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Extending the applicability of the O-ring theory to protein–DNA complexes

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ABSTRACT

Many biological processes depend on protein-based interactions, which are governed by central regions with higher binding affinities, the hot-spots. The O-ring theory or the "Water Exclusion" hypothesis states that the more deeply buried central regions are surrounded by areas, the null-spots, whose role would be to shelter the hot-spots from the bulk solvent. Although this theory is well-established for protein–protein interfaces, its applicability to other protein interfaces remains unclear. Our goal was to verify its applicability to protein–DNA interfaces. We performed Molecular Dynamics simulations in explicit solvent of several protein–DNA complexes and measured a variety of solvent accessible surface area (SASA) features, as well as, radial distribution functions of hot-spots and null-spots. Our aim was to test the influence of water in their coordination sphere. Our results show that hot-spots tend to have fewer water molecules in their neighborhood when compared to null-spots, and higher values of ΔSASA, which confirms their occlusion from solvent. This study provides evidence in support of the O-ring theory with its applicability to a new type of protein-based interface: protein–DNA.

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1. Introduction

Nature consists of a big number of biological systems, in the micro and macro scales, which interactions are the basis of endless processes. Proteins are one of its fundamental elements, acting as catalysts, carriers, providing mechanical support and immune protection, transmitting nerve impulses among others (Chothia and Janin, 1975; Janin, 1995; Jones and Thornton, 1996). The vast majority of proteins tend to bind and associate with other macromolecules, forming stable complexes that are the basis of many cellular functions. To that purpose protein–protein interactions (PPI), protein–DNA interactions (PDI) or protein–ligand interactions (PLI) are essential. The protein binding interface is composed of two large macromolecular surfaces that generally show good geometric and chemical complementary, and are governed by central regions with high binding affinities, the hot-spots (HS) (Clackson et al., 1998; DeLano, 2002; DeLano et al., 2000). HS, which are considered the most important residues for complex formation and for its stability, are defined as residues that upon alanine mutation generate a binding free energy difference ($\Delta\Delta G_{binding}$) higher than 2.0 kcal/mol; residues that cause a binding free energy difference lower than 2.0 kcal/mol were defined as null-spots (NS) (Moreira et al., 2007c; Thorn and Bogan, 2001). The characterization of protein-binding interfaces has been achieved through computational techniques, mainly Alanine-Scanning Mutagenesis (Clackson et al., 1998; DeLano, 2002; DeLano et al., 2000; Huo et al., 2002; Massova and Kollman, 1999; Moreira et al., 2006a,b, 2007a). It was proposed by Guharoy, Chakrabarti and co-workers that the interface could be separated in two different regions: a core and a rim. The rim is formed of residues that have only partial accessibility to the solvent, similar to the protein's surface, having few HS; on the other hand, the core is formed by residues deeply buried in the interface and with a composition distinct from the rest of the protein surface, having a large number of HS. Moreover, they proposed a direct relation between the buried surface area of core residues and the contribution to the binding free energy (Bahadur et al., 2003; Chakrabarti and Janin, 2002; Guharoy and Chakrabarti, 2005). Effectively, years before, Bogan and Thorn proposed a similar theory in which HS would be surrounded by regions with higher packing density, more deeply buried. This leads to solvent exclusion around them and results in a lower local dielectric constant environment and enhancement of specific electrostatic and hydrogen bond interactions. This region would be surrounded by another one formed by NS, whose role would be to shelter the HS from bulk solvent. This theory became known as the "O-ring theory" (since it resembled an O-ring) or the "Water Exclusion" hypothesis (Bogan and Thorn, 1998). This subject was later explored by many authors such as Li et al. that proposed a "double water exclusion" theory in which they accepted the existence of a ring surrounding the HS protecting them from the solvent, but stated that this ring of residues was itself water free (Li and Liu, 2009); and many others (Kosloff et al., 2011; Moreira et al., 2007b; Rajamani et al., 2004).

