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Dy-Bendix: Visual Analysis approach of α helices molecular dynamics simulations

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Abstract

α helices are one of the most common folding patterns found in proteins. They are of great importance in the context of molecular dynamics simulations, as they contribute to structural stability, conformational dynamics and molecular interactions, providing crucial information on protein behavior and function at the atomic scale. Here is presented Dy-Bendix (Dynamic Bendix), a novel representation of helices dynamics based on an intuitive helix geometry abstraction named Bendix. Indeed, in this work, we considered α helices fluctuation to quantify and represent the movement amplitude of α helices during the molecular dynamics. To do so, we used UnityMol, an open source molecular viewer and prototyping platform. We looked at the amplitude of movement of the residues that make up the helix during a simulation. These movement amplitudes are represented by a coloured heat map on the Bendix surface. This representation allows to detect instinctively helices with big movements and facilitate the comparison of helices movement using the heat-map color throughout the trajectory visualization. It also allows the visualization of the molecular dynamics in static image.

CCS Concepts

•***Computing methodologies*** → *Modeling methodologies; Computer graphics;* •***Applications*** → *Scientific visualization;*

1. Introduction

Structural biology studies the structure of macromolecules and the way they behave and fold. It also looks at the structural modifications that can affect the way they function. Proteins adopt a specific 3D structure (also called tertiary structure) that depends on their basic composition (primary structure) as well as their folding into secondary structures (α helices, β sheets and turns) [Pal19]. Visualising the structure of these molecules is essential in order to better understand how they perform their functions.

In this sens, we can find in the literature many visualization approaches that either depict the global structure of the molecule representing atoms and bonds, named atomistic representations, or represent some parts of the molecule structure with a specific shape due to chemical interactions that can't be easily seen in the atomistic models, named abstract models. Kozlíková *et al.* provided a review with more details about the existing representation modes [KKF*17].

Most of these approaches were first designed for static visualization and were later adapted for frame by frame visualization of molecular dynamics. Consequently, beyond the changing of the structures positions, they do not take these dynamics into account. In this work, we are interested in the visualization of α helices in the context of molecular dynamics simulations.

In fact, α helices play a crucial role in proteins as key structural components. They contribute to the stability of the protein's 3D structure during molecular dynamics simulation. Intramolecular interactions, such as hydrogen bonds and electrostatic interactions, maintain the α helix in its characteristic helical conformation. In addition, α helices can interact with other structural elements of the protein, such as beta-sheets and turns/loops. These interactions can be important for the overall stability and functional activity of the protein [Pal19].

α helices can undergo fluctuations and movements, which is important for understanding how the protein can change conformation and interact with other molecules in a biological environment. They can be also subjected to deformation, torsion and movement in response to changes in environmental conditions or interactions with other molecules. Analysis of these deformations and movements in the context of molecular dynamics simulations is essential for understanding the flexibility and plasticity of proteins as well as their interactions and conformation changes.

We present here, a graphic representation called Dy-Bendix that allows the visualization and the analysis of α helices in the context of molecular dynamics simulations. Dy-Bendix is based on Bendix [DCS12], an α helix representation, that quantifies the helix

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axis evolution over time. We studied the fluctuation of α helices by calculating the movement amplitude of the residues that constitutes them. This allows to compare α helices and detect big fluctuations.

This representation is developed under the molecular viewer and prototyping platform UnityMol [LTDS*13]. We describe in following, the Bendix α helix representation and the used approach to develop Bendix on UnityMol. After that we detailed the Dy-Bendix representation, the general principles, the developed algorithms, then we present some results we discuss and finally a conclusion.

2. Bendix representation

Bendix is a graphic representation of helices. It was developed by Dahl *et al.* [DCS12] as VMD (Visual Molecular Dynamics) [WH96] plugin. Bendix visualises helices as cylinders that follow the helix axis, and quantifies helix distortion. It uses a sliding window of four residues and a vector algebra of their α carbons, to give local helix axes that are joined by a spline. This window slides along the length of the helix in steps of one α carbon. The used algorithm generates a helix axis that is three residues short of the original helix length; one at the N-terminus and two at the C-terminus (i.e. the N-terminus and the C-terminus refer to the two ends of a polypeptide chain [Pal19]). To remedy this, Bendix computes the local helix vector at the ends of the helix, and extends the helix by one residue's worth in each direction. Bendix uses the Catmull-Rom [CR74] to calculate the helix axis curve. The generated curve by the spline algorithm is only between the middle-most coordinates in the 4-point window. Thus, spline application shortens the helix length. To counter this issue, Bendix generates Phantom knots, artificial helix axis extensions, prior to spline-calculation to preserve the helix axis length.

