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► **To cite this version:**

M. Trellet, Nicolas Férey, M. Baaden, P. Bourdot. Content-guided Navigation in Multimeric Molecular Complexes. BIOIMAGING 2014 - Proceedings of the International Conference on Bioimaging, ESEO, Angers, Loire Valley, France, 3-6 March, 2014, 2014, Angers, France. pp.76–81, 10.5220/0004914300760081 . hal-01498053

HAL Id: hal-01498053

<https://hal.science/hal-01498053>

Submitted on 5 Jan 2023

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Content-guided Navigation in Multimeric Molecular Complexes

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Keywords: Molecular Visualization, Constrained Navigation, Structural Biology.

Abstract: In the field of structural biology, molecular visualization is a critical step to study and understand 3D structures generated by experimental and theoretical techniques. Numerous programs are dedicated to the exploration and analysis of structures in 3 dimensions. However, very few of them offer navigation algorithms that deal in an intelligent way with the content they display and are adapted to the specific task to be performed. This observation is emphasized in the case of navigation in immersive environments where users are immersed in their molecular systems, without any spatial landmark to guide their exploration. Starting from this observation, we propose to take into account some geometrical features found in multimeric molecular complexes to provide the users with navigation guides during the exploration process. This can be achieved using the common symmetrical layout molecular complexes present. Beyond the biological meaning and importance that symmetric layouts have in proteins, they allow us to orient and guide the exploration of molecular complexes in an intelligent and meaningful manner. We present navigation paradigms based on the content and the intended task in the context of molecular visualization and exploration.

1 INTRODUCTION

Structural biology comprises several indispensable steps leading to the deciphering of molecular complexes. One of these steps is the visualization and exploration of molecular structures. Several techniques are able to generate accurate 3-dimensional structures of molecules. One can cite NMR spectroscopy and X-ray crystallography as well as molecular modelling programs as main sources of structural data. To fully understand the function and the role that structure plays in molecular assemblies, visualization is a mandatory step. Broadly used molecular visualization programs very efficiently display 3D structures of molecules. However, navigation paradigms to explore such 3D models remain undeveloped.

Here, we investigate other ways to render and interact with 3D models, aiming to put the scientist in the center of the exploration process, bringing the ensemble of the user's senses to focus on his task using multimodal rendering (Férey et al., 2009). Stereoscopic solutions as well as intuitive and natural ways to interact with a molecular system are

used in this purpose. Several works on the intake of such immersive environments for scientific visualization have been carried out (Van Dam et al. 2000). Numerous issues linked to the navigation in immersive environments were addressed along the last years (Christie et al. 2008) but rarely by taking into account both the content of the scene and the tasks that will be performed in it. This immersion goes together with perception issues. Several studies have been carried out to evaluate the impact of immersive techniques during the exploration of virtual scenes. When dealing with oriented and realistic environments, user comfort can be quite well managed. However, the exploration of abstract scientific data, where no implicit or explicit orientations exist, raises several issues with respect to the user experience and efficiency. Simple navigation tasks can be perturbed by a phenomenon called "cybersickness" (LaViola Jr 2000), significantly reducing the user comfort and his efficiency to perform a specific task in a virtual environment. This observation is emphasized in the context of interactive molecular simulations where users manipulate the 3D structures during a

simulation in progress (Dreher et al. 2013). Consequently, the need for alternative ways to navigate in virtual environments has been emphasized by Hanson et al. (Hanson et al. 1997) who cited several families of navigation paradigms significantly increasing the user experience.

