RACHEL™

SOPHISTICATED TOOLS FOR OPTIMIZATION OF LEAD COMPOUNDS

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Lead optimization is still something of an art. Structural modifications that logically should enhance affinity often decrease it. Project duration can be lengthy, the process uncertain, and progress intermittent. RACHEL is an application designed to streamline this laborious task.

Starting from a ligand/receptor structure, RACHEL performs automated combinatorial optimization of lead compounds by systematically derivatizing user-defined sites on the ligand. These compounds are conformationally searched within the active site, evaluated, and only those that bind tightly with the receptor are retained. This new population of compounds is then processed to form the next generation of derivatives. Over time, a lead compound is iteratively refined into a set of high affinity structures.

Applications

- Combinatorially enumerate user-defined sites on a lead scaffold to optimize binding within a receptor
- Bridge high-affinity ligand fragments positioned within the active site

Generation of the Fragment Database

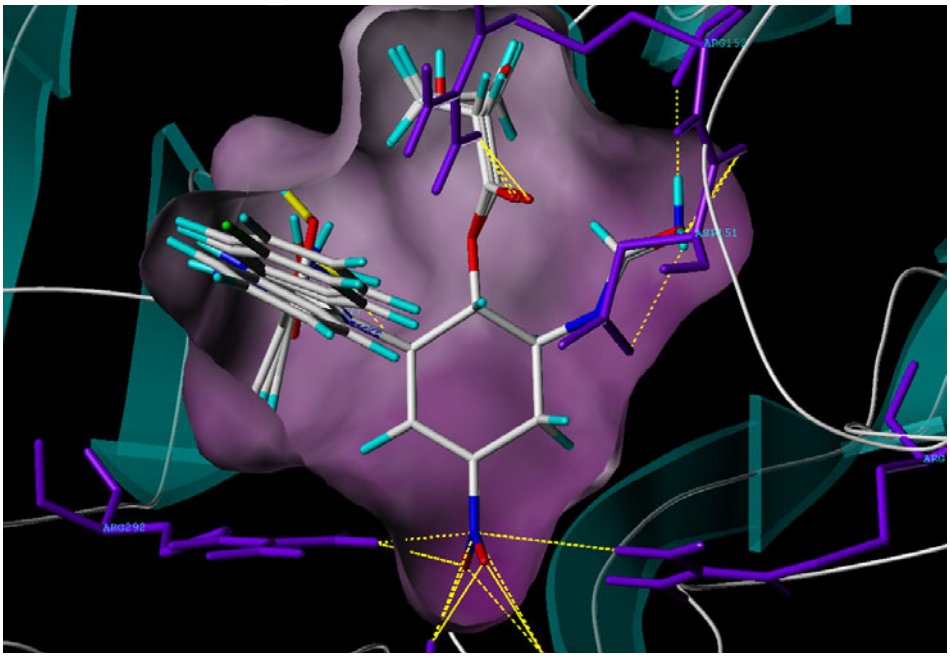
RACHEL obtains chemical fragments by extracting structures directly from a corporate or commercial database, dividing them along their rotatable bonds, and storing the atomic coordinates of those that are unique. This enables the compression of a massive database into a much smaller and manageable form, and allows intellectual property such as patented compounds, synthetic expertise, and biochemical data to be leveraged for a competitive advantage. This unique functionality has the added benefit that structures generated by RACHEL are easier to patent and synthesize because proprietary chemistry is often directly incorporated.

Intelligent Component Selection

During component extraction, a *fragment property index* is created integrating characteristics such as size, atom composition, connectivity, ring structure, and electrostatic charge for each structure that is stored. Additionally, a *heuristic active site mapping algorithm* is used to determine the chemical characteristics of the receptor.[1,2] These characteristics are verified and updated as RACHEL discovers new ligand derivatives. During the search, this knowledge base enables RACHEL to quickly isolate and utilize components that complement regions of the active site by cross-referencing the *fragment property index* with the *active site map*.

User-defined Structure Generation

Unique to RACHEL is an automated method to generate structurally diverse compounds using Markush-like templates that allow the user to specify invariant scaffolds along with potential sites for combinatorial enumeration. Chemical descriptors can be employed to constrain the enumeration by the number and size of the components, ring structure, atom and bond types, as well as the presence of defined pharmacophoric elements.[1,3] These descriptors afford the user complete control over the structure generation process.