Helix geometry data are visualised, the angle along the helix is computed and displayed using visual analytics, directly onto the helix area in question, using heatmap colour-coding. This is facilitated by the helix abstraction of Bendix, which follows the helix axis. The angle along the helix axis is evaluated using a triangle with side length equal to the spline control point interval. The unit for angle side length is therefore number of α carbons. Angle-values for helix ends can not be evaluated for axis points that are located less than one angle side's distance from a helix end. Instead, the nearest angle that it is possible to compute is evaluated, and angle measurements along helix ends are made to decrease linearly to 0 at the tip.

3. Proposed approach

To develop our representation, we used UnityMol [LTDS*13], a molecular viewer and prototyping platform that allows easy development of new molecular representations. This is thanks to its structure and the use of the Unity game engine [Uni05], which is known for its versatility and user-friendly interface, making it quick and easy to develop visualisation approaches. We present here the development of Bendix on UnityMol, then the novel feature Dy-Bendix we introduce to the Bendix representation to visualise the fluctuation of helices during a molecular dynamics simulation.

Smoothness: 0.50
Metallic: 0.00
Alpha: 0.80
Tube size: 2
Turn resolution: 4
Resolution: 16
Splines: 16

Frequency 15
Stride 3
Smoothness: 0.50
Metallic: 0.00
Alpha: 0.80
Tube size: 2
Turn resolution: 4

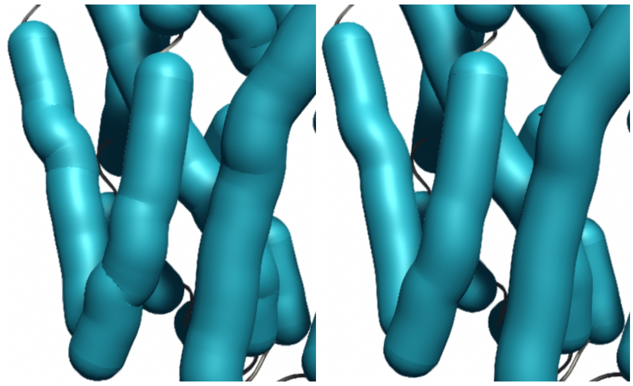
(a) (b)

Figure 1: Dy-Bendix user interface on UnityMol. a) Bendix parameters. b) Dy-Bendix specificity configuration.

3.1. Bendix in UnityMol

To develop Bendix on UnityMol, we used the Unity C# Job System [Uni21] which allows to write simple and safe multithreaded code that interacts with the Unity Engine to enhance the visualization performance. We've set up a user-friendly interface, with a number of user-configurable parameters (see Figure 1a). Indeed, the user can change the Bendices colors using the color picker or by choosing a coloring method (coloring by: chain, residues, hyperbolicity, residues types and the angular heat-map). He can also modify the smoothness, the metalic properties and the transparency of the visualization. The user can modify the Bendices diameter through the "Tube size" slider. The "Turn resolution" slider allows to configure a stride to reduce the number of the helices axis points. The "Splines" slider configures the number of spline points between two axis points. Finally, the "Resolution" slider increases and/or decreases the number of vertices. We developed Bendix using the Catmull-Rom [CR74] algorithm to calculate the axis curve, which gives the helices a wrinkled visual appearance (see Figure 2a). However the visual appearance improves when one point in four of the helix axis is used (Turn resolution = 4). For smoother helices, we developed the Basic-Spline [DB76] algorithm instead of Catmull-Rom (see Figure 2b). The user can choose between the two algorithms.

We developed various Bendix coloring options, such as coloring by residues, by hyperbolicity, by chain..etc. Figure 3 shows some results of the lactose permease monomer, (PDB ID: 1pv7_B), Bendix visualization with different coloring options. The first image (Figure 3a) shows the helices hyperbolicity which can be important in determining the stability and function of proteins. The



(a) (b)

Figure 2: Zoom on the lactose permease visualization, (PDB ID: 1pv7), using Bendix mode. a) Shows the result with the Catmull-Rom algorithm and Turn Resolution = 1. b) Shows the result with the Basic-Spline algorithm and Turn Resolution = 1.

