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

49 This representation is developed under the molecular viewer and
 50 prototyping platform UnityMol [LTDS*13]. We describe in follow-
 51 ing, the Bendix α helix representation and the used approach to de-
 52 velop Bendix on UnityMol. After that we detailed the Dy-Bendix
 53 representation, the general principles, the developed algorithms,
 54 then we present some results we discuss and finally a conclusion.

55 2. Bendix representation

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

75 Helix geometry data are visualised, the angle along the helix is
 76 computed and displayed using visual analytics, directly onto the
 77 helix area in question, using heatmap colour-coding. This is facil-
 78 itated by the helix abstraction of Bendix, which follows the helix
 79 axis. The angle along the helix axis is evaluated using a triangle
 80 with side length equal to the spline control point interval. The
 81 unit for angle side length is therefore number of α carbons. Angle-
 82 values for helix ends can not be evaluated for axis points that are
 83 located less than one angle side's distance from a helix end. Instead,
 84 the nearest angle that it is possible to compute is evaluated, and an-
 85 gles along helix ends are made to decrease linearly to
 86 0 at the tip.

87 3. Proposed approach

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



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

97 3.1. Bendix in UnityMol

98 To develop Bendix on UnityMol, we used the Unity C# Job Sys-
 99 tem [Uni21] which allows to write simple and safe multithreaded
 100 code that interacts with the Unity Engine to enhance the visual-
 101 ization performance. We've set up a user-friendly interface, with
 102 a number of user-configurable parameters (see Figure 1a). Indeed,
 103 the user can change the Bendices colors using the color picker or
 104 by choosing a coloring method (coloring by: chain, residues, hy-
 105 perbolicity, residues types and the angular heat-map). He can also
 106 modify the smoothness, the metallic properties and the transparency
 107 of the visualization. The user can modify the Bendices diameter
 108 through the "Tube size" slider. The "Turn resolution" slider allows
 109 to configure a stride to reduce the number of the helices axis points.
 110 The "Splines" slider configures the number of spline points be-
 111 tween two axis points. Finally, the "Resolution" slider increases
 112 and/or decreases the number of vertices. We developed Bendix us-
 113 ing the Catmull-Rom [CR74] algorithm to calculate the axis curve,
 114 which gives the helices a wrinkled visual appearance (see Fig-
 115 ure 2a). However the visual appearance improves when one point
 116 in four of the helix axis is used (Turn resolution = 4). For smoother
 117 helices, we developed the Basic-Spline [DB76] algorithm instead
 118 of Catmull-Rom (see Figure 2b). The user can choose between the
 119 two algorithms.

We developed various Bendix coloring options, such as color-
 ing 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 im-
 age (Figure 3a) shows the helices hyperbolicity which can be im-
 portant in determining the stability and function of proteins. The

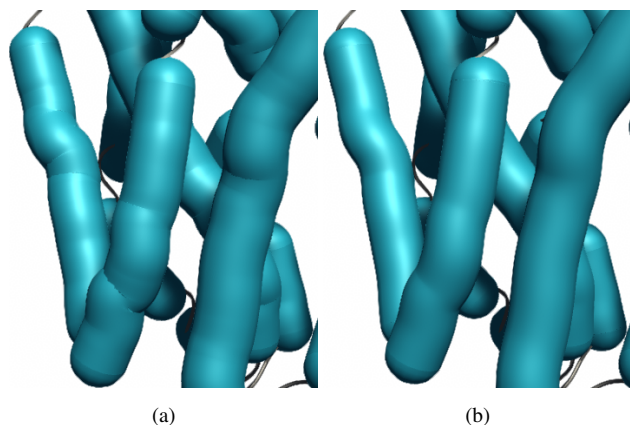


Figure 2: Zoom on the lactose permease visualization, (PDB ID: 1pv7), using Bendix mode. a) Shows the result with the Catmull-Rom algorithm and Turn Resolution = 1. b) Shows the result with the Basic-Spline algorithm and Turn Resolution = 1.

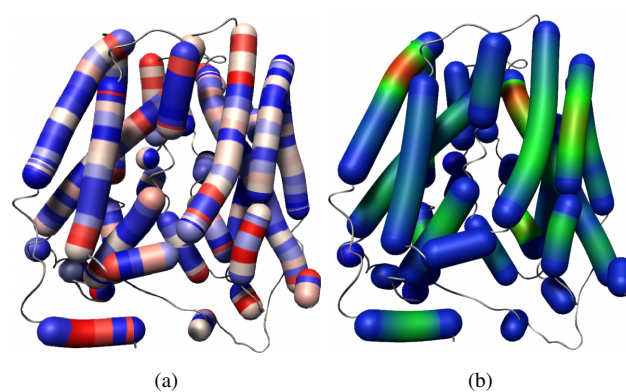


Figure 3: Example of the lactose permease monomer, (PDB ID: 1pv7_B), with different Bendix visualization mode (Turn resolution = 4). a) Coloring by hyperbolicity b) Heat-map color according to the local angle of the helix axis.