Based on these observations, we designed new navigation paradigms with the aim to fill the gap between virtual and immersive environments and molecular visualization. To do so, we took into account the importance of geometry in structural biology. Indeed, it has been shown that most large 3D structures are constructed around specific symmetry layouts (Goodsell & Olson 2000). Symmetry is a spatial feature of these molecular complexes governing their architecture and stability, but furthermore it may play a significant role in the biological function. Our algorithm takes as input the symmetry of a multimeric complex and the geometrical transformation linking each symmetry-related monomer. This symmetry can be manually set up or automatically approximated. Automatic approaches may use principal component analysis to detect the main orientations of monomers or call upon specific software dedicated to this analysis (Kim et al. 2010). Such information is sufficient to provide a spatial basis to orient the virtual world for exploration. Through the symmetric nature of molecular complexes and by identifying the tasks a scientist would have to perform in molecular exploration, we will setup several navigation paradigms aiming to improve the user experience and efficiency.

2 CONTENT FORMALISATION IN STRUCTURAL BIOLOGY

Development of camera models has to take into account both the constraints linked to the visualization in immersive conditions and the navigation possibilities extractable from the molecular complexes of interest.

The notion of symmetry is of first importance in structural biology. As soon as a complex is formed of more than two identical chains, a symmetric configuration has significant chances to intervene in the structuration of the monomers. These particular layouts, found in large molecular complexes, play a crucial role in most of the biological functions accomplished by these structures. They are involved in complex stability but sometimes also in the primary function of the complex itself. As a

particular example we chose the GLIC ion channel, one of many transmembrane proteins that present a pore where ions will pass through to transmit electrical signals of a cell (Figure 1A). Most of the times, this pore will coincide with the exact symmetry axis of the protein. Each monomer of the complex will present a symmetric transformation to fit another monomer. Several other types of symmetries can be found among molecular complexes and we listed two of them in Figure 1B and C. Each of these symmetries can be used as a basis for a navigation system, providing a first step to orient the complex. Any orientation of an abstract element in a virtual scene provides a new spatial landmark for the user and allows reducing the discomfort that could appear when dealing with such large and non-oriented structures.

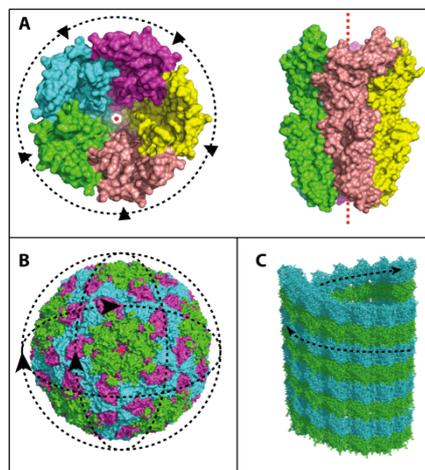


Figure 1: Several types of symmetries found in molecular complexes. (A) GLIC, transmembrane protein composed of 5 elements with a single symmetry axis. On the left, top view of the protein, on the right, transversal view. (B) Virus capsid with two types of components presenting a symmetry center overlaying the gravity center of the virus. (C) Tubulins tangle shaping a microtubule with a screw-like symmetry.

We already cited the axial symmetry and it is one of the most represented symmetries among large molecular complexes. The ensemble of monomers is often organized in a circular manner around the symmetry axis that is coincident with the pore of the protein (Figure 1A).

Viruses present an important number of different symmetries, most of them central but for which angles and distances of rotation are very variable and give rise to an important list of possible structures (Figure 1B).

Molecular complexes presenting important structural roles in the cell often adopt so-called “helical” symmetries (Figure 1C). The transformation to pass from one monomer to another can be associated to a screw-like movement. We can take the example of microtubules that are constituted of hundreds of subunits called tubulin and arranged with respect to each other in a helical way. Microtubules are part of the cell skeleton and are involved in maintaining the structure of the cell.

Despite their importance in the cell and the numerous functions that we just cited in a non-exhaustive manner, very few algorithms are dedicated to the identification of symmetry axes or centres in molecular complexes. Among them, only SymD (Kim et al. 2010) is available online and can be applied on a structural complex from a PDB structure. SymD is based on a fitting and permutation of monomers algorithm to identify the symmetries. In spite of its relative efficiency, SymD cannot deal with structures of more than 10 000 atoms and misses most of the large complexes with the most remarkable symmetries. Moreover, the program outputs only symmetry axes, whereas several structures rather present centres of symmetry. Symmetries being the starting point for the design of navigation guides that will be described, the automatic detection of these geometric features have been developed by our team but will not enter in the scope of this study.

