PRINCIANE: A Web Tool For Docking Simulations

Bonalumi, C.E.[1],da Silveira, N.J.F.[2], de Azevedo Jr., W.F.[3]

[1]IBILCE/UNESP, Rua Cristóvão Colombo, 2265, São José do Rio Preto, SP, Brasil, bonalumi@ibilce.unesp.br
[2]UNIVAP/FCC, Rua Shishima Hifumi, 2911, São José dos Campos, SP, Brasil, nelsonjfs@univap.br
[3]PUCRS/Faculdade de Biociências, Av. Ipiranga, 6681, Porto Alegre, RS, Brasil, walter.junior@pucrs.br

Abstract - The era of hit-or-miss searching for lifesaving drugs is giving way to the age of computationally tailored molecules. Finding molecular docking sites by computer is a computationally intensive problem. To determine how two molecules will bind, the computer performs an search through the relative translations and rotations of the molecules. In the present work, we will present the software PRINCIANE, a tool for docking implemented in a *Beowulf cluster*. We performed the docking simulation of Roscovitine against CDK2, using PRINCIANE. The result of the docking simulation presented good agreement with the crystallographic structure, with a rmsd of 1.3 Å, and with the inhibitor occupying the ATP-binding pocket of the CDK2 in approximately same orientation observed in the crystallographic structure. PRINCIANE allowed a substantial reduction of the processing time of docking simulations. This web tool is available at: http://www.biocristalografia.df.ibilce.unesp.br/tools.

Palavras-chave: docking, protein structure, drug design, therapeutic targets.
Área do Conhecimento: Computation Science

Introdução

Protein molecules " dock " one another like Lego blocks, with the bumps, ridges, and electrical potentials of one molecule matching the contours and charge of another to construct temporarily a larger, loosely bound structure (Figure 1 and Figure 2). This docking activity gives proteins the ability to promote and inhibit chemical reactions, and to accelerate or prevent the processes that keep cells alive -- or that allow bacteria and viruses to infect other organisms. Most drugs work by docking with target molecules and interfering with their functions, and the specific effects of a drug depend on the structure of the molecular aggregate.

The era of hit-or-miss searching for lifesaving drugs is giving way to the age of computationally tailored molecules. Knowledge of the structure of a critical molecule -- for example, a component of a virus -- now gives computational biologists the ability to design another molecule that will interfere with its activity. Even when the interfering molecule is a toxin that attacks a protein essential for human life, researchers have found that structural analysis of the docking can provide unexpected benefits by revealing the mechanisms of fundamental biological processes.

Finding molecular docking sites by computer is a computationally intensive problem. To determine how two molecules will bind, the computer performs an exhaustive 6-dimensional search through the relative translations and rotations of the molecules, far too many to check by brute force even with a supercomputer. (Olson *et al*., 1996).

In the present work, we will present the software PRINCIANE, a tool for docking implemented in a Beowulf cluster.

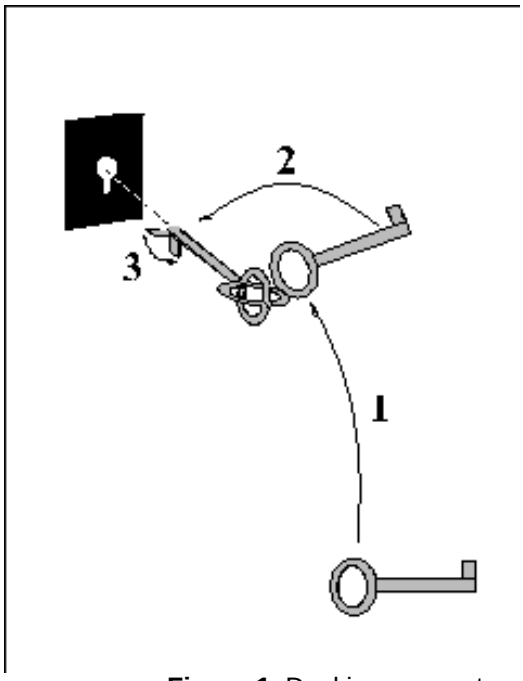

Figure 1. Docking concept

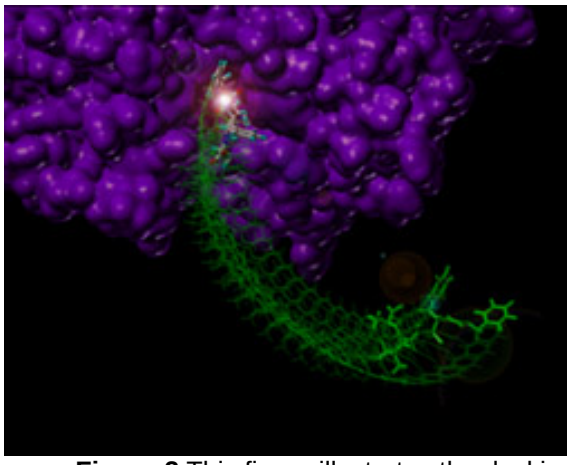

Figure 2. This figure illustrates the docking procedure

Materiais e Métodos

Docking Protein

The docking methodology is an empirical approach to smoothing the intermolecular energy function by changing the range of the atom-atom potentials (Katchalski-Katzir *et al*., 1992) implemented in the program GRAMM (Tovchigrechko *et al*., 2002). The technique locates the area of the global minimum of intermolecular energy for structures of different accuracy. The figure 1 shows the docking concept.

