

EA-Inventor™

INVENT NEW COMPOUND IDEAS AND LEAD HOP
USING NOVEL *de novo* DESIGN ENGINE



EA-Inventor is a new and different approach to *de novo* design. It enables researchers to "invent" new compounds (for *in silico* lead discovery), new R-groups around a fixed scaffold (for lead exploration), or new scaffolds (for lead- or scaffold-"hopping"). Unlike typical *de novo* design programs, EA-Inventor gives the user control over how the new structures are generated and scored. EA-Inventor is a general *de novo* design engine and can be used for both receptor-based and ligand-based design. Invented structures are usually worthy of synthesis but, in all cases, serve to spark and complement the imagination of both CAMD scientists and bench chemists. EA-Inventor is a *de novo* design engine which can be used in conjunction with any desired scoring function (or composite scoring function).

EA-Inventor modifies structures by applying a very complete set of mutation operators. The user has full control over the probability with which each operator will be selected — although many users are content to use the default probabilities encoded in EA-Inventor. This provides the user with optimal control over the evolutionary process, specifically over structures that are produced and the optimal rate of convergence.

Benefits

- Uses an Evolutionary Algorithm (analogous to a Genetic Algorithm) to generate new chemical structures which evolve via "survival of the fittest" so as to optimize a user-specified scoring function
- Ideally suited for inverse-QSAR, for extending leads based on a common scaffold, or for lead-hopping to new scaffolds, etc.
- Store preferred chemistry and substructures and use EA-Inventor to suggest new ideas that preserve these chemical features
- Easy to use with any scoring function (or composite scoring function)
- Provided with a very effective BCUT-similarity scoring function
- Offers a very complete palette of chemical structure mutation operators
- Enables user control over relative probabilities of all structural mutations
- Never produces chemically invalid structures
- Enables specification of molecular substructures which must be preserved through the evolutionary process

Unique *de novo* Design "Engine"

EA-Inventor utilizes an Evolutionary Algorithm that operates on the connection tables of an initial population (generation) of structures to **Invent** new structures with improved "scores" related to properties desired for optimization. The nature of the evolutionary process (relative probabilities of various evolutionary "operators" and outcomes thereof) can be tailored to best suit individual projects and/or preferences.

The structure-modifying EA-Inventor "engine" can be used with literally any desired scoring function or composite scoring function. It is recognized that users may never agree on a single "best" scoring function and that different discovery projects are best addressed using different scoring functions. Although some very useful scoring functions are provided with EA-Inventor, the focus is not on the best possible scoring function, but rather on the best possible structure modifying "engine".

Chem-evolutionary Operators

EA-Inventor offers a very complete palette of 34 different, chemically-aware operators that never make a chemically invalid structural change. The operators enable generation of any desired chemical structure thereby ensuring that no substructural change is impossible.

The operators also enable making very small changes to individual atoms and bonds — not just large changes of fragments or groups. Therefore, users can apply "fine-tuning" to optimize desired properties and faster convergence. However, the operators can only make changes if the resulting structure is valid with respect to valence rules. Hydrogens may also be automatically added or deleted as necessary.

Undesirable structures are avoided by rules, as well as by reducing probabilities such as: fragments are classified as either changeable or non-changeable to avoid unlikely structures, ring operators are biased based on ring-size, other operators are biased to avoid undesirable Hetero-Hetero situations, etc.

Probabilistic Evolutionary Process

Relative probabilities determine which operator to apply to each selected compound and which outcome of each selected operator should be achieved (e.g., change sp² ... to sp³ or to sp?)

EA-Inventor operator decisions are all controlled by "spinning" variable-probability "roulette wheels" on which all relative probabilities can be controlled by the user and, optionally, set to zero — i.e. turned off. Probabilities do not only control operators

and outcomes — they also control (indirectly) the nature of the evolved population of compounds. EA-Inventor's default probabilities were chosen based on the relative frequency of various substructures found in MDDR.

Fixed "Core" Preservation

With EA-Inventor, users can indicate substructural features that should be included (preserved) in any invented structures. This is useful for keeping R-groups "constant" and "lead-hopping" to evolve new scaffold ideas. Also, users may keep a scaffold "constant" and modify R-groups for late-phase lead follow-up.

Features

EA-Inventor Library (shared object library):

- performs all of the structure modifications
- controls the evolutionary process

Complete palette of 34 carefully selected, chemically-aware operators, including:

- add fragment, delete fragment or group, swap fragments, swap groups, ...
- make or break ring, change ring size, ...
- change atomic number, hybridization, chirality, ...

Useful with any scoring function (often derived from separately licensed products) for "grading" each invented structure:

- apply a single scoring function such as:
 - distance to known leads in BCUT chemistry-space, MACCS vector-space, or both
 - docking-score
 - 3D-QSAR score (CoMFA[®]-like, pharmacophore-like, etc.)
- apply a composite scoring function; e.g. one or more of the above combined with:
 - ADME-related score
 - toxicity (selectivity) score
 - synthesizability score
- apply proprietary scoring functions

EA-Inventor Program (executable):

- runs directly from IRIX[®]/Linux[®] prompt
- runs from within script, protocol, or C-code
- runs through interactive questionnaire-style GUI which provides easy control over all options and sets up control file for non-interactive use in future

Hardware and Software Requirements

EA-Inventor requires a separate license, and runs on workstations operating under IRIX[®] (SGI[®]) or Linux[®] (x86). Utilization of scoring functions derived from other Tripos products requires a separate license agreement for each product.

Complementary Software

- **Advanced CoMFA** for refining and enhancing 3D QSAR models.
- **DiverseSolutions**[®] for designing, comparing, or selecting compound libraries.
- **FlexX**[™] for flexibly docking ligands into a binding site.
- **FlexS**[™] for performing shape-based screening of ligands in the absence of receptor structure.
- **GASP**[™] for developing pharmacophore hypothesis using full conformational flexibility.
- **HQSAR**[™] for performing automated QSAR analyses.
- **StructureFilter**[™] for filtering lists of structures using user-specified criteria.
- **Tuplets**[™] for pharmacophore-based virtual screening.
- **UNITY**[®] for locating compounds in databases that match a pharmacophore or fit a receptor site.

*EA-Inventor also interfaces with other vendors' software such as Catalyst[®] and MOE[™].



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