examination of the crossed f_{NAT} values between the six interfaces (Table 2) reveals the position where ATP hydrolysis takes place, corresponding to the interface between chains E and F, where the f_{NAT} value falls below 0.5. The value remains however close to 0.5, suggesting that the cost of recovering the initial interface when ATP hydrolysis propagates further around the ring will not be very high.

Interface	AB	BC	CD	DE	EF	FA
AB	1.00	0.85	0.86	0.82	0.44	0.67
BC		1.00	0.90	0.85	0.45	0.63
CD			1.00	0.88	0.44	0.65
DE				1.00	0.42	0.60
EF					1.00	0.70
FA						1.00

Table 2: Cross-comparison of the six interfaces present in the crystal structure of the Rho transcription termination factor, PDB code 3ICE, in terms of f_{NAT} values. The values were obtained by systematically comparing all pairs of interfaces.

3.4. Tailoring oligomeric assemblies: from spiral to ring

In the general case, regularly assembling macromolecular subunits leads to helical architectures: cyclic assemblies are but specific cases of screw assemblies. Therefore, the odds that a predicted geometry for the assembly of two copies of a protein will correspond to a helix rather than a ring are high. Determining the structure of regular cyclic assemblies within integrative modeling pipelines can reasonably start with the prediction of the interface geometry, which can be obtained using docking methods among which recent deep-learning methods such as AlphaFold [34] produce increasingly reliable results.

The Heligeom webserver offers the possibility to “flatten” helices, i.e. to generate a cyclic assembly starting from a pair of interacting subunits that Heligeom indicates would form a helix with a low pitch value and a nearly integral number of monomers per turn. The cyclic geometry is obtained employing rigid-body subunit moves in a Monte Carlo approach, exploiting a coarse-grained protein-protein interaction energy [30] implemented in PTools.

The helix flattening function was successfully used in recent integrative modeling studies [9,18,35]. In Figure 1E, we illustrate the use of this functionality to produce a cyclic arrangement of the C-terminal domains in the DnaB structure 4ESV, starting from the spiral arrangement found in the crystal structure. In the ring structure shown in Figure 1E, right panel, the individual proteins have been displaced by 4Å with respect to their initial position/orientation shown in the left panel and the interfaces retain 93% of their initial contacts ($f_{\text{NAT}} = 0.93$).

Helix flattening by the Heligeom webserver can also be used to investigate transitions between cyclic and helical assemblies, examples of which have been documented in the literature for example in cyclic motor assemblies [11,32,36].

4. Conclusions

With the capacities described here, the Heligeom server should provide a helpful companion to the study and integrative modelling of large-scale assemblies. With it, a researcher may analyze and visualize assembly patterns seen in structural data for local monomer-monomer interactions and use them to understand and explore the morphology of larger assemblies as well as sources of their potential variability and plasticity. Such explorations may be carried out directly on the server, without having to pass through a programming library, although the open-source nature of the PTools library, written in Python, of course allows this possibility for more detailed applications.

Credit author statement

Hubert Santuz: Software, Methodology, Data curation, Writing - Review & editing. **Benoist Laurent:** Software, Methodology, Data curation. **Charles H. Robert:** Software, Methodology, Data curation, Investigation, Project administration, Conceptualization, Writing - Original draft, review & editing. **Chantal Prévost:** Methodology, Investigation, Conceptualization, Project administration, Writing - Original draft, review & editing.

Data and Code availability

The source code of the Heligeom webserver is available at https://github.com/ptools/heligeom_webserver/ and is archived in Software Heritage ([swh:1.dir:af308bc8009c2d889d6cd42c29198ecb50e7fd25](https://swh.1.dir:af308bc8009c2d889d6cd42c29198ecb50e7fd25)). The source code of the PTools library used by the webserver is also available at <https://github.com/ptools/ptools>.

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