Parallel Programming

PRINCIANE has been developed using PERL, C++ and MPI programming (Figure 3 and Figure 4). The PERL (Wall *et al*., 2000) provides a WEB interface, stores in a database and prepares the archives for docking (Figure 5). The MPI (Message Passing Interface) provides a software environment for message passing between homogeneous or heterogeneous computers and has a collection of library routines that the user can employ with C or FORTRAN programs (Wilkinson and Allen, 1999). An important factor in developing MPI is the desire to make message passing portable and easy to use, therefore we used MPI routines from the C language.

The SPMD (Simple Data Multiple Program) is ideal where each process will actually execute the same code.To create the parallel program, the source code was compiled once in the front-end. In the source code is defined the calling to the MPI routines and the group of computers that will perform the tasks. In this group there are slaves and the master. The master is represented by the front-end and it is the machine that distributes the processes to slaves. The slaves are the nodes that will process the modeling.

Data base design

A MySQL database was developed to archive the all performed docking. The database contents receptors, ligands, parameters of docking session and results.

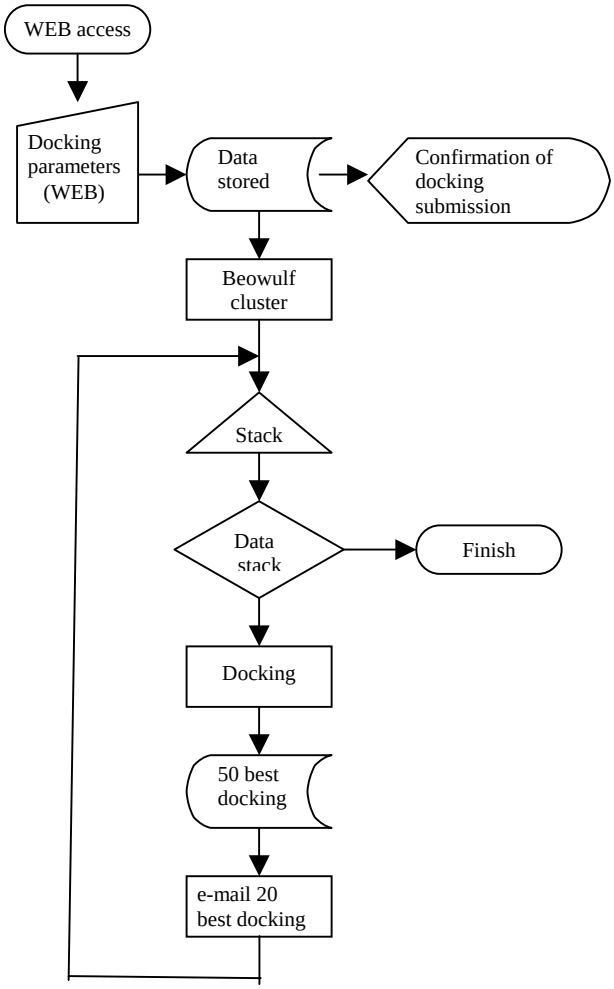

Figure 3. Fluxogram of docking protein

Figure 4. Parallel computing

Resultados and Discussion

We performed the docking simulation of Roscovitine against CDK2, using PRINCIANE. The atomic coordinates of CDK2 were obtained from the crystallographic structure of the complex between CDK2 and Roscovitine (de Azevedo *et al*., 1997). The processing times of the docking simulation running on a single-processor PC was compared with that obtained using a beowulf cluster (Figure 5). Figure 6 shows the superposition of the docking simulation onto the crystallographic structure. The result of the docking simulation presented good agreement with the crystallographic structure, with a rmsd of 1.3 Å, and with the inhibitor occupying the ATP-binding pocket of the CDK2 in approximately same orientation observed in the crystallographic structure.