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

135 3.2. Dynamic Bendix

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

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

158 Once the amplitudes of movement of the residues that make up
 159 the α helix have been calculated, we calculate the amplitude of

160 movement of each point on the axis that makes up the helix. This
 161 corresponds, for each point on the axis, to the average of the ampli-
 162 tudes of the residues used to calculate it. These amplitude values are
 163 used to calculate the heat map. To do this, we chose the turbo map
 164 color, an improved rainbow color-map for visualization. It varies
 165 from blue to red through shades of green, yellow and orange. Once
 166 the movement's amplitude for each axis point is calculated, we as-
 167 sign it a color according to this value. Blue color indicates small
 168 movements whereas red color indicates large movements.

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

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

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

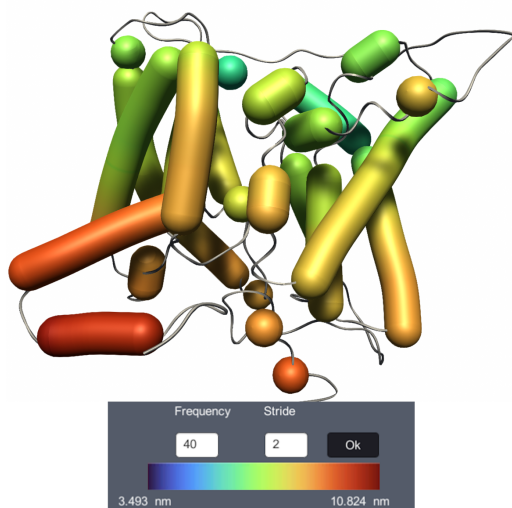


Figure 4: Visualization of membrane transport protein, UT-B Urea, dynamics, using the Dy-Bendix representation with local amplitude threshold = 10.824 nm. Frame = 257, Frequency = 40, Stride = 2. Turn resolution = 4.

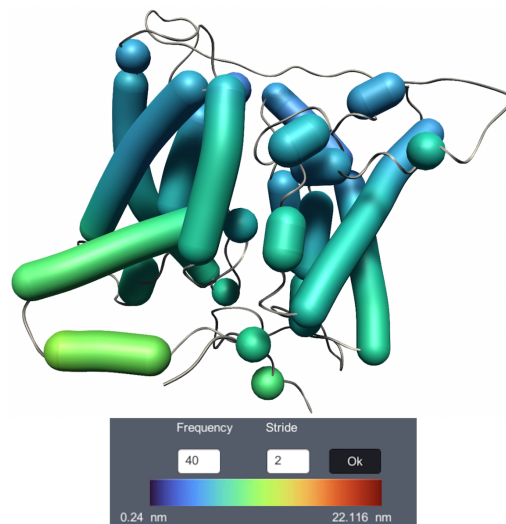


Figure 5: Visualization of membrane transport protein, UT-B Urea, dynamics, using the Dy-Bendix representation with the global amplitude threshold = 22.116 nm. Frame = 257, Frequency = 40, Stride = 2. Turn resolution = 4

196 Bendix representation using the global amplitude threshold
 197 calculated over the entire trajectory, i.e. 1350 frames, with the same param-
 198 eters that we used for the local amplitude threshold. By compar-
 199 ing the two images (Figure 4 and 5) we can see that the hot parts
 200 (which move the most) remain the same, however the colour of the
 201 Figure 5 is cooler globally which means that the appreciation of the
 202 movement remains the same locally as globally, however the quan-
 203 tification of the movement is different. In fact, the local threshold
 204 can be considered less important on the overall trajectory.

205 4. Performance Metrics

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

219 This work is developed in C#, under version 2019.4.26 of Unity
 220 3D, using visual studio 2019. The computer performances consist
 221 in 8.00 GB of memory, the CPU is 11th Gen Intel(R) Core(TM) i5-
 222 11400H @ 2.70GHz - 2.69 GHz and the graphic card is NVIDIA
 223 GeForce RTX 3050 Laptop GPU. The tests we carried out on the
 224 visualization of a membrane transport protein simulation resulted
 225 in graphics rendering that varied between 30 and 40 FPS, with a
 226 job processing time of 0.7ms to 1ms.

227 5. Conclusion

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

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

240 After that, we studied the fluctuation of the residues making up
 241 the helix, and applied a heat map to the bendix representation ac-
 242 cording to the movements amplitudes of residues. This is important
 243 for understanding how the protein can change conformation and in-
 244 teract with other molecules in a biological environment.

245 Dy-Bendix makes it easy to study the α helices fluctuation, to
 246 compare the helices with each other intuitively and to easily de-
 247 tect big movements which are a sign of a potential conformation
 248 change. The use of a local amplitude threshold makes it possible to
 249 study the helices movement on a preconfigured window. When us-
 250 ing a global amplitude threshold, allows to analyze the movement
 251 of the helices over the entire trajectory.

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

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