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Nowadays it is generally accepted that water plays a crucial role in the protein interface due to its interaction with the energetically important residues, and that the O-ring theory is a well-established theory. But one could argue about the applicability of the O-ring theory to other interfaces, protein on non-protein related, since it was, to the best of our knowledge, only applied for protein–protein interfaces. The protein–DNA interface, for example, has as much biological interest as the protein–protein. However, the information regarding experimentally detected HS in protein–DNA complexes or the application of the alanine scanning mutagenesis method to this type of interface is still scarce. It probably occurs due to the difficulties in energetic characterizing of this type of system as it possesses a highly charged character. Regardless, it was observed the same organization of HS in the central region of the interface but with a different composition. For protein–DNA interfaces there is a higher occurrence of positively charged residues (Arginine and Lysine), as well as, a lower occurrence of hydrophobic and negatively charged residues (Ahmad et al., 2008). With this in mind, and to test the applicability of the O-ring theory to protein–DNA interfaces, we subjected ten different protein–DNA complexes to Molecular Dynamics (MD) simulations in explicit solvent and measured different solvent accessible surface area (SASA)

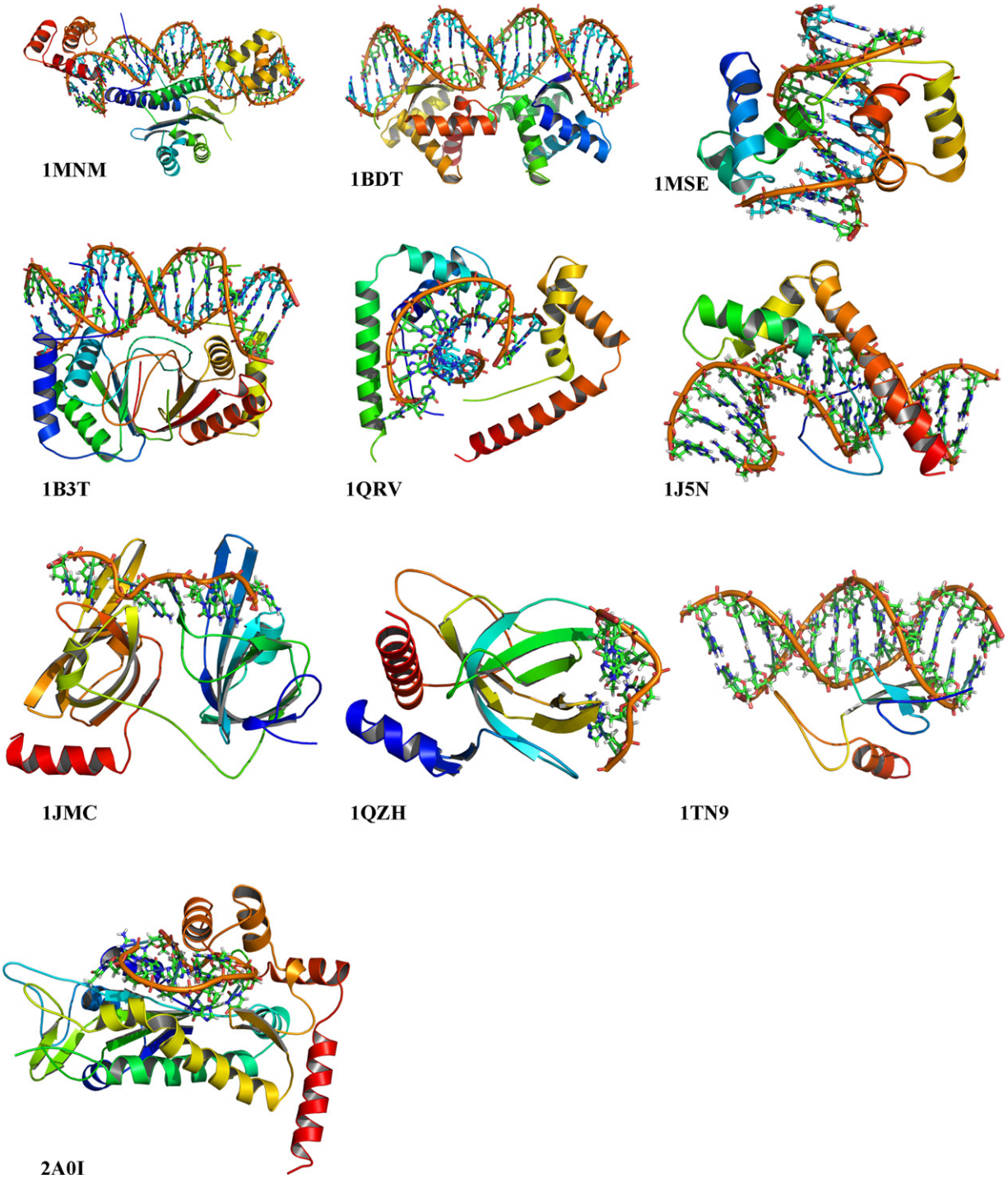

Fig. 1. Representation of the 10 protein–DNA complexes studied in this work. Protein and DNA are in cartoon and stick representation, respectively.

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