3 USERS’ NEEDS IN STRUCTURAL BIOLOGY

3.1 Context support

Visualisation of molecular complexes has been brought to everyone’s hands thanks to numerous programs such as PyMol (DeLano 2002) or VMD (Humphrey et al. 1996). As a first step to assess navigation paradigms we chose to develop a PyMol plugin based on the python language, using the API available for this program. PyMol was chosen because it is recognized as broadly used software in the structural biology community and could thus be easily evaluated by scientists in this field. Our developments are, however, completely independent of the visualization software used and we expect to port the paradigm on a large-scale visualization platform very soon. A short-term use case will see the integration of our paradigm in the specific and emergent case of visual analytics. This development

will take place in an immersive context represented by a CAVE-like system. Together, the immersion and visual analytics features highlight the need for proper algorithms addressing specific navigation tasks that we listed in a non-exhaustive way in the following section.

3.2 Navigation tasks

The first steps of complex visualisation take place through the external exploration of the overall shape of a molecular assembly. These steps require a distant position of the camera as well as a specific orientation of the complex for the user. This orientation will be fixed during the whole exploration process and any movements of the camera will be made to avoid that the user loses this orientation setup with respect to the complex.

It is particularly difficult to precisely visualise a specific region, repeated along the different monomers of a complex. Navigation without constraints renders the quick and uniform observation of these regions very difficult to achieve. The movements to reach these regions involve quick and precise motions to be performed in order to simultaneously keep some spatial landmarks and find the good point of view in the middle of thousands of particles. The feeling to jump from one monomer to the other in a smooth and quite instantaneous way is particularly interesting in the aim to compare binding sites or dynamic structures involved in complex stability. Selection of similar and repeated regions of complex monomers allows the extraction of atoms as graphic objects used to perform certain standard geometrical analyses such as Root Mean Square Deviation (RMSD) calculation. Several other comparisons like the number of bonds among a region, the size of accessible binding pockets or the distances between atoms or groups of atoms are additional elements used to study a complex.

On top of the sequential navigation along the monomer, we cannot dissociate the importance of the point of view a user will adopt to analyse the region of interest. This is particularly true in the case of regions completely embedded and hardly accessible in the structure. We can then add an algorithm to compute the best point of view from a user position toward an interesting region.

As indicated for the GLIC example, some molecular structures present unique internal arrangements that participate to their function. These functions may comprise passage of water molecules or ions being exchanged between the inside and the outside of a cell membrane through a pore that also

plays the role of the symmetry axis around which the different monomers constituting the transmembrane protein stand. Pores are then particular structural arrangements where many biological events such as permeation, gating and desensitization occur and are therefore of first importance for scientists. They are interesting to visualize but not so easy to reach and follow because they are buried deep within the protein. We setup the possibility to easily anchor the camera to the entrance or exit of these biological “corridors” to let the user explore them via specific navigation paths.

Proteins are hierarchically structured in tertiary and quaternary structures that obey specific rules, providing geometrical patterns that are useful to guide the exploration of their shape. In this exploration, we chose to use the metaphor of the rollercoaster to minimize the interaction with the user. In this setup, the user only controls the speed and direction of motion (forward or backward) but neither the path nor the orientation.

4 CAMERA MODEL

Our camera model must address the different requirements listed above in order to be pertinent for the scientists. This will be achieved through putatively coupled navigation modes that we will describe now.

4.1 Navigation modes

When a centre or axis of symmetry is detected, the molecular system is re-oriented to have its symmetry axis merged with the $\{0, 1, 0\}$ axis of the $\{x, y, z\}$ orthonormal reference frame. A translation is applied to merge the basis of the complex with the origin of the coordinate system.

