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COMPUTER SOFTWARE REVIEWS

ReCore. BioSolveIT GmbH, An der Ziegelei 75, 53757 Sankt Augustin, Germany. www.biosolveit.de/ReCore. See Web site for pricing information.

Twenty years ago, Paul Bartlett introduced CAVEAT as a means for designing rigid bioactive molecules, starting from the known conformation of a flexible bioactive molecule, like a peptide (see Bartlett, P. A.; Shea, G. T.; Telfer, S. J.; Water, S. CAVEAT: A Program to Facilitate the Structure-derived Design of Biologically Active Molecules. In *Molecular Recognition: Chemical and Biological Problems*; Roberts, S. M., Ed.; Royal Society of Chemistry: London, 1989; pp 182−196 and Lauri, G.; Bartlett, P. A. *J. Computer-Aided Molecular Design* **1994**, *8*, 51−66). The general idea was to look for rigid scaffolds by searching a 3D database to find molecules with points of attachment having both the proper intramolecular distance and the proper orientation of vectors to present side chains similar to what is observed in the bioactive conformation of the original flexible molecule. CAVEAT was one of a number of techniques that arose almost simultaneously to automate the process of ligand design, including pharmacophore-based 3D database searching (see Martin, Y. C. *J. Med. Chem.* **1992**, *35*, 2145−2154) and de novo design (see Moon, J. B.; Howe, W. J. *Proteins* **1991**, *11*, 314−328 and Böhm, H.-J. *J. Comput. Aided Mol. Des*. **1992**, *6*, 61−78).

Bartlett's original software has fallen into disuse, although the principle is still valid. As long as chemists are designing bioactive molecules, they will pose the question "What molecule should be made next?" Such software can help to answer that question.

ReCore from the German software company BioSolveIT implements the basic idea of CAVEAT, in a slick new package suitable for Windows (and Unix) computers; it also incorporates some additional twists. It emerged from collaboration between the drug design group at Roche/Basel and the academic group of M. Rarey at the Center for Bioinformatics in Hamburg (see Maass P.; Schulz-Gasch, T.; Stahl, M.; Rarey, M. *J. Chem. Inf. Model*. **2007**, *47*, 390−399). This lineage ensures that the quality of the science underlying ReCore is first-rate; the way this software leads the user to think about the design of bioactive molecules is very appealing.

To test this software's ability to devise novel molecules, I presented it with three similar problems, to see if the software was useable and if it could discover interesting molecules. The first problem was one we faced years ago (Martin, 1992), where we used 3D database searching to discover a novel D1 agonist scaffold, given knowledge of competitors' compounds. Using ReCore's graphical user interface, I entered a conformation of SKF-38393 and identified which substituents I wanted to hold fixed, and it came up with the very scaffold we identified long ago, which led to A-68930. The second problem was to take a peptide bound to an HIV protease, as shown in an early X-ray structure (see Erickson, J.; Neidhart, D.; Van Drie, J.; Kempf, D.; Wang, X.; Norbeck, D.; Plattner, J.; Rittenhouse, J.; Turon, M.; Wideburg, N.; Kohlbrenner, W.; Simmer, R.; Helfrich, R.; Paul, D.; Knigge, M. *Science*, **1990**, *249*, 527−533) and see if the software would suggest a scaffold along the lines that later emerged, e.g., saquinivir, indinavir. Alas, no such luck, although interesting suggestions did emerge. The third problem is one of current interest, where a preclinical candidate was publicly revealed along with an X-ray structure, and our goal was to look for novel scaffolds that might possess improved pharmacokinetic properties. ReCore did suggest some scaffolds that I had never thought of, which stimulated new thinking.

One of the limitations of this type of approach is that the ideas that emerge can only come from molecules already in its database of scaffolds. ReCore provides utilities that allow one to convert any molecular 3D database into a database of scaffolds, along the lines of the RECAP software described by Glaxo/UK a decade ago (see Lewell, X. Q.; Judd, D. B.; Watson, S. P.; Hann, M. M. *J. Chem. Inf. Comput. Sci.* **1998**, *38*, 511−522). Additional functionality available in ReCore includes the ability to define constraints beyond CAVEAT-style vector relationships; one can define pharmacophore-type constraints as well, so as to look for molecules that position certain types of features in specific geometric orientations.

The primary drawback of this software is that once it suggested a novel scaffold holding my side chains in place, I could not use this proposed molecule as a starting point to tweak interactively the molecule further, e.g., to devise something easier to synthesize. I'm not looking to this software to propose the ultimate molecule—I simply want it to present a new starting point for me to think about new molecules. This functionality is not provided, and one must use ReCore in conjunction with different modeling software. The second-biggest drawback is that this software assumes a chemist has the 3D structure of his or her initial molecule readily available. Again, either complementary modeling software must be at hand, or other tools must be available to extract 3D structures from databases like the Protein Data Bank.

In general, a chemist wishing to use this software alone, without some hand holding from a nearby modeler, would need to be unusually computer-savvy. As ReCore is used at Roche, it is usually employed in a team setting, with chemists and modelers working side-by-side. Also, at the moment the software is still in a "beta" release, and thus, the types of technical glitches one must deal with are more appropriate for those with the "early-adopter" mentality.

The software vendor is established and well-known in the world of scientific software; the team at BioSolveIT is responsive and eager to help users achieve success with this software. Refreshingly, they impose no constraints on what users do when using the demo of this software with the molecules that emerge, in contrast to some of their US-based counterparts, who bury in the fine print restrictions on doing useful work with the demo software. Furthermore, the underlying science has all been disclosed (Maass, P. et al., 2007); this software is not a mysterious "black box".

In my opinion, software of this sort belongs on the desk of any chemist designing bioactive molecules. It remains to be seen whether ReCore is the optimal answer to this problem, but it is definitely a step in the right direction. Anyone interested in designing bioactive molecules should consider investigating this.

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