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Bendix: intuitive helix geometry analysis and abstraction

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ABSTRACT

Summary: The flexibility of α-helices is important for membrane protein function and calls for better visualization and analysis. Software is presented that quantifies and projects the helix axis evolution over time, with the choice of uniform or analytic heatmap graphics according to the local geometry. Bendix supports static, molecular dynamics, atomistic and coarse-grained input.

Availability and implementation: Bendix source code and documentation, including installation instructions, are freely available at http://sbcb.bioch.ox.ac.uk/Bendix. Bendix is written in Tcl as an extension to VMD and is supported by all major operating systems.

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1 INTRODUCTION

α-Helix flexibility enables membrane protein functionality such as receptor activation, molecule transport and channel gating (Sansom and Weinstein, 2000). Examples of this can be seen in the voltage-gated potassium channels and the MscS mechanosensitive channel, where molecular hinges within channel-lining helices elicit gating (Akitake *et al*., 2007; Jiang *et al*., 2002). In addition, helix curvature ensures structural integrity by allowing close packing (Ceruso and Weinstein, 2002).

The dynamics of transmembrane α-helices can be explored through molecular dynamics (MD) simulations, which is becoming an increasingly important tool to complement experimental structural studies (Stansfeld and Sansom, 2011). However, improved methods for analysis and visualization of helix dynamics are needed. Considerations of helix flexibility are also somewhat compromised by their classical representation as idealized cylinders. The prevalence and importance of kinked helices therefore calls for improved helix abstraction and intuitive analysis tools. Furthermore, it is important to make such developments available to the wider community by incorporation into existing, publicly adopted visualization software (Goddard and Ferrin, 2007). We have therefore developed Bendix, a program that meets these demands.

2 PROGRAM FEATURES

Bendix features custom helix representation and geometry indicative graphics that assist analysis of both static structures and complex molecular dynamics simulation trajectories. Bendix uses a sliding window of four residues to give local helix axes that are joined by a spline (Dalton *et al*., 2003).

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The example provided in Figure 1 for the membrane protein Mhp1 shows how Bendix can be used to reveal the role of helix flexibility in a complex transport mechanism (Shimamura *et al*., 2010). The graphed helix axis captures crucial conformational information that is lost in classical, straight cylinders, besides offering a concise alternative to the spiraling ribbon backbone. Analysis is performed on this axis to give local angles along the length of the helix versus time. This helix distortion distribution is visualized across residues by heatmap colour-coding according to local angle magnitude, which highlights non-linear helix behaviour. In the example of Mhp1, this feature exposes important changes in helix TM10 as Mhp1 adopts its different functional and structural states (Fig. 1A–C). 2D and 3D graphs of the evolution of maximal and local angles over time are provided (Fig. 1D and E), with the choice to export data to other software. In particular, Bendix enables ready comparison of helix distortions in multiple X-ray structures with those observed in MD simulations.

Bendix comes with a user-friendly graphical user interface with customizable settings, e.g. resolution, helix diameter, angle side length, helix assignment and choice of uniform or angle-indicative graphics. A full list of features, technical detail, examples and tutorials are provided at http://sbcb.bioch.ox.ac.uk/Bendix. Bendix is platform-independent and distributed as a plugin for the widely used and freely available molecular graphics software Visual Molecular Dynamics (VMD; http://www.ks.uiuc.edu/Research/vmd/) (Humphrey *et al*., 1996). In addition to the structure and trajectory file formats supported by VMD, Bendix offers secondary structure representation for coarse-grained protein simulations (Monticelli *et al*., 2008). As a VMD plugin, Bendix uses in-built features such as secondary structure prediction, rendering options and VMD's flexible syntax for selecting subsets of atoms for Bendix characterization. The broad visualization, animation and analysis capabilities of VMD remain available alongside Bendix.

3 CONTRAST TO SIMILAR TOOLS

There are a number of dedicated analysis software for static helix structures, e.g. HELANAL (Bansal *et al*., 2000), but support for analysis of helix dynamics over time is restricted to global descriptors of helix geometry [see e.g. TRAJELIX (Mezei and Filizola, 2006)]. This limits applicability and lacks geometric context. Bendix resolves these issues and provides numeric results that are accompanied by axis-based helix visualization. This resembles a representation that is implemented in YASARA (http://www.yasara.org/), but is functionalized in Bendix by geometry-indicative graphics and analysis.