In a first, simple mode of navigation that we call “simple exploration”, the camera is oriented so that it always faces either the centre of symmetry or the centre of the symmetry axis while it is located at the complex level (Figure 2, area B). In the external areas (Figure 2, areas A), the camera *up* vector follows the global vector model (Khan et al. 2005) that keeps it fixed parallel to the symmetry axis if existing or fixed in a way to keep the user head at the same orientation with respect to the molecular system. Movements along the 3 dimensions are made in the same way, via the interaction with a unique button associated to each $\{x, y, z\}$ direction. A translation along the camera *forward* vector will create a “zoom-in”/“zoom-out” effect.

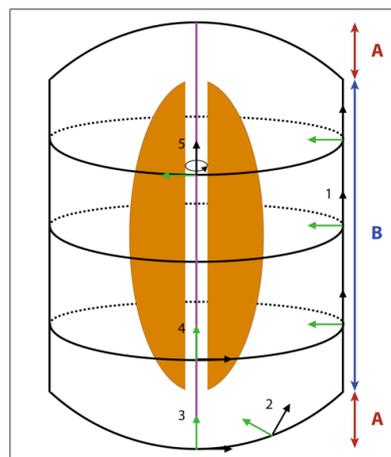


Figure 2: Schematic view of navigation paths and camera orientations with a symmetry axis (purple). The molecular complex is coloured in orange, areas A are outside the structure whereas area B encompasses the ensemble of the structure along the y axis. Each example of a camera position is associated to a number from 1 to 5. The camera *forward* vector is shown in green and the camera *up* vector in black.

A right translation will perform a turn around the structure while keeping the same distance between the camera and the symmetry centre. The user will have the possibility to go up and down along an axis parallel to the symmetry axis in area B (Figure 2, position 1) but will fly over the top or base of the complex when in areas A (Figure 2, position 2). During the hovering of one of the complex extremities, the camera *forward* vector will be focused on the closest complex extremity.

At the intersection between the hovering trajectory and a symmetry axis, a new mode of navigation can be activated and will offer the possibility to navigation along the symmetry axis (Figure 2, position 3). In this mode, the camera *up* vector will be kept in the same direction that it was when the user was flying over the structure to avoid any navigation issues in terms of orientation losses.

When the user is inside the complex, along the symmetry axis, the user has the choice to change the navigation mode for a free 360-turn around a specific position (Figure 2, position 5). In this mode, the camera *forward* vector will not be confounded with the symmetry axis anymore but will be perpendicular to it. The camera *up* vector will be along the axis and the user will have the possibility to look in every direction from his position. The movement might be associated to the one of a panoramic elevator allowing the exploration of the internal structure of a protein.

To answer the basic needs of the field experts, the possibility to target a specific region of a monomer can be split into 4 successive steps:

1. Constrained navigation as illustrated in Figure 2 to face the interesting region.
2. Selection of the interesting area and best point of view computing.
3. Memorisation of the point-of-view information in terms of camera parameters.
4. Jump to the following monomer thanks to the symmetry information.

4.2 Accessibility computing

The previous navigation mode includes a search for an optimal point-of-view relative to an interesting area pointed by the user. This algorithm operates in the following way: Starting with the center of an area identified by the user, a sphere is created around this point with a radius matching a configurable distance between the camera and the target. From each element of the sphere surface, a ray is cast toward the target. If a ray crosses a cell of the grid with an atom in it, the grid element corresponding to a surface starting point is considered as occulted.

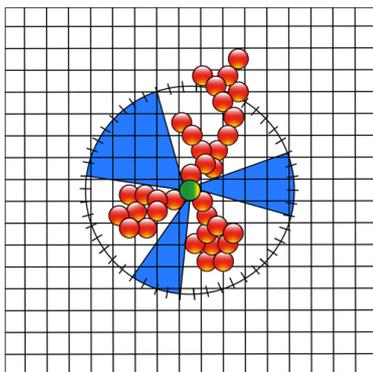


Figure 3: Grid splitting of the region surrounding an atom of interest (green). Each neighbouring atom (red) constitutes an occlusion for the camera view. The optimal point-of-view cones are represented in blue.

