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Applications Note

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Databases and ontologies

Cyclo-lib: a database of computational molecular dynamics simulations of cyclodextrins

Edgar Mixcoha[1,2,†], Roberto Rosende[1,†], Rebeca Garcia-Fandino[3] and Ángel Piñeiro[1,*]

[1]Soft Matter & Molecular Biophysics Group, Department of Applied Physics, Universidade de Santiago de Compostela, 15782 Santiago de Compostela, Spain, [2]CONACYT - Instituto Nacional de Psiquiatría Ramón de la Fuente Muñiz, 14370 Tlalpan, Distrito Federal, Mexico and [3]Centro Singular de Investigación en Química Biolóxica e Materiais Moleculares (CIQUS) and departamento de Química Orgánica, Universidade de Santiago de Compostela, 15782 Santiago de Compostela, Spain

*To whom correspondence should be addressed.
†The authors wish it to be known that, in their opinion, the first two authors should be regarded as Joint Authors.
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Abstract

Motivation: Cyclodextrins (CDs) are amongst the most versatile/multi-functional molecules used in molecular research and chemical applications. They are natural cyclic oligosaccharides typically employed to encapsulate hydrophobic groups in their central cavity. This allows solubilizing, protecting or reducing the toxicity of a large variety of different molecules including drugs, dyes and surfactant agents. In spite of their great potential, atomic level information of these molecules, which is key for their function, is really scarce. Computational Molecular Dynamics (MD) simulations have the potential to efficiently fill this gap, providing structural-dynamic information at atomic level in time scales ranging from ps to μs.

Results: Cyclo-lib is a database with a publicly accessible web-interface containing structural and dynamic analysis obtained from computational MD simulation trajectories (250 ns long) of native and modified CDs in explicit water molecules. Cyclo-lib currently includes 70 CDs typically employed for fundamental and industrial research. Tools for comparative analysis between different CDs, as well as to restrict the analysis to specific time-segments within the trajectories are also available. Cyclo-lib provides atomic resolution information aimed to complement experimental results performed with the same molecules.

Availability and Implementation: The database is freely available under http://cyclo-lib.mduse.com/.

Contact: Angel.Pineiro@usc.es

1 Introduction

Cyclodextrins (CDs) are cyclic oligosaccharides formed by 6 (α-CD), 7 (β-CD) or 8 (γ-CD) glucopyranoside groups (GPUs) that play a relevant role in different fields such as pharmacy, medicine, chemistry, materials design, food or agricultural science (Ain *et al.*, 2015). By taking advantage of the different accessibility and reactivity of the primary and secondary hydroxyl groups of the native (α, β, γ-)CDs, specifically designed chemical modifications allow their selective functionalization in order to affect their physicochemical and pharmaceutical properties (solubility, surface properties, complexation efficiency, control release, aggregation). New

and interesting perspectives for their use have emerged in recent years by the development of novel CD derivatives (Otero-Espinar *et al.*, 2014). Despite the increasing number of patents and articles based on CDs, only a tiny fraction of that literature contains atomic level structural/dynamic information and even less includes results from computational simulations. The development and optimization of applications using CDs has been traditionally based on trial and error essays supported by wet-lab experiments. While the pharmaceutical industry has successfully incorporated computational molecular modeling tools into the drug-design process, other chemical sectors where CDs are involved (textile, food, cosmetics, cleaning, painting, agriculture, etc.) have not extensively used this type of computational tools. It is worth noting that the chemical processes involved in all these industries, including the pharmaceutical, are similar.

In contrast to what is commonly assumed, it is known that CDs are not rigid (Dodziuk, 2002). Their flexibility is key in the way they interact to the surrounding molecules. Unlike other computational simulation methods, MD allows studying molecules in motion as well as to include the explicit interaction with the solvent and with other solutes, making the results more reliable.