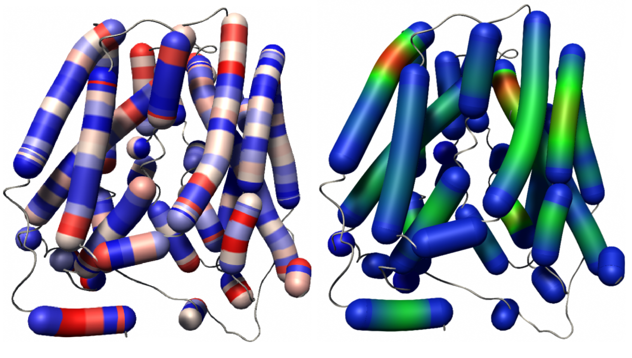
second image (Figure 3b) allows to see the heat-map coloring of the helices witch is calculated according to the local angle of the helices axes. The Bendix angular heat-map allows to study the helices flexibility during a molecular dynamic simulation. Indeed, α helices can undergo deformation, torsion and movement in response to changes in environmental conditions or interactions with other molecules. Analysis of these deformations and movements in the context of molecular dynamics simulations is essential for understanding the flexibility and plasticity of proteins.

3.2. Dynamic Bendix

Observing the fluctuation of the α helices communicates information on their stability and their potential interactions. We propose here a novel feature for Bendix representation, which integrates the time dimension in this α helices representation beyond the frame-by-frame approach. Indeed, we are interested in α helices fluctuation throughout the trajectory and the way to represent it. We are therefore looking for the movements of the residues throughout the trajectory. As the trajectory is read, we calculate the movement's amplitude for each residue belonging to the α helices over a sliding window, with a number of frames defined by the user. Indeed, for each frame read, we calculate the distance between the current position of an α carbon and its previous positions on the sliding window. The largest distance represents the movement amplitude of the residue. This calculation is performed for all residues belonging to an α helix.

To do this, we have added the "Frequency" parameter to the interface, which determines the size of the sliding window. In this way, we can calculate the amplitude of movement of the helix residues in this window. In order to reduce the calculation time, the user can define a "Stride" value, if this parameter is equal to two, for example, the algorithm will take into account every second frame of the sliding window (see Figure 1b).

Once the amplitudes of movement of the residues that make up the α helix have been calculated, we calculate the amplitude of movement of each point on the axis that makes up the helix. This corresponds, for each point on the axis, to the average of the amplitudes of the residues used to calculate it. These amplitude values are used to calculate the heat map. To do this, we chose the turbo map color, an improved rainbow color-map for visualization. It varies from blue to red through shades of green, yellow and orange. Once the movement's amplitude for each axis point is calculated, we assign it a color according to this value. Blue color indicates small movements whereas red color indicates large movements.



(a) (b)

Figure 3: Example of the lactose permease monomer, (PDB ID: 1pv7_B), with different Bendix visualization mode (Turn resolution = 4). a) Coloring by hyperbolicity b) Heat-map color according to the local angle of the helix axis.

To determine the colours corresponding to the amplitude values calculated, we need a reference value (a threshold) to define the big amplitude which would correspond to the red colour of our heat-map. To do so, we use the biggest value of the amplitudes calculated, on our sliding window, as the reference value, named "the local amplitude threshold". It allows us to determine the colours corresponding to the other calculated values. The use of the local amplitude threshold, allows to study the movement of the helices on the window defined beforehand. To make it easier to analyse and quantify the movement, we display on the user interface the value that corresponds to the biggest movement and the one that represents the smallest movement. (see Figure 1b).

Figure 4 shows the membrane transport protein, UT-B Urea, with the Dy-Bendix representation. In this image we can detect intuitively, the helices that make big movements. This representation allows us to compare helices easily. In addition, on a single image we have information related to dynamics. As the image was taken at frame 257, with a window of 40 frames, we can determine from this image the helices that fluctuate a lot over the previous 40 frames.

To allow the user to study the movement of the helices along the entire trajectory and not just over the defined sliding window, we propose the global amplitude threshold. For its calculation when reading the trajectory, we compare the local amplitude thresholds calculated each frame on the defined sliding window to determine the largest amplitude of motion over the entire trajectory. Figure 5 shows the membrane transport protein, UT-B Urea, with the Dy-

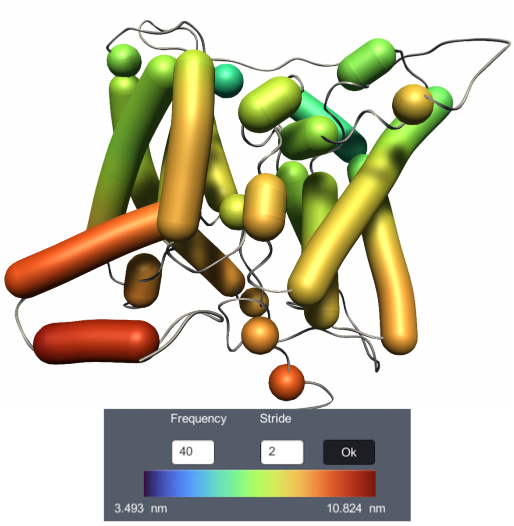

Frequency Stride
40 2 Ok

Figure 4: Visualization of membrane transport protein, UT-B Urea, dynamics, using the Dy-Bendix representation with local amplitude threshold = 10.824 nm. Frame = 257, Frequency = 40, Stride = 2. Turn resolution = 4.