At the end, each element of the surface is associated to a 2D table and we extract the area with less occulted neighbors (Figure 3). The centers of these areas, once re-transformed into 3D coordinates, yield the observation points with the least occultations to observe the target. The user is then able to choose among the optimal points of view calculated by modifying the position and the orientation of the camera.

This accessibility grid can also be used to follow the shape of protein surfaces or membranes. In this mode, the camera *up* vector is aligned onto the surface normal and any movement can be associated to navigation on a ground where the user is limited to 2 dimensional control with a rotational degree of freedom around the camera *up* axis.

4.3 Structure manipulation

The algorithm of optimal point-of-view determination reaches some limits when we reach protein areas that are completely buried within the structure or located at the interface of two monomers. In these situations, accessibility is null and there is no simple algorithm to visualize these regions. Based on this observation, we went further in the use of the symmetric layout found in molecular structures. In order to put into light hardy accessible regions, we decided to manipulate the 3D structure of the investigated protein. The user is able to control the 3D modification to fit his wishes. Translational movements are applied to each monomer in order to separate them from each other and thereby free several regions that were previously hidden in the structure (Figure 4). This is very similar to exploded views used in technical drawings.

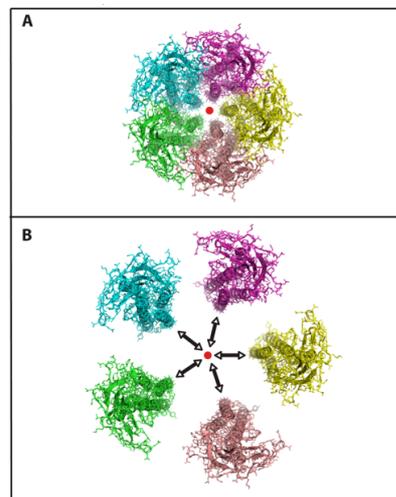


Figure 4: Top view of the GLIC protein. (A) Default layout of the different monomers. (B) Spreading of the different monomers by translation with respect to a vector linking the symmetry axis centre to each monomer centre of mass (exploded view).

By a simple interaction with a button or by letting the program compute the movement automatically according to the camera position we can move the

monomers apart along an axis starting from the symmetry centre/axis to the monomer centre of mass.

5 CONCLUSIONS

Immersion for molecular exploration provides an interesting dimension for the study of certain biological events. However, it also raises some navigation issues that can be easily extended to desktop environments. Without any specific navigation paradigm, the exploration of abstract and scientific data can easily lead to significant loss of spatial landmarks and hence hamper the user experience and efficiency. To tackle this problem, navigation guides can be setup. They are based on a common feature that many molecular assemblies share: a symmetric layout geometrically connecting monomers between them. Beyond the simple comfort of the user, the constraints extracted from any centre or axis of symmetry become useful tools for the execution of daily tasks in structural biology.

Next steps will be the evaluation of our paradigm by structural biology experts. We will base our assessments on the broadly accepted evaluation benchmark proposed by Bowman et al (Bowman et al. 1997). The criteria used to assess the navigation paradigms group, in a non-exhaustive way: the task execution speed, its accuracy, the user spatial awareness in the virtual scene during and after the experience, the comfort of the user, etc...

It is important to notice that our paradigms are completely independent of the navigation technique or the visualisation system used. Indeed, they can be applied from immersive environments like CAVE systems to desktop ones and with mouse/keyboard devices as well as 3D mice or tracking solutions (Chen et al. 2013). A navigation control can easily be substituted to one other while keeping a behaviour consistency of the camera defined as a function of the scene content.

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