Here, we present a web-based database with structural and dynamic analysis results obtained from computational MD simulation trajectories of native and modified CDs in explicit water molecules. Tools to easily compare the behaviour of different CDs obtained from the corresponding MD trajectories are included in Cyclo-lib. Due to their interesting physicochemical properties, there is a growing interest by the research community in using CDs for a number of applications based on their ability to encapsulate hydrophobic groups or to form nanoaggregates (Ryzhakov *et al.*, 2016). The lack of information about these molecules at atomic scale seriously limits the capacity of researches to rationally modify their structure and also to predict their behaviour at different levels. Cyclo-lib provides not only the most probable structures and a detailed analysis of a large number of CDs in aqueous solution but also the parameter files required to perform more complex simulation studies including docking, aggregation or adsorption to interfaces. So, we do expect that the new insight provided by this database will significantly contribute to the ongoing efforts worldwide to design novel CD derivatives as well as to widen the range of applications based on these molecules (Fig. 1).

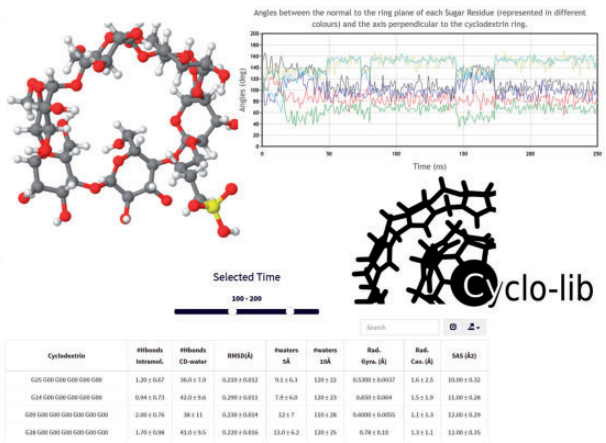

Fig. 1. Representative results shown in Cyclo-lib

2 Methods

The simulations of all CDs contained in the database were carried out with GROMACS 4.6 package (Hess *et al.*, 2008). The topologies were generated using the 53a6 version of the GROMOS force field (Oostenbrink *et al.*, 2004). Each system was solvated using the SPC water model, partially optimized, thermalized and equilibrated, followed by unrestrained simulations for 250 ns (time step = 2 fs). The simulation parameters and protocol were the same employed in a recent work for the simulations in aqueous solution (Mixcoha *et al.*, 2014). RMSD, H-bond, number of water molecules in different spheres around CDs, rotation angles of the GPUs and cluster analysis were carried out using GROMACS tools or locally written code. All data are stored in a database, using the structured query language (SQL) to ensure portability. The website is created with HTML5 and PHP for the server side operations and Javascript for the client side to represent CDs and graphics. Cyclo-lib uses Jmol (an open-source Java viewer for chemical structures in 3D. http://www.jmol.org) to show the molecular structures of CDs.

3 Discussion

Cyclo-lib freely provides detailed analysis of long MD simulation trajectories for a set of over 70 modified CDs. The CDs are identified by their GPU chemical composition. All features, including structures, plots, movies and even trajectories and simulation parameter files are available. Among the basic functionalities, three-dimensional visualization of the CDs and their constitutive GPUs, a chemical description, and a search engine of structures are included. More advanced functionalities allow comparative analyses of different properties of molecules averaged over different time periods that can be easily selected by the user. The properties that can be analyzed include: the number of both intramolecular hydrogen bonds both and those between the molecule and the solvent, the mean square deviation with respect to the initial structure, the number of water molecules in spheres centered in the CD cavity with radii of 0.5 and 1.0 nm, the radius of gyration of the molecule, the radius of the cavity, accessible to the solvent surface areas and the angle between each GPU and the symmetry axis of the CD. A dynamic analysis is also shown for each CD, representing these properties as a function of time along the different trajectories, a description of the simulation conditions and a selection of the representative structures obtained from cluster analysis based on quadratic mean deviations.

Presently, all the simulations are based on one of the most widely used force fields (GROMOS56a6). There are plans to include models based on other force fields. Further simulations with modified CDs will be added to the database in the future and the inclusion of other molecules such as cyclic peptides or calixarenes are not discarded. Our aim is to build up a large database of MD simulations of modified CDs that can be used to provide structural/dynamic information at atomic resolution aimed to complement experimental results performed with the same molecules in the wet-lab as well as to contribute in the design of new CDs derivatives.

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Conflict of Interest: Roberto Rosende Dopazo, Edgar Mixcoha, Angel Pineiro and and Rebeca Garcia-Fandino are shareholders of MD. USE Innovative Solutions S.L., a company engaged in the computational simulation of molecular systems. This article was not supported by MD. USE Innovative Solutions S.L.

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