Computer Software Review

eHiTS 5.1.6 SimBioSys Inc., 135 Queen's Plate Drive, Unit 420, Toronto, Ontario M9W 6V1, Canada. http://simbiosys.ca/index.html. For pricing information, contact company.

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eHiTS 5.1.6 is an electronic high-throughput screening software and a flexible ligand-docking program that is both easy to use and highly customizable. SimBioSys has been updating and improving this software on a continuing basis, and new versions have appeared frequently in the last year. This version offers a practical, simple means of addressing the conformational flexibility of ligands in a reasonably time-efficient way, although it does not take into account the conformational flexibility of the receptor. The key features of this docking program include a proprietary systematic exhaustive algorithm that does not involve any stochastic or evolutionary components. SimBioSys claims that this algorithm is guaranteed to find the best pose and conformation of the ligand according to the scoring function. Another feature is the highly customizable nature of the scoring function and the docking parameters. The empirical scoring function is used several times during the algorithm and contains components for favorable hydrogen bonding, electrostatic, van der Waals, π-stacking, and metal ion interactions, and penalties for incompatible contacts, steric clashes with the receptor, and unfavorable intramolecular interactions. Parameters defining each of these individual components can be easily modified, as can their individual weights in calculating the overall score. A "fast mode" allows quick yet relatively accurate docking of entire virtual libraries of ligands, while a more time-intensive "accurate mode" provides results that in many cases are in excellent agreement with experimentally determined poses. This version incorporates improved algorithms and a very useful training feature that can be used to optimize the scoring function to best recapture experimentally determined poses. The software functions both on Silicon Graphics R10000 workstations running the IRIX 6.5 operating system and on X86-architecture PCs with Linux. It supports 64-bit processing on both of these platforms, as well as multiple processors and distributed processing. Minimal documentation is provided with the software, but additional information is available from the company's Web site or by contacting the company by e-mail.

The software is very easy to install and use and requires no preprocessing of receptor or ligand files prior to docking. The site of interest is defined by the presence of a ligand in the receptor input file or via a separate clip file, which can simply consist of a subset of the receptor residues flanking the site of interest. Alternatively, docking can be run on the entire receptor surface, allowing eHiTS to detect the protein pockets automatically, although this is extremely slow. eHiTS automatically adds hydrogen atoms to the receptor, assigns partial charges, and determines protonation states by considering all alternatives in a single docking run. The insulation of the user from these issues facilitates quick use of the program; however, this can also limit the user's ability to employ his or her chemical knowledge of the receptor site. The user has the option of retaining or deleting water molecules from the receptor. It is also possible to retain a ligand bound to the receptor if the user is interested in doing tertiary docking, as in the case of fragment-based methods to expand upon a previously identified ligand.

Support is provided for only a few input file types: pdb, mol, mol2, and sd. Output structure files are in sdf format. The software is less forgiving of nonstandard input file formats than most visualization programs. While many programs will correctly assign atom connectivity and bond types using just heavy atom three-dimensional pdb coordinates, eHiTS requires full connectivity in the input receptor and ligand pdb files. Even when connectivity information is present in these input pdb files, eHiTS occasionally has difficulty in the correct assignment of bond types, resulting in incorrect ligand structures. In addition to the structure output files, eHiTS produces a number of output text files and various other files for internal use by the program. In some cases, these files are overwritten, requiring the user to rename them prior to running the program with new inputs. In other cases, previous internal files are used even when the program is invoked with different arguments. For example, when docking to a receptor with different clip files, one must rename the input receptor file in order to employ a new clipping file. When the program terminates with errors, an error output file is produced that can be e-mailed to SimBioSys for troubleshooting. The software organizes all of these output files in an easily navigable directory tree structure.

The software was tested against a variety of crystallographically determined receptor−ligand complexes from the protein databank. In the case of relatively nonflexible ligands, eHiTS preformed extremely well. Docking runs required a few minutes at most, and the most favorable predicted poses were extremely close to those determined crystallographically, with RMSD typically less than 1.5 Å. Interestingly, when using the separated receptors and ligands as inputs along with a clip file defining the binding pocket, the docking results were slightly worse. Docking studies of known receptor-flexible ligand complexes using the default settings required much longer run times and the predicted conformations and poses deviated more from those determined crystallographically; however, in some cases the results were very accurate, even for very flexible (i.e., with nine rotatable bonds) ligands. Docking on a modestly sized database of small, fragmentlike ligands was also carried out. When the "fast" option was used, the docking required just a few minutes for each ligand. The results of these searches include an output file containing the top-scoring poses of each ligand. While the results seemed reasonable, no effort was made to determine how many of the highest-scoring ligands were true "hits".

Overall, eHiTS is an easy to use flexible docking program that may appeal to both academic and industrial chemists who

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want to perform docking studies rapidly on individual ligands and on virtual databases of ligands. The most appealing aspect of this software is its ease of use. Other nice features include the customizable scoring function that can be optimized for specific receptor complexes, and the speed and accuracy of docking, particularly of moderately flexible or rigid ligands. Docking of very flexible ligands is slower and not as accurate. Although the documentation is limited, SimBioSys provides excellent support and is continuously updating the program with new features and improvements.

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