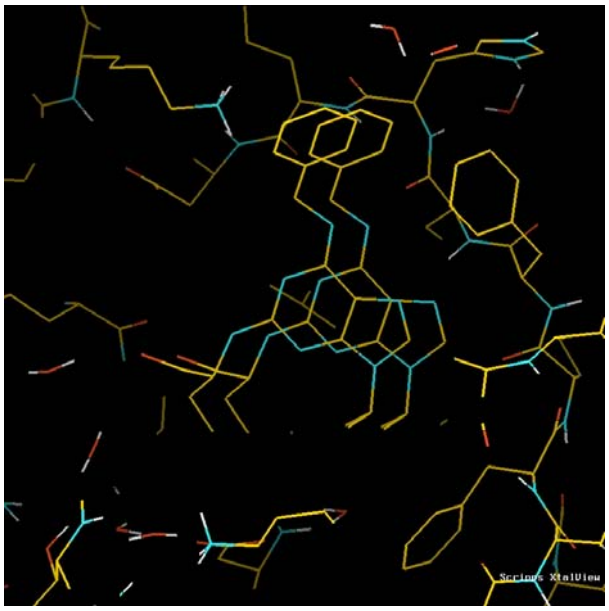

Figure 6. Docking CDK2-Roscovitine

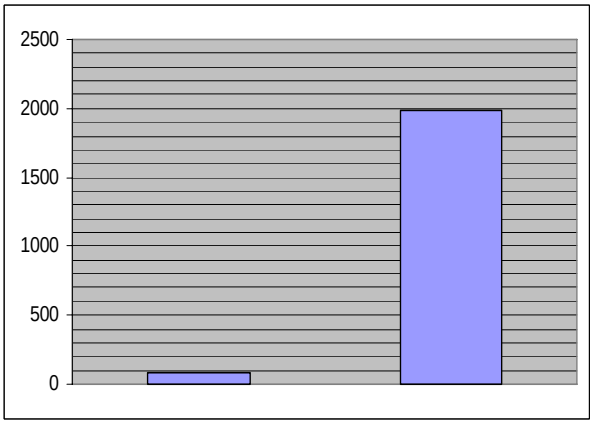

Figure 5. Comparison of processing time, single processor PC and cluster.

Conclusion

PRINCIANE allowed a substantial reduction of the processing time of docking simulations. Using rigid docking protocols, PRINCIANE was able to correctly predict the orientation of Roscovitine in the ATP-binding pocket of CDK2. We are using the present protocol to assess the structure of complexes between CDK2 and several different inhibitors, in order to understanding the strucutural basis for inhibition of this important target for drug development. Furthermore, the user-friendly interface of PRINCIANE (Figure 7) allows inexperienced users to have access to powerful docking protocols, which may speed up the process of drug discovery.

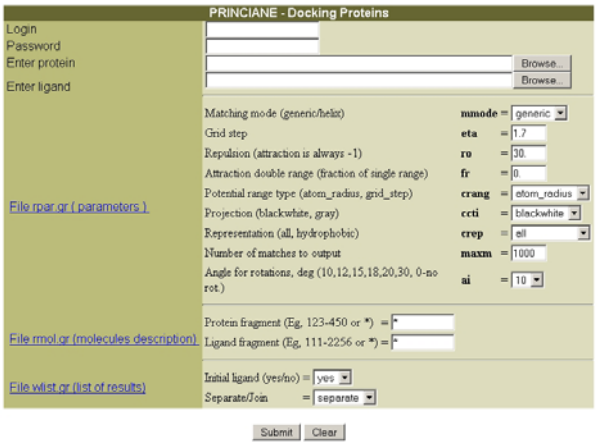

Figure 7. Parameters for docking session

Agradecimentos

This work was supported by grants of FAPESP (02/10239-6, SMOLBNet 01/07532-0, 02/04383-7, 04/00217-0), CNPq, CAPES and Instituto do Milênio (CNPq-MCT).

Referências

- De Azevedo, W.F.; Leclerc, S.; Meijer, L.; Havlicek, L.; Strnad, M.; Kim, S.-H. Inhibition of cyclin-dependent kinases by purine analogues: crystal structure of human cdk2 complexed with roscovitine. Eur. J. Biochem., 243, 518-526, 1997.

- Katchalski-Katzir, E.; Shariv, I.; Eisenstein, M.; Friesem, A.A.; Aflalo, C.; Vakser, I.A.. Molecular surface recognition: Determination of geometric fit between proteins and their ligands by correlation techniques, Proc. Natl. Acad.Sci. USA, 89:2195-2199, 1992.

- Olson, A.J.; Taylor, P.; Belew, R.K.; Ten Eyck, L.; Bailey, M. Docking Proteins inside the Computer. Biology, vol12, no.3; 1996.

- Tovchigrechko, A.; Wells, C.A.; Vakser, I.A. Docking of protein models, Protein Sci., 11:1888-1896, 2002.

- Wall, L.; Christiansen,T.; Orwant, J. Programming PERL, O'Reilly; 2000.

- Wilkinson, B.; Allen M. *Parallel Programming.* Prentice Hall, 1999.