The X-ray structure of wildtype tern N9 influenza virus neuraminidase (2QWK) shown with five ligands generated using RACHEL that are predicted to be active. Hydrogen bonds between the ligands and residues are indicated by dashed yellow lines. The surface was rendered using MOLCAD™ and color-coded according to hydrogen acceptor/donor density. Dark purple regions contain a greater acceptor/donor density and light purple regions indicate areas where hydrogen bonding is less likely to occur.

Bridge Generation

CHARLIE™, a RACHEL module, allows the user to generate scaffolds to link separate, docked, high-affinity structures into complete compounds within the confines of the active site.[1,4] The previously described technologies pertaining to component selection and structure generation are also applicable to bridge generation.

Automated Scoring Function Elucidation

RACHEL incorporates the statistical and analytical tools necessary to generate *focused* scoring functions based on structure-activity data. This enables companies that have characterized the receptor binding of a number of lead compounds to utilize this knowledge to guide derivative generation.

Automated Target Function Elucidation

If the user-supplied training set is either too small or lacks the variability to generate a predictive scoring function, RACHEL will instead employ a *target function.* A target function is formed by averaging the descriptor values of the highest affinity training set complexes. These *ideal* descriptor values are then used to guide the selection of derivatives, thereby fostering the generation of alternate chemical architecture that retains optimal binding characteristics.

Features

- Component database generation, registration, and management
- Advanced conformational search engine capable of sampling nearly 10^6 conformers per second[5]
- User defined Markush-like templates and chemical descriptors to direct the generation of structures
- Pseudo-receptor generation using the active analog approach
- Monitoring functions to provide feedback during the optimization

Advantages

- Chemical fragments are obtained directly from personal, corporate, or commercial databases increasing the likelihood of synthetically accessible results
- Building block components are selected for use based on favorable interaction with the active site
- Templates and chemical descriptors can be independently configured for each substitution site enabling complete user control of structure generation
- Focused scoring functions can be automatically generated based on user supplied structure-activity data

Complementary Software

- **Biopolymer** for predicting, building, and visualizing macromolecular 3D structure.
- **Composer™** for constructing 3D homology models of proteins.
- **Concord®** for generating accurate 3D coordinates.
- **CScore™** for ranking the affinity of compounds bound to a target with consensus scoring.
- **FlexS™** for performing shape-based screening of ligands in the absence of receptor structure.
- **FlexX™** for flexibly docking ligands into a binding site.
- **GeneFold®** for identifying protein function from sequence.
- **LeapFrog®** for performing *de novo* ligand design.
- **MOLCAD™** for visualizing molecular surfaces and molecular properties.
- **QSAR with CoMFA®** for building predictive structure-activity and structure-property models.
- **VolSurf™** for predicting ADME properties.

Acknowledgements

Software Partner: Drug Design Methodologies, LLC, St. Louis, MO
Scientific Partner: Chris Ho, M.D., Ph.D.

Hardware and Software Requirements

RACHEL requires a SYBYL®/Base license, and is accessible through the SYBYL expert molecular modeling environment. SYBYL and RACHEL run on workstations operating under IRIX® (SGI®) or Linux® (x86).

References

1. For detailed information regarding the technology, please see www.newdrugdesign.com

2. Ho, C.M.W.; Marshall, G.R. "CAVITY SEARCH: An Algorithm for the Isolation and Display of Cavity-like Binding Regions." *J. Comp.-Aided Mol. Des.* **1990**, *4*, 337-354.

3. Ho, C.M.W.; Marshall, G.R. "DBMAKER: A Set of Programs to Generate Three-Dimensional Databases Based upon User-Specified Criteria." *J. Comp.-Aided Mol. Des.* **1995**, *9*, 65-86.

4. Ho, C.M.W.; Marshall, G.R. "SPLICE: A Program to Assemble Partial Query Solutions from Three-Dimensional Database Searches into Novel Ligands." *J. Comp.-Aided Mol. Des.* **1993**, *7*, 623-647.

5. Dammkoehler, R.A.; Karasek, S.F.; Shands, E.F.B.; Marshall, G.R. "Constrained Search of Conformational Hyperspace." *J. Comp.-Aided Mol. Des.* **1989**, *3*, 3-21.

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