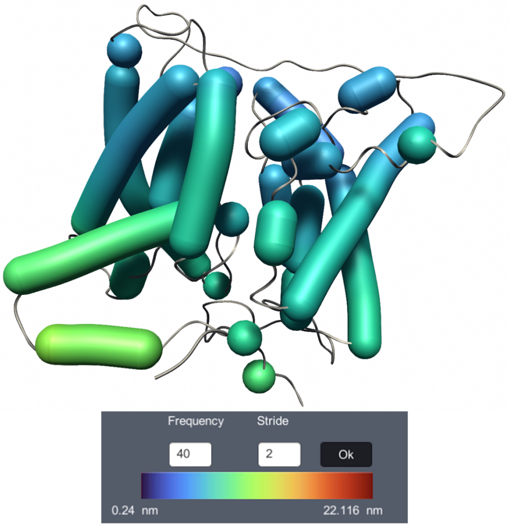

Frequency Stride
40 2 Ok

Figure 5: Visualization of membrane transport protein, UT-B Urea, dynamics, using the Dy-Bendix representation with the global amplitude threshold = 22.116 nm. Frame = 257, Frequency = 40, Stride = 2. Turn resolution = 4

Bendix representation using the global amplitude threshold calculated over the entire trajectory, i.e. 1350 frames, with the same parameters that we used for the local amplitude threshold. By comparing the two images (Figure 4 and 5) we can see that the hot parts (which move the most) remain the same, however the colour of the Figure 5 is cooler globally which means that the appreciation of the movement remains the same locally as globally, however the quantification of the movement is different. In fact, the local threshold can be considered less important on the overall trajectory.

4. Performance Metrics

In this paper, we present images from the Dy-Bendix visualization of a simulation of a membrane transport protein, UT-B Urea. The molecular system contains a total of 14177 atoms in 516 residues, of which 198 belong to α helices (i.e. 25 helices of different sizes). The used parameters are a turn resolution equals to 4 resulting in a total of 124 α helices axis points, 16 spline points between each two α helix axis point and a resolution equal to 16 which corresponds to the number of vertices around an axis point two draw a cylinder. These parameters provide over 25k vertices and 160k triangles for the helices representation. Depending on data size and machine performance, the user can modify the number of spline points and the resolution to reduce calculation time or increase visualization quality.

This work is developed in C#, under version 2019.4.26 of Unity 3D, using visual studio 2019. The computer performances consist in 8.00 GB of memory, the CPU is 11^{th} Gen Intel(R) Core(TM) i5-11400H @ 2.70GHz - 2.69 GHz and the graphic card is NVIDIA GeForce RTX 3050 Laptop GPU. The tests we carried out on the visualization of a membrane transport protein simulation resulted in graphics rendering that varied between 30 and 40 FPS, with a job processing time of 0.7ms to 1ms.

5. Conclusion

In this paper, we are interested in the representation of the α helices dynamics. Therefore, we propose Dy-Bendix visualization that provides new feature to the Bendix representation. Dy-Bendix, allows to visualize the α helices fluctuation during molecular dynamics.

We first developed the Bendix representation on UnityMol. This representation offers an intuitive helix geometry analysis and abstraction. The Bendix heat-map is based on the local angles of the helix axis. Visualizing this heat map in a molecular dynamics simulation enables study of helix flexibility. We have subsequently added some visualization options, such as hyperbolicity coloring and residue coloring, which can be useful when studying molecular simulations.

After that, we studied the fluctuation of the residues making up the helix, and applied a heat map to the bendix representation according to the movements amplitudes of residues. This is important for understanding how the protein can change conformation and interact with other molecules in a biological environment.

Dy-Bendix makes it easy to study the α helices fluctuation, to compare the helices with each other intuitively and to easily detect big movements which are a sign of a potential conformation change. The use of a local amplitude threshold makes it possible to study the helices movement on a preconfigured window. When using a global amplitude threshold, allows to analyze the movement of the helices over the entire trajectory.

Finally, Dy-Bendix allows you to visualize in a static image the fluctuation of helices during a molecular dynamics trajectory. Indeed, the colors of the heat-map make it possible to determine in a simple image, which helices are stable and which move a lot.

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