Confort™

GENERATE SETS OF DIVERSE, LOW ENERGY CONFORMERS

Tripos™
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Confort is a powerful conformational analysis tool that performs exhaustive yet rapid analysis of drug-sized molecules. It can be used to identify the global minimum energy conformer, all local minima within a user-specified energy range, or a maximally diverse subset of conformers. Confort can be applied to entire molecular structures or to user-specified substructures and is equally adept at searching rings as well as acyclic rotatable bonds.

Applications

- Generate diverse conformers for receptor-ligand docking
- Perform 3D database searches starting from multiple conformations
- Produce diverse conformers for improved pharmacophore perception
- Enable multi-confromer methods for 3D-QSAR
- Identify global minimum and low-energy conformations of drug candidates
- Generate diverse conformers for ADME and other physical property predictions

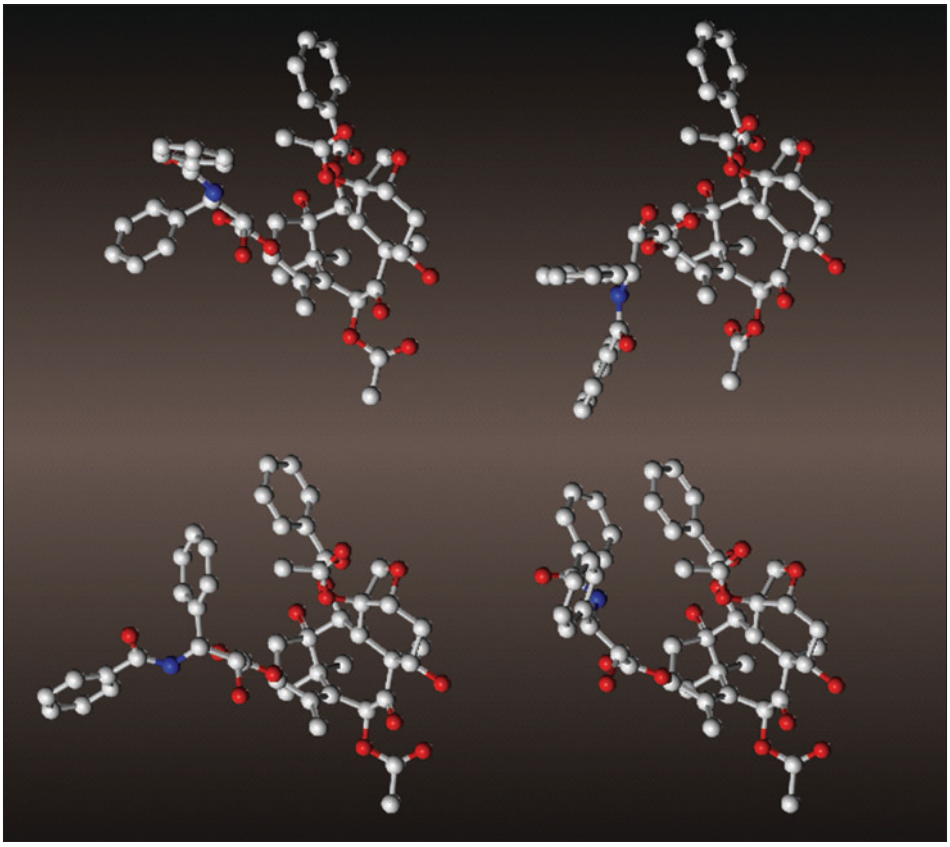
Confort is based on a novel algorithm for conformational searching. Rather than examining all combinations of dihedral angles for each rotatable bond (rotor), it examines all combinations of "worthy" dihedral ranges for each rotor.

Confort's algorithm guarantees that each of these ranges brackets a single local minimum. At each step of Confort's search process, these ranges are updated and completely explored by energy minimization, making the search truly exhaustive.

Following the removal of duplicates, conformers are output subject to user specifications with respect to total number, energy, and diversity. Diverse sets of conformers are selected based on interconformer distance in a conformational-space that is defined in terms of interatomic distances, rather than dihedral angles. When using Confort for diverse conformer selection, optional pre-search heuristics greatly increase speed without loss of diversity.

Advantages

- Confort searches rotatable bonds in rings and complex ring systems as well as those in simple acyclic structures
- Confort allows the user to specify rotors to be excluded from the conformational search
- Confort's search algorithm does not use "poling", or distort the energy surface in any other way



A sampling from larger Confort-generated set of diverse conformers of taxol. This analysis identified conformers within 10kcal of taxol's global minimum and included all 23 acyclic rotatable bonds.

Features

- Input and output in a variety of formats (SMILES, UNITY hitlist/SLN, mol2, MDL SDfile)
- Tripos Force Field with optional electrostatics
- BFGS minimization algorithm using analytic gradients computed in internal (not cartesian) coordinates
- Adjustable minimization convergence criteria and conformational search parameters to control the accuracy and speed of the search
- Full flexibility of rings and complex ring systems
- User control of which rotors to search and which to hold rigid enables constrained searches and constrained optimizations

A 2D view of the molecule sampling from a larger Confort-generated set of diverse conformers of taxol.

- Confort uses a novel interatomic distance-based definition of conformational-space to generate diverse conformer subsets
- Unoptimized 3D structures can be used as input because Confort refines structures prior to conformational search. With an additional license, 2D input can be used
- Confort performs all relaxations and optimizations in internal coordinates using analytic gradients, resulting in faster and more reliable energy minimizations
- Confort is much faster than other exhaustive search algorithms and just slightly slower than non-exhaustive methods that fail to identify all local minima

Validation

Confort's conformational search results have been compared[1] with the results reported in the well known benchmark papers by Saunders, et al.[2] and Goto and Osawa.[3] In all cases, the number of conformers and energies of conformers generated by Confort agree with those previously published results.

Acknowledgements

Confort was developed by Professor Robert Pearlman and Dr. Renzo Balducci at the Laboratory for Molecular Graphics and Theoretical Modeling at the University of Texas at Austin.

Hardware and Software Requirements

Confort requires a separate license. The standalone version of Confort runs directly from the UNIX command line. With a SYBYL®/Base license, Confort can be accessed through the SYBYL molecular modeling environment. An additional license is required to use 2D structures as input. SYBYL/Base and Confort run on workstations operating under IRIX® (SGI®) or Linux® (x86).

Complementary Software

- **DISCOtech™** for generating pharmacophore hypothesis from precomputed sets of conformers
- **FlexS™** for shape-based screening in the absence of receptor structure, using candidate bound conformers as reference
- **QSAR with CoMFA®** and **Advanced CoMFA®** for multi-conformer 3D QSAR analysis
- **UNITY®** for 3D searching starting from a database of multiple conformations

References

1. Pearlman, R.S.; Balducci, R. "Confort: A Novel Algorithm For Conformational Analysis." *National Meeting of the American Chemical Society, New Orleans*, **1998**.
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3. Goto, H.; Osawa, E. "An Efficient Algorithm For Searching Low-Energy Conformers of Cyclic And Acyclic Molecules." *J. Chem. Soc. Perkin Trans.* **1993**, *II*, 187.

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