As part of VMD, Bendix incorporates important features of existent helix analysis software and complements them with

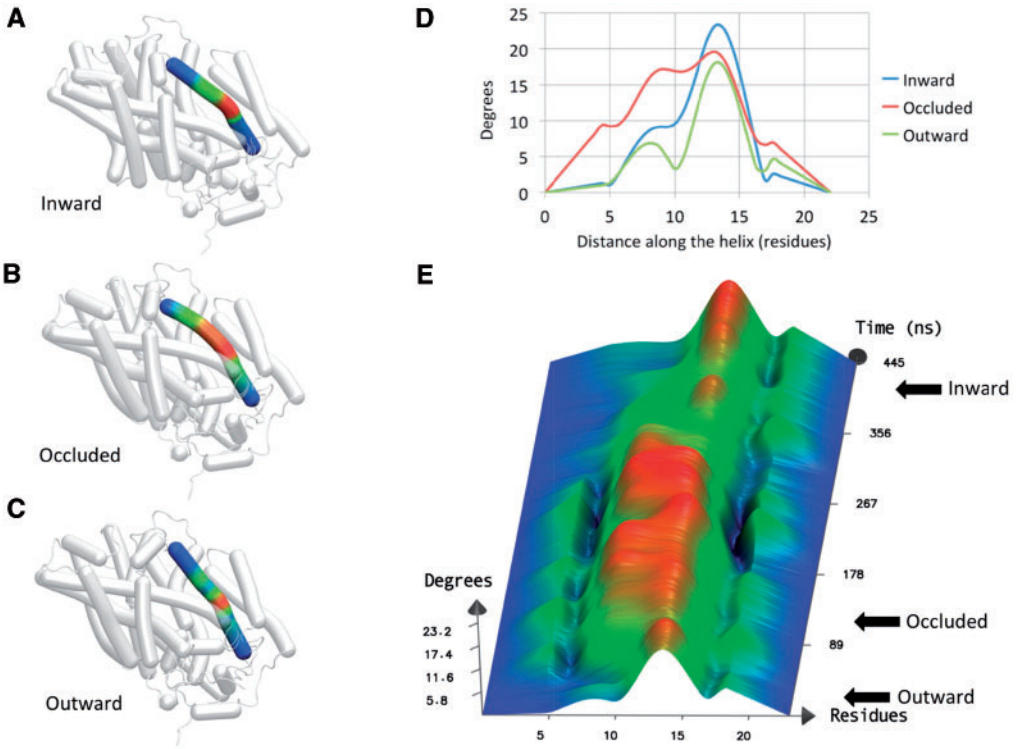

Fig. 1. Bendix analysis of the membrane transport protein Mhp1. (**A–C**) Crystal structures of Mhp1 (PDB ids 2X79, 2JLO and 2JLN), rendered in Bendix, showing the inward facing, occluded and outward facing conformations. The functional flexibility of helix TM10 is highlighted using angle-indictive heatmapping. (**D**) Helix curvature profiles along the length of TM10 for the three crystal structures of Mhp1. (**E**) Heatmap surface of the TM10 trajectory from an MD simulation of Mhp1, using GROMACS (van der Spoel *et al.*, 2005) as detailed in Shimamura *et al.* (2010). This shows the time evolution of the helix curvature profile of TM10, with the arrows signifying the times in the trajectory that best correspond to the three crystal structures

intuitive, real-time data visualization, a clear interface and extended data type support and user control.

4 CONCLUSION

Curved α-helices are prevalent in membrane protein structures, and their flexibility plays a key role in biological function. Despite this demonstrated importance, methods for helix motion analysis are limited. We have developed a new tool for analysis of helix conformational change. Thus, helix characterization in Bendix aids structure comprehension and allows interactive analysis, visualization and manipulation of both atomistic and coarse-grained simulations. Intuitive heatmap display of helix curvature at the point of interest allows the user to more readily detect potentially relevant helix distortions over time, thus aiding analysis of the relationship between structure, dynamic conformational changes and biological function.

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