

Chapter 5

Molecular Docking of Biologically Active Substances to Double Helical Nucleic Acids: Problems and Solutions

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ABSTRACT

Molecular docking of ligands to DNA-targets is of great importance for the design of new anticancer drugs. Unfortunately, most docking programs were developed for protein-ligand docking which raises a question about their applicability for the DNA-ligand docking. In this study, the popular docking programs AutoDock Vina, AutoDock4 and AutoDock3 were compared for a test set of 50 DNA-ligand complexes taken from the Nucleic Acid Database. It was shown that the version 3.05 of the AutoDock program was the most successful in reproducing the structures of intercalation and minor-groove complexes. The program AutoDock4 was able to re-dock to within 2 Å RMSD most of the intercalation complexes of the test set, but showed poor performance for minor groove binders. While Vina, on the contrary, failed to construct six intercalation complexes of the test set, but showed satisfactory results for DNA-ligand minor-groove complexes when small search space was used.

INTRODUCTION

Molecular docking method allows one to construct the optimal complex - the complex with the minimum energy – of macromolecule-target and small biologically active substance (BAS)-ligand. Proteins are used usually as macromolecules-targets nucleic acids-targets are less common. At the same time, there is no doubt that nucleic acids (NA) are attractive targets for small molecules (Dailey et al., 2009; Hermann & Tor, 2005). One can hardly overestimate the role they play in biological processes, with the

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most important being probably the storage and propagation of genetic information. Many anticancer drugs exert their biological activity by binding to DNA (Brana, Cacho, Gradillas, de Pascual-Teresa, & Ramos, 2001). Drugs targeting NA can be even more effective than those targeting proteins in view of the fact that number of NA-targets is much less compared to protein-targets (Holt, Buscaglia, Trent, & Chaires, 2011). Each DNA gene-target is transcribed into multiple mRNAs-targets, and each mRNA-target is translated into multiple protein-targets. So blocking of a single gene will cause blocking of multiple protein-targets.

The docking of nucleic acids and BAS has a number of peculiarities compared to protein docking. The reason of them is primarily the differences in the structure of proteins and nucleic acids. Unlike the proteins, there are no clearly confined binding pockets for ligands in DNA duplexes. The polyanionic NA-targets have higher charge density compared to proteins and the treatment of solvent plays an important role in the evaluation of NA-ligand interactions. Another problem of NA docking is that the empirical energy scoring functions in many docking programs were calibrated using a set of protein-ligand complexes. Taking into account that the contribution of individual interactions (van der Waals, hydrogen bonds, electrostatic) to the total energy of docking complex may be different for BAS-protein complexes and BAS-NA complexes, the use of such programs for docking of NA and BAS does not always allow one to obtain the optimal complex for the given target and ligand. Nevertheless, in the literature, there are a number of successful examples of BAS-NA docking using programs designed for proteins (Chen, Shafer, & Kuntz, 1997; Detering & Varani, 2004; Evans & Neidle, 2006; Holt, Chaires, & Trent, 2008; Ricci & Netz, 2009; Li et al., 2010; Srivastava, Chourasia, Kumar, & Sastry, 2011). Protein docking programs that were successfully used for docking of ligands to NA-targets are listed in Table 1. At the same time, the application of protein-designed scoring functions for NA-ligand docking revealed some scoring problems: for the majority of studied complexes the crystal ligand pose had lower score than the best scored pose and the hydrogen bonding pattern was different in the crystal complex and in the docking top-ranked complex (Gilad & Senderowitz, 2014; Deligkaris, Ascone, Sweeney, & Greene, 2014). Recently several docking programs and scoring functions appeared that were specially designed for RNA-targets: MORDOR (Guilbert & James, 2008), RiboDock (Morley & Afshar, 2004), DrugScore^{RNA} (Pfeffer & Gohlke, 2007), DOCK6 (Lang et al., 2009). Unfortunately, there is a lack of scoring functions designed for DNA-duplexes.

This study was focused on docking of small ligands to DNA-duplexes. Since the most of the reported DNA-ligand docking studies were done using AutoDock software (Morris et al., 1998), this program

Table 1. Protein docking programs that were successfully applied to NA-ligand docking

Program	Description	Reference
AutoDock	Free program based on Lamarckian genetic algorithm and empirical force-field based scoring function	Morris et al., 1998; Morris et al., 2009
DOCK	Free anchor-and-grow based docking program	Lang et al., 2009
Surflex	Commercial docking program using molecular similarity-based search algorithm	Jain, 2003
GLIDE	Commercial exhaustive search-based docking program	Friesner et al., 2004
GOLD	Commercial genetic algorithm-based docking program	Verdonk, Cole, Hartshorn, Murray, & Taylor, 2003
CDOCKER	Commercial CHARMM-based molecular dynamics docking program	Wu, Robertson, Brooks III, & Vieth, 2003

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